**Name of journal: World Journal of Cardiology**

**ESPS Manuscript NO: 4266**

**Columns: Review**

# Hyponatremia in patients with heart failure

Filippatos TD *et al*. Hyponatremia and heart failure

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**Received:** June 23, 2013 **Revised:** July 30, 2013

**Accepted:** August 16, 2013

**Published online:**

# Abstract

The present review analyses the mechanisms relating heart failure and hyponatremia, the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and presents treatment options focusing on the role of arginine vasopressin (AVP)-receptor antagonists. Hyponatremia is the most common electrolyte disorder in the clinical setting and in hospitalized patients. Patients with hyponatremia may have neurologic symptoms since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with major neurologic complications. Patients with heart failure often develop hyponatremia owing to the activation of many neurohormonal systems leading to decrease of sodium levels. A large number of clinical studies have associated hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure. Treatment options for hyponatremia in heart failure, such as water restriction or the use of hypertonic saline with loop diuretics, have limited efficacy. AVP-receptor antagonists increase effectively sodium levels and their use seems promising in patients with hyponatremia. However, the effects of AVP-receptor antagonists on hard outcomes in patients with heart failure and hyponatremia have not been thoroughly examined.

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**Key words**: Heart failure; Hyponatremia; Sodium; Vasopressin; Vasopressin-receptor antagonists; Tolvaptan; Conivaptan; Lixivaptan

**Core tip:** Patients with heart failure and hyponatremia have increased morbidity and mortality compared with subjects with normal sodium levels. Established treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. Arginine vasopressin (AVP)-receptor antagonists increase sodium levels and exhibit beneficial effects on hemodynamic variables in patients with heart failure. However, double-blind, placebo-controlled trials examining the effects of AVP-receptor antagonists on mortality, quality of life and length of hospital stay in patients with heart failure and hyponatremia are missing.

Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure.

**Available from: URL:**

**DOI:**

# INTRODUCTION

Hyponatremia is defined as a serum sodium concentration lower than 136 mmol/L[[1](#_ENREF_1)]. It is recognized as the most common electrolyte disorder both in the clinical setting and in hospitalized patients[[2](#_ENREF_2), [3](#_ENREF_3)]. The prevalence of hyponatremia in hospitalized patients varies depending on the sodium level used to define the condition and the patient population[[4-13](#_ENREF_4)]. Patients with hyponatremia may suffer major neurologic complications since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with increased morbidity and mortality[[14-18](#_ENREF_14)]. It should be mentioned that elderly women and subjects who also have hypokalemia are characterized by an increased risk for neurologic complications following rapid correction of hyponatremia[[19-24](#_ENREF_19)]. The mortality rates associated with hyponatremia range from 5% to 50% depending on severity and acuity of onset[[25](#_ENREF_25)].

Heart failure is a disabling and growing disease, associated with high morbidity and mortality rates and with annually increasing costs[[26-29](#_ENREF_26)]. Hyponatremia is often encountered in patients with heart failure[[30-33](#_ENREF_30)]. In a study of our group, 33.7% of patients with congestive heart failure had hyponatremia, which was the most common electrolyte abnormality in the study population[[34](#_ENREF_34)]. Aim of the present review is to present the mechanisms relating heart failure and hyponatremia, the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and to describe treatment options focusing on the role of arginine-vasopressin (AVP)-receptor antagonists.

