Outcome Differences in Community- Versus Hospital-
Acquired Hyponatremia in Patients With a Diagnosis
of Heart Failure

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Background—Hyponatremia at hospital admission is a well-known risk factor of morbidity and mortality in patients with heart failure (HF). However, there are few data about hyponatremia developing during hospitalization in patients with HF. The present study compares hospital-acquired hyponatremia (HAH) with community-acquired hyponatremia (CAH) in HF patients with respect to outcome.

Methods and Results—A total of 5347 consecutive hospitalized patients with a diagnosis of HF were analyzed. CAH was defined as a serum sodium value of ≤135 mEq/L at the time of hospital admission. HAH was defined as development of a serum sodium level of ≤135 mEq/L during hospitalization in the setting of a serum sodium value >135 mEq/L on admission. In-hospital mortality, length of stay, worsening kidney function, and discharge to short-/long-term care facilities were analyzed. CAH and HAH were identified in 1039 patients (19.4%) and in 1302 patients (24.4%) of the 5347 patients admitted, respectively. Both types of hyponatremia were associated with increased mortality, length of stay, rate of discharge to short-/long-term care facilities, and worsening kidney function. In-hospital mortality did not differ between CAH and HAH, but differences in demographics and comorbidities were present.

Conclusions—The present results identified HAH as a risk factor for increased mortality in HF as has been previously described for CAH. HAH was associated with increased length of stay, discharge to short-/long-term care facilities, and development of cardio-renal failure. Thus, hyponatremia in hospitalized patients with a diagnosis of HF, either on admission or during hospitalization, is a prognostic marker for poor outcomes. (Circ Heart Fail. 2013;6:379-386.)

Key Words: heart failure □ hyponatremia □ renal disease

There are ≈1 million hospitalizations each year in the United States for acute decompensated heart failure (HF). Patients with a hospitalization for decompensated HF have a poor prognosis. In-hospital mortality occurs in 3% to 4% of these patients, and 60- to 90-day postdischarge mortality and rehospitalization rates have been reported to be 35% to 50%.1-5 Hyponatremia, defined as a serum sodium concentration of ≤135 mEq/L, is the most common electrolyte disorder among hospitalized patients, occurring in 15% to 22% of admissions. It is a frequent finding in patients with HF, with prevalence rates ranging from 8% to 28%, depending on HF severity.8-11

Clinical Perspective on p 386

Hyponatremia in patients with HF at hospital admission is an important marker for hemodynamic deterioration, prolonged hospital stay, and higher rates of rehospitalization.12-15 Moreover, hyponatremia is a marker for increased short-term and long-term mortality in patients with HF.4,16-29 In the OPTIMIZE-HF (Organized Program To Initiate life-saving treatMent In hospitaliZEd patients with Heart Failure) registry, a mortality risk increase was observed at admission serum sodium levels <130 mEq/L.4

To date, however, data are scarce for hospital-acquired hyponatremia (HAH) in patients with HF. In a large single-center cohort study, community-acquired hyponatremia (CAH) and HAH in unselected hospitalizations were associated with increased hospital length of stay (LOS), increased in-hospital mortality, and increased rate of discharge to a short-/long-term care facility.30 The objective of our current study was to further characterize and compare in-hospital outcomes of patients with HF and HAH versus CAH in the parent cohort, in terms of in-hospital mortality, worsening kidney function, and among survivors, hospital LOS and discharge disposition to home setting or short-/long-term care facilities.

Methods

Data Source

This was a single-center retrospective cohort study using a dataset that contained fully deidentified hospital discharges at a community-based
tertiary acute care facility (St. Elizabeth’s Medical Center, Boston, MA) during a 7-year period (2000–2007). Information was provided on patient’s age, sex, race, admission service, and comorbidities, as measured by the Deyo–Charlson Comorbidity Index. Multivariable logistic regression was used to evaluate the association between hyponatremia subtype and the outcomes of in-hospital death, worsening kidney function, and discharge to short-/long-term care facility, whereas negative binomial regression was used to evaluate the association between hyponatremia subtype and LOS in days. The odds ratio generated by this analysis reflects the proportional change in the LOS compared with the reference category. Patients who died in the hospital were excluded from all analyses involving discharge disposition and LOS. To explore the consistency of the findings, sensitivity analyses were performed that were restricted to hospitalized subjects with a primary diagnosis of HF, based on ICD-9-CM diagnosis code ranking, as well as to subjects with a primary diagnosis of HF and hospitalization on the cardiology service. All of the analyses were generated using SAS version 9.2 (Cary, NC). The restrictive cubic spline was generated in R version 2.11 (Free Software Foundation, Boston, MA). \( P<0.05 \) was considered statistically significant.

