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Short-Term Efficacy and Safety of Vasopressin Receptor Antagonists for Treatment of Hyponatremia: A Meta-Analysis

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Abstract

Background—We performed a meta-analysis to systematically measure efficacy and safety of vasopressin receptor antagonists (VRAs) tested in randomized controlled trials for treatment of hyponatremia.

Methods—MEDLINE, ClinicalTrials.gov, and scientific abstracts were searched without language restriction. Two authors independently screened citations, and extracted data on patient characteristics, quality of reports, and efficacy and safety endpoints.

Results—11 trials were identified (1094 patients). By meta-analysis, VRAs achieved a net increase in serum sodium concentration ($[Na^+]_{serum}$) relative to placebo of 3.3 mEq/L at day 1 (95% CI, 2.7, 3.8), and 4.2 mEq/L at day 2 (95% CI, 3.6, 4.8), persisting at days 3–5. Larger net increases in $[Na^+]_{serum}$ at days 1–4 were observed in euvolemic hyponatremia and with higher doses. VRAs induced a net increase in effective water clearance relative to placebo of 1,244 mL at day 1 (95% CI, 920, 1,567), persisting at days 2 and 4. VRAs were associated with odds ratios of 3.0 for overly rapid correction of $[Na^+]_{serum}$ ($P<0.001$), 7.8 for development of hypernatremia ($P<0.001$), 3.3 for thirst development ($P<0.001$), and 2.2 for postural hypotension ($P=0.04$).

Conclusions—Short-term use of VRAs in treating hyponatremia was successful at raising $[Na^+]_{serum}$. Additional experience is required to guide their optimal use and minimize safety concerns.

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Keywords

hyponatremia; conivaptan; tolvaptan; lixivaptan; satavaptan

INTRODUCTION

Hyponatremia is the most common electrolyte disorder encountered in clinical practice.¹⁻³ Both the disorder itself and its management are associated with considerable morbidity and mortality.^{1,4,5} Dilutional hyponatremia, by far the commonest form of the disorder, is generated by water retention that usually results from a water-excreting defect of the kidneys. This defect largely reflects elevated levels of arginine vasopressin (AVP).¹

Depending on the body's sodium stores, dilutional hyponatremia is designated as hypovolemic, euvolemic, or hypervolemic. Hypovolemic hyponatremia is managed with volume repletion. By contrast, the cornerstone of treating mildly-to-moderately symptomatic euvolemic or hypervolemic hyponatremia has been water restriction. At best, this treatment compensates for, rather than addresses, the underlying pathophysiology. It is poorly tolerated and therefore ineffective, especially when the water-excreting defect requires stringent water restriction.

Vasopressin receptor antagonists (VRAs) represent a new class of agents that offers a pathophysiologically directed approach to managing euvolemic or hypervolemic hyponatremia. By binding to the V₂ receptor of the principal cell of the collecting duct, VRAs competitively antagonize the renal action of AVP, thereby promoting water excretion and increasing [Na⁺]_{serum}.^{6,7} Conivaptan, a mixed V_{1a}/V₂ receptor antagonist (V_{1a}/V₂RA), and tolvaptan, a selective V₂ receptor antagonist (V₂RA) have recently been approved in the U.S. for treatment of hyponatremia with mild to moderate symptomatology. Other V₂RAs include satavaptan and lixivaptan. Several randomized controlled trials have examined the efficacy and safety of VRAs in treating hyponatremia. We conducted a meta-analysis of available randomized controlled trials to assess the clinical efficacy and safety of this novel therapeutic modality and evaluate potential sources of heterogeneity among studies.

