OPEN

Current treatment practice and outcomes. Report of the hyponatremia registry

Arthur Greenberg[1], Joseph G. Verbalis[2], Alpesh N. Amin[3], Volker R. Burst[4], Joseph A. Chiodo III[5], Jun R. Chiong[6], Joseph F. Dasta[7], Keith E. Friend[5], Paul J. Hauptman[8], Alessandro Peri[9] and Samuel H. Sigal[10]

[1]Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA; [2]Division of Endocrinology and Metabolism, Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia, USA; [3]Department of Medicine, University of California, Irvine, California, USA; [4]Department II of Internal Medicine: Nephrology, Rheumatology, Diabetes and General Internal Medicine, University Hospital of Cologne, Cologne, Germany; [5]Otsuka America Pharmaceutical, Princeton, New Jersey, USA; [6]Department of Medicine, Loma Linda University Medical Center, Loma Linda, California, USA; [7]University of Texas College of Pharmacy, Austin, Texas, USA; [8]Department of Medicine, Saint Louis University School of Medicine, St Louis, Missouri, USA; [9]Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy and [10]Division of Gastroenterology, Department of Medicine, NYU Langone Medical Center and School of Medicine, New York City, New York, USA

Current management practices for hyponatremia (HN) are incompletely understood. The HN Registry has recorded diagnostic measures, utilization, efficacy, and outcomes of therapy for eu- or hypervolemic HN. To better understand current practices, we analyzed data from 3087 adjudicated adult patients in the registry with serum sodium concentration of 130 mEq/l or less from 225 sites in the United States and European Union. Common initial monotherapy treatments were fluid restriction (35%), administration of isotonic (15%) or hypertonic saline (2%), and tolvaptan (5%); 17% received no active agent. Median (interquartile range) mEq/l serum sodium increases during the first day were as follows: no treatment, 1.0 (0.0–4.0); fluid restriction, 2.0 (0.0–4.0); isotonic saline, 3.0 (0.0–5.0); hypertonic saline, 5.0 (1.0–9.0); and tolvaptan, 4.0 (2.0–9.0). Adjusting for initial serum sodium concentration with logistic regression, the relative likelihoods for correction by 5 mEq/l or more (referent, fluid restriction) were 1.60 for hypertonic saline and 2.55 for tolvaptan. At discharge, serum sodium concentration was under 135 mEq/l in 78% of patients and 130 mEq/l or less in 49%. Overly rapid correction occurred in 7.9%. Thus, initial HN treatment often uses maneuvers of limited efficacy. Despite an association with poor outcomes and availability of effective therapy, most patients with HN are discharged from hospital still hyponatremic. Studies to assess short- and long-term benefits of correction of HN with effective therapies are needed.

Correspondence: *Arthur Greenberg, Division of Nephrology, Duke University Medical Center, 2424 Erwin Road, Suite 605, Durham, 27705 North Carolina, USA. E-mail: arthur.greenberg@duke.edu*

Received 15 July 2014; revised 24 November 2014; accepted 5 December 2014; published online 11 February 2015

Kidney International (2015) **88,** 167–177; doi:10.1038/ki.2015.4; published online 11 February 2015

KEYWORDS: acid-base and electrolytes; geriatric nephrology; vasopressin; water and volume homeostasis

Hyponatremia (HN), defined as a serum sodium concentration ($[Na^+]$) below the lower limit of normal, is the most common electrolyte disorder in hospitalized patients, with a prevalence as high as 30–42%.[1,2] HN is independently associated with mortality in congestive heart failure (CHF), cirrhosis, and hospitalized patients in general[3–7] and with increased hospital costs and readmission rates.[8,9] Chronic HN has been linked to impaired gait and balance, increased falls and fracture rates, and osteoporosis.[10–13] However, a causal role of HN for these associations is largely unproven.[14]

Correction of severe HN of sudden onset can be genuinely lifesaving,[15,] and treatment of chronic HN associated with neurological symptoms is undeniably beneficial. Despite the widespread clinical impression that correction of less severe chronic HN is also worthwhile, evidence-based data demonstrating clinical benefit are limited.[10,16–18]

Hypovolemic HN responds readily to volume repletion. Until recently, treatment of hypervolemic HN has been limited to fluid restriction (FR) and correction of the underlying disorder. Treatment modalities for euvolemic HN have included FR, hypertonic saline (HS), loop diuretics, demeclocycline, and urea. With the approval of the vasopressin-receptor antagonists conivaptan and tolvaptan, more targeted treatment for euvolemic and hypervolemic HN became available. It remains uncertain how treatment options are employed, and how correction magnitude and incidence of adverse outcomes are affected by the type of therapy. With this background, the multinational HN

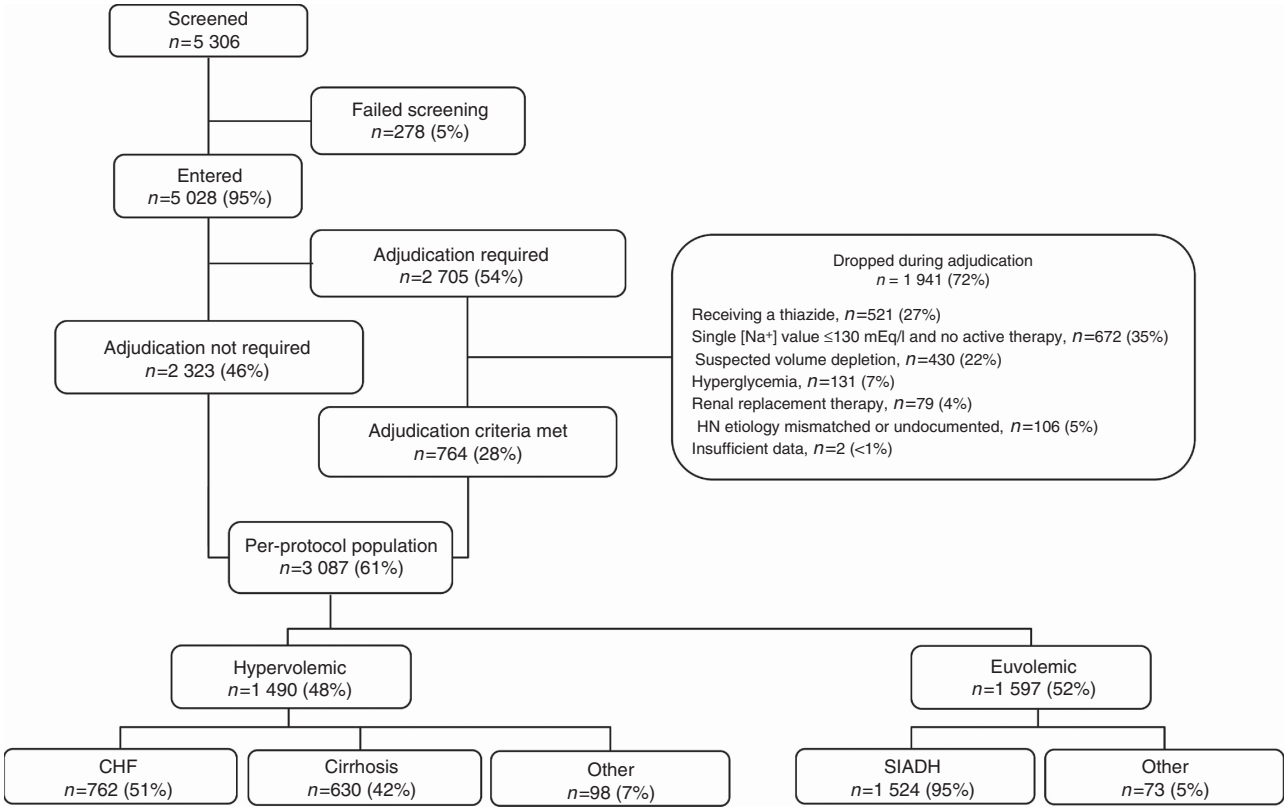

Figure 1 | Consort diagram showing patient flow. The 3087 patients in bottom row constitute the per-protocol group. All analyses are based on this group. Note: patients reporting multiple comorbidities were counted in the "Other" group. See Materials and Methods section and Supplementary Table S4 online for description of the adjudication process. CHF, congestive heart failure; HN, hyponatremia; [Na^+], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Registry was initiated to assess the current state of treatment of euvolemic and hypervolemic HN in diverse, real-world hospital settings. Its specific purpose was 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 [Na^+]. An additional goal was to determine which treatments posed the greatest risk of overly rapid correction and osmotic demyelination.[19]

