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Accepted Manuscript

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PII: S0002-9343(15)01049-9

DOI: 10.1016/j.amjmed.2015.11.005

Reference: AJM 13258

To appear in: *The American Journal of Medicine*

Received Date: 26 June 2015

Revised Date: 29 October 2015

Accepted Date: 3 November 2015

Please cite this article as: Verbalis J, Greenberg A, Burst V, Haymann JP, Johannsson G, Peri A, Poch E, Chiodo JA III, Dave J, Diagnosing and Treating the Syndrome of Inappropriate Antidiuretic Hormone Secretion, *The American Journal of Medicine* (2015), doi: 10.1016/j.amjmed.2015.11.005.

Diagnosing and Treating the Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Running head:

Treatment of SIADH

Keywords: fluid restriction, hyponatremia, isotonic saline, hypertonic saline, syndrome of inappropriate antidiuretic hormone secretion (SIADH), tolvaptan

Word count (not including abstract): 4,339

Number of figures and tables: 6 (plus 4 supplemental tables)

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Conflict of Interest Statement:

Author Conflict of Interest Disclosures: Dr. Verbalis is a consultant, and his institution received research support for his role as investigator for the HN Registry and for investigator-sponsored trials from Otsuka. He has received travel support and fees for data review activities and educational presentation development, and has served on a speakers' bureau for Otsuka. He is also a consultant and received fees for expert testimony from Ferring Pharmaceuticals. Dr. Greenberg is a consultant and his institution received research support for his role as investigator for the HN Registry from Otsuka. He has received travel support and fees for data review activities, and has

served on a speakers' bureau for Otsuka. Drs. Burst, Haymann, Johannsson, Peri and Poch are consultants and their respective institutions have received research support for their roles as investigators for the HN Registry from Otsuka. They have received fees for expert testimony and review activities, and travel support, and have served on a speakers' bureau for Otsuka. Dr. Chiodo is an Otsuka employee. Dr. Dave is a Consultant Physician working with Otsuka. No payment was provided to any author for the development of the manuscript.

Funding/Support: The academic co-authors take full responsibility for study design, data analysis plan, and drafting of the manuscript. They had unlimited access to the data. All authors meet the ICMJE authorship criteria. Statistical analysis was performed by employees of TCM Group and Mapi Group. Funding for study design and conduct, statistical analyses, and study oversight was provided by Otsuka America Pharmaceutical, Inc. (OAPI).

Abstract

Background

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in clinical practice, but current management of hyponatremia and outcomes in patients with SIADH are not well understood. The objective of the Hyponatremia Registry was to assess the current state of management of hyponatremia due to SIADH in diverse hospital settings, specifically: which diagnostic and treatment modalities are currently employed and how rapidly and reliably they result in an increase in serum [Na^+]. A secondary objective was to determine whether treatment choices and outcomes differ across the United States (US) and the European Union (EU).

Methods

The HN Registry recorded selected diagnostic measures and utilization, efficacy, and outcomes of therapy for euvolemic HN diagnosed clinically as SIADH in 1,524 adult patients with serum sodium concentration ([Na^+]) ≤130 mEq/L (1,034 from 146 US and 490 from 79 EU sites). A subgroup of patients with more rigorously defined SIADH via measurement of relevant laboratory parameters was also analyzed.

Results

The most common monotherapy treatments for hyponatremia in SIADH were fluid restriction (48%), isotonic (27%) or hypertonic (6%) saline, and tolvaptan (13%); 11% received no active agent. The mean rate of [Na^+] change (mEq/L/d) was greater for all active therapies than no active treatment. Hypertonic saline and tolvaptan produced the greatest mean rate of [Na^+] change (IQR both 3.0(6.0) mEq/L/d), compared to lower

IQR rates of [Na^+] change for isotonic saline (1.5(3.0) mEq/L/d) and fluid restriction (1.0(2.3) mEq/L/d). The general pattern of responses was similar in both the US and EU cohorts. At discharge, [Na^+] was <135 mEq/L in 75% of patients and ≤130 mEq/L in 43%. Overly rapid correction occurred in 10.2%.

Conclusions

1) Current treatment of hyponatremia in SIADH often employs therapies with limited efficacy; the most commonly chosen monotherapy treatments, fluid restriction and isotonic saline, failed to increase the serum [Na^+] by ≥5 mEq/L in 55% and 64% of monotherapy treatment episodes, respectively. 2) Appropriate laboratory tests to diagnose SIADH were obtained in <50% of patients; success rates in correcting hyponatremia were significantly higher when such tests were obtained. 3) Few outcome differences were found between the US and EU. A notable exception was hospital length of stay; use of tolvaptan was associated with significantly shorter length of stay in the EU but not the US. 4) Despite the availability of effective therapies, most patients with SIADH were discharged from the hospital still hyponatremic.

Introduction

Hyponatremia is the most common electrolyte abnormality, affecting up to 30-42% of hospitalized patients across numerous studies throughout the world over the last several decades.[1,2] Hyponatremia is important because it is associated with worse clinical outcomes across the entire range of inpatient care,[3] and with increased hospital costs and readmission rates.[4,5] In every disease studied, hyponatremia has been found to be an independent risk factor for increased mortality.[6] Chronic hyponatremia has been linked to impaired gait and balance, falls, osteoporosis and increased fracture rates,[7-10] though its causal role for these associations remains unproven.[11] Despite the widespread clinical impression that correction of hyponatremia is beneficial, evidence-based data demonstrating clinical benefit of correction of hyponatremia are limited,[7,12-14] and treatment practices vary widely.

The multinational Hyponatremia Registry assessed the current state of treatment of euvolemic and hypervolemic hyponatremia in diverse, real-world hospital settings; it was designed to determine which diagnostic and treatment modalities are currently employed, how effective they are, and how rapidly and reliably they result in an increase in serum sodium concentration ($[Na^+]$). A recent publication summarized the results of the Hyponatremia Registry for all hyponatremic patients[15]; the current report focuses on the more homogeneous subgroup of patients with the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH). A secondary objective is to determine whether treatment choices and outcomes for SIADH differ across the United States (US) and the European Union (EU).

Materials and Methods

Study Plan. The study design was described previously in detail.[16] Patients with euvolemic or hypervolemic hyponatremia were enrolled from 146 US sites and patients with euvolemic hyponatremia were enrolled from 79 EU sites. For the present publication, only patients initially assessed as clinically euvolemic by the treating physicians were analyzed. At each site, approval was sought from the appropriate research ethics review boards as required. After informed consent or waiver, investigators recorded patient data. The study was exclusively observational: no diagnostic or treatment protocols were imposed.

Inclusion and Exclusion Criteria. To assure that hyponatremia was clinically significant, the Registry required an entry [Na^+] ≤130 mEq/L. Patients were excluded if <18 years old, hypovolemic, using an investigational agent or device, if hyperglycemic enough to interfere with assessment of [Na^+], or receiving renal replacement therapy while hyponatremic. Euvolemia and a clinical diagnosis of SIADH were determined by the treating physician's clinical assessment. A complete listing of inclusion and exclusion criteria is found in Supplemental Table 1.