METHODS

Data Sources and Searches

We searched MEDLINE (1950-May 2010) using the following MeSH database search terms: “Receptors, Vasopressin”, “5-fluoro-2-methyl-N-(4-(5H-pyrrolo(2,1-c)-(1,4)benzodiazepin-10-(11H)-ylcarbonyl)-3-chlorophenyl)benzamide”, “argipressin, beta-mercapto-beta,beta-cyclopentamethylenepropionic acid(1)-Ile(2)-Abu(4)-”, “argipressin, beta mercapto-beta,beta-cyclopentamethylenepropionic acid(1)-O-methyl-Tyr(2)-TyrNH2(9)-”, “satavaptan”, “lixivaptan”, “conivaptan”, “tolvaptan”, and “relcovaptan”. The search was limited to human randomized controlled trials with no language restrictions. We also searched ClinicalTrials.gov for completed trials using similar search terms, and reviewed the *American Society of Nephrology* abstracts (2003-2009 meetings) and the bibliographies of retrieved articles.

Study Selection

We included randomized controlled trials that examined efficacy (as measured primarily by changes in [Na⁺]_{serum}) and safety endpoints (as defined below) of VRAs in treating hyponatremia. Studies of approved and non-approved VRAs were included. Reports of VRA trials in heart failure were excluded, as only a minority of participants had hyponatremia. If

more than one publication appeared on the same study, data from the most inclusive report were used.

Since the majority of trials reported data over 4-5 days of intervention, the short-term efficacy of VRAs was assessed by the net change in $[\text{Na}^+]_{\text{serum}}$ and effective water clearance (EWC) ⁸ in the VRA-treated group relative to the placebo group, at daily intervals for days 1-5 of study. We considered it important to present daily outcome values, as the initial two days of intervention represent a critical period during which overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ must be avoided to prevent osmotic demyelination. ¹ Furthermore, we wanted to assess the temporal evolution of the treatment effect. In 2 trials reporting data for up to 30 days of intervention, net change in $[\text{Na}^+]_{\text{serum}}$ could also be formally assessed at day 30 of study.

Safety of VRAs was assessed by the following adverse events that were pre-specified in individual studies: overly rapid correction of hyponatremia, development of hypernatremia, postural hypotension, hypotension, nausea, headache, thirst, renal impairment, infusion site phlebitis, and death.

Data Extraction and Quality Assessment

Data were extracted from full-text articles by 2 of the authors (LA and LB) independently. Disagreements were resolved through consensus and arbitration by a third author (VFS or BLJ). Corresponding authors of 2 trials were contacted for data clarification.

Data extracted from full-text articles included the following: country of origin, year of publication, study sponsor, study design, hyponatremia type, percent female, mean age, amount of fluid restriction in each arm (if any), VRA type, VRA route of administration, VRA dose, and duration of intervention.

Study quality was assessed using a modified version of the Jadad scale, ⁹ which assesses adequacy of randomization, blinding, and attrition. ¹⁰

Data Synthesis and Analysis

We performed random-effects model meta-analyses ¹¹ to assess the net change in $[\text{Na}^+]_{\text{serum}}$ and EWC in the VRA-treated group relative to the placebo group. For two studies we imputed the missing standard deviation data with the median standard deviations from other studies at the same time-point.

We performed Peto fixed-effect model meta-analyses ¹² to assess the aforementioned safety endpoints. This method was used due to the low number of events. The odds ratio (OR) and rate difference (with 95% confidence interval [CI]) for each adverse event was computed in the VRA-treated group relative to the placebo group.

Existence of heterogeneity among effect sizes estimated by individual studies was tested using the I^2 index and the Tau² test's P value. An I^2 index $\geq 50\%$ was used to indicate medium-to-high heterogeneity. ¹³ Potential causes of heterogeneity were explored by performing subgroup analyses based on *a priori* selected study characteristics. The Student *t*-test was used to compare subgroups. The weighted incidence rate for each adverse event was calculated using random-effects models. Finally, publication bias was formally assessed using funnel plots and the Egger's test.

All analyses were performed using MetaAnalyst beta version 3.1 (Tufts University, Boston, MA), ¹⁴ and the Metan command in Stata version 11. ¹⁵

RESULTS

Study Characteristics

1,198 potentially relevant citations in Medline were identified and screened (Figure 1). We retrieved 51 full-text articles for detailed evaluation, of which 8 reports satisfied the selection criteria. In addition, the abstract search yielded 7 reports, of which 2 met criteria. A total of 10 reports were included,¹⁶⁻²⁵ representing 11 trials, as 1 publication reported on the results of 2 trials.¹⁸ In addition, 1 parent study²² had a subsequent report on a subset of patients with euvolemic hyponatremia,²⁶ which was used for a subgroup analysis (see below).

