Vasopressin-receptor antagonists in heart failure

Teresa A. Schweiger and Martin M. Zdanowicz

Purpose. The role of arginine vasopressin in heart failure and the use of vasopressin receptor antagonists in the treatment of heart failure are reviewed.

Summary. Arginine vasopressin (AVP) functions in the regulation of plasma osmolarity and blood pressure. In heart failure, AVP worsens heart failure by causing vasoconstriction of arteries and veins, potentially contributing to remodeling of the left ventricle and causing fluid retention and worsening of hyponatremia. Two V2-receptor antagonists, tolvaptan and lixivaptan, and one combined V1a- and V2-receptor antagonist, conivaptan, have shown promise for use in patients with heart failure. All three agents have been shown to increase free water excretion and increase serum sodium levels while maintaining serum potassium levels. They have not been shown to decrease renal function or the glomerular filtration rate and are well tolerated, with thirst being the major adverse effect during clinical trials. Because of their effects on sodium, vasopressin antagonists need to be carefully monitored to ensure that serum sodium levels do not increase too quickly and put the patient at risk for overcorrection or osmotic demyelination syndrome. In addition, patients need to be monitored for signs of dehydration secondary to increased urine excretion. To date, studies have not consistently shown improvements in patient symptoms or weight reduction. However, early data suggest that at least one agent, tolvaptan, does not alter mortality.

Conclusion. Based on data from available clinical trials, vasopressin antagonists may offer a new treatment option for patients with congestive heart failure. However, these agents do not currently appear to delay the progression of heart failure or decrease mortality.

Index terms: Cardiac drugs; Conivaptan; Heart failure; Lixivaptan; Mechanism of action; Tolvaptan; Toxicity; Vasopressin antagonists

Heart failure results from the inability of the heart to pump enough blood to meet the oxygen demands of the rest of the body. It is one of the most common medical diagnoses in the United States. Heart failure can be classified as secondary to diastolic or systolic dysfunction. Diastolic dysfunction is usually characterized by a heart ventricle’s inability to fill properly. Systolic dysfunction is caused by a decrease in myocardial contraction and usually a decrease in left ventricular ejection fraction (LVEF). It is estimated that the prevalence of heart failure in the United States is 5.2 million and that at the age of 40, 20% of Americans will be at risk for developing congestive heart failure (CHF). Coronary artery disease, hypertension, and diabetes are considered risk factors for heart failure. Hypertension precedes the diagnosis of heart failure in 75% of patients.

Heart failure is one of the most costly diseases in the United States both in dollars and deaths. The direct and indirect costs of the disease were an estimated $33.2 billion in 2007. Hospital discharges secondary to heart failure increased 175% between 1979 and 2004. Nearly 290,000 patients died in 2003 with heart failure as the underlying cause of or contributor to death. Further, heart failure is the most common reason for hospitalizations in Medicare beneficiaries.

Heart failure may be further classified as systolic heart failure and diastolic heart failure. Systolic heart failure is characterized by contractile dysfunction of the left ventricle and is the most common type of symptomatic heart failure. Patients with diastolic heart failure have preserved left ventricular systolic function but impaired ventricular relaxation, ventricular filling, or both. As car-
Cardiac output begins to decrease as a result of heart failure, a number of physiological compensatory mechanisms become active (Figure 1). The compensatory mechanisms include increased stroke volume (via the Frank-Starling mechanism), activation of both the sympathetic nervous system and renin–angiotensin system, and pathological cardiac remodeling. These compensatory mechanisms may initially appear helpful since they can delay the appearance of overt symptoms of heart failure; however, the increased workload they place on the failing heart will eventually worsen overall function and hasten cardiac failure. A number of therapeutic interventions used to treat heart failure are targeted at blunting the detrimental effects of these compensatory mechanisms.

Many treatments have been beneficial in the treatment of chronic heart failure. Unloading of high-pressure baroreceptors (blue circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (black) that stimulate cardio regulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (green). The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thus activating the renin–angiotensin–aldosterone system. Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constrains blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The blue lines designate circulating hormones. Reproduced, with permission, from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999; 341:577-85. Copyright © 1999, Massachusetts Medical Society.