Data Collection. Principal data collection items are as recently described.[15]

Adjudication. To assure data consistency, data from patients who met pre-specified review thresholds were subject to review by two members of the study steering committee. Discrepancies were resolved by review by the committee co-chairmen. Pre-specified criteria triggering adjudication are have been published.[16] Although not a specified exclusion criterion originally, we subsequently excluded any patient receiving a thiazide at the time the treating physician made a diagnosis of SIADH, because it

would be difficult to assure that such patients were not in fact hypovolemic,[17] and diuretic use is generally considered to be an exclusion to the proper diagnosis of SIADH.[18] This decision was made prior to data analysis.

Subgroup Analysis. Because initial data analysis showed that many patients with a clinical diagnosis of SIADH did not have measurement of key laboratory parameters necessary to confirm this diagnosis, a subgroup was created to better assure the veracity of this diagnosis. This cohort consisted of only those patients with a clinical diagnosis of SIADH who also met the following criteria: urine osmolality measured and found to be >100 mOsm/kg H_2O; urine [Na^+] measured and found to be ≥30 mmol/L; if measured, TSH <10 mIU/ml; if done, ACTH stimulation test normal (unstimulated or stimulated cortisol level ≥18 mg/dl).

Statistical Methods. Therapy periods are defined as the time interval during which a patient received only a single therapy (monotherapy), or a specified combination. Patients could have had multiple hyponatremia episodes and multiple hyponatremia therapies during their hospital stay. Mild hyponatremia was defined as [Na^+] above 125 mEq/L, moderate hyponatremia as [Na^+] between 121 and 125 mEq/L, and severe hyponatremia as [Na^+] below 121 mEq/L. Overly rapid correction of [Na^+] was defined as an increase >12 mEq/L in any 24-hour interval or >18 mEq/L in any 48-hour interval.[16] Rate of change of [Na^+] was calculated as the total increment in [Na^+] during the period the treatment was utilized divided by the number of treatment days. For patients who received no treatment, the interval during which the patient was hyponatremic was used. Duration of the course of hyponatremia monotherapy was

168 determined by the formula: (hospital day number the treatment ended – hospital day
169 number the treatment started) + 1.

170 Categorical variables were compared using a chi-square test. In the case of more
171 than two comparison groups, an overall chi-square test was done before performing
172 individual pairwise chi-square tests. Analysis of correction criteria to test for treatment
173 differences was done using the Cochran-Mantel-Haenszel (CMH) method to adjust for
174 the baseline [Na^+] levels of mild, moderate, and severe for achievement of a serum
175 [Na^+] ≥130 mEq/L and ≥135 mEq/L, but not for achievement of an increase in serum
176 [Na^+] ≥5 mEq/L. Overall tests for raw mean score differences, relative risk, and odds
177 ratios were calculated from the CMH analysis. Confirmatory analyses of the correction
178 criteria were done using a logistic regression with the actual baseline [Na^+] as a
179 covariate. Both, the CMH and the logistic regressions were done to compare treatments
180 with the “no active hyponatremia therapy” treatment as a reference.

181 Nonparametric analysis was performed for continuous variables. When there
182 were more than two comparison groups, a Kruskal-Wallis test was done to generate an
183 overall test for equality of medians, and pairwise group comparisons were then done.
184 For comparisons of only two groups, medians were compared using the Wilcoxon Rank
185 Sum Test.

186

187 **Results**

188 A total of 5,028 patients were entered into the Hyponatremia Registry between
189 September 2010 and February 2013. After adjudication 3,087 individual patients
190 comprised the per-protocol data set (see CONSORT diagram[15]). A majority of the

patients in the per-protocol data set had euvolemic hyponatremia (1,597, 52%); the 1,524 (95%) of these who were diagnosed clinically as having SIADH constituted the primary pre-specified analysis group (Clinician Diagnosed SIADH). After excluding patients who did not have the necessary laboratory results to assure a diagnosis of SIADH, a subgroup of 729 patients constituted the secondary analysis group (Laboratory Diagnosed SIADH).

Patient demographics and baseline characteristics are shown in Table 1 for the combined Clinician Diagnosed SIADH group and for US and EU cohorts separately. Patients with SIADH were older and more likely to be female, but there were no significant differences between the regional cohorts. Serum [Na^+] was significantly lower and BUN and creatinine were significantly higher in EU compared to US patients. A prior episode of hyponatremia was known to have occurred significantly more often in US patients (28%) compared to EU patients (23%). A majority of patients were under the care of a generalist rather than a hyponatremia subspecialist, especially in US (78%) as compared to EU (29%). Conversely, a hyponatremia subspecialist was consulted significantly more frequently in US (54%) than in EU (25%).

Serum osmolality was measured in 66%, urine osmolality in 68%, and urine [Na^+] in 63%; all three tests were performed in 47%, and none in 11% (Table 2). Cortisol was measured in 33% of patients and thyroid-stimulating hormone in 63%. All five of these measurements were made in 21% of patients. Serum uric acid was measured in 28%. Of all these measures, 4 differed significantly in frequency of measurement between US and EU: urine osmolality, urine sodium and plasma cortisol were measured slightly less frequently and serum uric acid was measured somewhat more frequently in the EU

cohort (Table 2). TSH levels were abnormal in 4.5% of all SIADH patients (5.2% US, 2.8% EU). Cortisol levels were <18 µg/ml in 395 patients (62% of those tested) and <5 ug/ml in 67 patients (11% of those tested). ACTH stimulation tests were performed in 138 patients (including 24% of those with cortisol levels <18 µg/ml) and were abnormal in 26 (19%) of the patients tested (27% US, 15% EU).

Etiologies of SIADH were similar in both US and EU patients (Supplementary Table 2). The only significant differences were a higher incidence of tumors in EU compared to US patients (31% vs 20%, p<0.001), and a higher incidence of idiopathic or unknown etiology in US patients (38% vs 32%, p=0.003). Analysis of drug-induced SIADH revealed an expected preponderance (68%) of antidepressant, antiepileptic and antipsychotic therapies (Supplemental Table 3).

For monotherapy episodes in all Clinician Diagnosed SIADH patients, fluid restriction alone was selected most frequently (48.0%), followed closely by isotonic saline alone (26.9%) or in conjunction with fluid restriction (16.6%). Hypertonic saline was used less frequently (5.3%), and was utilized more often in patients with lower baseline [Na^+]. Pharmacological therapies were also used much less frequently: salt tablets (7.7% alone, 18% in combination with other therapies including 0.3% in association with loop diuretics), tolvaptan (12.7%), conivaptan (0.7%), loop diuretics (1.1%), demeclocycline (3.2%) and urea (0.2%). No active hyponatremia therapy was chosen in 11.2% of all SIADH patients. Of note, 51% of the patients who did not undergo active hyponatremia therapy received a medication that produces hyponatremia, which was stopped in 39%. Selection of therapies was not substantively different between US and EU cohorts, but US patients had a significantly greater

number of unique therapies per patient admission (2.3±1.1 vs 1.9±1.0, p<0.0001). More rigorous fluid restriction (≤1,000 ml/d) was not associated with a significantly greater [Na^+] increase than lesser degrees of fluid restriction (p=0.091).