The trials were published over 6 years and were all industry sponsored (Table 1). The 11 trials included 1,094 patients. The percentage of women ranged from 29-63%, and mean age from 51-74 years. Mean baseline $[\text{Na}^+]_{\text{serum}}$ in the control arm ranged from 123-129 mEq/L. Patients with euvolemic/hypervolemic hyponatremia were enrolled in 8 studies,^{16-18,21-23,25} patients with euvolemic hyponatremia in 2 studies^{19,20} and 1 sub-study,²⁶ and patients with hypervolemic hyponatremia (cirrhosis) in 1 study.²⁴

Conivaptan was used in 3 trials,^{17,22,25} tolvaptan in 3 trials,^{18,21} satavaptan in 4 trials,^{19,20,23,24} and lixivaptan in 1 trial (Table 2).¹⁶ Treatment duration ranged from 4-30 days. In 2 studies, no fluid restriction was imposed although fluid limitation was encouraged.¹⁸ In another trial, fluid restriction was confined to the placebo arm.²¹ In the remaining studies, fluid restriction, ranging from 1.5 to 2 L/day, was imposed in both arms.

Study Quality

Overall study quality scores were fair to good (Jadad score of 3-4). Ten of the 11 trials were double-blinded, and randomization was adequately described in 4 trials.^{16,18,25} The attrition rate was reported in 10 trials,^{16-19,21-25} ranging from 2.9 to 39.1%, and allocation concealment was reported in 8 trials.^{16,18,19,21,22,24,25} Finally, the intention-to-treat principle was used in the 3 trials.^{20,22,24}

Effect of VRAs on Net Change in $[\text{Na}^+]_{\text{serum}}$

Ten studies reported changes in $[\text{Na}^+]_{\text{serum}}$ levels at days 1, 2, and 3,^{16-19,21-25} 11 studies at day 4,¹⁶⁻²⁵ and 5 studies at day 5.^{16,17,19,21,25} By meta-analysis (Figure 2), at day 1, use of VRAs resulted in a net increase in $[\text{Na}^+]_{\text{serum}}$ level of 3.3 (95% CI, 2.7, 3.8) mEq/L relative to the control group ($P<0.001$). Although trials differed considerably in size and quality score, there was no evidence of statistical heterogeneity ($I^2=0\%$, $P=0.51$). Use of VRAs resulted in a net increase in $[\text{Na}^+]_{\text{serum}}$ level of 4.2 (95% CI, 3.6, 4.8) mEq/L at day 2, 4.4 (95% CI, 3.5, 5.3) mEq/L at day 3, 4.9 (95% CI, 4.1, 5.8) mEq/L at day 4, and 5.7 (95% CI, 4.1, 7.4) mEq/L at day 5, relative to the control group ($P<0.001$ for all analyses; Figure 3). The tests for heterogeneity were significant at day 3 ($I^2=59\%$, $P=0.001$), day 4 ($I^2=51\%$, $P=0.004$), and day 5 ($I^2=55\%$, $P=0.02$). When assessed at day 30 in 2 of the trials,¹⁸ the net increase in $[\text{Na}^+]_{\text{serum}}$ level in the VRA-treated group remained significant at 4.6 (95% CI, 3.6, 5.5) mEq/L relative to the control group (Figure 3; $P<0.001$).

In subgroup analyses, trials of euvolemic hyponatremia displayed significantly higher net increases in $[\text{Na}^+]_{\text{serum}}$ at day 1 than trials of hypervolemic and euvolemic/hypervolemic hyponatremia (5.5 vs. 2.6 vs. 3.3 mEq/L; Figure 4A). This trend persisted at days 2 through 4. No significant differences existed among the various types of hyponatremia at day 5. Similarly, pooled point estimates for net increases in $[\text{Na}^+]_{\text{serum}}$ at days 1-5 in the VRA-treated group relative to the control group had larger effects in studies of high-dose VRA

(vs. low-dose VRA; Figure 4B) and those with a higher Jadad score (≤ 3 vs. >3 ; Figure 4C). Funnel plots obtained at days 1 and 4 revealed no evidence of publication bias.