RESULTS

Characteristics of study population

A total of 5028 patients were entered (Figure 1) between September 2010 and February 2013. One or more criteria requiring adjudication were met by 2705 patients (54% of those entered), and 1941 of those (72%) failed adjudication. The 764 patients (28%) retained after adjudication and the 2323 (46% of those entered) not requiring adjudication comprise the 3087 individuals of the per-protocol data set. A sensitivity analysis performed with and without the 951 potentially hypovolemic patients excluded because of thiazide use or evidence of volume depletion showed no significant differences in rates of [Na^+] change or achievement of [Na^+] correction benchmarks. The syndrome of inappropriate antidiuretic hormone (SIADH), CHF, and cirrhosis data sets include patients in whom these diagnoses were made by treating physicians.

Patient demographics and baseline characteristics are shown in Table 1. Patients with cirrhosis were younger and more likely to be male compared with patients with SIADH or CHF. A prior episode of HN was known to have occurred in 909 patients (29%) and was most likely in patients with cirrhosis and least likely in those with SIADH. Most patients (71%) were under the care of a generalist rather than an internal medicine subspecialist.

Diagnosis

In the 1524 patients with SIADH, 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%. Cortisol was measured in 33% of patients and thyroid-stimulating hormone in 64%. All five of these measurements were made in 21% of patients.

Treatment selection

As shown in Table 2, 17% of patients received no active HN therapy. Utilization varied with [Na^+]. Only 3% of patients with severe HN received no therapy compared with 13% with

Table 1 | Baseline demographic characteristics by comorbidity

	All Patients[a] ($N = 3087$)	SIADH ($n = 1524$)	CHF ($n = 762$)	Cirrhosis ($n = 630$)
Age distribution, n *(%)*[b]				
⩽50 years	479 (16)	186 (12)	76 (10)	190 (30)
51–64 years	937 (30)	373 (25)	164 (22)	339 (54)
65–74 years	587 (19)	339 (22)	127 (17)	81 (13)
⩾75 years	1084 (35)	626 (41)	395 (52)	20 (3)
Men, *n* (%)[c]	1558 (51)	695 (46)	352 (46)	419 (67)
Race distribution: US only, n *(%)*[b]				
White	1927 (74)	770 (75)	575 (76)	455 (72)
African American	309 (12)	108 (10)	123 (16)	58 (9)
Asian	57 (2)	29 (3)	10 (1)	13 (2)
Other	154 (6)	61 (6)	30 (4)	53 (9)
Unknown	149 (6)	66 (6)	24 (3)	51 (8)
Median initial [Na +] (IQR), mEq/l[d]	125.0 (120.0–128.0)	124.0 (119.0–127.0)	126.0 (122.0–129.0)	125.0 (121.0–128.0)
Median initial BUN (IQR), mg/dl[b]	15.83 (10.0–25.0)	12.0 (9.0–17.0)	22.0 (14.0–36.0)	20.0 (13.0–33.0)
Median initial creatinine (IQR), mg/dl[e]	0.85 (0.6–1.2)	0.70 (0.6–0.9)	1.10 (0.8–1.6)	1.03 (0.8–1.5)
Initial BUN:creatinine ratio (IQR),[b]	17.8 (13.3–23.4)	16.7 (12.2–21.9)	20.0 (15.2–26.0)	18.2 (14.1–24.0)
Median initial blood glucose (IQR), mg/dl	112 (97.0–134.0)	110 (96.0–130.0)	116 (101.0–141.0)	109 (95.0–133.0)
Prior HN, n *(%)*[b,f]				
Yes	909 (29)	407 (27)	209 (27)	240 (38)
No	1176 (38)	687 (45)	253 (33)	178 (28)
Unknown	1001 (32)	430 (28)	299 (39)	212 (34)
HN at admission, n *(%)*[g]				
Yes	2532 (82)	1252 (82)	605 (79)	549 (87)
No	531 (17)	253 (17)	153 (20)	81 (13)
Unknown	24 (1)	19 (1)	4 (1)	0 (0)
Primary physician specialty, n *(%)*				
Nephrologist	104 (3)	82 (5)	10 (1)	8 (1)
Endocrinologist	108 (4)	106 (7)	2 (<1)	0
Cardiologist	321 (10)	49 (3)	247 (32)	7 (1)
Hepatologist	260 (8)	3 (<1)	4 (1)	246 (39)
Oncologist	111 (4)	92 (6)	5 (1)	11 (2)
Generalist	1844 (60)	944 (62)	466 (61)	315 (50)
Other	338 (11)	247 (16)	28 (4)	43 (7)
HN subspecialist consulted, n *(%)*[h,i]				
No	1989 (64)	839 (55)	530 (70)	501 (80)
Yes	1096 (36)	683 (45)	232 (30)	129 (21)

Abbreviations: BUN, blood urea nitrogen; CHF, congestive heart failure; HN, hyponatremia; [Na^+], sodium concentration; IQR, interquartile range; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Median (IQR) B-type natriuretic peptide value in the CHF patients was 733.5 pg/ml (1465.0), $n = 410$.
[a]Includes 171 either patients without a diagnosis of SIADH, cirrhosis, or CHF or with multiple comorbidities.
[b]SIADH versus CHF and cirrhosis, and CHF vs. cirrhosis: $P < 0.001$.
[c]SIADH versus CHF: $P = 0.79$; and SIADH and CHF versus cirrhosis: $P < 0.001$.
[d]SIADH versus CHF and cirrhosis: $P < 0.001$; CHF versus cirrhosis: $P = 0.01$.
[e]SIADH versus CHF and cirrhosis: $P < 0.001$; and CHF versus cirrhosis: $P = 0.005$.
[f]HN during previous hospital admission in prior 12 months.
[g]Data missing for 24 patients in all, 19 in SIADH and 4 in CHF populations; SIADH versus CHF: $P = 0.04$; SIADH versus cirrhosis: $P = 0.001$; and CHF versus cirrhosis: $P < 0.001$.
[h]SIADH versus CHF and cirrhosis: $P < 0.001$; and CHF versus cirrhosis: $P = 0.01$.
[i]HN specialist defined as nephrologist or endocrinologist.

moderate HN and 25% with mild HN ($P < 0.001$). Stopping a medication that may induce SIADH could also be considered an active treatment; of the 509 patients who received no active HN therapy, 265 (52%) were receiving a potentially HN-inducing medication (see Supplementary Table S1 online for list), which was discontinued in 29 (11%).

The therapies utilized, according to underlying diagnosis or severity of HN, are shown in Figures 2 and 3. Overall, 55% of patients were treated with FR or isotonic saline (NS) or both. Treatments more likely to result in an increase in [Na^+]—HS or tolvaptan—were used in 7% of patients.

FR alone was selected most frequently. NS alone or with FR was used significantly more often in patients with SIADH (30%) than with CHF (7%) or cirrhosis (10%). Patients with lower baseline [Na^+] were more likely to receive HS.

