A Review of the State of the Science in Heart Failure

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Heart Failure: The Clinician’s Perspective from 40,000 ft.
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Director, Cardiology, Einstein Campus
Montefiore-Einstein Medical Center
Bronx, NY
Chair CLLCD AHA
Disclosures

- Advisory Board: Relypsa, modest
- Speakers Bureau: None
- FDA Senior Staff Fellow
- Medscape: Heart Failure editor/blog

*Today my comments are purely my own and speak as a clinician with over 20 years of HF/Transplant/LVAD experience.*
**HFReF clinical goals**

- **When are my patients the happiest?**
  - When they feel better
    - Independence
    - Self care
    - More function ADL’s
    - Better appetite
  - Out of the hospital
    - Stretch out their visits
    - No arrhythmias, especially AFib
  - When they are told they don’t need an ICD because their LV is better
  - Their heart has improved
  - When I simplify their med regimen
    - Limit diuretics
  - When they meet their life milestones
  - Health status including QOL

- **When am I the happiest?**
  - See reverse remodeling
    - Equates to lower mortality
    - No need for ICD
    - Less MR
  - Keep them out of the hospital
    - Last hospitalization
    - No arrhythmias
  - When I can medicate them to my standards
    - Keep them euvolemic
    - When adherent to meds
    - Limit diuretics
    - Minimize side effects
  - When I hear how much they can do—walk as much as they want
  - Loosing weight (not muscle mass)
  - Increased activity levels
  - Na and K are stable
  - Stretch out their visits
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  - Increased activity levels
    - Na and K are stable
    - Stretch out their visits
Continuity of the syndrome forgotten

NYHA classification

NYHA I

NYHA II

NYHA III

NYHA IV

STAGE B

NYHA classification

Compensated

Chronically decompensated

Acutely decompensated

Clinical status

First myocardial injury

First episode of AHF with hospitalization

ED

CCU

Telemetry

DC

Early Post DC

Outpatient

DEATH
“Failure” of Usual Care in Heart Failure

- Failure to prescribe evidence-based medications
- Failure to discontinue medication that may exacerbate HF
- Failure to titrate medications to target doses
- Failure to adhere to prescribed medications
- Failure to adequately address comorbidities
- Failure to consider device therapies
- Failure to provide adequate dietary counseling
- Failure to comply with dietary regimen
- Failure to seek early care with escalating symptoms
- Failure of adequate discharge planning
- Failure of adequate follow-up
- Failure of adequate monitoring
- Failure of patient social support systems
- Failure to address patient and care-giver needs

Hospitalizations: An important outcome for HFReF at a minimum, 30, 60 and 90 days | The Why’s

Why do I believe in reducing hospitalizations (all kinds)

- Increased mortality
- The revolving door
- Good drugs removed and Good drugs not given
- Bad drugs given
- Loss of function in bed
- Poor physical therapy or rehab
- No consistent pattern of care determined by attending (often not even Cardiology)
- LOS usually not sufficient to reverse the storm and adequately decongest. Pressure to discharge

- Hospitalizations (all cause) should be an OUTCOME
- HF Hospitalizations should be an OUTCOME
- Hospitalization equivalents (ED visit, unscheduled HF office visit) should be an OUTCOME
Outcomes in Patients Hospitalized with HF

Hospital Readmissions

- 30 days: 20%
- 6 months: 50%

Median hospital LOS: 6 days

Mortality

- 30 days: 12%
- 12 months: 33%
- 5 years: 50%

Annual mortality rate
- NYHA class III HF: 12% [COPERNICUS DATA]
- NYHA class II HF: 7% [SCD-HeFT DATA]
Survival After HF Hospitalizations

Median Survival Years

Setoguchi et al
Am Heart J 2007

11,110 3264 5472 4098
Typical List of Meds: BB Clinic
What am I confident of?

- GDMT
- Reverse remodeling should mean improvement in outcomes
- Exercise therapy can improve health outcomes, safe
- Capturing health status clinically
- Other prognostic factors, e.g., serum sodium, Pro BNP, VO2
Why do I insist on GDMT?

