Impact of Change in Serum Sodium Concentration on Mortality in Patients Hospitalized With Heart Failure and Hyponatremia

Vinay D. Madan, MD; Eric Novak, MS; Michael W. Rich, MD

**Background**—Hyponatremia is a common electrolyte abnormality among patients hospitalized with heart failure and it is a marker for increased short-term and long-term mortality. However, little is known about the time course of hyponatremia and whether changes in serum sodium levels affect clinical outcomes.

**Methods and Results**—Patients (n=322) hospitalized with decompensated heart failure and serum sodium <135 mmol/L were evaluated. After hospital discharge, the first sodium value obtained within a 60- to 270-day period was recorded, and patients were classified into 3 groups, based on whether the serum sodium value increased (≥2 mmol/L), decreased (≤2 mmol/L), or remained unchanged (±1 mmol/L) relative to the baseline value. Kaplan–Meier survival curves were constructed to illustrate mortality as a function of change in sodium concentration over time, and a Cox-proportional hazards model was constructed to determine if change in serum sodium concentration predicted mortality after adjusting for relevant covariates. The mean age of the population was 66 years, 45% were women, and 55% were white. The mean baseline sodium level was 131 mmol/L and the mean ejection fraction was 32.5%. Two hundred twenty-two patients (68.9%) exhibited an increase in sodium during follow-up; in 57 patients (17.7%) the level was unchanged and in 43 patients (13.4%) there was a decrease in sodium level. During a median follow-up of 610 days, there was a strong positive association between change in sodium level and survival (P for trend 0.001); that is, increased sodium was associated with decreased mortality. In multivariable analysis, change in sodium concentration and higher blood urea nitrogen were the strongest predictors of mortality (both P<0.001).

**Conclusions**—Among patients hospitalized with heart failure and hyponatremia, change in serum sodium concentration over time is a strong predictor of long-term survival. *(Circ Heart Fail. 2011;4:637-643.)*

**Key Words:** heart failure ■ hyponatremia ■ prognosis

Hyponatremia, commonly defined as a serum sodium concentration <135 mmol/L, is the most common electrolyte disorder among hospitalized patients, occurring in 15% to 22% of admissions. It is also a frequent finding in patients with heart failure, with prevalence rates ranging from 8% to 28%, depending on heart failure severity. Hyponatremia in patients with heart failure is a marker for impaired renal perfusion and excessive neurohormonal activation, including arginine vasopressin (AVP), which promotes water retention. Hyponatremia has also emerged as an important risk factor for hemodynamic deterioration, prolonged hospital stay, and higher rates of rehospitalization. Moreover, hyponatremia is a marker for increased short-term and long-term mortality in patients with heart failure. However, despite the fact that hyponatremia is a potent marker for adverse outcomes in patients with heart failure, the value of serum sodium as a potential therapeutic target is unknown.

To date, no study has examined the prognostic significance of a change in serum sodium concentration after hospital discharge; in particular, it is unknown whether an increase in serum sodium over time is associated with improved outcomes in heart failure patients with hyponatremia. The objective of this study was to determine the effect of change in serum sodium concentration over time on mortality in patients hospitalized with heart failure and hyponatremia. We hypothesized that an increase in serum sodium concentration would be associated with improved survival, whereas a further decline in the sodium level would be associated with increased mortality relative to patients with stable sodium levels.

**Methods**

**Study Design**

We conducted a retrospective chart review of patients admitted to Barnes-Jewish Hospital between January 2002 and December 2007 with a primary diagnosis of heart failure and documented hyponatremia.
tremia at the time of admission. Patients were included if they met the following criteria: age ≥18 years, admission with a primary diagnosis of heart failure (DRG 127, ICD-9 code 428), admission serum sodium <135 mmol/L, an assessment of left ventricular ejection fraction by echocardiogram (within 1 year of the index admission), and at least 1 repeat determination of serum sodium concentration available in the hospital clinical database in the 60- to 270-day period after hospital discharge. We elected to exclude sodium levels obtained within the first 60 days after discharge because our primary objective was to assess the impact of changes in sodium levels during intermediate to long-term follow-up.

