Hyponatremia, Natriuretic Peptides, and Outcomes in Acutely Decompensated Heart Failure
Results From the International Collaborative of NT-proBNP Study

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Background—Hyponatremia is a well-known predictor of mortality in patients with acutely decompensated heart failure. Associations between hyponatremia and other prognostic variables in acutely decompensated heart failure, such as amino-terminal pro-B type natriuretic peptide remain unclear.

Methods and Results—Six hundred twenty-eight patients presenting to the emergency department with acutely decompensated heart failure were studied. All were hospitalized. Serum sodium (Na) concentration at presentation was examined as a function of mortality at 1 year, alone and relative to other predictors of death. Hyponatremia (Na ≤135 mmol/L) was diagnosed in 24% (n=149) patients. Compared with those without hyponatremia, those affected were less likely to be male or to have hypertension or coronary artery disease but were more likely to have severe symptoms, to be anemic, and to have higher amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations (all P<0.05). When examined as a function of Na deciles (ranging from Na <132 mmol/L to Na ≤142 mmol/L), a U-shaped association was found between Na level and 1-year mortality. In multivariate Cox proportional hazards analysis, hyponatremia was an independent predictor of 1-year mortality (hazards ratio=1.72; 95% CI=1.22 to 2.37; P=0.001) as was an NT-proBNP concentration above the median value of 4690 pg/mL (hazards ratio=1.49; 95% CI=1.10 to 2.00; P=0.009). Those with hyponatremia and more elevated NT-proBNP were more likely to develop worsening renal function during their hospitalization and had highest rates of 1-year death. Notably, however, hyponatremia predicted only 1-year mortality in those with an elevated NT-proBNP.

Conclusion—Hyponatremia is associated with adverse outcome in patients with acutely decompensated heart failure; however, the prognostic value of low Na is mainly evident in those with more pronounced elevation of NT-proBNP concentrations. (Circ Heart Fail. 2010;3:354-361.)

Key Words: heart failure ▪ hyponatremia ▪ natriuretic peptides

Hyponatremia (conventionally defined as a serum sodium [Na] concentration ≤135 mmol/L), is a common phenomenon in patients suffering from acutely decompensated heart failure (ADHF), with an incidence from 20% to 25%. Based on landmark studies of Na and heart failure (HF), it is known that hyponatremia is more common in severe HF and low Na has been repeatedly described as a predictor of adverse short-term outcomes in affected patients; indeed, important predictive models of mortality in patients with ADHF have included serum Na alongside other traditional variables predictive of adverse outcome. Notably, however, no data exist on the longer-term prognostic role of hyponatremia in the setting of ADHF, and the predictive power of hyponatremia in combination with other more novel biomarkers of risk, such as natriuretic peptides, remains undefined.

Clinical Perspective on p 361

B-type natriuretic peptide (BNP) and amino-terminal pro-B type natriuretic peptide (NT-proBNP) are cardiac peptides secreted by the myocardium in response to myocardial stretch such as that occurs in the setting of volume overload; results from natriuretic peptide testing are useful for the diagnostic evaluation of ADHF; Importantly, natriuretic peptide testing not only provides important diagnostic information but it is useful for prognosis in the setting of ADHF; although both BNP and NT-proBNP are only partially dependent on volume status for

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their synthesis and release in ADHF, the potential association between Na and natriuretic peptides is compelling and underexplored. Moreover, with the development of aquaretic agents that may resolve hyponatremia, a better understanding of the risks associated with low Na is relevant.

Accordingly, we used data from the International Collaborative of NT-proBNP (ICON) study to better understand the association among admission serum Na, NT-proBNP levels, and outcomes among patients with ADHF admitted to hospital.