- It works!
  - Consistent
  - Gradual
  - Know pharmacology
  - Confident with dosing
  - Follow biomarkers

- The inability to medicate (by experts) = Outcome

- Not a checkbox without doses or reasons

- Can it be done?
Incremental Benefits with HF Therapies
(Cumulative % Reduction in Odds of Death at 24 Months)

Reverse Remodeling?

- Remodeling is an adverse myocardial process
- Advanced remodeling ______ worse outcomes
- Remodeling involves not only myocytes
- Surrogates of remodeling or its true reversal:
  - LVEDV, LVEDVi
  - LVESV, LVESVi
  - Mass
  - EF
  - Reduction or resolution of MR
- Remodeling is a time related process
- Reverse remodeling is a time related process
- May serve as a response to specific therapies

*Reverse remodeling should be linked to favorable outcomes: Causal relationship*

*Should reverse remodeling be an outcome: YES*
### Heart Failure Clinic Stats  CWRU 2002-2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Pt Visits</th>
<th>Admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1630</td>
<td>42</td>
</tr>
<tr>
<td>2003</td>
<td>1800</td>
<td>48</td>
</tr>
<tr>
<td>2004</td>
<td>1600</td>
<td>42</td>
</tr>
</tbody>
</table>

- **Age**: 59 ± 16 years
- **Gender**: 49% women
- **Etiology**: 41% ICM
- **Wt**: 175 lbs
- **B/P**: 133/70
- **HR**: 78
- **NYHA**: 2.4 ± 0.8
## Beta blocker use in CASE HF clinic

<table>
<thead>
<tr>
<th></th>
<th>Improved LVEF</th>
<th>Non-Improved</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=37</td>
<td>N=48</td>
<td></td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>40</td>
<td>48</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Caucasian (%)</strong></td>
<td>47</td>
<td>44</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Nonischemic (%)</strong></td>
<td>77</td>
<td>58</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Initial LVEDD (mmHg)</strong></td>
<td>6.4</td>
<td>6.3</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>ACEI Use (%)</strong></td>
<td>95</td>
<td>83</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Mean Dose of ACEI (mg/day)</strong></td>
<td>36</td>
<td>35</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>β-Blocker Use (%)</strong></td>
<td>81</td>
<td>77</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Initial Pulmonary Artery Systolic Pressure (mmHg)</strong></td>
<td>37</td>
<td>45</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Initial Peak Oxygen Uptake (ml/kg/min)</strong></td>
<td>13.8</td>
<td>13.6</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Cardiac Index (L/min/m²)</strong></td>
<td>2.3</td>
<td>2.5</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Initial NYHA Class</strong></td>
<td>2.4</td>
<td>2.5</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*HFSA 2002*
Beta blocker use in CASE HF clinic

Figure 2: Changes in LVEF

<table>
<thead>
<tr>
<th>Improved LVEF (N=37)</th>
<th>Not Improved (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LVEF</td>
<td>Post LVEF</td>
</tr>
<tr>
<td>Improved LVEF (N=37)</td>
<td></td>
</tr>
<tr>
<td>Initial LVEF (N=37)</td>
<td>44%</td>
</tr>
<tr>
<td>Post LVEF (N=48)</td>
<td>26%</td>
</tr>
<tr>
<td>Initial LVEF (N=37)</td>
<td>23%</td>
</tr>
<tr>
<td>Post LVEF (N=48)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3: Changes in LVEDD

<table>
<thead>
<tr>
<th>Improved LVEF (N=37)</th>
<th>Not Improved (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LVEDD (mmHg)</td>
<td>Post LVEDD (mmHg)</td>
</tr>
<tr>
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<td>6.4</td>
</tr>
<tr>
<td>Initial LVEDD (mmHg)</td>
<td>5.3</td>
</tr>
<tr>
<td>Post LVEDD (mmHg)</td>
<td>6.3</td>
</tr>
<tr>
<td>Improved LVEF (N=37)</td>
<td>5.9</td>
</tr>
<tr>
<td>Initial LVEDD (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Post LVEDD (mmHg)</td>
<td></td>
</tr>
</tbody>
</table>
Beta blocker use in CASE HF clinic