**Hyponatremia Definitions**

CAH was defined as a serum sodium value of \( \leq 135 \) mEq/L at the time of hospital admission (either on the day of or before admission). HAH was defined as development of a nadir serum sodium level of \( \leq 135 \) mEq/L during hospitalization in the setting of a serum sodium value \( >135 \) mEq/L on admission.

Due to the confounding effect on serum sodium of water translocated from cells to the extracellular fluid with hyperglycemia, serum sodium values were adjusted upward by 2 mEq/L for each 100 mg/dL increment in serum glucose \( >100 \) mg/dL.\(^{31,32} \)

**Outcomes of Interest**

In-hospital mortality, hospital LOS, worsening kidney function, and patient disposition were evaluated. Worsening kidney function was defined as an increase in serum creatinine \( \geq 0.3 \) mg/dL using the difference between the peak and nadir (see below) value during hospitalization, in accordance with a previously published method. For disposition status, the event of interest was discharge to a short-/long-term care facility; discharges to home and departures from the hospital against medical advice comprised the reference category. LOS hospitalization, in accordance with a previously published method. For disposition status, the event of interest was discharge to a short-/long-term care facility; discharges to home and departures from the hospital against medical advice comprised the reference category.

**Description of Covariates**

The Deyo–Charlson Comorbidity Index was used to assess comorbidities.\(^{33,34} \) This index incorporates a patient’s history of comorbidities using ICD-9-CM diagnosis codes, with increasing numeric values reflecting greater comorbidity. For each hospitalization, the Deyo–Charlson Comorbidity Index was used to generate a score, and hospitalizations were categorized based on scores of 0 to 3 or higher.

Presence of acute respiratory infections (ICD-9-CM diagnosis codes 460–466), pneumonia and influenza (ICD-9-CM codes 480–488), psychosis (ICD-9-CM diagnosis codes 290–299), neurotic disorders, personality disorders, other nonpsychotic mental disorders (ICD-9-CM diagnosis codes 300–316), and malignant neoplasm of respiratory and intrathoracic organs (ICD-9-CM diagnosis codes 160–165) were used as additional covariates because of their potential confounding effect on serum sodium concentration.

The baseline serum creatinine was defined as the nadir value in the first 3 days of hospitalization.\(^{35} \) Using this baseline serum creatinine, the baseline estimated glomerular filtration rate was calculated using the CKD-EPI equation.\(^{36} \)

**Statistical Analyses**

Continuous variables are described as mean (with SDs) or median (with 25th and 75th percentiles) as appropriate. Categorical variables are expressed as frequencies (with percentages). For continuous variables, comparisons between groups were made by the \( t \) test and ANOVA for normally distributed data, and by the Wilcoxon rank-sum test and Kruskal–Wallis test for non-normally distributed data, and for categorical variables by the \( \chi^2 \) test.

We constructed a restrictive cubic spline to ascertain the crude relationship between the admission serum sodium \( \leq 145 \) mEq/L and in-hospital mortality. The independent association of the hyponatremia subtypes (community- and hospital-acquired) with in-hospital mortality, worsening kidney function, hospital LOS, and discharge to a short-/long-term care facility were evaluated after adjustment for age, sex, race, admission service, and comorbidities, as measured by the Deyo–Charlson Comorbidity Index. Multivariable logistic regression was used to evaluate the association between hyponatremia subtype and the outcomes of in-hospital death, worsening kidney function, and discharge to short-/long-term care facility, whereas negative binomial regression was used to evaluate the association between hyponatremia subtype and LOS in days. The odds ratio generated by this analysis reflects the proportional change in the LOS compared with the reference category. Patients who died in the hospital were excluded from all analyses involving discharge disposition and LOS. To explore the consistency of the findings, sensitivity analyses were performed that were restricted to hospitalized subjects with a primary diagnosis of HF, based on ICD-9-CM diagnosis code ranking, as well as to subjects with a primary diagnosis of HF and hospitalization on the cardiology service. All of the analyses were generated using SAS version 9.2 (Cary, NC). The restrictive cubic spline was generated in R version 2.11 (Free Software Foundation, Boston, MA). \( P<0.05 \) was considered statistically significant.

