Managing Heart Failure
What’s old, What’s new?

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Cox South Hospital

Presentation Objectives

• Be Familiar with the utilization of new pharmacotherapy in concert with the tried and true

• Know the benefits and drawbacks of various monitoring options, both invasive and noninvasive

The Epidemic of Heart Failure

• 5 million patients with HF in US\textsuperscript{1}
• 550,000 new cases/year
• 6.6\%–9.8\% aged >65 years have HF

\textsuperscript{1} American Heart Association. 2014 Heart and Stroke Statistical Update.
Projected increase in the US population 65 years of Age or Older

Heart Failure: A Public Health Crisis
Hospitalizations Have Tripled in last 25 Years

Classification of Recommendations and Levels of Evidence

Heart Failure: A Public Health Crisis
Hospitalizations Have Tripled in last 25 Years

Classification of Recommendations and Levels of Evidence
Stages, Phenotypes and Treatment of HF

ACC/AHA Guidelines 2013

Asymptomatic

A At high risk for HF but without structural heart disease or symptoms of HF (e.g., patients with HTN or CAD)

B Structural heart disease but without symptoms of HF

C Structural heart disease with prior or current symptoms of HF

D Refractory/advanced HF requiring specialized interventions

Symptomatic

NYHA Class

Class I Asymptomatic: No limitation of physical activity. Ordinary activity does not cause sxs.

II Symptomatic with moderate exertion. Ordinary physical activity causes SOB, fatigue

III Symptomatic with minimal exertion. Less than usual activity causes sxs

IV Symptomatic at rest. Unable to carry on any activity without discomfort.

NYHA Class and Mortality

NYHA Class

Class I Asymptomatic: No limitation of physical activity. Ordinary activity does not cause sxs.

Class II Symptomatic with moderate exertion. Ordinary physical activity causes SOB, fatigue

Class III Symptomatic with minimal exertion. Less than usual activity causes sxs.

Class IV Symptomatic at rest. Unable to carry on any activity without discomfort

1-Yr Mortality

<table>
<thead>
<tr>
<th>Class</th>
<th>1-Yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>5-10%</td>
</tr>
<tr>
<td>Class II</td>
<td>5-10%</td>
</tr>
<tr>
<td>Class III</td>
<td>10-25%</td>
</tr>
<tr>
<td>Class IV</td>
<td>25-60%</td>
</tr>
</tbody>
</table>
### New York Heart Association Classification of Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>• No limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>• No undue fatigue, palpitation or dyspnea</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>• Slight limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>• Comfortable at rest</td>
</tr>
<tr>
<td></td>
<td>• Less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>• Marked limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>• Comfortable at rest</td>
</tr>
<tr>
<td></td>
<td>• Less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>IV</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>• Unable to carry out any physical activity without discomfort</td>
</tr>
<tr>
<td></td>
<td>• Symptoms of cardiac insufficiency at rest</td>
</tr>
<tr>
<td></td>
<td>• Physical activity causes increased discomfort</td>
</tr>
</tbody>
</table>

Criteria Committee of the New York Heart Association, 1964.

### Stage C: Nonpharmacological Interventions

- **Continuous positive airway pressure (CPAP)** can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.

- Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.

### Pathophysiology and Mechanisms in Heart Failure


Pathologic remodeling
Low ejection fraction
Death
Pump failure
Symptoms: Dyspnea, Fatigue, Edema
Chronic heart failure

Neurohormonal stimulation
Endothelial dysfunction
Myocardial toxicity
Vasoconstriction
Renal sodium retention
Arrhythmia
Coronary artery disease

Underlying etiology in ~60% of CHF

Underlying etiology in ~40% of CHF

Pathophysiologic Progression of HF
Normal
Injury
Adaptation
Remodeling
Architectural distortion

Compensatory hypertrophy
Dilated and fibrotic

Neurohumoral Response: Renin-Angiotensin-Aldosterone (RAAS)

