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

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Background—The prognostic value of serum sodium in patients hospitalized for worsening heart failure has not been well defined.

Methods and Results—The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study randomized 949 patients with systolic dysfunction hospitalized for worsening heart failure to receive 48 to 72 hours of intravenous milrinone or placebo in addition to standard therapy. In a retrospective analysis, we investigated the relationship between admission serum sodium and the primary end point of days hospitalized for cardiovascular causes within 60 days of randomization, as well as the secondary end points of in-hospital mortality, 60-day mortality, and 60-day mortality/rehospitalization. The number of days hospitalized for cardiovascular causes was higher in the lowest sodium quartile: 8.0 (4.5, 18.5) versus 6 (4, 13) versus 6 (4, 11.5) versus 6 (4, 12) days (P=0.015 for comparison with the lowest quartile). Lower serum sodium was associated with higher in-hospital and 60-day mortality: 5.9% versus 1% versus 2.3% versus 2.3% (P<0.015) and 15.9% versus 6.4% versus 7.8% versus 7% (P=0.002), respectively. There was a trend toward higher mortality/rehospitalization for patients who were in the lowest sodium quartile. Multivariable-adjusted Cox proportional hazards analysis showed that serum sodium on admission, when modeled linearly, predicted increased 60-day mortality: sodium (per 3-mEq/L decrease) had a hazard ratio of 1.18 with a 95% CI of 1.03 to 1.36 (P=0.018).

Conclusions—In patients hospitalized for worsening heart failure, admission serum sodium is an independent predictor of increased number of days hospitalized for cardiovascular causes and increased mortality within 60 days of discharge. (Circulation. 2005;111:2454-2460.)

Key Words: heart failure • prognosis • sodium • risk factors

Although recent clinical trials1–4 demonstrated that hospitalized heart failure patients have relatively low inhospital mortality (3% to 4%), their readmission for cardiovascular causes and all-cause mortality rates within 60 days of discharge are as high as 25% and 10%, respectively. The mortality and morbidity appear to be significantly higher during this postdischarge phase than during a comparable period for patients with severe disease that does not require hospitalization.5 Despite the clinical significance of worsening heart failure that results in hospitalization, this phase of the syndrome has received little attention in the cardiovascular community,6 and risk stratification for these patients has not been well defined.

Serum sodium has been shown to be a prognostic factor in outpatients with heart failure7; however, its significance in hospitalized patients has not been well defined. In a retrospective analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), we investigated the association between serum sodium and all-cause mortality and readmissions for cardiovascular causes in hospitalized patients with heart failure.

Methods

Study Design

The study design8 and primary results of OPTIME-CHF have been published previously.1 The OPTIME-CHF study randomized 949 patients with systolic dysfunction hospitalized for worsening heart failure to receive 48 to 72 hours of intravenous milrinone or placebo in addition to standard therapy.
patients with systolic dysfunction and worsening heart failure to receive 48 to 72 hours of intravenous milrinone (0.5 μg·kg⁻¹·min⁻¹ without a loading dose) or placebo in a double-blinded fashion. Patients requiring inotropic support and those with evidence of active myocardial ischemia within the prior 3 months, serum creatinine >3.0 mg/dL, systolic blood pressure <80 mm Hg, or unstable arrhythmias were excluded. Background therapy was left to the discretion of the treating physician, but specific recommendations for optimal medical therapy based on published guidelines were included with the study protocol. The primary end point was the total number of days hospitalized for cardiovascular causes within 60 days of randomization. Days lost to follow-up and days deceased were included prospectively in the primary end point to avoid bias toward a therapy with increased mortality. For instance, a patient hospitalized initially for 7 days after randomization who then died on day 45 of the 60-day follow-up would have 22 days as the primary end point. Important secondary end points were 60-day mortality, the composite of death and rehospitalizations at 60-days, the ability to reach target dosing of ACE inhibitors at discharge, and quality of life (QOL). The latter was assessed with a visual analog scale from 0 (worst) to 100 (best) and a subjective health status questionnaire that assessed activity limitations, symptoms, and emotions as better, worse, or the same. End points for the present analysis were the same as those in the overall OPTIME-CHF study, as described previously.