**Results**

**Analytic Dataset**

There were 97,472 hospitalizations during the 7-year study period, representing 51,207 subjects. A total of 84,042 hospitalizations (representing 47,301 subjects) were excluded upfront for any of the following reasons: absence of a diagnosis of HF (ICD-9 code 428.xx) or being admitted to 1 of the following services: newborn, obstetrics, psychiatry, neonatology, or missing data on service. Of the remaining 13,430 hospitalizations, which represented 7042 subjects, 4606 subjects experienced a single hospitalization. For the remaining 2436 subjects who were hospitalized more than once, the first hospitalization was selected. Among these 7042 subjects, 1695 were excluded because of the absence of admission serum sodium measurement (n=1383) or because the admission serum sodium value was \( >145 \) mEq/L (n=312). The final analytic dataset thus comprised 5347 subjects with a diagnosis of HF. Approximately 30% of patients were discharged within 3 days of admission. Nadir-to-peak serum creatinine could be calculated on 89% of patients (n=4764).

**CAH Versus Normonatremia**

CAH was identified in 1039 patients with a diagnosis of HF (19.4%). Median serum sodium in this group was 133 mEq/L (131 135). Patients with CAH did not differ significantly from normonatremic patients in terms of age and sex, but there was a significant difference in racial breakdown (\( P=0.0003; \) Table 1). Patients with a diagnosis of HF and CAH had a higher prevalence of comorbidities, as evidenced by a higher mean Deyo–Charlson Comorbidity Index (\( P=0.0001 \)). CAH was associated with increased in-hospital mortality (9.7% vs 5.7%; \( P<0.0001 \)), prolonged LOS (median 6 days [4, 10] vs 4 days [3, 7]; \( P<0.0001 \)) and increased discharge to short-/long-term care facility (48.6% vs 40.4%; \( P<0.0001 \); Table 2). The figure displays the restrictive cubic spline examining the crude relationship between admission serum sodium \( \leq 145 \) mEq/L and in-hospital mortality (Figure). As shown in the Figure, a \( U \)-shaped relationship was observed, with a serum sodium value of 140 mEq/L associated with the lowest mortality risk.

**HAH Versus Normonatremia**

HAH was identified in 1302 patients with a diagnosis of HF (30.2% of the 4308 normonatremic patients at admission). Median serum sodium in this group was 134 (132–135) mEq/L.
and median time for developing HAH was 4 days. Patients with a diagnosis of HF and HAH were younger, more likely to be men, and more likely to be nonwhite compared with normonatremic patients. However, patients with HAH had more comorbidities, as evidenced by a higher Deyo–Charlson Comorbidity Index (P<0.0001; Table 1). Significantly more patients with a diagnosis of HF and CAH were admitted to the medical service (94.4% vs 86.6%; P<0.0001). Patients with a diagnosis of HF and HAH had a significantly higher Deyo–Charlson Comorbidity Index (2.4±1.5 vs 2.3±1.6; P=0.03), with more patients having a score of ≥ 3 (34.5% vs 28.9%; P=0.004) compared with patients with a diagnosis of HF and CAH. Patients with HAH had a higher prevalence of low baseline estimated glomerular filtration rate of <60 mL/ min per 1.73 m² (7.8% vs 5.6%; P=0.03) and a history of myocardial infarction (37.1% vs 23.8%; P<0.0001).

**CAH Versus HAH**

There were some differences among patients with a diagnosis of HF and community-versus HAH. Compared with HAH, patients with a diagnosis of HF and CAH tended to be older (75.9±12.4 vs 74.6±12.0; P=0.01) and were more likely to be women (55.3% vs 48.0%; P=0.0005; Table 1). Significantly more patients with a diagnosis of HF and CAH were admitted to the medical service (94.4% vs 86.6%; P<0.0001). Patients with a diagnosis of HF and HAH had a significantly higher Deyo–Charlson Comorbidity Index (2.4±1.5 vs 2.3±1.6; P=0.03), with more patients having a score of ≥ 3 (34.5% vs 28.9%; P=0.004) compared with patients with a diagnosis of HF and CAH. Patients with HAH had a higher prevalence of low baseline estimated glomerular filtration rate of <60 mL/ min per 1.73 m² (7.8% vs 5.6%; P=0.03) and a history of myocardial infarction (37.1% vs 23.8%; P<0.0001).

