Rational and Practical Approaches For Treating Hyponatremia

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Disclosure

Research grant from Otsuka for the study:

Tolvaptan in the treatment of volume overload in hyponatremic patients with heart failure (AQUA-AHF).
“His contributions to the field of heart failure are near legendary and place him in an iconic status. He has consistently been among the most highly cited investigators in the country, he has mentored countless students and residents and has initiated and completed innumerable clinical trials. His impact on the field will remain for many years to come.”
Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure
A Randomized Controlled Trial

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Frank A. McGrew, MD
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for the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators

Context Nearly 1 million hospitalizations for chronic heart failure occur yearly in the United States, with most related to worsening systemic congestion. Diuretic use, the mainstay therapy for congestion, is associated with electrolyte abnormalities and worsening renal function. In contrast to diuretics, the vasopressin antagonist tolvaptan may increase net volume loss in heart failure without adversely affecting electrolytes and renal function.

Objective To evaluate the short- and intermediate-term effects of tolvaptan in patients hospitalized with heart failure.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 trial conducted at 45 centers in the United States and Argentina and enrolling 319 patients with left ventricular ejection fraction of less than 40% and hospitalized for heart failure with persistent signs and symptoms of systemic congestion despite standard therapy.

Intervention After admission, patients were randomized to receive 30, 60, or 90 mg/d of oral tolvaptan or placebo in addition to standard therapy, including diuretics. The study drug was continued for up to 60 days.

Main Outcome Measures In-hospital outcome was change in body weight at 24 hours after randomization; outpatient outcome was worsening heart failure (defined as death, hospitalization, or unscheduled visits for heart failure) at 60 days after randomization.
**ACTIVE in CHF**

*Figure 2. Median Changes in Body Weight Over Time*

<table>
<thead>
<tr>
<th>Change in Body Weight From Baseline, Kg</th>
<th>30 mg Tolvaptan</th>
<th>60 mg Tolvaptan</th>
<th>90 mg Tolvaptan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last Visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates $P = .002$; †, $P = .009$; ‡, $P = .006$; and §, $P = .008$ for comparisons with placebo group. Error bars indicate interquartile range.

*Figure 3. Mean 24-Hour Urine Volumes at Day 1 and at Hospital Discharge*

- **30 mg Tolvaptan**
- **90 mg Tolvaptan**
- **60 mg Tolvaptan**
- **Placebo**

- **Day 1**
- **Discharge**

$P < .001$ for all comparisons of tolvaptan regimens and placebo.
Hyponatremia (serum sodium < 135 mEq/L) is common in patients hospitalized with HF.
Hyponatremia Is Associated With Death and Rehospitalization in HF Patients*

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

PROGNOSTIC VALUE OF HYPONATREMIA VS. BNP
PARK ET AL JACC 2014;63:A786
HYPONATREMIA and diuretic resistance

- Retrospective cohort study in 499 hospitalized AHF patients treated with intravenous loop diuretics for ≥48 hours

<table>
<thead>
<tr>
<th>Nadir Sodium, mEq/L</th>
<th>≥135</th>
<th>130-134</th>
<th>&lt; 130</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose, mg/d</td>
<td>65±43</td>
<td>75±84</td>
<td>71±55</td>
<td>0.276</td>
</tr>
<tr>
<td>Mean hourly UO, mL/h</td>
<td>79±37</td>
<td>85±43</td>
<td>80±36</td>
<td>0.234</td>
</tr>
</tbody>
</table>

Ng T, Cao D, Elkayam U et al. J Am Coll Cardiol 2012;59(13 suppl A):A249.
Hyponatremia in ADHF

Treatment
Treatments for Hyponatremia In Patients With HF

• Improving hemodynamics.
• ACE inhibitors.
• Fluid restriction (poorly tolerated, only 1-2 mEq/L per day).
• Diuresis (Hypertonic saline).
• Vasopressin receptor antagonists.
HSS added to furosemide increased total urine output, sodium excretion, urinary osmolality, and furosemide urine delivery in all patients and at all time points.
Hypertonic saline with furosemide for the treatment of acute HF: A systematic review and meta-analysis

Gandhi S et al Int J Cardiol 2014;173:139-45

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HSS</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Issa 2011</td>
<td>10</td>
<td>20</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Licata 2002</td>
<td>24</td>
<td>53</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>Paterna 2000</td>
<td>3</td>
<td>30</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>Paterna 2005</td>
<td>0</td>
<td>48</td>
<td>3</td>
<td>46</td>
</tr>
<tr>
<td>Paterna 2011</td>
<td>114</td>
<td>881</td>
<td>212</td>
<td>890</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1032</td>
<td>1032</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>151</td>
<td>277</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.05; Chi² = 7.01, df = 4 (P = 0.14); I² = 43%

