Arginine Vasopressin Antagonists for the Treatment of Heart Failure and Hyponatremia

John J. Finley IV, MD; Marvin A. Konstam, MD; James E. Udelson, MD

Arginine vasopressin has attracted attention as a potentially important neurohormonal mediator of the heart failure (HF) syndrome and hyponatremic states in humans because vasopressin influences renal handling of free water, vasoconstriction, and myocyte biology. Several vasopressin antagonists are under development, and one of these agents, conivaptan, recently received US Food and Drug Administration approval for short-term intravenous treatment in patients with euvolemic or hypervolemic hyponatremia.

The Role of Vasopressin in HF and Hyponatremia

A neurohypophysial hormone, vasopressin (also called antidiuretic hormone [ADH]), affects free water reabsorption by the kidney, body fluid osmolality, blood volume, vasoconstriction, and myocardial contractile function. Vasopressin is synthesized by neurosecretory cells located predominantly in the supraoptic and paraventricular hypothalamic nuclei. These neurons have axons terminating in the neural lobe of the posterior pituitary (neurohypophysis) that release vasopressin and oxytocin.

Physiology of Regulation of Vasopressin Release

Normally, the dominant stimulant for vasopressin release is a change in plasma tonicity, plasma volume depletion, or blood pressure, the last 2 mediated by arterial baroreceptors. Osmoreceptors in the anterior hypothalamus sense the increase in serum osmolality and stimulate secretion of vasopressin from the posterior pituitary. In an attempt to normalize plasma osmolality, vasopressin acts on the V2 renal receptors, increasing free water reabsorption by insertion of protein water channels, aquaporins, in the luminal membranes of the principal cells of the renal collecting ducts.

Receptor/Effector Mechanisms

The 3 vasopressin receptor subtypes belong to a family of rhodopsin-like G-protein–coupled receptors. V1a (vascular) receptors are located on several cell types, including vascular smooth muscle cells and cardiomycocytes (Table 1), with effects on the maintenance and regulation of vascular tone and possibly myocardial function.

V1b (pituitary) receptors are expressed on the surfaces of corticotrophic cells in the anterior pituitary and the pancreas and adrenal medulla (Table 1). V1a and V1b receptors are linked to the phosphatidylinositol and 1,2-diacylglycerol signaling pathway (Figure 1). Activation of the V1 receptors causes influx of extracellular calcium by an unknown mechanism. Protein kinase C and calcium/calmodulin-activated protein kinases phosphorylate cell type-specific proteins, leading to a range of cellular responses, including vasoconstriction, glycogenolysis, platelet aggregation, adrenocorticotrophic hormone release, and growth of vascular smooth muscle cells.

V2 (renal) receptors, expressed on the basolateral membrane of the renal collecting ducts, mediate the antidiuretic effects of vasopressin. The intracellular effects of this receptor subtype are mediated by the adenylate cyclase signaling pathway (Figure 2). Intracellular events triggered by binding of vasopressin to the V2 receptor include increased de novo synthesis and “shuttling” of aquaporin 2 water channels (AQP-2) from cytoplasmic vesicles to the luminal surface of the renal collecting duct cells, where they are inserted into the cell membrane and facilitate water transport across the collecting duct cells (Figure 2).

Evidence for Elevated Vasopressin Levels in HF and/or LV Dysfunction

In addition to plasma osmolality, nonosmotic factors such as intracardiac pressures, intraarterial pressures, angiotensin II, pain, and adrenergic (α2) central nervous stimuli potentially influence vasopressin secretion. In normal homeostasis, these nonosmotic mechanisms are thought to play only a minor role. However, in edematous states, there appears to be a shift in regulation toward relatively greater influence of the nonosmotic mechanisms. The response to osmotic changes appears to occur at lower plasma osmolality levels in edematous states and is more pronounced, as demonstrated by a greater increment of vasopressin levels in patients with HF compared with non-HF subjects after an osmotic load of mannitol.

Several studies have shown a significant elevation in mean values of plasma vasopressin in populations of patients with HF and/or LV dysfunction. In the Studies of Left Ventricular Dysfunction (SOLVD), patients with asymptomatic left ventricular (LV) dysfunction had higher mean vasopressin levels compared with a control group. Patients with mild to moderate symptomatic HF had even higher mean levels than their asymptomatic counterparts. Wide variability...

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in vasopressin levels exists among individual patients and across studies, and not all HF patients in these studies demonstrate elevated levels compared with normal referents. However, these “normal” vasopressin levels may be inappropriately elevated in HF relative to the state of expanded plasma volume or diminished plasma osmolality, although studies are not often analyzed as such.15 Table 2 summarizes the extant published literature reporting vasopressin levels in patients with HF and/or LV dysfunction.11–23

Table 1. Vasopressin Receptors: Location and Function5,8

<table>
<thead>
<tr>
<th>Location</th>
<th>Mediates</th>
<th>Location</th>
<th>Mediates</th>
<th>Location</th>
<th>Mediates</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1a</td>
<td>Vasoconstriction, myocardial hypertrophy</td>
<td>V1b</td>
<td>ACTH release</td>
<td>V2</td>
<td>Free water resorption (insertion of AQP-2 water channels into apical membrane; induction of AQP-2 synthesis)</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td></td>
<td>Corticotroph cells of anterior pituitary</td>
<td>ACTH release</td>
<td>Basolateral membrane of renal collecting tubule</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Aggregation</td>
<td>...</td>
<td>...</td>
<td>Vascular endothelium</td>
<td>Releases von Willebrand factor and factor VIII</td>
</tr>
<tr>
<td>Myometrium</td>
<td>Uterine contraction</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

ACTH indicates adrenocorticotropic hormone.