**Figure 1.** The pathophysiology of heart failure. Unloading of high-pressure baroreceptors (blue circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (black) that stimulate cardio regulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (green). The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thus activating the renin–angiotensin–aldosterone system. Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constrains blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The blue lines designate circulating hormones. Reproduced, with permission, from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999; 341:577-85. Copyright © 1999, Massachusetts Medical Society.
heart failure including β-blockers, angiotensin-converting-enzyme (ACE) inhibitors, and aldosterone antagonists. However, heart failure continues to progress for many patients, who often require treatment for multiple episodes of acute decompensation (typically characterized by severe shortness of breath secondary to fluid overload and congestion).

Despite the number of medications available, including vasodilators and inotropes, loop diuretics remain the mainstay of therapy in acute decompensated heart failure for symptom and fluid management. While effective for fluid management, loop diuretics have not been shown to alter disease progression or improve survival in heart failure patients. Loop diuretics do decrease preload and cause natriuresis, which generally increases urine output and decreases edema and congestion. Loop diuretics, however, are not without risks. Electrolyte imbalance, especially hypokalemia and hypomagnesemia, can occur. Loop diuretics can also worsen hyponatremia, a very common condition in patients with severe heart failure that has been associated with increased rehospitalizations and mortality in these patients. In addition, loop diuretics decrease intravascular blood volume and can potentially worsen renal function by decreasing renal blood flow. Decreased renal perfusion leads to activation of the renin–angiotensin–aldosterone system and further worsening of heart failure. Renal failure in heart failure patients has also been associated with increases in mortality.

An ideal agent for the treatment of volume overload in heart failure would cause aquaresis without the complications associated with loop diuretics. In addition, an ideal agent would also maintain normal electrolyte levels, including serum sodium levels, and would not alter renal function. Arginine vasopressin (AVP) receptor antagonists may potentially be the agents to do this.

**Physiological actions of AVP**

AVP is also known as antidiuretic hormone. It is a nine amino-acid peptide hormone synthesized within the supraoptic and paraventricular nuclei of the hypothalamus. Structurally, AVP closely resembles oxytocin, which is produced in the same region of the hypothalamus but has very different physiological actions. Once synthesized in the hypothalamus, AVP is transported down nerve tracts running through the infundibulum and to nerve terminals in the posterior pituitary, from which it is released into circulation.

The major physiological actions of AVP include regulation of plasma osmolarity and blood pressure (Figure 2). A change in blood osmolarity is one of the key regulators of AVP release. When plasma osmolarity is in the normal range (approximately 280 mOsm/kg), plasma levels of AVP are low or undetectable. When plasma osmolarity begins to increase, osmoreceptors in the hypothalamus (near the region where AVP is produced) are activated. The activation of these osmoreceptors triggers the activation of neurosecretory cells involved in AVP synthesis and release. An increase of only 1% in plasma osmolarity leads to an increase in AVP release. The osmoreceptors involved in regulating AVP release are also extremely sensitive to changes in plasma sodium levels since the sodium ion contributes to the majority of osmotic activity of plasma.

Another factor affecting AVP synthesis and release is a change in blood pressure or blood volume. Baroreceptors located in the aortic arch, left atrium, and carotid sinus monitor blood pressure at strategic locations in the circulatory system. These baroreceptors send impulses back to the brain stem (via cranial nerves) and eventually to the hypothalamus. Decreases of 5–7% in mean arterial pressure and decreases of 8–10% in plasma volume are generally sufficient to trigger detectable increases in plasma AVP levels. Activation of the hypothalamus by osmoreceptors and baroreceptors also leads to increased

![Figure 2. Regulation of arginine vasopressin (AVP) release.](image-url)
thirst, which can drive increased fluid intake and thus help alleviate hyperosmolarity and hypovolemia. Changes in blood volume and serum sodium concentration may also stimulate the release of AVP through the activation of the renin–angiotensin system (Figure 3).

The mechanism by which AVP helps regulates serum osmolarity and blood volume centers on the ability to increase permeability of the distal renal tubules and collecting ducts to water. Increased resorption of water by the kidneys leads to an increased vascular volume, which decreases serum osmolarity and elevates blood pressure. AVP also exerts a constrictor effect on vascular smooth muscle, which can increase peripheral vascular resistance and blood pressure.

Several distinct AVP receptor subtypes have been identified (Table 1). The V$_2$ AVP receptor is found in the collecting ducts of the kidneys and mediates the effect of AVP on water resorption. The V$_2$ AVP receptor is a G$_s$-linked receptor whose activation leads to elevation in cellular cyclic adenosine monophosphate with subsequent increased expression and insertion of aquaporin-2 water channels in the distal renal tubules and collecting ducts. The V$_1$-receptor subtype a (V$_1$a) is found on vascular smooth muscle and mediates the vasoconstricting effects of AVP. The V$_1$a receptor is a G-protein-linked receptor that activates phospholipase C and increases the release of intracellular calcium. The V$_1$b receptor is also found on platelets and plays a role in platelet aggregation. The V$_1$-receptor subtype b (V$_1$b) is located on the anterior pituitary gland and is involved in regulating the release of ACTH and β-endorphins.