Renin
Angiotensinogen
Angiotensin I
Angiotensin II
AT I receptor
Vascular remodeling
LV remodeling
Cell Growth
Aldosterone
Angiotensin
Converting Enzyme
Neurohormonal Blockade Across the CV Disease Continuum

- Angiotensin II (Renin-Angiotensin System [RAS])
- Norepinephrine (Sympathetic Nervous System [SNS])

RAS Inhibition
Beta-Blockade
Disease Progression

Treatment of Post-MI Patients with Asymptomatic LV Dysfunction (LVEF ≤ 40%)

SAVE Study
- All-cause mortality ↓ 19%
- CV mortality ↓ 21%
- HF development ↓ 37%
- Recurrent MI ↓ 25%


SOLVD: Studies Of Left Ventricular Dysfunction

Effect of ACE Inhibitors on Mortality Reduction in Patients With LVD or Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CHF</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
<td></td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>46%</td>
<td>0.82 (0.70–0.97)</td>
<td></td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
<td></td>
</tr>
<tr>
<td>Post MI</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.50–0.99)</td>
<td></td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
<td></td>
</tr>
<tr>
<td>SMILE</td>
<td>6.5%</td>
<td>8.3%</td>
<td>0.74 (0.52–1.01)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>21%</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Neurohumoral Interventions Across the Continuum

Patients With Reduced Left Ventricular Ejection Fraction

Angiotensin-converting enzyme (ACE) inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated.
**Patients With Reduced Left Ventricular Ejection Fraction**

Angiotensin II Receptor Blockers

Angiotensin II receptor blockers are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE-inhibitor intolerant (see full text guidelines).

**Trials with Aldosterone Blockade**

*Primary Endpoint: All-Cause Mortality*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Aldosterone Blockade</th>
<th>Hazard Ratio</th>
<th>Log-rank P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS</td>
<td>554/3319</td>
<td>478/3313</td>
<td>0.85 (0.75, 0.96)</td>
<td>0.008</td>
</tr>
<tr>
<td>RALES</td>
<td>386/841</td>
<td>284/822</td>
<td>0.70 (0.60, 0.82)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Study Design

- NYHA Class III-IV (N=1663)
- EF ≤ 35%
- Frequent monitoring of potassium
- 30% reduction in death
- 35% risk of hospitalization


Probability of Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>0.88</td>
</tr>
<tr>
<td>6</td>
<td>0.80</td>
<td>0.78</td>
</tr>
<tr>
<td>9</td>
<td>0.70</td>
<td>0.68</td>
</tr>
<tr>
<td>12</td>
<td>0.60</td>
<td>0.58</td>
</tr>
<tr>
<td>15</td>
<td>0.50</td>
<td>0.48</td>
</tr>
<tr>
<td>18</td>
<td>0.40</td>
<td>0.38</td>
</tr>
<tr>
<td>21</td>
<td>0.30</td>
<td>0.28</td>
</tr>
<tr>
<td>24</td>
<td>0.20</td>
<td>0.18</td>
</tr>
<tr>
<td>27</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>30</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

RALES: Spironolactone Improves Survival


EPHESUS: Improved Survival and Decreased Hospitalization

<table>
<thead>
<tr>
<th>Event rate at 16 months (%)</th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.007</td>
<td>0.006</td>
</tr>
<tr>
<td>Mortality or Hospitalization</td>
<td>0.017</td>
<td>0.016</td>
</tr>
</tbody>
</table>

P value 0.008 0.002


Patients With Reduced Left Ventricular Ejection Fraction

The Risks of Aldosterone Antagonists

Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine 2.5 mg/dL or less in men or 2.0 mg/dL or less in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.
Neurohormonal Blockade Across the CV Disease Continuum

<table>
<thead>
<tr>
<th>Post-MI LV dysfunction</th>
<th>Mild CHF</th>
<th>Moderate CHF</th>
<th>Severe CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE/SAVE/TRACE (ramipril/captopril/trandolapril)</td>
<td>SOLVD Treatment (enalapril)</td>
<td>CONSENSUS (enalapril)</td>
<td></td>
</tr>
<tr>
<td>EPHEUS (eplerenone)</td>
<td>?</td>
<td>RALES (spironolactone)</td>
<td></td>
</tr>
</tbody>
</table>