Hemodynamic Effects of Vasopressin
The vasoconstrictive effects of vasopressin are not thought to be associated with appreciable changes in arterial blood pressure at plasma levels within physiological range.24 However, in patients with HF, infusion of vasopressin increases systemic vascular resistance and pulmonary capillary wedge pressure increase, whereas stroke volume and cardiac output decrease with dose-dependent increases in vasopressin infusion.25 These hemodynamic effects are thought to be mediated primarily by activation of V1a receptors.16,26

Evidence supporting the concept that vasopressin mediates some degree of hemodynamically unfavorable effects in the setting of HF comes from data using selective V1a receptor antagonists in vivo,15 where significant improvements in systemic vascular resistance and cardiac output were observed in humans after vasopressin antagonism but only when vasopressin levels were elevated. Similar findings have been reported in animal models.27,28

Vasopressin Effects on Myocyte Biology
In neonatal rat myocardial cells, cellular hypertrophy by means of enhanced protein synthesis has been observed as a result of vasopressin receptor stimulation.29,30 By means of exposure to V1a receptor antagonists, the observed hypertrophy was significantly inhibited.29,30 Myocardial V1a receptor agonism results in an increase in intracellular calcium concentration, causing activation of mitogen-activated protein kinase and protein kinase C,29–31 thought to be central in mediating the observed hypertrophic myocardial cell growth.

Figure 1. Vasopressin V1 receptor activation. The binding of arginine vasopressin (AVP) to its V1 receptor (V1R) stimulates membrane-bound phospholipase (PLCβ) via stimulation of a G-coupled protein (Gα), which in turn results in inositol triphosphate (IP3) formation and mobilization of intracellular Ca2+ (icCa2+). A separate phosphorylation cascade occurs via diacylglycerol (DAG) and protein kinase C (PKC), which has downstream effects, including vascular smooth muscle (VSM) vasconstriction, cell growth, adrenocorticotropic hormone (ACTH) release, and platelet aggregation.

Figure 2. Vasopressin V2 receptor activation. The binding of arginine vasopressin (AVP) to the V2 vasopressin receptor (V2R) stimulates a Gs-coupled protein that activates adenylyl cyclase, in turn causing production of cAMP to activate protein kinase A (PKA). This pathway increases the exocytosis of aquaporin water channel–containing vesicles (AQMCV) and inhibits endocytosis of the vesicles, both resulting in increases in aquaporin 2 (AQP2) channel formation and apical membrane insertion. This allows an increase in the permeability of water from the collecting duct (CD).
dial cell growth. In these experiments, vasopressin inhibition with an agent acting at both the V1a and V2 receptors inhibited the activity of mitogen-activated protein kinase on rat cardiac myocytes.

Vasopressin Role in Water Balance and Hyponatremia
Vasopressin directly alters sodium concentration and water balance by stimulating the renal V2 receptors through increased expression of AQP-2 inserted into the cell membranes of the principal cells of the renal collecting ducts, facilitating free water absorption and a subsequent decrease in sodium serum levels.

Elevated plasma vasopressin concentrations appear to be associated with impaired solute-free water excretion in the setting of HF.9,10 Rats with an elevated LV end-diastolic pressure and reduced plasma sodium had significantly increased expression of AQP-2 mRNA compared with rats with compensated HF.32

In this regard, specific antagonism of the vasopressin V2 receptor results in a potent aquaresis in dogs and rats.33 In humans, V2 receptor antagonism results in a dose-related increase in solute-free water excretion and elevation of serum sodium concentration and serum osmolality in patients with HF.22,34,35 In 1 study, an observed reduction in urinary AQP-2 protein levels suggested that aquaresis was associated with a reduction in AQP-2 expression at the level of the renal collecting duct.36

Moreover, as discussed further below, vasopressin antagonism at the level of the V2 receptor has been consistently associated with an improvement in serum sodium levels among patients with hyponatremia of multiple causes.37–40

Vasopressin Antagonists in Development
Several vasopressin antagonists are in various stages of clinical trials for treating hyponatremia and/or HF. These agents differ on the basis of their degree of specificity for the V1a and V2 receptors (Table 3).4,41–43

Conivaptan is a nonpeptide vasopressin antagonist with a high affinity for both V1a and V2 receptors. Conivaptan has been administered by oral and intravenous routes,44 although the clinical development and recent US Food and Drug Administration approval involve only the intravenous formulation. The effects of conivaptan on urinary parameters in rat models have included an increase in both urine volume and sodium concentration compared with placebo.45

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Mean AVP Levels, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creager et al16</td>
<td>HF, 10</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>Normal</td>
<td>1.1 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Nicod et al17</td>
<td>HF, 10</td>
<td>2.3 ± 0.8</td>
</tr>
<tr>
<td>Pruszczynski et al18</td>
<td>HTN, 8</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>CAD, 11</td>
<td>2.9 ± 0.1</td>
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</tr>
<tr>
<td>3.4 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldsmith et al19</td>
<td>HF, 31</td>
<td>9.5 ± 0.9</td>
</tr>
<tr>
<td>Normal, 51</td>
<td>4.7 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Goldsmith et al19</td>
<td>HF, 15</td>
<td>11.6 ± 5.5</td>
</tr>
<tr>
<td>Normal, 9</td>
<td>5.3 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>Szatalowicz et al13</td>
<td>HF, 9</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td>Kramer et al15</td>
<td>HF, 20</td>
<td>14.5 ± 8.8</td>
</tr>
<tr>
<td>“High AVP” for Posm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Low AVP” for Posm</td>
<td>3.9 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Rouleau et al20</td>
<td>Asx LVD, 534</td>
<td>1.8 ± 0.7</td>
</tr>
<tr>
<td>Gavras et al21</td>
<td>Normal, 12</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Francis et al23</td>
<td>HF, 80</td>
<td>3.5</td>
</tr>
<tr>
<td>Asx LVD, 147</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Normal, 54</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Uretsky et al22</td>
<td>HF, 42</td>
<td>3.0 ± 2.5</td>
</tr>
<tr>
<td>Normal, 10</td>
<td>1.0 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Udelson et al22</td>
<td>HF, 142</td>
<td>Median levels 2.1–2.9</td>
</tr>
<tr>
<td>Udelson et al23</td>
<td>HF randomized to TLV, 120</td>
<td>1.7 ± 1.9</td>
</tr>
<tr>
<td>HF randomized to PLC, 120</td>
<td>2.0 ± 1.8</td>
<td></td>
</tr>
</tbody>
</table>

AVP indicates arginine vasopressin; HTN, hypertension; CAD, coronary artery disease; Posm, plasma osmolality; Asx LVD, asymptomatic LV dysfunction; TLV, tolvaptan; and PLC, placebo.

