Short- and Long-Term Effect of Immediate Vasodilator Therapy in Acutely Decompensated Heart Failure: Results of the TRUE-AHF Trial

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on behalf of the TRUE-AHF Executive Committee and Investigators
Disclosures

Within past 2 years:

Consultant to Admittance, Amgen, AstraZeneca, Bayer, BioControl, Boehringer Ingelheim, Boston Scientific, Celyad, Cardiorentis, Daiichi Sankyo, GlaxoSmithKline, Novartis, NovoNordisk, Relypsa, Takeda, ZS Pharma
Potential Mechanisms in Acute Heart Failure

- Worsening heart failure events
- Acute ventricular distension
  - Increased intravascular volume
  - Sodium retention
    - Vasoconstriction
    - Transcapillary plasma shifts
- NT-proBNP
- Hemodilution
Potential Mechanisms in Acute Heart Failure

- Myocardial microinjury
- Accelerated rate of disease progression
- Increased rate of hospitalizations for heart failure
- Increased long-term risk of cardiovascular death

↑ Troponins
Are These Two Pathways Causally Related?

- Worsening heart failure events
- Increased intravascular volume
- Sodium retention
- Vasoconstriction
- Transcapillary plasma shifts
- Acute ventricular distension

↑ NT-proBNP

Hemodilution

?

↑ Troponins

Myocardial microinjury

Accelerated risk of hospitalization

Increased long-term risk of cardiovascular death
### Timing of Onset of Treatment in Trials of Acutely Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Planned Time From Admission to Start of Study Drug</th>
<th>Actual Time From Admission to Start of Study Drug</th>
<th>Did the Trial Report a Drug Effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND</td>
<td>≤ 48 hours</td>
<td>15.5 hours</td>
<td>No effect</td>
</tr>
<tr>
<td>EVEREST</td>
<td>≤ 48 hours</td>
<td>----</td>
<td>Transient effect</td>
</tr>
<tr>
<td>VERITAS</td>
<td>≤ 24 hours</td>
<td>11 hours</td>
<td>No effect</td>
</tr>
<tr>
<td>PROTECT</td>
<td>≤ 24 hours</td>
<td>----</td>
<td>No effect</td>
</tr>
<tr>
<td>RELAX-HF</td>
<td>≤ 16 hours</td>
<td>7 hours</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The TRUE-AHF trial determined if, in patients with acute heart failure, the urgent administration of the natriuretic peptide ularitide, in doses sufficient to provide meaningful decongestion and reduce cardiac wall stress, would reduce the long-term risk of cardiovascular death.
Unique Aspects of the TRUE-AHF Trial

- Worsening heart failure events
  - Acute ventricular distension
    - Increased intravascular volume
      - Sodium retention
      - Vasoconstriction
      - Transcapillary plasma shifts

- Extremely early time to intervention
  - Myocardial microinjury
    - Accelerated risk of hospitalization
      - Increased long-term risk of cardiovascular death
Ularitide is a synthetic analogue of urodilatin, which causes systemic and renal vasodilation, diuresis and natriuresis, and inhibition of the renin-angiotensin system.

Hemodynamic and symptomatic benefits in two randomized placebo-controlled heart failure trials (SIRIUS I and SIRIUS II).

- 15 ng/kg/min and 30 ng/kg/min produced similar improvement in dyspnea and global clinical status, but 30 ng/kg/min led to more frequent hypotension.

- Mortality at 30 days was 13.2% in the placebo group and 3.0% in the ularitide groups (total: 12 events).
Men or women, aged 18 to 85 years
Unplanned hospitalization or ED visit for acutely decompensated heart failure
Dyspnea at rest, worsened within the past week
Evidence of heart failure on chest X-ray
BNP > 500 pg/mL or NT-pro BNP > 2000 pg/mL
Persistence of dyspnea at rest despite ≥ 40 mg of IV furosemide (or equivalent)
Systolic BP ≥ 116 mmHg and ≤ 180 mmHg
Start of study drug infusion within 12 hours after initial clinical assessment
Eligibility Criteria

- Placebo
- Ularitide

Clinical Assessment
- 12hr

Eligibility Criteria

- 48 hr
- 120 hr
- 6 months
- 34 months

Hierarchical clinical composite

In-hospital heart failure events

Re-hospitalization

Mortality

Discharge

TRUE-AHF Design: Eur J Heart Fail (Today)
## Primary Endpoints (Short- and Long-Term)