Patients who did not have hyponatremia on admission but had subsequent development during the course of hospitalization were not included to avoid confounding by treatment (ie, diuretic therapy). Patients were also excluded if they had a comorbid condition known to affect serum sodium values, for example, adrenal insufficiency or syndrome of inappropriate antidiuretic hormone secretion; if they had an undetermined cause of heart failure (eg, cardiac amyloidosis, sarcoidosis, or surgically treated congenital heart disease); if they received a ventricular assist device or underwent orthotopic heart transplantation; or if they had a preexisting condition associated with a markedly limited life expectancy, such as metastatic cancer.

The baseline sodium value was defined as the first value recorded at the time of presentation for decompensated heart failure. We elected to use the initial sodium value rather than a later value to avoid the confounding effect of treatment. The follow-up sodium value was defined as the first sodium level obtained in the 60- to 270-day window after hospital discharge, either in the inpatient or outpatient setting. Of the 322 patients included in the analysis, 279 (86.7%) had follow-up sodium values that were charted on a subsequent hospital admission, with the remainder recorded in the outpatient setting.

On the basis of the change between the initial sodium value and the follow-up sodium value, patients were stratified into 1 of 3 groups: increased, decreased, or unchanged. An “increase” in serum sodium concentration from baseline to follow-up was defined as a net increment of ≥2 mmol/L; whereas a “decrease” was defined as a net decrement of ≥2 mmol/L; patients with a follow-up sodium concentration within ±1 mmol/L of the baseline value were considered as having “no change” in the sodium level.

Age, sex, race, comorbidities (diabetes, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, chronic lung disease, chronic kidney disease), etiology of heart failure, ejection fraction, medications, and treatment, if any, for hyponatremia were recorded for each patient. The patient’s body mass index, hemoglobin concentration, blood urea nitrogen, and creatinine were also recorded on presentation, and estimated glomerular filtration rate was calculated using the Cockcroft-Gault formula. The Social Security Death Index was used to identify patients who died during the follow-up period, which extended through August 2009. In the absence of documented death, patients were presumed to be alive at the time of analysis. Further elucidation of mode of death was not performed due to the inability to obtain complete records in all patients.

Statistical Analysis
One-way analysis of variance and the χ² test were used to compare patients across sodium change categories. Kaplan–Meier survival curves were constructed to illustrate mortality as a function of change in sodium concentration over time in 3 groups: increased, decreased, or unchanged. The log rank test was used to assess differences in survival between groups. Pairwise comparisons between groups were conducted and corrected probability values were calculated using the Tukey adjustment for multiple comparisons. Median survival times were determined from the Kaplan–Meier curves. A multivariable Cox proportional hazards model was created to examine sodium change while adjusting for other variables significantly associated with survival or potential confounders. All variables were considered and a stepwise variable selection technique was used to identify significant covariates. Potential confounders were identified from patient comparisons conducted across predefined groups. The proportionality assumption was assessed for sodium change. Results were presented as hazard ratios and 95% confidence intervals. Significance was set at α=0.05. In sensitivity analysis, we examined mortality rates based on sodium change from admission to follow-up as a continuous variable and by tertiles, as well as change in sodium from hospital admission to discharge. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results
Baseline Characteristics
Baseline characteristics of the study patients are described in Table 1. Patients had a mean age of 66 years, 54.7% were male, and 54.7% were white. Approximately half (48.1%) of patients had heart failure associated with an ischemic cardiomyopathy, and the mean ejection fraction was 32.5%. The mean serum sodium concentration at baseline was 130.7±3.8 mmol/L.