Effect of VRAs on Net Change in EWC

Only 3 studies reported on net change in EWC,^{17,22,25} which could be ascertained solely at days 1, 2, and 4. By meta-analysis (Figure 5), use of VRAs resulted in a net increase in EWC of 1,244 (95% CI, 920, 1,567) mL relative to the control group at day 1. No significant heterogeneity existed among effect sizes ($I^2=39\%$, $P=0.15$). Use of VRAs resulted in a net increase in EWC of 721 (95% CI, 525, 917) mL at day 2 and 672 (95% CI, 412, 932) mL at day 4, relative to the control group ($P<0.001$ for both). The tests for heterogeneity were not significant.

Safety Analyses of VRAs

Overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ was reported in 9 trials.^{16-19,22-25} Authors used variable definitions to characterize this endpoint ranging from a $[\text{Na}^+]_{\text{serum}}$ correction rate of >8 mEq/L over 8 hours on the first day of therapy, or >12 mEq/L in 24 hours;¹⁸ to >12 mEq/L in 1 day or >24 mEq/L in total.²⁶

Development of hypernatremia was reported in 6 trials, using variable definitions, including $[\text{Na}^+]_{\text{serum}} >142$ mEq/L¹⁶ or ≥ 145 mEq/L.^{17-19,24} Postural hypotension was reported in 4 studies,^{16,17,19,22} hypotension in 6 trials,^{17,18,22,23,25} nausea in 4 trials,¹⁷⁻¹⁹ headache in 3 trials,^{17,18} thirst in 3 trials,^{18,24} renal impairment in 5 trials,^{17,18,22,25} infusion site phlebitis in 1 study,²² and death in 6 trials.^{16-18,22,25}

As shown in Table 3, in the VRA-treated group, the weighted incidence rate of overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ was 10.5% and of development of hypernatremia was 5.5%. Thirst developed in 22% of VRA-treated patients and postural hypotension in 15.1%. The death rate in the VRA-treated group was 6.0%. By meta-analysis, use of VRAs was associated with a 3.0-fold increased odds of overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ ($P<0.001$), a 7.8-fold increased odds of development of hypernatremia ($P<0.001$), a 3.3-fold increased odds of thirst development ($P<0.001$), and a 2.2-fold increased odds of postural hypotension ($P=0.04$). By meta-analysis, 6.1% (95% CI, 2.6, 9.7) more patients in the VRA-treated group had an overly rapid correction of hyponatremia than in the control group ($P=0.001$). Similarly, 2.1% (95% CI, 0.4, 3.7) more patients in the VRA-treated group developed hypernatremia than in the control group ($P=0.02$). No significant difference in mortality existed between the 2 groups. The tests for heterogeneity were not significant for any of the adverse events. Finally, no case of osmotic demyelination was reported in any of the trials.

Notwithstanding the absence of significant heterogeneity among the trials for adverse events, *a priori* subgroup analyses found higher odds ratios for rapid $[\text{Na}^+]_{\text{serum}}$ correction with VRA among studies that used high-dose vs. low-dose VRA (6.21 [95% CI, 2.58, 4.93] vs. 2.10 [95% CI, 1.12, 3.93]; $P=0.04$). No difference in the odds of hypotensive episodes was found across studies based on VRA selectivity.

DISCUSSION

Our meta-analysis indicates that VRAs are effective at raising $[\text{Na}^+]_{\text{serum}}$ and EWC in hyponatremia during the first 5 days of study. Short-term efficacy was greater in euvoletic hyponatremia and high-dose VRAs. The effect on $[\text{Na}^+]_{\text{serum}}$ was sustained at day 30 of study. Although VRAs were associated with a higher risk of overly rapid correction of $[\text{Na}^+]_{\text{serum}}$, hypernatremia, and postural hypotension, these events were relatively rare.

