Advanced Heart Failure: Hyponatremia & Preventing Thromboembolic Complications

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Case Discussion

• 76 yr retired gentleman with previous MI and systolic HF, now admitted in failure

• After one dose of furosemide, you found that his [Cr] has risen (140->250), [Na] fallen (136->131)

• What would you do now for the patient?
  – 1. Withhold diuretics
  – 2. Give hypertonic saline intravenously
  – 3. Furosemide infusion
  – 4. Restrict fluid intake
  – 5. Consider vasopressin antagonist
Outcomes After Acutely Decompensated Heart Failure Hospitalization

- **Mortality**
  - 11.6% at 30 days\(^1\)
  - 33.1% at 12 months\(^1\)

- **Hospital readmissions**
  - 20% at 30 days
  - 50% at 6 months

In-hospital Mortality Risk Groups According to the ADHERE Risk Stratification

- BUN > 42 → 3.34 (3.08 – 3.62)
- SBP ≤ 115 → 3.09 (2.85 – 3.35)
- DBP ≤ 55 → 2.87 (2.62 – 3.14)
- Serum [Na⁺] < 134 → 2.26 (2.08 – 2.47)
- SCr > 3.2 → 1.99 (1.78 – 2.24)
- Age > 78 years → 1.88 (1.74 – 2.04)
- Dyspnea at Rest → 1.57 (1.45 – 1.70)
- HR > 84 → 1.20 (1.11 – 1.30)

Prevalence of Hyponatremia in ADHF

OPTIMIZE-HF Registry N=48,612 pts.

[Na] & Mortality in HF Cohort

Bettaro L, et al., J Cardiac Fail 2012; 18:74-81

Duke HF Database
Mean admission serum [Na⁺] in the total cohort was 138 ± 5 mmol/L, and 19.7% of patients had values <135 mmol/L.

**Treatment Algorithm for Acute HF**

- **AHF diagnosed, treatment initiated based on symptoms and signs**

**Volume overload**

- **Mild volume overload**
  - IV diuretics (IV furosemide bolus)
    - serum creatinine <200 µmol/L 40 mg
    - serum creatinine >200 µmol/L 80 mg

- **Moderate to severe volume overload**
  - IV diuretics + IV vasodilators
    - consider furosemide infusion
    - add IV nitroglycerin starting at 5-10 µg/kg/min, titrate to clinical status, BP or PCWP, if available

**Volume overload + low cardiac output**

- **Mild to moderate low output**
  - SBP >90 mmHg
    - milrinone 0.275 µg/kg/min or
    - dobutamine

- **Very low output**
  - SBP <90 mmHg
    - dobutamine 2-5 µg/kg/min or
    - may also require vasopressors

- **Erratum. Can J Cardiol 2006;22(3):271.**
List of Acute HF Trials that Reduced Mortality or Hospitalization

•

•

•
Acute Heart Failure (1 symptom AND 1 sign) <24 hours after admission

2x2 factorial randomization

Low Dose (1 x oral) Q12 IV bolus
Low Dose (1 x oral) Continuous infusion
High Dose (2.5 x oral) Q12 IV bolus
High Dose (2.5 x oral) Continuous infusion

48 hours

1) Change to oral diuretics
2) continue current strategy
3) 50% increase in dose

72 hours

Co-primary endpoints

60 days

Clinical endpoints
Death, Rehospitalization, or ED Visit

HR for Continuous vs. Q12 = 1.19
95% CI 0.86, 1.66, p = 0.30

HR for High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28
DOSE Trial Summary

• There was no evidence of benefit for continuous infusion compared to Q12 hour bolus on any secondary endpoint.

• Despite transient changes in renal function, there was no evidence for higher risk of clinical events at 60 days associated with the high intensification strategy.

• High intensification (2.5 x oral dose) was associated with trends towards greater improvement in multiple domains:
  – Symptom relief (global assessment and dyspnea)
  – Weight loss and net volume loss
  – Proportion free from signs of congestion
  – Reduction in NT-proBNP
Ultra-Filtration: External Fluid Removal
UNLOAD Trial

n = 200 with ADHF

IV Diuretics

Ultrafiltration for 48 hours

Costanzo MR. *J Am Coll Cardiol.* 2007;49:675-83
Ultrafiltration Improved Weight Loss But Not Symptoms

