1. Introduction

The prevalence of heart failure has increased in the past several decades (1), and congestive heart failure has now emerged as a major public health hazard with grave implications. Rosamond et al. reported that 2.5% of the adult American population (approximately 5.3 million men and women) suffer from congestive heart failure, and the medical costs of heart failure in the United States are estimated at approximately $60 billion per year (2). Despite advanced medical care for patients with heart failure, the average 5-year survival is about 50% (3). Currently, various types of therapeutic agents are used for chronic heart failure as standard treatment, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, β-adrenoceptor blockers, digitalis glycosides, and inotropic agents (4). Unfortunately, they are not enough to reduce mortality. Furthermore, therapeutic options in acute decompensated heart failure have not changed significantly over the past several decades despite advances in the management of chronic heart failure. Therefore, the discovery of novel agents is needed for successful treatment of heart failure.

2. Vasopressin in heart failure

Arginine vasopressin (AVP) is secreted from the posterior pituitary in response to high plasma osmolality and hypotension. AVP has important roles in circulatory and water homeostasis, which are mediated by oxytocin receptors and by AVP receptor subtypes: V₁a (mainly vascular), V₁b (pituitary), and V₂ (renal). Vaptans are orally and intravenously active nonpeptide vasopressin-receptor antagonists. Recently, subtype-selective nonpeptide vasopressin-receptor agonists have been developed. A selective V₁a-receptor antagonist, relcovaptan, has shown initial positive results in the treatment of Raynaud’s disease, dysmenorrhea, and tocolysis. A selective V₁b-receptor antagonist, nelivaptan, has beneficial effects in the treatment of psychiatric disorders. Selective V₂-receptor antagonists including mozavaptan, lixivaptan, satavaptan, and tolvaptan induce highly hypotonic diuresis without substantially affecting the excretion of electrolytes. A nonselective V₁a/V₂-receptor antagonist, conivaptan, is used in the treatment for euvolemic or hypervolemic hyponatremia. Recent basic and clinical studies have shown that AVP-receptor antagonists, especially V₂-receptor antagonists, may have therapeutic potential for heart failure. This review presents current information about AVP and its antagonists.

**Keywords:** arginine vasopressin, diuretic, heart failure, vasopressin receptor antagonist
Three subtypes of AVP receptors have been identified so far, which belong to rhodopsin-like G-protein–coupled receptors (6). The role of each AVP receptor subtype in the pathogenesis of heart failure is shown in Fig. 1. The V1a receptor is found on vascular smooth muscle cells, hepatocytes, and platelets. Binding of AVP to the V1a receptor activates Gq/phospholipase C-β, which results in an increase in intracellular calcium levels and activation of protein kinase C (5, 7), leading to vasoconstriction, platelet aggregation, and growth of the smooth muscle cells.

The V2 receptor is mainly located on the basolateral membrane of the collecting ducts in the renal medulla (6). Binding of AVP to the V2 receptor activates adenylate cyclase via Gs protein, which leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) (7). Elevation of intracellular cAMP facilitates translocation of aquaporin (AQP) channels from intracellular vesicles to the apical plasma membrane through activation of protein kinase A, leading to an increase in water permeability (8).

The V1b (V3) receptor is found predominantly in the anterior pituitary, where it mediates adrenocorticotropic release. It is still unknown what role the V1b receptor plays in heart failure.

Previous studies have documented the presence of elevated AVP levels in patients with heart failure (9 – 10). In addition, an increase in AVP levels has been associated with increasing severity of heart failure (9). The increase in AVP levels results in impaired excretion of free water in patients with heart failure due to an increase in the number of AQP channels in the collecting duct (8). This results not only in abnormal water retention but also in hyponatremia (11). Water retention has detrimental effect in patients with heart failure because it leads to increased congestion, while hyponatremia is associated with increased mortality (12).

Intravenous infusion of AVP in patients with heart failure increases systemic vascular resistance and pulmonary capillary wedge pressure, while it decreases stroke volume and cardiac output. These changes were thought to result from AVP-induced vasoconstriction mediated by the V1a receptor because no association with alteration in blood pressure or heart rate was observed (13). Furthermore, stimulation of the V1a receptor is associated with the development of cardiac hypertrophy in experimental animal models (14). Thus, chronic AVP stimulation could promote cardiac remodeling similarly to other neurohormonal systems. Elevated AVP levels activate the V2 receptor, increase the expression of AQP channels, and cause water retention. As a result, preload and pulmonary capillary wedge pressure are increased.

3. Vasopressin-receptor antagonists in heart failure

Selective AVP V2-receptor antagonists induce hypotonic diuresis without substantially affecting the excretion of electrolytes. Tolvaptan and lixivaptan, V2-selective antagonists with K_iV2:K_iV1a binding affinities of 29:1 and 100:1 in human cells, respectively, have been extensively studied in clinical trials and experimental animal models of heart failure. A small, randomized, placebo-controlled, crossover study showed a similar urine output in stable patients with heart failure with preserved renal function who received single doses of a loop diuretic (furosemide, 80 mg) or tolvaptan (30 mg) (15). There was no difference in the glomerular filtration rate between the two agents, although furosemide
increased urinary sodium and potassium excretion and decreased renal blood flow. Several studies have reported the effects of AVP-receptor antagonists on human and animal heart failure (16–17).

