Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

Jo E. Rodgers, Pharm.D., BCPS

One of Four Continuing Education Programs in the Series, “Acute Decompensated Heart Failure: Integrating Consensus Guidelines and Individual Patient Characteristics into Optimal Treatment Regimens”

Recorded August 1, 2006
Chicago, Illinois
Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

Target Audience

This continuing education program is beneficial for pharmacists and pharmacy managers in all practice settings who are involved in improving care for patients with ADHF.

Program Description

Acute decompensated heart failure (ADHF) accounts for almost one million hospitalizations per year, and rehospitalization within six months is as high as 50%. The annual mortality rate in patients frequently hospitalized with ADHF—those with New York Heart Association class III or IV symptoms—approaches 50%. While ADHF was traditionally viewed as a disorder associated with sodium and water retention and left-ventricular dysfunction, it is now understood to be associated with neurohormonal activation. This program will provide an overview of the pathophysiology of ADHF, including risk stratification criteria based on observational data of patients hospitalized with ADHF. The primary focus, however, will be on key clinical trials that guide treatment selection for patients with ADHF. Understanding the design and limitations of these studies is essential to offering optimal care to the ADHF population.

This program is the recommended starting point in the series for pharmacists who do not have a strong background in cardiology.

Learning Outcomes

After listening to this program, the participant should be able to:

- Identify the role of neurohormonal activation in ADHF.
- Describe in-hospital mortality risk based on risk stratification data for ADHF.
- Identify key factors in applying the results of clinical trials to various subpopulations of patients with ADHF.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This continuing education program provides 1.0 hours (0.1 CEUs) of continuing education credit (program number 204-000-06-424-H01). This program is provided free of charge. After participating in the program, pharmacists may complete the CE test online at the ASHP Advantage CE Testing Center (www.ashp.org/advantage/ce). A passing grade of 70% is required to receive continuing education credit for this program, and pharmacists can print their CE statement immediately. Continuing education credit for this program is available from September 15, 2006, through September 14, 2007.
Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

Program Faculty

Jo E. Rodgers, Pharm.D., BCPS
Clinical Assistant Professor
University of North Carolina at Chapel Hill
School of Pharmacy
Chapel Hill, North Carolina

Jo E. Rodgers, Pharm.D., is Clinical Assistant Professor at the University of North Carolina (UNC) at Chapel Hill School of Pharmacy. She maintains an active clinical practice with the UNC Cardiomyopathy and Cardiac Transplantation Service at UNC Hospitals. She serves as co-coordinator of the cardiology specialty residency, coordinator of the cardiology therapeutics module and the acute care and critical care electives, and advisor to both the UNC Clinical Scholars Program and Kappa Epsilon. Dr. Rodgers’ research interests focus on the care of heart failure and cardiac transplant patients.

After obtaining both her Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees at the University of North Carolina (UNC) at Chapel Hill, Dr. Rodgers completed a pharmacy practice and critical care specialty residency at the Medical College of Virginia. She then returned to UNC for a fellowship in cardiovascular pharmacotherapy.

Dr. Rodgers is a reviewer for Pharmacotherapy and Annals of Pharmacotherapy, and her research has recently been published in Critical Care Medicine and Journal of Thrombosis and Thrombolysis. She is an active member of the American College of Clinical Pharmacy, and she currently serves as chair-elect of the Cardiology PRN and secretary-elect of the Triangle College of Clinical Pharmacy. Dr. Rodgers received the 2004-05 national Outstanding Advisor Award from Kappa Epsilon Fraternity.

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Dr. Rodgers declares that she has served as a consultant for Abbott Laboratories and Scios Inc. and has been on the speakers bureau for Scios Inc.
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1. Type www.ashp.org/advantage/ce/ in your internet browser.

2. If you have previously logged in to the ASHP Advantage site, then you need only enter your e-mail address and password.

   If you have not logged in to the ASHP Advantage site before, click on “Create Account” and follow the brief instructions to set up a user account and password. You will only need to create your account once to have access to register, take CE tests, and process CE online from ASHP Advantage in the future.

