All Acute Heart Failure is Not Created Equal
Personalising Treatment for Your Patients

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Associate Director of Clinical Research
Wayne State University Department of Emergency Medicine
Disclosures

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  – Research support: Novartis Pharmaceuticals, Trevena Inc, Cardiorentis, BMEye Inc, Mespere
  – Grant support: NIH (5 R01 MD005849), Novartis Pharmaceuticals
  – Board of Directors: Society of Cardiovascular Patient Care
  – Ownership: Emergencies in Medicine LLC, Rosh Review LLC
Purpose of This Lecture

• To highlight the similarities and distinctions among patients who present with acute heart failure

• To show how such differences can be used to develop a more personalised approach to treatment
What is the Prevailing Model of Acute HF?

• Singular entity defined largely by congestion
  – Preload mediated
  – Afterload is an important contributor but most often not the solitary determinant

• Likelihood and severity of symptoms is a product of underlying ventricular dysfunction
  – Summarily denoted by ejection fraction
Unifying Theme Has Led To Search for Unifying Therapy

• String theory
  – “Theory of everything”
  – Attempts to unify natural forces
    • Gravitational
    • Electromagnetic
    • Nuclear

• String “therapy”
  – Single treatment that will benefit all acute HF patients
Exemplified by Nesiritide

[Graph showing the percentage of patients with congestive heart failure over time, with key events marked: Approval of Nesiritide August 2001, Publication 27 March 29, 2005, and Publication 28 April 20, 2005.]

Hauptman et al. JAMA 2006;296:1877-84.
Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

Death from Any Cause or Rehospitalization for Heart Failure at 30 Days

Percentage Point Difference (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nesiritide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Rehospitalization</td>
<td>-0.7 (-2.1 to 0.7)</td>
<td>-0.7 (-2.1 to 0.7)</td>
</tr>
<tr>
<td>Death</td>
<td>-0.4 (-1.3 to 0.5)</td>
<td>-0.4 (-1.3 to 0.5)</td>
</tr>
<tr>
<td>Rehospitalization for Heart Failure</td>
<td>-0.1 (-1.2 to 1.0)</td>
<td>-0.1 (-1.2 to 1.0)</td>
</tr>
</tbody>
</table>

P=0.31  Hazard ratio, 0.93 (95% CI, 0.8–1.08)

Diuretics for acute HF can depend on specialty of treating physician

<table>
<thead>
<tr>
<th>Evaluation or management</th>
<th>EM</th>
<th>IM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items included in history taking (n, mean)</td>
<td>4.01</td>
<td>4.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Items included at physical exam (n, mean)</td>
<td>4.26</td>
<td>4.22</td>
<td>0.65</td>
</tr>
<tr>
<td>Use of diuretics (% of cohort)</td>
<td>10.7</td>
<td>80.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of nitroglycerin (% of cohort)</td>
<td>17.3</td>
<td>9.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Oxygen (% of cohort)</td>
<td>33.3</td>
<td>36.9</td>
<td>0.284</td>
</tr>
<tr>
<td>BiPAP/intubation (% of cohort)</td>
<td>13.1</td>
<td>10.7</td>
<td>0.306</td>
</tr>
</tbody>
</table>
Acute HF is a Heterogeneous Condition

<table>
<thead>
<tr>
<th></th>
<th>ADHERE (N = 107,920)</th>
<th>EHFS (N = 11,327)</th>
<th>OPTIMIZE-HF (N = 34,059)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, (yr)</td>
<td>75</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>Women (%)</td>
<td>52</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>Prior HF (%)</td>
<td>75</td>
<td>65</td>
<td>87</td>
</tr>
<tr>
<td>LVEF 0.40 (%)</td>
<td>59</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>57</td>
<td>68</td>
<td>50</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>72</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>44</td>
<td>27</td>
<td>42</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>31</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>Renal insufficiency (%)</td>
<td>30</td>
<td>18</td>
<td>NA</td>
</tr>
</tbody>
</table>

Gheorghiade et al. Am J Cardiol 2005;96(suppl):11G-17G.
“CHF”
A Proposed Model for Initial Assessment and Management of Acute Heart Failure Syndromes

Mihai Gheorghiade, MD
Eugene Braunwald, MD

Clinical severity

- De novo or chronic heart failure
- Comorbidities
- Precipitants
- Blood pressure
- Heart rate and rhythm
Suspected acute heart failure

History/examination
(including blood pressure and respiratory rate)
- Chest X-ray
- Echocardiogram or NP (or both)
- Blood chemistry

ECG
- Oxygen saturation
- Full blood count

Simultaneously assess for
- Ventilation/systemic oxygenation inadequate
  - Oxygen
  - NIV
  - ETT and invasive ventilation
- Life-threatening arrhythmia/bradycardia
  - Electrical cardioversion
  - Pacing
- Blood pressure <85 mmHg or shock
  - Inotrope/vasopressor
  - Mechanical circulatory support (e.g., IABP)
- Acute coronary syndrome
  - Coronary reperfusion
  - Antithrombotic therapy
- Acute mechanical cause/severe valvular disease
  - Echocardiography
  - Surgical/percutaneous intervention