The responses to the most commonly employed monotherapies as well as the most commonly employed combinations compared to no active hyponatremia treatment is shown in Table 3. The median rate of [Na^+] change (mEq/L/d) was greater for all active therapies than no active treatment, including those patients who had a hyponatremia-inducing drug stopped. Hypertonic saline and tolvaptan produced the greatest median (Interquartile Range, IQR) rate of [Na^+] change (both 3.0 (6.0) mEq/L/d), compared to lower median rates of [Na^+] change for isotonic saline (1.5 (3.0) mEq/L/d) and fluid restriction (1.0 (2.3) mEq/L/d). The general pattern of responses was similar in both US and EU cohorts, with only minor differences across treatments.

Examined categorically, lack of correction, defined as a final [Na^+] within 2 mEq/L of the starting [Na^+] was more likely in patients who received fluid restriction (28.5%) or isotonic saline (36.2%) than with hypertonic saline (18.4%) or tolvaptan (12%) as monotherapy. [Na^+] was also more likely to decrease by >2 mEq/L in patients who received fluid restriction (7.1%) or isotonic saline (9.0%) than in patients who received hypertonic saline (2.0%) or tolvaptan (1.2%) as monotherapy. These percentages were not substantially different in the more rigorously defined Laboratory Diagnosed SIADH subgroup (Supplemental Table 4).

Overly rapid correction of [Na^+] occurred with greater frequency with hypertonic saline (16.9%) and tolvaptan (12.1%) compared to the slower acting therapies: fluid restriction (2.6%), isotonic saline (2.1%). Differences in overly-rapid corrections

between US and EU cohorts were minimal. Analysis of individual cases of overly rapid correction revealed substantial percentages of etiologies of SIADH likely to be transient (22%, including pneumonia, traumatic brain injury, subarachnoid hemorrhage, and postoperative pituitary surgery), simultaneous cessation of hyponatremia-inducing drugs with initiation of active therapies (20%), off label use of tolvaptan (7%, including starting dose of 30 mg and use of fluid restriction concomitant with tolvaptan initiation), use of sequential active therapies on successive days (6%), and use of desmopressin for treatment of diabetes insipidus concomitant with active therapies (2%). However, 43% of the cases of overly rapid correction had no apparent contributing factor other than the primary method used to correct hyponatremia. Patients with lowest starting [Na^+] were at greatest risk for overly rapid correction: 5.4% for mild hyponatremia (referent), 7.4% (relative risk 1.35 [95% CI 0.85-2.14]) for moderate hyponatremia, and 21.8% (4.04 [2.72-5.99]) for severe hyponatremia. No cases of osmotic demyelination syndrome were documented in the Hyponatremia Registry.

Overall success in reaching three correction benchmarks using the most commonly employed monotherapies is shown in Table 4 for all monotherapy episodes and frequently employed combination therapies. Overall, 57% of all Clinician Diagnosed SIADH patients reached a [Na^+] ≥130 mEq/L, and 25% reached a normal [Na^+] ≥135 mEq/L. For each of these benchmarks, tolvaptan was significantly more successful compared to all other therapies. Success at increasing serum [Na^+] ≥5 mEq/L was similar with hypertonic saline (60%) and tolvaptan (78%). Success rates for correction were better in EU than US with hypertonic saline for [Na^+] ≥130 mEq/L (47% vs 20%, $p<0.05$) and for [Na^+] ≥135 mEq/L (29% vs 8%, $p<0.05$), and with fluid restriction for

283 increase in serum [Na^+] ≥5 mEq/L (56% vs 39%, p<0.05). Achievement of correction
284 benchmarks were similar in the more rigorously defined Laboratory Diagnosed SIADH
285 subgroup with three exceptions: success at increasing serum [Na^+] ≥5 mEq/L was
286 increased in the patients who had a hyponatremia-inducing drug stopped as their only
287 therapy (78% vs 47%) and was reduced in patients receiving isotonic saline (29%
288 versus 36%) and tolvaptan (70% vs 78%). However, the success rate for correction to
289 [Na^+] ≥130 mEq/L and to [Na^+] ≥135 mEq/L using isotonic saline was equivalently low
290 (19-20% and 4% respectively) with isotonic saline as monotherapy in both the Clinician
291 Diagnosed and Laboratory Diagnosed SIADH groups.

292 Comparison of achievement of correction benchmarks in patients who had
293 Schwartz-Bartter criteria measured showed that patients who underwent measurement
294 of serum and urine osmolality and sodium were significantly more likely to achieve an
295 increase in [Na^+] ≥5 mEq/L (71% vs 58%, p=0.002) and a normal [Na^+] ≥135 mEq/L
296 (24% vs 14%, p=0.009) than those who did not. Achievement of a [Na^+] ≥130 mEq/L
297 was more likely in the US (58% vs 45%, p=0.013) but not the EU (49% vs 55%,
298 p=0.497). Virtually identical results were obtained for patients in whom cortisol and TSH
299 were also measured.

300 Because fluid restriction and isotonic saline were the most frequently prescribed
301 monotherapies, we separately analyzed the course of patients with Laboratory
302 Diagnosed SIADH who were first treated with either of these therapies. A total of 122
303 patients with a baseline [Na^+] ≤130 mEq/L were treated initially with fluid restriction as
304 monotherapy (Figure 1a). Approximately half of the patients did not correct [Na^+] by an
305 increment ≥ 5 mEq/L (52); the majority of those patients received an additional

treatment (72%), with an eventual correction success rate between 40-71%. A total of 162 patients with a baseline [Na^+] ≤130 mEq/L were initially treated with isotonic saline as monotherapy (Figure 1b). Approximately two-thirds of the patients did not correct [Na^+] by an increment ≥ 5 mEq/L (70%); the majority of those patients received an additional treatment (75%), with an eventual correction success rate between 25-83%.

Logistic regression analysis was performed to identify characteristics of responders versus non-responders for the initial therapies chosen in the Clinician Diagnosed SIADH group. For fluid restriction, significant predictors (OR (95% CI)) of an increase in [Na^+] ≥5 mEq/L included lower starting [Na^+] (0.426 (0.357, 0.507), $p<0.00001$); lower urine osmolality (0.620 (0.414, 0.928), $p=0.0203$); and lower BUN (0.448 (0.324, 0.734), $p=0.0006$). For isotonic saline, significant predictors of an increase in [Na^+] ≥5 mEq/L included lower starting [Na^+] (0.233 (0.159, 0.343), $p<0.0001$); and higher serum creatinine (1.543 (1.145, 2.080), $p=0.0044$). In addition, 8% of the responders to isotonic saline also had a hyponatremia-inducing medication stopped on admission as a potential contributing cause to their response.

The median length of stay was 7 days for the entire SIADH group and did not vary by category of [Na^+], diagnosis, or treatment employed (Figure 2). Median length of stay was significantly shorter in US (7 days) compared to EU patients (13 days). Although length of stay did not vary by treatment employed in the US cohort, it was significantly shorter in EU patients treated with tolvaptan (6 days) than the other major treatments (fluid restriction = 9 days, isotonic saline = 10.5 days, hypertonic saline = 11 days; $p<0.01$). Correction of hyponatremia to [Na^+] ≥130 mEq/L was not associated with

survival; 4% of patients who corrected vs 5% who did not correct died or were discharged to hospice care (p=0.23).

Discussion

The Hyponatremia Registry is the largest observational hyponatremia study to date, and is unique in its examination of the diagnosis, treatment, and outcome of hyponatremia in diverse hospital settings in both the US and EU. The current analysis of 1,524 patients with clinically diagnosed SIADH, and a more rigorously defined subgroup of 729 patients with laboratory diagnosed SIADH, represents the largest group of patients with this disorder ever studied.