Compared with the baseline sodium level, the first sodium level obtained during follow-up was increased in 222 patients (68.9%), unchanged in 57 patients (17.7%), and decreased in 43 patients (13.4%). Demographic and clinical characteristics were generally similar between the three groups. However, patients with increased sodium during follow-up were less likely to be white and had a higher baseline urea nitrogen level and slightly lower baseline sodium level than the other 2 groups; they were also less likely to be treated with spironolactone.

Mortality
The median duration of follow-up for all 322 patients was 610 days (20 months). Overall, 224 patients (69.6%) died during the follow-up period. The number of deaths in the decreased, unchanged, and increased sodium change categories were 41 (95.4%), 41 (71.9%), and 142 (64.0%), respectively. Kaplan–Meier survival curves for the 3 groups are shown in the Figure. Patients with increased sodium had the lowest mortality, whereas those with a decrement in the sodium level had the highest mortality (P<0.0001 for survival as a function of sodium change category). Survival differences between all paired groups were significant; decreased versus increased (P<0.0001), decreased versus unchanged (P=0.040), and unchanged versus increased (P=0.009). Median survival times in patients with decreased, unchanged, and increased sodium levels were 0.61 years, 1.58 years, and 2.67 years, respectively.

Multivariable Analysis
Predictors of mortality using the Cox proportional hazards model and adjusting for baseline differences between groups are shown in Table 2. Compared with the unchanged group, the hazard of death for the decreased group was greater (hazard ratio, 1.921; P=0.004), whereas it was lower for the increased group (hazard ratio, 0.622; P=0.011), indicating an association between increased sodium levels and decreased mortality. Sodium change category and blood urea nitrogen (10 mg/dL increment) were the strongest predictors of mortality (both P<0.001) in the model; additional predictors included nonprescription of a β-blocker and older age (per 10-year increment).
In sensitivity analysis using sodium change tertiles from admission to follow-up, the association of sodium change with mortality was less evident because of overlapping of the decreased and unchanged sodium groups. However, the lowest change tertile was associated with higher mortality compared with the other 2 tertiles (data not shown). A similar trend was noted when analyzing sodium change directly (ie, as a continuous variable; data not shown). Sodium change from hospital admission to discharge was not found to be a predictor of mortality (data not shown).

Discussion
This study demonstrates that the change in serum sodium concentration over time is a powerful predictor of mortality in patients hospitalized with heart failure and hyponatremia. Those who demonstrated an increase in serum sodium after hospital discharge had improved survival compared with those in whom the serum sodium concentration remained unchanged or decreased. These findings suggest that hyponatremia may serve as more than a simple marker for disease severity and increased risk for adverse outcomes; it may serve as a target for therapeutic intervention.

### Hyponatremia as a Marker for Adverse Outcomes
In patients with heart failure, those with hyponatremia have higher levels of circulating catecholamines, renin, angiotensin II, aldosterone, and vasopressin compared with those with normal serum sodium. In addition, hyponatremic patients have lower hepatic and renal plasma blood flow, a diminished response to orthostatic changes, higher hepatic enzyme levels, and more pronounced azotemia. These