Methods

Study Subjects
We used baseline and follow-up information from the ICON Study, a multicenter pooled analysis comprised of trial data assessing the role of NT-proBNP for the diagnosis and prognosis of ADHF. Patient cohorts from previously-published clinical studies of ADHF from Boston, Barcelona, and Christchurch New Zealand were included; these studies had comparable inclusion criteria, including dyspnea not known to be due to acute coronary syndrome or trauma, as well as the absence of severe renal failure (as evidenced by serum creatinine in excess of 2.5 mg/dL). In addition, patients from an ADHF registry from Maastricht, the Netherlands were included. All data sources obtained similar clinical information, including standard demographics, medical history and drug therapy, presenting symptoms and signs (including severity of breathlessness by the New York Heart Association [NYHA] classification), physical examination, and results of hematologic testing, serum chemistry tests, radiographic studies (typically plain chest radiographs), electrocardiography results, and the results of NT-proBNP testing. The assignment of diagnosis was based on current guidelines and made after review of the entire medical record and subsequent treatment course. Of the 1256 overall patients in ICON, 720 (57%) were judged to have ADHF. Of these, data on Na were lacking from the Barcelona site as well as for 12 more subjects evenly distributed between Christchurch and Maastricht. Thus, 628 (87.2%) had available admission serum Na data and were considered eligible for this analysis. The characteristics of the Barcelona site do not significantly differ from the rest of the cohort, as demonstrated in Table 1 of the initial report of these patients. Of the 628 subjects who were analyzed, 207 from the Boston cohort had follow-up Na results, taken closest to the time of death or discharge.

Baseline Data
Blood samples for the measurements of serum Na and NT-proBNP concentrations were obtained at the time of enrollment. Serum Na concentrations were measured in an unblinded fashion at each institution, using conventional laboratory methods. NT-proBNP was measured by using a validated, commercially available immunoassay (Elecsys ProBNP, Roche Diagnostics, Indianapolis, Ind), using established methodology. In the constituent studies in this report, this assay had inter-run coefficients of variation ranging from 0.9% to 5.5%. Historical information, physical findings, and the results of routine diagnostic testing obtained during the initial presentation were considered. Creatinine clearance values were calculated by using the simplified modified diet in renal disease equation.

End Points
The primary end point of this analysis was 1-year all-cause mortality, which was complete in 100% of subjects. Death was ascertained from hospital medical records, death certificates, and telephone follow-up with referring physicians. In addition, in an exploratory fashion, we examined the effect of hyponatremia at presentation on the phenomenon of worsened renal function (defined as a serum creatinine rise ≥0.3 mg/dL, any time during hospital admission).

Statistical Analysis
For statistical analyses, PASW Statistics 17.0 (SPSS Inc, Chicago, Ill) software was used. Patients were categorized into hyponatremia and non-hyponatremia based on serum Na level of ≤135 mmol/L and baseline characteristics compared with the Student t test or the χ² test as appropriate. For continuous variables, data are presented as medians with interquartile ranges for non-normally distributed variables (identified when skewness was more than double its standard error of the mean and compared by using the Wilcoxon rank sum test) and means±SD for all normally distributed continuous variables, which were compared using ANOVA. In addition, patients were subdivided into serum Na deciles for survival analysis, and a least-squares quadratic fit was generated based on mortality rates across Na categories.

Independent predictors of 1-year mortality were identified using Cox proportional hazards analysis with generation of a corresponding hazards ratio (HR) and 95% CI. Characteristics found to have association with mortality in univariable analyses were retained for possible inclusion to the final model and entered in a stepwise-forward manner; only those variables with significant association with mortality in multivariate models were retained for the final model. In addition to hyponatremia, NT-proBNP was considered as a function of the median for the group as a whole (4690 pg/mL); age and estimated glomerular filtration rate were entered dichotomously as a function of the means for the group as a whole (75 years and 60 mL/min per 1.73 m²); and troponin T was considered elevated when >0.01 ng/mL. All variables were tested for first-order interactions. To better understand the effect of NT-proBNP on the significance of Na as a predictor of outcome, Cox proportional hazards models examined the prognostic value of hyponatremia in those with submedian and supramedian NT-proBNP concentrations. Last, survival curves were calculated with the Kaplan–Meier method. All P values are 2-sided, with values <0.05 considered significant.

Results

Baseline Characteristics
Table 1 provides detailed information regarding study subjects with ADHF without hyponatremia (n=479, 76.2%) compared with those with hyponatremia (n=149, 23.8%). Compared with those without hyponatremia, those affected were less likely to be male, less likely to have hypertension or previous myocardial infarction, but were more likely to have more severe symptoms, to be anemic, and had higher NT-proBNP values (all P≤0.05).

Notably, although more likely to suffer NYHA class IV symptoms, patients with hyponatremia were not more likely to show signs of volume overload, such as elevated jugular venous pressure, gallop rhythms, peripheral edema or pulmonary rales and chest radiograph findings were similar between the 2 groups.