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<table>
<thead>
<tr>
<th>Vasopressin Antagonist</th>
<th>Tolvaptan (OPC-41061)4</th>
<th>Lixivaptan (VPA-985)4</th>
<th>Conivaptan (YM-087)4</th>
<th>Satavaptan (SR-121463)4</th>
<th>Mozavaptan (OPC-31260)4,43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>V2</td>
<td>V2</td>
<td>V1a/V2</td>
<td>V2</td>
<td>V1a/V2</td>
</tr>
<tr>
<td>Selectivity (KiV1a:KiV2)</td>
<td>29:1</td>
<td>100:1</td>
<td>10:1</td>
<td>112:1</td>
<td>10:1</td>
</tr>
<tr>
<td>Administration route</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous/oral</td>
<td>Oral</td>
<td>Intravenous/oral</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>6–8</td>
<td>7–10</td>
<td>14–17</td>
<td>14–17</td>
<td>1–8</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4/CYP6)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
<td>Feces</td>
</tr>
<tr>
<td>Clinical development</td>
<td>Hyponatremia, decompensated HF, PKCD</td>
<td>Hyponatremia, decompensated HF with hyponatremia</td>
<td>Hyponatremia, decompensated HF with hyponatremia</td>
<td>Hyponatremia, decompensated HF with hyponatremia</td>
<td>Hyponatremia (only SIADH)</td>
</tr>
</tbody>
</table>

PCKD indicates polycystic kidney disease.
intracellular free calcium and mitogen-activated protein kinase activity were observed to occur in a dose-dependent manner,29,30 suggesting a reduction in intracellular protein synthesis and possibly cardiomyocyte hypertrophy. Thus, in animal models, inhibition of both V1a and V2 vasopressin receptors may play a beneficial role in HF.

Tolvaptan, a selective nonpeptide V2 receptor antagonist, has potent aquaretic properties in animal models.46,47 In cloned human receptors, the V2:V1a receptor selectivity was 29:1.47 Dose-dependent responses demonstrated in rats include increased free water clearance, less urinary loss of sodium than furosemide, and no effect on serum creatinine.46 Compared with furosemide, serum sodium increased in a dose-dependent fashion in animals given tolvaptan.46 Unlike the administration of loop diuretics, antagonism of V2 receptors appeared not to increase activation of the renin-angiotensin-aldosterone system.46

Lixivaptan is a nonpeptide, highly specific antagonist of the V2 receptor. The binding affinity of lixivaptan for V2 receptors is \( \approx 100 \) times greater than for V1 receptors.2 Dose-dependent increases in urine output and solute-free water clearance and increased serum sodium concentration have been demonstrated in preliminary human studies of single doses of lixivaptan administered to patients with New York Heart Association class II and III HF.34

Satavaptan is highly specific for the V2 receptor, has a long half-life, and is under development for the treatment of hyponatremia in the syndrome of inappropriate secretion of ADH (SIADH) and cirrhosis.31

**Clinical Trials of Vasopressin Receptor Antagonists**

**Trials in Hyponatremia**

Hyponatremia is challenging to treat, with current approaches having significant limitations. Antagonism of vasopressin action at its receptor is attractive as an approach that directly addresses the pathophysiology. Table 4 summarizes the trials that have investigated the use of vasopressin antagonists in patients with hyponatremia of multiple origins.37,39,40,41,48

Two recently completed trials, Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT)-1 and SALT-2, investigated the effects of tolvaptan on serum sodium levels in patients with euvolemic or hypervolemic hyponatremia associated with HF, cirrhosis, or SIADH. This double-blind multicenter trial randomized 223 patients to placebo and 225 patients to tolvaptan at an initial dose of 15 mg daily. Dosing of tolvaptan (or matching placebo) was increased to 30 mg and then to 60 mg daily if sodium levels were not responding. Patients receiving tolvaptan had highly significant increases in serum sodium concentration at days 4 and 30. In the week after discontinuation of tolvaptan at day 30, hyponatremia recurred.37 In a prespecified analysis examining a patient-reported health status measure, tolvaptan had a favorable effect compared with placebo on the Mental Component Summary of the Short Form-12 Health Survey, particularly in patients with more severe hyponatremia.37

Of note, patients in the SALT trials were not fluid restricted; however, in 1 smaller study compared with placebo plus fluid restriction, tolvaptan appeared to be more effective at correcting hyponatremia in hospitalized patients.49

Lixivaptan also has been evaluated in 44 patients with hyponatremia from cirrhosis, HF, or SIADH receiving doses of 25, 125, or 250 mg orally twice daily for 7 days.40 The observed effects included an aquaretic response compared with placebo, with dose-related increases in free water clearance and serum sodium and without changes in orthostatic blood pressure or serum creatinine. Although effective at lower doses, the higher dose (250 mg) resulted in significant volume depletion requiring withholding of doses in 50% of patients.