Meaningful increases in $[\text{Na}^+]_{\text{serum}}$ occur by day 1 of VRA administration (Figure 2), practically without fluid restriction. Although most studies limited daily fluid to 1.5-2.0 liters, such amount hardly qualifies as fluid restriction. Most of the overall rise in $[\text{Na}^+]_{\text{serum}}$ occurred during day 1 of study, consistent with the concurrent, maximal increase in EWC.

Evaluation of the temporal evolution of the VRA effect on $[\text{Na}^+]_{\text{serum}}$ (Figure 3) should consider that a variable number of trials and participants were included at various time points. Both low- and high-dose VRAs were included, as well as oral and intravenous conivaptan therapy. No study rigorously controlled the intake of water, sodium, and potassium--factors involved in determining $[\text{Na}^+]_{\text{serum}}$. In this context, decreased efficacy of VRAs at longer time points, as suggested by Figure 3, might be unwarranted. The SALT trials in themselves showed undiminished efficacy of tolvaptan during the latter period of study.^{18,27} Open-label extension of VRA administration over 1-4 years supports continued efficacy.^{19, 28} Nonetheless, moderation of the initial rise in $[\text{Na}^+]_{\text{serum}}$ would not be surprising given development of thirst stimulation that promotes increased fluid intake.

As expected for a competitive antagonist, high-dose VRAs effected greater rises in $[\text{Na}^+]_{\text{serum}}$. Also, the efficacy of VRAs is greater in euvolemic hyponatremia (i.e., SIADH) than in hypervolemic hyponatremia (i.e., heart failure or cirrhosis). This difference might reflect decreased delivery of filtrate to the distal nephron in the edematous disorders secondary to decreased glomerular filtration and increased proximal reabsorption. Importantly, approximately 15% of SIADH patients do not respond to VRAs.²⁹ An established cause of such unresponsiveness is the nephrogenic syndrome of inappropriate antidiuresis.^{30,31}

Not unexpectedly, the risk of overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ was greater for high-dose VRAs. This risk might have been even higher if trials had used uniformly stringent criteria. It is comforting that no cases of osmotic demyelination were encountered. However, most reported cases of the syndrome occurred in patients with baseline $[\text{Na}^+]_{\text{serum}} < 115 \text{ mEq/L}$, patients excluded from VRA trials. It is unclear whether patients with increased susceptibility to osmotic demyelination (i.e., severe malnutrition, chronic alcoholism, advanced hepatic failure, and hypokalemia) were included. Shorter trials and the early phase of longer trials were completed in the hospital, thus enabling investigators to tailor medication dose and fluid administration. Fluid limitation would increase the risk of overly rapid correction of $[\text{Na}^+]_{\text{serum}}$ and development of hypernatremia.

Strengths of our synthesis include the observed robust findings on short-term efficacy of VRAs in a diverse patient population, and the absence of notable publication bias. Our findings generally agree with those of a recently published meta-analysis³² that appeared while our work was in progress. However, that meta-analysis did not report on the efficacy of VRAs at day 1 and day 2 of study, a crucial period in developing osmotic demyelination, or at any subsequent day individually. Rather, it described the short-term efficacy of VRAs by the aggregate net change in $[\text{Na}^+]_{\text{serum}}$ for days 3-7 of treatment. In contrast to the previous meta-analysis,³² we excluded the hyponatremic subgroups of VRA trials for treatment of heart failure. Only 8% and 21% of the enrolled patients were hyponatremic in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan trial³²⁻³⁵ and the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure trial,³⁶ respectively. Inclusion of these hyponatremic subgroups would have introduced selection biases and heterogeneity.

Limitations of our meta-analysis include significant heterogeneity among study-effect sizes, both for the net change in $[\text{Na}^+]_{\text{serum}}$ and EWC, which was explored through subgroup analyses. Eight of the 11 trials included mixed hyponatremic populations, confounding

optimal differentiation of VRA efficacy between hyponatremia types. Overly rapid correction of hyponatremia and development of hypernatremia were not uniformly defined in individual trials. Finally, studies had a relatively short-term follow-up and provided insufficient data to examine efficacy and safety of selective vs. non-selective VRAs in various types of hyponatremia.