Treatment efficacy and outcomes

When used as a monotherapy, FR was least effective, although more rigorous FR (⩽1000 ml/day) resulted in a more rapid

Table 2 | Treatment utilization according to diagnosis or severity of HN

	Number of therapy episodes or unique therapies employed			
	No therapy, *n* (%)	1 Episode, *n* (%)	⩾2 Episodes, n (%)	Median therapy episodes/patient (IQR), *n*
All patients ($n=3087$)	509 (17)	1148 (37)	1430 (46)	2.0 (1.0–3.0)
Comorbidity				
SIADH ($n=1524$)	170 (11)	451 (30)	903 (59)	2.0 (1.0–3.0)
CHF ($n=762$)	176 (23)	325 (43)	261 (34)	1.0 (1.0–3.0)
Cirrhosis ($n=630$)	125 (20)	298 (47)	207 (33)	1.0 (1.0–2.0)
Starting [Na^+], mEq/l				
<120 mEq/l ($n=653$)	22 (3)	207 (32)	424 (65)	2.0 (1.0–3.0)
120–125 mEq/l ($n=1048$)	139 (13)	379 (36)	530 (51)	2.0 (1.0–3.0)
>125–130 mEq/l ($n=1386$)	348 (25)	562 (41)	476 (34)	1.0 (1.0–2.0)

Abbreviations: CHF, congestive heart failure; HN, hyponatremia; IQR, interquartile range; [Na^+], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Episode of therapy refers to an interval during which a treatment or combination of treatments was given specifically for HN without interruption. For purposes of this analysis, treatment of CHF patients for congestion was not considered a specific treatment of HN as any patient with CHF would have been so treated.

No HN therapy: $P<0.001$, SIADH versus CHF and cirrhosis; $P=0.14$, CHF versus cirrhosis; $P<0.001$, mild versus moderate and severe, and moderate versus severe HN.

One episode: $P<0.001$, SIADH versus CHF and cirrhosis; $P=0.09$, CHF versus cirrhosis; $P=0.08$, mild versus severe HN; $P=0.03$, mild versus moderate HN; $P=0.06$, moderate versus severe HN.

⩾2 episodes: $P<0.001$, SIADH versus CHF and cirrhosis; $P=0.58$, CHF versus cirrhosis; $P<0.001$, mild versus moderate and severe, and moderate versus severe HN.

Therapy episode/patient: $P<0.001$, SIADH versus CHF and cirrhosis; $P=0.29$, CHF versus cirrhosis; $P<0.001$, mild versus moderate and severe, and moderate versus severe HN.

[Na^+] increase compared with a lesser degree of FR (Table 3). Addition of FR to the other monotherapies had a small effect, if any. Median (interquartile range) rate of change with NS alone was 2.0 (0.3–4.0) versus 2.4 (1.0–5.0) mEq/l/day with addition of FR ($P=0.004$), but rate of change, correction rate, or frequency of overly rapid correction did not change significantly with addition of FR to any other monotherapy. Examined categorically (Figure 4), correction of [Na^+], defined *de minimus* as a [Na^+] increase >2 mEq/l, was more likely and lack of correction, defined as a final [Na^+] within 2 mEq/l of the starting [Na^+], less likely with HS or tolvaptan than with FR or NS. [Na^+] was also less likely to decrease by >2 mEq/l in patients who received HS or tolvaptan than in patients who received FR or NS as monotherapy. For decrease >2 mEq/l: FR versus HS, $P=0.03$; FR versus tolvaptan, $P<0.01$; NS versus HS, $P=0.04$; NS versus tolvaptan, $P=0.01$.

Overall success in reaching various correction benchmarks is shown in Table 4 for initial monotherapy episodes. Overall, 22% of patients reached a normal [Na^+] ⩾135 mEq/l. Rate of correction by ⩾5 mEq/l with HS was similar to that of tolvaptan in the unadjusted analysis. However, the utilization of various treatments varied with baseline [Na^+] (Figure 3). When achievement of [Na^+] change benchmarks was adjusted for starting [Na^+] using logistic regression (Table 4), only tolvaptan produced a consistently higher rate of success in reaching all three benchmarks. Compared with FR, NS was worse in two of three benchmarks. HS was more likely to result in a [Na^+] ⩾5 mEq/l. When the [Na^+] interaction was examined categorically rather than continuously (Supplementary Table S2 online), the relative likelihood of reaching any of the three benchmarks for HS compared with FR was not different from unity for mild, moderate, or severe HN. In a similar categorical analysis comparing tolvaptan with FR, the relative likelihood of correction to [Na^+] >130 mEq/l was 3.131 (1.7324–5.658) with mild HN, 2.106 (1.435–3.092) with moderate HN, and 1.410 (1.007–1.974) with severe HN. The relative likelihood of correction >5 mEq/l was 2.202 (1.446–3.353) with mild HN and 3.533 (1.772–7.044) for moderate HN. The relative likelihood of correction to [Na^+] >135 mEq/l was 1.817 (1.340–2.464) for mild HN and 1.200 (1.021–1.409) for moderate HN. The relative likelihoods for other benchmarks or starting [Na^+] values did not differ from unity. In some categories, the number of cases was quite small.

As FR was the most frequently prescribed initial therapy, we separately analyzed the course of patients after FR. A total of 922 patients (30%) with a baseline [Na^+] <130 mEq/l were treated with FR initially (Figure 5). The majority did not correct [Na^+] by an increment ⩾5 mEq/l and the majority of those patients received no additional treatment.

Overly rapid correction of [Na^+] occurred in 7.9% of patients overall (Table 5) and was most likely in patients with SIADH (10.7%) and least likely with cirrhosis (3.6%; $P<0.001$, SIADH vs. cirrhosis). Of patients who received no active therapy, 1.4% experienced overly rapid correction. Compared with no therapy, the relative risk (95% confidence interval) for overly rapid correction was 1.6 (0.70–3.57) for FR, 2.35 (0.97–5.65) for NS, 12.01 (5.14–28.04) for HS, and 8.57 (3.84–19.12) for tolvaptan. Overall, 17.1% of patients receiving HS and 10.8% of patients receiving tolvaptan monotherapy at any time ($P=0.08$, HS vs. tolvaptan) experienced overly rapid correction, similar to the results for initial treatment responses (Table 3). Included among the overly rapid correction episodes that occurred with active therapy are one episode with HS and two with tolvaptan in patients

