THE NEW ARMENIAN
MEDICAL JOURNAL
Vol. 2 (2008), N 3, 20 - 27
www.ysmu.am

HYPONATREMIA AND ITS MANAGEMENT IN PATIENTS WITH HEART FAILURE

D. Farmakis, J. Parissis, G. Filippatos*.

Second Department of Cardiology and Heart Failure Unit,
Athens University Hospital Attikon, Athens, Greece

Abstract

In this review the new approaches of medical treatment of heart failure are discussed. Hyponatremia represents one of pathogenetic pathways of heart failure symptoms progression and results from the relative excess of water compared to sodium.

Arginine-vasopressin antagonists have a potency to prevent hyperntremia and suppress neurohumoral overactivity mechanisms.

Results of several trials, which showed clinical benefit of these agents in patients with chronic heart failure, are discussed in this article.

Keywords: hyponatremia, heart failure, arginine-vasopressin, tolvaptan, conivaptan, lixivaptan.

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 osmolarity 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*].

Addres for correspondense: *Second Department of Cardiology and Heart Failure UnitAthens University Hospital Attikon 1 Rimini Street, 12461, Athens, Greece*
Tel./fax: +30-210-5832195;
E-mail: geros@otenet.gr

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

[*Mebazaa A. et al., 2008; Nieminen M.S. et al., 2005*]. 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 V_{1a} and on V_2 receptors, while lixivaptan and tolvaptan are oral agents and are selective for V_2 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 aquaresis [*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; Zeltser 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 genrally well tolerated.

References

1. *Abraham W.T., Shamshirsaz A.A., McFann K., Oren R.M., Schrier R.W.* Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. J. Am. Coll. Cardiol. 2006; 47: 1615-1621.
2. *Adrogué H.J., Madias N.E.* Hyponatremia. N.Engl. J. Med. 2000; 342: 1581–1589.
3. *Ali F., Raufi M.A., Washington B., Ghali J.K.* Conivaptan: a dual receptor vasopressin v1a/v2 antagonist. Cardiovasc. Drug Rev. 2007; 25:.261-279.
4. *Anderson R.J., Chung H.-M., Kluge R., Schrier R.W.* Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann. Intern. Med. 1985; 102: 164 –168.
5. *Cawley M.J.* Hyponatremia: current treatment strategies and the role of vasopressin antagonists. Ann. Pharmacother. 2007;.41:.840-850.
6. *Chen M.C., Chang H.W., Cheng C.I., Chen Y.H., Chai H.T.* Risk stratification of in-hospital mortality in patients hospitalized for chronic congestive heart failure secondary to non-ischemic cardiomyopathy. Cardiology 2003;. 100:.136 –142.
7. *Chin M.H., Goldman L.* Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. Arch. Intern. Med. 1996;.156:.1814 –1820.
8. *Costello-Boerrigter L.C., Smith W.B., Boerrigter G., Ouyang J., Zimmer C.A., Orlandi C., Burnett J.C. Jr.* Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. Am. J. Physiol. Renal Physiol. 2006;.290: F273-F278.
9. *Cuffe M.S., Califf R.M., Adams K.F. Jr., Benza R., Bourge R., Colucci W.S., Massie B.M., O'Connor C.M., Pina I., Quigg R., Silver M.A., Gheorghiade M.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002; 287: 1541–1547.
10. *De Luca L., Klein L., Udelson J.E., Orlandi C., Sardella G., Fedele F., Gheorghiade M.* Hyponatremia in patients with heart failure. Am. J. Cardiol. 2005; 96:19L-23L.
11. *Dzau V.J., Packer M., Lilly L.S., Swartz S.L., Hollenberg N.K., Williams G.H.* Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia. N. Engl. J. Med. 1984; 310: 347–352.
12. *Fall P.J.* Hyponatremia and hypernatremia: a systematic approach to causes and their correction. Postgrad. Med. 2000; 107: 75– 82.
13. *Felker G.M., Leimberger J.D., Califf R.M., Cuffe M.S., Massie B.M., Adams K.F. Jr., et al.* Risk stratification after hospitalization for decompensated heart failure. J. Card. Fail. 2004; 10: 460–466.
14. *Francis G.S., Benedict C., Johnstone D.E., Kirlin P.C., Nicklas J., Liang C.S. et al.* Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990; 82: 1724-1729.
15. *Fried L.F., Palevsky P.M.* Hyponatremia and hypernatremia. Med. Clin. North Am. 1997; 81: 585– 609.
16. *Ghali J.K., Koren M.J., Taylor J.R., Brooks-Asplund E., Fan K., Long W.A., Smith N.* Efficacy and safety of oral conivaptan: a V_{1A}/V_2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J. Clin. Endocrinol. Metab. 2006;.91:.2145-2152.

17. *Gheorghiade M., Gattis W.A., O'Connor C.M., Adams K.F. Jr., Elkayam U., Barbagelata A.. et al.;* Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004; 291: 1963-1971.

18. *Gheorghiade M., Hellkamp A.S., Pina I.L. et al.* Hemodynamic characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial [abstract]. J. Am. Coll. Cardiol. 2005; 45(Suppl.): 145A.

19. *Gheorghiade M., Konstam M.A., 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. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007; 297: 1332-1343. 2 Bullets When added to standard therapy, Tolvaptan improves signs and symptoms of heart failure throughout hospitalization without affecting blood pressure, heart rate or renal function.