Hyponatremia elicits variable symptomatology, more so if acute or severe in nature.¹ Strikingly, chronic hyponatremia with $[\text{Na}^+]_{\text{serum}} > 120 \text{ mEq/L}$, previously considered asymptomatic, has now been associated with reversible attention deficit and gait instability, osteoporosis, and propensity to falls and bone fractures.³⁷⁻³⁹ Chronic hyponatremia induces osteoporosis in rats.^{39,40} Even in its mildest form, hyponatremia is associated with increased mortality and heightened resource consumption.^{4,5} Whether this relationship is merely associative or, at least in part, causative remains unclear. Long-term and appropriately powered studies are required to examine whether correction of hyponatremia with VRAs affects favorably the associated morbidity and mortality.

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Figure 1.
Literature search and selection.

Figure 2.

Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists (VRAs) vs. placebo on net change in serum sodium concentration ([Na⁺]_{serum}) at day 1 in patients with hyponatremia.

No. trials	10	10	10	11	5	2
No. participants	1018	1018	1018	1094	258	448

Figure 3. Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists (VRAs) vs. placebo on net change in serum sodium concentration ($[\text{Na}^+]_{\text{serum}}$) at days 1-5 and day 30 in patients with hyponatremia.

Figure 4.

Subgroup meta-analyses of randomized trials comparing the effect of vasopressin receptor antagonists (VRAs) vs. placebo on net change in serum sodium concentration ($[Na^+]_{serum}$) at days 1-5, stratified by (4A) hyponatremia type (euvoletic vs. hypervolemic vs. mixed), (4B) low- vs. high-dose VRA, and (4C) Jadad score. Where indicated, P values refer to Student *t*-tests comparing trials of euvoletic/hypervolemic vs. hypervolemic patients (*), euvoletic/hypervolemic vs. euvoletic (†) patients, and hypervolemic vs. euvoletic (**) patients. High-dose VRA was defined as follows: conivaptan >40 mg/day; tolvaptan >30 mg/day; satavaptan >25 mg/day; and lixivaptan >125 mg/day.

Figure 5. Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists (VRAs) vs. placebo on net change in effective water clearance (EWC) at day 1 in patients with hyponatremia.

Table 1

Baseline characteristics of participants in trials of VRAs included in the meta-analysis

Author	Year	Country	No. patients	Female gender (%)	Mean age (years)	Hyponatremia type	Mean [Na ⁺] _{serum} (mEq/L) *
Wong ¹⁶	2003	US, and Canada	44	29	51	Euvolemic/hypervolemic	127
Ghalji ¹⁷	2006	US, Canada, and Israel	74	49	69	Euvolemic/hypervolemic	123
Schrier SALT-1 ¹⁸	2006	US, and 50 other countries	205	44	60	Euvolemic/hypervolemic	129
Schrier SALT-2 ¹⁸	2006	US, and 50 other countries	243	40	63	Euvolemic/hypervolemic	129
Soupart ¹⁹	2006	4 European countries	34	63	67	Euvolemic	126
Decaux ^{20†}	2006	3 European countries	76	47	68	Euvolemic	128
Gheorghiad ²¹	2006	US	23	43	67	Euvolemic/hypervolemic	129
Zeltser ²²	2007	Israel, Canada, US, and South Africa	84	51	74	Euvolemic/hypervolemic	124
Aronson ^{23†}	2007	Israel, Germany, and Australia	118	42	69	Euvolemic/hypervolemic	129
Gines ²⁴	2008	US, Canada, Australia, Argentina, and 8 European countries	110	30	57	Hypervolemic (cirrhosis)	126
Anname ²⁵	2009	9 European countries	83	34	64	Euvolemic/hypervolemic	126

NR denotes not reported.