### Table 1. Profile of Hospitalized Patients With Heart Failure According to the Presence or Absence of Hyponatremia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normonatremia (n=3006)</th>
<th>Community-Acquired Hyponatremia (n=1039)</th>
<th>Hospital-Acquired Hyponatremia (n=1302)</th>
<th>P Value (Overall)</th>
<th>P Value (Community- vs Hospital-Acquired Hyponatremia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.5±12.2</td>
<td>75.9±12.4</td>
<td>74.6±12.0</td>
<td>&lt;0.0001</td>
<td>0.01</td>
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<td>Women, %</td>
<td>55.2</td>
<td>55.3</td>
<td>48.0</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0006</td>
</tr>
<tr>
<td>White</td>
<td>89.3</td>
<td>88.3</td>
<td>87.9</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Black</td>
<td>4.6</td>
<td>2.7</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6.1</td>
<td>9.0</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical service, %</td>
<td>96.4</td>
<td>94.4</td>
<td>86.6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deyo–Charlson Comorbidity Index Score</td>
<td>2.1±1.3</td>
<td>2.3±1.6</td>
<td>2.4±1.5</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Deyo–Charlson Comorbidity Index category, %</td>
<td></td>
<td>[0]</td>
<td>[0]</td>
<td>&lt;0.0001</td>
<td>0.004</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>37.8</td>
<td>33.8</td>
<td>28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37.9</td>
<td>37.3</td>
<td>37.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>24.3</td>
<td>28.9</td>
<td>34.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21.6</td>
<td>23.8</td>
<td>37.1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7.6</td>
<td>10.9</td>
<td>10.2</td>
<td>0.0007</td>
<td>0.60</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6.2</td>
<td>5.6</td>
<td>7.6</td>
<td>0.10</td>
<td>200</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>29.9</td>
<td>30.0</td>
<td>29.0</td>
<td>0.83</td>
<td>200</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.6</td>
<td>5.6</td>
<td>7.8</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.0</td>
<td>1.5</td>
<td>1.3</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.7</td>
<td>4.0</td>
<td>5.4</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4.8</td>
<td>7.9</td>
<td>7.0</td>
<td>0.0003</td>
<td>0.41</td>
</tr>
<tr>
<td>HIV</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>3.0</td>
<td>1.1</td>
<td>1.2</td>
<td>&lt;0.0001</td>
<td>0.83</td>
</tr>
<tr>
<td>Psychosis</td>
<td>22.2</td>
<td>17.0</td>
<td>13.8</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonpsychosis mental disorder</td>
<td>15.4</td>
<td>20.2</td>
<td>16.0</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Acute respiratory infection</td>
<td>1.1</td>
<td>1.8</td>
<td>1.5</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Pneumonia or influenza</td>
<td>15.9</td>
<td>19.9</td>
<td>19.7</td>
<td>0.001</td>
<td>0.87</td>
</tr>
<tr>
<td>Malignant neoplasm of respiratory or intrathoracic organs</td>
<td>0.9</td>
<td>1.5</td>
<td>1.3</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;30</td>
<td>10.7</td>
<td>13.6</td>
<td>14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–59</td>
<td>40.2</td>
<td>30.3</td>
<td>33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>49.1</td>
<td>56.2</td>
<td>51.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are displayed as mean±SD. eGFR indicates estimated glomerular filtration rate; and HF, heart failure.
In-hospital mortality was increased in both hyponatremic groups compared with normonatremic patients with a diagnosis of HF. However, there was no statistically significant difference in mortality between these hyponatremic subtypes (9.7% vs 9.1%; \(P=0.58\)). Patients with HAH had increased hospital LOS compared with patients with CAH (9 days [5, 14] vs 6 days [4, 10]; \(P<0.0001\)) and were more likely to be discharged to short-/long-term care facilities (54.7% vs 48.6%; \(P=0.005\)).