Conivaptan has been studied for short-term intravenous treatment of euvolemic and hypervolemic hyponatremia and has recently achieved US Food and Drug Administration approval for this indication. The data that formed the basis for approval were published by Zeltser et al.,39 who randomized 84 hospitalized patients with either euvolemic or hypervolemic hyponatremia (defined by serum sodium concentrations between 115 and 130 mEq/L) to receive a 20-mg loading dose of conivaptan over 30 minutes followed by a 4-day infusion at either 40 or 80 mg/d or to receive placebo loading and infusion. Conivaptan resulted in a significant increase in serum sodium of 6.3±0.7 mEq/L in the 40-mg/d group and an increase of 9.4 mEq/L in the 80-mg/d group.39 The rate of correction of serum sodium was within safe limits without evidence of excessive hypernatremia or feared complications of central pontine myelinolysis from too-rapid correction of serum sodium. Compared with placebo, the incidence of death, serious side effects, and discontinuations of treatment for any reason were not in excess compared with placebo. However, an increased incidence of adverse effects in dose-related infusion-site reactions was present among patients receiving conivaptan versus those receiving placebo.39

Satavaptan is highly specific for the V2 receptor and has the longest half-life (14 to 17 hours) of the agents studied so far. A trial of 34 patients with SIADH showed significant correction of hyponatremia after doses of either 25 or 50 mg versus placebo.45 In the long-term open-label extension of the trial, satavaptan demonstrated safety without adverse events over a 12-month period.

A larger trial in 110 cirrhotics with ascites and hyponatremia demonstrated improvement in serum sodium levels and ascites control.48 This multicenter, double-blind, randomized controlled trial compared 3 oral doses (5, 12.5, or 25 mg once daily) compared with placebo, in addition to spironolactone 100 mg daily for 14 days. A dose-dependent improvement in ascites was found with satavaptan, as indicated by a reduction in body weight and abdominal girth, as well as an improvement in serum sodium.48

Overall, the data surrounding tolvaptan, lixivaptan, conivaptan, and satavaptan have been consistent in demonstrating favorable effects on serum sodium among patients with hyponatremia of various causes but not in demonstrating effects on overall or disease-specific mortality. An effect in the tolvaptan trials has been seen on symptoms as reflected by the Mental Component Summary of the Short Form-12 Health Survey.37
HF With Hyponatremia

The presence of hyponatremia in the setting of volume overload and HF creates substantial management challenges. Treatment of the volume-overload state with loop diuretics can exacerbate the free water excess and result in maintaining or even worsening of the magnitude of hyponatremia. The presence of hyponatremia in patients admitted for HF exacerbation regardless of systolic dysfunction, even mild hyponatremia, portends a worse prognosis, as many trial registries (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Heart Failure [OPTIMIZE-HF], Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure [OPTIME-CHF], Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness [ESCAPE]) have demonstrated.50–52 Because such patients are thought to have vasopressin excess contributing to the pathophysiology, the potential use of vasopressin antagonists in this setting is attractive.

In a double-blind study conducted in 254 stable chronic HF patients (regardless of LV ejection fraction), 3 oral doses of tolvaptan (30, 45, or 60 mg) given daily for 25 days were compared with placebo administration.38 Throughout the full course of therapy, a significant decrease in body weight and edema was observed, as was an increased urinary volume. Seventy of the 254 patients (28%) had hyponatremia at

### Table 4. Vasopressin Receptor Antagonists in Hyponatremia: Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>n</th>
<th>Design</th>
<th>Drug</th>
<th>Inclusion Criteria</th>
<th>End Points</th>
<th>Results</th>
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<tbody>
<tr>
<td>SALT-1/SALT-237</td>
<td>448</td>
<td>Multicenter, placebo controlled, double</td>
<td>Tolvaptan</td>
<td>Euvolemic or hypovolemic hyponatremia</td>
<td>Change in the average daily AUC for serum sodium from baseline to day 4 and the change from baseline to day 30</td>
<td>Serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 d ($P&lt;0.001$) and after 30 d of therapy ($P&lt;0.001$)</td>
</tr>
<tr>
<td>Wong et al40</td>
<td>44</td>
<td>Multicenter, placebo controlled, double</td>
<td>Lixivaptan</td>
<td>Hyponatremic patients</td>
<td>Free water clearance and serum sodium</td>
<td>Increase in serum sodium; increased aquaretic response without significant changes in orthostatic blood pressure or serum creatinine levels; higher dose (250 mg) led to dehydration</td>
</tr>
<tr>
<td>Zeitser et al39</td>
<td>84</td>
<td>Multicenter, placebo controlled, double</td>
<td>Conivaptan</td>
<td>Euvolemic or hypervolemic hyponatremia ($Na&lt;135$ mEq/L)</td>
<td>Change in the AUC for serum sodium during the infusion</td>
<td>Dose-dependent increase in serum sodium</td>
</tr>
<tr>
<td>Ghali et al70</td>
<td>74</td>
<td>Multicenter, placebo-controlled, double,</td>
<td>Conivaptan</td>
<td>Euvolemic or hypervolemic hyponatremia ($Na&lt;130$ mEq/L)</td>
<td>Change in the AUC for serum sodium</td>
<td>Dose-dependent increase in serum sodium</td>
</tr>
<tr>
<td>Soupert et al41</td>
<td>34</td>
<td>Multicenter, placebo controlled, double</td>
<td>Satavaptan</td>
<td>SIADH</td>
<td>Percent normalization or increase of ≥5 mmol/L sodium</td>
<td>Dose-dependent correction in serum sodium (second, long-term arm showed safety)</td>
</tr>
<tr>
<td>Gines et al48</td>
<td>110</td>
<td>Multicenter, placebo controlled, double</td>
<td>Satavaptan</td>
<td>Hyponatremic cirrhotics with ascites</td>
<td>Ascites control (abdominal girth and weight); change in serum sodium on day 5 from baseline</td>
<td>Improved control of ascites; increased serum sodium</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; heart failure.
Table 5. Vasopressin Receptor Antagonists in Heart Failure With Hyponatremia: Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Design</th>
<th>Drug</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gheorghiade et al (subgroup analysis)</td>
<td>Placebo controlled, double blind, multidose (30, 45, or 60 mg orally daily for 25 d)</td>
<td>Tolvaptan</td>
<td>HF patients regardless of LVEF</td>
<td>Body weight</td>
<td>Normalization of mean serum sodium by day 1 and maintained</td>
</tr>
<tr>
<td></td>
<td>Subgroup of 28% (of 254 total) with hyponatremia (Na⁺ &lt;136 mEq/L) at baseline</td>
<td>...</td>
<td>...</td>
<td>Urine volume (day 1), edema, serum sodium</td>
<td>Decrease in body weight and edema; increased urinary volume</td>
</tr>
<tr>
<td>ACTIV in HF (subgroup analysis)</td>
<td>Multicenter, placebo controlled, double blind (30, 60, or 90 mg orally daily up to 60 d)</td>
<td>Tolvaptan</td>
<td>Decompensated HF with LVEF ≤40% and 2 clinical signs of volume overload</td>
<td>Secondary end point: sodium levels</td>
<td>In subgroup with hyponatremia, sodium levels increased and often normalized</td>
</tr>
<tr>
<td></td>
<td>Subgroup: 16% (of 319 total) with hyponatremia (Na &lt;136 mEq/L)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>EVEREST (subgroup analysis)</td>
<td>Multicenter, placebo controlled, double blind, single dose (30 mg orally daily for up to 60 d)</td>
<td>Tolvaptan</td>
<td>Decompensated HF patients with LVEF ≤40%</td>
<td>All-cause mortality</td>
<td>In subgroup with hyponatremia, no effect on mortality or HF morbidity</td>
</tr>
<tr>
<td></td>
<td>Subgroup: 28% (of 4133 total) with hyponatremia (Na &lt;137 mEq/L)</td>
<td>...</td>
<td>...</td>
<td>First occurrence of cardiovascular mortality or heart failure hospitalization</td>
<td>Significant increase in mean serum sodium</td>
</tr>
<tr>
<td>BALANCE</td>
<td>Multicenter, placebo controlled, double-blind</td>
<td>Lixivaptan</td>
<td>Decompensated HF with hyponatremia</td>
<td>...</td>
<td>Pending</td>
</tr>
</tbody>
</table>