There was no association between serum Na and symptom severity as judged by the NYHA classification. A modest inverse relationship was noted between serum Na and NT-proBNP concentrations (r=−0.113; P=0.001) (Figure 1).

Considering patients as a function of serum Na and NT-proBNP, Table 2 demonstrates considerable differences between patients across groups; however, when examining patients with hyponatremia as a function of an NT-proBNP above the median value of 4690 pg/mL, few differences existed: patients with a high NT-proBNP were less likely to be wheezing on physical examination and were more likely to have more severe symptoms, lower left ventricular ejection fraction, worse renal function, and elevated troponin T values.

Notably, rates of worsened renal function (defined as a serum creatinine rise >0.3 mg/dL) after admission were noted to be higher among those patients with hyponatremia and elevated NT-proBNP (53.2%) compared with those with hyponatremia and an NT-proBNP below the median value of 4690 pg/mL (36.2%; P<0.001); this likely reflects differences in baseline renal function because those with low Na.
and elevated NT-proBNP had significantly worse estimated glomerular filtration rate compared with those with low Na but an NT-proBNP below the median (48.2 versus 65.1 mL/min per 1.73 m²; P<0.001).

**Table 1. Baseline Characteristics of Nonhyponatremic Patients vs Hyponatremic Patients**

<table>
<thead>
<tr>
<th></th>
<th>No Hyponatremia (Sodium &gt;135, N=479)</th>
<th>Hyponatremia (Sodium ≤135, N=149)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75±11</td>
<td>75±13</td>
<td>0.63</td>
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<tr>
<td>Male gender</td>
<td>251 (52)</td>
<td>65 (44)</td>
<td>0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±6</td>
<td>26±6</td>
<td>0.14</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>297 (62)</td>
<td>79 (53)</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>265 (55)</td>
<td>77 (52)</td>
<td>0.55</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>179 (37)</td>
<td>42 (29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>244 (51)</td>
<td>83 (56)</td>
<td>0.10</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>132 (28)</td>
<td>38 (26)</td>
<td>0.67</td>
</tr>
<tr>
<td>Tobacco use (present or past)</td>
<td>241 (50)</td>
<td>71 (48)</td>
<td>0.49</td>
</tr>
<tr>
<td>Loop diuretic use</td>
<td>292 (61%)</td>
<td>88 (60%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Symptoms/signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>133 (28%)</td>
<td>36 (24%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>224 (47%)</td>
<td>68 (46%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Chest pain</td>
<td>162 (34%)</td>
<td>51 (34)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cough</td>
<td>138 (29)</td>
<td>48 (32)</td>
<td>0.21</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>92±25</td>
<td>96±28</td>
<td>0.17</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>238 (50)</td>
<td>69 (46%)</td>
<td>0.23</td>
</tr>
<tr>
<td>S3 gallop</td>
<td>33 (7)</td>
<td>8 (5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>265 (55)</td>
<td>82 (55)</td>
<td>0.86</td>
</tr>
<tr>
<td>Rales</td>
<td>323 (67)</td>
<td>91 (62)</td>
<td>0.36</td>
</tr>
<tr>
<td>Wheezing</td>
<td>70 (15)</td>
<td>18 (12)</td>
<td>0.44</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>38 (8)</td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>254 (53)</td>
<td>55 (37)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>187 (39)</td>
<td>82 (55)</td>
<td></td>
</tr>
<tr>
<td>EKG findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>295 (62)</td>
<td>87 (58)</td>
<td>0.14</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>161 (34)</td>
<td>52 (35)</td>
<td>0.88</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>52 (11)</td>
<td>17 (11)</td>
<td>0.90</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>72 (15)</td>
<td>30 (20)</td>
<td>0.09</td>
</tr>
<tr>
<td>Chest radiography findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial edema</td>
<td>148 (31)</td>
<td>47 (31)</td>
<td>0.98</td>
</tr>
<tr>
<td>Infiltrate/pneumonia</td>
<td>54 (11)</td>
<td>20 (13)</td>
<td>0.83</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>125 (28)</td>
<td>41 (27)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cephalization of vessels</td>
<td>117 (24)</td>
<td>35 (23)</td>
<td>0.77</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>149 (31)</td>
<td>50 (34)</td>
<td>0.98</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>44±17</td>
<td>42±18</td>
<td>0.73</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13±2</td>
<td>12±3</td>
<td>0.01</td>
</tr>
<tr>
<td>GFR ml/min per 1.73 m²</td>
<td>58±25</td>
<td>58±28</td>
<td>0.67</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>3907 (1653 to 9565)</td>
<td>7214 (2847 to 15320)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin T, ng/mL</td>
<td>0.19±0.9</td>
<td>0.19±0.5</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Values are presented as absolute n (%), means (±SD) or medians (IQR). COPD indicates chronic obstructive pulmonary disease; EKG, Electrocardiogram; GFR, Glomerular Filtration Rate.

