ORIGINAL RESEARCH

Current Management of Hyponatremia in Acute Heart Failure: A Report From the Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry)

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***Background*—**Hyponatremia (HN) occurs commonly in patients with acute heart failure and confers a worse prognosis. Current HN treatment varies widely, with no consensus. This study recorded treatment practices currently used for patients hospitalized with acute heart failure and HN.

***Methods and Results*—**Data were collected prospectively from 146 US sites on patients hospitalized with acute heart failure and HN (serum sodium concentration [Na^+] ≤130 mEq/L) present at admission or developing in the hospital. Baseline variables, HN treatment, and laboratory values were recorded. Of 762 patients, median [Na^+] was 126 mEq/L (interquartile range, 7) at baseline and increased to 130 mEq/L at discharge. Fluid restriction was the most commonly prescribed therapy (44%), followed by no specific HN treatment beyond therapy for congestion (23%), isotonic saline (5%), tolvaptan (4%), and hypertonic saline (2%). Median rate of change in [Na^+] varied by treatment (0.5 [interquartile range, 1.0] to 2.3 [8.0] mEq/L/d) and median treatment duration ranged from 1 (interquartile range, 1) to 6 (5) days. Fluid restriction and no specific HN treatment resulted in similar changes in [Na^+], and were least effective in correcting HN. Few patients (19%) had [Na^+] ≥135 mEq/L at discharge.

***Conclusions*—**The most commonly used treatment approaches for HN (fluid restriction and no specific treatment) in acute heart failure increased [Na^+] minimally, and most patients remained hyponatremic at discharge. **(*J Am Heart Assoc*. 2017;6:e005261. DOI: 10.1161/JAHA.116.005261.)**

Key Words: acute heart failure • fluid restriction • hypertonic saline • hyponatremia • saline • sodium • tolvaptan

In chronic heart failure (HF), as cardiac output and systemic blood pressure fall, secretion of neurohormones, such as renin, vasopressin, and norepinephrine, increases.[1–3] The degree of neurohormonal activation is generally related to severity of cardiac dysfunction,[4] and many neurohormones limit sodium and water excretion in a short-term adaptive attempt to return perfusion pressure to normal. Vasopressin directly enhances water reabsorption in the kidney collecting tubules, and angiotensin II and norepinephrine limit distal water delivery by lowering the glomerular filtration rate mediated by a reduction in renal perfusion, and by increasing proximal sodium and water reabsorption. Whereas the pathophysiology of hyponatremia (HN) is multifactorial, these changes are among the most important leading to hypervolemic HN.[5]

In the acute hospital setting, both HN on admission and hospital-acquired HN are frequent.[6,7] HN acquired during an HF hospitalization is associated with substantially increased hospital length of stay (LOS) and cost. Presence of HN has been shown to be a significant predictor of poor clinical outcomes in both acute and chronic HF, especially in the elderly.[8–12] In patients hospitalized with worsening HF, HN is associated with increased readmissions and poor health-related quality of life.[13–17] This increased risk occurs most notably when HN is persistent, which occurs commonly in spite of significant clinical and hemodynamic improvement.[18]

Although interventions that can lead to the (partial) correction of HN in HF have been studied,[19] little is known about how HN is evaluated and treated in the "real world," outside the clinical trial setting. Therefore, we evaluated the processes of

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Clinical Perspective

What Is New?

- Hyponatremia (HN) is common in patients hospitalized with acute heart failure and is associated with worse outcomes.
- We examined current practices for the management of HN in 762 patients with acute heart failure.
- Fluid restriction was the most commonly used strategy for correcting HN; however, nearly one quarter received no specific therapy.

What Are the Clinical Implications?

- Most patients with HN remained hyponatremic at discharge.
- Further studies are needed to determine optimal approaches to effectively correct HN the inpatient setting.

care associated with HN in patients admitted with HF in the context of a large clinical registry.

Methods

The Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry) (NCT01240668) is a prospective, observational, multicenter study of patients hospitalized with euvolemic or hypervolemic HN in the United States (146 sites) and with euvolemic HN in Europe (79 sites). A detailed description of the study design has been published previously,[20] and the results for the overall cohort and the euvolemic cohort have been published.[21] The present analysis focuses on the hypervolemic HF subset of patients with HN in the United States. Hypervolemic patients with cirrhosis were not included in this analysis.

In brief, observational chart data were collected retrospectively by investigators at each site throughout the duration of a patient's hospitalization. No prospective diagnostic or treatment algorithm or protocol was imposed, nor was consecutive enrollment required for entry. Hospitalized patients aged ≥18 years were eligible if they had hypervolemic HN characterized by serum sodium concentration ($[Na^+]$) ≤130 mEq/L, a current diagnosis of HF documented in the medical record, and hypervolemia as determined by the site investigative team based on medical record review. A cutoff of $[Na^+]$ ≤130 mEq/L was chosen to focus on patients more likely to be receiving therapy specifically for HN. Patients were excluded if they were hypovolemic, had a random blood glucose level >250 mg/dL, or 180–250 mg/dL together with a $[Na^+]$ of 127–130 mEq/L at entry, or received renal replacement therapy while they had HN. Patients were also excluded if they were receiving an investigational drug or device for any reason in a clinical trial setting.

Data collected on hospital admission included date of hospitalization, admitting diagnosis, demographics (age, sex, and race), details on HF condition (left ventricular ejection fraction [LVEF] and New York Heart Association classification), and history of HN (including number of hospitalizations in the past year and acuity of onset of HN, when available). Additional data points collected are described in the methods paper.[20] Creatinine clearance was used as a measure of renal function in order to standardize data collection across international sites. "No specific treatment" was used to describe patients who received no specific therapy for HN.

