Management Strategies for Acute Heart Failure

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Management of Acute Heart Failure in 2017

- Magnitude of the problem and outcomes
- Current approaches to therapy
- New therapies
- Are we going about this in the wrong way?
- Available treatment strategies that improve outcomes
Burden of Acute Heart Failure (AHF) on the Healthcare System

- Currently ~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 \( \geq 65 \) 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

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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.

Current Treatment of AHF

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

Congestion at Rest

Low Perfusion 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

Inotropic Drugs
Dobutamine
Milrinone
Levosimendan

Diuretics
Nitroprusside
Nesiritide

Cl=cardiac index
PCWP=pulmonary capillary wedge pressure
SVRI=Systemic Vascular Resistance Index
**Therapies in the Hospitalized HF Patient**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF patients hospitalized with fluid overload should be treated with IV diuretics</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>HF patients receiving loop diuretic therapy, should receive an initial parenteral dose greater than or equal to their chronic oral daily dose, then should be serially adjusted</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>HF-REF patients requiring HF hospitalization on GDMT should continue GDMT unless hemodynamic instability or contraindications</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of IV agents</strong></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF</strong></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Serum electrolytes, urea nitrogen, and creatinine should be measured during the titration of HF medications, including diuretics</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

COR = class of recommendation; LOE = level of evidence; IV = intravenous; GDMT = guideline-directed medical therapy.

Therapies in the Hospitalized HF Patient (cont)

<table>
<thead>
<tr>
<th>Recommendation</th>
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<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>When diuresis is inadequate, it is reasonable to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Give higher doses of IV loop diuretics; or</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>b) add a second diuretic (e.g., thiazide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose dopamine infusion may be considered with loop diuretics to improve</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>diuresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with obvious volume overload</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>IV nitroglycerin, nitroprusside or nesiritide may be considered an adjuvant</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>to diuretic therapy for stable patients with HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients hospitalized with volume overload and severe hyponatremia,</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>vasopressin antagonists may be considered</td>
<td></td>
<td></td>
</tr>
</tbody>
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COR = class of recommendation; LOE = level of evidence.
Diuretics
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

None of these has been shown to improve outcomes!
Vasodilators and Inovasodilators
Nesiritide Effects on Dyspnea in ASCEND
Co-Primary Endpoint: 6 and 24 h Dyspnea

6 Hours

P=0.030*

42.1% 44.5%

13.4 15.0%

28.7 29.5%

34.1 32.8%

3444 Placebo

3416 Nesiritide

21.7 20.3%

6 Hours

P=0.007*

66.1% 68.2%

27.5 30.4%

38.6 37.8%

3398 Placebo

3371 Nesiritide

Markedly Better

Moderately Better

Minimally Better

Minimally Worse

No Change

42.1% 44.5%

13.4 15.0%

28.7 29.5%

34.1 32.8%

3444 Placebo

3416 Nesiritide

21.7 20.3%
Nesiritide Effects on 30-day All-Cause Mortality or HF Rehospitalization

ASCEND-HF

Hazard Ratio 0.93 (95% CI: 0.8, 1.08)

Risk Diff (95% CI)
- 0.7 (-2.1; 0.7)
- 0.4 (-1.3; 0.5)
- 0.1 (-1.2; 1.0)

P = 0.31
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.

Intravenous Inotropic Agents During Hospitalization for AHF

**OPTIME-CHF**

- **Adverse Event:**
  - Milrinone: 12.6%
  - Placebo: 2.1%
  - **HR 6.0**
  - **P < 0.001**

- **Sustained Hypotension:**
  - Milrinone: 10.7%
  - Placebo: 3.2%
  - **HR 3.3**
  - **P < 0.001**

- **Acute MI:**
  - Milrinone: 1.5%
  - Placebo: 0.4%
  - **HR 3.8**
  - **P = 0.18**

- **Afib:**
  - Milrinone: 4.6%
  - Placebo: 1.5%
  - **HR 3.1**
  - **P = 0.004**

- **Mortality:**
  - Milrinone: 3.8%
  - Placebo: 2.3%
  - **HR 1.7**
  - **P = 0.19**

**HR** = heart rate; **MI** = myocardial infarction; **Afib** = atrial fibrillation.

New Therapies For Acute Heart Failure

- Rolophylline
- Nesiritide
- Milrinone
- Serelaxin
- Ularitide
- Levosimendan
- TRV027
The Fate of New Therapies for Acute Heart Failure

- Levosimendan
- Ularitide
- Serelaxin
- TRV027
- Rolophylline
- Nesiritide
- Milrinone
- Ultrafiltration
- Low Dose Dopamine
- ET Inhibitors
- Ularitide
- TRV027
- Serelaxin
High Noon for AHF Drugs....

Serelaxin
Serelaxin Reduced Mortality in RELAX-AHF

Kaplan-Meier plot of CV deaths through Day 180

- Placebo: 55 CV deaths (9.6%)
- Serelaxin: 35 CV deaths (6.1%)
- HR 0.63 (95% CI 0.41, 0.96)
- p = 0.028

Number at risk:
- Serelaxin: 581, 573, 563, 555, 546, 542, 536, 463
- Placebo: 580, 567, 559, 547, 535, 523, 514, 444

Kaplan-Meier plot of all-cause deaths through Day 180

- Placebo: 65 deaths (11.3%)
- Serelaxin: 42 deaths (7.3%)
- HR 0.63 (95% CI 0.43, 0.93)
- p = 0.02

Number at risk:
- Serelaxin: 581, 573, 563, 555, 546, 542, 536, 463
- Placebo: 580, 567, 559, 547, 535, 523, 514, 444

