Vaptans as Therapy for Hypervolumic Hyponatremia

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Disclosures: None
Hyponatremia in Heart Failure

- Nearly 1 million hospitalizations and 12-15 million outpatient office visits for HF occur annually in the US.
- Hyponatremia is common in patients with heart failure.
- Hyponatremia is associated with cognitive impairment, gait instability, and falls.
- Hyponatremia is associated with longer length of stay, higher in-hospital mortality, higher post-discharge mortality, and higher rates of rehospitalization.
- There are new therapeutic options for treating hyponatremia.

Hyponatremia (serum sodium < 135 mEq/L) is common in patients hospitalized with HF.

Prevalence of Hyponatremia in HF

11% of EVEREST placebo patients were hyponatremic at baseline, and by Day 7/Discharge 17% of patients were hyponatremic.
Physiology of Fluid Balance
Differences Between Euvolemic and Hypervolemic Dilutional Hyponatremia

• Euvolemic hyponatremia
  - Normal or near normal total body sodium
  - Increase in total body water
  - Absence of edema

• Hypervolemic hyponatremia
  - Elevations in both total body sodium and total body water
  - Increase in total body water exceeds increase in total body sodium
  - Edema

Mechanisms of Hyponatremia

- Failure to achieve a maximally dilute urine
- Excessive AVP secretion is the dominant problem under most conditions, although the presence of agents, such as loop diuretics and extremely low flow states, may contribute in conditions such as severe CHF.
Na⁺ and Water Retention in CHF

• Na⁺ retention in CHF is primarily mediated by renal mechanisms
  – Decrease in renal blood flow and glomerular filtration rate
  – Increase in tubular reabsorption of NaCl
  – Elevation of renin-angiotensin-aldosterone
  – Inadequate natriuretic mechanisms

• Water retention is a parallel process
  – Obligatory water reabsorption accompanies salt reabsorption
  – Elevated angiotensin II stimulates thirst and provokes release of AVP, the major controller of water reabsorption
  – Reduced renal tubular flow increases free-water absorption
  – Diuretics exacerbate this condition

Arginine Vasopressin (AVP) Stimulation and Effects

1. ↑ Osmolality
2. Angiotensin II/NE
3. ↓ Arterial pressure/cardiac volume

Vasoconstriction
Myocardial stimulation

V1a Receptors

V2 Receptors

1. ↓ Osmolality
2. Natriuretic peptides
3. ↑ Arterial pressure/cardiac volume

Renal H2O reabsorption

The Vaptans: Mechanism of Action

- Block effects of AVP in the kidney
- Fewer AQP$_2$ channels in apical membrane
- Fewer water molecules retained, more water excreted in urine
- Plasma osmolality increases
- Safe, effective, predictable rise in serum [Na$^+$]

Goldsmith SR. *Am J Cardiol.* 2005;95(suppl):14B-23B.  
Figure Leiden University. From Dubois EA et al.  
Vasopressin

**Effector Mechanisms**

Vasopressin effects mediated by:

- **$V_{1a}$ receptors** (blood vessels, myocardium)
  - Peripheral and coronary vasoconstriction
  - Cell growth, increased intracellular calcium

- **$V_2$ receptors** (renal tubules)
  - Water retention

Inappropriate Elevation of Vasopressin in HF

\[ p < 0.01 \]

Goldsmith et al. JACC. 1983.
Neuroendocrine Activation in LV Dysfunction
SOLVD: Prevention and Treatment


**Median plasma norepinephrine (pg/mL)**

- Control: (242–450) N = 54
- Prevention: (312–566) N = 151
- Treatment: (368–644) N = 81

**Median plasma renin activity (ng/mL/hr)**

- Control: (0.3–0.9) N = 56
- Prevention: (0.3–1.6) N = 151
- Treatment: (0.5–3.8) N = 80

**Median plasma ANF (pg/mL)**

- Control: (31–65) N = 54
- Prevention: (69–139) N = 147
- Treatment: (91–203) N = 80

**Median plasma AVP (pg/mL)**

- Control: (1.4–2.3) N = 56
- Prevention: (1.7–3.0) N = 151
- Treatment: (2.3–4.4) N = 80
Diagnostic Algorithm for Hyponatremia