Role of AVP in heart failure

Two key physiological features of heart failure are fluid overload (due to reduced renal output) and increased peripheral resistance (caused by overactivation of the sympathetic nervous and renin–angiotensin systems). Since AVP release can potentially affect both of these factors, a considerable body of recent research has focused on the role of this peptide in heart failure. Normally, hyponatremia and low osmolarity will inhibit the release of AVP; however, in patients with heart failure, numerous studies have found increased plasma AVP levels despite the presence of excess fluid volume and decreased plasma sodium levels. This paradoxical effect on AVP levels in heart failure may be due to abnormalities in the normal feedback regulation of AVP release. It appears that the volume regulation (and thus baroreceptor regulation) of AVP release overrides the osmotic regulation (via osmoreceptors) of AVP in patients with heart failure. Baroreceptor response to heart failure appears to vary depending on the location of the baroreceptors involved. Baroreceptors in the carotid sinus detect a decrease in pressure (caused by reduced cardiac output), and those in the atrium detect an increase in pressure (caused by atrial overfilling). The

![Figure 3. Renin–angiotensin system. AVP = arginine vasopressin.](image-url)
carotid baroreceptors appear to be the predominant responders in heart failure since the ultimate outcome is increased AVP release.

Elevated AVP levels in heart failure lead to overactivation of \( V_1a \) receptors, resulting in increased water retention and hyponatremia. This increased fluid volume increases the workload on the failing heart and drives compensatory hypertrophy and pathological myocyte remodeling. The presence of hyponatremia in heart failure indicates a more severe stage of the disease process. Likewise, activation of \( V_{1a} \) receptors in response to elevated AVP levels further increases peripheral resistance and workload on the failing myocardium. The effects of elevated AVP levels in heart failure also potentiate the detrimental compensatory actions of the sympathetic nervous system and renin–angiotensin system, which are already overactivated in heart failure.

Mounting evidence also points to a key role for AVP in the pathological remodeling processes that occur in the myocardium of patients with heart failure.\(^{23-25}\) Both in vitro and animal studies have shown that AVP is capable of inducing structural changes and hypertrophy in cardiac myocytes.\(^{23-25}\) The development of AVP-induced hypertrophy appears to occur primarily through increased levels of intracellular calcium and protein kinase C. Activation of G-protein-linked \( V_{1a} \) receptors leads to the formation of the second messengers inositol-1,4,5-triphosphate and diacylglycerol, which causes elevations in the levels of cellular calcium and protein kinase C. Activated protein kinase C has been shown to mediate increased expression of specific growth-regulating genes, such as c-Fos in cultured cardiac myocytes, supporting the role of AVP in cardiac remodeling.\(^{23-25}\)

There are many potential clinical benefits of vasopressin antagonism in heart failure. Regardless of the mechanism by which AVP is elevated in heart failure, blockade of its effects on the renal tubules should blunt the retention of water and the subsequent hyponatremia that accompanies this condition. Vasopressin antagonism may also potentiate the beneficial effects of loop diuretics, which are mainstays in heart failure therapy. Although they are potent, loop diuretics can significantly deplete electrolytes, alter renal function, and affect neurohumoral regulation of blood pressure. Blockade of AVP effects can potentially reduce fluid accumulation without the adverse effects on renal function or electrolyte balance seen with loop diuretics. Blockade of AVP effects on systemic vascular resistance has a positive effect on left ventricular filling pressure, pulmonary capillary wedge pressure, and afterload. Accompanying reductions in cardiac workload due to the above effects should reduce the main cause of cardiac hypertrophy. Reduced cardiac workload coupled with the cellular and molecular effects of AVP blockade on myocyte protein synthesis, growth, and gene expression should also blunt the effects of this substance on pathological cardiac remodeling.

