Keynote Address II
Managing Acute Heart Failure: What Can We Do to Improve Outcomes?

24th Annual San Diego Heart Failure Symposium
June 1-2, 2018
La Jolla, CA

Barry Greenberg, MD
Distinguished Professor of Medicine
Director, Advanced Heart Failure Treatment Program
University of California, San Diego
Managing Acute Heart Failure: What Can We Do to Improve Outcomes?

• Magnitude of the problem and outcomes.
• Current approaches to therapy.
• What can we do to improve outcomes?
Burden of Acute Heart Failure (AHF) on the Healthcare System

• ~6 million U.S. adults have heart failure and each year there are about 1 million hospitalizations with heart failure as the primary diagnosis.
• HF is the most common DRG for patients ≥65 years of age.
• Approximately 2/3 of the annual $30+ billion dollar cost for heart failure management is spent on acute heart failure (AHF) hospitalization or post-hospitalization care.
• By 2030, the number of heart failure patients will rise to over 8 million and the cost to nearly $70 billion.
Goals of AHF Therapy

• Alleviate symptoms
• Reduce extracellular fluid volume excess (“congestion”)
• Improve hemodynamics
  • Decrease left and right ventricular filling pressures
  • Increase cardiac output (?)
• Maintain renal function and perfusion to vital organs
• Avoid worsening the underlying disease state
• Reduce length of stay
• Improve post-discharge outcomes including re-hospitalization rates and mortality
Goals of AHF Therapy

• Alleviate symptoms
• Reduce extracellular fluid volume excess (“congestion”)
• Improve hemodynamics
  • Decrease left and right ventricular filling pressures
  • Increase cardiac output (?)
• Maintain renal function and perfusion to vital organs
• Avoid worsening the underlying disease state
• Reduce length of stay
• Improve post-discharge outcomes including re-hospitalization rates and mortality
Drugs Used to Treat AHF

- **Diuretics**: Reduce Fluid Volume
- **Vasodilators**: Decrease Preload and Afterload
- **Inotropes**: Augment Contractility
Patient Selection and Treatment

**Congestion at Rest**

- **No**
  - **Warm & Dry**
    - PCWP normal
    - CI normal (compensated)
    - RARE
  - **Cold & Dry**
    - PCWP low/normal
    - CI decreased
    - RARE
- **Yes**
  - **Warm & Wet**
    - PCWP elevated
    - CI normal
    - COMMON
  - **Cold & Wet**
    - PCWP elevated
    - CI decreased
    - COMMON

**Low Perfusion at Rest**

- **No**
- **Yes**

**Diuretics**
- NTG
- Nitroprusside
- Nesiritide

**Vasodilators**
- Normal SVRI
- High SVRI

**Inotropic Drugs**
- Dobutamine
- Milrinone
- Levosimendan

CI=cardiac index
PCWP=pulmonary capillary wedge pressure
SVRI=Systemic Vascular Resistance Index
Acute Heart Failure
Have We Made Progress?

The good news:
- In-hospital mortality has been reduced to <5%
- Mean length of stay 5-6 days

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 month
Nearly 1 in 4 AHF Patients Readmitted within 30 Days

1-year Mortality Rates Haven't Changed over the Last Decade

*Risk-adjusted rates relative to 1999.
What Can Be Done To Improve Outcomes in AHF?

• Avoid injury to vital organs during the acute phase by avoiding inappropriate therapies
Impact of Worsening Biomarkers On Survival

RELAX-AHF

A. Troponin T

B. Cystatin C

C. AST

D. ALT

E. NT-proBNP

F. Worsening heart failure

Data from Metra et al. J Am Coll Cardiol 2013
Adverse Effects of Milrinone in Patients with Ischemic Etiology
When to Use Inotropic Support

**Until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.**

**Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.**

**Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.**

What Can Be Done To Improve Outcomes in AHF?

- Avoid injury to vital organs during the acute phase by avoiding inappropriate therapies
- Aim for more complete resolution of congestion
Most Patients Have Little or No Weight Loss During Hospitalization

![Bar graph showing patients' weight loss percentages.]