Clinical Implications of Hyponatremia

- Hyponatremia is an indicator of the severity of HF
- Decrease in serum $[\text{Na}^+]$ is often associated with
  - Elevated levels of norepinephrine, plasma renin, serum urea nitrogen, AVP
  - Regional blood flow derangements
  - Markedly impaired hemodynamics
  - Increased diuretic requirements
  - Ventricular arrhythmias

Hyponatremia and Cognitive Function

- 122 patients with serum $[\text{Na}^+]$ 125±5 mEq/L: 25 adjusted odds ratio for falling compared to 244 controls $= 67$ ($p<0.001$)

- Patients with normal mini-mental status had abnormal formal psychometric testing that returned to normal with correction of hyponatremia

- Impaired cognition and gait from hyponatremia is comparable to a blood alcohol level of 0.06%

Hyponatremia Results in Gait Instability

serum [Na⁺] = 130 mEq/L

serum [Na⁺] = 139 mEq/L

serum [Na⁺] = 124 mEq/L

serum [Na⁺] = 135 mEq/L

### Increased Risk of Falls with Mild Hyponatremia

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>% Falls</th>
<th>Odds Ratio</th>
<th>Adjusted Odds Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Asymptomatic&quot; Chronic Hyponatremia</td>
<td>122</td>
<td>21.3%</td>
<td>9.45</td>
<td>67.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.64-34.09)</td>
<td>(7.48-607.42)</td>
</tr>
<tr>
<td>P &lt; .001</td>
<td></td>
<td></td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Normonatremic controls</td>
<td>244</td>
<td>5.35%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*adjusted for age, sex, and covariates

Hyponatremia and Hospital Length of Stay in Heart Failure: EVEREST

Reference: Hospitalized HF patients with normal sodium concentrations

Hyponatremia Is Associated With Death and Rehospitalization in HF Patients

*OPTIMIZE-HF registry data; N=48,612.

Hyponatremia When Corrected During Hospitalization is Associated with Better Outcomes


Values are 95% confidence intervals.

LEVEL 1 - NO OR MINIMAL SYMPTOMS: headache, irritability, inability to concentrate, altered mood, depression

LEVEL 2 - MODERATE SYMPTOMS: nausea, confusion, disorientation, altered mental status

LEVEL 3 - SEVERE SYMPTOMS: vomiting, seizures, obtundation, respiratory distress, coma

fluid restriction, treat underlying condition

fluid restriction, demeclocycline, urea

hypertonic NaCl w loop diuretic

Challenges in Treatment of Hypervolemic Hyponatremia

- **Fluid restriction:**
  - difficult to maintain effectively
  - Not usually effective unless severe (≤ 1 L/day) => very difficult to tolerate and maintain

- **Demeclocycline, urea**
  - Difficult to use and toxicities

- **Hypertonic saline and loop diuresis**
  - Challenging to perform, requires adequate diuresis, may exacerbate volume overload
  - Some data support use

Sec 6: Nonpharm Management of Chronic HF:
- Restriction of daily fluid intake to <2 L with severe hypoNa (serum sodium <130 mEq/L) (SoE C)

Sec 12: Eval and Management of ADHF:
- Fluid restriction (<2 L/day) with moderate hypoNa (<130 mEq/L)
- In pts with severe (<125 mEq/L) or worsening hypoNa, stricter fluid restriction may be considered (SoE C)

Sec 12 text:
- VP antagonists improve serum Na with either a V2-selective or a nonselective VP antagonist. Longer term Rx with a V2 antagonist does not improve mortality but appears to be safe
## Nonpeptide AVP Receptor Antagonists

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tolvaptan</th>
<th>Lixivaptan</th>
<th>Satavaptan</th>
<th>Conivaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td>Urine volume</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Na(^+) excretion/24 h</td>
<td>↔</td>
<td>↔ for low dose</td>
<td>↑ for high dose</td>
<td>↔</td>
</tr>
<tr>
<td>Company</td>
<td>Otsuka</td>
<td>CardioKine</td>
<td>sanofi-aventis</td>
<td>Astellas</td>
</tr>
</tbody>
</table>

Effect of Conivaptan on Urine Output

Udelson et al, *Circulation* 2001
Serum [Na\(^+\)] Over 4 Days After Continuous IV Infusion of Conivaptan

ECLIPSE Trial

Primary Hemodynamic Finding After a Single Oral Tolvaptan Dose

All tolvaptan dosages were associated with significant and sustained increases in urine output ($P < .01$ vs placebo) that were most pronounced at the 60-mg level and least pronounced at 15 mg.

