Recent Advances in Heart Failure

Heart Failure in 2016
- Only CVD with stagnant/ increasing incidence, prevalence, morbidity (hospitalizations), mortality
- 20+ mil patients worldwide (6 mil in US)
  - One and 5 years survival: 90% and 50%
  - One year hospitalization rate 20-25%
- HF reduced EF (HFrEF) – EF < 40%
  - Lots of medications, devices
- HF preserved EF (HFpEF) – EF > 50%
  - No medications, devices
- HF borderline or improved EF – EF 40-50%
- Remote management needed to decrease costs and serve an increasing number of patients

Current Management of HFrEF

<table>
<thead>
<tr>
<th>Treat Clinical Congestion:</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow Disease Progression:</td>
<td>ACE-I/BB/MRB/CRT ARB</td>
</tr>
<tr>
<td>Sudden Death:</td>
<td>BB/MRB/ICD</td>
</tr>
<tr>
<td>Treat Residual Symptoms:</td>
<td>Digoxin, ARB, CRT Hy-ISDN</td>
</tr>
<tr>
<td>Advanced Disease:</td>
<td>Heart transplant LVAD</td>
</tr>
</tbody>
</table>

Drugs Associated with Improved Survival in HFrEF

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers; BB: beta-blockers; MRB: mineralocorticoïd receptor blockers; Hy-ISDN: hydralazine/isosorbide dinitrate; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; LVAD: left ventricular assist devices
Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

- Increased activity or response to maladaptive mechanisms
- Decreased activity or response to adaptive mechanisms

Evolution and progression of heart failure

New Drugs: Mechanisms of Action

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

- Increased activity or response to maladaptive mechanisms
- Decreased activity or response to adaptive mechanisms

Evolution and progression of heart failure

PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

LCZ696 400 mg daily
Enalapril 20 mg 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 Inclusion

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40%
- BNP ≥ 150 (or NT-proBNP ≥ 600)
- 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
- SBP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization

PARADIGM-HF Trial Design

Randomization

Single-blind run-in period

Double-blind period

(1:1 randomization)

4187 pts. (375 mg daily)

4212 pts. (18.9 mg daily)

PARADIGM-HF Endpoints

- CVD death or first HF hospitalization
  - Trial powered for 15% CVD mortality reduction
- All-cause mortality
- Change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Time to new onset of atrial fibrillation
- Time to first occurrence of a decline in renal function

PARADIGM-HF Baseline Char.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/mL)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>21.9%</td>
<td>21.4%</td>
</tr>
</tbody>
</table>
PARADIGM-HF Results: CV Death or 1st HF Hospitalization


<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death or 1st HF Hospitalization</td>
<td>9.7</td>
<td>11.8</td>
<td>0.80 (0.73-0.87)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.9</td>
<td>7.3</td>
<td>0.80 (0.71-0.89)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>1st HF Hospitalization</td>
<td>5.7</td>
<td>6.9</td>
<td>0.79 (0.71-0.89)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

PARADIGM-HF Results: Sudden Cardiac Death


PARADIGM-HF Results: Heart Failure Death

**PARADIGM-HF Results:**

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized, no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>


**PARADIGM-HF Summary:**

In HFrEF, compared to high doses of enalapril:

- LCZ696 was more effective than enalapril in . . .
  - Reducing the risk of CV death, sudden death and HF death by incremental 20%
  - Reducing the risk of HF hospitalization by incremental 21%
  - Reducing all-cause death by incremental 16%
  - Incrementally improving symptoms and physical limitations

- LCZ696 was better tolerated than enalapril . . .
  - Less likely to cause cough, hyper K or renal impairment
  - Less likely to be discontinued due to an adverse event
  - Not more likely to cause serious angioedema
  - More hypotension, but no increase in drug discontinuation


**ARNI Doubles Survival in HFrEF Compared to ACE-I/ ARBs**

- Stop ACE-I for 48 hrs. prior
- Make sure patient is not “dry” (adjust diuretics)
- Start with low dose (24/26 mg BID) and increase dose slowly (every 7-10 days) as tolerated if patients’ baseline BP < 120 mmHg
- If BP > 120 mmHg, one can start at higher dose (49/51 mg BID) and titrate up faster
- For patients that cannot achieve target dose (98/102 mg BID), check NT-pro BNP and echocardiogram (LV size, LVEF) after 3 months on therapy to assess benefit


**Caveats of Using ARNI**

- Stop ACE-I for 48 hrs. prior
- Make sure patient is not “dry” (adjust diuretics)
- Start with low dose (24/26 mg BID) and increase dose slowly (every 7-10 days) as tolerated if patients’ baseline BP < 120 mmHg
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Future Management of HFrEF