Determining the cause of hyponatremia is crucial to guiding correct management.[18-20] Proper diagnosis of SIADH requires measurement of urine and plasma osmolality, and urine [Na^+] at a minimum, as well as cortisol and thyroid hormone concentrations in selected cases.[18,20,21] Only 47% of patients with SIADH diagnosed by treating physicians had all 3 cardinal tests performed, and only 21% of patients had measurements of all the criteria necessary for this diagnosis. Testing results were virtually identical for the EU and US cohorts (Table 2), indicating that failure to make a precise diagnosis of SIADH is widespread, which potentially has important consequences with regard to choice of therapy. Of particular significance is the finding that success rates in achieving benchmark criteria for correction of [Na^+] were significantly better in patients in whom all or some subset of the Schwartz-Bartter criteria were measured.

Despite evidence from multiple studies[4,6.7,22-25] that hyponatremia is deleterious, the results of the Registry infer that correction is not felt to be important, since 75% of patients were discharged still hyponatremic, including 43% with [Na^+] ≤130 mEq/L at the time of discharge.

In the Hyponatremia Registry, the choice of treatment was left up to the treating physicians. Fluid restriction was used most often as the initial therapy. Fluid restriction used as monotherapy in patients with SIADH led to a modest rise in [Na^+], with a median (IQR) rate of 1.0 (2.5) mEq/L/d. The second most frequent treatment chosen was isotonic saline, despite long-standing knowledge that this therapy is generally considered to be ineffective or counterproductive for treatment of SIADH.[21] Responses to isotonic saline were also modest and statistically equivalent to fluid restriction, with a median (IQR) rate of 1.5 (3.0) mEq/L/d. Categorical responses of individual patients showed that 7% treated with fluid restriction and 9% with isotonic saline actually experienced further decreases in [Na^+] (Supplemental Table 4), indicating that reliance on these treatments can be detrimental. Patients who responded to fluid restriction with an increase in [Na^+] ≥5 mEq/L generally had lower levels of [Na^+], urine osmolality and BUN. This supports previous data that fluid restriction is unlikely to result in a significant increase in [Na^+] if urine osmolality is high, (i.e., >500 mOsm/kg H_2O) or the ratio of urine to plasma electrolyte concentrations is >1.0,[18,19,26,27] but these parameters were not evaluated in the majority of SIADH patients. Those who responded to isotonic saline had higher levels of creatinine, a finding suggesting unrecognized volume depletion, which is supported by the lower achievement increases in [Na^+] ≥5 mEq/L with isotonic saline in the more rigorously defined Laboratory Diagnosed SIADH subgroup (Table 4).

The finding that 29% of patients who met laboratory criteria for a diagnosis of SIADH responded to isotonic saline with an increase in [Na^+] ≥5 mEq/L but only 4% achieved a normal [Na^+] ≥135 mEq/L supports recommended use of a limited (i.e., 1.0 L) therapeutic challenge with isotonic saline in cases where there is uncertainty about the patient's volume status (e.g., clinical signs of dehydration, high BUN, creatinine or uric acid levels, borderline urine [Na^+]),[18] but not continuation of this therapy when responses are absent, negative, or reach a plateau of [Na^+] prior to normalization.of the [Na^+] level.

Hypertonic saline and tolvaptan worked more consistently and significantly faster than fluid restriction and isotonic saline in patients with SIADH (Tables 3 and 4). These agents also had very low rates of decreases in [Na^+] (Supplemental Table 4). Hypertonic saline and tolvaptan had similar efficacy in increasing [Na^+] by ≥5 mEq/L and were each more effective than no active therapy, fluid restriction, or isotonic saline. However, in the Laboratory Diagnosed SIADH subgroup, stopping a hyponatremia-inducing medication alone was the most effective monotherapy, albeit in a small number of patients (Table 4). After adjustment for baseline [Na^+] using logistic regression, hypertonic saline was no better than no active therapy in achieving specific [Na^+] correction benchmarks of [Na^+] >130 or ≥135 mEq/L. This is consistent with clinical practice in which hypertonic saline is used to effect an initial correction in symptomatic patients with the most severe hyponatremia, followed by other modalities to raise [Na^+] further, but was also influenced by a high spontaneous correction rate in the untreated patients (Table 3), likely as result of stopping medications associated with hyponatremia and spontaneous reversal of transient etiologies of SIADH.

Also of interest are the hyponatremia therapies not chosen. Despite recent recommendations by a European Guidelines group for use of urea and the combination of loop diuretics with NaCl tablets as second-line therapies for hyponatremia,[20] the very low frequency of use of these therapies (0.2% and 0.3% of all hyponatremia treatment episodes in this Registry, respectively) suggests that these therapies are not being utilized very widely in either the US or EU at this time.

The rate of [Na^+] rise with tolvaptan was more rapid than reported previously in clinical trials,[14,28] and the rate of overly rapid correction was higher as well. A [Na^+] increase >12 mEq/L/24h or >18 mEq/L/48h, predisposing patients to development of osmotic demyelination syndrome, was observed more often in patients receiving hypertonic saline or tolvaptan than receiving other treatments (Table 3). The relatively high percentages of etiologies where SIADH may be transient and resolve suddenly or where hyponatremia-inducing drugs were stopped concomitantly with initiation of active therapies in the patients with overly rapid correction in the Registry suggests that use of active therapies to correct hyponatremia in these situations poses an increased risk for overly rapid correction, and supports more frequent monitoring of [Na^+] in such cases. Although well described with hypertonic saline, only one case of osmotic demyelination syndrome with the use of vasopressin-receptor antagonists as monotherapy to correct hyponatremia has been reported to date,[18,29] and no cases of osmotic demyelination syndrome were observed in the SIADH patients in the Registry.

Previously reported results from the Hyponatremia Registry failed to show any association between treatment modality and hospital length of stay.[15] However, the results from the SIADH subgroup analysis showed that length of stay was significantly

shorter in EU patients treated with tolvaptan than other treatments. The likely reason for this was the marked difference in length of stay between the US and EU. Overall median length of stay was 6 days longer in the EU compared to the US; consequently, the time frame to observe a reduction in length of stay with any hyponatremia therapy was significantly shorter in the US compared to the longer time frame for observation in the EU. Although this indicates that hyponatremia patients are discharged more quickly in the US, the [Na^+] at the time of discharge was not significantly different between the US and EU (Table 1).

The Hyponatremia Registry has a number of limitations, most of which derive from its observational design,[12] as described in detail in the previously published report of the combined Hyponatremia Registry cohort.[15] Of particular note, the selection of diagnostic studies and treatments was left up to the clinicians responsible for patients; neither a fluid challenge nor urine sodium determination was required as an entry criterion for putatively euvolemic patients. This limited the ability to confirm the presence of SIADH with precision, and the study relied on treating clinicians to make the diagnosis. However, since the study's intent was to capture "real-world" practice, this limitation does not detract from observing how clinician-diagnosed SIADH is treated. Although the lack of major differences in achievement of successful corrections between the clinician diagnosed and laboratory diagnosed groups suggests that for the most part the clinical diagnoses identified patients with true SIADH, the high rate of adjudication failures likely eliminated most of the patients who were volume depleted despite a clinical diagnosis of SIADH. Indeed, a principal conclusion of the Registry is that diagnostic rigor in the case of SIADH is severely lacking. Although the length of

stay data suggests that more effective treatment with vasopressin receptor antagonists was associated with shorter hospitalization stays, the numbers of patients treated with tolvaptan are too small to draw meaningful conclusions.