A PubMed/Scopus search was performed up to June 2013 using combinations of “heart failure” with the following keywords: sodium, hyponatremia, vasopressin, aldosterone, diuretics, morbidity, mortality, hospital stay, water restriction, vaptans, vasopressin-receptor antagonists, tolvaptan, conivaptan, lixivaptan, electrolyte. Randomised controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

# MECHANISMS OF HYPONATREMIA IN PATIENTS WITH HEART FAILURE

## Neurohormonal mechanisms

Many factors are implicated in the pathogenesis of hyponatremia in patients with heart failure (Figure 1)[[6](#_ENREF_6)]. Heart failure reduces cardiac output and results in arterial underfilling, which induces the activation of the sympathetic nervous system (SNS). This leads to peripheral and renal vasoconstriction and decreases glomerular filtration rate, effects that combined with arterial underfilling result in increased reabsorption of sodium and water and induce the activation of the renin-angiotensin-aldosterone system (RAAS)[[31](#_ENREF_31), [32](#_ENREF_32), [35](#_ENREF_35)]. The subsequent increase of angiotensin II results in peripheral and renal vasoconstriction and induces aldosterone release from the adrenal gland causing further sodium retention[[36-43](#_ENREF_36)]. Arterial underfilling and the activation of both SNS and RAAS lead to increased release of AVP. Angiotensin II also stimulates the thirst center of the brain and increases water intake and the release of AVP[[44-46](#_ENREF_44)]. AVP binds to the vasopressin-2 (V2) receptor subtype and increases the number of aquaporin-2 water channels, leading to increased permeability of water in the collecting duct and enhanced free water retention[[47-50](#_ENREF_47)]. Aquaporin water channels consist of six membrane-spanning domains that form water channels within collecting duct membranes[[50-52](#_ENREF_50)].

In agreement with the above mechanisms patients with heart failure and hyponatremia have higher levels of plasma renin, angiotensin II, aldosterone, epinephrine, norepinephrine, and dopamine compared with patients with normal sodium levels[[40](#_ENREF_40), [53](#_ENREF_53), [54](#_ENREF_54)]. It has been shown that heart failure patients exhibit increased AVP production and generally a dysregulation of AVP characterised by an elevation of its levels despite the presence of volume overload, atrial distension and low plasma osmolality[[55-61](#_ENREF_55)]. Furthermore, the urinary excretion of aquaporin-2 is increased in heart failure patients with elevated AVP[[48](#_ENREF_48)]. Notably, the elevated plasma AVP levels are not appropriately reduced even with acute water loading in hyponatremic patients with advanced heart failure[[62](#_ENREF_62)]. These observations led to the hypothesis that hyponatremia may be a marker of neurohormonal activation that reflects the severity of heart failure[[63](#_ENREF_63)].

AVP plays an important role in the development of hyponatremia in heart failure but unfortunately it cannot reliably determined by the current laboratory methods. Copeptin, the C-terminal part of the AVP precursor peptide, is secreted in an equimolar ratio to AVP and is a sensitive and stable surrogate marker for its release[[64](#_ENREF_64)]. Copeptin levels have been used as a prognostic marker in patients with acute diseases such as lower respiratory tract infection, heart disease and stroke. Copeptin is also a promising marker in the differential diagnosis of hyponatremia[[64](#_ENREF_64)]. In a study plasma copeptin and N-terminal pro-B-type natriuretic peptide were evaluated in 340 patients with left ventricular systolic dysfunction, who were divided into 3 groups according to copeptin tertiles and followed for 55 months[[65](#_ENREF_65)]. Copeptin, although it did not predict the future development of hyponatremia, was a significant predictor of hospitalization or death (HR = 1.4, 95%CI: 1.1-1.9, *P <* 0.019) even after adjustment for plasma sodium, loop diuretic dose, and N-terminal pro-B-type natriuretic peptide levels[[65](#_ENREF_65)]. However, a secondary analysis of three prospective studies of patients with lower respiratory tract infections and acute cerebrovascular events showed that plasma copeptin levels did not add significant information to the investigation of sodium imbalance states in hospitalized patients[[66](#_ENREF_66)]. It should be mentioned that this analysis was based on a small sample size and did not focus on patients with heart failure[[66](#_ENREF_66)].