Data Analysis
Continuous variables are presented as median values with 25th and 75th percentiles, whereas categorical variables are shown as percentages of nonmissing values. The data are displayed in quartiles. All analyses were performed on the basis of the intention-to-treat principle.

Contingent on the assumptions of normality, ANOVA or Kruskal-Wallis tests were used to explore the relationship between continuous baseline and outcomes variables and serum sodium across quartiles. Because of the nonnormality of the primary end point, the Kruskal-Wallis test was used for this outcome. Pearson χ² statistics or Fisher exact test were used to examine the association between serum sodium quartiles and baseline categorical variables. If the overall test for differences among quartiles was significant at the 0.05 level, we examined the differences between the first and the other quartiles. For dichotomous outcomes measures, logistic regression analysis was used to examine the overall association of serum sodium and outcome with indicator variables for the higher 3 quartiles. If the overall model was significant at the 0.05 level, we examined the significance of the higher 3 quartiles using the first quartile as the referent group. A similar approach was used to test the association between serum sodium and 60-day mortality with Cox proportional hazards regression. Multivariable analysis was used to assess the independent risk of serum sodium on clinical end points. For the multivariable analysis, 41 candidate variables were considered that reflected demographics, cardiac history, comorbidities, bedside clinical assessment, and laboratory studies. Within each category, the most likely predictors were identified by backwards-variable selection, and variables were removed from the model at a probability value >0.05. The significant predictors from each of these 5 groups were combined, and 6 prespecified covariates were added if they had not already been included: age, gender, ethnicity, ejection fraction, etiology, and systolic blood pressure. These covariates were included on the basis of the high theoretical likelihood that they would be associated with outcomes. Backward stepwise variable selection was again performed, and a final model was generated. Two-sided values of P<0.05 were considered significant for all analyses. Analyses were performed with SAS version 8.2 (SAS Institute Inc).

Results
Baseline Characteristics
The baseline characteristics of the study patients across serum sodium quartiles are presented in Table 1. Patients with lower serum sodium were more likely to have more severe heart failure (higher number of admissions in the previous year) and tended to have a longer duration of their disease. These patients also had lower systolic blood pressure and higher blood urea nitrogen (BUN). However, left ventricular ejection fraction, degree of congestion, symptoms (New York Heart Association [NYHA] functional class), and heart failure score were similar across quartiles.

Outcomes by Serum Sodium Concentrations
The primary end point of days hospitalized for cardiovascular causes within 60 days of randomization was higher in the lowest sodium quartile than in the other quartiles: 8.0 (4.5, 18.5) versus 6 (4, 13) versus 6 (4, 11.5) versus 6 (4, 12) days (P<0.001 overall; P<0.015 for any quartile compared with first; Table 2). The in-hospital and 60-day mortality rates were also increased in the lowest quartile of serum sodium: 5.9% versus 1% versus 2.3% versus 2.3% (P=0.015) and 15.9% versus 6.4% versus 7.8% versus 7% (P=0.002), respectively (Figure 1). Patients in the lowest sodium quartile trended toward higher rates of death or rehospitalization at 60 days: 41% versus 30.4% versus 33.5% versus 33.6% (P=0.095). The primary end point had a moderate correlation with the 60-day mortality and 60-day death/rehospitalization rates (r=0.48 and 0.64, respectively, by Spearman rank correlation).

There were no differences observed across serum sodium quartiles in the rates of treatment failure (defined as sustained hypotension for >30 minutes that required intervention, myocardial ischemia and arrhythmias, worsening heart failure, and failure to achieve adequate clinical improvement at 48 hours after study-drug infusion) while patients were taking the study drug. However, significantly more patients with low serum sodium developed sustained hypotension that necessitated intervention (Table 2). There was no association between serum sodium concentration and the ability to reach target dosing of ACE inhibitors by discharge.

Baseline QOL scores were comparable across sodium quartiles, and all patients had substantial and similar improvement over baseline in the visual analog QOL by hospital discharge that was maintained at 60-day follow-up. There was no difference in the QOL by the subjective health status questionnaire in the 4 quartiles, with an equal percentage of patients feeling better or the same by 60 days (Table 2).

