Acute Decompensated Heart Failure: Can We Do Better In Improving Outcomes?

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Acute Decompensated Heart Failure

Magnitude of the Problem

- 1 million admissions annually in the U.S. (↑50% over the past 10 years)
- Most common admitting diagnosis for patients ≥ 65 years
- Hospitalization costs are considerable (>60% of amount spent on heart failure)
- Mean length of stay 5-6 days
- In-hospital mortality 5%
Acute Decompensated Heart Failure
Have We Made Progress?

• The good news:
  – In-hospital mortality 5% (↓ 40% in 10 years)
  – Mean length of stay 5-6 days (↓ 30% in 10 years)

• The bad news:
  – Readmission rates remain high
    • 25% within 30 days
    • 50% within 6-12 months
  – High mortality rates persist
    • 5-10% at 30 days
    • 20-40% at 6-12 months
## Acute Decompensated Heart Failure: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHERE N = 105,388</th>
<th>OPTIMIZE-HF N = 48,612</th>
<th>Euro-HF N = 11,327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>72.4</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>&gt; 75 years (%)</td>
<td>50</td>
<td>ND</td>
<td>30 men</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51 women</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>72</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Prior HF history (%)</td>
<td>75</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>Systolic dysfunction (%)</td>
<td>54</td>
<td>46</td>
<td>45</td>
</tr>
</tbody>
</table>

Acute Decompensated Heart Failure: Patient Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ADHERE N = 105,388</th>
<th>OPTIMIZE-HF N = 48,612</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any dyspnea (%)</td>
<td>89</td>
<td>ND</td>
</tr>
<tr>
<td>Dyspnea at rest (%)</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Dyspnea on exertion (%)</td>
<td>ND</td>
<td>61</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>31</td>
<td>ND</td>
</tr>
<tr>
<td>Rales (%)</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>Peripheral edema (%)</td>
<td>66</td>
<td>65</td>
</tr>
</tbody>
</table>

Which Patients Are At the Highest Risk For In-Hospital and Post-Discharge Mortality?
ADHERE CART: Predictors of Mortality

BUN 43
N = 33,324

Less than

2.68%
n = 25,122

SBP 115
n = 24,933

<

SBP 115
N = 7150

> Greater than

8.98%
n = 7202

5.49%
n = 4099

2.14%
n = 20,834

SCr 2.75
2045

12.42%
n = 1425

15.28%
n = 2048

Highest to lowest risk cohort
OR 12.9 (95% CI 10.4–15.9)

12.42%
n = 620

21.94%
n = 20,834

CART, classification and regression tree
# Impact of Worsening Renal Function on Outcomes in Heart Failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RF not worse</th>
<th>RF worse</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>3%</td>
<td>7%</td>
<td>2.7 (1.6–4.6)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>6%</td>
<td>10%</td>
<td>1.9 (1.3–2.8)</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>19%</td>
<td>25%</td>
<td>1.6 (1.2–2.1)</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>6.93</td>
<td>9.14</td>
<td></td>
</tr>
</tbody>
</table>

Variables Associated with Higher 60-day Mortality

* Edema, dyspnea, and jugular venous distention at baseline.

High PCWP at Hospital Discharge Is Associated with Higher Long-term Mortality

Current Treatment of Acute Decompensated Heart Failure

Diuretics
- Reduce fluid volume

Vasodilators
- Decrease preload and afterload

Inotropes
- Augment contractility
Diuretics
Most Common IV Medications
All Enrolled Discharges (n=105,388) October 2001-January 2004

ADHERE data base
Loop Diuretics Impair Glomerular Filtration Rate

GFR (% change)

Urine Output (mL) 0-8h

Placebo

IV furosemide 80 mg

Acute Effects of IV Furosemide

**Heart rate**

**SVR**

**LV filling pressure**

**Plasma norepinephrine levels**

**Plasma renin activity**

**Plasma AVP levels**

* P < .05; ** P < .01.