Another molecule that may play role in the development of hyponatremia in patients with heart failure is apelin, which is an endogenous ligand of the orphan APJ receptor. Apelin has a wide tissue distribution and is implicated in the regulation of body fluid homeostasis, cardiovascular functions, glucose homeostasis, cell proliferation, and angiogenesis[[67](#_ENREF_67)]. Apelin has diuretic properties and it has been shown that it is regulated in opposite directions with AVP to maintain body fluid homeostasis[[67](#_ENREF_67), [68](#_ENREF_68)]. There is evidence of apelin dysregulation in patients with cardiac failure since it has been shown that the observed increase in plasma apelin cannot compensate for the higher levels of AVP and may contribute to the corresponding water metabolism defect[[69](#_ENREF_69)].

## Diuretics

Diuretics are one of the most common causes of drug-induced hyponatremia[[70](#_ENREF_70), [71](#_ENREF_71)]. The great majority of cases of diuretic-induced hyponatremia are caused by thiazide diuretics, which act solely in the distal tubules and do not interfere with urinary concentration and the ability of AVP to promote water retention[[24](#_ENREF_24), [70](#_ENREF_70), [72](#_ENREF_72), [73](#_ENREF_73)]. Thiazide-induced hyponatremia is usually mild, but acute severe hyponatremia is occasionally developed as an idiosyncratic reaction[[70](#_ENREF_70), [72](#_ENREF_72), [74](#_ENREF_74)].

It should also be mentioned that the hydrochlorothiazide and amiloride combination appears to increase the risk of hyponatremia. This increment is probably because of the direct effect of amiloride on the collecting tubule increasing sodium loss[[75-77](#_ENREF_75)]. Moreover, amiloride spares potassium and, hence, aggravates thiazide-induced hyponatremia as a consequence of potassium retainment by exchanging it for sodium in the distal tubule. Indapamide administration has also been associated with hyponatremia[[78-80](#_ENREF_78)].

# EFFECTS OF HYPONATREMIA IN THE PROGNOSIS OF PATIENTS WITH HEART FAILURE

A large number of clinical studies have confirmed the association of hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure[[10](#_ENREF_10), [11](#_ENREF_11), [42](#_ENREF_42), [81-94](#_ENREF_81)]. A recent meta-analysis that included 14,766 patients from 22 studies and used as endpoint the death from any cause at 3 years showed that the risk of death is linearly increasing with serum sodium levels < 140 mmol/L[[95](#_ENREF_95)]. Moreover, hyponatremia was predictive of death in both patients with reduced or preserved ejection fraction[[95](#_ENREF_95)]. Another recent study, which enrolled 1,000 consecutive patients with heart failure of any cause and severity for a median duration of 5.1 years, showed that hyponatremia was associated with a significantly increased mortality risk (HR = 2.10, 95%CI: 1.60-2.77)[[96](#_ENREF_96)]. Notably, it was shown that serum sodium within the reference range has a U-shaped association with mortality risk; specifically, sodium levels of 135-139 mmol/L indicated an increased mortality risk, whereas sodium levels of 140-145 mmol/L were associated with the best prognosis[[96](#_ENREF_96)]. Hyponatremia has also been found to be an important predictor of survival in several risk models in patients with heart failure[[83](#_ENREF_83), [84](#_ENREF_84), [97-101](#_ENREF_97)].

Hyponatremia is associated with increased rate of re-hospitalization[[102](#_ENREF_102)], increased length of stay[[10](#_ENREF_10), [84](#_ENREF_84), [103](#_ENREF_103)], increased hospital resource use[[104](#_ENREF_104)], increased complications[[81](#_ENREF_81), [105](#_ENREF_105)] and increased costs[[106-108](#_ENREF_106)]. Furthermore, the presence of hyponatremia in patients with acute ST-elevation myocardial infarction is associated with the development of acute heart failure and with in-hospital adverse outcomes[[109](#_ENREF_109)]. Moreover, the risk of in-hospital mortality was associated with the severity of hyponatremia in patients with acute ST-elevation myocardial infarction[[109](#_ENREF_109), [110](#_ENREF_110)].