<table>
<thead>
<tr>
<th>End points</th>
<th>Ultrafiltration</th>
<th>Diuresis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss, primary end point (mean kg)</td>
<td>5.0</td>
<td>3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnea score, primary end point (mean)</td>
<td>6.4</td>
<td>6.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Net fluid loss (mean L)</td>
<td>4.6</td>
<td>3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>K&lt;3.5 mEq/L (%)</td>
<td>1</td>
<td>12</td>
<td>0.018</td>
</tr>
<tr>
<td>Need for vasoactive drugs (%)</td>
<td>3</td>
<td>13</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Costanzo MR. *J Am Coll Cardiol.* 2007;49:675-83
Role of Ultrafiltration

- Patient with acute decompensated heart failure and significant volume overload
- Unresponsive to IV diuretics
- Adequate blood pressure and perfusion
- Reasonable renal function
- Can tolerate full anticoagulation
- Local nephrology expertise and support
Cost-Effectiveness of UF

Neurohormonal Pathophysiology of HF

Plasma Vasopressin According to HF Severity

Data from 72 subjects with CHF admitted to Omiya Medical Center in Japan.

Copeptin & Survival in HF Pts (BACH)

Maisel A, Anker S, et al., Circ Heart Fail 2011; 4:613-20
Action of Vasopressin
Samsca® (Tolvaptan)
Mechanism of Action
**EVEREST Outcomes Trial Design**

**Randomisation**
- ≤48 hours

**Treatment Period**
- Median 9.9 months

**Safety Follow-up**
- 60 days
- 14 days

**Hospitalisation for Worsening HF**

**TLV (n=2072)**
**Placebo (n=2061)**

**Tolvaptan 30 mg QD + Standard Therapy**
(n=2072)

**Placebo QD + Standard Therapy**
(n=2061)

**Dual Primary Endpoints:**
- All-cause mortality
- CV death or HF hospitalisation

**Short-Term Endpoints:**
- Composite of change in weight and VAS between baseline and Day 7 or discharge

**1065 Deaths**

### Distribution of Baseline Serum $[Na^+]$ in the EVEREST Trial

<table>
<thead>
<tr>
<th>Baseline Serum $[Na^+]$ Level (mmol/L)</th>
<th>No. of Subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>n=92</td>
<td>2.2%</td>
</tr>
<tr>
<td>Mild</td>
<td>n=383</td>
<td>9.3%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>n=475</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

**Hyponatremia**

- Placebo: Tolvaptan 30 mg
- Placebo: Tolvaptan 30 mg

Neutral Effect on Outcomes – All Patients

All-Cause Mortality

HR 0.98; 95%CI (0.87–1.11)
Meets criteria for non-inferiority

CV Mortality or HF Hospitalisation

HR 1.04; 95%CI (0.95–1.14)

CV Mortality/Morbidity in Pts with Hyponatremia (Sodium < 130 mmol/L)

**Subjects with Baseline Sodium ≥130 mmol/L (ITT Population)**

- **Hazard Ratio:** 0.603
- **95% CI Limits:** 0.372, 0.979

**Subjects with Baseline Sodium <130 mmol/L (ITT Population)**

- **Hazard Ratio:** 1.065
- **95% CI Limits:** 0.973, 1.165

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Overall CV Mortality/Morbidity (ITT) HR 1.04; 95% CI (.95–1.14).

Change in Serum $[\text{Na}^+]$ Concentrations – Hyponatremic Subgroup

Mean ($\pm$ SE) Serum $[\text{Na}^+]$ Concentration (mmol/L)

**Inpatient**

- BSL
- Day 1
- Day 7

**Outpatient Week**

- Week 1
- Week 4
- Week 8
- Week 16
- Week 24
- Week 32
- Week 40
- Week 48
- Week 56

- Tolvaptan 30 mg (n=235)
- Placebo (n=226)

*P<.05

Dyspnea Improvement With Tolvaptan

Overall HF (n=3664) - Δ 6.4% P<.0001

HF/Hyponatremia (n=409) - Δ 13.5% P=.028

Body Weight Reduction – Hyponatremic Subgroup

<table>
<thead>
<tr>
<th>Change From Baseline in Body Weight (kg)</th>
<th>Day 1</th>
<th>Day 7/Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ 0.7 kg</td>
<td>Δ 0.8 kg</td>
</tr>
</tbody>
</table>

P < .001 (n=460)  
P < .05 (n=463)

OC Analysis
Adjusted Mean Lengths of Stay in Pts with Normal Sodium & Hyponatremia