Figure 1: Differences in Beta Blocker Doses in Metoprolol Equivalent Doses in mg/day

- Improved LVEF Group (N=37) 139
- Non-Improved (N=48) 98

P=0.007

HFSA 2002
Predicted Change in KCCQ at 12 Months

More patients had clinically meaningful improvement at 12 months in the exercise arm than usual care.
## Results

### Demographics

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51 ± 8 years</td>
</tr>
<tr>
<td>Men</td>
<td>49</td>
</tr>
<tr>
<td>Women</td>
<td>37</td>
</tr>
<tr>
<td>Caucasian</td>
<td>40</td>
</tr>
<tr>
<td>African-American</td>
<td>31</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
</tr>
<tr>
<td>EF (%)</td>
<td>19.8 ± 8.1%</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Physical Limitation</th>
<th>Total Symptom</th>
<th>Self-Efficacy</th>
<th>QoL</th>
<th>Social Limitation</th>
<th>Overall Summary</th>
<th>Clinical Summary</th>
<th>EF (%)</th>
<th>VO$_2$ ml/min /kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.00</td>
<td>76.23</td>
<td>74.62</td>
<td>61.62</td>
<td>50.08</td>
<td>55.15</td>
<td>64.23</td>
<td>75.62</td>
<td>21.54</td>
<td>16.31</td>
</tr>
<tr>
<td>3.00</td>
<td>48.94</td>
<td>47.00</td>
<td>73.71</td>
<td>36.12</td>
<td>37.00</td>
<td>42.35</td>
<td>48.24</td>
<td>19.29</td>
<td>13.59</td>
</tr>
<tr>
<td>4.00</td>
<td>29.25</td>
<td>31.00</td>
<td>34.50</td>
<td>10.25</td>
<td>16.00</td>
<td>21.75</td>
<td>30.50</td>
<td>18.33</td>
<td>13.26</td>
</tr>
<tr>
<td>Total</td>
<td>57.06</td>
<td>55.68</td>
<td>64.47</td>
<td>38.41</td>
<td>41.47</td>
<td>48.29</td>
<td>56.62</td>
<td>20.09</td>
<td>14.56</td>
</tr>
</tbody>
</table>

Results are in mean values
Kansas City Cardiomyopathy Questionnaire at CASE
# Brown Bag Clinic: Montefiore

<table>
<thead>
<tr>
<th>Parameter (n=32)</th>
<th>Mean ± Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 14</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>25%</td>
</tr>
<tr>
<td>HF-PEF (n)</td>
<td>8</td>
</tr>
<tr>
<td>EF (%)</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>Pro BNP</td>
<td>1382.5 ± 159 pg/ml</td>
</tr>
<tr>
<td>HF-REF (n)</td>
<td>24</td>
</tr>
<tr>
<td>EF (%)</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>Pro BNP</td>
<td>7008 ± 7905 pg/ml</td>
</tr>
<tr>
<td><strong>KCCQ overall Score</strong></td>
<td><strong>52.14 ± 20.46</strong></td>
</tr>
</tbody>
</table>
HFPeF
Why Do HFPEF Patients Decompensate?

- Excess salt
- Inadequate diuretic Rx
- Worsening hypertension
- Medications: NSAIDs, thiazolidinediones, CCBs, alpha-blockers
- Atrial fibrillation
- Worsening renal function
- Myocardial ischemia
- Anemia
- Iatrogenic volume overload