Patients were excluded from analysis if $[Na^+]$ was ≤130 mEq/L for a duration <24 hours to avoid individuals with spurious laboratory values, and if the diagnosis of HF was accompanied by a diagnosis of euvolemia. The prespecified definitions of correction (ie, "clinically meaningful") included: achievement of $[Na^+]$ ≥130 or ≥135 mEq/L, or an increase ≥5 mEq/L. Therapy periods were defined as the time interval during which a patient received only the single therapy (monotherapy) or specified combination. Initial therapy refers to the first treatment given specifically for HN.

For purposes of categorizing initial $[Na^+]$ within the context of the HN Registry, HN was analyzed according to 3 ranges of $[Na^+]$: >125–130, between 120 and 125, and <120 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 consistent with current guidelines.[22] For each HN treatment received by patients, LOS was calculated from the day HN was first treated to better understand the impact of treatment for HN, and was not calculated for patients receiving no specific therapy for HN. Data analyses included comparisons for age, race, HF with preserved LVEF (HFpEF) versus reduced LVEF (HFrEF; defined as LVEF ≤45%), rate of $[Na^+]$ change, and HN on admission versus HN developed in the hospital. Creatinine clearance comparisons were made at the start and end of an episode, and at both admission and discharge as long as values were available for weights and creatinine values at both time points. The database recorded an age of 90 years for all patients >89. No data were collected postdischarge.

Data are presented as median value (interquartile range; IQR). The IQR is the difference between the first and third quartiles. Categorical variables were compared using either a chi-square test or Fisher's exact test (sparse tables). Comparisons between baseline and follow-up evaluations were evaluated using paired *t* tests. Nonparametric analysis was performed for continuous variables. Medians were compared using the Wilcoxon rank-sum test for comparisons of only 2 groups. Analysis of >2 groups was performed using the Kruskal–Wallis test. Statistical test probabilities were not adjusted for multiple comparisons, and no hypothesis testing was performed. SAS software (version 9.4; SAS Institute Inc, Cary, NC) was used for statistical analyses.

Results

Of the 2596 patients in the US cohort from the overall HN Registry meeting protocol requirements after adjudication,

Table 1. Baseline Demographic Characteristics

Characteristic	HF (N=762)
Age distribution, n (%)	
≤50 y	76 (10)
51 to 64 y	164 (21)
65 to 74 y	127 (17)
≥75 y	395 (52)
Sex, n (%)	
Men	352 (46)
Race distribution, n (%)	
White	575 (75)
Black	123 (16)
Asian	10 (1)
Other	30 (4)
Unknown	24 (3)
Past HN, n (%)	
Yes	209 (27)
No	253 (33)
Unknown	299 (39)
HN at admission, n (%)	
Yes	605 (79)
No	153 (20)
Unknown	4 (1)
Day of HN onset, n (%)	
Day 1 (present on admission or at first [Na+] value)	571 (75)
Day 2	62 (8)
Day 3	41 (5)
Day 4	25 (3)
Day 5	12 (2)
Day ≥6	51 (7)
Primary physician specialty, n (%)	
Cardiologist	247 (33)
Generalist	466 (61)
Nephrologist	10 (1.3)
Median SBP at admission, mm Hg (IQR)	128 (108–149)
Median DBP at admission, mm Hg (IQR)	70 (60–80)
Median HR at admission, beats/min (IQR)	82 (70–90)
Median LVEF, % (IQR)	40.0 (22–55)
ACEI/ARB, n (%)	
Prior to/at time of hospitalization	90 (12)
Prescribed/ongoing at discharge	63 (8)
Both hospitalization and discharge	280 (37)
β-blocker, n (%)	
Past to/at time of hospitalization	86 (11)
Prescribed/ongoing at discharge	81 (11)
Both hospitalization and discharge	390 (51)

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; DBP, diastolic blood pressure; HF, heart failure; HN, hyponatremia; HR, heart rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

762 (29%) were identified as having HF with hypervolemic HN. The demographics for this group are shown in Table 1. The majority were aged ≥75, women, and white. One third of patients were managed primarily by cardiologists, with most of the balance managed by generalists (mainly internists and hospitalists); 27% were known to have had past episodes of HN. Most patients received neurohormonal blockers (angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and β-blockers) either before, during, or at hospital discharge, with greater proportions of patients with HFrEF versus HFpEF receiving these agents (data not shown).

Key laboratory values at baseline and discharge are presented in Table 2. Median [Na^+] was 126 (IQR, 122–129) mEq/L on entry into the HN Registry and increased at time of discharge to 130 (128–134). Blood urea nitrogen also increased significantly, whereas creatinine and brain natriuretic peptide remained unchanged. Hematocrit decreased slightly, but significantly, and the blood urea nitrogen/creatinine ratio increased. Weight decreased from 76.2 (IQR, 63.6–90.7) kg at admission to 73.5 (62.2–87.5) at discharge ($P<0.001$). In the patients who had serum osmolality measured within 48 hours of the onset of HN (n=194), urine sodium was more likely to be measured and the patients were more likely to be severely hyponatremic ([Na^+ 122±8 versus 127±5).