In summary, despite the high prevalence of hyponatremia[1,2] and published guidance on its diagnosis and treatment,[18-20,30] numerous shortcomings in current management of hyponatremia in SIADH are evident. SIADH is often diagnosed clinically without sufficient attention to accepted diagnostic criteria, but success rates in correcting hyponatremia are higher in patients in whom these tests are measured. Many patients diagnosed with SIADH receive no specific treatment for hyponatremia. Fluid restriction was predictably the most frequent initial therapy, but was ineffective in more than half of cases. Isotonic saline was used nearly as frequently and was ineffective in more than two-thirds of cases, and also was more likely to decrease [Na^+] than to correct [Na^+] to normal ranges. When unsuccessful, fluid restriction and isotonic saline were often not followed with an additional therapy. Despite the availability of active therapies to correct [Na^+], clinicians typically discharge patients with unresolved hyponatremia. From this study, we conclude that there is a need to focus educational efforts on how to diagnose SIADH with rigor, the lack of uniform efficacy of fluid restriction and isotonic saline and the potential for [Na^+] to fall with fluid restriction and isotonic saline, the use of active treatments to raise [Na^+] urgently when needed, and on increasing awareness of situations where overly rapid correction of [Na^+] is more likely. Given the persisting uncertainty about whether hyponatremia contributes to the observed poor outcomes or is only a marker of severe underlying disease,[6,7,11,22-24]

464 future research efforts should focus on which patients with SIADH will directly benefit

465 from correction of hyponatremia.

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Acknowledgments

We thank Stephen Ball, MBBS, PhD, FRCP, Newcastle University, Newcastle, United Kingdom, Jean-Philippe Haymann, MD, Hôpital Tenon, Paris, France, Gudmundur Johannsson, MD, PhD, University of Göteborg, Sweden, Jens Otto Lunde Jørgensen, MD, Aarhus University Hospital, Aarhus, Denmark, and Esteban Poch, MD, University of Barcelona, Spain for their participation on the European Steering Committee for the Hyponatremia Registry, with funding by Otsuka. We thank Alpesh Amin, MD, Jun Chiong, MD, Joseph Dasta, PharmD, Paul Hauptman, MD, and Samuel Sigal, MD for their participation on the US Steering Committee for the Hyponatremia Registry, with funding by Otsuka. Statistical analysis was performed by Ronald Copp, MPH and Stuart Nichols of the Mapi Group, Lexington, KY, with funding from Otsuka. Susan Boklage, MS, MPH of Otsuka provided additional statistical advice. Sandra Chase, PharmD, and Jamie Jarecki-Smith of Otsuka provided continuing support for reviewing data entered in preparation for analysis and for accuracy. Catherine Fontana, MSc, and Geoff Marx of BioScience Communications, New York, NY, formatted tables, figures, text, and references to comply with Journal requirements, with funding from Otsuka.

571 **Figure Legends**

572

573 **Figure 1.** Outcomes and Use of Second Therapies in Patients with Baseline Serum
574 Sodium Concentrations <130 mEq/L Treated with Fluid Restriction or Isotonic Saline as
575 Monotherapy.

576

577 Panel A: Patients with Laboratory Diagnosed SIADH initially treated with fluid restriction
578 as monotherapy. Panel B: Patients with Laboratory Diagnosed SIADH initially treated
579 with isotonic saline as monotherapy. The decision to initiate a second treatment or not
580 and the selection of any such treatments were made by the patients' treating physicians
581 without input from the investigators. All serum [Na^+] values are mean ± standard
582 deviation in mEq/L. HS, hypertonic saline; NS, isotonic saline; TO, tolvaptan.
583 [a]Pretreatment value; [b]success defined as proportion of patients with [Na^+] increase in
584 [Na^+] ≥5 mEq/L.

585

586 **Figure 2.** Median Length of Hospital Stay for all SIADH Patients and the United States
587 (US) and European Union (EU) Cohorts Separately.

588

589 P-values <0.05:
590 EU- FR vs Tolvaptan; HS vs Tolvaptan.

Table 1. Baseline Demographic Characteristics for all Clinician Diagnosed SIADH Patients and the United States (US) and European Union (EU) Cohorts Separately.

	All (n=1524)	**US (n=1034)**	**EU (n=490)**
Age distribution, n (%)[a]			
≤50 y	186 (12)	139 (13)	47 (10)
51–64 y	373 (25)	259 (25)	114 (23)
65–74 y	339 (22)	229 (22)	110 (22)
≥75 y	626 (41)	407 (39)	219 (45)
Men, n (%)[b]	695 (46)	469 (45)	226 (46)
Median initial [Na+] (IQR), mEq/L[c]	124.0 (8.0)	124.0 (8.0)	122.0 (9.0)
Median discharge [Na+] (IQR), mEq/[c]	131.0 (7.0)	131.0 (6.0)	132.0 (8.0)
Median initial BUN (IQR), mg/dL[c]	12.0 (8.0)	12.0 (7.0)	14.0 (12.9)
Median discharge BUN (IQR), mg/dL[c]	13.0 (9.0)	13.0 (9.0)	16.2 (13.8)
Median initial creatinine (IQR), mg/dL[d]	0.70 (0.3)	0.71 (0.3)	0.69 (0.3)
Median initial BUN:creatinine ratio (IQR),[c]	16.7 (9.6)	16.2 (8.8)	19.2 (16.7)
Median Initial Urine Sodium (IQR) mmol/L[e]	72.0 (61.0)	75.0 (63.0)	68.0 (57.0)
Median Initial Urine Osmolality	404.0 (266.0)	402.0 (270.0)	411.5 (234.5)

(IQR), mmol/kg[f]			
Median Initial Uric Acid (IQR)[g]	166.56 (107.07)	169.53 (107.07)	166.56 (107.99)
Prior HN, n (%)[c, h]			
Yes	407 (27)	293 (28)	114 (23)
No	687 (45)	405 (39)	282 (58)
Unknown	430 (28)	336 (33)	94 (19)
HN at admission, n (%)[d,i]			
Yes	1,252 (82)	869 (84)	383 (78)
No	253 (17)	160 (16)	93 (19)
Unknown	19 (1)	5 (1)	14 (3)
Primary physician specialty, n (%)[c]			
Nephrologist	82 (5)	23 (2)	59 (12)
Endocrinologist	106 (7)	2 (<1)	104 (21)
Cardiologist	49 (3)	40 (4)	9 (2)
Hepatologist	3 (<1)	2 (<1)	1 (<1)
Oncologist	92 (6)	47 (5)	45 (9)
Generalist	944 (62)	802 (78)	142 (29)
Other	247 (16)	118 (11)	129 (26)
HN subspecialist consulted, n (%)[c,j]			
No	839 (55)	472 (46)	367 (75)
Yes	683 (45)	562 (54)	121 (25)

Abbreviations: BUN, blood urea nitrogen; HN, hyponatremia; [Na^+], sodium concentration; IQR, interquartile range; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a]US SIADH vs EU SIADH: *P* = 0.08.