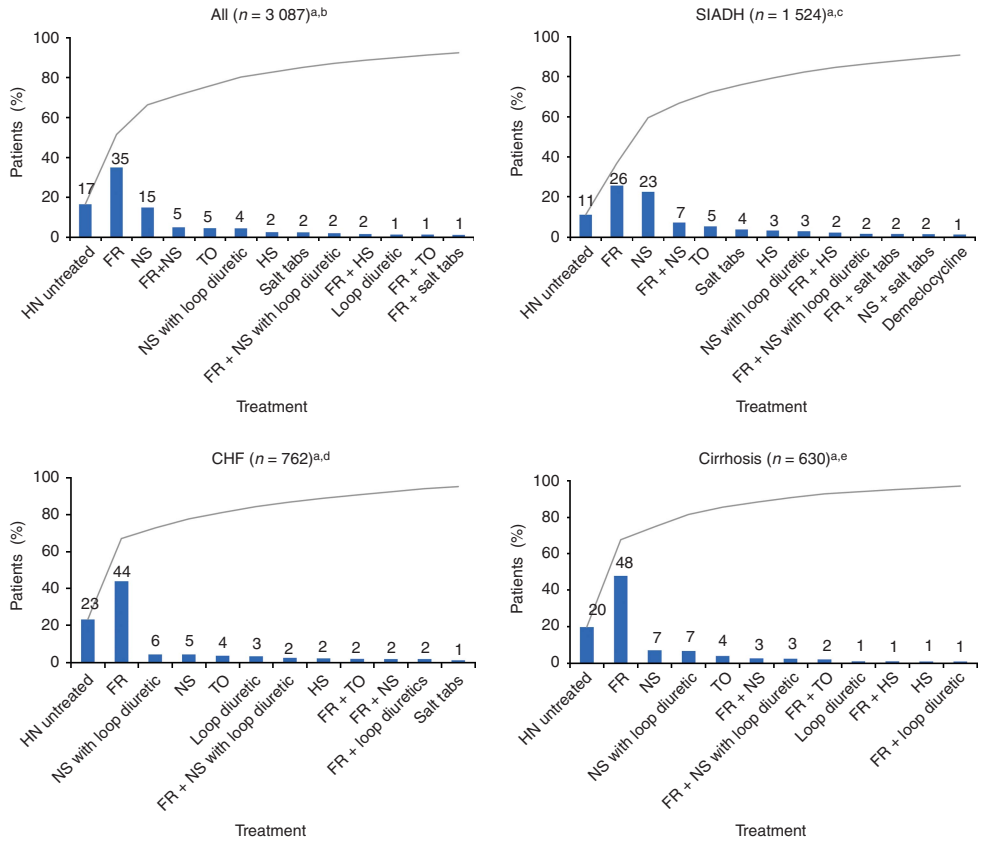

Figure 2 | Initial therapy of hyponatremia. Bars show percentages of patients receiving specified therapy. Lines show cumulative proportions of patients receiving therapies shown. CHF, congestive heart failure; FR, fluid restriction; HN untreated, no specific treatment targeted at hyponatremia at any time during hospitalization; HS, hypertonic saline; NS, isotonic saline; SIADH, syndrome of inappropriate antidiuretic hormone; TO, tolvaptan. [a]Therapies given to ⩾1% of patients; [b]7.6.0%, [c]9.3%, [d]5.2%, and [e]3.1% of patients received other unique therapies.

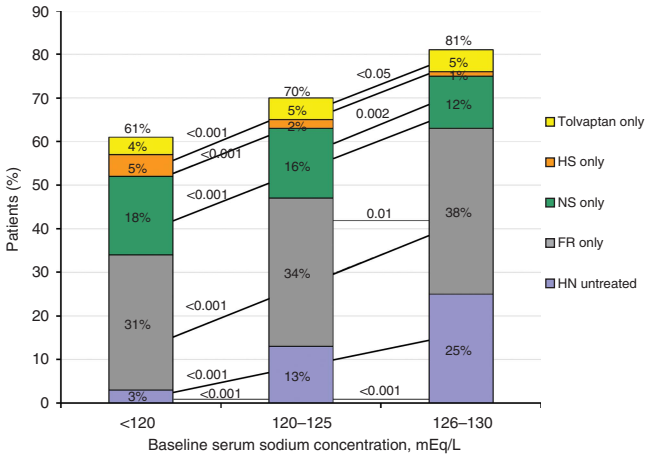

Figure 3 | Choice of initial therapy according to baseline serum sodium concentration: all patients. *P*-values shown for comparisons where $P<0.05$; all other intergroup comparisons did not reach statistical significance. Dotted lines indicate *P*-value comparisons for <120- vs. 126–130-mEq/l groups. FR, fluid restriction; HN, hyponatremia; HS, hypertonic saline; NS, isotonic saline. [a]No prescribed therapy specifically targeting HN.

who were also receiving variable doses of desmopressin to treat diabetes insipidus post parasellar surgery. A further six episodes with tolvaptan occurred after suprasellar or pituitary procedures alone. In total, six of these postoperative cases occurred at a single center. The group with the lowest starting $[Na^+]$ was at greatest risk for overly rapid correction: 3.6% for mild HN (referent), 5.0% (relative risk 1.39 (95% confidence interval 0.94–2.06)) for moderate HN, and 19% (5.34 (3.86–7.40)) for severe HN. No cases of the osmotic demyelination syndrome were documented in the HN Registry.

A generalist or specialist other than an HN specialist (i.e., nephrologist or endocrinologist) served as attending physician for 2775 patients. Of this subset, 619 of 1035 patients (60%) for whom a HN specialist was consulted versus 767 of 1720 (45%) for whom no HN specialist was consulted were discharged with $[Na^+] > 130$ mEq/l ($P<0.001$).

The mean length of stay was 10.3 ± 9.2 days for the group as a whole and did not vary by category of $[Na^+]$, diagnosis, or treatment employed. Comparisons of median length of stay for patients on any monotherapy tended to be longer for the group of patients not discharged until $[Na^+]$ was >130 mEq/l (Supplementary Figure S1 online). Correction of HN to $[Na^+] > 130$ mEq/l was not associated with survival; 7% of all patients who corrected versus 8% who did not correct ($P=0.58$) died or were discharged to hospice care.

Table 3 | Response to therapy for initial monotherapy episodes

Treatment	Patients, *n*	Median baseline [Na^+] (IQR), mEq/l	Median rate of [Na^+] change (IQR), mEq/l/day[a]	Median first day change (IQR), mEq/l/day[b]	Mean duration of Rx (IQR), days[c]	Overly rapid correction, *n* (%)	
						24 or 48 h[d]	24 Hours[e]
No treatment	507	127.0 (125.0–129.0)	0.4 (0.0–1.0)	1.0 (0.0–4.0)	6.0 (4.0–9.0)	7 (1.4)	7 (1.4)
Fluid							
restriction	992	125.0 (121.0–127.0)	1.0 (0.0–2.0)	2.0 (0.0–4.0)	4.0 (2.0–7.0)	15 (1.4)	13 (1.2)
⩽1000 ml	399	123.0 (120.0–126.0)	1.2 (0.3–2.5)	2.0 (0.0–4.0)	3.0 (1.0–5.0)	4 (1.0)	4 (1.0)
>1000 ml	529	126.0 (122.0–128.0)	0.7 (0.0–2.0)	2.0 (0.0–4.0)	4.0 (2.0–7.0)	7 (1.3)	6 (1.1)
Normal saline	428	123.0 (119.0–127.0)	2.0 (0.3–4.0)	3.0 (0.0–5.0)	1.0 (1.0–2.0)	13 (2.9)	10 (2.2)
Hypertonic saline	72	118.5 (114.5–124.0)	3.1 (1.7–7.8)	5.0 (1.0–9.0)	2.0 (1.0–3.0)	12 (16.0)	11 (14.7)
Tolvaptan	131	124.0 (120.0–128.0)	3.3 (1.4–7.0)	4.0 (2.0–9.0)	2.0 (1.0–4.0)	16 (11.6)	12 (8.7)

Abbreviations: HN, hyponatremia; [Na^+], sodium concentration; IQR, interquartile range; Rx, treatment.
Table comprises results of the first treatment given specifically to treat HN if only a single modality was used.
[a]Calculated as total increment in [Na^+] during the period of treatment utilization/no. of treatment days (interval of HN used for no treatment group).
[b]Calculated incremental change during the first 24 ± 12 h window. The actual interval for any individual patient ranged from 12 to 36 h, depending on the timing of the reported laboratory values.
[c]Duration of HN therapy is defined as the last day of initial HN therapy episode minus the start of the initial HN therapy episode + 1.
[d]Defined as increment in [Na^+] >12 mEq/l in 24 h or 18 mEq/l in 48 h.
[e]Defined as increment in [Na^+] >12 mEq/l in 24 h.