Treatment of HN

Of the 762 patients enrolled with HF, 465 (65%) were initially treated for HN with a single modality for HN, 176 (23%) received no specific HN treatment, and 91 (12%) received multiple therapies as the initial therapy to treat HN. Fluid restriction was the most commonly prescribed initial monotherapy for HN (44%), followed by no specific treatment beyond treatment of congestion (23%). Other initial monotherapies prescribed specifically for HN included isotonic saline (5%), tolvaptan (4%), loop diuretics (3%), hypertonic saline (2%), and salt tablets (1%). In all, 556 patients (73%) were identified as receiving either 1 major initial monotherapy or no specific therapy for HN and had both baseline and end of episode [Na^+] needed to complete

Table 2. Baseline and Discharge Laboratory Values

	Baseline*		Discharge	
Parameter	Patients, n	Median (IQR)	Patients, n	Median (IQR)
Serum sodium, mmol/L†	762	126 (122–129)	742	130 (128–134)
Serum potassium, mmol/L†	759	4.3 (3.9–4.8)	740	4.2 (3.9–4.6)
Blood glucose, mg/dL†	754	116 (101–141)	727	100 (90–120)
Serum creatinine, mg/dL	757	1.1 (0.8–1.6)	737	1.1 (0.8–1.5)
Creatinine clearance†,‡,§	511	57.2 (39.4–84.2)	511	55.5 (38.2–81.3)
BUN, mg/dL†	758	22 (14–36)	736	24 (16–38)
Serum albumin, g/L†	546	33 (29–37)	209	30 (26–34)
Total bilirubin, μmol/L†	486	15.4 (10.3–24.0)	146	13.7 (8.6–22.2)
Serum osmolality, mmol/kg†	204	264 (255–272)	32	270 (259–280)
Urine osmolality, mmol/kg	222	306 (237–413)	25	311 (232–364)
Hematocrit, proportion of 1†	731	0.34 (0.30–0.39)	607	0.32 (0.29–0.36)
Hemoglobin, g/dL†	735	11.4 (9.9–12.9)	610	10.7 (9.4–12.0-)
BNP pg/mL	446	734.0 (367.0–1706.2)	129	733.0 (303.0–2176.0)
NT-proBNP pg/mL	112	4744.0 (1733.5–10927.0)	12	2331.0 (1513.5–6440.5)
Weight, kg†,‡	511	76.2 (63.6–90.7)	511	73.5 (62.2–87.5)

BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; IQR, interquartile range; NT-proBNP, N-terminal pro-BNP.
*Baseline serum sodium concentration defined as earliest value ≤130 mEq/L; for other laboratory parameters, baseline defined as value closest to baseline serum sodium concentration taken within 48 h of baseline serum sodium; if multiple values with same interval from baseline serum sodium, earlier value was used.
†$P<0.05$.
‡Weight was measured and creatinine clearance calculated based on patients with values for both measures at baseline and discharge.
§Creatinine clearance=[(140–age [y])•weight (kg)]/[72•serum creatinine (mg/dL)] (multiply by 0.85 for women).

the analysis (Table 3). Median rate of change in [Na^+] varied by treatment from 0.5 (IQR, 0.0–1.0) to 2.3 (1.0–9.0) mEq/L/day and median duration of therapy varied from 1 (IQR, 1–2) to 6 (4–9) days. The rate of change in [Na^+] was significantly lower in patients who received no specific treatment or fluid restriction compared with isotonic saline, hypertonic saline, or tolvaptan (all $P<0.05$). Similarly, duration of treatment was longer with no specific treatment and fluid restriction than with the other monotherapies. Figure 1 shows changes in [Na^+] over time by the type of treatment received.

Successful Correction of HN

Serum sodium concentration increased to ≥130 or by ≥5 mEq/L at the time of discharge in approximately half of patients (Table 3). Correction to [Na^+] ≥135 mEq/L at discharge occurred in 19% of patients. A higher percentage of the 25 patients treated with tolvaptan reached prespecified correction benchmarks than those receiving no specific treatment, fluid restriction, or isotonic saline. Overly rapid correction of HN was uncommon in the group as a whole, but tended to occur more often with hypertonic saline (2 of 15 patients).

HN in Prespecified Subgroups

Patients with HFpEF were older (67% versus 38%; $P<0.001$), more often women (54% versus 37%; $P<0.001$), and less likely to be black (12% versus 20%; $P=0.02$) than were those with HFrEF. In univariate analysis, patients with HFpEF had lower baseline [Na^+] and creatinine (median, 125 [IQR, 121.0–128.0] versus 127 [123.0–129.0] mEq/L and 1.0 [IQR, 0.8–1.5] versus 1.2 [0.9–1.7] mg/dL, respectively; both $P<0.001$), but there was an interaction with age ($P=0.09$ and 0.02, respectively). Brain natriuretic peptide was also lower in patients with HFpEF (median, 524.5 [IQR, 250.0–858.0] versus 1232.2 [533.0–2483.5] pg/mL; $P<0.001$), with no interaction with age. By time of discharge, [Na^+] was slightly higher in HFpEF (median, 131 [IQR, 128–134] versus 130 [127–133] mEq/L; $P=0.01$). Patients with HFpEF had more-rapid rates of change in [Na^+] with both fluid restriction (median, 1.0 [IQR, 0.0–2.0] versus 0.4 [−0.1–1.5] mEq/L/day; $P=0.02$) and no specific therapy (0.7 [0.3–1.4] versus 0.4 [0.0–0.7]; $P=0.001$ [Figure 2]). A greater number of patients with HFpEF who received no specific therapy had more clinically meaningful change in [Na^+] (52% versus 32%; $P=0.01$). Although patients with HFpEF had a shorter LOS compared with HFrEF (median, 7 versus 8 days), multivariate