Changes in Serum Sodium Concentration
Although on average, serum sodium increased by discharge in the lowest admission quartile, it decreased in the other 3 quartiles: +1 (−2, 3) versus −1 (−3, 1) versus −2 (−3, 0) versus −3 (−6, −2; P<0.001). Thirty-eight percent (93/244) of the patients who were in the lowest serum sodium quartile at baseline were discharged with serum sodium concentration >135 mEq/L. Their 60-day mortality rate was 10.75% compared with 17.22% among patients who remained hyponatremic at discharge (P=0.19). The 60-day mortality rates in the other 3 quartiles were 6.4% versus 7.8% versus 7%, respectively.
Effect of Milrinone Treatment

There was no difference observed in the number of days hospitalized for cardiovascular causes within 60 days of randomization regardless of the treatment assignment (milrinone or placebo) for any of the serum sodium quartiles. The 60-day mortality rate was also similar across sodium quartiles among patients treated with milrinone compared with placebo (Table 3). The interaction between treatment assignment and serum sodium was not significant for any outcome ($P > 0.35$), which indicates that the relationship

### TABLE 1. Baseline Characteristics by Serum Sodium Quartiles

<table>
<thead>
<tr>
<th>Demographics</th>
<th>1st Quartile (n=256)</th>
<th>2nd Quartile (n=207)</th>
<th>3rd Quartile (n=220)</th>
<th>4th Quartile (n=260)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68 (53–76)</td>
<td>65 (55–74)</td>
<td>68 (57–76)</td>
<td>69 (59–77)</td>
<td>0.06</td>
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<tr>
<td>Women, %</td>
<td>32</td>
<td>35</td>
<td>33</td>
<td>36</td>
<td>0.92</td>
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<tr>
<td>Ethnicity, %</td>
<td>White</td>
<td>72</td>
<td>66</td>
<td>64</td>
<td>58</td>
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<tr>
<td></td>
<td>Black</td>
<td>25</td>
<td>32</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Medical history</td>
<td>Ischemic etiology, %</td>
<td>55</td>
<td>50</td>
<td>55</td>
<td>45</td>
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<tr>
<td></td>
<td>Myocardial infarction, %</td>
<td>45</td>
<td>51</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Coronary artery bypass surgery, %</td>
<td>38</td>
<td>29</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Hypertension, %</td>
<td>62</td>
<td>68</td>
<td>69</td>
<td>71</td>
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<tr>
<td></td>
<td>Atrial fibrillation, %</td>
<td>31</td>
<td>30</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia, %</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>8</td>
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<tr>
<td></td>
<td>Months since heart failure diagnosis</td>
<td>39.5 (17.5–75)</td>
<td>37 (11–69)</td>
<td>39 (12–70)</td>
<td>30.5 (9–65)</td>
</tr>
<tr>
<td></td>
<td>Hospitalizations in prior 12 months, n</td>
<td>2 (1–3)</td>
<td>1 (0–3)</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Ejection fraction, %</td>
<td>21 (17.5–30)</td>
<td>22 (17–30)</td>
<td>22.5 (19.5–30)</td>
<td>24.5 (20–30)</td>
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<td></td>
<td>NYHA class, %</td>
<td>47</td>
<td>45</td>
<td>49</td>
<td>42</td>
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<tr>
<td></td>
<td>III</td>
<td>49</td>
<td>49</td>
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<td></td>
<td>IV</td>
<td>76</td>
<td>72</td>
<td>73</td>
<td>70</td>
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<tr>
<td></td>
<td>Systolic blood pressure, mm Hg</td>
<td>114 (100–130)</td>
<td>120 (105–136)</td>
<td>120 (107–132)</td>
<td>123 (110–138)</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 (60–78)</td>
<td>70 (60–80)</td>
<td>70 (62–80)</td>
<td>70 (60–80)</td>
</tr>
<tr>
<td></td>
<td>Baseline heart rate, bpm</td>
<td>84 (72–96)</td>
<td>84 (72–97)</td>
<td>85 (76–95)</td>
<td>81 (70–94)</td>
</tr>
<tr>
<td></td>
<td>Jugular venous pressure &gt;6 cm, %</td>
<td>76</td>
<td>72</td>
<td>73</td>
<td>70</td>
</tr>
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<td></td>
<td>Pulmonary edema, %</td>
<td>83</td>
<td>79</td>
<td>80</td>
<td>82</td>
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<td></td>
<td>Systolic murmurs, %</td>
<td>52</td>
<td>47</td>
<td>43</td>
<td>51</td>
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<td>Third heart sound, %</td>
<td>59</td>
<td>61</td>
<td>56</td>
<td>58</td>
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<td></td>
<td>Heart failure score (4–10)</td>
<td>6 (5–7)</td>
<td>6 (5–7)</td>
<td>6 (5–7)</td>
<td>6 (5–7)</td>
</tr>
<tr>
<td>Laboratory values</td>
<td>Serum sodium, mEq/L</td>
<td>134 (132–135)</td>
<td>138 (137–138)</td>
<td>140 (139–140)</td>
<td>142 (141–144)</td>
</tr>
<tr>
<td></td>
<td>Serum potassium, mEq/L</td>
<td>4.2 (3.9–4.6)</td>
<td>4.1 (3.8–4.5)</td>
<td>4 (3.8–4.4)</td>
<td>4 (3.8–4.4)</td>
</tr>
<tr>
<td></td>
<td>Serum BUN, mg/dL</td>
<td>33 (20–49)</td>
<td>24 (17–39)</td>
<td>23 (16–37)</td>
<td>24 (18–35)</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine, mg/dL</td>
<td>1.4 (1.1–1.8)</td>
<td>1.4 (1.1–1.8)</td>
<td>1.3 (1–1.7)</td>
<td>1.4 (1.1–1.7)</td>
</tr>
<tr>
<td>Admission medications, %</td>
<td>Diuretics</td>
<td>92</td>
<td>93</td>
<td>89</td>
<td>88</td>
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<tr>
<td></td>
<td>ACE inhibitors</td>
<td>70</td>
<td>70</td>
<td>67</td>
<td>74</td>
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<tr>
<td></td>
<td>Angiotensin receptor blockers</td>
<td>13</td>
<td>14</td>
<td>17</td>
<td>8</td>
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<tr>
<td></td>
<td>β-Blockers</td>
<td>21</td>
<td>20</td>
<td>25</td>
<td>23</td>
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<tr>
<td></td>
<td>Digoxin</td>
<td>77</td>
<td>82</td>
<td>71</td>
<td>63</td>
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<td></td>
<td>Calcium channel blockers</td>
<td>12</td>
<td>10</td>
<td>15</td>
<td>17</td>
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<tr>
<td></td>
<td>Amiodarone</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (interquartile range). ANOVA or Kruskal-Wallis test was used to test for overall differences between continuous variables. Pearson $\chi^2$ statistics or Fisher exact test was used to test differences between categorical variables.