3. After logging in, you will see the list of activities for which CE is available. To process CE for one of the activities in the list, click on the “Start” button next to the name of the activity. This activity is listed under “ADHF Series.”

4. Click on the radio button next to the correct answer for each question. Once you are satisfied with your selections, click “Finish CE” to process your test and complete the remaining steps to print your CE statement.

5. Repeat the above steps for each Podcast activity in which you participate.

If you have any problems processing your CE, contact ASHP Advantage at support@ashpadvantage.com.

*Except that this site does not support the AOL Web browser.
Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

Jo E. Rodgers, Pharm.D., BCPS, BCPS
Clinical Assistant Professor
Division of Pharmacotherapy, School of Pharmacy
University of North Carolina at Chapel Hill

Learning Objectives

• Describe the epidemiology of acute decompensated heart failure (ADHF).
• Identify the role of neurohormonal activation in ADHF.
• Describe in-hospital mortality based on risk stratification for ADHF.
• Identify key factors in applying the results of clinical trials to various subpopulations of patients with ADHF.

Epidemiology

Incidence:
550,000 new cases/yr

Prevalence:
≈5 million
(continues to increase)


Scope of the Problem

Mortality:
≈50% at 5 years

Economic costs:
≈$29.6 billion
(direct and indirect)

Morbidity:
≈1 million hospitalizations/yr.


Economic Impact

60.6% Hospitalization
$23.1 billion

38.6% Outpatient care
$14.7 billion

0.7% Transplants
$270 million

Total = $38.1 billion
(5.4% of total health care costs)

Hospitalization

Initial episode
21%

Repeat visit 79%

Rates of readmission
• 2% within 2 days
• 20% within 1 month
• 50% within 6 months
Pathophysiology and Etiology

Neurohormonal Hypothesis

↓ LV function → Cardiac output → Abnormal reflexes → Neurohormone activation → RAAS, SNS, AVP, BNP, ET-1, TNF-α, IL-6

↑ Progression of heart failure (HF) → Impedance → Salt and water retention → ↑ Cardiac output → Abnormal reflexes → ↑ Neurohormone activation

RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system; AVP = arginine vasopressin; BNP = B-type natriuretic peptide; ET-1 = endothelin-1; TNF-α = tissue necrotizing factor α; IL-6 = interleukin-6; LV = left ventricular

Neurohormonal Imbalance

- Norepinephrine
- Angiotensin-II
- Aldosterone
- Endothelin
- Vasopressin

Vasoconstriction → Tachycardia → Fluid retention

- ANP
- BNP
- Nitric oxide
- Bradykinin
- Prostacyclin

Vasodilation → Suppress SNS/RAAS → Natriuresis and diuresis

Common Causes of ADHF

- Dietary noncompliance 24%
- Medication noncompliance 24%
- Inappropriate prescribing 19%
- Failure to seek care 17%
- Other 16%

ADHF: Signs and Symptoms

**Fluid Overload**
- Weight gain
- Dyspnea on exertion
- Paroxysmal nocturnal dyspnea (PND)
- Orthopnea
- Rales
- Peripheral edema
- Jugular venous distension
- Ascites
- Hepato-/splenomegaly

**Low Cardiac Output**
- Fatigue
- Nausea and vomiting
- Early satiety
- Weight loss
- Increased serum creatinine


B-type Natriuretic Peptide: Usefulness in ADHF Diagnosis

- Correlation with ↑ BNP level
  - ADHF diagnosis, disease severity, mortality
- Breathing Not Properly study (n=1,586)
  - Patients presenting with dyspnea → BNP assay
  - BNP > 100 pg/mL - 83% accuracy for diagnosis

Evaluate BNP in context of clinical picture

- BNP < 100 pg/mL: HF highly unlikely
- BNP 100 – 500 pg/mL: Consider HF history and other potential causes
- BNP > 500 pg/mL: HF highly likely