Diuretic Based Clinical Strategies Are Not Always EFFECTIVE in Reducing Weight (n=25,799)

All Enrolled Discharges in the Last 12 Months (04.01.2003-03.31.2004) Who Were Discharged Home (including home with additional and/or outpatient care)

ADHERE Database

Note: For the chart, n represents the number of patients who have both baseline and discharge weight, and the percentage is calculated based on the total patients in the corresponding population. Patients without baseline or discharge weight are omitted from the histogram calculations.
ESCAPE: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness

### UNLOAD: Ultrafiltration vs Standard Diuresis

<table>
<thead>
<tr>
<th></th>
<th>Ultrafiltration</th>
<th>Diuresis</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight loss (kg)</td>
<td>5 (n = 83)</td>
<td>3.1 (n = 84)</td>
<td>.001</td>
</tr>
<tr>
<td>Rehospitalization (%)</td>
<td>18</td>
<td>32</td>
<td>.022</td>
</tr>
<tr>
<td>at 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization days (mean) at 90 days</td>
<td>1.4</td>
<td>3.8</td>
<td>.022</td>
</tr>
<tr>
<td>Unscheduled office/ED visits (%) at 90 days</td>
<td>21</td>
<td>44</td>
<td>.009</td>
</tr>
</tbody>
</table>

**UNLOAD, Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF.**

UNLOAD Trial Safety Endpoints

Change in Serum Creatinine

Improving Outcomes in Acute Decompensated Heart Failure Patients

• Although diuretics (and ultrafiltration) are effective in relieving congestion they have adverse effects including worsening renal function that may adversely affect post-discharge outcomes.
Inotropic Agents and Vasodilators
Profiles and Therapies of Advanced Heart Failure

Congestion at Rest

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and Dry PCW and CI normal</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cold and Dry PCW low/normal CI decreased</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Vasodilators
Nitroprusside
Nitroglycerine
Nesiritide

Inotropic Drugs
Dobutamine
Milrinone
Calcium Sensitizers

### OPTIME-CHF: Increase in Adverse Events in Milrinone-treated Patients

<table>
<thead>
<tr>
<th>Index hospitalization</th>
<th>Control (n = 472)</th>
<th>Milrinone (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall adverse events</td>
<td>2.1%</td>
<td>12.6% *</td>
</tr>
<tr>
<td>Sustained hypotension</td>
<td>3.2%</td>
<td>10.7% *</td>
</tr>
</tbody>
</table>

#### Adverse events within 60 days post-discharge

| Days of hospitalization for CV-related causes | 5.9 (12.5) | 5.7 (12.6) |
| Rehospitalization or death                   | 35.3%      | 35.0%      |
| Death                                         | 8.9%       | 10.3%      |

OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure. *P < .001.

### Vasodilating Agents Currently Used to Treat ADHF

<table>
<thead>
<tr>
<th>Agent</th>
<th>HR</th>
<th>BP</th>
<th>CO</th>
<th>PAW</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>↑</td>
<td>↓</td>
<td>→</td>
<td>↓↓</td>
<td>Headache, ↓ BP, tachyphylaxis</td>
</tr>
<tr>
<td>NP</td>
<td>↑</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>Thiocyanate toxicity, ↓ BP</td>
</tr>
<tr>
<td>NESiritide</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>Sustained ↓ BP</td>
</tr>
</tbody>
</table>
VMAC Primary Endpoint: **PCWP through 3 Hours**

Mean observed value (mmHg) | Mean change (mmHg)
--- | ---

**Placebo** | **Nitroglycerin** | **Nesiritide**

**Mean observed value (mmHg):**

- **Placebo:**
  - BL: 28
  - 15 m: 26
  - 30 m: 24
  - 1 hr: 22
  - 2 hr: 20
  - 3 hr: 18

- **Nitroglycerin:**
  - BL: 18
  - 15 m: 16
  - 30 m: 14
  - 1 hr: 12
  - 2 hr: 10
  - 3 hr: 8

- **Nesiritide:**
  - BL: 30
  - 15 m: 28
  - 30 m: 26
  - 1 hr: 24
  - 2 hr: 22
  - 3 hr: 20

**Mean change (mmHg):**

- **Placebo:**
  - BL: -10
  - 15 m: -8
  - 30 m: -6
  - 1 hr: -4
  - 2 hr: -2
  - 3 hr: 0

- **Nitroglycerin:**
  - BL: -7
  - 15 m: -5
  - 30 m: -3
  - 1 hr: -1
  - 2 hr: 0
  - 3 hr: 1