Can absence of any of these be Outcomes? E.g., Afib, renal function
### Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
Echocardiographic parameters in select HFpEF trials.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>TOPCAT(62)</th>
<th>PARAMOUNT(65)</th>
<th>RELAX(20)</th>
<th>I-PRESERVE(17,64)</th>
<th>CHARMES(65,66)</th>
<th>Aldo-DHF(6)</th>
<th>PEP-CRF(18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>935</td>
<td>292</td>
<td>216</td>
<td>745</td>
<td>312</td>
<td>422</td>
<td>880</td>
</tr>
<tr>
<td>Definition of diastolic heart failure</td>
<td>LVEF ≥45%, HF hospitalization, or BNP ≥100 or NT-proBNP ≥600 pg/mL</td>
<td>LVEF ≥45%, NT-proBNP ≥400 pg/mL</td>
<td>LVEF ≥50%, NT-proBNP ≥400, pVO2 &lt; 80% of predicted</td>
<td>LVEF ≥45%, recent HF hospitalization or other objective signs of HF</td>
<td>LVEF &gt;40%</td>
<td>LVEF ≥50%, echocardiographic diastolic dysfunction or AF pVO2 &lt;25</td>
<td>LVEF &gt;40%, HF by clinical criteria</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70±10</td>
<td>71±9</td>
<td>69 (62–77)</td>
<td>72±7</td>
<td>66±11</td>
<td>67±8</td>
<td>75 (72–79)</td>
</tr>
<tr>
<td>Women</td>
<td>49%</td>
<td>50%</td>
<td>48%</td>
<td>62%</td>
<td>34%</td>
<td>35%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>LV structure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>4.80±0.58</td>
<td>4.64±0.48</td>
<td>4.6 (4.3–5.1)</td>
<td>4.8±0.6</td>
<td>5.4±0.7</td>
<td>4.6±0.62</td>
<td>4.6 (4.2–5.1)</td>
</tr>
<tr>
<td>EDV (mL/m2)</td>
<td>49.9±15.5</td>
<td>61.4±15.4</td>
<td>NA</td>
<td>49±14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MWT (cm)</td>
<td>1.18±0.20</td>
<td>0.91±0.16</td>
<td>NA</td>
<td>0.93±0.15</td>
<td>NA</td>
<td>NA</td>
<td>1.3 (1.2–1.5)</td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>113±31</td>
<td>79.1±22.2</td>
<td>78 (62–94)</td>
<td>NA</td>
<td>117±42</td>
<td>109±28</td>
<td>NA</td>
</tr>
<tr>
<td>RWT</td>
<td>0.49±0.10</td>
<td>0.28±0.08</td>
<td>NA</td>
<td>0.40±0.08</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>LV geometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14%</td>
<td>72%</td>
<td>NA</td>
<td>40%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Concentric remodeling</td>
<td>34%</td>
<td>14%</td>
<td>NA</td>
<td>25%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Concentric hypertrophy</td>
<td>43%</td>
<td>7%</td>
<td>NA</td>
<td>29%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Eccentric hypertrophy</td>
<td>9%</td>
<td>7%</td>
<td>NA</td>
<td>0%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>59.6±8.0</td>
<td>57.7±7.9</td>
<td>60 (56–65)</td>
<td>64±9</td>
<td>50 (18–65)</td>
<td>67±8</td>
<td>65 (56–66)</td>
</tr>
<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAVi (mL/m2)</td>
<td>29.8±12.5</td>
<td>35.0±13.5</td>
<td>44 (36–59)</td>
<td>NA</td>
<td>41.3±14.7</td>
<td>28.0±8.4</td>
<td>NA</td>
</tr>
<tr>
<td>LA diameter (cm)</td>
<td>4.3±0.6</td>
<td>3.7±0.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.5 (4–1.8)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.2±0.7</td>
<td>1.1±0.62</td>
<td>1.5 (1.0–2.1)</td>
<td>1.05±0.74</td>
<td>1.1±0.7</td>
<td>0.92±0.33</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>TDI E- septal (cm/s)</td>
<td>6.1±2.2</td>
<td>5.8±2.0</td>
<td>6 (5–8)</td>
<td>ND</td>
<td>ND</td>
<td>5.9±1.3</td>
<td>NA</td>
</tr>
<tr>
<td>TDI E- lateral (cm/s)</td>
<td>8.2±3.2</td>
<td>7.5±2.8</td>
<td>NA</td>
<td>9.1±3.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>E/E’ ratio (septal)</td>
<td>15.6±9.8</td>
<td>15.9±7.3</td>
<td>16 (11–24)</td>
<td>NA</td>
<td>NA</td>
<td>12.8±4.0</td>
<td>NA</td>
</tr>
</tbody>
</table>
Incident Atrial fibrillation: A growing problem and concern

- Often coexists with HFpEF presentation
- May be the causation of decompensation
- Meta-analysis of > 54,000 patients,
- A significantly higher risk of death in AF patients with HFrEF compared to those with HFpEF.
  - There was a crude mortality rate of 24% versus 18% respectively, over 2 years.
  - No significant difference in incident stroke or heart failure hospitalization between the two groups.