20. *Gheorghiade M., Niazi I., Ouyang J., Czerwiec F., Kambayashi J., Zampino M., Orlandi C.;* Tolvaptan Investigators. Vasopressin V_2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;.107: 2690-2696. 1 Bullet In outpatients with mild heart failure the addition of Tolvaptan to standard therapy in patients with systolic and diastolic heart failure reduces body weight and decreases edema without effecting heart rate, blood pressure or renal function

21. *Gheorghiade M., Orlandi C., Burnett J.C., Demets D., Grinfeld L., Maggioni A.. et al.* Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). J. Card. Fail. 2005; 11: 260-269.

22. *Greenberg A..* Diuretic complications. Am. J. Med. Sci. 2000; 319: 10 –24.

23. *Hawkins R.C.* Age and gender as risk factors for hyponatremia and hypernatremia. Clin. Chim. Acta 2003; 337: 169 –172.

24. *Janicic N., Verbalis J.G.* Evaluation and management of hypo-osmolality in hospitalized patients. Endocrinol. Metab. Clin. North Am. 2003; 32: 459–481.

25. *Kearney M.T., Fox K.A., Lee A.J., Brooksby W.P., Shah A.M., Flapan A.. et al.* Predicting sudden death in patients with mild to moderate chronic heart failure. Heart 2004; 90: 137–1143.

26. *Klein L., O'Connor C.M., Leimberger J.D., Gattis-Stough W., Pina I.L., Felker G.M. et al. for the OPTIME-CHF investigators.* Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the OPTIME-CHF study. Circulation 2005; 111: 2454 –2460.

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.

28. *Krumholz H.M., Chen Y.T., Bradford W.D., Cerese J. V*ariations in and correlates of length of stay in academic hospitals among patients with heart failure resulting from systolic dysfunction. Am. J. Manag. Care 1999; 5: 715–723.

29. *Lee C.R., Watkins M.L., Patterson J.H., Gattis W., O'connor C.M., Gheorghiade M., Adams K.F.* Jr. Vasopressin: a new target for the treatment of heart failure. Am. Heart J. 2003; 146: 9-18.

30. *Lee D.S., Austin P.C., Rouleau J.L.* Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003; 290: 2581–2587.

31. *Lee W.H., Packer M.* Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986; 73: 257–267.

32. *Lilly L.S., Dzau V.J., Williams G.H., Rydstedt L., Hollenberg N.K.* Hyponatremia in congestive heart failure: implications for neurohormonal activation and responses to orthostasis. J. Clin. Endocrinol. Metab. 1984; 59: 924–930.

33. *Martin P.Y., Abraham W.T., Lieming X., Olson B.R., Oren R.M., Ohara M., Schrier R.W.* Selective V2-receptor vasopressin antagonism decreases urinary aquaporin-2 excretion in patients with chronic heart failure. J. Am. Soc. Nephrol. 1999; 10: 2165-2170.

34. *Mebazaa A., Gheorghiade M., Piña. I.L., Harjola V.P., Hollenberg S.M., Follath F. et al.* Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit. Care Med. 2008; 36(1 Suppl.): S129-S139.

35. *Mehra M.R., Rockman H.A., Greenberg B.H.* Highlights of the 2007 Scientific Meeting of the Heart Failure Society of America. J. Am. Coll. Cardiol. 2008; 51: 320-327.

36. *Movig K.L., Leufkens H.G., Lenderink A.W., Egberts A.C.* Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia. J. Clin. Epidemiol. 2003;.56: 530 –535.

37. *Nieminen M.S., Böhm M., Cowie M.R., Drexler H., Filippatos G.S., Jondeau G., et al.;* ESC Committee for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur. Heart J. 2005; 26: 384-416.

38. *O'Connor C.M., Adams K.F., Gattis W.A., et al.* Predictors of mortality in patients hospitalized with worsening heart failure: insight from the ACTIV in CHF trial [abstract]. J. Am. Coll. Cardiol. 2005; 45(Suppl.):151A.

39. *Oren R.M.* Hyponatremia in congestive heart failure. Am. J. Cardiol. 2005; 95: 2B-7B.

40. *Rich M.W., Beckham V., Wittenberg C., Leven C.L., Freedland K.E., Carney R.M.* A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N. Engl. J. Med. 1995; 333:1190 –1195.

41. *Rossi J., Bayram M., Udelson J.E., Lloyd-Jones D., Adams K.F., Oconnor C.M., et al.* Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. Acute Card. Care 2007; 9: 82-86.

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

43. *Sica D.A.* Hyponatremia and heart failure-Pathophysiology and implications. CHF 2005; 11: 274-277.

44. *Udelson J.E., McGrew F.A., Flores E., Ibrahim H., Katz S., Koshkarian G., et al.* Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. J. Am. Coll. Cardiol. 2007; 49: 2151-2159.

45. *Udelson J.E., Smith W.B., Hendrix G.H., Painchaud C.A., Ghazzi M., Thomas I. et al.* Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 2001; 104: 2417-2423.

46. *Verbalis J.G., Goldsmith S.R., Greenberg A., Schrier R.W., Sterns R.H.* Hyponatremia treatment guidelines 2007: Expert panel recommendations. Am. J. Med. 2007; 120 (11 Suppl. 1): S1-S21.

47. *Verbalis J.G., Zeltser D., Smith N., Barve A., Andoh M.* Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolemic hyponatremia: subgroup analysis of a randomized, controlled study. Clin. Endocrinol. (Oxf) 2008 [in press].

48. *Wong F., Blei A.T., Blendis L.M., Thuluvath P.J.* A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology 2003; 37: 182-191.

49. *Zeltser D., Rosansky S., van Rensburg H., Verbalis J.G., Smith N.;* Conivaptan Study Group. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am. J. Nephrol. 2007; 27: 447-457.