- **Nesiritide:**
  - BL: -10
  - 15 m: -8
  - 30 m: -6
  - 1 hr: -4
  - 2 hr: -2
  - 3 hr: 0

* # p < 0.05 versus placebo
* * p < 0.05 versus NTG

Young JB et al. *AHA Meeting 2000 Late Breaking Trials Session*
Primary Endpoint

Dyspnea at 3 hours

Improved (%)  Worsened (%)

Nesiritide  NTG  Placebo

No change

P=0.034  P=0.191

p-values are based on Van Elteren Test with 7-point ordinal scale

Young JB et al. AHA Meeting 2000 Late Breaking Trials Session
Odds Ratios Of Worsening Serum Creatinine (>0.5 mg/dl) By Nesiritide Dose Group

Nesiritide Better

Nesiritide 0.01 mcg/kg/min

Nesiritide 0.015 mcg/kg/min

Nesiritide 0.03 mcg/kg/min

Nesiritide Worse

Odds Ratio (and 95% confidence intervals)

P = 0.17

P = 0.02

P = 0.001

Data on file, Scios Inc.
Improving Outcomes in Acute Decompensated Heart Failure Patients

• Inotropic agents should be avoided unless there is evidence of hypoperfusion.

• Vasodilators unload the ventricle and are most useful in patients with well maintained blood pressure who remain symptomatic due to congestion.

• Nesiritide is effective in relieving congestion but has uncertain effects on renal function and long-term outcomes.
Emerging Therapies for Treating Acute Decompensated Heart Failure

- AVP inhibitors
- Continuous aortic flow augmentation (CAFA-Cancion Device)
Vasopressin Effector Mechanisms

Vasopressin effects mediated by:

• $V_{1a}$ receptors (blood vessels, myocardium)
  – Peripheral and coronary vasoconstriction
  – Cell growth, increased intracellular calcium

• $V_2$ receptors (renal tubules)
  – Water retention
Effect of Single Dose Conivaptan on Urine Output in Advanced HF

Change in Urine Output 0–4 h

- Placebo
- 10 mg
- 20 mg
- 40 mg

* P < .005

SALT 1 and 2: Mean Sodium Concentration Over Time

SALT-2 and SALT-2, Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2.

*P < .001 for tolvaptan vs. placebo; tolvaptan was discontinued on day 30.

Physician-assessed Signs and Symptoms
(% Patients with Improvement)

Dyspnea

Orthopnea

Fatigue

Edema

P<0.05

Changes in Renal Function

**BUN (mg/dL)**

- Inpatient
  - Day 1: 1980
  - Day 7 or Discharge: 1987

- Outpatient
  - Day 1: 1828
  - Day 7 or Discharge: 1874

**Serum Cr (mg/dL)**

- Inpatient
  - Day 1: 1912
  - Day 7 or Discharge: 1864

- After Discharge (wk)
  - 1 Week: 1755
  - 8 Weeks: 1865

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Continuous Aortic Flow Augmentation

Orqis® Cancion®
Ax – Fem graft
Cath : Fem:Fem
single Fem

- a – inflow (fem artery)
- b – pump
- c – pump motor
- d – controller
- e – flow sensor
- f – outflow (desc thoracic aorta)
Mechanism of Action

Continuous Aortic Flow Augmentation

Ventricular Unloading

Vasodilation

Renal Effects

Nitric Oxide
Other mediators

Hemodynamic improvement
Diuresis

Clinical Benefit
Effects of CAFA on Hemodynamics and Renal Function

Hospital Readmission Is Reduced By HF Disease Management

Summary RR = 0.76 (95% CI .68-.87)
Summary RR for randomized only = 0.75 (CI = .60-.95)
Benefits and Drawbacks of Heart Failure Disease Management Programs

Benefits

- Improved use of evidence-based therapy
- Improved symptom status and functional capacity
- Improved QOL
- Reduction in hospitalization
- Decrease in total medical costs
- Improved survival suggested in some studies

Drawbacks

- Usual Care 96%
- HF Disease Management Program 4%

Improving Care of Patients With Decompensated Heart Failure

- Diurese to reduce volume overload.
- Vasodilators and inotropes useful in refractory patients.
- AVP antagonists correct hyponatremia and relieve signs/symptoms of congestion.
- CAFA improves hemodynamic in decompensated heart failure patients.
- Disease management programs improve outcomes.