Use of Vasopressin Receptor Antagonists in the Treatment of Heart Failure

TIEN M.H. NG, PHARM.D., FHFA, FCCP, BCPS AQ CARDIOLOGY
ASSOCIATE PROFESSOR OF CLINICAL PHARMACY AND MEDICINE
DIRECTOR, PGY2 RESIDENCY IN CARDIOLOGY
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA
Arginine Vasopressin

Hyperosmolarity → Hypothalamus
Decreased atrial receptor firing Baroreceptors → Hypothalamus
Angiotensin II → Hypothalamus
Sympathetic stimulation → Hypothalamus

Hypothalamus → Posterior Pituitary

Posterior Pituitary → Vasopressin

V_1A → Myocytes (Growth) → Remodeling
V_1A → Blood Vessels (Constriction) → Increased Systemic Vascular Resistance
V_2 → Kidneys (Fluid Reabsorption) → Increased Blood Volume
V_1B → ACTH
Vasopressin in HFrEF


Vasopressin Hemodynamics in HF

### Vasopressin Receptor Antagonists “Vaptans”

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Route of Administration</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conivaptan</strong></td>
<td>$V_{1A}/V_2$</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Tolvaptan</strong></td>
<td>$V_2$</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Lixivaptan</strong></td>
<td>$V_2$</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Mozavaptan</strong></td>
<td>$V_2$</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Satavaptan</strong></td>
<td>$V_2$</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Relcovaptan</strong></td>
<td>$V_{1A}$</td>
<td>PO</td>
</tr>
</tbody>
</table>
Vaptans and HF in 2017
PAST
ACUTE AND CHRONIC THERAPEUTIC IMPACT OF A VASOPRESSIN ANTAGONIST IN CONGESTIVE HEART FAILURE (ACTIV IN CHF)

- 319 AHF patients with LVEF < 40%, 21.6% hyponatremia
- Tolvaptan (30, 60, 90) vs. placebo x 60 days

![Graph showing 24-hour urine volume and patients with improvement from baseline.](image)

P = 0.04

EFFICACY OF VASOPRESSIN ANTAGONISM IN HEART FAILURE OUTCOME STUDY WITH TOLVAPTAN (EVEREST)

- 4133 patients within 2 short-term clinical status studies
- Tolvaptan 30mg daily vs. placebo x 9.9 mo

HR 0.98; 95%CI (.87-1.11)
Meets criteria for non-inferiority

Median follow-up 9.9 months
Peto-Peto Wilcoxon Test: P=0.68

JAMA. 2007 Mar 28;297(12):1319-31
EVEREST short-term clinical status

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tolvaptan</td>
<td>Placebo</td>
</tr>
<tr>
<td>Changes in patient-assessed global clinical status at day 7,* mean VAS score (SD) [No.]</td>
<td>18.25 (22.26) [903]</td>
<td>17.73 (22.47) [910]</td>
</tr>
<tr>
<td>Changes in body weight at day 1, mean (SD) [No.], kg</td>
<td>-1.71 (1.80) [978]</td>
<td>-0.99 (1.83) [997]</td>
</tr>
<tr>
<td>Changes in body weight at day 7,* mean (SD) [No.], kg</td>
<td>-3.35 (3.27) [997]</td>
<td>-2.73 (3.34) [1007]</td>
</tr>
<tr>
<td>Change in patient-assessed dyspnea at day 1, % showing improvement in dyspnea score (No.),§</td>
<td>76.74 (894)</td>
<td>70.61 (915)</td>
</tr>
<tr>
<td>Change in edema scores at day 7,* % showing at least a 2-grade improvement (No.),§</td>
<td>73.83 (772)</td>
<td>70.25 (790)</td>
</tr>
</tbody>
</table>

Trial B

- Markedly
- Moderately
- Minimally
- No Change
- Worse

P < .001 for Overall Comparison

Self-assessed Dyspnea

Tolvaptan (n = 941) vs Placebo (n = 914)
PRESENT
Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF)

- Randomized, double-blind, placebo-controlled, multicenter
- N= 257 (6 lost to follow-up)
- Inclusion criteria:
  - Within 24h of presentation
  - Dyspnea at rest or with minimal exertion
  - BNP > 400, NT-proBNP > 2000 pg/mL
  - Orthopnea, peripheral edema, JVD, rales, CXR pulmonary congestion
- Exclusion criteria:
  - Na > 140
  - SBP < 90 mmHg
  - Scr > 3.5 mg/dL or RRT

