Monitoring the Safety and Efficacy of Acute Decompensated Heart Failure Treatment

Cynthia A. Sanoski, Pharm.D., Program Chair

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
Monitoring the Safety and Efficacy of Acute Decompensated Heart Failure Treatment

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

Given the complex therapeutic regimens that are currently available for the treatment of acute decompensated heart failure (ADHF), it is essential that practitioners are aware of the parameters that can be used to monitor the safety and efficacy of these therapies. Using the results of key clinical studies as the guide, this program provides an up-to-date analysis of information regarding potential safety issues of treatment options for ADHF. In addition, various methods for assessing efficacy of these treatment regimens, including noninvasive clinical assessment strategies as well as pulmonary artery catheters, will be discussed. Options for monitoring safety of ADHF treatments within health systems, such as medication-use evaluations, will also be discussed.

Learning Outcomes

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

- Describe the key safety issues regarding the use of intravenous positive inotropes and vasodilators in patients with ADHF.
- Describe noninvasive, clinical assessment parameters for evaluating efficacy of treatment in patients with ADHF.
- Identify the role of pulmonary artery catheters for monitoring efficacy of treatment in patients with ADHF.
- Describe the potential usefulness of a medication-use evaluation for monitoring the safety of ADHF treatment within health systems.

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 204-000-06-426-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.
Cynthia A. Sanoski, PharmD, is Associate Professor of Clinical Pharmacy in the Philadelphia College of Pharmacy at the University of the Sciences in Philadelphia, Pennsylvania. In addition, Dr. Sanoski serves as Cardiovascular Clinical Specialist in the Coronary Care Unit at Presbyterian Medical Center in Philadelphia.

After earning her Bachelor of Science in Pharmacy degree at Duquesne University in Pittsburgh and her Doctor of Pharmacy degree from The Ohio State University College of Pharmacy in Columbus, Dr. Sanoski completed a two-year fellowship in cardiovascular pharmacotherapy at the University of Illinois College of Pharmacy in Chicago. A frequent national lecturer, Dr. Sanoski speaks on numerous topics in cardiovascular disease management, including cardiac arrhythmias, acute coronary syndromes, dyslipidemias, and acute decompensated heart failure.

As an author, Dr. Sanoski has published in a number of journals, including Archives of Internal Medicine, Formulary, Pharmacotherapy, Chest, Journal of Pharmacy Practice, and The Journal of Applied Research. She has also written several book chapters on the management of acute and chronic arrhythmias and medication-induced cardiovascular side effects. Dr. Sanoski is a reviewer for several medical journals, including Pharmacotherapy, Clinical Therapeutics, Journal of Pharmacy Practice, and the American Journal of Managed Care.

Dr. Sanoski is a member of the American College of Clinical Pharmacy, American Society of Health-System Pharmacists, and the American Association of Colleges of Pharmacy, for which she serves on several program and publications committees.

Faculty Disclosure Statement

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Dr. Sanoski declares that she has served as a consultant and on the speakers bureau for Scios Inc.
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Instructions for Receiving Your CE Credit and Statements Online for Podcast Activities

The online ASHP Advantage CE Testing Center allows participants to obtain their CE statements conveniently and immediately using any computer with an Internet connection.* To take the CE test and obtain your CE statement for this ASHP Advantage Podcast activity, please follow these steps:


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.
Monitoring the Safety and Efficacy of Acute Decompensated Heart Failure Treatment

Cynthia A. Sanoski, Pharm.D.
Associate Professor of Clinical Pharmacy
Philadelphia College of Pharmacy
University of the Sciences in Philadelphia

Learning Objectives

- Describe noninvasive, clinical assessment parameters for evaluating efficacy of treatment in patients with acute decompensated heart failure (ADHF)
- Discuss the role of pulmonary artery catheters for monitoring efficacy of treatment in patients with ADHF
- Characterize the key safety issues regarding the use of intravenous positive inotropes and vasodilators in patients with ADHF
- Describe the potential usefulness of a medication-use evaluation for monitoring the safety of ADHF treatment within health systems

ADHF: Goals of Therapy

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

Non-Invasive Assessment of Efficacy for ADHF Treatment

Hemodynamic Subsets in ADHF

Hemodynamic Subsets: Predictors of Outcomes in Heart Failure (HF)

