Early Management of Acute Heart Failure: Time is also muscle

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Athens, GR
Disclosures

Principal Investigator or Committee member in trials sponsored by Novartis, Bayer, Cardiorentis, Vifor, European Union
Outcome in acute HF is still poor

**DOSE**

Death, Rehospitalization or ER visit

Hazard ratio with high-dose strategy, 0.83 (95% CI, 0.60–1.16)
P = 0.28

40% at 60 days

**CARRESS-HF**

Death or HF Rehospitalization

HR = 1.01 (0.62, 1.64)
P = 0.9556
EURObservational Research Program: The Heart Failure Pilot Survey

All-cause death or hospitalization

1-year all cause mortality:
- Acute HF: 35.1%
- Chronic HF: 17.2%

Acute HF – 16.8%
Chronic HF – 6.8%

Days from enrollment

A. Maggioni, U Dahlstrom, G, Filippatos et al EJHF2011
Management of acute heart failure: why so difficult?

Clinical Factors:
- Underlying causes: multifactorial, precipitating factor often not identified
- Clinical presentation: spectrum of various conditions, heterogeneous pathophysiology
- Cardiovascular and non-cardiovascular comorbidities

Pathophysiologically targets: uncertain

Courtesy of Piotr Ponikowski
Acute Exacerbations May Contribute to the Progression of the Disease

MECHANISMS OF DISEASE PROGRESSION

Cardiac and Renal Injury
Cell death by necrosis and apoptosis
Tn Release
Fibrosis

Progression of Heart and Kidney Failure

Hemodynamic Deterioration

Neurohormonal Activation

Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section

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¹Cardiology Division, Mas Hospital Attikon, Athens, University Feinberg Schoc

Proteolysis or turnover of myocardial contractile proteins

Direct toxicity of circulating neurohormones, inflammation, infiltrative processes, etc.

Supply demand mismatch with subendocardial ischaemia

Selected causes of reduced oxygen supply:
• Anaemia
• Hypotension

Selected causes of increased myocardial oxygen demand:
• Increased transmural wall stress
• Dilated left ventricular chamber size
• Elevated pressures in cardiac chambers
• Left ventricular hypertrophy
• Diastolic stiffening of the myocardium

Myocardial apoptosis or autophagy

Coronary ischaemia due to epicardial CAD or endothelial dysfunction
Increases from baseline in hs-cTnT levels are associated with increased mortality in patients with AHF

- Increased hs-cTnT levels from baseline were associated with increased 180-day mortality
- At Day 2, an increase in hs-cTnT $\geq 20\%$ over baseline, indicative of substantial additional myocardial necrosis, nearly doubled the risk of mortality through Day 180

*Graph*

**Troponin T**

- <20% increase
- $\geq 20\%$ increase

Cumulative risk (all-cause mortality)

<table>
<thead>
<tr>
<th>Study day</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
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</thead>
<tbody>
<tr>
<td>Cumulative risk</td>
<td></td>
<td></td>
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</table>

HR 1.80 (95% CI 1.16, 2.78)  
p = 0.0076

Number at risk:
- <20% increase: 825, 810, 799, 790, 782, 775, 771, 762, 759, 654
- $\geq 20\%$ increase: 231, 219, 218, 216, 210, 207, 204, 200, 199, 174

Data from the RELAXin in Acute Heart Failure (RELAX-AHF study); AHF = acute heart failure; CI = confidence interval; HR = hazard ratio; hs-cTnT = high sensitivity cardiac troponin T; KM = Kaplan-Meier

Potential pathogenetic pathways linking heart failure with renal dysfunction.

Filippatos G et al. Eur Heart J 2014
Acute Kidney Injury Timeline
Relationship between time to treatment and the reduction in mortality and extent of salvage.