**Worsening Kidney Function**
As shown in Table 2, 41.4% of patients with a diagnosis of HF and CAH experienced in-hospital worsening kidney function, compared with 55.4% among patients with HAH, and 30.0% among those who were normonatremic (\(P<0.0001\)). Worsening kidney function was associated with increased hospital LOS in all 3 groups (normonatremia 7 [4, 11] vs 4 [3, 7], \(P<0.0001\); CAH 10 [6, 14] vs 6 [4, 8], \(P<0.0001\); HAH 11 [7, 18] vs 7 [5, 10], \(P<0.0001\)).

**Multivariable Analyses**
After adjustment for age, sex, race, hospital service, and the Deyo–Charlson Comorbidity Index, patients with a diagnosis of HF and either CAH or HAH had a higher risk of in-hospital mortality compared with normonatremic patients with a diagnosis of HF, with an adjusted odds ratio of 1.7 (95% confidence interval, 1.3–2.3) and 1.6 (95% confidence interval, 1.3–2.1), respectively (Table 3). In addition, patients with a diagnosis of HF and either CAH or HAH experienced a heightened likelihood of discharge to a short-/long-term care facility (adjusted odds ratio, 1.4 [95% confidence interval, 1.2–1.7] and adjusted odds ratio, 1.8 [95% confidence interval, 1.6–2.1], respectively) compared with normonatremic patients with a diagnosis of HF. Patients with CAH or HAH had an increased likelihood of LOS prolongation (adjusted odds ratio, 1.4 [95% confidence interval, 1.2–1.7] and adjusted odds ratio, 1.8 [95% confidence interval, 1.6–2.1], respectively) compared with normonatremic patients with a diagnosis of HF. Both CAH and HAH were associated with worsening kidney function (1.6 [1.3–1.9] and 2.7 [2.3–3.1], respectively). All these effect estimates remained significant after expanding the multivariable models with the addition of several covariates, including the presence of psychosis, mental illness, and pneumonia/influenza (Table 3).

**Sensitivity Analyses**
After adjustment for age, sex, and the Deyo–Charlson Comorbidity Index, these multivariable associations persisted on sensitivity analyses restricted to hospitalized patients with a primary diagnosis of HF, based on ICD-9-CM diagnosis code ranking (Table 3), as well as among patients with a diagnosis of HF hospitalized on the cardiology service (data not shown). Of note, hospitalized patients with a primary diagnosis of HF did not significantly differ in terms of demographic characteristics compared with patients with a nonprimary diagnosis of HF (Table 4). However, patients with a primary diagnosis of HF had significantly fewer comorbidities, as evidenced by a lower Deyo–Charlson Comorbidity Index, and specific comorbidities, such as myocardial infarction, cerebrovascular disease, liver disease, malignancies, and neurologic and psychiatric illnesses, as well as acute respiratory infections. By contrast, patients with a primary diagnosis of HF had more advanced stages of chronic kidney disease (estimated glomerular filtration rate, <60 mL/min per 1.73 m²). In-hospital mortality was significantly lower in patients with a primary diagnosis of HF.
diagnosis of HF compared with patients with a nonprimary diagnosis of HF (2.4% vs 7.3%), which might have been, in part, attributable to the presence of fewer comorbidities.

## Discussion

In the present subanalysis of 5347 hospitalized patients with a diagnosis of HF, we demonstrate that HAH is even more common than CAH. Moreover, similar to CAH, HAH is associated with poor outcomes compared with patients with a diagnosis of HF who are normonatremic at hospital admission. Our study is the first to analyze the implications of HAH in patients with a diagnosis of HF in juxtaposition with the CAH cohort.

In agreement with previous reports, the prevalence of CAH in hospitalized patients with a diagnosis of HF in our study was 19.4%. Notably, no <30.2% of our patients developed HAH, for an aggregate prevalence of 49.6%. Thus, more than half of the hyponatremic cases in hospitalized patients with a diagnosis of HF are hospital acquired. Both hyponatremic cohorts fared worse than their normonatremic counterpart. Compared with each other, the HAH cohort had the same poor prognosis as the CAH cohort in terms of hospital mortality, but had a longer median LOS and more discharges to special-care facilities. The data indicate that both hyponatremic presentations in patients with a diagnosis of HF are independently associated with increased in-hospital mortality and heightened resource consumption.