Neurohormonal Blockade Across the CV Disease Continuum

↑ Angiotensin II (Renin-Angiotensin System [RAS])

↑ Norepinephrine (Sympathetic Nervous System [SNS])

RAS Inhibition

β-Blockade

Disease Progression

Deleterious Effects of Norepinephrine in CV Disease

Injury to the heart (e.g., MI, HTN, DM)

Levels of norepinephrine

Negative cardiac effects

Negative vascular effects

Negative renal effects

Cardiac injury

Vasoconstriction

Sodium retention

Disease progression
Survival Benefits of Beta Blockers

**MERIT-HF**

- Beta-blocker: n=1100
- Placebo: n=1101

**COPERNICUS**

- Beta-blocker: n=1156
- Placebo: n=1133

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**P = 0.0002**

Risk ↓ 34%

Effect of Beta-Blockade on Outcome in Patients With Heart Failure and Post-MI LVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>HF Severity</th>
<th>Target Dosage (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol</td>
<td>carvedilol</td>
<td>mild to moderate</td>
<td>6.25 to 25 bid</td>
<td>↓48% disease progression</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>bisoprolol</td>
<td>moderate to severe</td>
<td>10 qd</td>
<td>↓34% mortality (P = 0.0001)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>metoprolol</td>
<td>mild to moderate</td>
<td>200 qd</td>
<td>↓34% mortality (P = 0.0062)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>carvedilol</td>
<td>severe</td>
<td>25 bid</td>
<td>↓35% mortality (P = 0.0014)</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>carvedilol</td>
<td>Post-MI LVD</td>
<td>25 bid</td>
<td>↓25% mortality (P = 0.031)</td>
</tr>
</tbody>
</table>

Neurohormonal Interventions Across the Continuum

- **AIRE/SAVE/TRACE** (ramipril/captopril/trandolapril)
- **SOLVD Treatment** (enalapril)
- **CONSENSUS** (enalapril)
- **CAPRICORN** (carvedilol)
- **US Carvedilol Trials** (carvedilol)
- **COPERNICUS** (carvedilol)
- **MERIT-HF** (metoprolol)
- **CIBIS II** (bisoprolol)
Patients With Reduced Left Ventricular Ejection Fraction

Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated.

Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yang, M.D., Peter Carson, M.D., Rajin D'Agostino, Ph.D., Keith Ferdinandy, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Wocner, M.D., Jay N. Cohn, M.D., and the African-American Heart Failure Trial Investigators

N Engl J Med
Volume 351;20:2049-2057
November 11, 2004
Conclusions

- The addition of a fixed dose of isosorbide dinitrate/hydralazine to standard therapy for African Americans with heart failure
  - 43% Reduction in mortality (P = .012)
  - 39% Risk of 1st Hospitalization (P<.001)
  - Improvement in Minnesota Living with Heart Failure Questionnaire

Patients With Reduced Left Ventricular Ejection Fraction

Recommendations for Hydralazine and Nitrates

The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, beta blockers, and diuretics.

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta blocker for symptomatic HF and who have persistent symptoms.
The Impact of Neurohormonal Interventions on SCD in Heart Failure: Are We Making Any Progress?

Medical Therapy for Stage C HF\textsubscript{a}EF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

Mortality Reduction with Pharmacotherapy

Optimal pharmacologic therapy (OPT) is effective in reducing mortality

- Beta-blockers: 40%
- ACE inhibitors: 30%
- Spironolactone (RALES): 30%
- Eplerenone (News): 21%

1. Mean mortality reduction from major β-blocker trials
2. Mean mortality reduction from major ACE inhibitor trials
3. Eplerenone (RALES) 3
4. Spironolactone (News) 2
5. Eplerenone (News) 1
6. Beta-blockers 4
7. ACE inhibitors 3
8. Spironolactone (RALES) 2
SCD in Heart Failure 1, 2

- Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of premature death in the first 2.5 yrs after diagnosis.