Primary Endpoint Results for RELAX-AHF2:
CV mortality through Day 180

- Serelaxin: 285/3274 (8.7%)
- Placebo: 290/3271 (8.9%)
- Hazard ratio (95% CI): 0.98 (0.83, 1.15)
- p-value (log-rank): 0.3857
Lessons From Recent RCTs in AHF - #2

- RELAX-AHF2 (and many, many others) evaluated the long-term effects of drug therapy that was administered for a limited period of time during AHF hospitalization.
- Whether this is a reasonable approach is debatable.
Patients with AHF Are Heterogeneous

- 50% HFrEF and 50% HFpEF
- 75% worsening existing HF and 20-25% new onset HF
- Wide variety of precipitating causes (e.g. arrhythmias, infection, myocardial ischemia, WRF, anemia)
- Multiple co-morbidities (e.g. diabetes, CKD, CAD, HTN, COPD, depression)
AHF is a Syndrome Caused by Different Diseases

- **Acute Vascular Failure**: (Elderly, female=male, preserved EF, mild chronic CHF)
  - Rapidly evolving pulmonary congestion + ↑ blood pressure
  - rapid respiratory failure, multi-organ failure and death.

- **Acute Cardiac Failure**: (Younger, male, low EF, significant background CHF)
  - Slow deterioration in severe chronic HF
  - slowly progressive pulmonary congestion and peripheral hypoperfusion accompanied by relatively ↓ blood pressure, peripheral edema and weight gain.

- **Other**:
  - ACS, arrhythmias (mostly A.Fib), high output failure, RV failure
Definition of Insanity

• Doing the same thing over and over again and expecting different results.
  - Albert Einstein

Future clinical trials will need to address issues regarding heterogeneity of the AHF population and focus on 48 hour drug administration in order to be successful in improving outcomes
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 in RELAX-AHF

**A. Troponin T**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0076

**B. Cystatin C**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0004

**C. AST**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0987

**D. ALT**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0162

**E. NT-proBNP**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0001

**F. Worsening heart failure**
- Cumulative Risk
- Number at risk: 2012
- p-value: 0.0164
Adverse Effects of Milrinone in Patients with Ischemic Etiology

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

Clinical Status at Time of Discharge

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

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
• Use available therapies
BG062444 Improves Outcomes in Worsening Chronic HF

**Figure Legend:**
- **NYHA III-IV**
  - Hazard ratio (95% CI): 0.65 (0.57–0.75); p<0.001
- **EF < 0.25**
  - Hazard ratio (95% CI): 0.61 (0.53–0.71); p<0.001
- **CTR >0.55**
  - Hazard ratio (95% CI): 0.65 (0.57–0.75); p<0.001

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Placebo</th>
<th>BG 062444</th>
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<tbody>
<tr>
<td>0-3 months</td>
<td>1105</td>
<td>338</td>
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<tr>
<td>3-6 months</td>
<td>792</td>
<td>795</td>
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<tr>
<td>6-9 months</td>
<td>674</td>
<td>700</td>
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<tr>
<td>9-12 months</td>
<td>597</td>
<td></td>
</tr>
<tr>
<td>12-15 months</td>
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<tr>
<td>15-18 months</td>
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<tbody>
<tr>
<td>0-3 months</td>
<td>1129</td>
<td>127</td>
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<tr>
<td>3-6 months</td>
<td>840</td>
<td>956</td>
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<tr>
<td>6-9 months</td>
<td>713</td>
<td>830</td>
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<tr>
<td>9-12 months</td>
<td>626</td>
<td>739</td>
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<tr>
<td>12-15 months</td>
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<tbody>
<tr>
<td>0-3 months</td>
<td>1170</td>
<td>1175</td>
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<tr>
<td>3-6 months</td>
<td>853</td>
<td>973</td>
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<tr>
<td>6-9 months</td>
<td>731</td>
<td>837</td>
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<tr>
<td>9-12 months</td>
<td>650</td>
<td>742</td>
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</tr>
</tbody>
</table>
BG062444 = Digoxin

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

**Central Illustration:** Influence of LCZ696 on Readmission: Rates After Investigator-Reported HF Hospitalization According to Treatment Assignment

- 30-day All-cause Readmission:
  - Enalapril: 21.0%
  - LCZ696: 17.8%

- 30-day Heart Failure Readmission:
  - Enalapril: 13.4%
  - LCZ696: 9.7%

- 60-day All-cause Readmission:
  - Enalapril: 30.5%
  - LCZ696: 27.8%

- 60-day Heart Failure Readmission:
  - Enalapril: 20.3%
  - LCZ696: 17.1%

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>
</tbody>
</table>
| 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. | I   | B   |
| Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended | I   | B   |
| A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge is reasonable | IIa | B   |
| Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable | IIa | B   |

Performance Improvement Initiatives Can Improve Quality of Patient Care

Significant reduction in mean length of stay
P<0.001

In-hospital mortality
Post-discharge death
Post-discharge death + rehospitalization

Data from 259 participating hospital centers enrolled in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) prospective registry

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
Interventions During Ambulatory Pulmonary Artery Pressure Monitoring

Cumulative HF Hospitalizations Reduced
At 6 Months and Full Duration of Randomized Study

- **≤ 6 Months**: 28% RRR, p = 0.0002
- **> 6 Months**: 45% RRR, p < 0.0001
- **Study Duration**: 37% RRR, p < 0.0001
Managing Acute Heart Failure in 2017

• AHF is a common, costly public health burden that is associated with high rates of re-admission and post-discharge mortality.
• Therapies currently in use have not been shown to improve outcomes in patients with AHF.
• Clinical trials in AHF should consider designs other than those that have dominated the field for the past decades.
• Currently available therapies and strategies can improve outcomes and should be emphasized both during hospitalization and in the transition to out-patient care.