**Na Level and 1-Year Mortality**

When examined as a function of Na deciles (ranging from Na <132 mmol/L to Na ≥142 mmol/L), a “U”-shaped association was found between Na level and 1-year mortality (Figure 2), with the highest mortality rates at the extremes of Na concentrations as depicted by the least-squares quadratic fit line. Considering time-to-event as a function of normal versus abnormal Na (including both hypo- or hypernatremia), those subjects with an abnormal Na value at presentation had clearly higher event rates by 1 year, compared with those with normal Na (supplemental Figure I).
Predictors of 1-Year Mortality
In multivariate Cox proportional hazards analysis, hyponatremia was an independent predictor of 1-year mortality (HR = 1.72; 95% CI = 1.22 to 2.37; \( P = 0.001 \)) as was NT-proBNP above the median value of 4690 pg/mL (HR = 1.49; 95% CI = 1.10 to 2.00; \( P = 0.009 \)). Age at or above the mean of 75 years, measurable troponin T, and glomerular filtration rate below 60 mL/min per 1.73 m² were also found to be significant independent predictors of death within this period (Table 3). The relationship between low Na and risk for death was strongest early, and fell to the end of follow-up, but remained significant nonetheless (Table 4).

An interaction was detected between hyponatremia and NT-proBNP as a function of death at 1 year; this is reflected in time-to-event analyses. For those with low NT-proBNP values, the mean survival was 315 days and 294 days (\( P = 0.55 \)) for those without and with hyponatremia, whereas for those with high NT-proBNP values, the mean survival was 277 and 213 days (\( P = 0.001 \)) for those without and with hyponatremia. This is well demonstrated in Kaplan–Meier survival curves (Figure 3), which demonstrate that hyponatremia was clearly predictive of death only among those patients with an NT-proBNP above the median value of 4690 pg/mL. Patients with hyponatremia and a more elevated NT-proBNP had mortality rates of 51.7%, while patients with hyponatremia and lower NT-proBNP concentrations had 1-year rates of death that were considerably lower (25.0%; \( P = 0.001 \) for difference). In NT-proBNP adjusted Cox proportional hazards analyses, the HR for hyponatremia was 1.92 (95% CI = 1.44 to 2.97; \( P < 0.001 \)) for those with high NT-proBNP, whereas it was only 1.09 (95% CI = 0.55 to 1.93; \( P = 0.66 \)) for those with NT-proBNP concentrations below the median.

Of the 207 subjects with follow-up Na data, 58 had hyponatremia; resolution of hyponatremia by discharge was noted in 35 of these subjects. Kaplan–Meier analysis demonstrates that resolution of hyponatremia was associated with lower 1-year mortality rates (Supplemental Figure II).

Discussion
In this post hoc analysis from the ICON study,13 we confirmed that admission hyponatremia and NT-proBNP levels, previously individually recognized independent predictors of mortality in patients with HF, additively predict mortality out to 1 year in patients with ADHF. Serum Na was associated with mortality in a “U”-shaped fashion, and importantly, we found a significant interaction between serum Na and NT-proBNP levels, with hyponatremia being a predictor of 1-year mortality only in patients with an elevated NT-proBNP concentration.