<table>
<thead>
<tr>
<th>Cardiovascular Mortality $(\alpha = 0.04)$</th>
<th>Hierarchical Clinical Composite at 48 Hours $(\alpha = 0.01)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cardiovascular death</td>
<td>Moderate or marked improvement in symptoms at 6, 24 and 48 hours without in-hospital worsening heart failure or death</td>
</tr>
<tr>
<td></td>
<td>Modest improvement or unchanged symptoms</td>
</tr>
<tr>
<td></td>
<td>Worsening of symptoms at 6, 24 or 48 hours</td>
</tr>
<tr>
<td>Cardiovascular death (time-to-event)</td>
<td>Persistent or worsening heart failure (in-hospital) requiring IV or mechanical interventions during first 48 hours</td>
</tr>
<tr>
<td></td>
<td>Death during first 48 hours</td>
</tr>
</tbody>
</table>
Secondary Endpoints (Short- and Long-Term)

- Length of stay of index hospitalization
- Length of stay in intensive care during the first 120 hours
- Number of episodes of persistent or worsening heart failure requiring an intervention during the first 120 hours
- Proportion of patients with persistent or worsening heart failure requiring an intervention during the first 120 hours
- Change of N-terminal pro-BNP after 48 hours
- Time to completion of last dose of intravenous treatment for heart failure
- Change in serum creatinine during first 72 hours
- Risk of rehospitalization for heart failure within 30 days after initial hospital discharge
- Risk of death for any reason or rehospitalization for a cardiovascular reason during first 180 days
TRUE-AHF: Study Organization

**Executive Committee**
- M. Packer (chair)
- W. Abraham, S. Anker,
- K. Dickstein, H. Krum, G. Filippatos,
- R. Holcomb, A. Maggioni,
- J. McMurray, A. Mebazaa,
- C. O’Connor, F. Peacock,
- P. Ponikowski, F. Ruschitzka,
- D.J. van Veldhuisen

**Data Monitoring Committee**
- K. Swedberg (SW), chair
- J. Borer (US)
- H. Wedel (SW)
- L. Tavazzi (IT)

**Clinical Events Committee**
- J. McMurray, E. Connolly
- P. Jhund, M. MacDonald
- M. Petrie, M. Walters

**Medical Review Committee**
- D. McGuire, J. de Lemos
- M. Packer

**Independent Statistical Analysis**
- J. Wittes, L. Kowarski,
- M. Schactman

**Cardiorentis /Quintiles Operations**

**Investigative Sites**

**National Leaders**
2351 patients screened at 156 centers in 23 countries

Screening failures (n=194)

2157 patients randomized for ITT analysis

**Placebo** (n=1069)
- 1056 received treatment
- 1 lost to follow-up
- after median 6.1 hours

**Ularitide** (n=1088)
- 1072 received treatment
- median 15.0 months
- 0 lost to follow-up
## TRUE-AHF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1069)</th>
<th>Ularitide (n=1088)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (n=1069)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ularitide (n=1088)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>68.3 ± 11.3</td>
<td>68.7 ± 11.4</td>
</tr>
<tr>
<td><strong>Men/women</strong></td>
<td>706/363</td>
<td>714/374</td>
</tr>
<tr>
<td><strong>Non-black, n (%)</strong></td>
<td>973 (91.0%)</td>
<td>989 (90.9%)</td>
</tr>
<tr>
<td><strong>LV ejection fraction &lt; 40%, n (%)</strong></td>
<td>449 (65.9%)</td>
<td>445 (64.5%)</td>
</tr>
<tr>
<td><strong>Time to treatment ≤ 6 hours, n (%)</strong></td>
<td>528 (49.4%)</td>
<td>533 (49.0%)</td>
</tr>
<tr>
<td><strong>Coronary artery disease, n (%)</strong></td>
<td>549 (51.4%)</td>
<td>556 (51.1%)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>429 (40.1%)</td>
<td>414 (38.1%)</td>
</tr>
<tr>
<td><strong>Prior heart failure (n,%)</strong></td>
<td>806 (75.6%)</td>
<td>825 (75.9%)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>135.1 ± 17.9</td>
<td>134.2 ± 17.8</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>85.6 ± 19.1</td>
<td>85.4 ± 18.8</td>
</tr>
<tr>
<td><strong>N-terminal proBNP (pg/mL), median (25,75 percentiles)</strong></td>
<td>7121 (3974,12599)</td>
<td>7156 (4230,13238)</td>
</tr>
<tr>
<td><strong>Cardiac troponin T (pg/ml), median, (25,75 percentiles)</strong></td>
<td>33 (21, 54)</td>
<td>34 (22, 54)</td>
</tr>
<tr>
<td><strong>Intravenous nitrates at baseline</strong></td>
<td>110 (10.3%)</td>
<td>101 (9.3%)</td>
</tr>
</tbody>
</table>

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**TRUE-AHF: Baseline Characteristics**

Placebo (n=1069) vs Ularitide (n=1088) significantly different in baseline characteristics.
Ularitide Exerted Expected Effects on Cardiac Distension and Intravascular Congestion