In-Hospital Mortality: Risk Stratification

- BUN
  - < 43: 2.7%
  - ≥ 43: 9%
- SBP
  - < 115: 2.1%
  - ≥ 115: 6.4%
- SCr
  - < 1.25: 12.4%
  - ≥ 1.25: 22%

BUN = blood urea nitrogen
SBP = systolic blood pressure
SCr = serum creatinine


Patient Selection and Treatment

Cardiac Index (L/min/m²)

- Subset I (Normal) 5 – 4
  - "Warm and dry"
- Subset II (Congestion) 3
  - "Warm and wet"
- Subset III (Hypoperfusion) 2 – 1
  - "Cold and dry"
- Subset IV (Congestion and hypoperfusion) 1
  - "Cold and wet"

PCWP = pulmonary capillary wedge pressure
CI = cardiac index
SVR = systemic vascular resistance

Adapted from Nohria A et al. JAMA. 2002; 287:628-40.

ADHF: Therapeutic Options

- Diuretics
  - Furosemide
  - Bumetanide
  - Torsemide
- Inotropes
  - Dobutamine
  - Milrinone
- Vasodilators
  - Nitroglycerin
  - Nitroprusside
  - Nesiritide

ADHF: Goals of Therapy

- Improve signs and symptoms of congestion or hypoperfusion or both
- Identify etiology and precipitating factors
- Minimize adverse effects
- Optimize chronic oral drug therapy

Diuretic Therapy in Fluid Overload
ADHF: Signs and Symptoms

**Fluid Overload**
- Weight gain
- Dyspnea on exertion
- PND
- Orthopnea
- Rales
- Peripheral edema
- Jugular venous distension
- Ascites
- Hepato-splenomegaly

**Low Cardiac Output**
- Fatigue
- Nausea and vomiting
- Early satiety
- Weight loss
- Increased serum creatinine

---

**Patient Selection and Treatment**

- **Cardiac Index (L/min/m²)**
  - Subset I (Normal): 4.0 - 5.0
  - Subset II (Congestion): 2.2 - 4.0
  - Subset III (Hypoperfusion): 1.0 - 2.2
  - Subset IV (Congestion and hypoperfusion): < 1.0

- **Pulmonary Capillary Wedge Pressure (mmHg)**
  - Subset I (Normal): 15-18
  - Subset II (Congestion): > 18

- **Diuretics**

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**Diuretics**

- Primarily used to reduce congestion
- Limited literature supporting impact on outcomes
- Diuretic resistance frequently limits efficacy
- Association with increased mortality

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**Chronic Diuretic Therapy: Mortality**

<table>
<thead>
<tr>
<th>SCr (&lt; 2 mg/dL)</th>
<th>No Diuretic</th>
<th>Diuretic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHERE Registry</td>
<td>2.7</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both p &lt; 0.0001</td>
<td>2.4</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Acute Diuretic Therapy: Mortality, LOS, and ICU LOS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>I.V. Diuretics (n=50,882)</th>
<th>No I.V. Diuretics (n=5,602)</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2.3%</td>
<td>2.0%</td>
<td>1.29 (1.04-1.59)</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS &gt; 4 day</td>
<td>52.1%</td>
<td>40.8%</td>
<td>1.49 (1.40-1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS &gt; 3 day</td>
<td>30%</td>
<td>19.7%</td>
<td>1.59 (1.26-2.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Ultrafiltration (UF)**

- **Principles and benefits**
  - Provides an additional modality for fluid removal
  - Rapidly removes salt and water (up to 500 mL/hr)
  - Allows for a predictable amount of fluid to be removed
  - Safer than diuretics because removal of sodium and water is isotonic

- **Potential indications**
  - Patients with diuretic resistance
  - Patients with renal impairment
UNLOAD Trial
Ultrafiltration versus I.V. Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

Design: Prospective, randomized trial in patients with ADHF due to volume overload

Population: n=200, ≥ 2 signs of volume overload, randomized within 24 hours of admission, hemodynamically stable, and no prior i.v. vasoactive drugs

Treatment: Ultrafiltration vs. aggressive i.v. diuretic therapy

Endpoints: Weight loss and dyspnea score at 48 hours

Costanzo MR et al. ACC scientific sessions. 2006 March 14.