Clinical trials of AVP receptor antagonists

**\( V_{1a} \) antagonists.** Theoretically, \( V_{1a} \) antagonists would benefit patients with heart failure by promoting arterial vasodilation and potentially reducing left ventricular remodeling and failure.\(^{23}\) However, most \( V_{1a} \) antagonists studied to date have exhibited partial \( V_{1a} \) agonist effects in humans. One agent, relcovaptan, which is considered highly selective, has not been studied in any published human trials in chronic heart failure.\(^{25}\)

**\( V_2 \) antagonists.** Tolvaptan. Several large studies have examined the effectiveness of tolvaptan, an oral \( V_2 \) antagonist, in heart failure and euvolemic hyponatremia.\(^{26-28}\) Phase III studies of both indications are ongoing.\(^{29}\) Tolvaptan has been shown to increase aquaresis without activating the renin–angiotensin system or worsening renal function.\(^{30}\)

Gheorghiade et al.\(^{31}\) enrolled 254 patients in a double-blind, placebo-controlled, multicenter study to examine the effects of adding tolvaptan to furosemide therapy in patients with CHF. Patients with CHF, regardless of LVEF, were eligible for inclusion in the study if they had CHF symptoms for 30 days accompanied by signs of volume overload and a stable dosage of oral furosemide for 7 days before study enrollment. Patients were followed for a total of 28 days: a 3-day run-in period and a 25-day treatment period. Patients also received standard CHF treatment. Patients were randomly assigned to receive 30, 45, or 60 mg of oral tolvaptan or placebo daily for 25 days as outpatients. The primary outcome of the study was assessment of body weight change from baseline to day 14 of treatment. Secondary outcomes included edema measurements, urine sodium excretion, urine osmolality, and urine volume. A total of 221 patients...
completed the study; 23 withdrew due to adverse effects. The most common reasons for study withdrawal were worsening CHF (n = 9), myocardial infarction (n = 3), and polyuria (n = 3). The number of patient withdrawals between treatment groups did not significantly differ. The percentage of hospitalizations for heart failure or the increase in medication secondary to worsening heart failure did not significantly differ between tolvaptan and placebo groups. Body weight decreased on day 1 in all tolvaptan-treated groups (mean ± S.D. change of –0.79 ± 0.99 kg, –0.96 ± 0.93 kg, and –0.84 ± 0.02 kg in the 30-, 40-, and 60-mg groups, respectively) (p < 0.001 for all groups versus placebo) and was maintained for the duration of the study. Patients who received placebo had an increase in body weight (mean ± S.D. change of 0.32 ± 0.46 kg). On the first day of treatment, urine volumes and the mean net fluid losses were greater in the tolvaptan groups (3.9 ± 0.6 L, 4.2 ± 0.9 L, 4.6 ± 0.4 L, and 2.3 ± 0.2 L in the 30-, 45-, and 60-mg groups and the placebo group, respectively) (p < 0.001 for all groups versus placebo) and was maintained throughout the study. In addition, improvement in ankle edema was seen in the tolvaptan-treated groups, but this improvement only reached statistical significance in the tolvaptan 45-mg daily group at all time points (p < 0.05 versus placebo). The most common adverse effects reported during tolvaptan therapy were dry mouth, thirst, and urinary frequency, as expected.

Tolvaptan was then studied in hospitalized patients with worsening heart failure in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase II, dose-ranging study. Patients were eligible for study inclusion if they were admitted to the hospital with worsening heart failure that did not improve after administration of standard therapy, had a ventricular ejection fraction of <40%, and showed evidence of systemic congestion. A total of 319 patients were randomized to receive 30, 60, or 90 mg daily of tolvaptan or placebo. Patients were evaluated as inpatients for up to 10 days and then for seven weeks as outpatients. The primary inpatient outcome, change in body weight, was evaluated 24 hours after the first dose of tolvaptan during hospitalization. The primary outpatient outcome was time to worsening of heart failure (i.e., death, hospitalization for heart failure, unscheduled visit due to heart failure requiring a change in drug therapy) and was evaluated for 60 days after randomization. Secondary outcomes included changes in CHF symptoms (dyspnea, jugular venous distension, rales, edema, and body weight), urine output during hospitalization, serum electrolyte levels, length of hospital stay after randomization, use of diuretics, and scores on patient- and physician-assessed symptom scales. All 319 randomized patients were included in the analysis of the inpatient primary endpoint, and 266 patients were included in the analysis of the outpatient primary endpoint. There was a decrease in body weight in all groups at 24 hours, including the placebo group. However, there was a significantly greater reduction in body weight in patients in the tolvaptan-treated groups compared with placebo (p < 0.05). This effect appeared to be independent of tolvaptan dosage. Urine volume was also significantly greater for all tolvaptan groups compared with placebo for the entire hospitalization period (p < 0.05). Dyspnea was the only symptom that improved significantly in patients receiving tolvaptan compared with placebo (p = 0.04). Global assessment scales and length of hospital stay did not significantly differ between treatment and placebo groups. The outpatient phase of the trial showed no difference in time to worsening of heart failure in either the treatment or placebo groups. Post hoc analysis revealed that patients with increased blood urea nitrogen (BUN) concentrations (>29 mg/dL) or severe systemic congestion and receiving tolvaptan had a lower total mortality rate compared with those patients with increased BUN levels or severe congestion receiving placebo. Of those patients with increased BUN levels in the tolvaptan group, 10% (10 of 100) died, compared with 23% (7 of 31) in the placebo group (p = 0.07). Six percent of patients in the tolvaptan group (6 of 108) with severe congestion died, compared with 18% of the placebo group (5 of 28) (p = 0.03). The most common adverse effect reported in the tolvaptan groups was thirst. Tolvaptan use was not associated with any increase in hypotension, worsening renal function, or hypokalemia. However, 128 patients withdrew from the study before completion; 68 (53%) did so because of adverse effects. The most common adverse effects were thirst, dry mouth, dizziness, nausea, and hypotension. The adverse ef-
fects that specifically caused patient withdrawals from the trial were not reported.