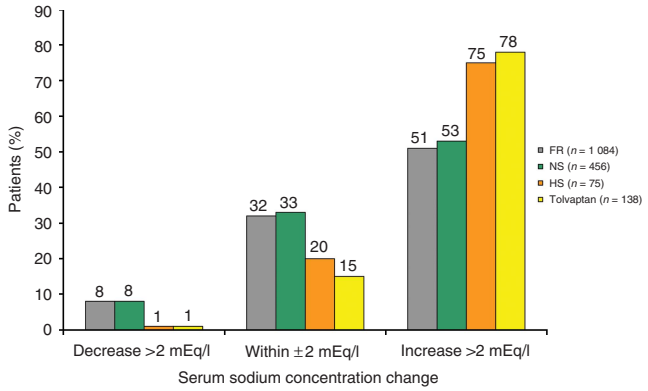

Figure 4 | Change in serum sodium concentration from baseline by initial monotherapy. FR, fluid restriction; HN, hyponatremia; NS, isotonic saline.

DISCUSSION

The HN Registry is the largest observational HN study to date and unique in its examination of the diagnosis, treatment, and outcome of HN in diverse hospital settings in the US and EU. Several important and novel findings have emerged from analysis of the results.

Determining the cause of HN is the first step in evaluating patients with HN and is crucial to guiding correct management.[20–22] Specific testing is generally not required with hypervolemic HN, but proper diagnosis of SIADH requires measurement of urine and plasma osmolality and urine [Na^+] at a minimum.[20,22,23] Only 47% of patients with SIADH as identified by treating physicians had all three cardinal tests performed, and 11% underwent none. The full diagnostic criteria include normal thyroid and adrenal function,[24] but only 21% of identified SIADH patients underwent cortisol and thyroid hormone determinations, along with the required electrolyte and osmolality measurements. These results confirm previous findings of smaller single-center studies.[25,26] The failure to make a precise diagnosis could have important sequelae.

HN has been associated with poor outcomes and higher hospital costs.[3,4,6–8,10] Correction of HN in selected patients with CHF is associated with improved survival,[16,17] and improved long-term survival following correction of HN in patients in general has been observed.[27] Experimentally, HN has been shown to have direct effects on cardiac fibrosis and myocyte function.[28,29] HN at hospital discharge is associated with risk of readmission.[17] Despite the suggestion from these studies that HN is deleterious, the results of the HN Registry strongly infer that clinicians are not presently convinced that correction of HN is worthwhile. Fully 17% of patients received no specific treatment for HN beyond discontinuing potentially HN-inducing medicines or treating conditions like pain, pneumonia, or CHF that may lead to HN. Furthermore, more than three quarters of patients were discharged still hyponatremic. Even using a less stringent criterion, only half of the patients overall reached a [Na^+] >130 mEq/l by the time of discharge. Among the 56% of patients treated initially with FR alone who failed to increase [Na^+] by >5 mEq/l, the treating physicians selected a second treatment in only 44%.

In the HN Registry, the choice of treatment, like the choice of diagnostic studies, was left up to the treating physicians. FR was used most often as the initial therapy irrespective of the etiology of the HN. This therapy is unlikely to result in an 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, but these parameters were rarely evaluated.[20,21,30,31] Among patients in the HN Registry, over the first day of its use as monotherapy, FR led only to a very modest rise in [Na^+], 2.0 mEq/l. Characterization of the categorical responses of individual patients showed that 8% treated initially with FR or NS actually

Table 4 | Achievement of correction benchmarks

	$[Na^+] > 130$ mEq/l	$\Delta[Na^+] \geqslant 5$ mEq/l	$[Na^+] > 135$ mEq/l
By diagnosis			
Diagnosis, *n* (%)[a]			
All ($N = 2948$)	1494 (51)	1790 (61)	635 (22)
SIADH ($n = 1422$)	809 (57)	981 (69)	361 (25)
CHF ($n = 742$)	357 (48)	395 (53)	139 (19)
Cirrhosis ($n = 618$)	239 (39)	316 (51)	100 (16)
By initial monotherapy episode, unadjusted for baseline sodium concentration			
Initial treatment, *n* (%)[b]			
No treatment ($n = 507$)	210 (41)	195 (39)	93 (18)
Fluid restriction ($n = 922$)	269 (29)	402 (44)	93 (10)
$\leqslant 1000$ ml ($n = 386$)	93 (24)	180 (47)	31 (8)
> 1000 ml ($n = 474$)	137 (29)	185 (39)	46 (10)
Normal saline ($n = 397$)	66 (17)	162 (41)	17 (4)
Hypertonic saline ($n = 71$)	18 (25)	46 (65)	7 (10)
Tolvaptan ($n = 122$)	80 (66)	95 (78)	41 (34)
By initial monotherapy episode, baseline sodium concentration $\leqslant 120$			
Initial treatment, *n* (%)[b]			
No treatment ($n = 22$)	12 (55)	21 (95)	6 (27)
Fluid restriction ($n = 189$)	42 (22)	122 (65)	16 (8)
Normal saline ($n = 116$)	6 (5)	78 (67)	3 (3)
Hypertonic saline ($n = 37$)	5 (14)	29 (78)	1 (3)
Tolvaptan ($n = 29$)	13 (45)	24 (83)	6 (21)
By initial monotherapy episode, baseline sodium concentration 120–125			
Initial treatment, *n* (%)[b]			
No treatment ($n = 138$)	47 (34)	81 (59)	25 (18)
Fluid restriction ($n = 382$)	91 (24)	181 (47)	31 (8)
Normal saline ($n = 170$)	20 (12)	63 (37)	6 (4)
Hypertonic saline ($n = 25$)	9 (36)	14 (56)	4 (16)
Tolvaptan ($n = 47$)	30 (64)	40 (85)	11 (23)
By initial monotherapy episode, baseline sodium concentration > 125–130			
Initial treatment, *n* (%)[b]			
No treatment ($n = 347$)	151 (44)	93 (27)	62 (18)
Fluid restriction ($n = 351$)	136 (39)	99 (28)	46 (13)
Normal saline ($n = 111$)	40 (36)	21 (19)	8 (7)
Hypertonic saline ($n = 9$)	4 (44)	3 (33)	2 (22)
Tolvaptan ($n = 46$)	37 (80)	31 (67)	24 (52)
By initial monotherapy episode, relative likelihood of correction, referent, fluid restriction[c]			
Normal saline	0.849 (0.800–0.902)	0.953 (0.863–1.052)	0.939 (0.912–0.968)
Hypertonic saline	0.949 (0.823–1.093)	1.602 (1.162–2.207)	0.997 (0.921–1.080)
Tolvaptan	2.057 (1.605–2.637)	2.548 (1.818–3.572)	1.354 (1.191–1.539)

Abbreviations: CHF, congestive heart failure; $[Na^+]$, sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
[a]Achievement of correction benchmark determined at discharge for diagnoses.
[b]Achievement of correction benchmark determined at the end of initial therapy episode.
[c]Logistic regression to control for baseline $[Na^+]$, relative likelihood (95% confidence interval).

experienced further decreases in $[Na^+]$ exceeding 2 mEq/l, indicating that relying on these treatments alone can be detrimental. HS and tolvaptan worked more consistently (Figure 4) and significantly faster compared with FR (Table 3). These agents also had very low rates of decreases in $[Na^+]$ (Figure 4). When examined in the patients as a whole, HS and tolvaptan had similar efficacy in increasing $[Na^+]$ by $\geqslant 5$ mEq/l and were each more effective compared with FR or NS. Baseline $[Na^+]$ varied significantly between treatments, in some cases with little overlap (Table 3). Achievement of correction benchmarks was high with no therapy (Table 4), likely because of confounding by indication; clinicians probably added specific treatment for patients whose $[Na^+]$ did not rise spontaneously concomitant with resolution of the precipitant for HN. Indeed, detailed review of response according to categorical baseline $[Na^+]$ (data not shown) demonstrated that the majority of such patients underwent withdrawal of an agent that would interfere with water excretion or underwent treatment for congestion in CHF, events that would not be captured as specific therapy for HN in the computerized analysis. After adjustment for baseline $[Na^+]$ using logistic regression, tolvaptan was consistently better compared with FR in achieving all of the prespecified $[Na^+]$ correction benchmarks, and HS was more often associated with a $[Na^+]$ increment $\geqslant 5$ mEq/l. This is consistent with clinical practice in which HS is used to