Test for overall effect: Z = 3.63 (P = 0.0003)
Treatments for Hyponatremia in Patients With HF

- Improving hemodynamics.
- ACE inhibitors.
- Fluid restriction (poorly tolerated, only 1-2 mEq/L per day).
- Diuresis (Hypertonic saline).
- Vasopressin receptor antagonists.
Arginine Vasopressin (AVP, ADH)
Stimulation and Effects

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

V1b-Ant pituitary
Pancreas, Adrenal medula

V1a Receptor (VSMC, cardiomyocytes)
V2 Receptors (collecting ducts)

Vasoconstriction
Myocardial stimulation
Renal H2O reabsorption

# 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></td>
<td>$V_2$</td>
<td>$V_2$</td>
<td>$V_2$</td>
<td>$V_{1a}/V_2$</td>
</tr>
<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>

Change in Serum [Na⁺] After 4 Days of Continuous IV Infusion of Conivaptan


No Myelinolysis

*P<.001, †P=.034 vs placebo.
Effects of Tolvaptan in patients with HF
Increased Vasopressin in HF

Increased Plasma Arginine Vasopressin Levels in Patients With Congestive Heart Failure

STEVEN R. GOLDSMITH, MD, FACC, GARY S. FRANCIS, MD, FACC,
ALLEN W. COWLEY, Jr., PhD, T. BARRY LEVINE, MD, JAY N. COHN, MD, FACC

*Milwaukee, Wisconsin*

31 patients with HF vs 51 comparable normals. Mean vasopressin level 9.5+/-0.6 vs 4.7 +/- 0.7
The EVEREST trial

4202 Patients at 432 Sites Screened

69 Patients Excluded (Did Not Meet Inclusion Criteria)

4133 Patients at 359 Sites Randomized

2072 Patients Randomized to Receive Tolvaptan

1018 Patients (179 Sites) Assigned to Trial A

32 Discontinued Study
8 Died
10 Adverse Events
13 Withdrew Consent
1 Investigator Decision

986 Completed Study Through Inpatient Day 7 or Discharge (if Earlier)

890 Included in Primary Efficacy Analysis
128 Excluded
32 Discontinued Study
96 Missing ≥1 Component of Composite Outcome

1015 Included in Safety Analysis
3 Excluded (Did Not Receive at Least 1 Dose of Study Drug)

1054 Patients (180 Sites) Assigned to Trial B

22 Discontinued Study
6 Died
3 Adverse Events
10 Withdrew Consent
2 Investigator Decision
1 Protocol Violation

1008 Completed Study Through Inpatient Day 7 or Discharge (if Earlier)

900 Included in Primary Efficacy Analysis
130 Excluded
22 Discontinued Study
108 Missing ≥1 Component of Composite Outcome

1027 Included in Safety Analysis
6 Excluded (Did Not Receive at Least 1 Dose of Study Drug)

2061 Patients Randomized to Receive Placebo

1030 Patients (179 Sites) Assigned to Trial A

25 Discontinued Study
9 Died
2 Adverse Events
13 Withdrew Consent
1 Investigator Decision

1029 Completed Study Through Inpatient Day 7 or Discharge (if Earlier)

921 Included in Primary Efficacy Analysis
133 Excluded
25 Discontinued Study
108 Missing ≥1 Component of Composite Outcome

1048 Included in Safety Analysis
6 Excluded (Did Not Receive at Least 1 Dose of Study Drug)

1031 Patients (180 Sites) Assigned to Trial B

25 Discontinued Study
11 Died
1 Adverse Events
13 Withdrew Consent

1006 Completed Study Through Inpatient Day 7 or Discharge (if Earlier)

888 Included in Primary Efficacy Analysis
143 Excluded
25 Discontinued Study
118 Missing ≥1 Component of Composite Outcome

1028 Included in Safety Analysis
3 Excluded (Did Not Receive at Least 1 Dose of Study Drug)
EVEREST Trial

CV Mortality or HF Hospitalization

Peto-Peto Wilcoxon Test: $P=0.55$

<table>
<thead>
<tr>
<th>Proportion Without Event</th>
<th>Months In Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>2072</td>
</tr>
<tr>
<td>TLV 30 mg</td>
<td>2061</td>
</tr>
</tbody>
</table>