Udelson and colleagues reported the effects of tolvaptan, furosemide, and both drugs combined in patients with congestive heart failure. Eighty-three patients with New York Heart Association (NYHA) class II or III heart failure and signs of congestion were randomized to receive placebo, tolvaptan 30 mg daily, furosemide 80 mg orally daily, or both for seven days. Standard heart failure therapy was continued during the study. Body weight decreased significantly from baseline in the tolvaptan group (mean ± S.D. change of –1.37 ± 1.61 kg) and the tolvaptan plus furosemide group (mean ± S.D. change of –1.13 ± 1.49) (p < 0.01 for both comparisons). A mean ± S.D. decrease in weight of 0.54 ± 1.59 kg was observed in patients receiving furosemide, but the change was not statistically different from baseline. An increase in body weight was observed in the placebo group (mean ± S.D. change of 0.72 ± 2.42 kg). Mean ± S.D. urine output per 24 hours increased from baseline in all three treatment groups (2646 ± 1503 mL, 894 ± 853 mL, and 2585 ± 2119 mL in the tolvaptan group, furosemide group, and tolvaptan plus furosemide group, respectively) (p < 0.01 for all comparisons). Significant increases in urine production also were observed in the tolvaptan group (p < 0.01 versus baseline and p < 0.001 versus furosemide alone) and the furosemide plus tolvaptan group (p < 0.01 versus baseline and p < 0.001 versus furosemide alone) compared with that observed in patients receiving furosemide alone. Serum sodium levels increased to normal range in a greater number of patients receiving tolvaptan than those receiving placebo (p < 0.02) or furosemide alone (p < 0.01). No patients developed hypokalemia, hypotension, or decreased renal functioning. Patients receiving tolvaptan reported reduced congestive symptoms (leg edema, dyspnea, jugular venous pressure, rales, and hepatomegaly) compared with patients receiving placebo. The authors did not report whether this reduction in symptoms reached statistical significance.

In addition to increased urine output and decreased body weight, some evidence suggests that tolvaptan may protect against the decline in renal function compared with what is typically seen with loop diuretics in heart failure patients. An open-label, randomized, placebo-controlled, crossover study was conducted with 14 patients with NYHA class II or III heart failure and an ejection fraction of <40%. Diuretics, β-blockers, and ACE inhibitors were discontinued for eligible patients three days before study initiation until the end of the study (eight days later). The primary aim of the study was to assess the effects of tolvaptan and furosemide on renal function. Patients received one dose of placebo or tolvaptan 30 mg on day 1. On day 3, they received the other medication. On day 5, all patients received furosemide 80 mg. Urine excretion rates did not significantly differ between treatment groups. Tolvaptan did not alter neurohormonal concentrations of AVP, plasma renin, aldosterone, atrial and B-type natriuretic peptides, or norepinephrine. Furosemide did significantly increase plasma renin activity (p = 0.02) and norepinephrine (p = 0.005) compared with placebo. Furosemide significantly decreased renal blood flow (–12.6%, p < 0.001) and effective renal plasma flow (–7.4%, p < 0.001) compared with placebo. There were trends toward a decline in the glomerular filtration rate with furosemide and an increase in the glomerular filtration rate with tolvaptan; however, these changes were not statistically significant. Tolvaptan significantly improved renal blood flow (9.6%, p < 0.05) and effective renal plasma flow (9%, p < 0.05) and significantly decreased renal vascular resistance (–8.3%, p < 0.05) compared with placebo.