[b]US SIADH vs EU SIADH: *P* = 0.78.

[c]US SIADH vs EU SIADH: *P* <0.001.

[d]US SIADH vs EU SIADH: *P* = 0.05.

[e]US SIADH vs EU SIADH: *P* = 0.44.

[f]US SIADH vs EU SIADH: *P* = 0.29.

[g]US SIADH vs EU SIADH: *P* = 0.84.

[h]HN during previous hospital admission in prior 12 months.

[i]Data missing 9 in SIADH.

[j]HN specialist defined as nephrologist or endocrinologist.

Table 2. Diagnostic Tests Obtained in Patients Diagnosed with SIADH by the Treating Physicians (Clinician Diagnosed SIADH).

Test	All (%) n=1524	US (%) n=1034	EU (%) n=490
No Test Performed[a]	168 (11)	116 (11)	52 (11)
All Bartter diagnostic criteria[b]	721 (47)	506 (49)	215 (44)
• Serum osmolality[c]	1012 (66)	685 (66)	327 (67)
• Urine osmolality[d]	1043 (68)	749 (72)	294 (60)
• Urine sodium[d]	962 (63)	688 (67)	274 (56)
All of the above plus TSH and Cortisol[a]	324 (21)	222 (22)	102 (21)
Serum Uric Acid[e]	422 (28)	262 (25)	160 (33)

[a]US SIADH vs EU SIADH: P = 0.79.

[b]US SIADH vs EU SIADH: P = 0.07.

[c]US SIADH vs EU SIADH: P = 0.86.

[d]US SIADH vs EU SIADH: P <0.001.

[e]US SIADH vs EU SIADH: P = 0.003.

Table 3. Response to Therapy for All Monotherapy Episodes, and Rate of Overly Rapid Correction of [Na^+] during Any 24- or 48-Hour Period of Therapy.

Treatment	Patients, n	Median Baseline [Na^+] (IQR), mEq/L	Median Rate of [Na^+] Change (IQR), mEq/L/d[a]	Median 24-h Rate of Change (IQR), mEq/L/d[b]	Median Duration of Rx (IQR), d[c]	Overly Rapid Correction, n (%) 24 or 48 h[d]
No active treatment	168	127 (5.0)	0.4 (1.0)	2.0 (4.5)	7.0 (8.0)	4 (2.4)
• No treatment	138	127 (5.0)	0.4 (1.0)	1.5 (4.0)	7.0 (8.0)	1 (0.7)
• HN-inducing med stopped	30	128.0 (7.0)	0.5 (0.9)	2.0 (6.0)	8.0 (14.0)	3 (10.0)
Fluid restriction	748	125 (8.0)	1.0 (2.3)	2.0 (5.0)	3.0 (4.0)	23 (2.6)
FR +NS	263	123.0 (8.0)	2.0 (4.0)	1.5 (5.0)	2.0 (1.5)	7 (2.5)
FR+Salt tabs	151	126.0 (6.0)	1.0 (2.7)	1.0 (5.0)	3.0 (3.0)	5 (3.0)
Isotonic	437	124 (8.0)	1.5 (3.0)	2.0 (5.0)	1.0 (1.0)	10 (2.1)

saline						
Hypertonic saline	86	121 (10.0)	3.0 (6.0)	4.0 (8.0)	1.0 (2.0)	15 (16.9)
Tolvaptan	225	127 (7.7)	3.0 (6.0)	4.0 (8.0)	2.0 (3.0)	30 (12.1)

P-values <0.05:

Baseline Sodium: No active treatment vs FR, FR+NS, NS, HS; FR vs FR+NS, NS, HS, Tolvaptan; NS vs FR+Salt tabs, HS, Tolvaptan; HS vs FR+NS, FR+Salt tabs, Tolvaptan. FR+NS vs FR+Salt tabs, Tolvaptan.

Overall Rate of Change: No active treatment vs FR, FR+NS, FR+Salt tabs, NS, HS, Tolvaptan; FR vs FR+NS, NS, HS, Tolvaptan; NS vs HS, Tolvaptan. HS vs FR+NS, FR+Salt tabs; Tolvaptan vs FR+NS, FR+Salt tabs; FR+NS vs FR+Salt tabs.

First 24 hour change: No active treatment vs HS, Tolvaptan; FR vs HS, Tolvaptan; NS vs HS, Tolvaptan; HS vs FR+NS, FR+Salt tabs; Tolvaptan vs FR+NS, FR+Salt tabs.

Duration of therapy: No active treatment vs FR, FR+NS, FR+Salt tabs, NS, HS, Tolvaptan; FR vs FR+NS, NS, HS, Tolvaptan; NS vs FR+Salt tabs, Tolvaptan; HS vs FR+Salt tabs, Tolvaptan; Tolvaptan vs FR+NS, FR+Salt tabs; FR+NS vs FR+Salt tabs.

Overcorrection: No active treatment vs HS, Tolvaptan; FR vs HS, Tolvaptan; NS vs HS, Tolvaptan; HS vs FR+NS, FR+Salt tabs; Tolvaptan vs FR+NS, FR+Salt tabs.

Baseline Sodium US vs EU-No active treatment, fluid restriction, Normal saline, FR+NS

First 24 hour change US vs EU-Tolvaptan

Durations of therapy US vs EU-No active treatment, Fluid Restriction, Normal saline, FR+NS

Table 4. Achievement of Correction Benchmarks by Monotherapy Episode.

	Δ[Na^+] ≥5 mEq/L		[Na^+] >130 mEq/L		[Na^+] >135 mEq/L	
Monotherapy Episode Treatment	**Clinician Diagnosed SIADH**	**Laboratory Diagnosed SIADH**	**Clinician Diagnosed SIADH**	**Laboratory Diagnosed SIADH**	**Clinician Diagnosed SIADH**	**Laboratory Diagnosed SIADH**
No active treatment (n=168, 46)	41%	44%	45%	46%	20%	24%
• No treatment (n=138, 37)	39%	35%	43%	38%	19%	16%
• HN-inducing med stopped (n=30, 9)	47%	78%	57%	78%	27%	56%
Fluid Restriction (n=625, 352)	44%	43%	29%	28%	10%	9%
Fluid Restriction+Isotonic Saline (n=241, 148)	42%	46%	25%	24%	8%	7%
Fluid Restriction+Salt tabs (n=129, 81)	46%	42%	37%	42%	11%	11%
Isotonic Saline (n=384, 206)	36%	29%	20%	19%	4%	4%
Hypertonic Saline (n=78, 40)	60%	60%	26%	25%	13%	15%
Tolvaptan (n=183, 76)	78%	70%	74%	67%	40%	28%

Abbreviations: [Na^+], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Supplementary Table 1. Inclusion and Exclusion Criteria

Inclusion criteria

1. Adults aged ≥18 y who are hospitalized
2. Euvolemic or hypervolemic hyponatremia with serum [Na^+] ≤130 mEq/L
3. For euvolemic hyponatremia:
    - Euvolemia defined as absence of clinical and historical evidence of extracellular fluid volume depletion or sequestration, and absence of edema and ascites; or
    - Physician diagnosis of SIADH
4. For hypervolemic hyponatremia (US sites only):
    - Hypervolemia defined as excess extracellular fluid volume manifesting as dependent edema or ascites
    - Patients may have ≥1 of following underlying comorbid conditions:
        - Congestive heart failure
        - Cirrhosis or liver failure
        - Nephrotic syndrome

Exclusion criteria

1. Hypovolemic hyponatremia
2. Use of any investigational drug, biologic, or device during study
3. Random blood glucose >250 mg/dL, or between 180 and 250 mg/dL with serum [Na^+] of 127–130 mEq/L at entry
4. Receiving renal replacement therapy for chronic kidney disease or acute kidney injury while hyponatremic

Abbreviations: [Na^+], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

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Supplemental Table 2. Underlying Etiology of SIADH for all SIADH Patients and the United States (US) and European Union (EU) Cohorts Separately.