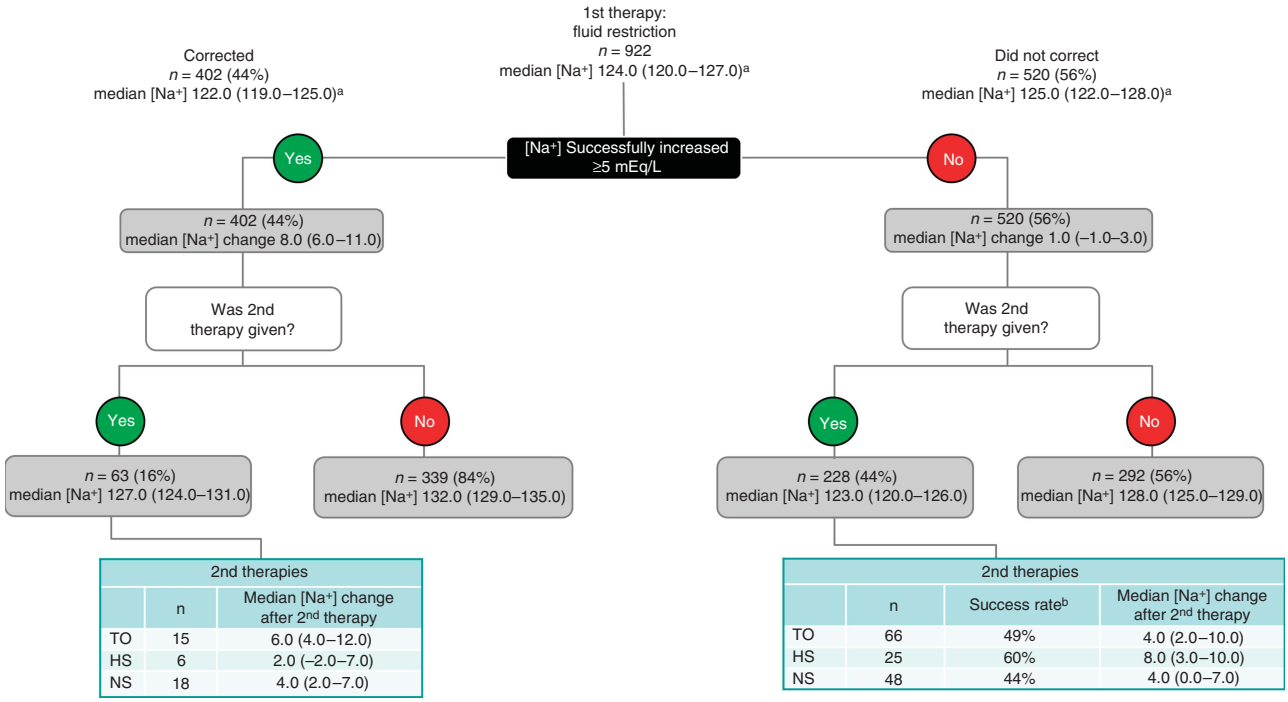

Figure 5 | Outcomes and the use of second therapies in patients with baseline serum sodium concentrations <130 mEq/l initially treated with fluid restriction alone. The decision to initiate a second treatment or not and the selection of any such treatments were made by the patients' treating physicians without input from the investigators. All serum sodium concentration [Na^+] values are median (IQR) in mEq/l. HS, hypertonic saline; NS, isotonic saline; TO, tolvaptan. [a]Pretreatment value; [b]success defined as proportion of patients with [Na^+] increase by 5 mEq/l or more from baseline.

Table 5 | Rate of overly rapid correction of [Na^+] during any 24- or 48-hour period of therapy

	Initial Rx, *n/N* (%)[a]	Any monotherapy, *n/N* (%)[b]	Any use, *n/N* (%)[c]
All	58/2033 (2.9)	119/2399 (5.0)	203/2578 (7.9)
By Rx			
No Rx	7/509 (1.4)	NA	NA
Fluid restriction	15/1084 (1.4)	43/1614 (2.7)	106/1960 (5.4)
Isotonic saline	13/456 (2.9)	19/564 (3.4)	57/1150 (5.0)
Hypertonic saline	12/75 (16.0)	20/117 (17.1)	57/353 (16.1)
Tolvaptan	16/138 (11.6)	34/314 (10.8)	68/582 (11.7)

Abbreviations: NA, not applicable; [Na^+], sodium concentration; Rx, treatment.
Overly rapid correction is defined as [Na+] >12 meq/l in any 12 h period or >18 mEq/l in any 48 h period.
[a]Initial therapy refers to first treatment modality selected for hyponatremia. Only episodes during which a patient received only a single modality (or no treatment) during that initial interval are included.
[b]Monotherapy includes any interval, initial or subsequent, during which only the single listed treatment was received.
[c]Any use includes any therapy period during which specified treatment was received irrespective of whether another treatment was also received.

effect an initial correction, followed by other modalities to raise [Na^+] further.

The rate of [Na^+] rise with tolvaptan was more rapid than reported in clinical trials.[18,32] With greater efficacy came greater risk. A [Na^+] increase >12 mEq/l per 24 h or >18 mEq/l per 48 h, predisposing patients to the development of osmotic demyelination syndrome, was observed more often in patients receiving HS or tolvaptan compared with receiving other treatments. Pituitary surgery, a situation where SIADH may be transient and resolve suddenly, as well as concomitant use of desmopressin for diabetes insipidus appear to pose a particular risk for overly rapid correction when active therapies are used as well. Although well described with HS, only one case of osmotic demyelination syndrome with the use of a vasopressin-receptor antagonist as monotherapy to correct HN has been reported to date.[20,33] No cases of osmotic demyelination syndrome were observed in the 5028 patients in the HN Registry.

The HN Registry has a number of limitations, most of which derive from its observational design.[16] Patients with hypovolemic HN were excluded, as were those with hypervolemic HN in the EU cohort. A large number of patients were excluded at the time of adjudication. Sensitivity analysis showed no difference in the major outcomes when patients with suspected hypovolemia were restored to the analysis. We believe that the exclusion of these patients represents a conservative approach. Ascertainment varied from center to center; enrollment of consecutive cases was not required. Consequently, the study provides no information about relative prevalence of different etiologies of HN.[34] Accurate determination of clinical volume status is difficult under the best of circumstances. The selection of diagnostic studies and treatments was left up to the clinicians responsible for patients, and the study relied on treating clinicians to make a diagnosis. Neither a fluid challenge nor a urine sodium determination was required as an entry criterion for putatively

euvolemic patients. This limited our ability to exclude hypovolemia and independently confirm the presence of SIADH with precision. Because the study's intent was to capture 'real-world' practice, this limitation did not detract from observing how clinician-diagnosed SIADH is treated. Indeed, a principal conclusion is that diagnostic rigor in the case of SIADH is severely lacking, even in a study situation where some treating physicians were aware that their diagnostic choices were being observed. Some therapies were used too infrequently to assess. For example, urea, a treatment shown to be effective in SIADH,[35] and recommended in recent EU guidelines,[22] was used in only 10 patients. Because of the large number of combinations used at low frequency, analysis focused on monotherapy and initial therapy episodes. The study did not specify, much less randomize, treatment choices. We were unable to determine the rationale for choosing a particular treatment. In particular, we could not determine how often NS was used initially in a diagnostic trial to exclude volume depletion in patients suspected of SIADH, a reasonable strategy for its use.[20] Choice of treatments was likely confounded by indication, and the study cannot accurately assess whether any particular treatment shortened hospital stay. We were not able to fully assess how maneuvers such as discontinuation of a HN-inducing medication or treatment of CHF affected $[Na^+]$ changes or the decision to add another treatment maneuver. As a result, even the limited comparisons showing superiority or inferiority of particular treatments that were feasible must be interpreted with much circumspection.