End points – 48 hours

<table>
<thead>
<tr>
<th></th>
<th>UF</th>
<th>Diuresis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (kg)</td>
<td>5.0</td>
<td>3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnea score (mean)</td>
<td>6.4</td>
<td>6.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Net fluid loss (L)</td>
<td>4.6</td>
<td>3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Potassium &lt; 3.5 mEq/L (%)</td>
<td>1</td>
<td>12</td>
<td>0.018</td>
</tr>
<tr>
<td>Need for vasoactive therapy (%)</td>
<td>3</td>
<td>13</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Costanzo MR et al. ACC scientific sessions. 2006 March 14.

End points – 90 days

<table>
<thead>
<tr>
<th></th>
<th>UF</th>
<th>Diuresis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehospitalization (%)</td>
<td>18</td>
<td>32</td>
<td>0.022</td>
</tr>
<tr>
<td>Rehospitalization days (mean)</td>
<td>1.4</td>
<td>3.8</td>
<td>0.022</td>
</tr>
<tr>
<td>Unscheduled office or emergency department (%)</td>
<td>21</td>
<td>44</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Costanzo MR et al. ACC scientific sessions. 2006 March 14.

ADHF: Signs and Symptoms

Fluid Overload
- Weight gain
- Dyspnea on exertion
- PND
- Orthopnea
- Rales
- Peripheral edema
- Jugular venous
- distension
- Ascites
- Hepato-splenomegaly

Low Cardiac Output
- Fatigue
- Nausea and vomiting
- Early satiety
- Weight loss
- Increased serum
- creatinine

Inotropic Therapy
in Low Cardiac Output

Patient Selection and Treatment

Pulmonary Capillary Wedge Pressure (mmHg)

Cardiac Index (L/min/m²)
- Subset I (Normal)
- Subset II (Congestion)
- Subset III (Hypoperfusion)
- Subset IV (Congestion and hypoperfusion)

Inotropes
- Dobutamine
- Milrinone

Limitations of Positive Inotropes

- Increased mortality
  - Milrinone
  - Enoximone
  - Imazodan
  - Vesnarinone
  - Dobutamine
  - Xamoterol
  - Ibopamine

Arrhythmias
- Neurohormonal activation
- Tachyphylaxis
- Physiologic effects
  - antagonized by β-blockade

OPTIME-CHF Trial

Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure

Design: Double-blind, placebo-controlled trial

Population: n=951 patients with ADHF

Treatment: Intravenous milrinone vs. placebo for 48 hrs

Endpoint: Rehospitalization for cardiovascular events at 60 days


OPTIME-CHF Trial: Study Results

There was no significant difference in hospitalization for cardiovascular events within 60 days.

<table>
<thead>
<tr>
<th></th>
<th>Milrinone (n = 477)</th>
<th>Control (n = 472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>477</td>
<td>472</td>
</tr>
<tr>
<td>Median hospital stay (days)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean hospital stay (days)</td>
<td>12.3 ± 14</td>
<td>12.5 ± 14</td>
</tr>
<tr>
<td>Days until discharge</td>
<td>5.7 ± 13</td>
<td>5.9 ± 13</td>
</tr>
</tbody>
</table>

Total mortality rates (in hospital and at 60 days) were not significantly different between the two treatment groups.