*All individual quartiles vs first quartile, $P < 0.05$. 
between serum sodium and end points did not differ between treatment groups (Table 3).

**Multivariable Analysis**

The findings of the Cox proportional hazards model were consistent with those of the unadjusted analysis for the primary end point and for the 60-day mortality rate. After adjustment for baseline differences, serum sodium on admission remained a significant predictor of the number of days hospitalized for cardiovascular causes within 60 days of randomization ($P=0.03$). Serum sodium, when modeled linearly, remained a significant predictor of increased 60-day mortality (hazard ratio [HR] 1.18 per 3-mEq/dL decrease, 95% CI 1.03 to 1.36, $P=0.018$). This translates into an 18% relative increase in the probability of death within 60 days of randomization for every 3-mEq/dL decrease in admission sodium values (Figure 2). Other predictors of 60-day mortality were increasing age (HR = 1.26 per 10-year increase, 95% CI 1.06 to 1.51, $P=0.01$), lower systolic blood pressure (HR = 1.28 per 10-mm Hg decrease, 95% CI 1.12 to 1.46, $P<0.001$), NYHA class IV symptoms (HR = 1.93, 95% CI 1.22 to 3.04, $P=0.004$), and elevated BUN (HR = 1.33 per 5-mg/dL increase, 95% CI 1.19 to 1.47, $P<0.001$).