Patients (%)

-20 to -15: 7%
-15 to -10: 6%
-10 to -5: 13%
-5 to 0: 24%
0 to 5: 33%
5 to 10: 15%
>10: 3%
>10: 2%

Evidence of Incomplete Relief From Congestion

- Asymptomatic: 44%
- Improved (but still symptomatic): 40%
- No Mention: 11%
- No Change: <1%
- Not Applicable: 4%
- Worse: <1%

All Enrolled Discharges (n=150,745) October 2001 to December 2004
High PCWP at Hospital Discharge Is Associated with Higher Long-Term Mortality

PCWP = pulmonary capillary wedge pressure; CI = cardiac index.
Post-Discharge Freedom of Congestion Is Associated with Better Prognosis

Symptoms of congestion: orthopnea, jugular venous distention, weight gain ≥2 lbs in a week, need to increase diuretic dose, leg edema

Predischarge BNP and Cumulative Incidence of Death or Re-admission

Diuretic Therapy of ADHF

• Vast majority of patients with ADHF have signs/symptoms of volume overload.
• IV diuretics are effective in removing excess fluid and relieving congestive symptoms.
• Diuretics are less effective when cardiac output or renal perfusion pressure is low and when renal impairment is present.
• Diuretic resistance may occur.
Diuretic Strategies:

- Combined Diuretic Rx
- High vs Low Dose
- Intermittent Bolus vs Continuous Drip
- Addition of Dopamine or Nesiritide?
- Ultrafiltration
Causes of Diuretic Resistance

<table>
<thead>
<tr>
<th>Table 1. Causes of Diuretic Resistance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate dose of diuretic</td>
</tr>
<tr>
<td>Nonadherence</td>
</tr>
<tr>
<td>Not taking drug</td>
</tr>
<tr>
<td>High sodium intake</td>
</tr>
<tr>
<td>Pharmacokinetic factors</td>
</tr>
<tr>
<td>Slow absorption of diuretic because of gut edema</td>
</tr>
<tr>
<td>Impaired secretion of diuretic into the tubule lumen</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs*</td>
</tr>
<tr>
<td>Probenecid</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Antinatriuretic drugs</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs*</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
</tr>
<tr>
<td>Low renal blood flow</td>
</tr>
<tr>
<td>Nephron remodeling</td>
</tr>
<tr>
<td>Neurohormonal activation</td>
</tr>
</tbody>
</table>

* These drugs inhibit the efficacy of loop diuretics through several mechanisms.

# Stepped Care Approach for Using Diuretics

## Table 2. Stepped-Care Pharmacologic Approach.

<table>
<thead>
<tr>
<th>Level</th>
<th>Previous Oral Dose</th>
<th>Furosemide</th>
<th>Infusion Rate</th>
<th>Metolazone†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80 mg</td>
<td>40 mg</td>
<td>5 mg/hr</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>81–160 mg</td>
<td>80 mg</td>
<td>10 mg/hr</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240 mg</td>
<td>80 mg</td>
<td>20 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>&gt;240 mg</td>
<td>80 mg</td>
<td>30 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

* The goal of treatment is a daily urine volume of 3 to 5 liters until clinical euvoolemia is reached. The initial approach may involve the intravenous administration (in two doses) of 2.5 times the patient’s previous oral daily dose of furosemide or alternatively the infusion approach described above. The diuretic level can be increased daily to achieve urinary output between 3 and 5 liters per day by moving to the next step if the urinary output remains less than 3 liters. NA denotes not applicable.

† Hydrochlorothiazide (at a dose of 50 mg twice daily) or chlorthalidone (at a dose of 50 mg daily) may be substituted for metolazone. Adapted from Grodin et al. and Bart et al. The full algorithm includes additional considerations for vasodilator, inotropic, or mechanical therapy in patients who do not have a response within 48 hours.

