Hyponatremia in Heart Failure. Hyponatremia is defined as a serum sodium ion concentration below 136 mmol/L (mild-moderate: 121-135 mmol/L; severe: <121 mmol/L) [Anderson R.J. et al., 1985; Adrogué H.J., Madias N.E., 2000;]. Hyponatremia is the most frequently encountered electrolyte abnormality in hospitalized patients, with a prevalence ranging between 15% and 28% [Janicic N., Verbalis J.G., 2003; Hawkins R.C., 2003]. In patients with heart failure, hyponatremia ranges between 5% and 27%, depending on the applied cutoffs, patients’ age, and heart failure severity [Fried L.F., Palevsky P.M., 1997; Klein L. et al., 2005; Gheorghiade M. et al., 2005; Sica D.A., 2005;]. However, its frequency is generally believed to be underestimated in those patients [Movig K.L., 2003].

Pathophysiology of hyponatremia in heart failure. In general, hyponatremia results from a relative excess of water compared to sodium and according to the underlying mechanism it is classified into dilutional or depletional. The first is the most common one and results from a water excess, with sodium being low, normal, or increased [Adrogué H.J., Madias N.E., 2000]; the patients may be either hypervolemic or euvolemic. Depletional hyponatremia, in contrast, is caused by a reduction in sodium stores, because of renal, gastrointestinal, cutaneous or blood losses [Adrogué H.J., Madias N.E., 2000]; the patient is often hypovolemic. In heart failure, hyponatremia is usually dilutional, with the patient being hypervolemic.

In heart failure, hyponatremia results from a combination of mechanisms, including the reduction of glomerular filtration rate, the activation of the sympathetic nervous (SNS) and the renin-angiotensin-aldosterone (RAAS) systems and the inappropriate release of arginine vasopressin (AVP), as well as by the heart failure therapy, especially the thiazide diuretics [Sica D.A., 2005; Oren R.M., 2005]. The activation of AVP, in particular, is an important pathogenetic component of fluid retention and hyponatremia in heart failure. In general, arginine vasopressin is secreted by the hypothalamus in response to volume depletion and increased plasma osmolality and leads to fluid retention, vasoconstriction and platelet aggregation [Greenberg A., 2000]. However, several conditions characterized by fluid retention, including heart failure, are associated with inappropriately high AVP levels, even in the presence of volume overload and reduced plasma osmolality [Francis G.S. et al., 1990; Ali F. et al., 2007].
Hyponatremia seems to be associated with neurohormonal activation and more specifically with stimulation of SNS and RAAS, as shown by the enhanced plasma renin activity and the increased norepinephrine and epinephrine levels, compared to patients with normal sodium concentration [Lilly L.S. et al., 1984; Dzau V.J. et al., 1984]. In this context, the importance of the RAAS activation is implied by the fact that hyponatremic patients had a significantly better outcome when treated with angiotensin converting-enzyme inhibitors than with vasodilators [Lee W.H., Packer M., 1986]. Furthermore, it seems that hyponatremia is related to a resistance to diuretic therapy, as patients with low serum sodium levels in the ESCAPE trial had higher pulmonary capillary wedge and right atrial pressures after treatment compared to patients with normal sodium, despite the fact that they had received higher diuretic doses and had underwent similar reductions in body weight [Gheorghiade M. et al., 2005]. Hyponatremia was furthermore associated with an impaired response of neurohormones and regional blood flow to orthostatic stress, which was not encountered in heart failure patients without hyponatremia [Lilly L.S. et al., 1984].

**Hyponatremia as a predictor of prognosis in heart failure.** Although hyponatremia is usually mild, severe hyponatremia may lead to significant morbidity and mortality. The most important complication is the development of cerebral edema, with headache, nausea, vomiting, seizures and coma and a mortality of 5-50% [Fall P.J., 2000].

In heart failure, hyponatremia has been related to adverse outcome and it is considered to be an independent predictor of poor prognosis [De Luca L. et al., 2005]. According to several reports, serum sodium concentration is associated with increased in-hospital [Hawkins R.C., 2003; Chin M.H., Goldman L., 1996; Chen M.C. et al., 2003], short-term and long-term mortality [Lee W.H., Packer M., 1986; Lee D.S. et al., 2003; Felker G.M. et al., 2004; O’Connor C.M. et al., 2005; Klein L. et al., 2005], increased rehospitalization rate [Rich M.W. et al., 1995], as well as a longer hospital stay in hospitalized patients with heart failure [Krumholz H.M. et al., 1999]. In addition, it is also related to a higher mortality rate in heart failure outpatients [Kearney M.T. et al., 2004].