Magnitude of SCA in the US

The #1 Cause of Death

- SCA claims more lives each year than these other diseases combined.
- 450,000 Sudden Cardiac Arrest

In people diagnosed with CHF, sudden cardiac arrest occurs at 6-9 times the rate of the general population

CHF predicts increased sudden death and overall mortality. During a 39-year follow-up of subjects in the Framingham heart study, the presence of CHF significantly increased sudden death and overall mortality in both men and women 1.
Relationship of SCD and Left Ventricular Dysfunction

- Reduced left ventricular ejection fraction (LVEF) remains the single most important risk factor for overall mortality and sudden cardiac death\(^1\).
- Increased risk is measurable at ejection fractions above 30%, but an ejection fraction ≤ 30% is the single most powerful independent predictor for SCD\(^2\).

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\(^1\) Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J. 2001;22:1374-1450.

Etiology of Sudden Cardiac Death

Coronary Heart Disease

- An estimated 13 million people had CHD in the U.S. in 2002. ¹
- Sudden death was the first manifestation of coronary heart disease in
  50% of men and 63% of women. ¹
- CHD accounts for at least 80% of sudden cardiac deaths in Western cultures.²

80% Coronary Heart Disease

5% Other³

15% Cardiomyopathy

* ion-channel abnormalities, valvular or
congenital heart disease, other causes

Etiology of Sudden Cardiac Death²³

References:
Conditions Predisposing to Ventricular Arrhythmia in Heart Failure Patients

• Electrophysiological abnormalities
  – Cellular hypertrophy & interstitial fibrosis can result in prolongation of the action potential
  – Increases propensity for early after depolarizations (Torsades de Pointes)

• Neurohormonal Activation
  – Persistent adrenergic stimulation of the failing heart is maladaptive & arrhythmogenic

Singh S. J Cardiovasc Electrophysiol 1997;8:89-97

Conditions Predisposing to Ventricular Arrhythmia in Heart Failure Patients

• Electrolyte abnormalities
  – Predisposition to hypokalemia is caused by diuretic therapy, activation of the renin-angiotensin-aldosterone system, and sympathetic activation
  – The effects of hypokalemia on ventricular arrhythmias are amplified in the setting of structural heart disease

Sweeney MO. PACE 2001;24:871-888.

Underlying Arrhythmias of Sudden Cardiac Arrest

- VT 62%
- Primary VF 8%
- Bradycardia 17%
- Torsades de Pointes 13%

Implantable Cardioverter Defibrillator (ICD)

ICD Survival Benefit: Secondary Prevention Studies

Overall Death
Arrhythmic Death

Urgency of Sudden Cardiac Arrest

Resuscitation Success vs. Time

% Mortality Reduction

Overall Death
Arrhythmic Death

SUCCESS

% Success

Time (minutes)

Chance of success reduced 7-10% every minute

The Epidemic of Heart Failure

- 5 million patients with HF in US
- 550,000 new cases/year
- 6.6%–9.8% aged >65 years have HF

1. AHA. 2004 Heart and Stroke Statistical Update.

Despite medical advances, Heart Failure hospitalization is a worsening epidemic

THE PROBLEM:
Unless focused, dramatic measures are taken, the clinical and financial burden to society is only going to escalate.

Cardiomems: another mode to help patients and reduce rehospitalization

Clinical trial and early commercial use demonstrates that PA-pressure guided therapy:
- Prevents Acute Decompensation
- Effectively Lowers PA Pressures
- Lowers Hospitalization and Readmission Rates
- Improves Quality of Life

1. Graph adapted from NIH, Accessed 2016.
Goal of heart failure management:
slow disease progression by preventing decompensation

Each Event Accelerates Downward Spiral of Myocardial Function
With each subsequent HF-related admission, the patient leaves the hospital with a further decrease in cardiac function.

THE GOAL: Maintain fluid volume to avoid acute decompensation and hospitalization, using proven drug and device therapies.

Current HF Management:
how well do current tools KEEP PATIENTS STABLE and out of the hospital?