HR 1.04; 95%CI (.95-1.14)
**EVEREST Trial**

**Composite Change in Global Status and Body Weight (Day 7 or Discharge)**

- **Study A**
  - Tolvaptan: 1.06
  - Placebo: 0.99
  - Sample Size: n = 890
  - *P* = .0004

- **Study B**
  - Tolvaptan: 1.07
  - Placebo: 0.97
  - Sample Size: n = 921
  - *P* < .0001

Based on rank-sum analysis.
Does Tolvaptan Have a Role in the Management of AHF?
Recent Trials

- AQUAMARINE
- TACTICS – HF.
- SECRET of CHF
Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction

Matsue Y et al JCF 2016;22:423
### Table 2. Summary of Primary and Secondary End Points

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conventional Group (n = 109)</th>
<th>Tolvaptan Group (n = 108)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48-hour urine volume (mL)</td>
<td>4997.2 ± 2101.4</td>
<td>6464.4 ± 3173.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of renal function (%)</td>
<td>30 (27.8)</td>
<td>26 (24.1)</td>
<td>.642</td>
</tr>
<tr>
<td>Dose of diuretics use within 48 h (mg)</td>
<td>120 (80–180)</td>
<td>80 (40–150)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Net fluid loss within 48 h (mL)</td>
<td>3697.9 ± 2112.0</td>
<td>4700.1 ± 2443.3</td>
<td>.004</td>
</tr>
<tr>
<td>Change in BNP from baseline to 48 h (pg/mL)</td>
<td>−306.1 (−153.7 to −662.1)</td>
<td>−285.3 (−110.7 to −650.9)</td>
<td>.602</td>
</tr>
<tr>
<td>Change in body weight from baseline to 48 h (kg)</td>
<td>−1.99 ± 2.17</td>
<td>−3.16 ± 2.66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>14.6 (10.3–27.2)</td>
<td>14.2 (8.9–20.3)</td>
<td>.36</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6 (5.5)</td>
<td>10 (9.3)</td>
<td>.313</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>5 (4.6)</td>
<td>4 (3.7)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SD, n (%), or median (interquartile range). BNP, B-type natriuretic peptide.
Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction
Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction

![Graph showing the clinical effectiveness of Tolvaptan over time with Conv group and Tolvaptan group compared.]
Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure

G. Michael Felker, MD, MHS, a,b Robert J. Mentz, MD, a,b Robert T. Cole, MD, c Kirkwood F. Adams, MD, d Gregory F. Egnaczyk, MD, e Mona Fiuza, PHARMd, a,b Chetan B. Patel, MD, a,b Melvin Echols, MD, a Michel G. Khouri, MD, a James M. Tauras, MD, f Divya Gupta, MD, c Pamela Monds, MBA, a,b Rhonda Roberts, MPH, a,b Christopher M. O’Connor, MD a

257 patients with AHF regardless of EF, Na < 140 mg/Dl randomized within 24 h of presentation to either 30 mg of tolvaptan or placebo given at 0, 24, and 48 h, with a fixed-dose furosemide regimen as background therapy.
Efficacy and Safety of Tolvaptan in Patients Hospitalized With AHF
The TACTICS-HF Study

257 patients with AHF within <24 hours presentation regardless of EF
randomized
to tolvaptan 30 mg or placebo given at 0, 24 and 48 hours

Primary end point: dyspnea at 7 and 24 hrs without rescue therapy
### Efficacy and Safety of Tolvaptan in Patients Hospitalized With AHF
#### The TACTICS-HF Study