3.1. Clinical trials (Table 1)

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial evaluated the short- and intermediate-term effects of tolvaptan in hospitalized patients with heart failure (18). In addition to the standard therapy, tolvaptan was administered to patients with the signs and symptoms of congestive heart failure and left ventricular ejection fraction of less than 40%. Compared with the standard-therapy group, the treatment group showed an increase in the net fluid loss resulting in decreased body weight. Although tolvaptan had no adverse effects such as changes in blood pressure, heart rate, or electrolytes, it did not improve the rate of worsening heart failure.

Table 1. Recent clinical trials using AVP antagonists in heart failure

<table>
<thead>
<tr>
<th>AVP antagonist</th>
<th>Design, Setting, and Participants</th>
<th>Effect</th>
<th>Reference No.</th>
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<tr>
<td>Tolvaptan (Oral)</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 trial conducted at 45 centers in the United States and Argentina and enrolling 319 patients with left ventricular ejection fraction of less than 40% and hospitalized for heart failure with persistent signs and symptoms of systemic congestion despite standard therapy.</td>
<td>· Increase in the net fluid loss, decrease in body weight, and improvement in the rate of worsening heart failure. · No adverse effects such as changes in blood pressure, heart rate, or electrolytes.</td>
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<td>Tolvaptan (Oral)</td>
<td>Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST). A total of 4133 patients hospitalized with heart failure and congestion were studied.</td>
<td>· Improvement in body weight, peripheral edema, and patient-assessed dyspnea. · No changes in morbidity or mortality.</td>
<td>19</td>
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<td>Tolvaptan (Oral)</td>
<td>A total of 181 patients with advanced heart failure on standard therapy were randomized to double-blind treatment with tolvaptan at a single oral dose (15, 30, or 60 mg) or placebo.</td>
<td>· Increase in urine output and serum sodium levels in a dose-dependent manner. · No changes in blood pressure, heart rate, systemic and pulmonary vascular resistance, or cardiac index.</td>
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<td>Tolvaptan (Oral)</td>
<td>Patients with heart failure, systolic dysfunction, and signs of congestion were removed from baseline diuretic therapy and placed on a low-sodium diet. After a 2-day run-in period, 83 patients were randomized to placebo (n = 21), monotherapy with tolvaptan 30 mg (n = 20), monotherapy with furosemide 80 mg (n = 22) or combination therapy with both agents (n = 20) once daily for 7 days.</td>
<td>· Reduction in body weight. Well tolerability. · No changes in serum electrolytes, other laboratory values, or blood pressure.</td>
<td>21</td>
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<td>Lixivaptan (Oral)</td>
<td>The effects of lixivaptan in 42 diuretic-requiring patients with mild-to-moderate heart failure in a randomized, double-blind, placebo-controlled, ascending single-dose study were examined. After overnight fluid deprivation, patients received single-blind placebo on day-1 and double-blind study medication (n = 12) or lixivaptan 10, 30, 75, 150, 250, or 400 mg (n = 5 per dose group) on day 1, followed by 4 h of continued fluid restriction and additional 20 h with ad libitum fluid intake.</td>
<td>· Increase in urine output in a dose-dependent manner. · Increase in serum sodium level at higher doses.</td>
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<td>Conivaptan (intravenous)</td>
<td>In a double-blind, multicenter trial, 170 patients hospitalized for worsening heart failure and given standard therapy were randomly assigned to treatment with conivaptan (20-mg loading dose followed by 2 successive 24 h continuous infusions of 40, 80, or 120 mg/day) or placebo.</td>
<td>· Improvement in urine output. Well tolerability. · No changes in vital signs, electrolyte disturbances, or cardiac rhythm.</td>
<td>23</td>
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The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) evaluated the short- and long-term effects of tolvaptan added to standard therapy within 48 h of hospital admission for heart failure (19). A 60-day treatment with tolvaptan, in addition to standard therapy with diuretics, improved numerous signs and symptoms of heart failure without any serious side effects. An improvement in body weight, peripheral edema, and patient-assessed dyspnea was observed on days 1 and 7 of tolvaptan treatment, but the primary outcome variable, mortality, was not affected.

The Effect of Tolvaptan on Hemodynamic Parameters in Subjects with Heart Failure (ECLIPSE) trial investigated the effect of tolvaptan on hemodynamic parameters in patients with heart failure (20), including symptomatic heart failure and decreased ejection fraction. Tolvaptan increased urine output and serum sodium levels in a dose-dependent manner. However, no significant differences were reported for the secondary endpoints of blood
pressure, heart rate, systemic and pulmonary vascular resistance, or cardiac index.