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**Table 1. Baseline Characteristics of Study Patients According to Change in Serum Sodium From Baseline to Follow-Up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=322)</th>
<th>Decreased (n=43)</th>
<th>Unchanged (n=57)</th>
<th>Increased (n=222)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, y</td>
<td>66.0±15.8</td>
<td>66.7±16.0</td>
<td>64.0±16.4</td>
<td>66.4±15.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Female</td>
<td>45.3</td>
<td>48.8</td>
<td>35.1</td>
<td>47.3</td>
<td>0.23</td>
</tr>
<tr>
<td>White, %</td>
<td>54.7</td>
<td>69.8</td>
<td>61.4</td>
<td>50.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic etiology, %</td>
<td>48.1</td>
<td>60.5</td>
<td>52.6</td>
<td>44.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>32.5±16.5</td>
<td>29.4±15.4</td>
<td>29.4±15.3</td>
<td>33.9±16.9</td>
<td>0.078</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>48.1</td>
<td>39.5</td>
<td>45.6</td>
<td>50.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>78.0</td>
<td>67.4</td>
<td>82.5</td>
<td>78.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>49.1</td>
<td>39.5</td>
<td>43.9</td>
<td>52.3</td>
<td>0.21</td>
</tr>
<tr>
<td>CAD, %</td>
<td>60.6</td>
<td>67.4</td>
<td>61.4</td>
<td>59.0</td>
<td>0.58</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>46.0</td>
<td>48.8</td>
<td>54.4</td>
<td>43.2</td>
<td>0.30</td>
</tr>
<tr>
<td>COPD, %</td>
<td>27.6</td>
<td>16.3</td>
<td>28.1</td>
<td>29.7</td>
<td>0.20</td>
</tr>
<tr>
<td>CKD, %</td>
<td>40.7</td>
<td>41.9</td>
<td>28.1</td>
<td>43.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4±7.7</td>
<td>27.6±7.7</td>
<td>27.5±6.8</td>
<td>28.8±7.9</td>
<td>0.40</td>
</tr>
<tr>
<td>BMI ≥30 kg/m², %</td>
<td>33.2</td>
<td>32.6</td>
<td>31.6</td>
<td>33.8</td>
<td>0.95</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.1±2.0</td>
<td>12.1±2.0</td>
<td>12.5±2.1</td>
<td>12.0±1.9</td>
<td>0.15</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>35±25</td>
<td>32±20</td>
<td>29±21</td>
<td>38±27</td>
<td>0.048</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.9±1.9</td>
<td>2.0±2.4</td>
<td>1.4±0.8</td>
<td>2.1±2.0</td>
<td>0.057</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>64±44</td>
<td>61±46</td>
<td>74±49</td>
<td>61±42</td>
<td>0.16</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>130.7±3.8</td>
<td>131.7±2.9</td>
<td>131.6±3.1</td>
<td>130.2±4.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic, %</td>
<td>80.7</td>
<td>76.2</td>
<td>80.7</td>
<td>81.5</td>
<td>0.72</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>35.7</td>
<td>41.9</td>
<td>49.1</td>
<td>31.0</td>
<td>0.03</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>64.0</td>
<td>58.1</td>
<td>52.6</td>
<td>68.0</td>
<td>0.07</td>
</tr>
<tr>
<td>ACEI/ARB, %</td>
<td>70.8</td>
<td>65.1</td>
<td>66.7</td>
<td>73.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>44.4</td>
<td>55.8</td>
<td>47.4</td>
<td>41.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Hydralazine, %</td>
<td>17.0</td>
<td>9.3</td>
<td>15.8</td>
<td>18.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Nitrates, %</td>
<td>27.0</td>
<td>25.6</td>
<td>28.1</td>
<td>27.0</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and eGFR, estimated glomerular filtration rate (Cockcroft-Gault).
Observations indicate that hyponatremia is a marker for greater disease severity in the heart failure population.

Hyponatremia has also emerged as a powerful predictor of adverse outcomes in patients with heart failure. More specifically, hyponatremia is a risk factor for hemodynamic deterioration, prolonged hospital stay, higher rate of rehospitalization, and mortality. For example, in a retrospective review of 4031 patients hospitalized with heart failure, hyponatremia predicted both 30-day and 1-year mortality rates. Similarly, analysis of data from randomized clinical trials has consistently shown that hyponatremia is a predictor of increased long-term mortality.

**Hyponatremia as a Modifiable Risk Factor**

Given the high morbidity and mortality of patients hospitalized with decompensated heart failure, identification of modifiable risk factors is of paramount importance. In this study, we investigated whether changes in serum sodium concentration, specifically whether improvement over time, results in decreased mortality. To our knowledge, this is the first study to directly address this question during long-term follow-up.