Hyponatremia in HF is dilutional in nature and is termed hypervolemic hyponatremia. With a decrease in cardiac output the arterial stretch baroreceptors in the carotid sinus and aortic arch are unloaded. Thus, the normal tonic inhibitory effect to the central nervous system via the vagus and glossopharyngeal nerves is removed with a resultant increase in sympathetic efferent activity. In turn, increased sympathetic activity is associated with stimulation of the renin–angiotensin–aldosterone system and the nonosmotic release of arginine vasopressin. The resultant systemic and renal vasoconstriction, as well as the sodium and water retention, attenuate the arterial underfilling, but ultimately at the expense of hyponatremia, pulmonary congestion, and diminished kidney function. In addition to the proposed baroreceptor-mediated arterial underfilling stimulating arginine vasopressin, direct central effects of the sympathetic and renin–angiotensin systems on arginine vasopressin synthesis and release must also be considered. More severe HF produces more severe hyponatremia. The longer the duration of impaired circulation and neurohumoral activation, the more prolonged the hyponatremia. Results of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial reported CAH in 23.8% of hospitalized patients with HF. The hyponatremia was an independent predictor of mortality and rehospitalization even when adjusted for clinical and hemodynamic improvements similar to those in HF patients without hyponatremia. In another study, patients with HF who demonstrated persistent hyponatremia for up to 60 to 270 days after discharge had the worst long-term survival.

Development of HAH in patients with HF could reflect worsening hemodynamics and aggravation of neurohumoral alterations because of comorbidities or complications during the hospital course. Medications and increased intake of electrolyte-free water might also be implicated. In the present study, patients with a diagnosis of HF and HAH tended to be more ill at baseline, with more comorbidities, including a higher prevalence of chronic kidney disease and myocardial infarction, compared with patients with a diagnosis of HF and either normonatremia or CAH. Approximately 15% of patients with a diagnosis of HF and HAH were admitted to nonmedical services as compared with 4% of normonatremic patients and 6% of patients with CAH. Median time for developing HAH was 4 days of hospitalization. In the present study, a strong association was observed between hyponatremia (both HAH and CAH).

### Table 3. Multivariable Analyses Examining the Association Between Hyponatremia Subtypes in Hospitalized Patients With a Diagnosis of Heart Failure and Hospital-Based Outcomes

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>Adjusted Relative Prolongation In-Hospital Length of Stay (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a diagnosis of HF</td>
<td>In-Hospital Mortality</td>
<td>Discharge to Short-/Long-Term Care Facility</td>
</tr>
<tr>
<td><strong>Community-acquired hyponatremia (vs normonatremia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic model</td>
<td>1.73 (1.33–2.25)</td>
<td>1.43 (1.22–1.67)</td>
</tr>
<tr>
<td>Expanded model</td>
<td>1.69 (1.29–2.21)</td>
<td>1.51 (1.29–1.78)</td>
</tr>
<tr>
<td><strong>Hospital-acquired hyponatremia (vs normonatremia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic model</td>
<td>1.64 (1.27–2.11)</td>
<td>1.80 (1.55–2.09)</td>
</tr>
<tr>
<td>Expanded model</td>
<td>1.55 (1.19–2.01)</td>
<td>2.07 (1.77–2.42)</td>
</tr>
<tr>
<td>Patients with a primary diagnosis of HF*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Community-acquired hyponatremia (vs normonatremia)</strong></td>
<td>6.77 (2.24–20.47)</td>
<td>1.39 (1.21–1.62)</td>
</tr>
<tr>
<td><strong>Hospital-acquired hyponatremia (vs normonatremia)</strong></td>
<td>7.61 (2.57–22.58)</td>
<td>1.79 (1.56–2.05)</td>
</tr>
</tbody>
</table>

The basic model for the entire cohort was adjusted for age, sex, race, hospital service, and Deyo–Charlson Comorbidity Index. The expanded model for the entire cohort was adjusted for age, sex, race, hospital service, Deyo–Charlson Comorbidity Index, psychosis, mental illness, and pneumonia/influenza. Patients who died in hospital were excluded from the analysis of hospital length of stay and discharge disposition. HF indicates heart failure.

*The model for patients with a primary diagnosis of HF (n=984) was adjusted for age, sex, and Deyo–Charlson Comorbidity Index.
and CAH) in hospitalized patients with HF and worsening kidney function. Not surprisingly, worsening kidney function in hyponatremic (hospital- or community-acquired) and in normonatremic patients with a diagnosis of HF was associated with increased LOS. Moreover, the incidence of worsening kidney function was increased in patients with HAH compared with those with CAH (55.4% vs 41.4%). It is likely that worsening kidney function contributed to the development of HAH by aggravating hemodynamics and neurohumoral stimulation, as well as limiting the amount of filtrate that reaches the collecting duct.