Recent studies have also shown the role of copeptin in the prognosis of heart failure. In the Biomarkers in Acute Heart Failure (BACH) trial, which enrolled 1641 patients with acute dyspnea, of whom 557 patients had acute heart failure, copeptin concentrations in the highest quartile were associated with increased 90-day mortality (HR 3.85, *P <* 0.001)[[111](#_ENREF_111)]. The combination of elevated copeptin and hyponatremia was associated with a higher risk of 90-day mortality (HR = 7.36, *P <* 0.001). Of note, no correlation was found between copeptin and sodium concentration[[111](#_ENREF_111)]. Similarly, marked elevations of copeptin were independent predictors of poor outcomes in a cohort of 157 patients with class III or IV heart failure prospectively evaluated for 2 years[[112](#_ENREF_112)]. Furthermore, the combination of increased copeptin levels with hyponatremia was a stronger predictor[[112](#_ENREF_112)].

# TREATMENT OF ACUTE SYMPTOMATIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In acute symptomatic hyponatremia serum sodium concentrations decrease rapidly resulting in the appearance of neurologic symptoms[[25](#_ENREF_25), [113](#_ENREF_113)]. These neurologic symptoms are due to brain edema resulting from fluid shifts from the hypotonic extracellular fluid into the more hypertonic brain[[1](#_ENREF_1)]. In acute symptomatic hyponatremia with severe neurologic symptoms (for example seizures and/or obtundation) immediate treatment is required to reduce the risk of neurologic complications[[1](#_ENREF_1), [114](#_ENREF_114)]. The proposed treatment for symptomatic hyponatremia is the infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L/h until symptoms subside[[54](#_ENREF_54)]. After this emergency intervention, the treatment should continue with the measures that are analysed below for the correction of chronic hyponatremia. Notably, in any case the rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-hour period.

# TREATMENT OF CHRONIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In patients with chronic hyponatremia the rate of correction of sodium levels should not exceed the rate of 8 mEq/L/d during the first 24 h[[115](#_ENREF_115), [116](#_ENREF_116)]. A more rapid correction increases the danger of central pontine myelinolysis[[1](#_ENREF_1), [117](#_ENREF_117), [118](#_ENREF_118)]. Central pontine myelinolysis is a neurological disease caused by the rapid rise in serum sodium levels during treatment in individuals with hyponatremia. It is characterised by severe damage of the myelin sheath of nerve cells in the pons area in the brainstem, leading to confusion, horizontal gaze paralysis, spastic quadriplegia, dysphagia, dysarthria and other neurological symptoms. The neurologic deterioration occurs 48-72 h after the rapid correction of hyponatremia. Death is common, but if the patient survives chronic neurologic deficits including locked-in syndrome and spastic quadriparesis are usually observed[[117-120](#_ENREF_117)]. Brain MRI is used to reveal the demyelination in the brainstem pons[[121](#_ENREF_121), [122](#_ENREF_122)].

## Fluid restriction

Fluid is restricted to amounts less than 800-1000 mL/d in order to achieve a negative water balance[[54](#_ENREF_54)]. It is the least expensive treatment option. In a randomized study, patients with hyponatremia (serum sodium ≤ 137 mg/dL) received usual care (*n =* 26) or 1000 mL/d fluid restriction (*n =* 20) at discharge[[123](#_ENREF_123)]. After 60 d patients in the group of fluid restriction had significantly better scores of symptom burden, total symptoms and overall quality of life. In this study there were no differences in thirst or adherence to fluid restriction between groups[[123](#_ENREF_123)]. However, many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction[[54](#_ENREF_54)].