In the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure (ACTIV in CHF) trial, 319 patients with decompensated heart failure were randomized to 1 of 3 tolvaptan doses. A post hoc analysis showed that among the 69 (21.6%) patients who had hyponatremia on admission, those with an improvement in serum sodium level (≥2 mmol/L) before discharge had a significant improvement in mortality at 60 days after discharge (11.1% compared with 21.7% in those with no improvement). After adjustment for other covariates, change in plasma sodium concentration during hospitalization was a significant predictor of mortality 60 days after discharge.

In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Heart Failure (OPTIME-CHF) trial, 949 patients with systolic dysfunction hospitalized for worsening heart failure were randomly assigned to receive 48- to 72-hour infusions of intravenous milrinone versus placebo in addition to standard therapy. A retrospective analysis examined the relationship between admission serum sodium level (≥2 mmol/L) before discharge and 60-day mortality. Lower serum sodium was associated with higher in-hospital and 60-day mortality, with an 18% relative increase in the probability of death within 60 days for every 3 mmol/L decrease in admission sodium levels. Furthermore, among the 244 patients in the lowest quartile of serum sodium, 93 (38%) were discharged with a serum sodium <135 mmol/L, whereas the remaining patients remained hyponatremic on discharge.

**Table 2. Cox Proportional Hazards Regression Model for Time Until Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>P Value</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium change category*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>0.653</td>
<td>&lt;0.001</td>
<td>1.921 (1.236–2.985)</td>
</tr>
<tr>
<td>Increased</td>
<td>−0.475</td>
<td>0.011</td>
<td>0.622 (0.430–0.898)</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>0.111</td>
<td>0.016</td>
<td>1.118 (1.021–1.224)</td>
</tr>
<tr>
<td>BUN, per 10 mg/dL</td>
<td>0.098</td>
<td>&lt;0.001</td>
<td>1.103 (1.052–1.156)</td>
</tr>
<tr>
<td>β-blocker use</td>
<td>−0.459</td>
<td>0.001</td>
<td>0.632 (0.481–0.831)</td>
</tr>
<tr>
<td>Baseline sodium</td>
<td>−0.015</td>
<td>0.396</td>
<td>0.985 (0.951–1.020)</td>
</tr>
<tr>
<td>Race, white vs other</td>
<td>0.034</td>
<td>0.811</td>
<td>1.034 (0.784–1.364)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>−0.027</td>
<td>0.853</td>
<td>0.973 (0.728–1.300)</td>
</tr>
</tbody>
</table>

*BUN indicates blood urea nitrogen; CI, confidence interval.

*Versus unchanged; for increased versus decreased (hazard ratio, 0.324; P<0.001).
discharge. The group that achieved normalization of serum sodium levels at discharge had a trend toward lower mortality (10.7% versus 17.2%) compared with those who remained persistently hyponatremic, but the difference was not significant.17

In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial,23 433 patients hospitalized with New York Heart Association class IV heart failure were randomly assigned to use of a pulmonary artery catheter in addition to clinical assessment versus clinical assessment alone in guiding therapy. In patients with hyponatremia on admission (n=103, 23.8%), the association between change in serum sodium during the hospital course and 6-month postdischarge mortality was evaluated.16 Among patients with hyponatremia on admission, 71 (68.9%) had “persistent hyponatremia” throughout the hospital course and 32 (31.1%) had “corrected hyponatremia” (ie, the sodium concentration improved to >134 mmol/L during hospitalization). After controlling for baseline characteristics, patients with persistent hyponatremia were found to have an increased risk of all-cause mortality (31% versus 16%), rehospitalization for heart failure (62% versus 43%), and death or rehospitalization (73% versus 50%) compared with the 327 patients with normonatremia. However, the differences between patients with persistent and corrected hyponatremia were not statistically significant, possibly because of the small sample size.