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Decongestion and Renal Endpoints</th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 128)</td>
<td>Tolvaptan (n = 129)</td>
<td></td>
</tr>
<tr>
<td>Change in weight, lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>−1.2 ± 13.2</td>
<td>−4.4 ± 6.6</td>
<td>0.005</td>
</tr>
<tr>
<td>48 h</td>
<td>−3.5 ± 6.3</td>
<td>−6.1 ± 7.4</td>
<td>0.004</td>
</tr>
<tr>
<td>72 h</td>
<td>−5.5 ± 7.0</td>
<td>−8.2 ± 9.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Fluid loss, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>1,541 ± 1,525</td>
<td>2,182 ± 1,844</td>
<td>0.006</td>
</tr>
<tr>
<td>48 h</td>
<td>1,419 ± 1,379</td>
<td>1,948 ± 1,636</td>
<td>0.01</td>
</tr>
<tr>
<td>72 h</td>
<td>1,401 ± 1,387</td>
<td>1,757 ± 1,670</td>
<td>0.11</td>
</tr>
<tr>
<td>Change in serum sodium, mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.2 ± 2.5</td>
<td>3.2 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>48 h</td>
<td>−0.2 ± 2.8</td>
<td>3.3 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>72 h</td>
<td>−0.4 ± 2.9</td>
<td>2.8 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Freedom from congestion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>9</td>
<td>7</td>
<td>0.47</td>
</tr>
<tr>
<td>48 h</td>
<td>17</td>
<td>19</td>
<td>0.59</td>
</tr>
<tr>
<td>72 h</td>
<td>16</td>
<td>25</td>
<td>0.12</td>
</tr>
<tr>
<td>Change in creatinine, mmol/l</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24 h</td>
<td>0.04 ± 0.3</td>
<td>0.13 ± 0.4</td>
<td>0.052</td>
</tr>
<tr>
<td>48 h</td>
<td>0.05 ± 0.4</td>
<td>0.10 ± 0.4</td>
<td>0.094</td>
</tr>
<tr>
<td>72 h</td>
<td>0.06 ± 0.4</td>
<td>0.03 ± 0.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Worsening renal function by 72 h</td>
<td>27</td>
<td>39</td>
<td>0.037</td>
</tr>
<tr>
<td>Over diuresis</td>
<td>2</td>
<td>5</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload

Marvin A. Konstam, MD, a Michael Kiernan, MD, MS, a Arthur Chandler, MD, b Ravi Dhingra, MD, MPH, c Freny Vaghaiwala Mody, MD, d Howard Eisen, MD, e W. Herbert Haught, MD, f Lynne Wagoner, MD, g Divya Gupta, MD, h Richard Patten, MD, i Paul Gordon, MD, j Kenneth Korr, MD, k Russell Fileccia, MD, l Susan J. Pressler, PhD, RN, j Douglas Gregory, PhD, m Patricia Wedge, RN, m Douglas Dowling, BS, m Matthew Romeling, MHA, m Jeremy M. Konstam, MS, m Joseph M. Massaro, PhD, n James E. Udelson, MD, a for the SECRET of CHF Investigators, Coordinators, and Committee Members

251 patients with AHF and at least one of the following risk factors: GFR < 60, NA < 134 mEq/L, Urine output < 125 ml/h following lasix 40 mg. Randomized to placebo or tolvaptan 30 mg / for 7 days. Primary end point : change in dyspnea score at 8 an 16 hours.
Short Term Effects of tolvaptan in Patients with AHF and Volume Overload- SECRET of CHF Study

Konstam MA et al JACC 2017;69:1409-19
Short Term Effects of tolvaptan in Patients with AHF and Volume Overload - SECRET of CHF Study

250 patients with AHF
Mean EF 34% 32% > 45%
Randomized within 36 h after hospitalization to Tolvaptan 30 mg/d or placebo for 7 days

A Likert dyspnea scale responses over 3 days

Konstam MA et al JACC 2017;69:1409-19
Short Term Effects of tolvaptan in Patients with AHF and Volume Overload - SECRET of CHF Study

Konstam MA et al JACC 2017;69:1409-19
There is a disconnect between weight/fluid loss and dyspnea.

It may be time to abandon the dyspnea endpoint in acute heart failure trials.

Starling & Young JACC 2017:69;1407-8
Figure 3. Percent changes in plasma volume (PV) (upper) and plasma refilling rate (PRR) (lower) during extracorporeal ultrafiltration (UF). *p < 0.01 vs. 1 L.
The transcapillary mobilization of expanded interstitial space fluid into the intravascular compartment accounts for this disparity and identifies the major contribution to fluid loss with diuresis.
7.7. Arginine Vasopressin Antagonists

CLASS IIb

1. In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a $V_2$ receptor selective or a nonselective vasopressin antagonist (330,331). (Level of Evidence: B)
Hyponatremia and ADHF

Summary

- Hyponatremia is common.
- Very strong prognostic biomarker.
- Vasopressin receptor antagonists are the most effective treatment for correction of hyponatremia and volume overload.
Hyponatremia and vasopressin antagonists in ADHF

Summary

- The drugs have not been shown to improve long term prognosis in patients with chronic HF or early symptoms in AHF.
- Enhance the effect of diuretics in patients with renal insufficiency, hyponatremia and diuretic resistance.