Table 3. Response to Therapy for Initial Monotherapy Episodes

Treatment	Median Baseline [Na^+], mEq/L (IQR)	Median Rate of [Na^+] Change, mEq/L/d (IQR)*	Median [Na^+] Change in First 24 h, mEq/L/d (IQR)†	Median Duration of Treatment, d (IQR)‡	Median LOS, d§	Overly Rapid Correction, n (%)‖	Achievement of Correction Benchmark¶	
							[Na^+] >130 mEq/L, n (%)	Δ[Na^+] ≥5 mEq/L, n (%)
No specific treatment (n=176)	127 (124–129)	0.5 (0.0–1.0)	2 (1–4)	6 (4–9)	NA	1 (<1)	77 (44)	72 (41)
Fluid restriction (n=304)	126 (122–128)	0.7 (0.0–1.9)	2 (0–4)	5 (2–8)	6	5 (1.6)	91 (34)	121 (45)
Isotonic saline (n=36)	122 (125–130)	2.0 (1.0–5.0)	3 (1–4)	1 (1–2)	6	0	3 (9)	18 (55)
Hypertonic saline (n=15)	120 (118–125)	2.3 (1.0–9.0)	5 (1–9)	1 (1–3)	3	2 (13)	6 (40)	9 (60)
Tolvaptan (n=25)	125 (121–127)	2.3 (0.8–5.0)	2 (2–5)	3 (1–4)	4	0	12 (48)	17 (68)

Table comprises results of first treatment given specifically to treat HN if only single modality was used. HN indicates hyponatremia; IQR, interquartile range; NA, not applicable.
*Calculated as total increment in serum sodium concentration ([Na^+]) during period of treatment/no. of treatment days (interval of HN used for no-treatment group); $P<0.05$: no specific treatment vs isotonic saline, hypertonic saline, and tolvaptan; and fluid restriction vs isotonic saline, hypertonic saline, and tolvaptan.
†Calculated as change from baseline after first 24±12 h depending on timing of laboratory draw; $P<0.05$: no specific treatment vs hypertonic saline; and fluid restriction vs hypertonic saline.
‡Defined as 1+number of last day of initial HN therapy episode minus number of day of start of initial HN therapy episode; $P<0.05$: no specific treatment vs fluid restriction, isotonic saline, hypertonic saline, and tolvaptan; fluid restriction vs isotonic saline, hypertonic saline, and tolvaptan; isotonic saline vs tolvaptan; and hypertonic saline vs tolvaptan.
§Calculated from day HN was first treated.
‖Defined as increment in [Na^+] >12 mEq/L in 24 h; $P<0.05$: no specific treatment vs hypertonic saline; and fluid restriction vs hypertonic saline.
¶Correction at end of initial treatment: [Na^+] >130 mEq/L, $P<0.05$: no specific treatment vs isotonic saline; fluid restriction vs isotonic saline; isotonic saline vs hypertonic saline; and isotonic saline vs tolvaptan; Δ[Na^+] ≥5 mEq/L, $P<0.05$: no specific treatment vs fluid restriction, isotonic saline, hypertonic saline, and tolvaptan; fluid restriction vs isotonic saline, hypertonic saline, and tolvaptan; and isotonic saline vs hypertonic saline and tolvaptan.

analysis showed that these differences were driven largely by age. Differences in LOS by age persisted regardless of HN severity.

A total of 80% of patients had HN on admission, which was more frequently observed in older than younger ones (84% versus 75%; $P=0.002$) and also more frequently observed in those with HFrEF (82% versus 77%; $P=0.02$). Compared with patients who developed HN in the hospital, those with HN on admission had lower [Na^+] (median, 125 [IQR, 121–128] versus 129 [128–130] mEq/L; $P<0.001$), creatinine (median, 1.1 [IQR, 0.8–1.6] versus 1.3 [0.9–1.9] mg/dL; $P=0.002$), blood urea nitrogen (median, 21 [IQR, 14–34] versus 27 [17–42] mmol/L; $P=0.005$), and serum osmolality (median, 264 [IQR, 253.5–271.0] versus 269 [261.0–286.0] mOsm/kg; $P=0.02$).

HN Treatment and LOS

Fluid restriction and no specific treatment resulted in more-rapid rates of change in [Na^+] in patients with HN on admission than in those who developed HN in the hospital (median, 1.0 [IQR, 0.1–2.0] versus 0.0 [−0.5–1.0] and 0.6 [0.2–1.2] versus 0.2 [−0.2–0.5] mEq/L/day, respectively; both $P<0.001$ [Figure 3]). Median values for LOS from start of HN treatment were 6, 6, 3, and 4 days for fluid restriction, isotonic saline, hypertonic saline, and tolvaptan, respectively, and was longer for fluid restriction than for either hypertonic saline or tolvaptan (both $P<0.001$). Patients who developed HN in the hospital had a longer LOS than those with HN on admission regardless of HN severity (median 12 versus 7 days; $P<0.001$).

Most patients (78%) received diuretics before and during the episode of HN. At baseline, [Na^+] was similar between patients not receiving diuretics and those receiving diuretics before HN onset, although LOS was shorter in the 11% of patients not receiving diuretics before HN onset and during the HN episode than in those who were receiving diuretics during these 2 time periods (median, 7 versus 8 days; $P=0.001$). At discharge, [Na^+] was the same regardless of whether patients were receiving diuretics at discharge. Because diuretic dose was not captured in the registry, we could not determine whether or not efficacy of diuresis modified the rate or degree of improvement in [Na^+].