	All (n=1524)	**US (n=1034)**	**EU (n=490)**
Underlying SIADH Etiology Known[a]	979 (64.2%)	646 (62.5%)	333 (68.0%)
Etiology:			
Tumors[b]	360 (23.6%)	208 (20.1%)	152 (31.0%)
CNS disorder[c]	129 (8.5%)	86 (8.3%)	43 (8.8%)
Drug induced[d]	271 (17.8%)	188 (18.2%)	83 (16.9%)
Pulmonary diseases[e]	163 (10.7%)	121 (11.7%)	42 (8.6%)
Other[f]	214 (14.1%)	149 (14.4%)	65 (13.3%)
Idiopathic or Unknown[b]	543 (35.6%)	396 (38.3%)	157 (32.0%)
Missing	2 (0.1%)	2 (0.2%)	0 (0.0%)

[a]US SIADH vs EU SIADH: $P = 0.003$.

[b]US SIADH vs EU SIADH: $P < 0.001$.

[c]US SIADH vs EU SIADH: $P = 0.48$.

65 [d]US SIADH vs EU SIADH: *P* = 0.94.

66 [e]US SIADH vs EU SIADH: *P* = 0.17.

67 [f]US SIADH vs EU SIADH: *P* = 1.00.

68

Supplementary Table 3. Patients with HN Inducing Med SIADH by Drug Category

Drug Category	N	Percentage of Patients (%)
Antidepressant	119	35.1
Antiepileptic	76	22.4
Antipsychotic	35	10.3
Diuretic[a]	25	7.4
Opiate	19	5.6
NSAID	13	3.8
ACEI/ARB	12	3.5
PPI	7	2.1
Antidiuretic	6	1.8
Anxiolytic	6	1.8
Chemotherapy	4	1.2
Unknown	4	1.2
Other[b]	13	3.8

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

[a]All patients on thiazide diuretics were excluded from the per-protocol SIADH group (see Methods). Patients on non-thiazide diuretics were allowed to remain in the per-protocol group if their clinical picture was consistent with a diagnosis of SIADH.

[b]Includes those drugs that were given to <1% of patients (n=13, Ethanol=3, Hallucinogenic=2, Hypnotic=2, Beta Blocker=1, Glucocorticoid=1, Immunosuppressant=1, Muscle Relaxant=1, Nicotine Agaonist=1, Protease Inhibitor=1)

Supplemental Table 4. Categorical Change in Serum Sodium Concentration from Baseline by Monotherapy.

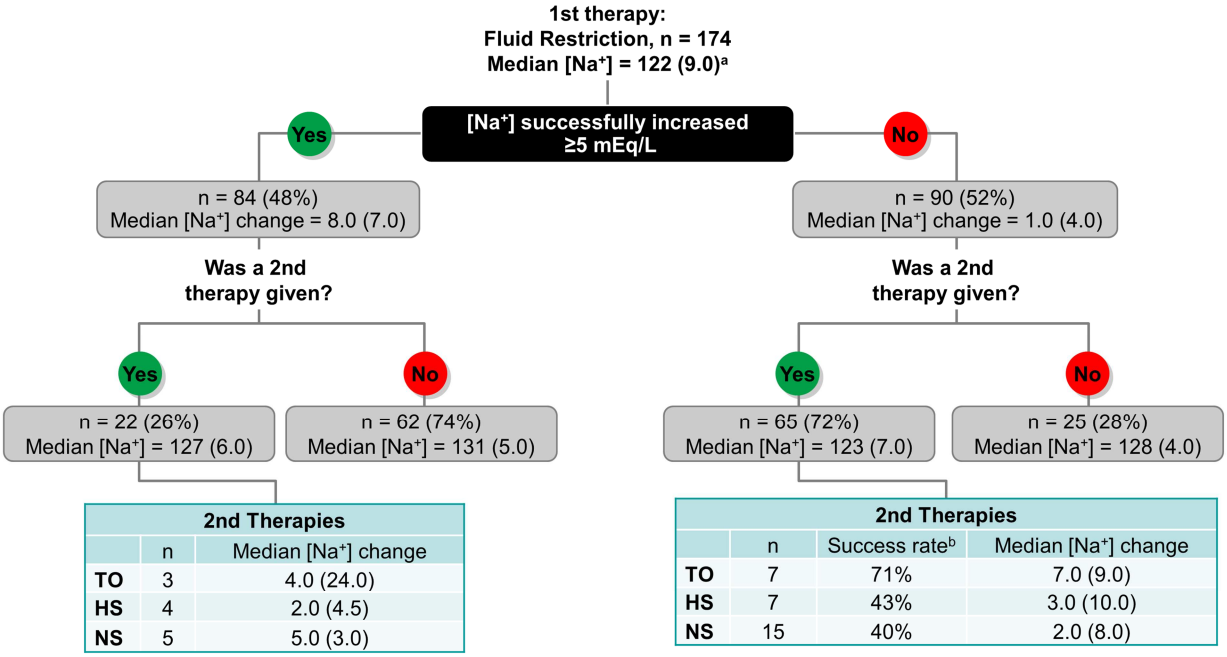
	Clinician Diagnosed SIADH (n=1524)	Laboratory Diagnosed SIADH (n=729)
No Active Therapy	170	46
Increase > 2 mmol/L	91 (53.5%)	27 (58.7%)
Within +/- 2 mmol/L	61 (35.9%)	15 (32.6%)
Decrease > 2 mmol/L	16 (9.4%)	4 (8.7%)
Unknown	2 (1.2%)	0 (0.0%)
No Therapy	140	37
Increase > 2 mmol/L	73 (52.1%)	20 (54.1%)
Within +/- 2 mmol/L	53 (37.9%)	14 (37.8%)
Decrease > 2 mmol/L	12 (8.6%)	3 (8.1%)
Unknown	2 (1.4%)	0 (0.0%)
HN Inducing Med Stopped	30	9
Increase > 2 mmol/L	18 (60.0%)	7 (77.8%)
Within +/- 2 mmol/L	8 (26.7%)	1 (11.1%)
Decrease > 2 mmol/L	4 (13.3%)	1 (11.1%)
Unknown	0 (0.0%)	0 (0.0%)
Fluid Restriction	393	206
Increase > 2 mmol/L	209 (53.2%)	113 (54.9%)