Tolvaptan’s effect on long-term progression of left ventricular dilation and remodeling in patients with heart failure was also assessed in a randomized, placebo-controlled trial. Patients with NYHA class II or III heart failure with documented ejection fraction values of ≤30% were eligible for study inclusion. Patients (n = 40) were randomized to receive tolvaptan 30 mg daily or placebo and followed for up to 54 weeks. Other heart failure therapies were continued. The primary outcome evaluated was change in left ventricular end-diastolic volume (LVEDV) over one year of treatment. Secondary outcomes included changes in left ventricular end-systolic volume (LVESV), ejection fraction, quality of life, and combined mortality and worsening of heart failure at one year. Quantitative radionuclide ventriculography (RVG) was performed at baseline and after one year of treatment to determine left ventricular volumes and ejection fractions. RVG was performed again after 54 weeks when patients had discontinued tolvaptan or placebo for 2 weeks. There was no significant difference in LVEDV, LVESV, ejection fraction, or quality of life between the tolvaptan and placebo groups after one year of treatment. In addition, there were no significant changes after treatment had been discontinued for 2 weeks. There was, however, a significant improvement with tolvaptan in the combined secondary endpoint of death or worsening of heart failure at one year (p = 0.027).

Until recently, most studies of vasopressin receptor antagonists in heart failure patients have relied on surrogate markers as their primary outcomes to prove their efficacy. However, the results of the EVEREST trial, a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of tolvaptan in heart failure and its ef-
fect on mortality, were recently made available. This trial included three parts: two short-term trials examining the efficacy of tolvaptan in patients admitted for acute decompensated heart failure and one long-term study evaluating tolvaptan’s effect on mortality. To be eligible for enrollment, adult patients with chronic heart failure must have had a LVEF of ≤40%, evidence of heart failure symptoms at rest or with minimum exertion, signs of congestion, and been admitted to the hospital for an exacerbation of chronic heart failure within 48 hours. Overall, 4133 patients were randomized to receive tolvaptan 30 mg daily or placebo for at least 60 days. Other heart failure treatments were implemented as ordered by the treating physician. The short-term trials’ primary endpoint was a composite of the change from baseline in a Kansas City Cardiomyopathy Questionnaire (KCCQ) score and body weight at day 7 (or discharge). Secondary short-term endpoints included patient-assessed change in dyspnea at day 1, change in the KCCQ score from baseline and day 7 (or discharge), and peripheral edema at day 7 (or discharge). There was a significant improvement in the short-term trials’ primary composite endpoint in the tolvaptan groups compared with patients receiving placebo (p < 0.001 for both short-term trials). There was no change at seven days in KCCQ scores in either of the tolvaptan or placebo groups in both short-term trials. Mean body weight reduction was significantly greater in the tolvaptan groups of both trials when compared with placebo (p < 0.001) at day 1 and day 7. Dyspnea was significantly less in the tolvaptan groups at day 1 compared with placebo (p < 0.001). There was an improvement seen in edema scores at day 7; however, the difference was not statistically significant. The long-term study then combined the patients enrolled in the two short-term trials into one trial examining long-term outcomes of tolvaptan after patients were discharged from the hospital. The long-term study had two primary outcomes that included time to first event, which included all-cause mortality, and the composite of cardiovascular death or hospitalization for heart failure. In addition, secondary endpoints included a composite of cardiovascular mortality or cardiovascular hospitalization, frequency of cardiovascular mortality, and frequency of clinical worsening of heart failure. Tertiary endpoints of the long-term trial included the change in KCCQ at outpatient weeks 1 and 24 and end of treatment. There was no difference in all-cause mortality in the trial. In addition, tolvaptan was considered noninferior to placebo. There was no difference in the composite endpoint of cardiovascular death or hospitalization for heart failure between the tolvaptan and placebo groups. The long-term secondary endpoints did not differ between the tolvaptan and placebo groups. The KCCQ overall summary score was significantly improved from baseline (p = 0.02) at the end of treatment. Adverse effects were common in both groups (89% in the tolvaptan group and 86.1% in the placebo group). As a result, 6.5% of patients in the tolvaptan group and 5.5% of patients in the placebo group discontinued the drug. Thirst and dry mouth were the only adverse effects that occurred significantly more often in the tolvaptan group than in the placebo group (p = 0.02).