## Diuretics

The use of diuretics is the mainstay of treatment in patients with heart failure with fluid overload. Loop diuretics are preferred because they increase electrolyte-free water clearance[[71](#_ENREF_71)]. It has been shown that the addition of a loop diuretic to an angiotensin-converting enzyme inhibitor reversed hyponatremia in heart failure patients[[124](#_ENREF_124)]. Furthermore, a study of our group showed that the combination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia[[125](#_ENREF_125)]. Specifically, six patients with congestive heart failure and serum sodium of 125-128 mmol/L treated with furosemide received captopril in progressively increasing doses. The addition of captopril resulted in clinical improvement and induced a significant increase in serum sodium levels, which was associated with a rise in the diluting ability of the kidney[[125](#_ENREF_125)].

It has also been shown that the infusion of hypertonic saline combined with high-dose diuretics was associated with increase in serum sodium levels and a potential improvement in outcomes in heart failure patients[[126](#_ENREF_126), [127](#_ENREF_127)]. One study enrolled 60 patients with New York Heart Association Class IV heart failure, who received infusion of furosemide (500 to 1000 mg) plus hypertonic saline (150 mL 1.4%-4.6% NaCl) in 30 min for 6 to 12 d. The combination of furosemide and hypertonic saline increased serum sodium levels and decreased length of stay and re-admissions compared with furosemide infusion alone[[126](#_ENREF_126)]. In a larger study, which enrolled 107 patients with heart failure, the infusion of furosemide plus hypertonic saline was associated with improvement in symptoms and reduction of re-admissions and mortality[[127](#_ENREF_127)].

## AVP-receptor antagonists

AVP has three different receptor subtypes[[128](#_ENREF_128)]. V1A receptors are found in vascular smooth muscle and cardiac myocytes causing vasoconstriction and hypertrophy, as well as in platelets and hepatocytes regulating platelet aggregation and glycogen metabolism[[129-135](#_ENREF_129)]. V1B receptors are found in the anterior pituitary gland and are associated with adrenocorticotropic hormone (ACTH) and b-endorphin release[[136](#_ENREF_136)]. Interestingly, these receptor subtypes have been also linked to the regulation of glucose homeostasis[[137](#_ENREF_137)]. V2 receptors are found on the renal collecting ducts and cause free-water reabsorption leading to increased water retention[[50](#_ENREF_50), [51](#_ENREF_51), [138](#_ENREF_138)]. V2 receptors are mainly linked to the development of hyponatremia in heart failure patients.

The central role of AVP in hyponatremia is targeted with the AVP-receptor antagonists (vaptans) conivaptan, tolvaptan and lixivaptan, which differ in their affinity for the V1A and V2 receptor[[139](#_ENREF_139)].

### Tolvaptan: Tolvaptan is an orally active, selective V2-receptor blocker. It is recommended to initiate the drug in hospital for safety reasons, although patients have been receiving tolvaptan safely as long as 3 years[[140](#_ENREF_140)].

Tolvaptan has been extensively studied in patients with heart failure. The administration of tolvaptan at a single oral dose (15, 30, or 60 mg) in 181 patients with advanced heart failure on standard therapy resulted in favourable changes in filling pressures and a significant increase in urine output[[141](#_ENREF_141)]. The low-dose (7.5 mg/d) tolvaptan for seven days improved hemodynamic parameters and resulted in significant fluid removal in 22 patients with chronic heart failure[[142](#_ENREF_142)]. Tolvaptan administration for 7 consecutive days reduced body weight and improved symptoms compared with placebo in patients with heart failure and volume overload despite the use of conventional diuretics[[143](#_ENREF_143), [144](#_ENREF_144)]. Tolvaptan administration in 254 stable patients with heart failure decreased body weight and increased urine volume[[145](#_ENREF_145)]. Similarly, in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial tolvaptan administration in hospitalized patients with systolic heart failure (*n =* 319) resulted in a significant decrease in body weight at 24 h without any changes in heart rate or blood pressure or increase in the rates of hypokalemia or worsening renal function[[146](#_ENREF_146)]. Of note, a lower 60-day mortality was observed in post hoc analyses in patients with renal dysfunction or severe systemic congestion[[146](#_ENREF_146), [147](#_ENREF_147)]. In the Multicenter Evaluation of Tolvaptan Effect on Remodeling (METEOR) study tolvaptan for 54 wk did not show any beneficial or detrimental effects on remodeling compared with placebo in 240 patients with stable systolic heart failure[[148](#_ENREF_148)]. Moreover, tolvaptan administration prevented the worsening of renal function compared with conventional therapy in patients with acute decompensated heart failure and high risk of renal failure[[149](#_ENREF_149)].