**Discussion**

Worsening heart failure that results in hospitalization represents a major public health problem because of the high postdischarge mortality rate, large number of hospital readmissions, and significant associated costs. Several recent studies have tried to identify predictors of mortality or rehospitalization that could potentially aid clinical decision making in this population.9–14 The present analysis, conducted in a sample derived from a large clinical trial, identifies a substantial risk of short- and intermediate-term clinical events associated with decreasing serum sodium concentration in patients hospitalized for worsening heart failure. Lower concentrations of serum sodium on admission remained a predictor of increased number of days hospitalized for cardiovascular causes and increased mortality within 60 days of discharge after adjustment was made for a variety of baseline variables.

In heart failure, decreased stimulation of mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal
afferent arterioles leads to increased sympathetic discharge, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin, among other neurohormones. Increased sympathetic drive contributes to avid sodium and water retention through renal vasoconstriction, stimulation of the renin-angiotensin-aldosterone system, and a direct effect on the proximal convoluted tubule. Increased angiotensin II and aldosterone levels in heart failure lead to decreased sodium and water delivery to the collecting duct, which, combined with resistance to the action of natriuretic peptides, result in impairment of free-water excretion and hyponatremia. Finally, the nonosmotic stimulation of vasopressin release leads to elevated vasopressin concentration, which results in an increased number of aquaporin water channels in the collecting duct of the kidney that promote abnormal free water retention and contribute to the development of hyponatremia.

In several studies from the early 1980s, Dzau et al observed that patients with heart failure and low serum sodium had higher circulating levels of catecholamines, renin, angiotensin II, aldosterone, and vasopressin than normonatremic patients. Hyponatremic patients had an impaired neurohormonal response to orthostasis, lower hepatic and renal plasma flows, elevated liver enzymes, and prerenal azotemia compared with normonatremic patients. These studies raised the hypothesis that low serum sodium may be a marker of neurohormonal activation, reflecting the severity of the disease. Indeed, the degree of neurohormonal activation and the prevalence of low serum sodium (21% versus 7%) are markedly higher in hospitalized patients with worsening heart failure than in outpatients with stable disease.

Low serum sodium has also been correlated with ventricular ectopy, an increase in sudden death and increased in-hospital mortality. A clinical risk model derived from a retrospective review of medical records has shown a significant 50% increase in 30-day all-cause mortality in patients with serum sodium below 136 mEq/L, risk that was also maintained at 1 year, compared with patients with normal serum sodium.

Hyponatremic patients have a greater immediate improvement in the cardiac index and left ventricular filling pressures in response to ACE inhibitors, and although they may initially have more symptomatic hypotension in response to ACE inhibitors, they have significant improvement in serum sodium and survival compared with normonatremic patients.

Many prior reports examining the prognostic value of serum sodium in hospitalized heart failure patients were either small or consisted of retrospective medical records review. The present retrospective analysis is the first to examine this relationship using data from a prospective, randomized clinical trial that had an extensive standardized assessment of baseline characteristics and outcomes and a 99% complete follow-up rate. In addition, we were able to analyze changes in serum sodium between admission and discharge. In the present analysis, lower serum sodium on admission was associated with more severe heart failure (longer duration of the disease and more hospitalizations in the previous year) but not with higher degree of congestion (similar prevalence of rales, jugular venous pressure, and edema across groups; Table 1). Lower serum sodium was also associated with a lower blood pressure and higher BUN (Table 1). Reduction in renal perfusion, renin-angiotensin-aldosterone, and sympathetic activation lead to increased sodium and water reabsorption that is coupled with enhanced urea reabsorption in the proximal tubules. Vasopressin, on binding to V2 receptors in the inner medullary collecting ducts, increases urea permeability through activation of urea transporters, which enables its reabsorption. The marked activation of neurohormonal systems, particularly vasopressin, may be the cause of both low serum sodium and high BUN in patients with decompensated heart failure. Use of neurohormonal blockade with ACE inhibitors and β-blockers may blunt some of these effects and may explain why hyponatremic patients in the OPTIME-CHF study had much lower BUN levels than in studies done in the 1980s, in which the use of ACE inhibitors and β-blockers was significantly lower.