90% of HF hospitalizations due to symptoms of pulmonary congestion
Post-hoc analysis of 463 acute decompensated HF patients from GOAL-HF and CARRESS-HF

TODAY’S TOOLS ARE INADEQUATE at relieving congestion (inpatient) and preventing re-congestion and readmission (outpatient) — even at well-established HF management programs and with the best HF-trained specialists.

Current HF Management:
Can we reliably use weight change as an indicator of rising pressure?

Body Weight and RV Diastolic Pressure

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 kg weight gain</td>
<td>9%</td>
<td>97%</td>
</tr>
<tr>
<td>2% weight gain</td>
<td>17%</td>
<td>94%</td>
</tr>
<tr>
<td>3 lbs in 1 day</td>
<td>22.5%</td>
<td>-</td>
</tr>
<tr>
<td>5 lbs in 3 days</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NO CORRELATION
Daily weights do not correlate with filling pressures.
**Current HF Management:**

**How reliable are clinical examinations in assessing **RISING** pressure?**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate of Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>48</td>
<td>78</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Edema</td>
<td>10</td>
<td>94</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Pulse Press</td>
<td>Cardiac Index</td>
<td>27</td>
<td>69</td>
<td>52</td>
</tr>
<tr>
<td>S3</td>
<td>36</td>
<td>81</td>
<td>69</td>
<td>54</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>PCWP</td>
<td>50</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>Rales</td>
<td>13</td>
<td>90</td>
<td>60</td>
<td>48</td>
</tr>
</tbody>
</table>

**RESULTS**

Data from clinical evaluations have poor sensitivity and predictive value in determining hemodynamic profile.

Clinical examination has **LIMITED RELIABILITY** in assessing filling pressures.

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**The CLINICAL burden:**

Heart failure is a **GROWING GLOBAL CONCERN** for patients, providers and health care systems.

**UNITED STATES**

- **PREVALENCE:** 2.2% prevalence
- **INCIDENCE:** 915,000 people ≥ 45 years of age are newly diagnosed each year with HF
  - Projected to increase to > 1M people ≥ 18 years of age with HF by 2030
- **MORTALITY:**
  - 50% will die within 5 years
  - 50% of the costs are attributed to hospitalization

High incidence, high prevalence and poor prognosis despite advances in the treatment of heart failure over the past few decades.

**The ECONOMIC burden:**

Heart failure is a significant and growing contributor to overall health system costs.

**UNITED STATES**

- **HOSPITALIZATIONS & READMISSIONS**
  - > 1,100,000 hospitalizations for HF
  - > 3,000,000 hospitalizations include HF as a contributor
  - > 25% all-cause readmission within 30 days, > 50% within 6 months

Despite advances in medical therapies to treat heart failure, the hospitalization rate has not changed significantly from 2003. As a result, heart failure continues to be a MAJOR DRIVER OF OVERALL HEALTH CARE COSTS.

- **COSTS**
  - Cost of medications for HF are projected to increase to ≥ $70B by 2030, a 2x increase from 2013
  - 50% of the costs are attributed to hospitalization

---

1. CDC NCHS National Hospital Discharge Survey, 2000-10.
**Current HF Management:**
How can we get ahead of symptoms associated with acute decompensation?


Delivers insight into the early onset of worsening HF to more proactively manage HF patients and improve outcomes

Cardiomems HF System:

**CHAMPION TRIAL design:** RANDOMIZED (Part 1) AND OPEN ACCESS (Part 2)

TRIAL HYPOTHESIS: In addition to basing treatment on signs and symptoms, adjusting medications based on PA pressures will reduce HF-related hospitalizations.

Previously hospitalized patients (at least one visit to HF clinic) with NYHA class III or IV heart failure for at least 3 months

All took daily readings.

**PART 1: RANDOMIZED ACCESS**

Cardiomems PA Sensor Implanted

- Treatment Group: n = 270
- Control Group: n = 280

- Study Start: n = 460
- Transition to Former Treatment Group: n = 177
- Transition to Former Control Group: n = 170

**PART 2: OPEN ACCESS**

Abraham WT, Lancet, 2011
CHAMPION TRIAL design:

**PART 1: Prospective, multi-center, randomized, controlled, single-blind clinical trial**

**Purpose:** Evaluate the safety and efficacy of the CardioMEMS™ HF System in reducing HF related hospitalizations in NYHA class III heart failure patients.

