Recent Advances in Heart Failure

Heart Failure in 2016
- Only CVD with stagnant/increasing incidence, prevalence, morbidity (hospitalizations), mortality
- 20+ million patients worldwide (6 million 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

| Treat Clinical Congestion: | Diuretics |
| Slow Disease Progression: | ACE-I/BB MRB CRT ARB |
| Sudden Death: | BB MRB ICD |
| Treat Residual Symptoms: | Digoxin, ARB, CRT |
| Advanced Disease: | Heart transplant LVAD |

Drugs Associated with Improved Survival in HFrEF

- Drugs that inhibit the renin-angiotensin system (RAS) have modest effects on survival
- 0%, 10%, 20%, 30%, 40% decrease in mortality

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta blockers; MRB: mineralocorticoid receptor blockers; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; LVAD: left ventricular assist device.
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

Enalapril
LCZ696

10 mg BID
100 mg BID
200 mg BID

2 weeks 1-2 weeks 2-4 weeks

4187 pts. (375 mg daily)
4212 pts. (18.9 mg daily)

Enalapril 10 mg BID

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>59.6%</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 (%)</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 (885-354)</td>
<td>1594 (886-3309)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-468)</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>93.2%</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</th>
<th>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</td>
<td>(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</td>
<td>(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</td>
<td>(0.71-0.89)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

PARADIGM-HF Results: Heart Failure Death
PARADIGM-HF Results:

<table>
<thead>
<tr>
<th>Prospective 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>16</td>
<td>9</td>
<td>NS</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
Future Management of HFrEF

- **Treat Congestion:** Diuretics
- **Progression:**
  - ARNi, BB, MRB, CRT
- **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 II receptor blockers; ARNi: angiotensin receptor blocker and neprilysin inhibitor; BB: beta blockers; MRB: mineralocorticoid receptor blockers; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; LVAD: left ventricular assist device

Stay tuned: fall 2019

ARNi in HFpEF: PARAMOUNT and PARAGON

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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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>79</td>
<td>58</td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>PND</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53</td>
<td>57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sign</th>
<th>Admission</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP &gt; 8 cm</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>Rales</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>S3 gallop</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Edema &gt; 2+</td>
<td>50</td>
<td>13</td>
</tr>
</tbody>
</table>
Poor Ability to Predict Elevated Intracardiac Filling Pressures

Sens. Spec. PPV NPV

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<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>


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**The Congestion Iceberg in Heart Failure**

- Systemic congestion (Increased PWP)
- Dyspnea
- Alveolar edema
- Redistribution in pulmonary vascular bed + interstitial edema
- Hemodynamic congestion (Increased PWP)
- Neurohormonal activation => increased blood volume, LV diastolic pressure

Abnormal LV function (Sys and/or Dia)

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Hemodynamic Directed Care

**Congestion Precedes Most Heart Failure Hospitalizations**

**Congestion Precedes Most Heart Failure Hospitalizations**

CardioMEMS HF System

Heart Failure Pressure Sensor

CHAMPION Trial: Baseline Char.
CHAMPION Trial: Results


CHAMPION Trial – Long Term Results


Success of a CHAMPION: Treatment Algorithm


CHAMPION Trial: Medications Changes

CHAMPION Trial: Diuretic Changes by PA Pressures

- Congestion is the lead cause of HF hospitalizations
- Congestion contributes to progression of HF
- Patients leave hospital with congestion, resulting in high rehospitalization rates
- 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

<table>
<thead>
<tr>
<th>Treat Congestion</th>
<th>Diuretics</th>
<th>Implantable/wearable hemodynamic monitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td>Sudden Death:</td>
<td>ARNI</td>
<td>BB MRB ICD</td>
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