1-Year Mortality and Urgent Transplantation

<table>
<thead>
<tr>
<th>Hemodynamic Subset</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and dry</td>
<td>Reference group</td>
<td>NA</td>
</tr>
<tr>
<td>Warm and wet</td>
<td>1.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Cold and dry</td>
<td>1.94</td>
<td>0.19</td>
</tr>
<tr>
<td>Cold and wet</td>
<td>2.48</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Clinical Assessment of Efficacy: Resolution of Signs and Symptoms

**Volume Overload**
- Dyspnea on exertion
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Early satiety
- Nausea and vomiting
- Rales
- Peripheral edema
- ↑ Jugular venous pressure (JVP)
- (+) hepatojugular reflex
- Hepato-/splenomegaly
- Ascites

**Hypoperfusion**
- Fatigue
- Altered mental status
- Narrow pulse pressure
- Hypotension
- Cool extremities
- Worsening renal function

Laboratory Assessment of Efficacy: B-type Natriuretic Peptide (BNP)

- Pre-pro BNP (134 AA)
- Signal Peptide (26 AA)
- Pro BNP (108 AA)
- NT-proBNP (1-76 AA)

- Biologically active
  - Cleared by natriuretic peptide receptors, endopeptidases, renal clearance
  - Half-life = 20 min
- Biologically inactive
  - Cleared renally (no receptors available)
  - Half-life = 1-2 hr

Diagnostic Usefulness of BNP in ADHF

- BNP
  - < 100 pg/mL: ADHF unlikely
  - 100-500 pg/mL: Consider other causes of dyspnea
    - Cor pulmonale, pulmonary embolism, LV dysfunction without acute exacerbation
  - > 500 pg/mL: ADHF very likely
- NT-proBNP
  - < 300 pg/mL: ADHF unlikely
  - 300-450 pg/mL (< 50 yrs) or 300-900 pg/mL (50-75 yrs): Consider other causes of dyspnea
  - > 450 pg/mL (< 50 yrs) or > 900 pg/mL (50-75 yrs): ADHF very likely
  - NT-proBNP target < 1700 pg/mL
  - NT-proBNP levels significantly ↓ in hormone-guided group (NS in clinically managed group)

BNP-Guided Therapy

- BNP-Guided Therapy (cont)
  - Responders: PCWP < 20 mmHg over first 24 hr
  - No significant correlation between PCWP and NT-proBNP

- BNP-Guided Therapy (cont)
  - Responders: > 30% ↑CI and > 30% ↓PCWP in first 24 hrs
  - PCWP BNP

Invasive Assessment of Efficacy for ADHF Treatment

Pulmonary Artery Catheters (PACs)
- Also known as right heart catheterization
- Used to
  - Provide insight regarding patient’s volume status and tissue perfusion
  - Guide therapy by monitoring cardiac filling pressures and systemic vascular resistance
- Specific hemodynamic goals
  - Right atrial pressure (RAP) ≤ 8 mmHg
  - PCWP ≤ 16 mmHg
  - Systemic vascular resistance (SVR) between 1000-1200 dyne•sec/cm$^5$

ESCAPE Trial
Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness

Design: Prospective, randomized, controlled; 26 HF centers in U.S. and Canada

Population: $n = 433$; advanced chronic systolic HF (despite standard therapy) with prior hospitalization for HF in past year, urgent emergency department visit or chronic high-dose diuretic therapy in preceding month

Treatment: Therapy guided by clinical assessment (CA) alone vs. therapy guided by CA + PAC

Endpoints: Primary: Days alive out of hospital during first 6 months
Secondary: Exercise, quality of life (QOL), BNP

ESCAPE Trial: Treatment Goals
- Resolution of signs and symptoms of congestion (both groups)
  - ↓ JVP, edema, orthopnea
- Hemodynamic goals (PAC group only)
  - PCWP 15 mmHg
  - RAP 8 mmHg

ESCAPE Trial: Treatment and Hemodynamics
- 100% use of i.v. diuretics
- Vasodilators
  - PAC = 37%
  - CA = 19%
- Inotropes
  - PAC = 44%
  - CA = 39%
- Both groups had significant improvement in clinical status
- No difference between groups