SALT 1 and 2: Mean Sodium Concentration Over Time

**SALT 1**

- Drug discontinued
- Serum sodium (mmol/liter)

**SALT 2**

- Drug discontinued
- Serum sodium (mmol/liter)

**Number of patients at risk**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day</th>
<th>Tolvaptan</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>84</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>71</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>20</td>
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<td>75</td>
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<td>30</td>
<td>119</td>
<td>115</td>
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<td></td>
<td>35</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>101</td>
<td>95</td>
</tr>
</tbody>
</table>

*P* < .001 for tolvaptan vs. placebo; tolvaptan was discontinued on day 30

SALT-2 and SALT-2 = Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2

Tolvaptan: Fluid Balance at Day 1
Patients with Hyponatremia and HF

Fluid Intake \(-\) Urine Output = Fluid Balance

\[ \Delta 251 \]
\[ \Delta 1301 \]
\[ \Delta 1073 \]
\[ p = 0.0002 \]
\[ N=114 \]
\[ p = 0.003 \]
\[ N=104 \]

SALT Trials-secondary endpoint subgroup
Tolvaptan Raises Serum [Na+] in Acute HF Patients (ACTIV Study)

Baseline Serum [Na+] <136 mEq/L

*P<.01 vs placebo.

EVEREST: 3 Trials in 1

OBJECTIVE:
Evaluate tolvaptan effects on signs/symptoms in-hospital

Short-term Clinical Status Trial A

Long-term Outcome Trial
Long-term drug administration

Separate Sites

Short-term Clinical Status Trial B

OBJECTIVE
Evaluate tolvaptan effects on morbidity/mortality

Changes From Baseline in Secondary Efficacy End Points (at day 7 or discharge)

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th>Trial B</th>
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<tbody>
<tr>
<td>Change in Mean Body Weight, kg</td>
<td>-5</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>P&lt;.001</td>
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</table>

<table>
<thead>
<tr>
<th>Change in Mean VAS Score, mm</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>P=0.51</td>
<td>P=0.52</td>
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</table>

<table>
<thead>
<tr>
<th>Global Clinical Status</th>
<th>Trial A</th>
<th>Trial B</th>
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<tbody>
<tr>
<td>n=997</td>
<td>n=1007</td>
<td>n=1031</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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</tr>
</tbody>
</table>

VAS = visual analog scale.
**All-Cause Mortality and Cardiovascular Mortality or Hospitalization for HF**

**All-Cause Mortality**
- HR 0.98; 95% CI (.87-1.11)
- Median follow-up 9.9 months
- Log-Rank Test: $P=.76$
- Peto-Peto-Wilcoxon Test: $P = .68$
- Stratified Peto-Peto-Wilcoxon Test: $P = .68$

**Cardiovascular Mortality or Heart Failure Hospitalization**
- HR 1.04; 95% CI (.95-1.14)
- Log-Rank Test: $P=.42$
- Peto-Peto-Wilcoxon Test: $P = .55$
- Stratified Peto-Peto-Wilcoxon Test: $P = .56$

**No. at Risk**
- **Tolvaptan** 2072 1812 1446 1112 859 589 404 239 97
- **Placebo** 2061 1781 1440 1109 840 580 400 233 95

Changes in Body Weight and Serum [Na\(^+\)] By Visit

**Adjudicated CV Mortality/Morbidity**

**EVEREST Trial: Patients with HF and Hyponatremia**

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

- **Tolvaptan**
- **Placebo**

Hazard Ratio: 1.065
95% CI Limits: 0.973, 1.165
(p<0.05)

Overall CV Mortality/Morbidity (ITT) HR 1.04; 95%CI (0.95-1.14)

DATA on File: Protocols 156-02-235 and 156-03-238.
Efficacy and Safety of Tolvaptan in Patients Hospitalized with Acute Heart Failure (TACTICS-HF)

**Background**  The oral vasopressin-2 receptor antagonist tolvaptan causes aquareasis in patients with volume overload, potentially facilitating decongestion and improving the clinical course of patients with acute heart failure (AHF).

**Objectives**  To address the acute use of tolvaptan to improve congestion in AHF, we conducted the Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF, NCT01644331) study.