Lixivaptan. Lixivaptan is another oral V2 receptor antagonist. Much of the data on lixivaptan show its benefits in the treatment of hyponatremia. Lixivaptan has been shown to increase serum sodium concentration, decrease urine osmolality, and significantly decrease body weight in patients with hyponatremia secondary to cirrhosis.10 Wong and colleagues11 studied lixivaptan’s effects on hyponatremia in patients with cirrhosis, conges-
to the placebo group. Urine volume, serum electrolyte levels, serum osmolality levels, serum creatinine values, urea nitrogen levels, and plasma neurohormone (renin, aldosterone, norepinephrine, endothelin-1, atrial natriuretic peptide) levels were measured at baseline and for 24 hours after drug administration. Urine volume increased significantly for lixivaptan doses greater than 10 mg ($p < 0.05$ versus placebo). Urine osmolality decreased significantly and free water secretion increased significantly in the lixivaptan groups ($p < 0.05$ for both comparisons versus placebo). There were no significant differences in urinary sodium, potassium, chloride, magnesium, or urea nitrogen excretion or serum chloride, magnesium, urea nitrogen, or potassium levels. Serum osmolality was significantly higher at lixivaptan dosages exceeding 75 mg ($p < 0.05$ versus placebo). Serum sodium levels increased significantly in patients receiving 150 and 250 mg of lixivaptan ($p < 0.05$ versus baseline). AVP levels were significantly higher in patients receiving $\geq 150$ mg of lixivaptan ($p < 0.05$ versus placebo). No difference in renal function was seen between treatment and control groups.

**Combined V$$_{1A}$- and V$$_2$-receptor antagonist: Conivaptan.** Conivaptan hydrochloride (Vaprisol, Astellas Pharma) is an i.v. V$$_{1A}$- and V$$_2$-receptor antagonist approved by the Food and Drug Administration in December 2005 for use in the treatment of euvolemic hyponatremia in hospitalized patients. There is a theoretical benefit to using an antagonist of V$$_{1A}$ and V$$_2$ in heart failure. Plasma AVP levels can increase during vasopressin receptor blockade, which can worsen heart failure symptoms, including fluid retention. If both V$$_{1A}$ and V$$_2$ receptors are blocked, the resultant increase in AVP levels may prevent any adverse outcome.

Conivaptan has demonstrated efficacy in the treatment of hyponatremia in patients with CHF. In patients with CHF, conivaptan (oral and i.v. continued for four to five days) increased serum sodium levels significantly compared with placebo without significantly increasing the rate of adverse effects.

In a randomized, prospective, placebo-controlled trial, the hemodynamic effects of conivaptan were studied in 142 patients with NYHA class III or IV heart failure. Eligibility criteria included a pulmonary capillary wedge pressure (PCWP) of $\geq 16$ mm Hg and a cardiac index of $\leq 2.8$ L/min/m$^2$ at baseline within 2 hours of study drug initiation. Patients were randomized to receive i.v. conivaptan hydrochloride 10, 20, or 40 mg or i.v. placebo. Hemodynamic values were measured over 12 hours. The primary endpoints were the peak change from baseline in PCWP at 3–6 hours after study drug initiation and area under the curve for the change from baseline PCWP over the 12-hour period after the drug was administered. In addition, peak change in cardiac index at 3–6 hours, systemic and pulmonary vascular resistance, right atrial pressure, and renal and electrolyte values were assessed. The peak change in PCWP and right atrial pressure at 3–6 hours was significantly decreased in the conivaptan hydrochloride 20- and 40-mg groups ($p < 0.05$ versus placebo). The decrease in PCWP remained below baseline for 12 hours. In addition, the areas under the curve for PCWP and right atrial pressure versus time were significantly smaller in these same groups ($p < 0.05$ for both comparisons versus placebo). A significant dose-dependent increase in urine output was seen with conivaptan ($\sim 11.3 \pm 17$ mL/hr, $88.9 \pm 17$ mL/hr, $152.2 \pm 19$ mL/hr, and $176.2 \pm 18$ mL/hr for placebo and conivaptan hydrochloride 10, 20, and 40 mg, respectively) ($p < 0.001$). Urine osmolality was significantly reduced in the conivaptan groups compared with patients receiving placebo ($p = 0.0001$). No difference was seen in cardiac index, pulmonary artery pressures, mean arterial pressure, systemic or pulmonary vascular resistance, heart rate, serum osmolality, or serum sodium or potassium levels between placebo and conivaptan groups. There was no significant difference in adverse effects between conivaptan and placebo groups; however, patients only received one dose of medication and were assessed for 12 hours.