Patients with heart failure, systolic dysfunction and signs of congestion (e.g., edema, rales), were removed from baseline diuretic therapy and placed on a low-sodium diet. And then, they were randomized to placebo, monotherapy with tolvaptan, monotherapy with furosemide, or both tolvaptan and furosemide once daily for 7 days (21). Tolvaptan monotherapy without concomitant loop diuretic therapy reduced body weight when compared to placebo without adverse changes in serum electrolytes, during a sodium restricted diet while on background medications including angiotensin-converting enzyme inhibitors and β-blockers.

A small study of stable patients with mild-to-moderate heart failure that examined the renal effects of lixivaptan showed that it increased urinary output in a dose-dependent manner. The increase in urine volumes was accompanied by significant increases in solute-free water excretion, and serum sodium level was significantly increased at higher doses (22). These observations suggest that the lixivaptan may be a promising therapeutic agent for the treatment of heart failure.

Trials on conivaptan showed that it significantly increased urine output and decreased body weight. Conivaptan, a nonselective V$_{1a}$/V$_{2}$-receptor antagonist, is a combined V$_{1a}$- and V$_{2}$-receptor antagonist with V$_{2}$:V$_{1a}$ binding affinity of 10:1. However, it failed to improve the clinical status of patients (23).

### 3.2. Experimental animal models

The beneficial effects of AVP-receptor antagonists in the treatment of heart failure have been demonstrated in experimental animal models. In dogs with heart failure induced by rapid right ventricular pacing, oral administration of OPC-21268, a selective V$_{1}$-receptor antagonist, significantly improved cardiac output and renal function (24). On the other hand, mozavaptan, a selective V$_{2}$-receptor antagonist, increased urinary output, serum sodium levels, as well as plasma renin and vasopressin levels, although it did not improve hemodynamic parameters. In a similar dog model, tolvaptan induced aquarexis with an increase in free water clearance, resulting in a significant increase in serum sodium concentrations and a decrease in cumulative water balance. Furthermore, it decreased pulmonary capillary wedge pressure without affecting systemic vascular resistance, glomerular filtration rate, or renal blood flow and did not affect plasma renin activity (25). Thus, the V$_{2}$-receptor antagonists may offer a novel approach to remove excess water congestion in patients with heart failure.

Unfortunately, the above clinical trials did not show that a V$_{2}$-receptor antagonist, particularly tolvaptan, could improve cardiac function and mortality. Moreover, as most of the patients received concomitant medications, it is difficult to elucidate whether tolvaptan can independently improve the ejection fraction in patients with chronic heart failure.

Recently, several studies have been published on the effects of tolvaptan in rat models of heart failure. The diuretic effects of tolvaptan were compared with those of furosemide in rats with chronic heart failure after autoimmune myocarditis (26). Tolvaptan increased the plasma sodium concentration in a dose-dependent manner, while furosemide tended to decrease it. Importantly, plasma renin activity and aldosterone concentration were significantly increased by furosemide, while they were not affected by tolvaptan, suggesting that the latter has a potential benefit for the treatment of chronic heart failure with edematous conditions by removing excess water from the body without activating the renin-angiotensin-aldosterone system or causing serum electrolyte imbalance. In hypertensive rats with heart failure, chronic tolvaptan treatment had beneficial effects by preventing the progression of left ventricular dysfunction and renal injury (27). Furthermore, in rats with left ventricular dysfunction after myocardial infarction (MI), long-term tolvaptan therapy improved left ventricular ejection fraction and reduced MI-induced macrophage infiltration and interstitial fibrosis in the left ventricle. At the same time, tolvaptan was shown to attenuate MI-induced mRNA expression of atrial and brain natriuretic peptides, which are reliable markers of heart failure (28), as well as monocyte chemotactic protein-1, transforming growth factor-β1, and endothelin-1 in the marginal infarct region (29). Furthermore, a 2-week treatment with tolvaptan improved the left ventricular ejection fraction and suppressed MI-induced left ventricular interstitial fibrosis and mineralocorticoid receptor expression in rats with acute heart failure after MI (30). These observations suggest that tolvaptan may have beneficial effects both on acute and chronic heart failure, which is partially mediated by the suppression of neurohumoral activation, the renin–angiotensin–aldosterone system, and inflammation.

### 4. Conclusions

AVP causes water retention, through the V$_{2}$ receptor, to maintain the blood pressure. However, AVP is responsible for cardiac hypertrophy and fibrosis at later stages of heart failure. Therefore, the timing of the therapy with AVP antagonists may be particularly important. AVP-receptor antagonists are beneficial for the treatment of hypotension in the setting of congestive heart failure. However, these agents have not been shown to improve
short- or long-term morbidity or mortality in clinical studies. On the other hand, in experimental animal models of heart failure, AVP-receptor antagonists have been shown to prevent cardiac remodeling. One of the reasons for the discrepancy between clinical trials and basic studies is that most of the clinical studies have focused on the effects of AVP antagonists in patients with heart failure who had been taking other diuretics and thus the results are difficult to interpret. Therefore, further studies are required to directly compare the effects of standard diuretic therapy with those of AVP antagonists in the clinical setting.

Conflicts of Interest
None declared.

References
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