Gersh B J, and Antman E M Eur Heart J 2006;27:761-763
Survival after Cardiac Arrest

Survival

CPR + Defibrillation

Time (min)
The Surviving Sepsis Campaign Resuscitation Bundle

Measure serum lactate

Obtain blood cultures prior to antibiotic administration

From the time of presentation, broad-spectrum antibiotics to be given within 1 h

Source of infection to be identified and drained within 6 h

In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL):

   deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)

   give vasopressors for hypotension not responding to initial fluid resuscitation to
   maintain mean arterial pressure ≥65 mmHg

In the event of persistent arterial hypotension despite volume resuscitation (septic shock)
and/or initial lactate >4 mmol/L (36 mg/dL):

   achieve central venous pressure of ≥8 mmHg

   achieve central venous oxygen saturation of ≥70%

Goals of Treatment in Acute Heart Failure

Immediate (ED/ICU/CCU)

- Treat symptoms
- Restore oxygenation
- Improve organ perfusion & haemodynamics
- Limit cardiac/renal damage
- Prevent thrombo-embolism
- Minimize ICU length of stay

Intermediate (in-hospital)

- Stabilise patient and optimise treatment strategy
- Initiate and up-titratre disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients
- Identify aetiology and relevant co-morbidities

Long-term and pre-discharge management

- Plan follow-up strategy
- Enrol in disease management programme, educate, initiate appropriate lifestyle adjustments
- Plan to up-titratre/optimize disease-modifying drugs
- Assess for appropriate device therapy
- Prevent early readmission
- Improve symptoms, quality of life and survival

Phases in the AHF management

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012
Recommendations for the treatment of acute heart failure in HFA – ESC 2012 guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pulmonary congestion/oedema without shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>High-flow oxygen is recommended in patients with a capillary oxygen saturation &lt;90% or PaO₂ &lt;60 mmHg (8.0 kPa) to correct hypoxaemia.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate &gt;20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure &lt;85 mmHg (and blood pressure should be monitored regularly when this treatment is used).</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>An i.v. opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure &gt;110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure &gt;110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure &lt;85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Acute Heart Failure management

Pharmacological therapy

1. **Acute management**
   - Oxygen
   - Diuretics
   - Opiates
   - Vasodilators
   - Nesiritide
   - Inotropes
   - Vasopressors

2. **After stabilization**
   - ACE inhibitor / ARB
   - Beta-blocker
   - Mineralocorticoid receptor antagonist
   - Digoxin

Non-pharmacological therapy

1. Sodium and fluid intake restriction
   - Ventilation
   - non-invasive
   - invasive
   - **Mechanical circulatory support**
   - IABP
   - VAD
   - **Ultrafiltration**

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012
Mortality benefit of CPAP/NIPPV in patients with ACPO

Mortality reduced from 22% to 11%

RR 0.53
(95% CI 0.35-0.81)
(Individual group sizes of n = 9 to 46)
Primary outcome: Mortality
Standard oxygen therapy versus non-invasive ventilation

Cumulative survival vs Days

- Non-invasive ventilation
- Standard oxygen therapy

p=0.685
Non-invasive ventilation in ACPO

Comparison of overall mortality and intubation rates in the 3CPO trial and a previous meta-analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>3CPO, 7-day rate (N=1069)</th>
<th>Meta-analysis, in-hospital rate (N=783)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>9.6</td>
<td>15.3</td>
</tr>
<tr>
<td>Intubation</td>
<td>2.9</td>
<td>21.9</td>
</tr>
</tbody>
</table>

A randomized study of out-of-hospital continuous positive airway pressure for acute cardiogenic pulmonary oedema: physiological and clinical effects

(A) PaCO2 arterial carbon dioxide tension evolution and (B) PaO2 arterial oxygen tension evolution.