Hemodynamic Changes (PAC Group)

<table>
<thead>
<tr>
<th>Hemodynamic Measurement</th>
<th>Baseline</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>CI (L/min/m$^2$)</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>SVR (dyne•sec/cm$^5$)</td>
<td>1500</td>
<td>1100</td>
</tr>
</tbody>
</table>

ESCAPE Trial: Primary Endpoint Results
- No significant difference in mortality at 180 days or total days hospitalized between the groups
ESCAPE Trial: Other Endpoints

- Secondary endpoints
  - QOL and exercise endpoints tended to improve to greater extent in PAC group (\(p=\text{NS}\))
  - Tended to be greater change in BNP in PAC group (\(p=\text{NS}\))
- Other endpoints
  - In-hospital adverse events
    - PAC (21.9%) vs. CA (11.5%); \(p = 0.04\)

Role of Invasive Hemodynamic Monitoring in Treatment of ADHF

- NOT recommended for routine use to adjust therapy in ADHF (Strength of Evidence = A)
- Should be considered in a patient (Strength of Evidence = C)
  - Who is refractory to initial therapy
  - Whose volume status and cardiac filling pressures are unclear
  - Who has clinically significant hypotension (typically systolic blood pressure (SBP) < 80 mmHg) or worsening renal function during therapy, or
  - In whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered

Safety Issues with ADHF Treatment

Potential Issues with I.V. Diuretics

- Electrolyte abnormalities
  - ↓Na\(^+\), ↓K\(^+\), ↓Mg\(^{++}\), ↓Ca\(^{++}\)
- Metabolic alkalosis
- ↑activation of renin-angiotensin-aldosterone system and sympathetic nervous system
- ↑risk of worsening renal function
- Development of diuretic resistance
- Potential risk for ↑mortality

Diuretics

Impact of I.V. Diuretics on Outcomes in Patients Hospitalized with ADHF: Insights from the ADHERE Registry

<table>
<thead>
<tr>
<th>Outcome</th>
<th>I.V. Diuretic Treated (n=50,882)</th>
<th>Non I.V. Diuretic Treated (n=5,602)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2.3%</td>
<td>2.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>3.2</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>5.3</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICU= intensive care unit; LOS = length of stay


Potential Issues with I.V. Inotropes

- Hypotension
  - Milrinone > dobutamine > dopamine
- Tachycardia
  - Dopamine > dobutamine > milrinone
  - ↑myocardial oxygen demand
- Proarrhythmia
  - Dopamine > dobutamine ~ milrinone
- ↑mortality
- Tachyphylaxis
OPTIME-CHF
Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure

Design: Prospective, randomized, double-blind, placebo controlled; 78 U.S. community and tertiary-care hospitals

Population: n = 951; exacerbation of systolic HF not requiring i.v. inotropic support; 92% baseline NYHA III or IV; mean left ventricular ejection fraction = 23%

Treatment: Milrinone 0.5 mcg/kg/min OR saline placebo

Endpoint: Cumulative days of hospitalization for cardiovascular (CV) cause within 60 days following randomization


OPTIME-HF: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Milrinone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of days hospitalized for CV event</td>
<td>6 days</td>
<td>7 days</td>
<td>0.71</td>
</tr>
<tr>
<td>Sustained hypotension</td>
<td>10.7%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New atrial arrhythmias</td>
<td>4.6%</td>
<td>1.5%</td>
<td>0.004</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>3.8%</td>
<td>2.3%</td>
<td>0.19</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>10.3%</td>
<td>8.9%</td>
<td>0.41</td>
</tr>
<tr>
<td>Death or readmission</td>
<td>35%</td>
<td>35.3%</td>
<td>0.92</td>
</tr>
</tbody>
</table>


Impact of Arrhythmias in ADHF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>(+) Arrhythmia</th>
<th>(-) Arrhythmia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of days hospitalized for CV event within 60 days</td>
<td>30.9 ± 22.7</td>
<td>11.3 ± 12.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Index hospitalization (days)</td>
<td>11.4 ± 7.6</td>
<td>6.8 ± 6.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>26%</td>
<td>1.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Death or readmission at 60 days</td>
<td>57%</td>
<td>34%</td>
<td>0.001</td>
</tr>
</tbody>
</table>