TACTICS-HF

AHF < 24h after presentation

- Fixed dose furosemide (1x PO or 40mg IV BID) +
  - Tolvaptan 30mg/d

- Fixed dose furosemide (1x PO or 40mg IV BID) +
  - Placebo

Open-label treatment

0h 24h 48h 72h 7d 30d

Rescue Tx:
- loop, thiazide, IV vasoactive, UF, MCS, resp support

# TACTICS-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=128)</th>
<th>Tolvaptan (N=129)</th>
<th>All Patients (N=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (y)</strong></td>
<td>63±16</td>
<td>66±13</td>
<td>65±14</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>33</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td><strong>Race C:AA (%)</strong></td>
<td>48:45</td>
<td>59:36</td>
<td>54:41</td>
</tr>
<tr>
<td><strong>Baseline diuretic dose (mg/d)</strong></td>
<td>72±46</td>
<td>71±53</td>
<td>71±49</td>
</tr>
<tr>
<td><strong>Mean LVEF (%)</strong></td>
<td>32±17</td>
<td>24±17</td>
<td>33±17</td>
</tr>
<tr>
<td><strong>LVEF &gt; 45% (%)</strong></td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>Mean Scr (mg/dL)</strong></td>
<td>1.44±0.6</td>
<td>1.48±0.7</td>
<td>1.46±0.6</td>
</tr>
<tr>
<td><strong>NT-proBNP BNP (pg/mL)</strong></td>
<td>10756±11735 1461±1073</td>
<td>9694±8509 1453±979</td>
<td>10246±10286 1457±1022</td>
</tr>
</tbody>
</table>
TACTICS-HF: Symptoms

% moderate or better improvement in dyspnea (Likert Scale)

*Dyspnea by numerical rating scale better with tolvaptan at 48h, p=0.05

J Am Coll Cardiol 2017;69(11):
TACTICS-HF: Responders

% responders
(dyspnea mod or better, and no rescue tx/death)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>48h</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>72h</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

*Tolvaptan pts less likely to need rescue therapy by 72 hours (39% for tolvaptan vs. 53% for placebo, p=0.047)

J Am Coll Cardiol 2017;69(11):
**TACTICS-HF: Fluid and Renal**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tolvaptan</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight change</strong> (lbs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24h</td>
<td>-1.2</td>
<td>-4.4</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>48h</td>
<td>-3.5</td>
<td>-6.1</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>72h</td>
<td>-5.5</td>
<td>-8.2</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Fluid loss</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24h</td>
<td>1541</td>
<td>2182</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>48h</td>
<td>1419</td>
<td>1948</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>72h</td>
<td>1401</td>
<td>1757</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>WRF by 72h (%)</strong></td>
<td>27</td>
<td>39</td>
<td><strong>0.037</strong></td>
</tr>
<tr>
<td><strong>Scr change</strong> (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24h</td>
<td>0.04</td>
<td>0.13</td>
<td>0.052</td>
</tr>
<tr>
<td>48h</td>
<td>0.05</td>
<td>0.10</td>
<td>0.094</td>
</tr>
<tr>
<td>72h</td>
<td>0.06</td>
<td>0.03</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Serum sodium significantly increased in tolvaptan treated patients*

J Am Coll Cardiol 2017;69(11):
In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the proportion of patients classified as responders at 24 hours, despite evidence of improved weight and fluid loss.

Trends towards greater dyspnea improvement at later time points (48 and 72 hours)

No differences in clinical endpoints such as LOS, days alive and out of the hospital within 30 days, 30-day all-cause mortality (underpowered)

“Worsening renal function” greater with tolvaptan but transient, and clinical relevance remains undetermined
Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET of CHF)

- Randomized, double-blind, placebo-controlled, multicenter
- **N= 250**
- Inclusion criteria:
  - Within 36h of presentation
  - Challenging decongestion:
    - Renal dysfunction (eGFR < 60 mL/min/1.73m²) or
    - Na ≤ 134 mEq/L or
    - UO ≤ 125 mL/h (furosemide 40mg IV or eq)
- Exclusion criteria:
  - SBP < 90 mmHg
  - Scr > 3.5 mg/dL or RRT
  - Na > 144 mEq/L

*Circ Heart Fail. 2015;8:997-1005*
SECRET of CHF

**Primary Endpoint:**
Self-assessed 7-point dyspnea score at 8 and 16 hours

**Secondary Endpoints:**
- Change in body weight
- In-hospital diuretic dose
- Change in eGFR
- Change in cognitive function
- Days alive and out of the hospital over 30 days
- Re-hospitalization for worsening heart failure or death at 30 days