LVEF indicates LV ejection fraction; BALANCE, Treatment of Hyponatremia Based on Lixivaptan in New York Heart Association Class III/IV Cardiac Patient Evaluation.

In these patients, tolvaptan at all doses was associated with normalization of the mean serum sodium levels in the treated patients for the entire duration of the study period in the absence of fluid restriction, although in this study the effect of tolvaptan on hyponatremia was not a primary study objective. Normalization of hyponatremia occurred in 82% of the treated patients even on day 1 compared with only 40% of placebo-treated patients, with similar findings observed on day 25.38

In the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF) trial, which evaluated decompensated HF patients, 68 patients (21%) had hyponatremia (again defined as sodium level <136 mEq/L) at randomization. Serum sodium concentrations were observed to rise and often normalize in this cohort.53 Of interest, among these patients admitted to hospital with decompensated HF, those with hyponatremia had a very high mortality rate at 60 days.

In a subgroup analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, ~8% of enrolled patients with decompensated HF had significant hyponatremia, defined as serum sodium <134 mEq/L. In these hyponatremic patients, serum sodium increased 5.5 mEq/L in the tolvaptan-treated patients compared with an increase of 1.8 mEq/L in the placebo-treated patients, and the improvement in the tolvaptan-treated patients was maintained throughout the long-term course of therapy.54 However, as with the larger cohort, no mortality outcome benefit in this subgroup and no association of improved hyponatremia with better outcomes were seen.

The published trials38,53–55 (Table 5) demonstrate the benefit of vasopressin antagonists in terms of raising or normalizing sodium levels in hyponatremic HF patients, most performed even without fluid restriction. In 1 trial that compared fluid restriction and tolvaptan, a significant improvement in hyponatremia with tolvaptan was demonstrated.49

The use of vasopressin antagonists, addressing both the pathophysiological state of hyponatremia and the volume-overload state simultaneously, could become an important approach in this clinical setting for this challenging group of patients.

Decompensated HF

In the ACTIV in CHF trial, 3 oral, once-daily doses of tolvaptan (30, 60, or 90 mg) or placebo were administered to patients hospitalized with acute decompensated HF.53 Body weight decreased significantly from baseline in all tolvaptan-treated groups on day 1 after admission (a primary end point) compared with placebo and decreased further during the course of hospitalization. This effect was not dose dependent. Similarly, urine volume on day 1 was significantly higher in all groups treated with tolvaptan than in those treated with placebo.

No significant differences were observed in rates of rehospitalization over the 60-day follow-up period, although a trend toward greater survival was found in the tolvaptan groups compared with placebo. In posthoc subgroup analyses, patients with elevated blood urea nitrogen and those with multiple signs of congestion who were treated with tolvaptan experienced lower mortality rates out to 60 days. Although this study was not sufficiently powered nor designed to assess
mortality, the results were provocative and supported the performance of a fully powered trial to assess these findings prospectively.

The EVEREST program evaluated short- and long-term end points among patients being admitted for acute decompensated HF, randomized to treatment with tolvaptan 30 mg daily in addition to routine standard care (including diuretics) or to placebo plus standard care.56 and followed up on continuing treatment with an assigned study drug after hospital discharge.54 The trial was structured so that the main trial incorporated 2 short-term trials of symptom assessment for the hospitalization period, whereas long-term morbidity and mortality outcome end points were assessed in the well-powered main trial over the longer follow-up period.57 The trial population sample size (ultimately 4133 patients) and duration of follow-up were event driven.

In the short-term trials, the primary end point was a composite of patient-assessed global clinical status (assessed as a visual analog score) and body weight reduction, both assessed at day 7 after randomization or at the time of discharge if earlier. This primary end point was positive in favor of treatment with tolvaptan, driven by the reductions in body weight beyond that achieved with standard therapy alone and not by changes in global clinical status because the scores were almost identical between the groups.