* Control group

† Abstract

Table 2
Characteristics of the control and treatment arms of the studies included in the meta-analysis

Author	No. arms	Control arm	VRA arm	VRA type	VRA route	VRA dose	Duration of intervention (days)	[Na ⁺] _{serum} extraction
Wong ¹⁶	4	Placebo (+ fluid restriction)	Lixivaptan (VPA-985) (+ fluid restriction)	Selective V ₂	Oral	25, 125 or 250 mg twice/day	7	Days 1-5
Ghali ¹⁷	3	Placebo (+ fluid restriction)	Conivaptan (+ fluid restriction)	Non-selective	Oral	40 or 80 mg/day	5	Days 1-5
Schrier SALT-1 ¹⁸	2	Placebo	Tolvaptan	Selective V ₂	Oral	15 mg/day (up to 60 mg/day)	30	Days 1-4, 30
Schrier SALT-2 ¹⁸	2	Placebo	Tolvaptan	Selective V ₂	Oral	15 mg/day (up to 60 mg/day)	30	Days 1-4, 30
Soupart ¹⁹	3	Placebo (+ fluid restriction)	Satavaptan (+ fluid restriction)	Selective V ₂	Oral	25 or 50 mg/day	5	Days 1-5
Decaux ^{20†}	3	Placebo (+ fluid restriction)	Satavaptan (+ fluid restriction)	Selective V ₂	Oral	25 or 50 mg/day	4	Day 4
Gheorghiad ²¹	2	Placebo (+ fluid restriction)	Tolvaptan	Selective V ₂	Oral	10 mg/day (up to 60 mg/day)	27	Days 1-5
Zeltser ²²	3	Placebo (+ fluid restriction)	Conivaptan (+ fluid restriction)	Non-selective	Intravenous	40 or 80 mg/day	4	Days 1-4
Aronson ^{23†}	3	Placebo (+ fluid restriction)	Satavaptan (+ fluid restriction)	Selective V ₂	Oral	25 or 50 mg/day	4	Days 1-4
Gines ²⁴	4	Placebo (+ fluid restriction)	Satavaptan (+ fluid restriction)	Selective V ₂	Oral	5, 12.5, or 25 mg/day	14	Days 1-4
Annane ²⁵	3	Placebo (+ fluid restriction)	Conivaptan (+ fluid restriction)	Non-selective	Oral	40 or 80 mg/day	5	Days 1-5

* Where indicated, fluid restriction 1.5-2.0 liters/day

VRA denotes vasopressin receptor antagonist

[†] Abstract

Table 3

Safety analysis of vasopressin receptor antagonists

Adverse event	No. trials (No. patients)	Summary odds ratio (95% CI)	P value	Summary rate difference (95% CI)	P value
Overly rapid correction of hyponatremia	9 (995)	3.03 (1.82, 5.05)	< 0.001	6.1% (2.6%, 9.7%)	0.001
Development of hyponatremia	6 (719)	7.75 (2.77, 21.65)	< 0.001	2.1% (0.4%, 3.7%)	0.02
Postural hypotension	4 (236)	2.17 (1.03, 4.56)	0.04	5.8% (-1%, 12.5%)	0.09
Hypotension	6 (807)	1.21 (0.71, 2.08)	0.48	1% (-1.8%, 3.9%)	0.48
Thirst	3 (558)	3.25 (1.87, 5.63)	< 0.001	7.9% (0.2%, 15.7%)	0.04
Nausea	4 (556)	1.32 (0.69, 2.50)	0.40	1.8% (-2.3%, 6.0%)	0.39
Headache	3 (522)	1.02 (0.53, 1.96)	0.94	-0.2% (-4.5%, 4.1%)	0.94
Renal impairment	5 (689)	2.64 (0.80, 8.79)	0.11	0.6% (-0.8%, 2.0%)	0.42
Infusion site phlebitis [*]	1 (84)	4.22 (1.59, 11.22)	0.004	20.2% (6.8%, 33.6%)	0.003
Death	6 (733)	0.67 (0.38, 1.18)	0.17	-2.0% (-5.3%, 1.3%)	0.23

CI denotes confidence interval

^{*} Specific to intravenous conivaptan.