Cyr PL, Hauptman PJ, et al., Am J Health System Pharm 2011; 68:328-33
Effect of Tolvaptan Rx on Mean Lengths of Stay in Pts with Hyponatremia

EVEREST Trial of Tolvaptan vs Placebo in ADHF

Cyr PL, Hauptman PJ, et al., Am J Health System Pharm 2011; 68:328-33
EVEREST: Summary

• In EVEREST, long-term tolvaptan treatment had no demonstrated effect on all-cause mortality or combined endpoint of CV mortality or subsequent hospitalisation for all comers with worsening HF

• Based on post-hoc analyses of hyponatremic cohort, treatment with tolvaptan was associated with
  – Improvements in serum [Na⁺]
  – Improvements in patient-assessed dyspnea
  – Improvements in survival
  – Trend towards decreased hospital lengths of stay

• Tolvaptan did not appear to have any clinically important effect on blood pressure or renal function
Question.
If the patient has systolic heart failure and sinus rhythm, What should be the approach of choice to prevent thromboembolic complications?
1. ASA
2. Coumadin
3. Neither
4. Both
5. Depends (individualize)
## Incidence of VTE in HF

### Table 1. VTE Incidence in HF RCTs

<table>
<thead>
<tr>
<th>RCT</th>
<th>No. Patients</th>
<th>LVEF, %</th>
<th>AF, %</th>
<th>VTE, %/y</th>
<th>Anticoagulants-Antiplatelet Agents, %</th>
<th>Follow-Up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD</td>
<td>6378</td>
<td>31</td>
<td>0</td>
<td>2.1</td>
<td>9 – 46</td>
<td>3.3</td>
</tr>
<tr>
<td>SAVE</td>
<td>2231</td>
<td>31</td>
<td>10</td>
<td>1.5</td>
<td>28 – 14</td>
<td>3.5</td>
</tr>
<tr>
<td>V-HeFT I</td>
<td>642</td>
<td>30</td>
<td>16</td>
<td>2.7</td>
<td>19 – 13</td>
<td>2.3</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>804</td>
<td>29</td>
<td>15</td>
<td>2.1</td>
<td>21 – 27</td>
<td>2.6</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>2114</td>
<td>25</td>
<td>9</td>
<td>3.4</td>
<td>28 – 59</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Bettari L, et al., Circ Heart Fail 2011;4;361-368
Warfarin vs ASA in HF

Bettari L, et al., Circ Heart Fail 2011;4;361-368
### WARCEF 1° Results

N = 2305 in 11 countries, FU of 3.5 years, NIH = sponsor

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, Stroke or IC Bleed</td>
<td>320 (7.9%)</td>
<td>302 (7.5%)</td>
<td>0.93 (0.79-1.10)</td>
<td>0.40</td>
</tr>
<tr>
<td>Deaths</td>
<td>268 (6.6%)</td>
<td>263 (6.5%)</td>
<td>1.01 (0.85-1.21)</td>
<td>0.91</td>
</tr>
<tr>
<td>Isch Stroke</td>
<td>29 (0.7%)</td>
<td>55 (1.4%)</td>
<td>0.52 (0.33-0.82)</td>
<td>0.005</td>
</tr>
<tr>
<td>IC Bleed</td>
<td>5 (0.12%)</td>
<td>2 (0.05%)</td>
<td>2.22 (0.43-11.66)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

### Guideline for Anticoagulation in HF

#### Table 3. Guidelines for Antithrombotic Therapy in HF

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendations</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA, 2009</td>
<td>Anticoagulants in patients with HF and paroxysmal or persistent AF or previous VTE</td>
<td>I-A</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet agents for MI and death prevention in patients with HF and CAD</td>
<td>I-B</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants in patients with underlying disorders that may be associated with increased VTE risk (eg, amyloidosis) and in patients with familial DCM and history of VTE in first-degree relatives</td>
<td>IIb-B</td>
</tr>
</tbody>
</table>
Conclusions

• Hyponatremia is frequent in HF pts, and is a new major risk factor for mortality
• Hyponatremia results from release of vasopressin, leading to vasoconstriction (V1a), & water resorption & low Na (V2R)
• Vasopressin antagonists have shown to be safe and effective in reducing body weight in HF patients, and raising serum [Na]
• Pt with systolic HF/NSR has thromboembolic risk of 2.5%/yr, and ASA or coumadin can be tailored to pt’s profile