The larger trial of tolvaptan is the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), which enrolled 4133 patients hospitalized with systolic heart failure. A significant reduction in body weight on day 7 after discharge was demonstrated[[150](#_ENREF_150)]. During a median follow-up of 9.9 mo a significant increase in sodium levels was observed in patients with hyponatremia[[151](#_ENREF_151)]. However, tolvaptan had no effect on long-term mortality or heart failure-related morbidity. Specifically, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (HR = 0.98, 95%CI: 0.87-1.11, *P =* 0.68). The composite of cardiovascular death or hospitalization for heart failure occurred in 42% of patients receiving tolvaptan and 40.2% of patients receiving placebo (HR = 1.04, 95%CI: 0.95-1.14, *P =* 0.55)[[151](#_ENREF_151)]. It should be mentioned that EVEREST did not enrol solely patients with heart failure and hyponatremia, who in theory could benefit from the administration of tolvaptan. A recent analysis of patients with hyponatremia from the EVEREST trial (*n =* 475) showed that tolvaptan was associated with greater likelihood of normalization of serum sodium, greater weight reduction and greater relief of dyspnea at discharge than placebo (all *P <* 0.05)[[152](#_ENREF_152)]. Tolvaptan did not reduce long-term outcomes compared with placebo among all patients with hyponatremia. However, the administration of tolvaptan in patients with pronounced hyponatremia (< 130 mEq/L; *n =* 92) resulted in a significant reduction in cardiovascular morbidity and mortality after discharge (*P =* 0.04)[[152](#_ENREF_152)].

A recent study showed that the use of a single dose tolvaptan in pediatric patients with heart failure (*n =* 28) significantly increased serum sodium concentration (*P <* 0.001)[[153](#_ENREF_153)]. Furthermore, urine output was significantly increased at 24 h (*P <* 0.001).

### Lixivaptan: Lixivaptan is an oral, highly selective V2-receptor antagonist[[154](#_ENREF_154)]. The administration of lixivaptan in 42 patients with mild to moderate heart failure was associated with significant increases in urine volume and solute-free water excretion without any significant change in plasma renin, norepinephrine, aldosterone, atrial natriuretic peptide and endothelin-1 levels[[155](#_ENREF_155)]. Treatment with lixivaptan 100 mg/d for eight weeks (in addition to standard therapy) in outpatients with heart failure and volume overload significantly reduced body weight and improved dyspnea and orthopnea[[156](#_ENREF_156)]. Lixivaptan was generally well tolerated but thirst and polyuria occurred more frequently in the active drug group compared with the placebo group[[156](#_ENREF_156)].

The effectiveness and safety of lixivaptan for 60 d in patients with heart failure and hyponatremia are being evaluated in a double-blind, placebo-controlled study, the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) study[[157](#_ENREF_157)]. Primary endpoint is the effect of lixivaptan on serum sodium in patients hospitalized with worsening heart failure (target *n =* 650), signs of congestion and serum sodium concentrations < 135 mEq/L. Other endpoints include assessment of dyspnea, body weight, cognitive function and days of hospital-free survival[[157](#_ENREF_157)].