	Clinician Diagnosed SIADH (n=1524)	Laboratory Diagnosed SIADH (n=729)
Within +/- 2 mmol/L	112 (28.5%)	52 (25.2%)
Decrease > 2 mmol/L	28 (7.1%)	16 (7.8%)
Unknown	44 (1.2%)	25 (12.1%)
Normal Saline	343	184
Increase > 2 mmol/L	166 (48.4%)	82 (44.6%)
Within +/- 2 mmol/L	124 (36.2%)	74 (40.2%)
Decrease > 2 mmol/L	31 (9.0%)	18 (9.8%)
Unknown	22 (6.4%)	10 (5.4%)
Hypertonic Saline	49	19
Increase > 2 mmol/L	37 (75.5%)	14 (73.7%)
Within +/- 2 mmol/L	9 (18.4%)	5 (26.3%)
Decrease > 2 mmol/L	1 (2.0%)	0 (0.0%)
Unknown	2 (4.1%)	0 (0.0%)
Tolvaptan	83	20
Increase > 2 mmol/L	68 (81.9%)	15 (75.0%)
Within +/- 2 mmol/L	10 (12.0%)	3 (15.0%)
Decrease > 2 mmol/L	1 (1.2%)	0 (0.0%)
Unknown	4 (4.8%)	2 (10.0%)

A.

Outcomes and Second Therapies in Patients Initially Treated with Fluid Restriction – Laboratory Diagnosed SIADH

(Patients baseline [Na^+] ≤130 mEq/L)



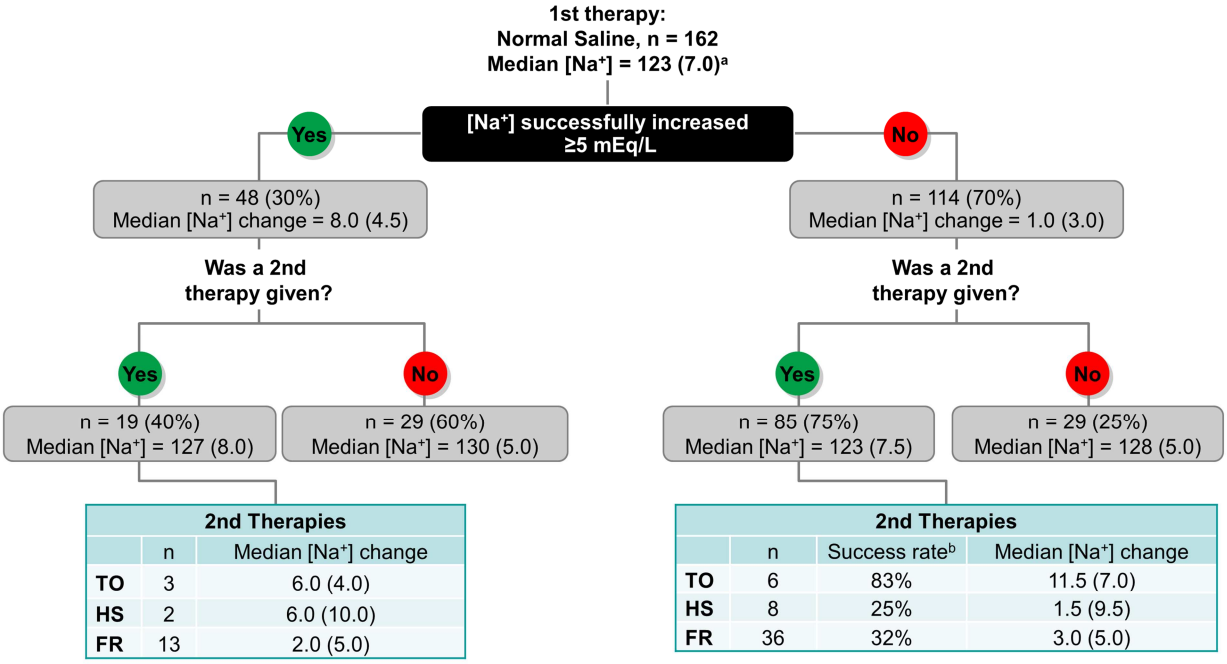
2nd Therapies		
	n	Median [Na^+] change
TO	3	4.0 (24.0)
HS	4	2.0 (4.5)
NS	5	5.0 (3.0)

2nd Therapies			
	n	Success rate[b]	Median [Na^+] change
TO	7	71%	7.0 (9.0)
HS	7	43%	3.0 (10.0)
NS	15	40%	2.0 (8.0)

B.

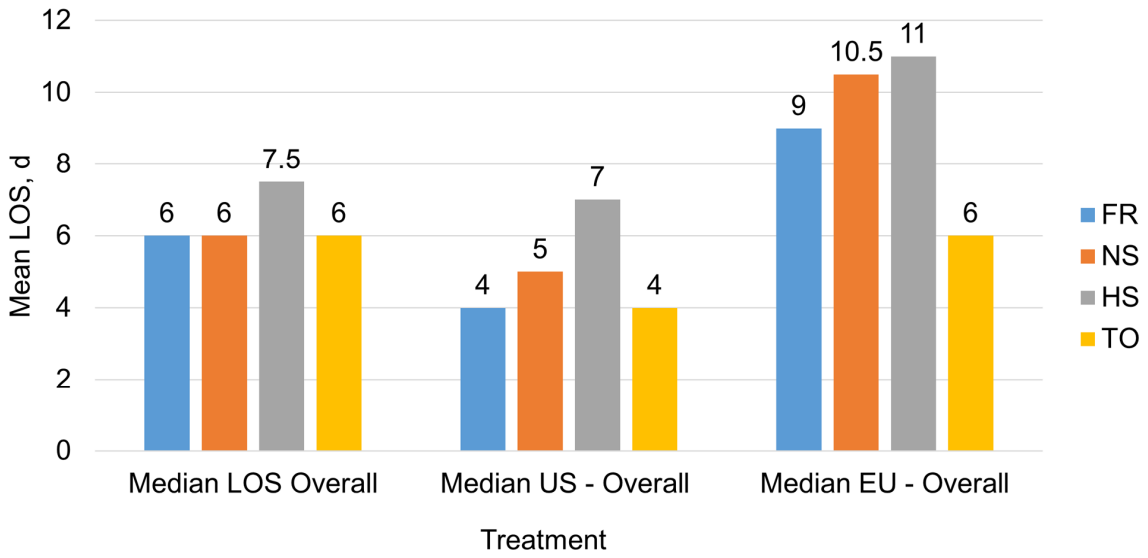
Outcomes and Second Therapies in Patients Initially Treated with Normal Saline – Laboratory Diagnosed SIADH

(Patients baseline [Na^+] ≤130 mEq/L)



2nd Therapies		
	n	Median [Na^+] change
TO	3	6.0 (4.0)
HS	2	6.0 (10.0)
FR	13	2.0 (5.0)

2nd Therapies			
	n	Success rate[b]	Median [Na^+] change
TO	6	83%	11.5 (7.0)
HS	8	25%	1.5 (9.5)
FR	36	32%	3.0 (5.0)



Hyponatremia in 1,524 hospitalized patients with SIADH was neither diagnosed nor treated successfully in more than half the cases studied across both the US and EU. Despite the availability of effective therapies, most patients with SIADH were discharged still hyponatremic. Success rates in correcting hyponatremia were significantly higher when appropriate laboratory tests were obtained and when pharmacological therapies were employed.