**Treatment Group**: n = 550
- Traditional HF management guided by PA pressure information
- Managed to target PA pressures:
  - Systolic: 15 – 35 mmHg
  - Diastolic: 8 – 20 mmHg
  - Mean: 10 – 25 mmHg

**Control Group**: n = 280
- Traditional HF management

**Secondary Endpoints:**
- Change in PA pressure at 6 months
- No. of pts admitted to hospital for HF
- Days alive outside of hospital
- QOL (MLHFQ)

**Study exits < 6 mos.**:
- Total: 26 (9.3%)
- Death: 20 (7.1%)
- Other: 6 (2.2%)


**PART 2: Confirming Effectiveness and Sustained Benefit of PA Pressure Monitoring**

**Purpose:** Given the Part 1 and Part 2 CHAMPION trial success, evaluate the impact of opening access to PA pressure information in the former control group.

**Transition to Former Treatment Group**: n = 177
- Traditional HF management guided by PA pressure information

**Transition to Former Control Group**: n = 170
- Traditional HF management guided by PA pressure information

**NEW ACCESS**
- to PA pressure information.

**Study exits**: 43
- Death: 21 (12.3%)
- Other: 22 (12.9%)

**Study exits**: 58
- Death: 31 (17.5%)
- Other: 27 (15.2%)

**CHAMPION Trial results:**

**Primary Endpoint**
- Patients managed with PA pressure data had **significant relative risk reduction** as compared to the control group.

**Patients managed with PA pressure data had significant relative risk reduction** as compared to the control group.

### CHAMPION Trial results:
#### Primary Safety Endpoints and Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n = 270)</th>
<th>Control (n = 280)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Safety Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related or system-related complications</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>= 0.0001</td>
</tr>
<tr>
<td>Pressure-sensor failures</td>
<td>0</td>
<td>0</td>
<td>= 0.0001</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in PA mean pressure mean-AUC (mm Hg x days)</td>
<td>-156</td>
<td>33</td>
<td>0.008</td>
</tr>
<tr>
<td>Number and proportion of patients hospitalized for HF (%)</td>
<td>35 (23%)</td>
<td>80 (29%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Days alive and out of hospital for HF (mean ± SD)</td>
<td>174.4 ± 31.1</td>
<td>172.5 ± 37.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Quality of life (Minnesota Living with Heart Failure Questionnaire, mean ± SD)</td>
<td>45 ± 26</td>
<td>51 ± 25</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**ALL ENDPOINTS MET.**

Both primary safety endpoints and all secondary endpoints were met at 6 months.

---

### CHAMPION Trial results:
#### PA PRESSURE MEAN CHANGE FROM BASELINE

By targeting PA pressure ranges and titrating medications, the overall mean PA pressure is reduced over time.

---

### CHAMPION Trial results:
#### Number Needed to Treat to Prevent One HF-related Hospitalization

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trial</th>
<th>Mean Duration of Randomized Follow-Up</th>
<th>Adjusted Reduction in HF Hospitalization Rates</th>
<th>NNT/Year to Prevent 1 HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>COPERNICUS</td>
<td>10 months</td>
<td>33%</td>
<td>7</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>RALES</td>
<td>24 months</td>
<td>35%</td>
<td>7</td>
</tr>
<tr>
<td>CRT</td>
<td>CARE-HF</td>
<td>24 months</td>
<td>52%</td>
<td>7</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>MERIT-HF</td>
<td>12 months</td>
<td>25%</td>
<td>15</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>SOLVD</td>
<td>41 months</td>
<td>35%</td>
<td>15</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>EMPHASIS-HF</td>
<td>21 months</td>
<td>38%</td>
<td>16</td>
</tr>
<tr>
<td>Diuretics</td>
<td>DIG</td>
<td>37 months</td>
<td>24%</td>
<td>17</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Valsartan</td>
<td>23 months</td>
<td>23%</td>
<td>18</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>CHARM</td>
<td>40 months</td>
<td>27%</td>
<td>19</td>
</tr>
<tr>
<td>PA pressure monitoring</td>
<td>CHAMPION</td>
<td>16 months</td>
<td>33%</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

Neprilysin breaks down important peptides that counter the negative consequences of the heart failure milieu.