Taken together, these studies suggest that an improvement in serum sodium concentration during the course of hospitalization tends to be associated with improved outcomes up to 6 months. However, these studies are limited by small sample size and relatively short-term follow-up. Moreover, none of these studies evaluated sodium levels during the postdischarge period. In contrast, our study was larger, the median follow-up was 1.7 years, and we evaluated sodium levels obtained during a 2- to 9-month period after hospital discharge.

Patients in this study represent a diverse heart failure population, including those with preserved or impaired left ventricular systolic function, as well as ischemic and nonischemic etiologies. Although patients who underwent advanced treatments for heart failure (ventricular assist devices or heart transplantation) were excluded, 7.8% of patients received intermittent or chronic intravenous inotropic therapy.

None of the patients in our study received specific pharmacotherapy to treat hyponatremia. The majority of patients were hospitalized before AVP antagonists were introduced as therapy for hyponatremia, and the utility of these agents in the heart failure population has not been established. Some patients were placed on free water restriction, but we suspect that this therapy was both underreported and poorly adhered to. Nonetheless, a large proportion of patients demonstrated an increase in serum sodium levels during the follow-up period. This suggests that treating symptoms of congestion and optimizing medications can be effective in raising serum sodium levels. Moreover, patients who respond to such therapeutic measures appear to have a better prognosis compared with those who do not. Therefore, analogous to a decline in the B-type natriuretic peptide level, an increase in serum sodium may serve as a marker for improved hemodynamic compensation and associated downregulation of neurohormones. In this regard, a study comparing the prognostic utility of changes in B-type natriuretic peptide levels and serum sodium concentrations, alone and in combination, would be of interest.

### Treatment Considerations

The results of this study indicate that change in serum sodium concentration over time predicts outcomes in patients hospitalized with heart failure and hyponatremia. Although hyponatremia may simply serve as a marker for disease severity, it is also possible that serum sodium represents a modifiable risk factor for adverse outcomes in the heart failure population. Accordingly, treatments tailored toward improving sodium levels in patients hospitalized with heart failure may be desirable, and future studies testing specific interventions are warranted. At the present time, therapeutic modalities for treating hyponatremia include free water restriction, hypertonic saline, demeclocycline, and AVP antagonists. Of these, AVP antagonists hold the most promise, in part because they directly antagonize the deleterious effects associated with upregulation of the arginine-vasopressin axis. In addition, clinical trials have shown that AVP antagonists are effective in ameliorating signs and symptoms of congestion without causing renal dysfunction or inducing electrolyte abnormalities.24 These agents also increase serum sodium levels in patients with hyponatremia even in the absence of free water restriction.24 However, their long-term effect on clinical outcomes remains unproven.

The recently published Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial revealed that while the oral V2-antagonist tolvaptan was more effective than placebo at providing short-term improvement in dyspnea and sustained improvements in body weight when added to standard medical therapy in patients admitted with decompensated heart failure, there was no benefit on heart failure-related morbidity or long-term mortality over a mean follow-up period of 9.9 months.5,6 Although only 8% of the 4133 patients (n=331) enrolled in the study had hyponatremia (defined as serum sodium <134 mmol/L), there was a significant increase of 5.5 mmol/L in the tolvaptan group compared with a 1.8 mmol/L increase in the placebo group that was maintained throughout the follow-up period. Although preliminary reports indicate favorable effects of tolvaptan in the hyponatremic subset, detailed analyses of clinical outcomes in these patients have not been published.24 In addition, the duration of follow-up in EVEREST was substantially shorter than in our study.