Exploratory (post-hoc): Placebo vs. Spiro by region

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)

Interaction p=0.122

Placebo: 280/881 (31.8%)
Placebo: 71/842 (8.4%)
Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction
A Randomized, Controlled, Single-Blind Trial

**Figure.** Individual and mean (■) responses of peak exercise VO\(_2\), following 16 weeks of supervised exercise training. Results are displayed in raw, nonindexed peak VO\(_2\), as this is uninfluenced by weight.
HFPeF: Key points

- HFPeF is common, especially among the elderly and in women.
- With an increasing prevalence of HTN, obesity, Afib, and diabetes, and the growing elderly segment of the general population, the prevalence of HFPEF is projected to increase.
- HFPEF = diagnostic challenge and studies differ widely in their reported incidence and mortality rates associated with this condition.
- There is agreement that between a third and one half of HF patients in the community have HFPEF.
- Prognosis is overall poor. Patients with HFPEF have substantial comorbidity, high rates of repeated hospitalizations, and a high mortality.
- Is the mortality often not related to the HFPEF but to the comorbidities?
- Are there different groups within the phenotypes?

OUTCOME:
- Reduction in all cause hospitalization
- Improvement in objective function: ability to rehab
- Improvement in symptoms (well captured)
- Absence of a fib
What is ADHF?

A semicolon in the total sentence...
Continuity of the syndrome forgotten

NYHA I → NYHA II → NYHA III → NYHA IV

First myocardial injury

Compensated

Chronically decompensated

Acutely decompensated

First episode of AHF with hospitalization

DEATH

ED → CCU → DC → Early Post DC → Outpatient
The Progression of Symptoms in ADHF

- Abnormal LV function (Sys and/or Dia)
- Orthopnea
- Dyshpnea
- Fatigue
- Edema

Systemic congestion (JVD, edema)

↑ RV + RA pressure

Increase PA pressure

Increased PCWP (congestion)

↑ LA and LV diastolic pressure

↑ LVDP + impaired volume regulation

Abnormal LV function (Sys and/or Dia)
Most Heart Failure Hospitalizations are due to Worsening Chronic Heart Failure

- ~70% Worsening chronic HF
  Associated with reduced or preserved left ventricular systolic function (LVEF)

- ~25% de novo HF
  After a large MI; sudden increase in blood pressure superimposed on a noncompliant LV

- ~5% Advanced HF
  Refractory to therapy; with severe LV systolic dysfunction, associated with a worsening low-output state

## Clinical Trials of ADHF

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study</th>
<th>Physiologic Target</th>
<th>Sx or outcome</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>DOSED</td>
<td>Hi vs. low continuous</td>
<td>Modest</td>
<td>NA</td>
</tr>
<tr>
<td>AVP blockers</td>
<td>EVEREST</td>
<td>AVP receptor</td>
<td>Neutral on dyspnea</td>
<td>No benefit</td>
</tr>
<tr>
<td>UF</td>
<td>UNLOAD</td>
<td>Volume</td>
<td>Relief of dyspnea</td>
<td>No benefit; renal fct worse</td>
</tr>
<tr>
<td></td>
<td>CARESS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seralaxin</td>
<td>RELAX-AHF</td>
<td>Vasodilation in ADHF</td>
<td>Modest dyspnea relief</td>
<td>No benefit in hospitalizations RELAX II almost complete</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>ASCEND-HF</td>
<td>Vasodilation</td>
<td>Modest Sx relief</td>
<td>No benefit</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>SURVIVE</td>
<td>Ca++ sensitization</td>
<td>Modest Sx relief</td>
<td>Possible harm</td>
</tr>
<tr>
<td></td>
<td>REVIVE II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ularitide</td>
<td>TRUE-AHF</td>
<td>Mortality In-hospital worsening</td>
<td>Lower ProBNP less hospital events.</td>
<td>No benefit on mortality but lowered BNP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No reduction in hospitalizations</td>
<td></td>
</tr>
</tbody>
</table>
Do we need to change our “injury” theory?