Urgent action if present
| Low perfusion at rest?  
<table>
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<tr>
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<tbody>
<tr>
<td>No</td>
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<td>No</td>
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<td>Yes</td>
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| Congestion at rest?  
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<tr>
<td>No</td>
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Adapted from Nohria et al. JAMA. 2002;287:628-40.
Suspected acute heart failure

History/examination
(including blood pressure and respiratory rate)

- Chest X-ray
- Echocardiogram or NP (or both)
- Blood chemistry
- ECG
- Oxygen saturation
- Full blood count

Simultaneously assess for

- Ventilation/systemic oxygenation inadequate
  - Oxygen
  - NIV
  - ETT and invasive ventilation

- Life-threatening arrhythmia/bradycardia
  - Electrical cardioversion
  - Pacing

- Blood pressure <85 mmHg or shock
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- Acute coronary syndrome
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  - Antithrombotic therapy

- Acute mechanical cause/severe valvular disease
  - Echocardiography
  - Surgical/percutaneous intervention

Urgent action if present
### Congestion at rest?
(e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, S3 gallop, edema)

<table>
<thead>
<tr>
<th>Low perfusion at rest? (e.g. narrow pulse pressure, cool extremities, hypotension)</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Warm and Dry</td>
<td>Warm and Wet</td>
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<tr>
<td>Yes</td>
<td>Cold and Dry</td>
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Adapted from Nohria et al. JAMA. 2002;287:628-40.
Can We Further Define Phenotypes?

- Hemodynamics
- Biomarkers
- Etiology and cardiac function?
Society of Chest Pain Centers Recommendations for the Evaluation and Management of the Observation Stay Acute Heart Failure Patient

A Report From the Society of Chest Pain Centers Acute Heart Failure Committee

**AHF patient with SBP > 160 mm Hg**
- Immediate sublingual NTG
- Topical/IV vasodilator (NTG, NES)
- Add IV loop diuretic if volume overloaded

If patient improves:
- Good response
- Good urine output
- SBP normalized
- Troponin negative

**Admit to ED observation unit**
- **Continued improvement**
  - Consider discharge
- **No improvement**
  - Consider additional therapy
- **Worsens**
  - Admit to hospital

**Reassess for clinical improvement**
- Poor response
- Poor urine output
- SBP < 90 or > 210 mm Hg
- Troponin elevated
- Respiratory embarrassment
Society of Chest Pain Centers Recommendations for the Evaluation and Management of the Observation Stay Acute Heart Failure Patient

A Report From the Society of Chest Pain Centers Acute Heart Failure Committee

AHF patient with SBP 120-160 mm Hg

- Partial response
- Elevated SBP

IV loop diuretic

Reassess for clinical improvement

- Good response
- Good urine output
- Good renal function
- Normal SBP
- Troponin negative

- Poor response
- Poor urine output
- Poor renal function
- Diuretic resistant
- Low SBP (< 90 mm Hg)
- Troponin elevated

Add IV vasodilator (NTG, NES)

- Good response

Admit to ED observation unit

- No improvement

Consider additional therapy

- Worsens

Admit to hospital

Consider discharge

Continued improvement
Can We Further Define Phenotypes?

- Hemodynamics
- Biomarkers
- Etiology and cardiac function?
Myocardial injury

Cardiac procedure

Non-cardiac major procedure

Tachy-/brady-arrhythmia

Heart failure

Renal failure

Clinical evidence of acute myocardial ischaemia with rise and/or fall of cardiac troponin

Myocardial infarction

Myocardial injury with cell death marked by cardiac troponin elevation

B-Type Natriuretic Peptide and the Effect of Ranolazine in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

Observations From the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary–Thrombolysis In Myocardial Infarction 36) Trial

Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

Cardiovascular Mortality or Heart Failure Hospitalization

Proportion Without Event

Months in Study

Log-Rank Test: $P = .42$
Peto-Peto-Wilcoxon Test: $P = .55$
Stratified Peto-Peto-Wilcoxon Test: $P = .56$

Tolvaptan
Placebo

<table>
<thead>
<tr>
<th>Months in Study</th>
<th>Tolvaptan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>2072</td>
<td>2061</td>
</tr>
<tr>
<td>21</td>
<td>1562</td>
<td>1532</td>
</tr>
<tr>
<td>18</td>
<td>1446</td>
<td>1137</td>
</tr>
<tr>
<td>15</td>
<td>834</td>
<td>819</td>
</tr>
<tr>
<td>12</td>
<td>607</td>
<td>597</td>
</tr>
<tr>
<td>9</td>
<td>396</td>
<td>385</td>
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<tr>
<td>6</td>
<td>271</td>
<td>255</td>
</tr>
<tr>
<td>3</td>
<td>149</td>
<td>143</td>
</tr>
<tr>
<td>0</td>
<td>58</td>
<td>55</td>
</tr>
</tbody>
</table>

Increased 90-Day Mortality in Patients With Acute Heart Failure With Elevated Copeptin
Secondary Results From the Biomarkers in Acute Heart Failure (BACH) Study

Urinary Angiotensinogen?
Can We Further Define Phenotypes?