Neprilysin 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)

**Neprilysin**

**Neprilysin inhibition**

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis
- Hypertrophy
- Sodium retention

- Inactive metabolites
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)

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF: Entry Criteria

- NYHA class II/IV heart failure
- LV ejection fraction ≤ 40%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization

PARADIGM-HF Was Designed to Show Incremental Effect on Cardiovascular Death

Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial

The sample size of the trial was determined by effect on cardiovascular mortality, not the primary endpoint

The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on cardiovascular mortality (in addition to the primary endpoint)

Difference in cardiovascular mortality of 15% between LCZ696 and enalapril was prospectively identified as being clinically important (n=8000 yielded 80% power)
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

(all comparisons are versus enalapril 20 mg daily, not versus placebo)

PARADIGM-HF: Cardiovascular Death

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

ENALAPRIL (n=4212)

LCZ696 (n=4187)

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

ENALAPRIL (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.71-0.89)
P = 0.00004
Number need to treat = 32
**PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.000002</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

**PARADIGM-HF: Effect of LCZ696 vs Enalapril on Secondary Endpoints**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Treatment effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCCQ clinical summary score at 8 months</td>
<td>−2.99 ± 0.36</td>
<td>−4.63 ± 0.36</td>
<td>1.64 (0.63, 2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New onset atrial fibrillation</td>
<td>84/2670 (3.2%)</td>
<td>83/2638 (3.2%)</td>
<td>Hazard ratio 0.97 (0.72, 1.31)</td>
<td>0.84</td>
</tr>
<tr>
<td>Protocol-defined decline in renal function</td>
<td>94/4187 (2.3%)</td>
<td>108/4212 (2.6%)</td>
<td>Hazard ratio 0.86 (0.65, 1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Dosing**

- Patients receiving initial daily dose of >50 mg of metoprolol erbumetate/olmetoprolol or another ACD, for example:
  - Lisinopril 10 mg
  - Ramipril 5 mg

- Patients receiving initial daily dose of ≤50 mg of metoprolol erbumetate/olmetoprolol or another ACD, for example:
  - Lisinopril 5 mg
  - Ramipril 2.5 mg

- Double the dose of LCZ696 every 2-4 weeks, as tolerated by the patient, to a maximum of 800 mg twice daily.

- Double the dose of Enalapril every 2-4 weeks, as tolerated by the patient, to a maximum of 40 mg twice daily.
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril** in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by incremental 20%
- Reducing the risk of HF hospitalization by incremental 21%
- Reducing all-cause mortality by incremental 16%
- Incrementally improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril** . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

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**PARADIGM-HF: Summary of Findings**

**Ivabradine (Corlanor)**

- Ivabradine is indicated to reduce the risk of hospitalization for worsening HF (systolic)
- For patients with stable, symptomatic chronic HF with
  - EF 35% or less
  - Sinus rhythms with HR >/= 70
  - receiving maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.

**Ivabradine (Corlanor)**

- Acts directly on sinus node, Na-K current
- No affect on blood pressure or cardiac conduction.
- No inotropic effect
- 5mg – 7.5 mg BID
Ivabradine (Corlanor)

Adverse events included bradycardia (10% for ivabradine versus 2.2% for placebo), hypertension (8.9% versus 7.8%), atrial fibrillation (8.3% versus 6.6%), and phosphenes (2.8% versus 0.5%).

Figure 2. Kaplan-Meier Cumulative Event Curve for Primary Composite Endpoint of Hospitalisation for Worsening Heart Failure or Cardiovascular Death (HFpEF Total)