Discussion

The HN Registry provides significant insights into current treatment practices for patients with volume overload and concomitant HN in the setting of acute decompensated HF, including the following: marked heterogeneity in treatment; frequent use of fluid restriction; persistence of HN at hospital discharge in most patients; and association with long LOS, especially in patients who developed HN during hospitalization.

Fluid restriction was used in most patients with HF and was also the most common therapy prescribed overall in the HN Registry.[21] In theory, limiting intake of free water should

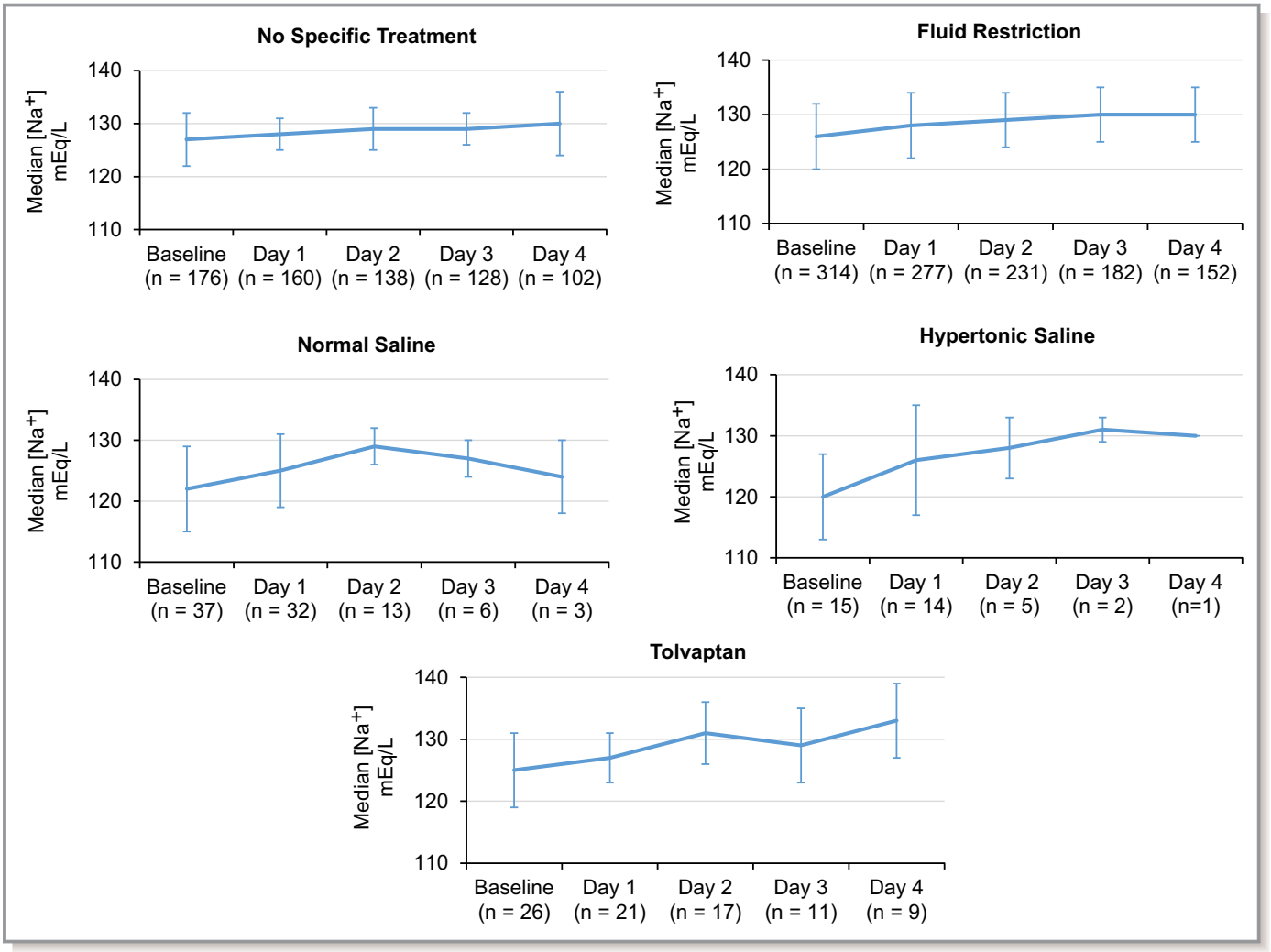

Figure 1. Changes in serum sodium concentration ([Na^+]) over time by treatment received. Bars represent the interquartile range.

result in an increased [Na^+]. Although [Na^+] did increase with fluid restriction, the effect was modest, with a median increase of only 2 mEq/L in the first 24 hours. In addition, the duration of fluid restriction was long, and no differences were noted in rate of change in [Na^+] and duration of therapy between patients receiving fluid restriction and those receiving no specific treatment for HN.

In addressing fluid intake for patients with advanced HF, the current American College of Cardiology/American Heart Association guidelines state that "Fluid restriction (1.5–2 L/d) is reasonable in stage D, especially in patients with HN, to reduce congestive symptoms (Class IIa, Level of Evidence: C)."[23] The low level of evidence underscores the lack of studies available to inform this recommendation. Data from the present study call into question these recommendations for fluid restriction as initial therapy for HN, given that the efficacy of this approach was poor, with most of these patients not reaching any measure of clinically meaningful response in [Na^+].