Similar to the rates described in the literature,4,5 hyponatremia was present in 24% of our patients with ADHF. Patients with HF with hyponatremia are thought to have a pathophysiologic profile that is different from that of patients with HF with nonhyponatremic because it may reflect more severe activation of the renin–angiotensin–aldosterone axis, up-regulation of the sympathetic nervous system, and excessive vasopressin release.6–24,25 This was noted in our study, where lower serum Na was more common among patients with severe HF with higher NT-proBNP levels. The effect of medications such as diuretics in the genesis of hyponatremia has also been discussed, although our study patients with low Na were not more likely to be taking loop diuretics at presentation. Interestingly, although the patients with hyponatremia in our analysis had more class IV symptoms and higher NT-proBNP values, they were not more likely to show signs of volume overload in either their history and physical examination or radiographic imaging, compared with those with normal Na values, reminiscent of other analyses such as ours.5 One explanation for the lack of association between the elevated NT-proBNP values and evidence of volume overload on physical examination is the relatively low negative predictive value of the physical findings of congestion in HF patients.26–30
Irrespective of mechanism, the association between serum Na and outcomes in HF is well-established but complex. As shown by the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)\textsuperscript{5} and the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE)\textsuperscript{4} trials, baseline hyponatremia was an independent predictor of mortality in ADHF patients, but the follow-up was limited to 60 days and 180 days, respectively. We now show that admission hyponatremia does in fact show predictive value for mortality when the time horizon for outcomes is extended further to 1 year from presentation; the relationship between hyponatremia and

<table>
<thead>
<tr>
<th></th>
<th>No Hyponatremia (Sodium &gt;135, N=479)</th>
<th>Hyponatremia (Sodium ≤135, N=149)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low NT-proBNP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N=257</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High NT-proBNP</td>
<td>N=222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>74.1±11.5</td>
<td>76.8±10.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Male gender</td>
<td>52.5</td>
<td>52.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>28.0±6.3</td>
<td>25.3±4.8</td>
<td>0.23</td>
</tr>
</tbody>
</table>

**History**

- Hypertension: 63.4 vs. 60.4, \(P=0.12\)
- Coronary artery disease: 55.6 vs. 55.0, \(P=0.88\)
- Myocardial infarction: 35.8 vs. 39.5, \(P=0.42\)
- Previous heart failure: 47.9 vs. 54.5, \(P=0.56\)
- COPD/Asthma: 34.2 vs. 19.9, \(P=0.88\)
- Tobacco use (present or past): 59.2 vs. 41.3, \(P=0.13\)

**Symptoms/signs**

- Paroxysmal nocturnal dyspnea: 27.6 vs. 27.9, \(P=0.67\)
- Orthopnea: 45.1 vs. 48.6, \(P=0.54\)
- Chest pain: 35.0 vs. 32.4, \(P=0.55\)
- Cough: 29.6 vs. 27.9, \(P=0.52\)

**Physical examination**

- Pulse: 91.7±27.3 vs. 92.3±22.9, \(P=0.70\)
- Jugular venous distention: 41.2 vs. 59.5, \(P=0.02\)
- S3 gallop: 8.2 vs. 5.4, \(P=0.55\)
- Lower extremity edema: 52.1 vs. 50.0, \(P=0.32\)
- Rales: 69.0 vs. 66.2, \(P=0.79\)
- Wheezing: 17.9 vs. 10.9, \(P=0.02\)

**NYHA class**

- II: 8.9 vs. 6.8, \(P=0.41\)
- III: 49.8 vs. 56.8, \(P=0.01\)
- IV: 41.2 vs. 36.5, \(P=0.02\)

**EKG findings**

- Sinus rhythm: 60.7 vs. 62.6, \(P=0.32\)
- Atrial fibrillation/flutter: 35.4 vs. 31.5, \(P=0.19\)
- Left ventricular hypertrophy: 9.3 vs. 12.7, \(P=0.45\)
- Left bundle-branch block: 13.2 vs. 17.1, \(P=0.45\)

**Chest radiography findings**

- Interstitial edema: 30.4 vs. 31.5, \(P=0.85\)
- Alveolar consolidation: 9.3 vs. 13.5, \(P=0.18\)
- Pleural effusion: 23.3 vs. 29.3, \(P=0.12\)
- Cephalization of vessels: 24.1 vs. 24.8, \(P=0.78\)
- Cardiomegaly: 30.7 vs. 31.5, \(P=0.35\)

**Left ventricular ejection fraction, %**

- 48.5±15.8 vs. 39.7±17.3, \(P=0.01\)

**Hemoglobin (mg/dL)**

- 12.6±6.4 vs. 13.0±6.2, \(P=0.10\)

**Estimated GFR, mL/min per 1.73 m\(^2\)**

- 65.9±25.6 vs. 50.0±21.9, \(P=0.001\)

**NT-proBNP, pg/mL**

- 2171 [964 to 2900] vs. 10082 [7319 to 18629], \(P=0.001\)

**Troponin T, ng/mL**

- 0.14±1.0 vs. 0.25±0.81, \(P=0.001\)

Values are presented as absolute n (%), means (±SD) or medians (IQR). COPD indicates chronic obstructive pulmonary disease; EKG, electrocardiogram; GFR, glomerular filtration rate.