• Hemodynamics

• Biomarkers

• Etiology and cardiac function?
Etiology Has Therapeutic Implications

Figure 2. Composite end point of death + rehospitalization by heart failure etiology and treatment assignment. p = 0.01 for etiology-treatment interaction.
Strain Echocardiography
Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims

A Scientific Statement From the American Heart Association

Neal L. Weintraub, MD, Chair; Sean P. Collins, MD, MSc, Co-Chair; Peter S. Pang, MD; Phillip D. Levy, MD, MPH; Allen S. Anderson, MD; Cynthia Arslanian-Engoren, PhD, RN, FAHA; W. Brian Gibler, MD, FAHA; James K. McCord, MD; Mark B. Parshall, PhD, RN; Gary S. Francis, MD, FAHA; Mihai Gheorghiade, MD; on behalf of the American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>ACS</th>
<th>AHFS</th>
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</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1 million/y</td>
<td>1 million/y</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehospital</td>
<td>High</td>
<td>?</td>
</tr>
<tr>
<td>In-hospital</td>
<td>3%-4%</td>
<td>3%-4%</td>
</tr>
<tr>
<td>60-90 d</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Targets of therapy</strong></td>
<td>Clearly defined-thrombosis</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Clinical trial results</strong></td>
<td>Beneficial</td>
<td>Minimal, no benefit, harmful</td>
</tr>
<tr>
<td><strong>ACC/AHA Guidelines</strong></td>
<td>Level A</td>
<td>Minimal level A/B, mostly C</td>
</tr>
</tbody>
</table>
AHFS phenotype defined (approximate incidence)

- Profoundly hypertensive (~25%)
  - Primary: afterload reduction with vasodilator therapy
  - Secondary: diuresis if associated volume overload

- Normal to moderately hypertensive (~50%)
  - Primary: volume reduction with diuretic therapy with possible ultrafiltration
  - Secondary: blood pressure reduction

- Hypotensive (5-10%)
  - Primary: output and perfusion increase with inotropes and vasopressors; fluids if overdiuresed
  - Secondary: mechanical ventricular assist devices

- Cardiogenic Shock (~1%)
  - Primary: improve cardiac function with inotropes and possibly mechanical ventricular assist devices
  - Secondary: anti-platelet and anti-coagulation medications; nitrates

- Acute coronary syndrome* (?
  - Primary: coronary artery reperfusion
    - Secondary: anti-platelet and anti-coagulation medications as per ACLS guidelines; cardioversion or pacing if unstable

- Arrhythmogenic* (?
  - Primary: rate or rhythm control with medications
  - Secondary: diuresis and blood pressure reduction as needed

- Right heart failure* (?
  - Primary: reperfusion if RV infarct; anti-coagulation (and possibly lytics) if pulmonary embolism; pulmonary artery pressure reduction; diuresis
    - Secondary: albuterol and ipratropium nebulizers; surgical intervention
The role of the emergency department in acute heart failure clinical trials—Enriching patient identification and enrollment

Sean P. Collins, MD, MSc, a Phillip D. Levy, MD, MPH, b Peter S. Pang, MD, c and Mihai Gheorghiade, MD d

<table>
<thead>
<tr>
<th>Trial and intervention</th>
<th>Year</th>
<th>No. of patients</th>
<th>When was patient enrolled?</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERITAS</td>
<td>2005</td>
<td>1448 (1760)*</td>
<td>After admission</td>
</tr>
<tr>
<td>Tezosentan vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIME-CHF</td>
<td>2002</td>
<td>951</td>
<td>After admission</td>
</tr>
<tr>
<td>Milrinone vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMAC</td>
<td>2002</td>
<td>489</td>
<td>After admission</td>
</tr>
<tr>
<td>Nesiritide vs nitrates vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVEREST</td>
<td>2007</td>
<td>Trial A, 2048; Trial B, 2085</td>
<td>After admission</td>
</tr>
<tr>
<td>Tolvaptan vs placebo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SURVIVE</td>
<td>2007</td>
<td>1327</td>
<td>After admission</td>
</tr>
<tr>
<td>Levosimendan vs dobutamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVIVE-II</td>
<td>2005</td>
<td>600</td>
<td>After admission</td>
</tr>
<tr>
<td>Levosimendan vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCEND-HF</td>
<td>2011</td>
<td>7141</td>
<td>Enrolled within 24 h of first intravenous therapy for AHF</td>
</tr>
<tr>
<td>Nesiritide vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROTECT</td>
<td>2010</td>
<td>2033</td>
<td>Within 24 h after admission for AHF hospitalization</td>
</tr>
<tr>
<td>Rolofylline vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RELAX-AHF</td>
<td>2012</td>
<td>1161</td>
<td>Randomized within 16 h of presentation for AHF</td>
</tr>
<tr>
<td>Relaxin vs placebo</td>
<td></td>
<td></td>
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</table>