Isotonic saline, hypertonic saline, and tolvaptan were the other monotherapies used initially to treat HN, although only 11% of patients in the HN Registry received any of these treatments. Each of these therapies resulted in a more-rapid rate of change in [Na^+] than either fluid restriction or no specific treatment. In addition, [Na^+] increased by ≥5 mEq/L in a majority of patients treated with any of these 3 therapies compared with only a minority treated with fluid restriction or no specific treatment. This held true even though the duration of therapy was shorter with each of the active treatments. Of note, a recent report suggested that concomitant administration of intravenous fluids and intravenous diuretics during the first 2 days of hospitalization in patients with acute decompensated HF is associated with worse outcomes, such as higher rates of subsequent critical care admission, intubation, renal replacement therapy, and hospital death compared with those who received only diuretics.[24] The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) study showed that tolvaptan led to rapid and safe correction of

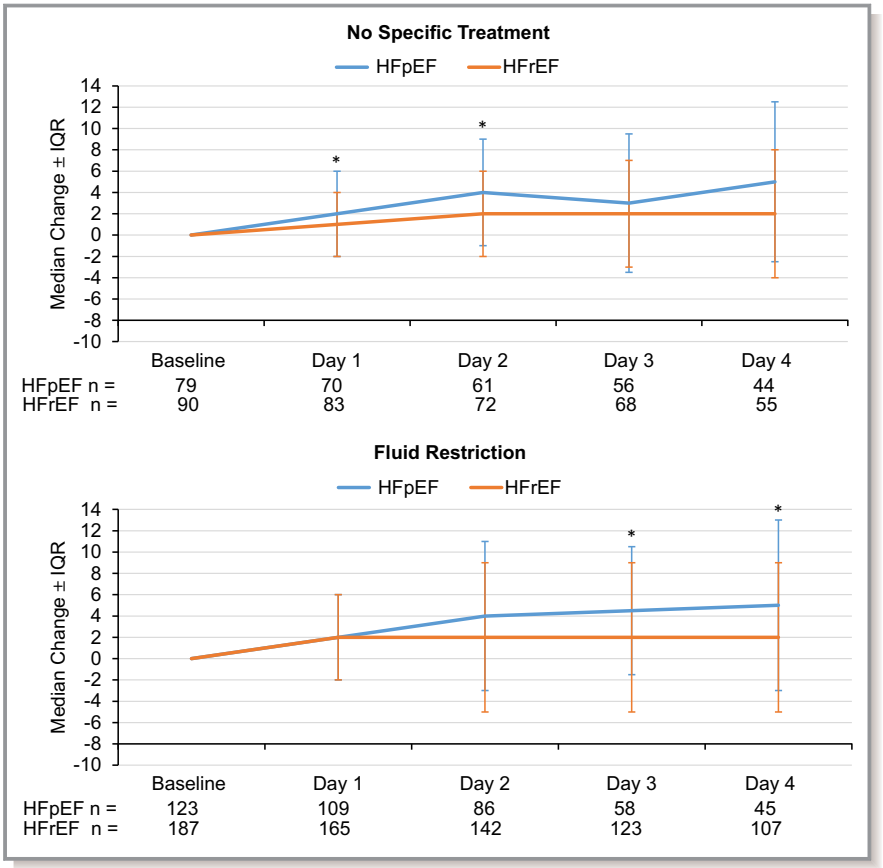

Figure 2. Rates of change in serum sodium concentration ([Na^+]) with no specific treatment or fluid restriction: preserved (HFpEF) vs reduced ejection fraction (HFrEF). IQR indicates interquartile range.

HN in the subset of patients with HN and acute HF, though the impact on outcomes could not be definitively determined in a post-hoc analysis of a small cohort.[25] Because of these uncertainties and cautionary notes, greater consensus is needed regarding best practices in the management of patients with HF, HN, and volume overload.

The median LOS of patients with HF in the HN Registry was 8 days, which likely understates the total hospital LOS given that we used onset of HN as day 0 rather than day of admission. This contrasts with a median LOS of 4 days in patients with acute HF reported by Get With The Guidelines®.[26] This longer LOS is similar to that reported previously in patients with moderate-to-severe HN.[27] Interestingly, severity of HN was not associated with higher LOS in the present study, with a median LOS of 7 days in patients with [Na^+] <125 mEq/L compared with 9 days in those with [Na^+] of 125–130 mEq/L. This suggests that there may be a "ceiling effect" on LOS once significant HN with HF has developed.

Based on the present exploratory analysis, there appear to be few clinical clues to guide clinicians in selecting patients more likely to achieve correction of HN during hospitalization. Univariate analysis showed that baseline [Na^+], blood urea nitrogen, creatinine, sex, LVEF, systolic blood pressure, and heart rate were predictors of improvement in [Na^+]. In the multivariate model, only baseline [Na^+] and sex remained significant predictors of correction; patients with lower baseline [Na^+] and women were more likely to achieve an increase in [Na^+] ≥5 mEq/L. Although the former may reflect greater clinical focus on HN when it is very severe, there are no clear pathophysiological reasons to explain a priori the latter.

Consistent with previous studies, patients with HFpEF in the HN Registry tended to be older than those with HFrEF. In general, older patients had a shorter LOS than younger patients. We performed exploratory analyses to determine the relative contributions of age and LVEF on [Na^+] by using both univariate and multivariate models. Although patients with HFpEF appeared to have a lower [Na^+] at presentation than those with HFrEF, this difference was largely driven by age rather than LVEF, as evidenced by a significant interaction between LVEF and age. Patients with HFpEF also had more-rapid rates of change in [Na^+] with both fluid restriction and no specific therapy than did those with HFrEF, and were more likely to have a clinically meaningful change in [Na^+].