- The “neurohormonal storm” not addressed with diuretics or vasodilators
- No guide after the early intervention
- Is it time for devices to treat or to prevent?
  - Safe if implanted
  - Durable (do not lose signal)
  - Cost effective
  - Who monitors the monitor?
    - Patient or providers?
  - How to respond to signals? Best drug, dose?

Figure 1. Suggested algorithm for continuation and initiation of long-term therapy during an admission for ADHF in which the patient is receiving IVAM. There are 7 cardinal points for decision making.
More than 50% of Patients Have Little or No Weight Loss During Hospitalization

<table>
<thead>
<tr>
<th>Change in Weight (lbs)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-20)</td>
<td>7%</td>
</tr>
<tr>
<td>(-20 to -15)</td>
<td>6%</td>
</tr>
<tr>
<td>(-15 to -10)</td>
<td>13%</td>
</tr>
<tr>
<td>(-10 to -5)</td>
<td>24%</td>
</tr>
<tr>
<td>(-5 to 0)</td>
<td>33%</td>
</tr>
<tr>
<td>(0 to 5)</td>
<td>15%</td>
</tr>
<tr>
<td>(5 to 10)</td>
<td>3%</td>
</tr>
<tr>
<td>(&gt;10)</td>
<td>2%</td>
</tr>
</tbody>
</table>

Current treatment options:
- Loop diuretics
- IV inotropes
- Nitrates
- Nesiritide
Congestion After Initial In-Hospital Therapy Is Associated with Higher 60-day Mortality

**60-Day All-cause Mortality**

<table>
<thead>
<tr>
<th></th>
<th>N =</th>
<th>%</th>
<th>Na &lt; 136</th>
<th>Na ≥ 136</th>
<th>BUN &gt; 29</th>
<th>BUN ≤ 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>319</td>
<td>21.6%</td>
<td>69 (21.6%)</td>
<td>250 (78.4%)</td>
<td>140 (44%)</td>
<td>179 (56%)</td>
</tr>
<tr>
<td>Severe congestion*</td>
<td>204</td>
<td>64%</td>
<td>7.8</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No severe congestion*</td>
<td>115</td>
<td>36%</td>
<td>6.3</td>
<td>4</td>
<td>11.4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Furosemide Monotherapy Causes a Significant Decline in Renal Function

Change in GFR after furosemide 80 mg IV
Class III HF, n = 16, age 61, LVEF 0.28, CAD 63%

Impact of IV Diuretics on Patients Hospitalized With ADHF

ADHERE: All Enrolled Discharges (n = 56,484) October 2001 to October 2003

Risk-adjusted data from ADHERE.
Diuretics Activate Neurohormonal Systems in HF

Adapted with permission from Bayliss J et al. Br Heart J. 1987;57:17
Background:
Limitations of diuretic therapy

- Deleterious acute hemodynamic effects
- Activation of neurohormonal axes
- Decline in renal function
- Tubuloglomerular feedback mechanisms
- High doses associated with worse outcomes
Acute Therapy = Acute Endpoints (24 hrs. → Until Discharge)

- Clinically important symptoms and/or signs
- Hemodynamics (BNP, NT-pro BNP? as surrogate)
- Myocardial injury (Tn? as surrogate)
- Renal function (BUN, BUN/Cr),
- Normalizing serum sodium, hemoglobin?

Long-term Safety Endpoints

- Readmissions
- Mortality
- Acute surrogate endpoints predicting long-term safety (Tn, BNP/NT-pro BNP, viability/remodeling assessment) should not worsen