In summary, despite the high prevalence of HN,[1,2] and published guidance on its diagnosis and treatment,[20–22] numerous shortcomings in current HN management are evident. HN in general and SIADH in particular are often diagnosed without attention to accepted diagnostic criteria. Strikingly, many patients receive no specific treatment for HN. FR was predictably the most frequent initial therapy but was ineffective in more than half of the cases. When unsuccessful, FR was often not followed with an additional therapy. Despite the availability of active therapies to correct $[Na^+]$, HS, and vasopressin-receptor antagonists, clinicians typically discharge patients with unresolved HN. From this study, we can conclude that educational efforts should focus on how to diagnose SIADH with rigor, on the lack of efficacy of FR alone and the potential for $[Na^+]$ to fall with FR alone, on the use of active treatments to raise $[Na^+]$ urgently when needed, and on increasing the awareness of situations where overly rapid correction is likely. One such circumstance highlighted in the present study is the immediate postoperative period after pituitary surgery where SIADH may occur but be transient and diabetes insipidus requiring desmopressin may supervene. Here, concomitant treatment with active therapies may pose a special risk. Randomized controlled trials of HN therapy are needed to compare relative efficacy, risks of over rapid correction, and overall costs, particularly for the active treatments. Given the strong association of HN with adverse outcomes, but persisting uncertainty about whether HN contributes to the poor outcomes or is only a marker of severe underlying disease,[3,4,6,7,10,14] research efforts should, in addition, focus on which patients are more likely to respond to specific therapies and which will directly benefit from correction of HN.

MATERIALS AND METHODS

Study plan

The study design has been described previously in detail.[19] Briefly, patients with euvolemic or hypervolemic HN were enrolled from 146 US sites and patients with euvolemic HN were enrolled from 79 EU sites. We excluded patients with hypovolemic HN because this disorder should respond readily and completely to treatment of volume deficits, and it therefore poses no therapeutic dilemma. We excluded patient with hypervolemic HN from the EU study centers because tolvaptan is only approved in the EU for euvolemic patients. Inclusion of hypervolemic patients treated with tolvaptan would have created a regulatory burden for the sponsor. At each site, approval was sought from the appropriate research ethics review boards as required. After informed consent, absent a waiver, investigators prospectively recorded patient data. To ascertain patients, some centers systematically reviewed hospital laboratory-generated lists of patients with HN. Others enrolled only patients referred to or managed by the investigator personally. The study was exclusively observational; no standardized diagnostic or treatment protocols were imposed. Investigators simply recorded the choices made by the physicians responsible for the patient's hospital care.

Inclusion and exclusion criteria

To assure that HN was clinically significant, the study required an entry $[Na^+] \leqslant 130$ mEq/l. Patients were excluded if <18 years old, hypovolemic, hypervolemic (EU only), using an investigational agent or device, or if hyperglycemic enough to interfere with assessment of $[Na^+]$ or receiving renal replacement therapy while hyponatremic. As indicated in Supplementary Table S3 online, euvolemia was defined as the absence of clinical and historical evidence of extracellular fluid volume depletion or sequestration, and the absence of edema and ascites, or on the basis of the treating physician's diagnosis of SIADH. Hypervolemia was defined as excess extracellular fluid volume manifesting as dependent edema or ascites. Although not a specified exclusion criterion originally, we subsequently decided to exclude any patient who was receiving a thiazide at the time the treating physician made a diagnosis of SIADH. It would be difficult to assure that such patients were not in fact hypovolemic,[36] and diuretic use is generally considered to be an exclusion to the proper diagnosis of SIADH.[20] This decision was made prior to data analysis. A complete listing of inclusion and exclusion criteria, as published previously, is provided as Supplementary Table S3 online.[19]

Data collection

Principal data collection items included the following: admitting diagnosis; volume status; time of hospitalization; demographics including age (in years of age, except as >89 years if $\geqslant 90$ years old) gender, and race; severity of the underlying condition using standard measures; etiology for SIADH including tumor, CNS disorder, drug induced, pulmonary disease, other specified cause, idiopathic (cause sought but not found), or unknown; history of prior HN; and acuity of onset of HN, if known. HN-inducing medications, HN treatment medications, diuretics, other medications, vital signs including blood pressure and heart rate at admission or onset of HN and

discharge, input and output measurements, daily weights, type and volume of intravenous fluids administered, and FR limits were also recorded. Any isonatric fluid was considered to be NS for purposes of analysis. Serum osmolality, [Na^+], blood urea nitrogen, creatinine, and glucose values were recorded daily as available, as were urine osmolality and [Na^+] and the results of testing performed to elucidate the cause of HN or to assess severity of comorbidities including serum potassium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, thyroid-stimulating hormone, cortisol, albumin, total bilirubin, and uric acid; adrenocorticotropic hormone, B-type natriuretic hormone, and N-terminal pro-B-type natriuretic peptide; hematocrit, hemoglobin, prothrombin time, and international normalized ratio; and urine urea nitrogen. Comorbidity procedures; HN symptoms; conditions developing during hospitalization; intensive care unit, intermediate care unit, and emergency department stay information; treating physician specialty and subspecialist consults for HN were also collected. Race was classified by the investigators (US only) and assessed to see whether race affected treatment or outcome. The following were also collected at discharge: timing of discharge, discharge diagnoses, disposition, discharge location, early termination reason (if applicable), and possibility of earlier discharge.

Adjudication

To assure that entry criteria were met and that duration of HN was evaluable, data from patients who met a prespecified review threshold were subject to review by two members of the study Steering Committee. Discrepancies were resolved by review by the Steering Committee co-chairmen. Prespecified criteria triggering adjudication are listed in Supplementary Table S4 online.[19] Among those who failed adjudication and were excluded were as follows: (1) individuals stated to be euvolemic but who presented with elevated blood urea nitrogen:creatinine ratios and/or low urine [Na^+]s whose HN responded to administration of NS alone coincident with a fall in blood urea nitrogen:creatinine ratio; (2) individuals who were stated to be euvolemic but whose admission findings included edema or anasarca; (3) individuals with only a single [Na^+] <130 mEq/l who did not receive an active treatment for HN, and (4) patients with a qualifying episode of euvolemic or hypervolemic HN who also had a separate episode of hypovolemic HN during the same hospitalization that would have interfered with computerized parsing of data.

Statistical methods

Therapy periods are defined as the time interval during which a patient received only the single therapy (monotherapy) or combination specified. Patients could have had multiple episodes and multiple therapies during the hospital stay. Initial therapy refers to the first treatment given specifically for HN. Conivaptan was used initially in only 6 patients and urea was used in only 10 but never as initial therapy. Thus, we were unable to quantitate response to these agents. For purposes of categorizing initial [Na^+], mild HN was defined as 130 mEq/l $\geqslant$[Na^+] >125 mEq/l, moderate HN as 125 mEq/l $\geqslant$[Na^+] $\geqslant120$ mEq/l, and severe HN as 120 mEq/l $>$[Na^+]. Overly rapid correction of [Na^+] was defined as an increase >12 mEq/l in any 24-h interval or >18 mEq/l in any 48-h interval.[19] 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. The incremental [Na^+] change during the first day of treatment was calculated as the difference in [Na^+] values at the end and the beginning of the first 24 ± 12 h window. The actual interval for any individual patient ranged from 12 to 36 h, depending on the timing of the reported laboratory values. Patients who lacked paired values during this interval were excluded from this analysis. Duration of the initial course of HN therapy was determined by subtracting the treatment day number of the first day the initial HN therapy was used from the treatment day number of the day the treatment ended and adding one.