**Systolic blood pressure**

- **Study drug infusion**
- **Placebo**
- **Ularitide**

**N-terminal pro BNP at 48 hours**

- **P < 0.001**
- **47% greater decrease**

Change from baseline

- Ularitide
- Placebo
Ularitide Exerted Expected Effects on Cardiac Distension and Intravascular Congestion

As compared with placebo, at 48 hours, ularitide led to significant increases in hemoglobin (P<0.001) and serum creatinine (P=0.005) and decreases in hepatic transaminases (P<0.001), indicative of **intravascular decongestion**.
Effect of Ularitide on In-Hospital Heart Failure Events During First 120 Hours

Study drug infusion

<table>
<thead>
<tr>
<th>Time Since Randomization</th>
<th>Placebo</th>
<th>Ularitide</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 hr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of In-Hospital Worsening Heart Failure Events

P=0.005
### TRUE-AHF: Treatment of Persistent or Worsening Events During First 48 Hours

<table>
<thead>
<tr>
<th>Intensity Level</th>
<th>Placebo</th>
<th>Ularitide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-intensity interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events requiring IV diuretics only (with or without low-dose dopamine)</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td><strong>Medium-intensity interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events requiring IV vasodilators (including morphine) and/or noninvasive ventilatory support; low-level interventions may be used</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td><strong>High-intensity interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events requiring IV positive inotropic agents or pressors and/or invasive ventilation, volume filtration and/or surgery; low- and medium-level interventions may also be used</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total number of events</strong></td>
<td>87</td>
<td>55</td>
</tr>
</tbody>
</table>
Are These Two Pathways Causally Related?

Worsening heart failure events → Acute ventricular distension → Increased intravascular volume → Sodium retention, Vasoconstriction, Transcapillary plasma shifts

NT-proBNP Hemodilution → Myocardial microinjury → Accelerated risk of hospitalization → Increased long-term risk of cardiovascular death

Troponins → Accelerated risk of hospitalization → Increased long-term risk of cardiovascular death
Increased intravascular volume

Acute ventricular distension

Myocardial microinjury

Ratio of high sensitivity cardiac troponin T (48 hours vs baseline)

Ularitide  Placebo
P=0.70

Will Rapid Reduction of Cardiac Distension Prevent Cardiac Microinjury?
TRUE-AHF: Cardiovascular Mortality

HR = 1.03
(96% CI: 0.85-1.25)
P = 0.75

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Months After Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ularitide</strong></td>
<td>1088 988 942 789 669 546 456 356 234 106 26 2 0</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>1069 987 934 786 668 547 444 338 219 104 19 5 0</td>
</tr>
</tbody>
</table>
TRUE-AHF: Clinical Composite

% Patients

Improved | Unchanged | Worse

P = 0.82
## TRUE-AHF: Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1069)</th>
<th>Ularitide (n=1088)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of stay (hr) in intensive care during first 120 hours,</strong></td>
<td>69.8 (50.3, 94.3)</td>
<td>68.0 (49.3, 93.6)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Length of stay (hr) in the hospital during first 30 days,</strong></td>
<td>148.2 (94.0, 216.8)</td>
<td>160.8 (96.0, 228.9)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Episodes of in-hospital worsening HF during first 120 hr</strong></td>
<td>126</td>
<td>115</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Proportion with in-hospital worsening HF during first 120 hr</strong></td>
<td>94 (8.8%)</td>
<td>90 (8.3%)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Rehospitalization for HF within 30 days of hospital discharge</strong></td>
<td>74 (7.0%)</td>
<td>75 (7.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Duration (hours) of IV therapy for HF during index admission,</strong></td>
<td>68.9 (44.6, 115.5)</td>
<td>70.5 (42.7, 115.4)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>All-cause mortality or CV hospitalization at 6 months</strong></td>
<td>398 (37.2%)</td>
<td>443 (40.7%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
## TRUE-AHF: Safety

### Most Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1056)</th>
<th>Ularitide (n=1072)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>107 (10.1%)</td>
<td>240 (22.4%)</td>
</tr>
</tbody>
</table>

### Renal Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1056)</th>
<th>Ularitide (n=1072)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>23 (2.2%)</td>
<td>24 (2.2%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>24 (2.3%)</td>
<td>15 (1.4%)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>18 (1.7%)</td>
<td>19 (1.8%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7 (0.7%)</td>
<td>13 (1.2%)</td>
</tr>
<tr>
<td>Serum creatinine at 30 days</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.5</td>
</tr>
</tbody>
</table>
It has been hypothesized that ventricular distension during acute heart failure leads to myocardial injury, explaining why such episodes are followed by acceleration of the downhill course of these patients.

Our findings indicate that early vasodilator therapy can produce meaningful decongestion and ameliorate cardiac wall stress as well as reduce the risk and number of in-hospital heart failure events.

However, this benefit does not reduce myocardial injury or change the natural history of these patients, including the long-term risk of cardiovascular death.