HN developed in the hospital was associated with minimal change in [Na^+] and longer LOS than when it was present on admission. These findings suggest that patients who develop

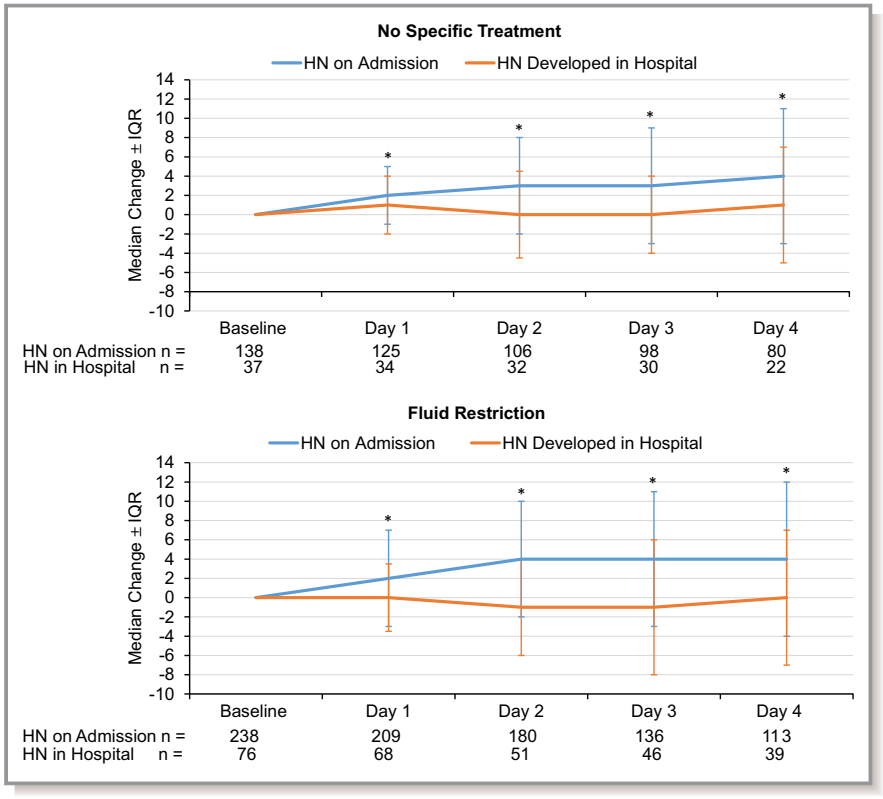

Figure 3. Rates of change in serum sodium concentration ([Na^+]) with no specific therapy or fluid restriction: HN (HN) on admission vs developed in hospital. IQR indicates interquartile range; HN, hyponatremia.

HN during hospitalization may be at higher risk for ineffective correction and prolonged LOS.

Limitations

There are several limitations of the HN Registry. First, only patients with [Na^+] ≤130 mEq/L were enrolled, although lesser degrees of HN are known to confer risk[16]; therefore, the efficacy of treatments used for milder degrees of HN could not be ascertained. Second, only outcomes that occurred while patients were hospitalized could be captured; attributed to regulatory constraints, outcomes following discharge were not recorded, and it was never the intent of the registry to capture postdischarge event rates.[20] Other studies have shown that HN occurring at admission or during hospitalization is associated with poor outcomes postdischarge in patients with acute HF. While it is not clear that correction of HN improves these outcomes,[15,16] the use of tolvaptan was associated with improved cardiovascular morbidity and mortality postdischarge in the subgroup with Na<130 at entry in EVEREST.[25,28] This uncertainty regarding the importance of correcting HN raises the possibility that HN may be a marker of poor prognosis rather than a target per se. Third, the observational nature of the registry and lack of randomization provides, at best, an overview into the frequency and efficacy of contemporary approaches to HN in hypervolemic patients with HF. While this approach provides insight into "real-world" management, the ability to meaningfully compare outcomes and efficacy of different treatments remains limited, for which a prospective, randomized trial would be needed. Fourth, no information was available on cost of treatment for HN because there was no access to hospital billing, although previous studies have shown that LOS is one of the most important determinants of costs during hospitalization with HN.[29] Finally, the intensity of fluid restriction was not analyzed because of the lack of valid data capture for this variable. A pilot study of 28 patients with hypervolemic and euvolemic HN showed, however, that fluid restriction of 1200 mL/day resulted in a mean change of only 0.7±2.1 mEq/L in [Na^+] on day 5 of treatment,[30] a finding consistent with results from the present study.

In conclusion, data reported here from the HN Registry suggest that fluid restriction, the therapy administered most frequently for HN in patients with HF, is relatively ineffective, often results in undercorrection of [Na^+], and is similar to no specific therapy for HN. Furthermore, most patients with HN

remain hyponatremic at hospital discharge. It remains unknown whether more-effective correction of [Na^+] results in better outcomes for patients with HN hospitalized with acute HF. Given the high prevalence and poorer outcomes of patients with acute HF and HN, however, further research is needed regarding decision making and optimal approaches to effectively correct [Na^+] in the inpatient setting.