Among the aforementioned reports, the OPTIME-CHF study, which assessed the effects of the PDE inhibitor milrinone in 949 patients with systolic dysfunction hospitalized for heart failure decompensation [Cuffe M.S. et al., 2002], showed that hyponatremia was an independent predictor of death at 60 days, along with advanced age, lower systolic blood pressure, New York Heart Association class IV and high blood urea nitrogen [Felker G.M. et al., 2004]. Data from the same trial also showed that patients in the lowest serum sodium quartile (132-135 mEq/L) had a higher number of days hospitalized for cardiovascular reasons within 60 days of discharge along with higher in-hospital and 60-day mortality [Klein L. et al., 2005]. Similarly, a retrospective study of 4031 patients hospitalized for heart failure in Canada reported that hyponatremia was one of the predictors of mortality at both 30 days and 1 year, along with advanced age, hypotension, tachypnea and high urea nitrogen levels [Lee D.S. et al., 2003]. Moreover, two subanalyses of the ACTIV-CHF [O’Connor C.M. et al., 2005] and ESCAPE [Gheorghiade M. et al., 2005] trials in 319 and 433 patients, respectively, confirmed the independent prognostic value of hyponatremia for post-discharge mortality and rehospitalization rate in heart failure. Finally, a retrospective study of 1046 patients with congestive heart failure showed that hyponatremia was independently associated with prolonged hospital stay [Krumholz H.M., 1999].

**Management of hyponatremia in heart failure.** Despite the recent therapeutic advances in the treatment of chronic heart failure that have resulted in a significant amelioration of patients’ prognosis and survival, the management of acute heart failure syndromes is still characterized by a significant unmet need for effective therapies that would improve long-term clinical outcome.
One of the recently emerged therapeutic targets in this field is hyponatremia, which is frequent in patients with congestion in the context of acute heart failure syndromes.

The non-peptide AVP receptor antagonists present a novel promising class of agents for the management of hyponatremia and congestion [Cawley M.J., 2007; Verbalis J.G. et al., 2007]. Three antagonists have mainly been tested in clinical settings: conivaptan, lixivaptan and tolvaptan. Conivaptan is administered intravenously and acts both on V₁ and on V₂ receptors, while lixivaptan and tolvaptan are oral agents and are selective for V₂ receptors, with lixivaptan being more selective than tolvaptan [Lee C.R. et al., 2003]. All three antagonists promote excretion of electrolyte-free water, an effect termed aquarexis [Lee C.R. et al., 2003]. All three agents are effective in the management of hyponatremia of variable aetiology and generally well tolerated and safe. Conivaptan has already been approved by the American Food and Drug Administration for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients [Costello-Boerrigter L.C. et al., 2006].

**Tolvaptan.** The effective management of hyponatremia of various aetiology by tolvaptan was documented by the SALT trials, two multicenter, randomized studies in patients with either euvolemic or hypervolemic hyponatremia [Schrier R.W. et al., 2006]. Nearly 500 patients were randomized to tolvaptan, at a dose of 15, 30 and 60 mg daily, escalated on the basis of response or placebo, for 30 days. Tolvaptan resulted in a higher serum sodium increase on days 4 and 30, while hyponatremia recurred soon after drug discontinuation. No serious adverse events were noticed, except for higher rates of thirst, dry mouth and urination. However, no improvement in clinical outcomes was observed.

Among AVP receptor antagonists, tolvaptan is the most studied agent in patients with heart failure. An early study in 254 patients with mild heart failure, tolvaptan if administered at 30, 45 or 60 mg, once daily for 25 days, induced a significant decrease in body weight, sustained throughout the whole study period, with a concomitant decrease in edema and a normalization of serum sodium in patients with hyponatremia, without affecting adversely blood pressure, serum potassium or renal function [Gheorghiade M. et al., 2003].

The ACTIV in CHF trial randomized 319 patients with acutely decompensated chronic heart failure and persistent congestion despite standard therapy and reduced left ventricular contractility, regardless of the presence of hyponatremia, to either tolvaptan at 30, 60, or 90 mg/d or placebo on top of standard care for up to 60 days [Gheorghiade M. et al., 2004]. Tolvaptan resulted in a significantly higher body weight reduction at 24 hours. Of note, tolvaptan was not followed by hypotension, hypokalemia or renal function worsening, despite the higher weight loss. However, 60-day survival free of heart failure worsening was not improved, although a later data analysis showed that the improvement of serum sodium during hospitalization in the tolvaptan arm was associated with lower 60-day mortality [Rossi J. et al., 2007].