### Conivaptan: Conivaptan is both a V1A- and a V2-receptor blocker; the aquaretic effect is due to antagonism of the V2 receptor[[158-161](#_ENREF_158)]. The drug is a substrate and potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may result in significant drug-drug interactions[[158](#_ENREF_158)]. The drug is given only intravenously (20 mg bolus, then continuous infusion 20–40 mg/24 h) over up to 4 days in hospital[[139](#_ENREF_139)]. It has been shown that volume status or the presence of congestive heart failure do not alter the pharmacokinetics of conivaptan 20 or 40 mg/d[[162](#_ENREF_162)].

The effects of conivaptan in hyponatremia of various origin were evaluated in 3 randomized double–blind, controlled studies which showed significant improvement in serum sodium levels[[163-165](#_ENREF_163)]. The acute hemodynamic effects of conivaptan (single intravenous dose of 10, 20, or 40 mg) in heart failure were examined in 142 patients with symptomatic heart failure (New York Heart Association class III and IV)[[166](#_ENREF_166)]. The administration of conivaptan resulted in favourable changes in hemodynamic variables and urine output without affecting blood pressure or heart rate[[166](#_ENREF_166)]. In a double-blind trial, which randomised 170 patients hospitalized for worsening heart failure receiving standard therapy to conivaptan (20 mg loading dose followed by 2 successive 24-hour continuous infusions of 40, 80, or 120 mg/d) or placebo, conivaptan significantly increased urine output at 24 h compared with placebo (1-1.5 L difference, *P* ≤ 0.02 for all doses)[[167](#_ENREF_167)]. Body weight was decreased with the 40 and 80 mg/d dose in parallel with the increase in urine output but this reduction was not significant. Global and respiratory status at 48 h did not differ significantly between conivaptan and placebo groups. Conivaptan was well tolerated with the most common adverse events being infusion-site reactions[[167](#_ENREF_167)]. Another study assessed the role of conivaptan, furosemide or their combination in 8 patients with chronic stable heart failure on standard medical treatment[[168](#_ENREF_168)]. Both conivaptan and furosemide monotherapy increased urine volume, but the combination treatment significantly augmented this effect. Although conivaptan did not increase urinary sodium excretion compared with furosemide, the combination led to a greater urinary sodium excretion compared with furosemide monotherapy. There were no significant effects of conivaptan, furosemide or their combination on heart rate, arterial pressure, systemic vascular resistance, cardiac output, glomerular filtration rate, renal blood flow, plasma catecholamines, renin activity, AVP and B-type natriuretic peptide levels[[168](#_ENREF_168)].

### Other considerations: Fluid should not be restricted in patients with hyponatremia who start AVP-receptor antagonists and serum sodium concentration should be monitored every 6–8 h in order to avoid rapid correction of sodium levels[[139](#_ENREF_139)]. Although osmotic demyelination has not been reported with the use of AVP-receptor antagonists in studies with heart failure patients, a warning letter was recently published concerning the occurrence of neurological sequelae in some patients treated with tolvaptan in whom the correction of serum sodium exceeded the suggested rate[[169](#_ENREF_169)].

AVP-receptor antagonists should not be used in patients with hypovolemic hyponatremia, who should instead be treated with isotonic saline. Adverse effects of AVP-receptor antagonists include dry mouth, thirst and increased urination in most patients. These agents may not be effective in patients with advanced acute or chronic renal failure[[139](#_ENREF_139)]. Furthermore, the United States Food and Drug Administration (FDA) based on a recent large clinical trial of tolvaptan in patients with autosomal dominant polycystic kidney disease[[170](#_ENREF_170)] has recently determined that tolvaptan should not administrated for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death[[171](#_ENREF_171)].

# CONCLUSION

Many patients with heart failure have decreased sodium levels due to neurohormonal mechanisms. Patients with heart failure and hyponatremia have increased morbidity and worse prognosis compared with subjects with normal sodium levels. Treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. AVP-receptor antagonists increase effectively sodium levels and their use seems promising in patients with hyponatremia. However, it is not clear whether normalization of serum sodium also leads to an improved prognosis. Furthermore, the effects of AVP-receptor antagonists on the mortality, quality of life and length of hospital stay, as well as their cost-effectiveness, have not been thoroughly examined in double-blind, placebo-controlled trials in patients with heart failure and hyponatremia.