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References

1. Leier CV, Dei Cas L, Metra M. Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: HN, hypokalemia, and hypomagnesemia. *Am Heart J*. 1994;128:564–574.
2. Benedict CR, Johnstone DE, Weiner DH, Bourassa MG, Bittner V, Kay R, Kirlin P, Greenberg B, Kohn RM, Nicklas JM, McIntyre K, Quinones MA, Yusuf S. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the Registry of Studies of Left Ventricular Dysfunction. SOLVD Investigators. *J Am Coll Cardiol*. 1994;23:1410–1420.
3. Lilly LS, Dzau VJ, Williams GH, Rydstedt L, Hollenberg NK. HN in congestive heart failure: implications for neurohumoral activation and responses to orthostasis. *J Clin Endocrinol Metab*. 1984;59:924–930.
4. Klein L, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF Jr, Califf RM, Gheorghiade M; OPTIME-CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail*. 2008;1:25–33.
5. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. HN in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol*. 2015;65:480–492.
6. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of HN. *Am J Med*. 2006;119:S30–S35.
7. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC;; OPTIMIZE-HF Investigators Coordinators. 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;8:980–988.
8. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217–2226.
9. Kearney MT, Fox KA, Lee AJ, Prescott RJ, Shah AM, Batin PD, Baig W, Lindsay S, Callahan TS, Shell WE, Eckberg DL, Zaman AG, Williams S, Neilson JM, Nolan J. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol*. 2002;40:1801–1808.
10. Senni M, De Maria R, Gregori D, Gonzini L, Gorini M, Cacciatore G, Gavazzi A, Pulignano G, Porcu M, Maggioni AP. Temporal trends in survival and hospitalizations in outpatients with chronic systolic heart failure in 1995 and 1999. *J Cardiac Fail*. 2005;11:270–278.
11. Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF Jr, Califf RM, Gheorghiade M; OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation*. 2005;111:2454–2460.
12. Herrero-Puente P, Marino-Genicio R, Martín-Sánchez FJ, Vázquez-Alvarez J, Jacob J, Bermudez M, Llorens P, Miró O, Pérez-Durá MJ, Gil V, Alonso-Morilla A; Members of the ICA-SEMES group (Annex 1). Characteristics of acute heart failure in very elderly patients – EVE study (EAHFE very elderly). *Eur J Intern Med*. 2014;25:463–470.
13. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Matsushima S, Sakakibara M, Ishimori N, Goto D, Tsutsui H. HN is an independent predictor of adverse clinical outcomes in hospitalized patients due to worsening heart failure. *J Cardiol*. 2014;63:182–188.
14. Amin A, Deitelzweig S, Christian R, Friend K, Lin J, Lowe TJ. Healthcare resource burden associated with HN among patients hospitalized for heart failure in the US. *J Med Econ*. 2013;16:415–420.
15. Hernandez MB, Schwartz RS, Asher CR, Navas EV, Totfalusi V, Buitrago I, Lahoti A, Novaro GM. Predictors of 30-day readmission in patients hospitalized with decompensated heart failure. *Clin Cardiol*. 2013;36:542–547.
16. Bettari L, Fiuzat M, Shaw LK, Wojdyla DM, Metra M, Felker GM, O'Connor CM. HN and long-term outcomes in chronic heart failure–an observational study from the Duke Databank for Cardiovascular Diseases. *J Cardiac Fail*. 2012;18:74–81.
17. Allen LA, Gheorghiade M, Reid KJ, Dunlay SM, Chan PS, Hauptman PJ, Zannad F, Konstam MA, Spertus JA. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. *Circ Cardiovasc Qual Outcomes*. 2011;4:389–398.
18. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007;167:1998–2005.
19. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007;297:1332–1343.
20. Hauptman PJ, Greenberg A, Verbalis JG, Amin A, Sigal S, Chiong J, Chase S, Dasta J. Design of a prospective, multinational registry to evaluate patients hospitalized with HN: the HN Registry. *Open Access J Clin Trials*. 2013;5:93–100.

21. Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo JA III, Chiong JR, Dasta JF, Friend KE, Hauptman PJ, Peri A, Sigal SH. Current treatment practice and outcomes. Report of the HN registry. *Kidney Int*. 2015; 88:167–177.
22. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of HN: expert panel recommendations. *Am J Med*. 2013;126:S1–S42.
23. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;2013:e147–e239.
24. Bikdeli B, Strait KM, Dharmarajan K, Li SX, Mody P, Partovian C, Coca SG, Kim N, Horwitz LI, Testani JM, Krumholz HM. Intravenous fluids in acute decompensated heart failure. *JACC Heart Fail*. 2015;3:127–133.
25. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. *JAMA*. 2007;297:1319–1331.
26. Whellan DJ, Zhao X, Hernandez AF, Liang L, Peterson ED, Bhatt DL, Heidenreich PA, Schwamm LH, Fonarow GC. Predictors of hospital length of stay in heart failure: findings from get with the guidelines. *J Cardiac Fail*. 2011;17:649–656.
27. Callahan MA, Do HT, Caplan DW, Yoon-Flannery K. Economic impact of HN in hospitalized patients: a retrospective cohort study. *Postgrad Med*. 2009;121:186–191.
28. Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, Krasa HB, Maggioni A, Ouyang J, Swedberg K, Zannad F, Zimmer C, Udelson JE; Everest Investigators. 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.
29. Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, Shorr AF. Epidemiology, clinical and economic outcomes of admission HN among hospitalized patients. *Curr Med Res Opin*. 2008;24:1601–1608.
30. Gheorghiade M, Gottlieb SS, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, Orlandi C; Tolvaptan Investigators. Vasopressin V(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of HN. *Am J Cardiol*. 2006;97:1064–1067.