Treat Congestion: Diuretics
Slow Disease Progression:
  - ARNI
  - BB
  - MRB
  - CRT
Sudden Death:
  - ARNI
  - BB
  - MRB
  - ICD
Treat Residual Symptoms:
  - Digoxin, ARB, CRT
Advanced Disease:
  - Heart transplant
  - LVAD

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers; ARNI: angiotensin receptor blocker and neprilysin inhibitor; BB: beta-blockers; MRB: mineralocorticoid receptor blockers; Hy-ISDN: hydralazine/isosorbide dinitrate; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; LVAD: left ventricular assist device

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ARNI in HFrEF: PARAMOUNT and PARAGON

Stay tuned: fall 2019

Heart Failure Hospitalizations: 1 Million and Counting....
Timing of Heart Failure Re-Hospitalizations:


Heart Failure Hospitalizations: All Roads Lead to Rome


High Mortality Post Discharge for Heart Failure Hospitalization


Heart Failure Signs/ Symptoms in Hospitalized Patients


Poor Ability to Predict Elevated Intracardiac Filling Pressures

Sens. Spec. PPV NPV

Congestion Does not Translate in **EARLY** Signs/Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial edema</td>
<td>60</td>
<td>73</td>
<td>78</td>
<td>53</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>43</td>
<td>79</td>
<td>76</td>
<td>47</td>
</tr>
</tbody>
</table>


The Congestion Iceberg in Heart Failure

- **Systemic congestion** (Leg edema, JVD, Hepatomegaly)
- **↑ LV diastolic pressure**
- **↑ Blood volume**
- **↑ PA Pressure**
- **Alveolar edema**
- **Redistribution in pulmonary vascular bed + interstitial edema**
- **Hemodynamic congestion (Increased PWP)**
- **Neurohormonal activation => ↑ Blood volume**
- **↑ LV diastolic pressure**

Abnormal LV function (Sys and/or Dia)

Hemodynamic Directed Care

Congestion Precedes Most Heart Failure Hospitalizations

CardioMEMS HF System

PA Sensor and Delivery System

Patient Electronics System

PA Pressure Database

Physician Access Via Secure Website

Heart Failure Pressure Sensor

\[ f = \frac{1}{2\pi \sqrt{L \cdot C(p)}} \]

Sensor Cross section

CHAMPION Trial: Baseline Char.


<table>
<thead>
<tr>
<th>Demographics</th>
<th>Treatment group (n=279)</th>
<th>Control group (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.3 (14.3)</td>
<td>61.8 (12.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (5.2)</td>
<td>28.0 (7.3)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>122.3 (19.5)</td>
<td>129.3 (23.9)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>72.4 (12.9)</td>
<td>73.0 (13.3)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.4 (0.6)</td>
<td>1.35 (0.6)</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>60.4 (22.5)</td>
<td>61.8 (23.2)</td>
</tr>
<tr>
<td>INR (mg/dL)</td>
<td>2.6 (1.5)</td>
<td>2.5 (1.6)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72.3 (23.6)</td>
<td>77.2 (26.4)</td>
</tr>
</tbody>
</table>

Arterial stiffness

Friction (cmH2O)

Humidifiers
CHAMPION Trial: Results


CHAMPION Trial – Long Term Results


Success of a CHAMPION: Treatment Algorithm


CHAMPION Trial: Medications Changes

Congestion in Heart Failure

- Congestion is the lead cause of HF hospitalizations
- Congestion contributes to progression of HF
- Patients leave hospital with congestion, resulting in high rehospitalization rate
- Congestion is often *subclinical* and difficult to assess when present
- Significant dissociation between *hemodynamic* and *clinical* congestion, even when hemodynamics are very abnormal
- Need for better monitoring of degree and changes in congestion (more accurate and sensitive)
Conclusions

• Monitoring PAP/ PWP can provide early warning of condition worsening/ decompensation much better than body weight and before symptoms
• Most changes occur over a few days - weeks
• Having a treatment algorithm based on PAP/PWP values is key to successful treatment and preventing heart failure readmissions
• Always treat to max: drive pressures down to patient’s normal

Future Management of HFrEF

Diuretics
Implantable/ wearable hemodynamic monitors

Sudden Death:
ARNI       BB       MRB       ICD

Treat Residual Symptoms:
Digoxin, ARB, CRT
Hy-ISDN

Advanced Disease:
Heart transplant, LVAD

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin 2 receptor blockers; ARNI: angiotensin receptor blocker and nephrilysin inhibitor; BB: beta-blockers; MRB: mineralocorticoid receptor blockers; Hy-ISDN: hydralazine/isosorbide dinitrate; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; LVAD: left ventricular assist devices