Numerous other secondary end points such as change in patient-assessed dyspnea at multiple time points were positively affected during tolvaptan treatment.56 On day 1, dyspnea improvement was reported, with the tolvaptan group improving 77% compared with 71% in the placebo in trial A and 72% versus 65% in trial B. Although these differences are modest, it is important to note that the changes were seen with study drug given in addition to all standard therapy.

The long-term follow-up trial was powered to assess coprimary end points of all-cause mortality (for either superiority or noninferiority) and cardiovascular death or HF hospitalization (for superiority). Over a median of 9.9 months of follow-up, no effect (neither favorable nor unfavorable) of tolvaptan was found compared with placebo without a significant change in cardiac index, pulmonary artery pressures, systemic or pulmonary vascular resistance, systemic arterial pressure, or heart rate. Urine output in the conivaptan-treated group was significantly increased in postdischarge body weight and improved serum sodium levels in hyponatremic patients.54 No excess adverse effects on renal function, heart rate, blood pressure, and serum potassium were reported.

Both groups were on optimal medical therapy for HF, yet some benefit was observed in signs and symptoms of HF without the increased risks that can occur with some treatments for acute HF. Thus, although not ultimately affecting natural history after admission for decompensated HF in a favorable way, the long-term EVEREST follow-up has provided substantial safety information to guide clinicians’ potential treatment strategy for use in improving symptomatology.

Hence, the EVEREST data suggest that vasopressin antagonism in the setting of decompensated HF has potential benefit, including decreasing body weight by increasing urine output associated with improvement in dyspnea, without fostering abnormalities in electrolytes or renal function (as can be seen with more aggressive loop diuretic therapy) and normalizing serum sodium concentration in hyponatremic patients.

The intravenous form of conivaptan as a several-day infusion also has undergone investigation for potential use in acute decompensated HF. A dose-ranging pilot study assessing the efficacy and safety of intravenous conivaptan in patients with acute decompensated HF found that conivaptan significantly increased urine output, was hemodynamically well tolerated, and had minimal excess adverse effects. However, no apparent significant change in respiratory symptoms or body weight was found.58

Data on the use of vasopressin antagonism in the setting of acute decompensated HF (see Table 6)53,54,58 suggest that the reductions in body weight, increases in urine output incremental to that resulting from standard therapy, and potentially more rapid improvement in symptoms can be achieved safely. The trials in this area, particularly EVEREST, also highlight the challenges inherent in studying this syndrome. This trial was designed as a “one size fits all” approach with a fixed-dose protocol, although in clinical practice such an agent would likely be titrated on the basis of clinical effects. Moreover, a new treatment strategy must be compared with “standard therapy,” ie, intravenous loop diuretics and other therapies, which are generally effective, so end points must be measured against a clinical background that is dynamic and usually improving with standard therapy, as seen in the placebo groups in trials such as Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) and again in EVEREST.54,59 Symptom-based end points such as dyspnea are highly subjective and incorporate substantial variability in their measurement scales. In designing trials in this area, researchers must account for this variability and the effects of standard therapy when designing the analysis and calculating sample sizes.

A sign such as change in body weight, although accepted by clinicians, is not yet on solid regulatory footing by itself as a basis for approval of a new agent for this syndrome. Thus, in EVEREST, change in body weight was a component of a composite, along with a patient-assessed symptom end point. Significant lessons have been learned from trials in this area, including EVEREST, to inform the design of future studies.

**Hemodynamics and Remodeling in Chronic HF**

In a study of 142 patients with advanced HF with systolic dysfunction, conivaptan was administered as a single intravenous dose (10, 20, or 40 mg) and compared with placebo.22 Pulmonary capillary wedge pressure was reduced, although modestly, and right atrial pressure was significantly reduced after drug administration in the 20- and 40-mg conivaptan groups compared with placebo without a significant change in cardiac index, pulmonary artery pressures, systemic or pulmonary vascular resistance, systemic arterial pressure, or heart rate. Urine output in the conivaptan-treated group demonstrated a dose-dependent increase that peaked 2 to 3 hours after dosing. Urine osmolality was significantly reduced by all doses of conivaptan. Of interest, no correlation could be established between conivaptan effects and baseline vasopressin or serum sodium levels.
Similar hemodynamic and urine output data have recently been presented in a dose-ranging, singe-dose administration study of tolvaptan\textsuperscript{35} in which modest reductions in wedge pressure and dose-dependent increases in urine output were observed. This increase in aquaresis may have been facilitated by the increase in serum osmolality seen in this study.

The data from these studies suggest that vasopressin receptor antagonism in patients with stable advanced HF (see Table 7)\textsuperscript{23,60–62} has favorable hemodynamic effects (with initial dosing), possibly mediated via increased urine output. The generally similar results noted for hemodynamics and urine output with single-dose studies of both conivaptan and tolvaptan suggest that the predominant effect of vasopressin receptor antagonism in these studies involves effects at the V2 receptor.

A preliminary study of oral conivaptan treatment for several months that examined the effects on exercise tolerance and functional capacity in stable HF patients demonstrated neutral results.\textsuperscript{60} Thus, the role of these agents in affecting clinical symptoms in patients with initially stable HF is uncertain at this time.

The effect of vasopressin receptor antagonism with tolvaptan on LV remodeling was evaluated in the Multicenter Evaluation of Tolvaptan Effect on Remodeling (METEOR) trial in 240 patients with chronic HF and systolic dysfunction and signs of volume excess.\textsuperscript{23} In this patient sample with very high use of evidence-based background HF therapies (>90% use of both angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as well as β-blockers), the primary end point, mean LV end-diastolic volume index (by quantitative radionuclide ventriculography), was unchanged over 1 year of follow-up in the tolvaptan-treated group compared with the placebo group. Although the results of the METEOR trial established that vasopressin antagonism (with a V2 receptor–specific agent) had no incremental benefit on remodeling over 1 year of therapy, the data indirectly addressed a potential issue with regard to long-term treatment. It had been suggested that long-term treatment with an agent more specific for the V2 vasopressin receptor may have unfavorable effects resulting from the unopposed vasopressin V1 receptor stimulation because vasopressin levels may rise during receptor antagonist therapy.\textsuperscript{63} The absence of any unfavorable effect on remodeling during long-term V2 receptor antagonist in the METEOR trial and the safety data accumulated in the EVEREST study suggest that if any such unfavorable effects exist, that they are not easily measurable.

