DISCLOSURES

• Consultant/speaker/honoraria: none

• JAMA Cardiology, Deputy Editor; Journal of the American College of Cardiology - senior associate editor (HF); American Journal of Cardiology - associate editor, supplements; American Heart Journal, Circulation; Circulation-Heart Failure - editorial boards

• Guideline writing committees: Chair, ACC/AHA, chronic HF; member, atrial fibrillation; hypertrophic cardiomyopathy; syncope guideline committees. Chair, Performance Measures, Sudden Cardiac Death

• Federal appointments: FDA: Immediate Past Chair, Cardiovascular Device Panel; ad hoc consultant; NIH – Scientific Management and Review Board; AHRQ- adhoc consultant; NHLBI- consultant; PCORI- former methodology committee member; IOM- writing group member

• Volunteer Appointments: American Heart Association- President, American Heart Association, 2009-2010; American College of Cardiology, Founder-CREDO
BIG TRIALS FOR BIG QUESTIONS: Short and long-term effects of vasodilator therapy for ADHF; results of TRUE AHF

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Professor, Medical Social Science
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Acute Decompensated Heart Failure; what do we know?

- High rate of recidivism- readmission rates remain (stubbornly) at 20% within 30 days and near 50% at 6 months
- Inflection point in the natural history of heart failure with subsequent one year mortality rates that approximate 25%
- Significant patient heterogeneity:
  - Both HFrEF & HFpEF at risk
  - New onset heart failure
  - Recrudescence of heart failure due to process of care challenges
  - Worsening heart failure
  - Advanced heart failure
  - Multiple co-morbidities, e.g., CKD, diabetes, AF, COPD, OSA

Is there evidence that a single intervention will change the natural history?
Treatment Options for Acute HF?

- **Diuretics**
  - AVP Antagonists/
    ultrafiltration

- **Vasodilators**

- **Inotropes**

- **Natriuretic Peptides**
  - Fluid volume
  - Preload and/or afterload
  - Contrac-
tility
  - Increase lusitropy

- Fluid volume

- Preload and/or afterload

- Contrac-
tility

- Increase lusitropy
## Evidence-based treatment of ADHF?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trial</th>
<th>Target</th>
<th>morbidity</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>DOSE</td>
<td>Hi &amp; Lo dose; Continuous infusion</td>
<td>modest</td>
<td>NA</td>
</tr>
<tr>
<td>AVP antagonists</td>
<td>EVEREST SECRETS TACTICS</td>
<td>AVP receptor type II &amp; free water excretion</td>
<td>No benefit on dyspnea</td>
<td>No mortality benefit</td>
</tr>
<tr>
<td>Ultrafiltration?</td>
<td>UNLOAD CARESS</td>
<td>Volume removal</td>
<td>Relief of dyspnea</td>
<td>No benefit; worsened renal fxn</td>
</tr>
<tr>
<td>Seralaxin</td>
<td>RELAX-AHF</td>
<td>Vasodilation Adequate BP Mild CRI</td>
<td>Modest dyspnea relief</td>
<td>No proven benefit; awaiting RELAX II</td>
</tr>
<tr>
<td>nesiritide</td>
<td>ASCEND- HF</td>
<td>Vasodilation Adequate BP</td>
<td>Modest symptom relief</td>
<td>No harm but also no benefit</td>
</tr>
<tr>
<td>levosimendan</td>
<td>SURIVE REVIVE II</td>
<td>Ca++ sensitization</td>
<td>Modest symptom relief</td>
<td>Possible harm</td>
</tr>
</tbody>
</table>

*Felker, NEJM 2011; Konstam JAMA 2007; Felker JACC 2016; Costanzo JCF, 2010; Bart, NEJM 2012; Teerlink Lancet 2013; O'Connor NEJM 2011*
A new natriuretic peptide

Na⁺ concentration

- Signal transduction involved: AC and PKC, intracellular ↑ Na⁺
- De novo synthesis of ANP-prohormone
- Processing of urodilatin (secretion into the urine)

Urodilatin binds to NPR-A receptors

- Inhibition of Na⁺-reabsorption
- Induction of natriuresis and diuresis

Processing of urodilatin

Pro-ANP → Enzyme ? → Urodilatin
Ularitide; TRUE-AHF

• Ularitide: synthetic urodilatin

• TRUE-AHF: Phase 3; Ularitide vs. Placebo (n = 2157)
  – Patients with unplanned hospitalization or emergency department visit for ADHF.
  – Infusion of the study drug within 6 h after initial clinical assessment performed by a physician.
  – Systolic blood pressure ≥110 mmHg.
  – Co-primary endpoints: CV mortality; Clinical composite; multiple 2° endpoints (powered for mortality)

Clinicaltrials.gov NCT01661634
TRUE-AHF: Cardiovascular Mortality

Placebo
225 deaths

Ularitide
236 deaths

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

Number at risk

<table>
<thead>
<tr>
<th>Months After Randomization</th>
<th>Placebo</th>
<th>Ularitide</th>
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<tbody>
<tr>
<td>0</td>
<td>1069</td>
<td>1088</td>
</tr>
<tr>
<td>6</td>
<td>987</td>
<td>988</td>
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<td>668</td>
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<tr>
<td>30</td>
<td>546</td>
<td>546</td>
</tr>
<tr>
<td>36</td>
<td>456</td>
<td>444</td>
</tr>
</tbody>
</table>

+ Censored
TRUE-AHF: Clinical Composite

% Patients

P=0.82
Are there alternatives?

New Drugs & Devices
Kaplan–Meier Curve for the Time to First Hospitalization for Heart Failure During First 30 Days After Randomization, According to Study Group

Hazard ratio 0.60 (0.38-0.94)
P = 0.027

Patients at Risk
<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>7</td>
<td>4174</td>
<td>4192</td>
</tr>
<tr>
<td>14</td>
<td>4153</td>
<td>4166</td>
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<tr>
<td>21</td>
<td></td>
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<tr>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Packer M et al. Circulation. 2015;131:54-61
Figure Legend:

Cumulative HF Hospital Stays

Cumulative heart failure (HF) hospital stays of the treatment and control groups throughout the duration of the study. RRR = relative risk reduction.
The Persistent Challenges of Acute Decompensated HF - 2016:

• A litany of failed therapies for ADHF
  – continuous infusion of loop diuretics
  – Ultrafiltration
  – Inotropes
  – AVP antagonists
  – Natriuretic Peptides- nesiritide & ularitide
  – Levosimendan
  – ? Seralaxin

• Do we need new drugs, better phenotyping or better targets?

• Is it worthwhile to pursue the injury hypothesis still?

• Might we return to neurohormonal targets known to be dysregulated in heart failure for which effective intervention improves outcomes?

• Do devices have a role?

• What’s next- *pause and reconsider the science & the premise*?
thank you!