The EVEREST trial addressed the effect of tolvaptan’s addition to standard medical therapy improved on clinical outcome and long-term prognosis in heart failure patients hospitalized for congestion, regardless of the presence of hyponatremia [Gheorghiade M. et al., 2005; Gheorghiade M. et al., 2007; Konstam M.A. et al., 2007]. Over 4000 patients were randomly assigned to oral tolvaptan at 30 mg/d or placebo within 48 hours of admission for a minimum of 60 days. Global clinical status and body weight at day 7 was more improved in the tolvaptan than in the placebo arm; body weight and dyspnea were also significantly improved on days 1 and 7 and day 1, respectively [Gheorghiade M. et al., 2007]. Moreover, in patients with hyponatremia on admission, serum sodium was effectively increased by tolvaptan [Gheorghiade M. et al., 2007]. However, after a median follow-up of 9.9 months, neither all-cause mortality nor the composite point of cardiovascular death and hospitalization for heart failure differ significantly between the
two arms [Konstam M.A. et al., 2007]. Although tolvaptan caused thirst and dry mouth, it was not followed by a higher rate of renal dysfunction, hypotension or other major adverse events compared with placebo [Gheorghiade M. et al., 2007, Konstam M.A. et al., 2007].

The METEOR study addressed the effects of long-term tolvaptan therapy on left ventricular geometry in 240 patients with mild to moderate heart failure and reduced left ventricular ejection fraction [Udelson J.E. et al., 2007]. Tolvaptan, at 30 mg/day for one year, caused a small reduction in left ventricular end-diastolic volume and end-systolic volume and a small increase in left ventricular ejection fraction, as documented by radionuclide ventriculography. However, none of those changes were statistically significant.

Finally, the ECLIPSE trial addressed the hemodynamic effects of tolvaptan, at 15, 30 or 60 mg, on top of standard care, in 181 patients with advanced heart failure, reduced systolic function and a PCWP of 18 mm or higher [Mehra M.R. et al., 2008]. Tolvaptan induced an early and sustained PCWP reduction and a modest reduction in mean pulmonary artery pressure and right atrial pressure, with no changes in blood pressure or cardiac output.

**Conivaptan.** Several studies have shown that a conivaptan regimen, consisting usually of a loading dose of 20 mg over a 30-min period followed by a continuous intravenous infusion at 40 mg or 80 mg/day, increases serum sodium concentration and it is generally well-tolerated [Ghali J.K. et al., 2006; Zeltsler D., 2007; Verbalis J.G. et al., 2008]. In heart failure, however, data is quite limited. A randomized study on 142 patients with New York Heart Association class III or IV symptoms of heart failure, conivaptan, as a single intravenous infusion of 10, 20, or 40 mg, increased urine output in a dose-dependent manner, while the higher 20 mg and 40 mg doses also reduced pulmonary capillary wedge pressure and right atrial pressure; effects lasted 4-6 hours after administration [Udelson J.E. et al., 2001].

**Lixivaptan.** The existing evidence on the use of lixivaptan in heart failure is also quite limited. An earlier study in patients with mild to moderate chronic heart failure used antibodies to aquaporin-2 water channels to show that lixivaptan induced water excretion through those channels [Martin P.Y. et al., 1999]. In a study on a mixed population of 44 hospitalized patients with hyponatremia, including 33 patients with cirrhosis, 6 with congestive heart failure and 5 with syndrome of inappropriate antidiuretic hormone secretion, lixivaptan at 25, 125 or 250 mg twice daily increased free water excretion and serum sodium concentration in a dose dependent manner, without inducing orthostatic hypotension or affecting serum creatinine [Wong F. et al., 2003]. Finally, in a later randomized trial, 42 patients with mild or moderate heart failure in need of diuretic therapy were randomly assigned to either lixivaptan, at 10, 30, 75, 150, 250, or 400 mg or placebo, as a single-dose [Abraham W.T. et al., 2006]; doses of 30 mg or higher increased effectively aquaresis and were generally well tolerated.


27. Konstam M.A., Gheorghiade M., Burnett J.C. Jr., Grinfeld L., Maggioni A.P., Swedberg K. et al.; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007; 297: 1319-1331. 2 bullets The addition of Tolvaptan to standard therapy after hospitalization for heart failure, do not effect survival or rehospitalization in spite of the fact that it is superior to placebo in reducing body weight and normalizing serum sodium in those patients with hyponatremia.


42. Schrier R.W., Gross P., Gheorghiade M., Berl T., Verbalis J.G., Czerwiec F.S, et al.; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N. Engl. J. Med. 2006; 355: 2099-2112. 2 bullets Tolvaptan is very effective in improving or normalizing serum sodium in patients with hyponatremia due to liver or heart failure and inappropriate secretion of ADH.