### Limitations

The present study has several limitations. The study is retrospective and based on data from a single center; prospective confirmation of our findings in larger and more diverse populations is needed. The time from hospital discharge to acquisition of the follow-up sodium level ranged from 60 to 270 days; in future prospective studies it would be desirable to measure follow-up sodium at fixed time points, such as 30
and/or 60 days after hospital discharge. The patients included in this analysis represented a “convenience sample” obtained in a nonconsecutive manner to meet the planned target enrollment of over 300 patients. As such, we observed a high rate of rehospitalization for heart failure during the follow-up period, probably a reflection of our inability to obtain outpatient values beyond those linked to our medical record. This methodology may have introduced a selection bias toward sicker patients. In addition, sodium levels obtained at the time of readmission may not have reflected patients’ usual baseline values.

Empirical classification of patients into 3 categories, based on an incremental change in sodium concentration ≥2 mmol/L from baseline, although consistent with prior reports, warrants further study; that is, additional analysis is needed to define what constitutes a clinically significant and meaningful change in sodium concentration. Nonetheless, our classification scheme clearly distinguished patients with more or less favorable outcomes, thus providing face validity for this approach.

Because of the observational nature of the study, we are unable to provide insights into the mechanisms underlying the association between change in serum sodium concentration and mortality. It is possible that the sodium level is a marker for circulating AVP, in which case selective AVP receptor blockade may be therapeutic. Conversely, if serum sodium is merely a marker for heart failure severity, treatment directed at the sodium level is unlikely to be beneficial.

Finally, although our findings are statistically robust, we cannot exclude the possibility of residual confounding by unmeasured or unknown variables. Serum glucose values were not obtained in our patient population and therefore serum sodium levels were not adjusted for the potential contribution these values may have had. We also did not have data on other longitudinal biomarkers of heart failure disease severity, such as B-type natriuretic peptide. Last, although we adjusted for multiple covariates during the index admission, we did not adjust for changes in these parameters during the follow-up period.

Conclusion
Among patients hospitalized with heart failure and hyponatremia, those who exhibited an improvement in serum sodium concentration after hospital discharge had markedly improved long-term survival compared with patients without an increase in the serum sodium level, and this effect remained significant after adjusting for other measured covariates. Our findings support the hypothesis that serum sodium levels in patients with heart failure and hyponatremia may serve not only as a marker for adverse clinical outcomes but also as a potential therapeutic target. Prospective studies, such as the ongoing lixivaptan trial,²⁵ are needed to test this hypothesis.

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Disclosures
None.

References
16. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Gattis-Stough W, O’Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe...


**CLINICAL PERSPECTIVE**

Hyponatremia is a marker for increased mortality in patients with heart failure. However, the relationship between change in serum sodium levels over time and subsequent mortality has not been well characterized. We studied 322 patients hospitalized with heart failure and an admission serum sodium concentration <135 mmol/L. The mean age was 66 years, 45% were women, 55% were white, the mean left ventricular ejection fraction was 32.5%, and the mean baseline serum sodium concentration was 131 mmol/L. On the basis of the first follow-up sodium level obtained within 60 to 270 days after hospital discharge, we classified patients into 3 groups: increased sodium (≥2 mmol/L increment; n=222), decreased sodium (≥2 mmol/L decrement; n=43), or unchanged sodium (±1 mmol/L compared with baseline; n=57). During a median follow-up period of 610 days, there were 224 deaths (69.6%). Mortality rates in patients with increased, unchanged, and decreased sodium levels were 64.0%, 71.9%, and 95.4%, respectively (P for trend <0.001). Median survival in the 3 groups was 2.67 years, 1.58 years, and 0.61 years. In multivariable Cox proportional hazards analysis, sodium change category and higher blood urea nitrogen (10-mg/dL increments) were the strongest predictors of mortality. These findings suggest that the change in serum sodium concentration over time is an important prognostic marker in patients hospitalized with heart failure and hyponatremia. Additional studies are needed to determine if treatment of hyponatremia in this population will reduce mortality rates and improve other clinical outcomes.
Impact of Change in Serum Sodium Concentration on Mortality in Patients Hospitalized With Heart Failure and Hyponatremia
Vinay D. Madan, Eric Novak and Michael W. Rich

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