Circ Heart Fail. 2015;8:997-1005
<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=128)</th>
<th>Tolvaptan (N=122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>67±13</td>
<td>70±11</td>
<td>0.08</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35</td>
<td>30</td>
<td>0.42</td>
</tr>
<tr>
<td>Race AA (%)</td>
<td>29</td>
<td>29</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>33±17</td>
<td>35±16</td>
<td>0.27</td>
</tr>
<tr>
<td>LVEF ≥ 45% (%)</td>
<td>30</td>
<td>34</td>
<td>0.51</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>1.7±0.6</td>
<td>1.7±0.5</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Serum Na ≤ 134 (%)</strong></td>
<td>21</td>
<td>18</td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>eGFR ≤ 60 (%)</strong></td>
<td>81</td>
<td>85</td>
<td>0.48</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>728</td>
<td>577</td>
<td>0.115</td>
</tr>
</tbody>
</table>

12% enrolled based on diuretic resistance alone

*Potential greater benefit early with tolvaptan in those without JVD or ascites.

Body Weight Change

DAY 1
-0.94

DAY 2
-2.36

DAY 3
-2.41

kg

Placebo
Tolvaptan

p<0.001
p<0.001
p=0.006

### Diuretic Doses

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tolvaptan</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRF (%)</td>
<td>25</td>
<td>31</td>
<td>0.298</td>
</tr>
<tr>
<td>Days alive/out of hospital</td>
<td>21.6±7.7</td>
<td>22.6±7.0</td>
<td>0.991</td>
</tr>
<tr>
<td>HF rehospitalization (%)</td>
<td>12.8</td>
<td>11.8</td>
<td>0.740</td>
</tr>
<tr>
<td>Death (%)</td>
<td>4.8</td>
<td>5.0</td>
<td>0.972</td>
</tr>
</tbody>
</table>

SECRET of CHF: Author Conclusions

- Despite significant early and sustained augmentation in weight reduction with tolvaptan, there was no between-group differences in the primary endpoint of dyspnea improvement at 8 and 16 h following initial tolvaptan dosing.

- Signal for improved dyspnea at day 3.

- Incongruity between the marked day 1 weight loss with tolvaptan and our neutral first-day dyspnea primary endpoint.

- Neutral effect on other clinical efficacy and safety outcomes.

- Subgroup findings suggest potential influence of right-sided HF on dyspnea

AQUAMARINE

- Multicenter, open-label, randomized controlled, parallel-group trial
- N=217 AHF with renal dysfunction (eGFR 15-30 mL/min/1.73m²)

ADHF ≤ 6h after admission

- Conventional Tx
- Conventional Tx + Tolvaptan 15mg/d

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carperitide</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Nitrate/ISDN</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Dopamine</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diuretic Dose within 48h, mg</td>
<td>120 (80-180)</td>
<td>80 (40-150)</td>
</tr>
</tbody>
</table>

AQUAMARINE

Changes in dyspnea within 48h

Neutral effect on all-cause mortality and event-free survival. IJC2016;221:188-93.

Potential niches continuing to be explored...

- Monotherapy
- Loop sparing/renal sparing
- HFpEF
- Transitional care
- Targeted use
AQuaresis Utility for hyponAtremic Acute Heart Failure (AQUA-AHF; NCT02183792)

- N=50, AHF with Na⁺ < 135 mEq/L
- Randomized, open-label, parallel-group

Endpoints: UO, Wt, NT-proBNP, cystatin C, PRA, copeptin A, NGAL, dyspnea, diuretic requirements
A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Tolvaptan Monotherapy Compared to Furosemide and the Combination of Tolvaptan and Furosemide in Patients With Heart Failure and Systolic Dysfunction
Randomized pilot trial comparing tolvaptan with furosemide on renal and neurohumoral effects in acute heart failure

- N=60 AHF dyspnea at rest
- Tolvaptan 7.5mg PO once daily vs Furosemide 40mg IV daily x 5 days
  - Background tx of carperitide and canrenoate potassium

Jujo K. ESC Heart Failure 2016; 3: 177–188
TACTICS, SECRET, and AQUAMARINE all have signals for greater symptom improvement with tolvaptan later rather than sooner, but no associated difference in 30 day readmission rates.

- Short course of vaptan therapy (2-3 days, up to 7 days)

- Perhaps we need to continue therapy longer?

Ng TM, Menon R, Hauptman PJ. JAMA Cardiol 2017
Targeted Use of Vaptans?

- Retrospective
- Response: urine aquaporin-2/serum AVP level > \(1.4 \times 10^3\) L/gCre

Vasopressin is intimately linked to the pathophysiology of HF

Addition of vaptans to conventional therapy for both chronic and acute HF has failed to impress thus far despite greater early weight loss.

Investigations into potential niches for vaptans in HF are ongoing