Categorical variables were compared using a chi-square test. In the case of more than two comparison groups, an overall χ^2-test was conducted before performing individual pairwise χ^2-tests. Analysis of correction criteria to test for treatment differences was performed using a logistic regression model to adjust for the baseline [Na^+] levels. Analyses were performed separately using 'no therapy' and 'fluid restriction' as references for comparisons with the other treatments.

Nonparametric analysis was performed for continuous variables. When there were more than two comparison groups, a Kruskal–Wallis test was conducted to generate an overall test for equality of medians. Pairwise group comparisons were then carried out. For comparisons of only two groups, medians were compared using the Wilcoxon rank-sum test. *P*-values were not adjusted for multiple comparisons. Data are reported as medians with interquartile range.

DISCLOSURE

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. He is also a consultant and has received fees for expert testimony from Cornerstone. 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 Cardiokine. Amin and Chiong are consultants for the HN Registry, have received travel support and fees for data review activities, and have served on a speakers' bureau for Otsuka. Burst and Peri 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. Chiodo and Friend are Otsuka employees. Dasta is a consultant for the HN Registry and has received travel support and fees for data review activities from Otsuka. Hauptman is a consultant, has received travel support and fees for data review activities, and has served on a speakers' bureau for Otsuka. His institution received funds for serving as an investigational site for the HN Registry from Otsuka. Sigal is a consultant, has received travel support and fees for data review activities, and has served on a speakers' bureau for Otsuka. His institution received research support for serving as an investigational site for the HN Registry and for an investigator-initiated trial from Otsuka. No payment was provided to any author for the development of the manuscript.

ACKNOWLEDGMENTS

We thank Stephen Ball, Newcastle University, Newcastle, UK, Jean-Philippe Haymann, Hôpital Tenon, Paris, France, Gudmundur Johannsson, University of Göteborg, Sweden, Jens Otto Lunde Jørgensen, Aarhus University Hospital, Aarhus, Denmark, and Esteban Poch, University of Barcelona, Spain, for their participation on the

European Steering Committee for the HN Registry, with funding by Otsuka. Robert McQuade, and Frank Czerwiec, of Otsuka provided critical review. Statistical analysis was performed by Ronald Copp, MPH and Stuart Nichols of the Mapi Group, Lexington, KY, and Michael Chen, of TCM Groups, Berkeley Heights, NJ, with funding from Otsuka. Susan Boklage, MPH of Otsuka provided additional statistical advice. Sandra Chase, and Jamie Jarecki-Smith of Otsuka provided continuing support for reviewing data entered in preparation for analysis and for accuracy. Melissa Pozun of Otsuka provided continuing administrative support for development of the manuscript. Rae Bretana, Catherine Fontana, and Geoff Marx of BioScience Communications, New York, NY, formatted tables, figures, text, and references to comply with Journal requirements, with funding from Otsuka. The academic co-authors take full responsibility for the study design, data analysis plan, and drafting of the manuscript. They had unlimited access to the data. Statistical analysis was performed by employees of the TCM Groups and the Mapi Group. Funding for study design and conduct, statistical analyses, and study oversight was provided by Otsuka America Pharmaceutical (OAPI).

SUPPLEMENTARY MATERIAL

Figure S1. Length of Stay From HN Diagnosis by HN Correction Status at Discharge and Monotherapy: All Patients.
Table S1. List of Medications Regarded by Authors to Be Likely to Contribute to Development of Hyponatremia.
Table S2. Relative Likelihood of Correction Benchmarks for Initial Monotherapy Episodes Categorized by Baseline [Na^+].
Table S3. Inclusion and Exclusion Criteria.
Table S4. Criteria Leading to Adjudication.
Hyponatremia: Current Treatment Practice and Outcomes.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003; **337**: 169–172.
2. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006; **119**: S30–S35.
3. Gheorghiade M, Abraham WT, Albert NM *et al.* Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007; **28**: 980–988.
4. Ruf AE, Kremers WK, Chavez LL *et al.* Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005; **11**: 336–343.
5. Kim WR, Biggins SW, Kremers WK *et al.* Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; **359**: 1018–1026.
6. Wald R, Jaber BL, Price LL *et al.* Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med* 2010; **170**: 294–302.
7. Corona G, Giuliani C, Parenti G *et al.* Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. *PLoS One* 2013; **8**: e80451.
8. Shea AM, Hammill BG, Curtis LH *et al.* Medical costs of abnormal serum sodium levels. *J Am Soc Nephrol* 2008; **19**: 764–770.
9. Amin A, Deitelzweig S, Christian R *et al.* Evaluation of incremental healthcare resource burden and readmission rates associated with hospitalized hyponatremic patients in the US. *J Hosp Med* 2012; **7**: 634–639.
10. Renneboog B, Musch W, Vandemergel X *et al.* Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006; **119**: 71–78.
11. Kinsella S, Moran S, Sullivan MO *et al.* Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clini J Am Soc Nephrol* 2010; **5**: 275–280.
12. Hoorn EJ, Rivadeneira F, van Meurs JB *et al.* Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. *J Bone Miner Res* 2011; **26**: 1822–1828.
13. Verbalis JG, Barsony J, Sugimura Y *et al.* Hyponatremia-induced osteoporosis. *J Bone Miner Res* 2010; **25**: 554–563.
14. Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. *Am J Kidney Dis* 2013; **62**: 139–149.
15. Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997; **102**: 67–77.
16. Hauptman PJ, Burnett J, Gheorghiade M *et al.* Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail* 2013; **19**: 390–397.
17. Rossi J, Bayram M, Udelson JE *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.
18. Schrier RW, Gross P, Gheorghiade M *et al.* Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; **355**: 2099–2112.
19. Hauptman PJ, Greenberg A, Verbalis JG *et al.* Design of a prospective, multinational registry to evaluate patients hospitalized with hyponatremia: the HN Registry. *Open Access Journal of Clnical Trials* 2013; **5**: 93–100.
20. Verbalis JG, Goldsmith SR, Greenberg A *et al.* Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; **126**: S1–S42.
21. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581–1589.
22. Spasovski G, Vanholder R, Allolio B *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014; **29**: i1–i39.
23. Schwartz WB, Bennett W, Curelop S *et al.* A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957; **23**: 529–542.
24. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; **42**: 790–806.
25. Huda MS, Boyd A, Skagen K *et al.* Investigation and management of severe hyponatraemia in a hospital setting. *Postgrad Med J* 2006; **82**: 216–219.
26. Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. *QJM* 2006; **99**: 505–511.
27. Waikar SS, Mount DB, Curhan GC *et al.* Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009; **122**: 857–865.
28. Barsony J, Manigrasso MB, Xu Q *et al.* Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. *Age (Dordr)* 2013; **35**: 271–288.
29. Movafagh S, Cleemann L, Morad M. Regulation of cardiac $Ca2+$ channel by extracellular $Na+$. *Cell Calcium* 2011; **49**: 162–173.
30. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356**: 2064–2072.
31. Furst H, Hallows KR, Post J *et al.* The urine/plasma electrolyte ratio: a predictive guide to water restriction. *Am J Med Sci* 2000; **319**: 240–244.
32. Verbalis JG, Adler S, Schrier RW *et al.* Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol* 2011; **164**: 725–732.
33. Malhotra I, Gopinath S, Janga KC *et al.* Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. *Case Rep Endocrinol* 2014; **2014**: 807054.
34. Anderson RJ, Chung HM, Kluge R *et al.* Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985; **102**: 164–168.
35. Soupart A, Coffernils M, Couturier B *et al.* Efficacy and Tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012; **7**: 742–747.
36. Fenske W, Stork S, Koschker AC *et al.* Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. *J Clinical Endocrinol Metab* 2008; **93**: 2991–2997.