In patients with stable chronic HF, highly specific V2 receptor antagonist with lixivaptan has been studied in a dose-ranging trial. Dose-dependent increases in urine output, solute-free water clearance, and serum sodium concentration have been demonstrated in a preliminary study of single doses of 10, 30, 75, 150, 250, and 400 mg lixivaptan administered to patients with New York Heart Association class II and III HF.\textsuperscript{54} End points were measured after 4 hours of fluid restriction followed by another 20 hours of liberal fluid intake. Significant dose-related increases in urinary flow were observed after 4 hours for all doses of lixivaptan compared with placebo. Clinical data on chronic HF management are limited to this small study for lixivaptan, and data from trials using conivaptan have not been published.

### Table 6. Vasopressin Receptor Antagonists in Decompensated HF: Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>n</th>
<th>Design</th>
<th>Drug</th>
<th>Inclusion/Exclusion Criteria</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
</table>
| ACTIV in HF\textsuperscript{33} | 319 | Multicenter, placebo controlled, double blind (30, 60, or 90 mg orally daily up to 60 d) | Tolvaptan | Decompensated HF patients with LVEF \(

\leq 40\%\) and 2 clinical signs of volume overload | Body weight; urine volume (day 1) | Decrease in body weight; increase in urine volume; no change in BUN, Cr, K |
| EVEREST\textsuperscript{54}   | 4133| Multicenter, placebo controlled, double blind, single dose (30 mg orally daily for a minimum of 60 d) | Tolvaptan | Decompensated HF patients with LVEF \(\leq 40\%\) | Short-term trials: composite of GCS and change in body weight at day 7 or discharge | Favorable effect on composite, driven by body weight change |
| Goldsmith et al\textsuperscript{58} | 162 | Placebo controlled, double blind (20 mg IV loading dose followed by 40, 80, or 120 mg/d for 2 d) | Conivaptan | Decompensated HF | Urine volume, body weight, visual analog score (respiratory symptoms) | Increase in urine volume; decrease in body weight; no change in clinical status |

LVEF indicates LV ejection fraction; BUN, serum urea nitrogen levels; Cr, creatinine; GCS, global clinical score assessed by the patient; ACM, all-cause mortality; and CV, cardiovascular.
Given the consistent increases in urine output seen with all agents in this class, it could be postulated that the administration of vasopressin receptor antagonists might allow “sparing” of loop diuretic dose. This concept was evaluated in a preliminary study in which patients with chronic HF and signs of congestion were withdrawn from background diuretic therapy, salt restricted, and randomized to short-term treatment with tolvaptan as monotherapy (30 mg/d), furosemide monotherapy (80 mg/d), or a combination for 7 days.61 Tolvaptan-treated patients demonstrated a significant decline in body weight and increase in urine output compared with furosemide alone without altering serum potassium. Results of studies such as this must be interpreted keeping in mind that furosemide lasts only ~6 hours; thus, once-daily diuretic dosing leaves ~18 hours per day of compensation for sodium and water loss in the first 6 hours. However, these preliminary data suggest that vasopressin receptor antagonism in HF patients who are stable on once-daily furosemide dosing may allow reduction or even discontinuation of loop diuretics in some cases, a finding that should be evaluated in future studies.

**Effects on Renal Function**

In contrast to the administration of loop diuretics, antagonism of vasopressin receptors appears not to increase activation of the renin-angiotensin-aldosterone system, and the increase in urine output without changes in systemic vascular resistance and cardiac output observed in the short-term studies suggests that volume reduction may be achieved with less effect on renal function than seen with loop diuretics. In many studies of patients with decompensated HF, higher-dose loop diuretic therapy is associated with unfavorable outcomes, as is worsening renal function during the course of therapy.64,65

One possible explanation for why the neurohormonal axis is apparently activated less53,61 with V2 receptor antagonists than loop diuretics despite the same volume of urine losses is that extracellular fluid is depleted less. With V2 receptor antagonists, solute-free urinary losses come from intracellular fluid (two thirds) and extracellular fluid (one third), whereas sodium loss from furosemide is exclusively via extracellular fluid. Thus, the impact on extracellular fluid is significantly greater with loop diuretic use, which in turn has greater potential effects on the renin-angiotensin-aldosterone system.

In an open-label, randomized, placebo-controlled, single-dose crossover study in patients with mild to moderate chronic HF designed to assess the effects of tolvaptan and furosemide on renal function and renal hemodynamics,62 tolvaptan was found to increase urine output and renal blood flow. In comparison, furosemide increased urinary output to a comparable degree but at the expense of electrolyte excretion (urinary sodium and potassium) and renal blood flow. Tolvaptan, furosemide, and placebo did not differ in respect to mean arterial pressure, glomerular filtration rate, or serum sodium and potassium.62 In EVEREST, at day 7 or day of discharge, a very slight but significantly higher serum creatinine level but a lower serum urea nitrogen level was found in the tolvaptan compared with the placebo group. This difference was observed at many long-term follow-up points through 56 weeks after discharge.54

In published studies to date,54,56 no significant adverse effects on renal function or electrolyte status have been noted. All of these results support the possibility that vasopressin receptor antagonism may be associated with preserved renal function.
function in HF patients while promoting volume loss and relief of congestion.