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**P-Reviewers** Esposito P, Giuffre M, Liu T  **S-Editor** Wen LL  **L-Editor**  **E-Editor**

**Figure 1 Mechanisms of hyponatremia in patients with heart failure.** RAAS: Renin-angiotensin-aldosterone system; AV*P*: Arginine-vasopressin.

**Table 1 Treatment options in patients with heart failure and hyponatremia**

|  |  |  |  |
| --- | --- | --- | --- |
| **Indication** | **Intervention** | **Comments** | **Citations** |
| Acute symptomatic hyponatremia with severe neurologic symptoms | Infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L/h until symptoms subside | The rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-hour period. | Adrogue *et al*[[1](#_ENREF_1)]  Ghali *et al*[[54](#_ENREF_54)]  Fraser *et al*[[114](#_ENREF_114)] |
| Chronic hyponatremia  (the rate of correction of sodium levels should not exceed 8 mEq/L/h the first 24 h, in order to avoid central pontine myelinolysis) | Fluid restriction (<800-1000 mL/d) | The least expensive option. Many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction. | Adrogue *et al*[[1](#_ENREF_1)]  Fraser *et al*[[114](#_ENREF_114)]  Ghali *et al*[[54](#_ENREF_54)]  Albert *et al*[[123](#_ENREF_123)] |
| Loop diuretics | The mainstay of treatment in patients with heart failure with fluid overload. The combination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia. | Chow *et al*[[71](#_ENREF_71)]  Dzau *et al*[[124](#_ENREF_124)]  Elisaf *et al*[[125](#_ENREF_125)] |
| Infusion of hypertonic saline (*e.g.*, 150 mL 1.4-4.6% NaCl in 30 minutes for 6 to 12 d) combined with high-dose diuretics (furosemide 500 to 1000 mg) | Two studies (167 patients with heart failure) showed increased serum sodium levels, improvement in symptoms, decreased length of stay and re-admissions compared with furosemide infusion alone. | Paterna *et al*[[126](#_ENREF_126)]  Licata *et al*[[127](#_ENREF_127)] |
| Tolvaptan | Oral, selective V2-receptor blocker. Many studies showed efficacy in increasing serum sodium levels and improving heart failure symptoms. The drug should be initiated in hospital for safety reasons. It should not be administrated for more than 30 days or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death. | Berl *et al*[[140](#_ENREF_140)]  Gheorghiade *et al*[[145](#_ENREF_145)]  Gheorghiade *et al*[[146](#_ENREF_146)]  Rossi *et al*[[147](#_ENREF_147)]  Udelson *et al*[[148](#_ENREF_148)]  Gheorghiade *et al*[[150](#_ENREF_150)]  Konstam *et al*[[151](#_ENREF_151)]  Hauptman *et al*[[152](#_ENREF_152)] |
| Lixivaptan | Oral, highly selective V2-receptor antagonist. Studies have shown improvement of heart failure symptoms. | Ghali *et al*[[154](#_ENREF_154)]  Abraham *et al*[[155](#_ENREF_155)]  Ghali *et al*[[156](#_ENREF_156)] |
| Conivaptan | Only intravenous administration. The drug is both V1A- and a V2-receptor blocker, but the aquaretic effect is due to antagonism of the V2 receptor. Studies have shown significant increase in urine volumes in the first 48 h. It is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. | Ali *et al*[[158](#_ENREF_158)]  Yatsu *et al*[[159](#_ENREF_159)]  Verbalis *et al*[[160](#_ENREF_160)]  Udelson *et al*[[166](#_ENREF_166)]  Goldsmith *et al*[[167](#_ENREF_167)]  Goldsmith *et al*[[168](#_ENREF_168)] |

V2: Vasopressin-2; V1A: Vasopressin-1A.