Potential Issues with I.V. Vasodilators

• Nitroglycerin (NTG)
  - Tachyphylaxis
  - Hypotension
  - Reflex tachycardia
  - Headache
  - May need to be administered in ICU (with higher doses)

• Nitroprusside
  - Toxic metabolites
    - Cyanide (liver), thiocyanate (renal) toxicity
  - Hypotension
  - “Coronary steal”
  - Reflex tachycardia
  - Needs to be administered in ICU (± arterial line)


Renal Effects of Nesiritide

• Meta-analysis reported “an increased risk of worsening renal function with nesiritide as compared with control groups, as defined as an increase in SCr of >0.5mg/dL.”
  - Incidence of symptomatic hypotension similar between nesiritide and Nitroglycerin (VMAC)
  - Not associated with proarrhythmia
  - Worsening renal function??
  - ↑ mortality??

• The authors’ conclusion: SCr elevations were observed “at FDA- approved doses of nesiritide (≤ 0.03 mcg/kg/min)” and doses ≤ 0.015 mcg/kg/min were referred to as “low-dose nesiritide.”

SCr = serum creatinine


Potential Issues with I.V. Vasodilators (cont)

• Nesiritide
  - Hypotension
    - Seen with higher doses
    - Incidence of symptomatic hypotension similar between nesiritide and Nitroglycerin (VMAC)
  - Not associated with proarrhythmia
  - Worsening renal function??
  - ↑ mortality??

Nesiritide and Renal Function

- Limitations of meta-analysis
  - Raw data not available
  - Heterogeneous trial design, population, dosing, analyses
  - Prior diuretic therapy unknown
  - Final creatinine levels unknown
  - Initial recommended infusion dose is 0.01 mcg/kg/min because of a known dose-dependent relationship to hypotension and increases in SCR
  - Four of the 5 trials initiated nesiritide at doses 50-300% higher than the FDA recommended initial dose
  - No outcomes presented


Renal Effects of Nesiritide: VMAC

<table>
<thead>
<tr>
<th>p=NS for all comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day SCR compared to baseline NTG Nesiritide and maximum SCR at any time (n=216) (n=273)</td>
</tr>
<tr>
<td>Less than baseline</td>
</tr>
<tr>
<td>Equal to baseline</td>
</tr>
<tr>
<td>Greater than baseline (and &lt; maximum SCR)</td>
</tr>
<tr>
<td>Greater than baseline (and = to maximum SCR)</td>
</tr>
<tr>
<td>↑ in SCR &gt; 0.5 mg/dL through 30 days</td>
</tr>
</tbody>
</table>

* 30-day SCR could have been obtained between study day 21-42

Data on file, Scios Inc.

Renal Effects of Nesiritide: Impact on 30-Day Mortality

<table>
<thead>
<tr>
<th>Nesiritide Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SCR ↑ &gt; 0.5 mg/dL</td>
</tr>
<tr>
<td>Mortality within 30 days of Treatment</td>
</tr>
<tr>
<td>p=0.059</td>
</tr>
</tbody>
</table>


Nesiritide and Potential Mortality Risk

Short-term Risk of Death after Treatment with Nesiritide for Decompensated Heart Failure

- Design: Meta-analysis of three trials (NSGET, VMAC, PROACTION); data obtained from the FDA and sponsor documents and corroborated with published articles, when available
- Population: n = 862; patients with ADHF
- Treatment: Nesiritide versus active controls; therapy administered as a single infusion (>6 hours) and inotropes not mandated as control
- Endpoint: 30-day survival

Sackner-Bernstein JD et al. JAMA. 2005; 293:1900-5

Nesiritide and Potential Mortality Risk (cont)

<table>
<thead>
<tr>
<th>Nesiritide Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SCR ↑ &gt; 0.5 mg/dL</td>
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<tr>
<td>Mortality within 30 days of Treatment</td>
</tr>
<tr>
<td>p=0.059</td>
</tr>
</tbody>
</table>

..., our finding should be viewed as hypothesis generating rather than as conclusive evidence of harm.