OPTIME-CHF Trial: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Milrinone (n = 477)</th>
<th>Control (n = 472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>12.6% **</td>
<td>2.1%</td>
</tr>
<tr>
<td>Sustained hypotension</td>
<td>10.7% **</td>
<td>3.2%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Atrial fibrillation (new-onset)</td>
<td>4.6% *</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

* p = 0.004
**p < 0.001


ADHERE Registry: Mortality Comparing Vasodilators vs. Inotropes

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio*</th>
<th>Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG vs. MIL</td>
<td>0.69</td>
<td>0.53–0.89</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NTG vs. DOB</td>
<td>0.46</td>
<td>0.37–0.57</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NES vs. MIL</td>
<td>0.59</td>
<td>0.48–0.73</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NES vs. DOB</td>
<td>0.47</td>
<td>0.39–0.56</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NES vs. NTG</td>
<td>0.94</td>
<td>0.77–1.16</td>
<td>0.58</td>
</tr>
<tr>
<td>DOB vs. MIL</td>
<td>1.24</td>
<td>1.03–1.55</td>
<td>0.027</td>
</tr>
</tbody>
</table>

NTG = nitroglycerin, NES = nesiritide, MIL = milrinone, DOB = dobutamine
*Adjusted for covariates and propensity score


Vasodilator Therapy in Fluid Overload and Low Output
**Cardiac Index (L/min/m²)**

- Subset I (Normal) “Warm and Dry”
- Subset II (Congestion) “Warm and Wet”
- Subset III (Hypoperfusion) “Cold and Dry”
- Subset IV (Hypoperfusion and Congestion) “Cold and Wet”

**Pulmonary Capillary Wedge Pressure (mmHg)**

- Subset II (Congestion) “Warm and Wet”
- Subset III (Hypoperfusion) “Cold and Dry”
- Subset IV (Congestion and Hypoperfusion) “Cold and Wet”

**Vasodilators**

<table>
<thead>
<tr>
<th>Nitroprusside</th>
<th>Nitroglycerin</th>
<th>Natriuretic peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Renin Angiotensin Aldosterone System**

- Vasoconstriction
- Sodium retention
- Increased aldosterone release
- Increased cellular growth
- Increased sympathetic nervous system activity

**Natriuretic Peptide System**

- Vasodilation
- Sodium excretion
- Decreased aldosterone release
- Decreased cellular growth
- Inhibition of sympathetic nervous system activity

**VMAC Trial: Design**

**Vasodilatation in the Management of Acute CHF**

- Active-controlled treatment period
- Placebo-controlled period

**Primary endpoint: PCWP through 3 hours**

**Nesiritide: Mortality Assessment**

- Meta-analysis assessing mortality of nesiritide vs. control
  - 3 trials: NSG-Efficacy, VMAC, PROACTION

<table>
<thead>
<tr>
<th>End point</th>
<th>Nesiritide (n = 485)</th>
<th>Control (n = 377)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>7.2 %</td>
<td>4 %</td>
<td>0.059</td>
</tr>
</tbody>
</table>

- Study limitations
  - 3 heterogeneous trials
  - Not designed to assess mortality
  - Nesiritide doses greater than labeled doses

- Author conclusion
  - “Hypothesis-generating rather than conclusive”

**VMAC Investigators. JAMA. 2002; 287:1531-40.**

**NAPA Trial**

**Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery**

- Design: Multicenter, randomized, placebo-controlled study
- Population: Undergoing coronary artery bypass graft (CABG) surgery requiring cardiopulmonary bypass, left ventricular ejection fraction (LVEF) < 40%
- Treatment: Intravenous nesiritide versus placebo for 24-96 hr
- Endpoints: Change in Scr and glomerular filtration rate (GFR)
  - Change in urine output (UOP) at 24 hr
  - Mean ICU/CCU and hospital LOS

**CCU = coronary care unit**

Hebeler RF Jr et al. 7th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. 2006 May 9.
**NAPA Trial: Design**