Although the OPTIME-CHF study excluded patients with active ischemia, renal failure, significant arrhythmias, or

![Figure 1. Kaplan-Meier survival curves to 60 days by serum sodium quartiles (unadjusted analysis). Probability value <0.05 for first quartile vs each of the other quartiles from Cox proportional hazards model.](http://circ.ahajournals.org/)

![Figure 2. Fourteen-day and 60-day mortality rates by serum sodium levels (unadjusted analysis). Survival estimates are product-limit estimates from Cox proportional hazards model.](http://circ.ahajournals.org/)
those who required inotropes,1,8 patients in the lowest serum sodium quartile had an event rate (death/rehospitalizations) of 41% within 60 days, which suggests that they are at particularly high risk (Table 2). Moreover, only 38% of these patients were able to normalize their serum sodium by the time of discharge. The 60-day mortality rate in this group was 11% compared with 17% in patients who remained persistently hyponatremic at discharge; however, this difference did not achieve statistical significance, probably owing to the small number of end points.

Milrinone is known to improve hemodynamics in heart failure patients,34 and it has been suggested that it might be useful especially in patients with more severe heart failure.35,36 In the present analysis, patients in the lowest serum sodium quartile (with more severe heart failure and presumably worse hemodynamics) experienced more sustained hypotension while using milrinone, despite having a similar improvement in QOL score.

It has also been suggested that heart failure patients with hyponatremia are more susceptible to the hypertensive and azotemic effects of ACE inhibitors, possibly because they are more dependent on neurohormones to sustain their blood pressure, and therefore initiation or uptitration of ACE inhibitors is particularly difficult in these patients.30,31 Nevertheless, in the present study, there were no significant differences in the percentages of patients able to achieve target doses of ACE inhibitors at discharge across serum sodium quartiles.

The high short-term mortality and morbidity rates in patients hospitalized with worsening heart failure underline the importance of identification of modifiable risk factors. Of the predictors of mortality in the OPTIME-CHF study (age, NYHA class, low blood pressure, high BUN, and hyponatremia), hyponatremia is potentially modifiable by an available treatment (ie, vasopressin antagonists).37,38

The present study has several limitations. The study sample is derived from a randomized, controlled trial and consists solely of patients with impaired systolic function and relatively preserved renal function. Whether serum sodium concentration would be predictive of outcomes in patients hospitalized for heart failure and more advanced renal dysfunction deserves further investigation. Patients enrolled in the OPTIME-CHF study, however, do appear to have a clinical profile similar to that of unselected registry patients hospitalized for heart failure who have left ventricular dysfunction: normotensive, with a high degree of congestion and relatively preserved renal function.39 Finally, although lower serum sodium is related to higher mortality, care must be observed in interpreting the exact shape of the relationship because of the relatively small number of deaths observed.

**Conclusions**

In this retrospective analysis, we found that in patients hospitalized for worsening heart failure and systolic dysfunction, serum sodium on admission is an important predictor of increased number of days hospitalized for cardiovascular causes and increased mortality within 60 days of discharge. The present study also raised the hypothesis that normalization of serum sodium during hospitalization may improve survival; however, this assumption needs to be tested further in randomized clinical trials.

**Acknowledgment**

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**References**


**TABLE 3. Outcomes by Serum Sodium Quartiles and Treatment Assignments**

<table>
<thead>
<tr>
<th>Serum Sodium Quartile</th>
<th>Primary End Point, d*</th>
<th>Mortality, %</th>
<th>Rehospitalization/Death at 60 Days§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Quartile</td>
<td>7 (4–19)</td>
<td>6.3</td>
<td>39.7</td>
</tr>
<tr>
<td>2nd Quartile</td>
<td>9 (5–18)</td>
<td>5.4</td>
<td>42.4</td>
</tr>
<tr>
<td>3rd Quartile</td>
<td>6 (4–10)</td>
<td>1</td>
<td>26.7</td>
</tr>
<tr>
<td>4th Quartile</td>
<td>6 (4–14)</td>
<td>1</td>
<td>26.7</td>
</tr>
</tbody>
</table>

*Continuous variables are presented as median (interquartile range). P value is of interaction of treatment and serum sodium from regression of log-transformed response.

†Raw percentages of patients followed up to 60-day visit. P value is of interaction of treatment and serum sodium level from Cox model.

§Raw percentages of patients followed up to 60-day visit. P value is of interaction of treatment and serum sodium level from logistic model.


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