Nesiritide and Mortality
Nesiritide-Controlled Trials with 30-day Mortality Data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Nesiritide n (%)</th>
<th>Control n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills et al.</td>
<td>2/74 (2.7%)</td>
<td>2/29 (7.5%)</td>
<td>0.38 (0.05, 2.67)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>5/85 (5.9%)</td>
<td>2/42 (4.8%)</td>
<td>1.25 (0.24, 6.45)</td>
</tr>
<tr>
<td>Comparative</td>
<td>14/203 (6.9%)</td>
<td>5/102 (4.9%)</td>
<td>1.43 (0.52, 3.97)</td>
</tr>
<tr>
<td>PRECEDENT</td>
<td>6/163 (3.7%)</td>
<td>5/83 (6.1%)</td>
<td>0.6 (0.18, 1.97)</td>
</tr>
<tr>
<td>VMAC</td>
<td>22/273 (8.1%)</td>
<td>11/216 (5.1%)</td>
<td>1.56 (0.75, 3.24)</td>
</tr>
<tr>
<td>PROACTION</td>
<td>5/120 (4.2%)</td>
<td>1/117 (0.9%)</td>
<td>4.99 (0.58, 42.73)</td>
</tr>
<tr>
<td>FUSION I</td>
<td>2/141 (1.4%)</td>
<td>2/89 (2.9%)</td>
<td>0.49 (0.07, 3.47)</td>
</tr>
</tbody>
</table>

Pooled (6 studies)* 54/918 (5.9%) 26/589 (4.4%) 1.34 (0.84, 2.15)
Pooled (7 studies) 56/1059 (5.3%) 28/658 (4.3%) 1.27 (0.81, 2.01)


Mortality Data: All Trials Pooled Unadjusted and Adjusted*

<table>
<thead>
<tr>
<th>30-Day (7 trials)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.42 (0.81 - 2.49)</td>
<td>P = 0.30</td>
<td>1.40 (0.79 - 2.49)</td>
</tr>
<tr>
<td>1.42 (0.79 - 2.56)</td>
<td>P = 0.31</td>
<td>1.41 (0.77 - 2.57)</td>
</tr>
</tbody>
</table>

6-Month (4 trials)

<table>
<thead>
<tr>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.26 (0.62 - 2.58)</td>
<td>P = 0.51</td>
</tr>
<tr>
<td>1.25 (0.61 - 2.59)</td>
<td>P = 0.51</td>
</tr>
</tbody>
</table>

* Adjusted for significant predictors of mortality: Baseline creatinine clearance ≤ 60 mL/min, SBP ≤ 100 mmHg, dopamine or dobutamine use prior to study, history of ventricular tachycardia, NYHA Class IV.

ADHERE Registry:
Vasodilator vs. Inotrope Mortality Analysis

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

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

Mortality Data: All Trials Pooled Unadjusted and Adjusted*

<table>
<thead>
<tr>
<th>30-Day (7 trials)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.26 (0.81 - 2.05)</td>
<td>P = 0.30</td>
<td>1.24 (0.77 - 1.98)</td>
</tr>
<tr>
<td>1.25 (0.77 - 2.01)</td>
<td>P = 0.31</td>
<td>1.24 (0.76 - 1.98)</td>
</tr>
</tbody>
</table>

6-Month (4 trials)

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Mortality Data: All Trials Pooled Unadjusted and Adjusted*

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6-Month (4 trials)

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Medication-Use Evaluations (MUEs)

MUE: Overall Purpose

- Evaluate and improve medication-use processes with the goal of optimal patient outcomes
- Can be used to
  - Identify actual and potential medication-related problems
  - Resolve actual medication-related problems
  - Prevent potential medication-related problems

MUE: Potential Objectives

- Promote optimal medication therapy
- Prevent medication-related problems
- Evaluate effectiveness and outcomes of medication therapy
- Improve patient safety
- Improve medication-use processes
- Identify areas for needed education
- Minimize costs of medication therapy
- Meet or exceed internally or externally established standards