‡ A dose of 40 mg of furosemide is considered to be equivalent to 1 mg of bumetanide or 20 mg of torsemide.
Effects of High vs Low Dose Diuretics on Symptoms In AHF Patients

DOSE Study

What Can Be Done To Improve Outcomes in AHF

• Avoid injury to vital organs during the acute phase by avoiding in appropriate therapies
• Aim for more complete resolution of congestion
• Use available therapies
Digoxin Improves Outcomes in Patients with Advanced Heart Failure

Gheorghiade et al. Eur J Heart Failure (2013); 15:551-9
Influence of LCZ696 on Readmission Rates After HF Hospitalization

35-40% lower likelihood of HF rehospitalization with sacubitril/valsartan

What Can Be Done To Improve Outcomes in AHF

• Avoid injury to vital organs during the acute phase by using appropriate therapies
• Aim for more complete resolution of congestion
• Use available therapies
• Optimize transitions of care
Strategies for Transition From Hospital to Home

<table>
<thead>
<tr>
<th>Recommendation or Indication</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed: a) initiation of GDMT if not done or contraindicated; b) causes of HF, barriers to care, and limitations in support; c) assessment of volume status and blood pressure with adjustment of HF therapy; d) optimization of chronic oral HF therapy; e) renal function and electrolytes; f) management of comorbid conditions; g) HF education, self-care, emergency plans, and adherence; and h) palliative or hospice care.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge is reasonable</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>

What Can Be Done To Improve Outcomes in AHF

- Avoid injury to vital organs during the acute phase by using appropriate therapies
- Aim for more complete resolution of congestion
- Use available therapies
- Optimize transitions of care
- Consider remote monitoring
HF Events Are Associated with PA Pressure

Probability of an HFE for 261 patients during a 6-month period in relation to chronic daily ePAD.

CardioMEMS™ PA Sensor Technology

The sensor is no larger than the size of a dime

The sensor is a hermetically sealed capsule containing an inductor coil and pressure-sensitive capacitor.

Reliable PA pressure monitoring without leads, batteries or active-fixation mechanisms. Nitinol (niti-n-6) wire loops extend from each end of the sensor to stabilize the sensor in the implant location.

The inductor coil and pressure-sensitive capacitor create a resonant circuit at a specific frequency. The blood pressure affects the resonant frequency, so that when the blood pressure changes, the resonant frequency changes. The external measurement system wirelessly tracks the resonant frequency and uses this to determine the pressure in the pulmonary artery.
Cumulative HF Hospitalizations Reduced
At 6 Months and Full Duration of Randomized Study

Cumulative Number of HF Hospitalizations

<table>
<thead>
<tr>
<th>Days from Implant</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>280</td>
</tr>
<tr>
<td>90</td>
<td>270</td>
<td>267</td>
</tr>
<tr>
<td>180</td>
<td>262</td>
<td>252</td>
</tr>
<tr>
<td>270</td>
<td>244</td>
<td>215</td>
</tr>
<tr>
<td>360</td>
<td>210</td>
<td>179</td>
</tr>
<tr>
<td>450</td>
<td>169</td>
<td>137</td>
</tr>
<tr>
<td>540</td>
<td>131</td>
<td>105</td>
</tr>
<tr>
<td>630</td>
<td>108</td>
<td>82</td>
</tr>
<tr>
<td>720</td>
<td>82</td>
<td>67</td>
</tr>
<tr>
<td>810</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>900</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Study Duration
37% RRR, p < 0.0001

≤ 6 Months
28% RRR, p = 0.0002

> 6 Months
45% RRR, p < 0.0001

No. at Risk
Treatment: 270, 262, 244, 210, 169, 131, 108, 82, 29, 5, 1
Control: 280, 267, 252, 215, 179, 137, 105, 67, 25, 10, 0
Managing Acute Heart Failure in 2018

- AHF is a common, costly public health burden that is associated with high rates of re-admission and post-discharge mortality.
- Currently available therapies and strategies can improve outcomes and should be emphasized both during hospitalization and in the transition to out-patient care.
- These include judicious use of inotropic agents, more complete decongestion, initiation of chronic therapies that improve outcomes, better transition of care and remote hemodynamic monitoring.