Conivaptan effects on exercise tolerance and functional capacity were also studied in a 12-week, multicenter, double-blind, placebo-controlled study in chronic heart failure patients. Investigators assessed the change from baseline to week 12 in time to reach 70% of peak oxygen consumption (VO$_2$) during treadmill exercise testing. Changes in 70% and peak VO$_2$ total exercise time, anaerobic threshold, exercise time to anaerobic threshold, heart rate multiplied by systolic blood pressure at peak exercise, heart failure symptoms, and the Minnesota Living with Heart Failure Questionnaire score were also compared with baseline values. A total of 343 patients with NYHA class II–IV heart failure, an ejection fraction of $\leq 35\%$, and a peak VO$_2$ of $\leq 18$ and $> 7$ mL/min/kg during exercise testing were enrolled. Patients were randomized to receive conivaptan hydrochloride 10, 20, or 40 mg orally twice daily for 12 weeks. Conivaptan did not significantly change or improve any of the values measured compared with placebo. An equal number of adverse effects were seen between treatment and placebo groups; however, there were more severe adverse effects in the conivaptan groups (12.8% versus 4.3%).

The exact nature of the adverse effects was not reported. The authors concluded that their endpoint of exercise tolerance may not have been ideal for determining conivaptan’s efficacy and that endpoints related to volume status should be used in the future.
Goldsmith\textsuperscript{54} conducted a multicenter, randomized, double-blind, pilot study of conivaptan in patients hospitalized for acute decompensated heart failure. A total of 162 patients were randomized to conivaptan hydrochloride 40, 80, or 120 mg daily via continuous infusion for two days. Primary outcomes measured were the changes in severity of respiratory symptoms, total urine output, and body weight. Conivaptan significantly increased total urine volume output ($p < 0.016$ for all conivaptan groups versus placebo). Body weight did not significantly decrease in the conivaptan group compared with the placebo group. There was no difference in patients' assessment of severity of their respiratory symptoms measured using a visual analogue scale. The most common adverse reaction was infusion site related. Adverse reactions caused discontinuation of conivaptan in 8% of patients (10 of 122), compared with 2.5% in the placebo group (1 of 40).

Another randomized pilot study was completed with 24 patients with NYHA class II or III heart failure receiving conivaptan.\textsuperscript{55} Endpoints included free water excretion, change in urine volume, urine osmolality, total urine sodium level, total urine potassium level, and adverse effects. Patients received 40 or 80 mg daily of furosemide for six days, and then conivaptan hydrochloride 20 or 40 mg daily for three days was added to the regimen. Urine volume increased, urine osmolality decreased, and urine sodium and potassium levels decreased in most groups when compared with baseline. There were no serious adverse events or need to withdraw secondary to conivaptan use. This pilot study found that conivaptan increased free water excretion in heart failure patients while blunting the effects of furosemide on sodium and potassium excretion. More data are needed to establish conivaptan's benefit in heart failure, regardless of the patient's serum sodium level and presence of hyponatremia.

**Summary**

Based on a growing body of recent clinical trials, vasopressin antagonists show significant promise in the treatment of heart failure. These agents appear to cause adequate aquareasis while maintaining or increasing serum sodium levels. Unlike loop diuretics, vasopressin receptor antagonists exert beneficial effects on fluid volume in heart failure without causing hypokalemia or renal dysfunction. They appear to be well tolerated, with thirst being the main adverse effect reported during clinical trials. Because of their effects on sodium, vasopressin receptor antagonists need to be carefully monitored to ensure that serum sodium levels do not increase too quickly and put the patient at risk for overcorrection or osmotic demyelination syndrome. In addition, patients need to be monitored for signs of dehydration secondary to increased urine excretion. Vasopressin antagonists, specifically tolvaptan, appear to show benefit in the relief of symptoms in decompensated heart failure without affecting long-term mortality. Vasopressin antagonists may have a role in the management of acute heart failure in the future.

**Conclusion**

Based on data from available clinical trials, vasopressin antagonists may offer a new treatment option for patients with CHF. However, these agents do not currently appear to delay progression of heart failure or decrease mortality.

**References**

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