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

ADHERE Registry:
Vasodilator vs. Inotrope Mortality Analysis

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<tr>
<th>Odds Ratio*</th>
<th>Confidence Interval</th>
<th>p Value</th>
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<td>NTG vs MIL</td>
<td>0.69</td>
<td>0.53-0.89</td>
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<tr>
<td>NTG vs DOB</td>
<td>0.46</td>
<td>0.37-0.57</td>
</tr>
<tr>
<td>NES vs MIL</td>
<td>0.59</td>
<td>0.48-0.73</td>
</tr>
<tr>
<td>NES vs DOB</td>
<td>0.47</td>
<td>0.39-0.56</td>
</tr>
<tr>
<td>NES vs NTG</td>
<td>0.94</td>
<td>0.77-1.16</td>
</tr>
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<td>1.03-1.55</td>
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Potential Reasons to Select a Medication or Medication-Use Process for MUE

- Known to cause adverse drug reactions (ADRs) that may pose significant health risk
- Used in patients at high-risk for ADRs
- Frequently prescribed or affects large number of patients
- Critical component of care for specific disease
- More effective when used in certain way
- Under consideration for formulary addition, retention, or deletion
- Suboptimal use would have negative impact on patient outcomes or health system costs
- Expensive

Potential Usefulness of MUE for ADHF Treatment

- Known to cause ADRs that may pose significant health risk
- Used in patients at high-risk for ADRs
- Frequently prescribed or affects large number of patients
- Critical component of care for specific disease
- More effective when used in certain way
- Under consideration for formulary addition or retention
- Suboptimal use would have negative impact on patient outcomes or health system costs
- Expensive

Nesiritide MUE Example

- Conducted at Mt. Sinai Medical Center
  - Records of patients receiving nesiritide from October 1, 2003 – March 31, 2004 examined
- Data collected
  - Demographics
  - Indications for nesiritide use
  - I.V. diuretic, vasodilator, and/or inotrope use
  - CV procedures
  - Lab values (electrolytes, SCr)
  - LOS (ICU and total)
- Total cost of nesiritide used (including cost of inappropriate use) calculated

Indications For Nesiritide

- ADHF
- Valve surgery
- Diuresis in non-cardiac condition
- Pulmonary hypertension
- Research study
- Other cardiac surgery
- Flash pulmonary edema
- Overall mean duration of therapy = 9.7 days (range 1-94 days)
- Mean duration of therapy for ADHF = 11 days (range 1-94 days)

I.V. Inotrope, Vasodilator, and Diuretic Use

- I.V. inotrope or vasodilator use
  - Milrinone = 12.3%
  - Dopamine = 8%
  - Dobutamine = 7.4%
  - Nitroglycerine = 5.6%
  - Nitroprusside = 1.2%
- I.V. diuretic use
  - Concurrent initiation of I.V. loop diuretic + nesiritide = 53.7%
  - Mean total dose of I.V. furosemide used before initiating nesiritide in other patients (46.3%) = 293 mg
- Total cost of nesiritide over 6 mo = $702,998
  - Cost of inappropriate (non-FDA approved) use = $70,943

Outcomes Associated with Vasoactive Therapy in ADHF

- Design: Retrospective cohort analysis of the University HealthSystem Consortium Clinical Database
- Population: n = 2130; patients with principle diagnosis of ADHF
- Treatment: Dobutamine, milrinone, or nesiritide; patients receiving more than one agent excluded
- Endpoints: In-hospital mortality, LOS, total health care costs, 30-day readmission rate

Results

The adjusted odds ratios for death with dobutamine and milrinone, as compared with nesiritide, were 3.5 and 3.9, respectively ($p < 0.001$).

In-Hospital Mortality Rate

- Dobutamine
- Milrinone
- Nesiritide

Length of Stay

- Dobutamine
- Milrinone
- Nesiritide

*The adjusted odds ratios for death with dobutamine and milrinone, as compared with nesiritide, were 3.5 and 3.9, respectively ($p < 0.001$).