*Administered for 24-96 hours (no bolus); nesiritide dose 0.01 mcg/kg/min

**NAPA Trial: Results**

<table>
<thead>
<tr>
<th>Endpoint*</th>
<th>Nesiritide (n=141)</th>
<th>Placebo (n=138)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak SCr increase (mg/dL)</td>
<td>0.15 (n=141)</td>
<td>0.34 (n=138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subjects with baseline</td>
<td>0.02 (n=141)</td>
<td>0.48 (n=138)</td>
<td>0.001</td>
</tr>
<tr>
<td>SCr &gt;1.2 mg/dL</td>
<td>-10.8 (n=141)</td>
<td>-17.2 (n=138)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximum decrease in GFR (mL/min/1.73 m²)</td>
<td>0.003 (n=141)</td>
<td>0.02 (n=138)</td>
<td></td>
</tr>
<tr>
<td>Subjects with baseline</td>
<td>-0.2 (n=29)</td>
<td>-0.9 (n=33)</td>
<td></td>
</tr>
<tr>
<td>SCr &gt;1.2 mg/dL</td>
<td>-10.8 (n=141)</td>
<td>-17.2 (n=138)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Mean change in SCr and GFR through discharge or hospital day 14, whichever came first.

**Optimizing Chronic Therapy**

- **IMPACT-HF Trial**
  - **Initiation Management PredischARGE: Process for Assessment of Carvedilol Therapy in Heart Failure**
  - Screening hospitalized patients
  - LVEF < 40%, hospitalized for ADHF
  - Pre-discharge initiation carvedilol 3.125 mg bid
  - Pre-discharge initiation carvedilol 3.125 mg bid
  - Physician discretion post-discharge (≥2 weeks)
  - Initiation of any β-blocker

**IMPACT-HF Trial: Results**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pre-discharge (n=185)</th>
<th>Post-discharge at MD Discretion (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with β-blocker (%)</td>
<td>91.2*</td>
<td>73.4</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Rehospitalization (%)</td>
<td>21.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Death or rehospitalization (%)</td>
<td>23.8</td>
<td>27.0</td>
</tr>
</tbody>
</table>

*p=0.0001; all other differences nonsignificant
IMPACT-HF Trial: Serious Adverse Effects

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pre-discharge (n=185)</th>
<th>Post-discharge at MD Discretion (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of β-blocker (%)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Withdrawal – hypotension (%)</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Withdrawal – bradycardia (%)</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal – HF worse (%)</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

All differences nonsignificant.


PHARM Trial

**Pharmacist Role in Heart Failure Assessment Recommendation and Monitoring**

**OR 0.218 (0.06-0.625), \( p=0.0048 \)**

Freedom from Death or NF HF

0.218 (0.06-0.625), \( p=0.0048 \)

NF HF = nonfatal heart failure


PHARM Trial: Death or Readmission

Death alone \( p=0.48 \)


ADHERE Registry: Conforming to HF Performance Indicators

<table>
<thead>
<tr>
<th>All Hospitals (n=223)</th>
<th>Academic Hospitals (n=87)</th>
<th>Non-Academic Hospitals (n=136)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge instructions (%)</td>
<td>31.5</td>
<td>22.1</td>
<td>35.5</td>
</tr>
<tr>
<td>Left-ventricular function tests (%)</td>
<td>84.2</td>
<td>86.3</td>
<td>83.3</td>
</tr>
<tr>
<td>Discharge ACE-inhibitor Rx (%)</td>
<td>71.9</td>
<td>75.4</td>
<td>70.4</td>
</tr>
<tr>
<td>Smoking cessation counseling (%)</td>
<td>45.5</td>
<td>41.5</td>
<td>47.2</td>
</tr>
</tbody>
</table>

81,142 hospital admissions for ADHF. ADHERE Registry Report Q2 2002 (7/1/02-12/31/03) of 233 U.S. hospitals.