Interventions to Relieve Congestion

- Sodium & fluid restriction
- **Diuretics***
  - Vasodilators
  - Ultrafiltration / dialysis

- BNP (nesiritide)
- Vasopressin antagonists

**Patients with pulmonary congestion/oedema without shock**

An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.
Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine
Decompensated chronic HF

• Consider higher dose of diuretics in renal dysfunction or with chronic diuretic use.
If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion.
Early intravenous heart failure therapy and outcomes among older patients hospitalized for AHF: Findings from the ADHERE-EM

![In-hospital Mortality Rate by Quartile of Time to Treatment](chart)

Observed in-hospital mortality rate by quartile of time to treatment.

Every hour delay in treatment was associated with a modest increased risk of in-hospital mortality (adjusted OR 1.01; 95% CI 1.00-1.02; P = .001) and an approximately 1.4-hour increase in index admission length of stay (P < .001).

If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF.
## ASCEND: Symptoms and Clinical Outcomes by Time to Start Therapy

### Post hoc ASCEND–HF analysis: Symptom and clinical outcomes by time to start of therapy

<table>
<thead>
<tr>
<th>End point</th>
<th>Treatment started &lt;15.5 h, n=3493</th>
<th>Treatment started &gt;15.5 h, n=3514</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with marked improvement in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea at 6 h</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Dyspnea at 24 h</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>&quot;Well-being&quot; at 6 h</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>&quot;Well-being&quot; at 24 h</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Clinical events at 30 days (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Death/HF hospitalization</td>
<td>8.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Death/all-cause hospitalization</td>
<td>13.4</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Christopher M O'Connor, ESC-HFA Hotline
TRUE-AHF

TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure

The first-ever acute heart failure (AHF) Phase III trial to be specifically designed to assess the effect of early treatment on cardiovascular mortality as a co-primary endpoint.

Study aim
• efficacy and safety of ularitide on clinical status and mortality in AHF
• build on the growing body of evidence to treat AHF patients as early as possible
Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

Effect of Serelaxin on Cardiac, Renal and Hepatic Biomarkers in the RELAX-AHF Development Program: Correlation with Outcome

J Am Coll Cardiol 2013
Organ Damage Hypothesis

Graphs showing changes in various biomarkers over time:

- **4a. Creatinine**: Concentration over days showing an increase in both placebo and Serelaxin groups.
- **4b. BUN**: Concentration over days showing a similar increase in both groups.
- **4c. Uric acid**: Concentration over days showing a higher increase in the placebo group.
- **4d. AST**: Activity over days showing a slight increase in the placebo group.
- **4e. ALT**: Activity over days showing a slight increase in the placebo group.
- **4f. Albumin**: Concentration over days showing a decrease over time in both groups.

**Legend:**
- Red: Placebo
- Blue: Serelaxin
# Inotropic Therapies

<table>
<thead>
<tr>
<th>Inotropic mechanism</th>
<th>Drugs</th>
</tr>
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<tbody>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Digoxin</td>
</tr>
<tr>
<td>β-Adrenoceptor stimulation</td>
<td>Dobutamine, dopamine</td>
</tr>
<tr>
<td>Phosphodiesterase inhibition</td>
<td>Enoximone, milrinone</td>
</tr>
<tr>
<td>Calcium sensitization</td>
<td>Levosimendan</td>
</tr>
<tr>
<td>Sodium-potassium-ATPase inhibition plus SERCA activation</td>
<td>Istaroxime</td>
</tr>
<tr>
<td>Acto-myosin cross-bridge activation</td>
<td>Omecamtiv mecarbil</td>
</tr>
<tr>
<td>SERCA activation</td>
<td>Gene transfer</td>
</tr>
<tr>
<td>SERCA activation plus vasodilation</td>
<td>Nitroxyl donor; CXL-1020</td>
</tr>
<tr>
<td>Ryanodine receptor stabilization</td>
<td>Ryanodine receptor stabilizer; S44121</td>
</tr>
<tr>
<td>Energetic modulation</td>
<td>Etomoxir, pyruvate</td>
</tr>
</tbody>
</table>

*Hasenfuss and Teerlink, EHJ 2011*
Effect of IV drugs given during the first 48 hours in AHF patients on in-hospital mortality
We recommend early treatment, including hemodynamic stabilization and treatment of the shock etiology.