**Methods**  TACTICS-HF randomized patients within 24 hours of AHF presentation in a prospective, double blind, placebo-controlled trial. Patients were eligible regardless of ejection fraction, and were randomized to either 30 mg of tolvaptan or placebo given at 0, 24, and 48 hours, with a fixed-dose furosemide regimen as background therapy. The primary endpoint was the proportion of patients considered responders at 24 hours. Secondary endpoints included symptom improvement, changes in renal function, and clinical events.

**Results**  A total of 257 patients were randomized. Dyspnea relief by Likert scale was similar between tolvaptan and placebo at 8 hours (25% moderately or markedly improved for tolvaptan vs. 28% placebo, p=0.59) and at 24 hours (50% tolvaptan vs. 47% placebo, p=0.80). Need for rescue therapy was also similar at 24 hours (21% tolvaptan, 18% placebo, p=0.57). The proportion defined as responders at 24 hours (primary study endpoint) was 16% for tolvaptan and 20% for placebo (p=0.32). Tolvaptan resulted in greater weight loss and net fluid loss compared to placebo, but tolvaptan-treated patients were more likely to experience worsening renal function during treatment. There were no differences in in-hospital or post-discharge clinical outcomes.

**Conclusions**  In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders at 24 hours despite greater weight loss and fluid loss.
Indications: Vasopressin Antagonism in Hypervolemic Hyponatremia

- **Conivaptan**: indicated for Rx of euvolemic and hypervolemic hypoNa in hospitalized patients, short-term IV Rx

- **Tolvaptan**: indicated for oral Rx of clinically significant hypervolemic and euvolemic hyponatremia [serum Na < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction]

- **Lixivaptan**: awaiting later phase trial data
## The Vaptans: Dosing

### Conivaptan
- **Loading dose:** 20 mg IV over 30 m
- **Continuous infusion:** 20 mg/d over 24 h for 2-4 d
- **After initial treatment day,** dosage may be increased to 40 mg/d
- **Decrease dose in patients with moderate hepatic impairment**

### Tolvaptan
- **Initiate and reinitiate in a hospital**
- **Initial oral dose:** 15 mg once daily without regard to meals
- **Dosage may be increased at intervals ≥ 24 h to 30 mg once daily**
- **Maximum dose:** 60 mg daily
- **Avoid fluid restriction during first 24 h of therapy**

Data from:
Common Side Effects With Tolvaptan

- Thirst
- Polydipsia/polyuria
- Dry mouth
- Frequent daytime urination
TEMPO: Potential for Liver Injury

- 3-year TEMPO trial of 1445 patients with ADPKD, kidney volume ≥750 mL, estimated creatinine clearance ≥60 mL/m
  - Patients randomized 2:1 to receive tolvaptan or placebo
  - Tolvaptan treatment (compared with placebo)
    - Slowed increase in total kidney volume and decline in kidney function
    - *Increased incidence of ALT >2.5x ULN: 4.9% vs 1.2% of placebo patients*

- FDA drug safety communication, updated drug label
  - Limit duration to 30 days
  - Do not use in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death

Approach to Hyponatremia

- Tolvaptan or Conivaptan provide prompt but safe correction of serum $[\text{Na}^+]$ in 24-48 h:
  - $\leq 12$ mEq/L in the first 24 h
  - $\leq 18$ mEq/L in the first 48 h
- Increased water excretion without electrolyte excretion ($\text{Na}^+$ and $\text{K}^+$)
- Elimination or decreased need for fluid restriction
- Predictable and reliable action

Current Status of AVP Antagonists for HF Treatment

- $V_{1a}/V_2$ and $V_2$ antagonists appear to facilitate diuresis/decongestion in acute decompensated HF.

- Thus far, no effect on mortality or hospitalization risk has been demonstrated.

- Chronic administration of a $V_2$ antagonist is safe, has modest effects on clinical congestion, but has no effect on morbidity and mortality in HF with low ejection fraction.

- Additional trials in targeted populations are needed.
Clinical Implications: Approaches to Managing Patients with Hyponatremia

- Hyponatremia is common in patients with heart failure.
- Low sodium is associated with cognitive and neuromuscular impairment and increased mortality.
- Vaptans increase Na+ levels in hypervolemic, hyponatremic patients.
- Vaptans can improve cognitive function, enhance diuresis and improve hemodynamics.
- These agents are generally well tolerated with low side effect profile.
- Effects on survival and other outcomes in hyponatremic heart failure patients are uncertain.
- Need for additional studies.