Strengths of our study include its large size, encompassing a population with HF and an array of comorbidities cared for at a single medical center. Hyponatremia was corrected for the effect of hyperglycemia. A unique feature of the analysis was that both CAH and HAH were examined and their impact on in-hospital mortality and resource use was contrasted.

Our study has several limitations. Individual comorbidities were identified using administrative codes that do not offer information on the severity of the corresponding condition (with the exception of chronic kidney disease). That deficiency coupled with the potential omission of certain comorbidities might be responsible for some unmeasured confounding in the multivariable analyses. Nevertheless, we used a well-validated instrument for representing the global burden of illness for each patient. In further reference to that limitation, we did not analyze patients admitted to the hospital because of decompensated HF but rather hospitalized patients whose codified discharge abstract included the diagnosis code of HF. We did not use generalized estimating equations that would have allowed us to analyze all evaluable hospitalizations of patients with HF rather compared with the approach that we adopted where we limited the analysis to the first HF-associated hospitalization per patient.

In conclusion, hyponatremia in hospitalized patients with a diagnosis of HF, either present on admission or developing during the in-hospital course, is common and independently associated with poor outcomes, including increased mortality, LOS, and likelihood of discharge to special-care facilities. As a corollary, is this independent association merely associative or causative? Indeed, the critical question is whether mild to moderate hyponatremia in HF (as well as in other chronic disorders) is simply a prognostic marker of poor outcomes as a reflection of the severity of the underlying condition or actually imparts risk contributing directly to morbidity and mortality. The prevailing view favors the former option. However, we are intrigued by the recent recognition that mild, seemingly asymptomatic, hyponatremia is associated with attention impairment, gait instability, falls, osteoporosis, and fractures. Strong evidence has been produced for the development of osteoporosis in an experimental model of the syndrome of inappropriate antidiuresis. We consider it conceivable that hyponatremia itself or associated factors (eg, hypotonicity, changes in cell composition and transport, increased levels of arginine vasopressin) might impart adversity on the cardiovascular and other organ systems and thus contribute directly to poor outcomes. For example, there is experimental evidence that hyponatremia impairs cardiomyocyte function.
Sources of Funding
Dr. Shchekochikhin’s cardiorenal fellowship was sponsored by Russian President’s Scholarship for Studying Abroad and Gambro Ultrafiltration Solutions, Inc.

Disclosures
Dr. Schrier is a consultant for Otsuka America Pharmaceutical and Janssen Pharmaceutical. Dr. Madias serves as a consultant for Otsuka America Pharmaceutical. Drs. Shchekochikhin, Lindenfeld, Price, and Jaber have no conflicts to report.

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**CLINICAL PERSPECTIVE**

There are ≈1 million hospital admissions for heart failure (HF) each year in the United States, and ≈30% of these patients are either readmitted or die within the 60 days post discharge. The presence of hyponatremia in decompensated HF patients on admission to hospital is known to be associated with increased morbidity and mortality. There is, however, little known about whether the development of hyponatremia after patients with HF are admitted to hospital has the same unfavorable implications. Our data in a large population of patients (n=5347) admitted to a community hospital with decompensated HF patients demonstrate that hyponatremia developing in hospital predicted an increased mortality, length of stay, and discharge to special care facilities of a similar magnitude as occurred with hyponatremia that was present on admission to hospital (referred to here as community-acquired). Moreover, both community- and hospital-acquired hyponatremia were associated with worsening renal function, a known predictor of mortality in HF patients. Thus, extant hyponatremia on admission or the development of hyponatremia during admission both identify higher-risk cohorts of patients. Whether improving hyponatremia improves the adverse outcome risk is not known.
Outcome Differences in Community- Versus Hospital-Acquired Hyponatremia in Patients With a Diagnosis of Heart Failure
Dmitry Y. Shchekochikhin, Robert W. Schrier, JoAnn Lindenfeld, Lori Lyn Price, Bertrand L. Jaber and Nicolaos E. Madias

Circ Heart Fail. 2013;6:379-386; originally published online March 19, 2013; doi: 10.1161/CIRCHEARTFAILURE.112.000106
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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