Best practice.
# Diagnosis and Management of Acute Heart Failure

Mihai Gheorghiade, Gerasimos S. Filippatos, and G. Michael Felker

| Demographics and Comorbidities of Patients Hospitalized with Acute Heart Failure from Various Registries |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                                 | ADHERE N = 105,388 | OPTIMIZE-HF N = 48,612 | EHFS II N = 3580 | ARGENTINA N = 2974 |
| Mean age, years                                 | 72                 | 73                 | 70                | 68                |
| Women, %                                        | 52                 | 52                 | 39                | 41                |
| Prior HF, %                                     | 76                 | 88                 | 63                | 50                |
| Preserved EF, %                                  | 40                 | 49                 | 52                | 26                |
| Medical history,%                                |                    |                    |                   |                   |
| CAD                                            | 57                 | 50                 | 54                | —                 |
| Hypertension                                    | 73                 | 71                 | 62                | 66                |
| Myocardial infarction                            | 31                 | —                  | —                 | 22                |
| Atrial fibrillation                              | 31                 | 31                 | 39                | 27                |
| Diabetes                                        | 44                 | 42                 | 33                | 23                |
| Renal insufficiency                              | 30                 | 20                 | 17                | 10                |
| COPD/asthma                                     | 31                 | 34                 | 19                | 15                |

*From: Braunwald’s Heart Disease. 9th ed. Philadelphia, Elsevier, 2011*
Randomization

**Acute HF**
- LVEF < 40%
- BNP > 400 pg/mL
- SBP ≥ 110 mmHg
- ~1,800 patients

Follow-up at Week 2, Month 1, 2 and 3, with on-going assessments every 3 months thereafter

**Primary outcome:** CV death or HF hospitalization at 6 months (381 events)

- **Aliskiren 150 mg**
- **Aliskiren 300 mg**
- **Placebo**
- **Conventional therapy**

In-hospital entry and initiation

2 weeks

~15 months (event-driven)*

*Except concomitant use of an ACEI *and* ARB

Follow-up at Week 2, Month 1, 2 and 3, with on-going assessments every 3 months thereafter
Non-steroidal MRAs: more selective for cardiac/vascular than renal tissue?
ARTS-HF
Safety and efficacy study of BAY 94-8862 in patients with WCHF and left ventricular systolic dysfunction and either type 2 diabetes mellitus with or without CKD or moderate CKD alone

Primary aim
Investigate efficacy [percentage of patients with a relative decrease in NT-proBNP of more than 30% from baseline to visit 8 (day 90±2)] and safety of BAY 94-8862

Secondary aims
- Analyse the composite endpoint of death from any cause, cardiovascular hospitalizations, or emergency presentations for WCHF until visit 8 (day 90±2)
- Monitor changes in health-related quality of life as assessed by the KCCQ and EQ-5D-3L

CoChairs: B. Pitt & G Filippatos

ARTS-DN
Safety and efficacy study of BAY 94-8862 in patients with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Primary aim
Investigate change in UACR after treatment with BAY 94-8862 once daily over 90 days versus placebo

Secondary aims
- Investigate the safety and tolerability by assessing effects of different doses of BAY 94-8862 on serum potassium and renal function
- Analyse changes in health-related quality of life as assessed by the KDQOL-SF and EQ-5D-3L
Conclusions

- The therapeutic approach to acute HF has not changed much in the last few decades.
- There is a need to identify treatment strategies and regimens that reduce mortality and the incidence of rehospitalization in AHF patients.
The main HF Congress in the world

THE MOST POPULAR CONGRESS ON HEART FAILURE

4,470 participants
Record of submitted abstracts in 2015

www.escardio.org/HFA
“only dead fish swim with the stream”

japanese proverb