**Adverse Effects**

Vasopressin antagonists used in the published trials have generally been well tolerated. An increase in thirst and dry mouth has consistently been reported in patients treated with vasopressin antagonists compared with placebo. In EVEREST, no difference was observed in major adverse events between the 2 randomized groups. Among numerous side effects and safety parameters examined in EVEREST, the largest database, a small but significant apparent increase in the risk of reported stroke was found, plus a small but significant reduction in the risk of reported myocardial infarction of similar magnitude. Hypotension has not occurred in excess relative to placebo. Hypokalemia was seen during long-term treatment in 8% of patients in EVEREST treated with tolvaptan and in 9.8% of placebo-treated patients, whereas hypernatremia occurred in 1.7% of tolvaptan-treated patients compared with 0.5% of placebo-treated patients. It has been a general finding in the vasopressin antagonist studies that serum sodium in normonatremic patients may rise \(3\) mEq/L during initial therapy and then return to baseline after several days.

Thus, substantial published data, especially with V2 receptor antagonism as reported in EVEREST, have established a safety profile for this treatment approach.

**Future Directions**

Other potential clinical uses for vasopressin antagonists are currently being explored, one of which is treatment for patients with polycystic kidney disease because vasopressin V2 receptors have been implicated in the pathogenesis of cyst formation and enlargement in polycystic kidney disease. Tolvaptan is being evaluated in a multicenter trial in patients with autosomal-dominant polycystic kidney disease that is examining the rate of renal volume change.

Many unanswered questions remain on the potential use of vasopressin antagonists with regard to HF. Such questions include the potential efficacy of longer-term treatment with nonselective receptor antagonism, the use in volume overload associated with HF in the setting of preserved ejection fraction with a nondilated ventricle, the impact of potential sparing of loop diuretic dosing, the duration of therapy in terms of need for short-term versus longer-term treatment, and dose-adjustment strategies.

**Conclusions**

Despite advances in neurohormonal antagonist therapies, HF patients continue to progress to more advanced stages of the HF syndrome, continue to be hospitalized for decompensation, and die at an unacceptable rate. This has spurred translational and clinical investigation into blockade of additional neurohormonal systems. Somewhat unexpectedly, many contemporary neurohormonal antagonist trials investigating approaches such as endothelin receptor blockade and cytokine inhibition have shown neutral or unfavorable results. In this light, the “vaptan” class of vasopressin receptor antagonists has shown promising results for the treatment of hyponatremia, for decompensated HF, and for HF complicated by hyponatremia. Improvement in serum sodium in patients with hyponatremia of several causes has consistently been documented with an acceptable safety profile. At the time of this writing, intravenous conivaptan has been approved by the US Food and Drug Administration for the short-term treatment of euvoletic or hypovolemic hyponatremia. In HF, consistent increases in urine output, a reduction in body weight, and an improvement in many signs and symptoms have been seen without unfavorable changes in blood pressure, heart rate, electrolytes, or renal function. Pivotal trials of oral tolvaptan in the setting of decompensated HF and hyponatremia have been completed, and pivotal trials of lixivaptan for hyponatremia of multiple causes and HF complicated by hyponatremia are underway. Treatment of polycystic kidney disease also is being evaluated.

Thus far, therapeutic use of vasopressin antagonists has safely and effectively been shown to reduce body weight in decompensated HF and to normalize sodium levels in hyponatremic patients. In HF, an ideal agent would improve both symptoms and long-term outcomes, and from this perspective, the neutral long-term outcome effects of tolvaptan can be thought of as disappointing. Nevertheless, the data from EVEREST, SAL-T-1, and SAL-T-2 plus the conivaptan data suggest that vasopressin antagonism may become a useful tool for clinicians in specific situations such as decompensated HF with volume overload and is potentially an important therapy in setting of HF with hyponatremia and for hyponatremia of any cause when improvement in serum sodium is a clinical goal.

**Disclosures**

Drs Konstam and Udelson have received consulting income and research support from Otsuka Pharmaceutical Development and Commercialization Inc and from Cardiokine Inc. Dr Udelson has received consulting income from Astellas. Dr Finley reports no conflicts.

**References**


Arginine Vasopressin Antagonists for the Treatment of Heart Failure and Hyponatremia
John J. Finley IV, Marvin A. Konstam and James E. Udelson

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/content/119/21/e552.full.pdf

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In the article by Finley et al, “Arginine Vasopressin Antagonists for the Treatment of Heart Failure and Hyponatremia,” which appeared in the July 22, 2008, issue of the journal (Circulation. 2008;118:410–421), the following corrections should be made:

In tables 5 and 6, the n number of patients in the EVEREST trial should be 4133, as correctly reported in the text, not 4113.

In the second paragraph on page 414, the reference after the line “In a double-blind study conducted in 254 stable chronic HF patients (regardless of LV ejection fraction), 3 oral doses of tolvaptan (30 mg, 45 mg, or 60 mg) given daily for 25 days were compared with placebo administration” should be reference number 38, not 53.

In paragraph 3 of the section, “Effects on Renal Function” on page 418, the statement relative to tolvaptan’s effects on glomerular filtration rate is incorrect. The passage should read, “In an open-label, randomized, placebo-controlled, single-dose crossover study in patients with mild to moderate chronic HF designed to assess the effects of tolvaptan and furosemide on renal function and renal hemodynamics, 62 tolvaptan was found to increase urine output and renal blood flow. In comparison, furosemide increased urine output to a comparable degree but at the expense of electrolyte excretion (urinary sodium and potassium) and renal blood flow. Tolvaptan, furosemide, and placebo did not differ in respect to mean arterial pressure, glomerular filtration rate, or serum sodium and potassium 62.”

In the Tables of clinical trial results, randomized, placebo-controlled, phase II trials that studied conivaptan in patients with euvolemic or hyponatremia were omitted. The study published by Ghali et al (Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long LA, Smith N. Efficacy and safety of oral conivaptan: a V1a/V2 vasopressin receptor antagonist assessed in a randomized, placebo-controlled trial in patient with euvolemic or hyponatremia. J Clin Endocrinol Metab. 2006;91:2145–2152) should have been included in Table 4.

These changes have been made to the current online version of the article. The authors regret these errors.

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