Patient Selection and Treatment

Pulmonary Capillary Wedge Pressure (mmHg)

Cardiac Index (L/min/m²)

- Subset I (Normal)
  - "Warm and dry" 4
  - "Cold and dry" 2
- Subset II (Congestion)
  - "Warm and wet" 3
  - "Cold and wet" 1
- Subset III (Hypoperfusion)
  - "Cold and dry" 2
- Subset IV (Congestion and hypoperfusion)
  - "Cold and wet" 1

15-18 mmHg

2.2 L/min/m²

Diuretics or Vasodilators
Nitroprusside
Nitroglycerin or Natriuretic Peptides
Nesiritide

10 20 30

Indraprop Dobutamine Milrinone

Conclusions

• ADHF is associated with significant morbidity and mortality and consumes a considerable portion of overall healthcare expenditures.
• Maintaining the neurohormonal balance is instrumental to preventing ADHF.
• Limited literature supports therapies currently being used to manage ADHF.
• It is critical to understand the underlying process (wet/dry, cold/warm) in ADHF to best select optimal drug therapy.
• Pharmacists are instrumental in preventing and managing ADHF.
Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

References


Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials


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Self-Assessment Questions

1. Which of the following is the most significant contributor to the cost of heart failure management?
   a. Medication.
   b. Transplantation.
   c. Outpatient care.
   d. Hospitalization.

2. Which of the following are involved in the neurhormonal imbalance that occurs in heart failure?
   a. Reduction in vascular impedance or resistance.
   b. Increase in sodium and water retention.
   c. Reduction in B-type natriuretic peptide (BNP) level.
   d. Reduction in tachycardia.

3. What is the most common cause of worsening heart failure?
   a. Failure to seek care.
   b. Inappropriate prescribing.
   c. Inadequate discharge planning.
   d. Noncompliance with diet and medication.

4. Which of the following signs and symptoms is consistent with low cardiac output?
   a. Increased serum creatinine.
   b. Orthopnea.
   c. Ascites.
   d. Rales.

5. Which of the following BNP concentrations is consistent with an unlikely diagnosis of acute decompensated heart failure (ADHF)?
   a. 50 pg/mL.
   b. 500 pg/mL.
   c. 5000 pg/mL.
   d. 50,000 pg/mL.

6. A patient is hospitalized for ADHF with a systolic blood pressure of 100 mmHg, blood urea nitrogen of 55 mg/dL, and a serum creatinine of 4.2 mg/dL. Which of the following percentages most closely corresponds to the in-hospital risk of mortality for this patient?
   a. 2%.
   b. 5%.
   c. 15%.
   d. 20%.
Acute Decompensated Heart Failure: Review of Pathophysiology and Key Clinical Trials

7. Which of the following therapies directly improves contractility in patients with ADHF?

a. Diuretics.
b. Inotropes.
c. Vasodilators.
d. Natriuretic peptides.

8. Which of the following statements regarding diuretic therapy in patients with ADHF is true?

a. Many well-controlled studies support the positive impact of i.v. diuretics on outcomes.
b. Intravenous diuretics have a limited adverse effect profile.
c. Diuretic resistance rarely occurs.
d. Retrospective studies suggest a negative impact of intravenous diuretics on outcome.

9. Compared with diuretics, ultrafiltration has been shown to result in

a. Greater net fluid and weight loss.
b. Greater hypokalemia.
c. Greater need for vasoactive therapy.
d. Greater reduction in dyspnea score.

10. All of the following are concerns regarding the use of inotropic therapy in patients with ADHF except

a. Arrhythmia.
b. Increased mortality.
c. Lack of response to milrinone in patients receiving β-blocker therapy.
d. Neurohormonal activation.

11. Compared with nitroglycerin, nesiritide has been demonstrated to reduce which of the following parameters

a. Symptoms as reported by patient.
b. Symptoms as reported by physician.
c. Pulmonary capillary wedge pressure through 24 hours.
d. Pulmonary capillary wedge pressure through 48 hours.

12. Controversy has arisen regarding nesiritide’s effect on which of the following outcomes?

a. Mortality at 30 days.
b. Hospital readmission within 180 days.
c. Hemodynamic parameters within 12 hours.
d. Length of stay for initial hospitalization.

13. Initiating β-blocker therapy before discharge for patients hospitalized with ADHF has been demonstrated to

a. Increase length of stay.
b. Increase outpatient treatment with a β-blocker.
c. Increase the number of readmissions within 60 days.
d. Increase the total hospitalization cost.