Conclusions

- Clinical assessment remains a vital tool for evaluating patients with ADHF and enables practitioners to
  - Tailor drug therapy to clinical presentation
  - Monitor the efficacy of initiated drug therapy
- Invasive hemodynamic monitoring should not be routinely used in patients with ADHF
  - Should be reserved especially for patients with refractory symptoms despite ongoing treatment

Conclusions (cont)

- Total health care costs significantly lower with nesiritide than milrinone ($p<0.001$)
  - No significant difference between nesiritide and dobutamine
- No significant difference between groups for 30-day readmission rates

- All drugs for the treatment of ADHF are associated with potential safety issues
  - Ongoing trials are needed to address recent concerns raised regarding ↑ mortality and worsening renal function with nesiritide
- MUEs are useful tools for monitoring ADHF therapy (i.v. diuretics, vasodilators, inotropes)
  - Evaluate appropriate and inappropriate use
  - Assess therapeutic outcomes (LOS, readmissions, mortality)
  - Monitor adverse events
  - Minimize costs
References


Monitoring the Safety and Efficacy of Acute Decompensated Heart Failure Treatment

Self-Assessment Questions

1. Which of the following is a sign of hypoperfusion (low cardiac output) in a patient with ADHF?
   a. Hepatomegaly.
   b. Increased jugular venous pressure.
   c. Narrow pulse pressure.
   d. Orthopnea.

2. A diagnosis of acute decompensated heart failure (ADHF) is very likely in a patient who presents with dyspnea and a B-type natriuretic peptide level of
   a. 50 pg/mL.
   b. 100 pg/mL.
   c. 300 pg/ml.
   d. 600 pg/mL.

3. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT pro-BNP) have been established as definitive non-invasive markers of the effectiveness of ADHF therapy.
   a. True.
   b. False.

4. When pulmonary artery catheters (PACs) are used to guide ADHF therapy, specific hemodynamic goals are
   a. Right atrial pressure (RAP) < 8 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 16 mmHg, and systemic vascular resistance (SVR) > 1200 dyne•sec/cm$^5$.
   b. RAP > 8 mmHg, PCWP ≤ 16 mmHg, and SVR = 1000-1200 dyne•sec/cm$^5$.
   c. RAP ≤ 8 mmHg, PCWP ≤ 16 mmHg, and SVR = 1000-1200 dyne•sec/cm$^5$.
   d. RAP > 8 mmHg, PCWP > 16 mmHg, and SVR > 1200 dyne•sec/cm$^5$.

5. The use of PACs in conjunction with clinical assessment in patients with ADHF has been associated with a significant reduction in mortality and adverse events when compared with clinical assessment alone.
   a. True.
   b. False.

6. It would be reasonable to consider using a PAC as a means of invasive hemodynamic monitoring in all of the following patients with ADHF except
   a. A patient who is refractory to initial therapy with i.v. furosemide and nesiritide.
   b. A patient whose volume status and cardiac filling pressures are unclear.
   c. A patient who develops worsening renal function during therapy with i.v. furosemide and i.v. nitroglycerin.
   d. A patient whose symptoms have been improving after being given several doses of i.v. furosemide.
7. A patient is admitted to the coronary care unit with “warm and wet” ADHF. Treatment is initiated with furosemide 80 mg i.v. twice daily. All of the following adverse effects can be associated with i.v. furosemide except
   
   a. Worsening renal function.  
   b. Hypokalemia.  
   c. Hypercalcemia.  
   d. Metabolic alkalosis. 

8. All of the following agents used for the treatment of ADHF have been associated with proarrhythmia except
   
   a. Dobutamine. 
   b. Nesiritide. 
   c. Dopamine. 
   d. Milrinone. 

9. Recently published meta-analyses provide clear and valid evidence regarding increased mortality and worsening renal function in patients with ADHF treated with nesiritide compared with control. 
   
   a. True. 
   b. False. 

10. All of the following would be an appropriate rationale for performing a medication-use evaluation in a health system for a new i.v. drug approved for the treatment of ADHF except
    
    a. To evaluate length of stay or readmissions associated with the use of this drug. 
    b. To assess appropriate or inappropriate use of this drug. 
    c. To minimize the costs associated with the use of this drug. 
    d. To assess the safety and efficacy of this drug in a very narrow niche of patients. 

11. A retrospective cohort analysis of over 2000 patients with a principle diagnosis of ADHF showed that the in-hospital mortality rate and length of stay were significantly less for nesiritide compared with dobutamine or milrinone. 
   
   a. True. 
   b. False.