*Refers to comparison to hyponatremia/low NT-proBNP.
outcomes is attenuated with a longer time horizon, such that the HR associated with low Na was highest early after presentation, as would be expected. Nonetheless, hyponatremia appeared to predict death out to 1 year.

Interestingly, a “U”-shaped association was found between serum Na level and 1-year mortality, with increased risk for 1-year mortality in both the 116 patients with hyponatremia and 113 patients with hypernatremia in our analysis. A similar “U”-shaped association of serum Na levels and mortality was reported in a HF registry; although hyponatremia is a well-recognized risk factor for death in ADHF, in aggregate, these results strengthen the case for hypernatremia as a risk factor as well. In our analysis, a serum Na >142 mmol/L appeared to be associated with an increment in risk; this is of interest given that a Na of 142 mmol/L remains (by most estimates) in the normal range. A better understanding of the characteristics of patients with ADHF with hypernatremia as well as a mechanistic understanding of the reasons for hypernatremia and its association with adverse outcomes is now needed.

A novel finding of our study is the consideration of serum Na in the context of NT-proBNP concentrations. In our prospective study of 628 patients admitted to hospital with ADHF, we showed that hyponatremia—well known predictor of mortality in HF patients—predicted long-term mortality only in patients with markedly elevated NT-proBNP concentrations; this would suggest that low Na is of limited prognostic significance for patients who have less severe HF (determined by below the median NT-proBNP levels). Despite the expectation that Na and NT-proBNP would be useful to identify those patients with an exaggerated degree of volume overload compared with those without these abnormal values, we found that Na values did not correlate with the severity of ADHF symptoms. Furthermore, with the exception of an association with elevated jugular venous pressure (a highly specific finding for volume overload), elevated NT-proBNP values were not clearly associated with other findings to suggest volume overload. This may be due to the fact that volume overload is a nearly universal finding among those with ADHF and that factors other than fluid retention may contribute to elevation in NT-proBNP.

On the other hand, NT-proBNP stratification in hyponatremic patients identified a higher risk patient cohort, with lower ejection fraction and biochemical features predictive of adverse outcomes. Therefore, it is not surprising that patients with hyponatremia with elevated NT-proBNP had a mortality rate that was more than double the rate in those patients with hyponatremia with a low NT-proBNP. The rates of death in these patients rose quickly, relative to those with lower NT-proBNP values, and were sustained to a year from presentation.

Taken together, the knowledge that patients with hyponatremia and elevated NT-proBNP have highest risks for adverse outcome may have therapeutic implications. Hyponatremia resolves by discharge in most patients with ADHF (as in our subanalysis, where 63% of the patients with hyponatremia had normalized their Na by discharge), suggesting it is amenable to correction, and may be an appropriate specific, predischarge therapeutic aim in management of patients with low Na at admission. Vasopressin receptor antagonists have been shown to be well tolerated and improve serum Na levels in patients with ADHF with hyponatremia, but it remains yet unclear whether increasing serum Na concentration will result in an improvement in clinical outcomes in ADHF. Our data would suggest that inclusion of the highest risk patients with hyponatremia (such as those with marked elevation of NT-proBNP) would be most likely to show a favorable association between aquaretic therapy and outcomes. Ongoing studies such as the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) study may provide further insight in this area.

Worsened renal function, a recognized marker of high risk in ADHF, was more likely to develop in those with hyponatremia and elevated NT-proBNP. This is presumably on the basis of worse baseline renal function in such patients; however, the connection between low Na and worsened renal function in HF has been previously identified; thus, a mechanistic relationship between hyponatremia and renal dysfunction is quite possible. It is known that in patients who develop worsening renal function, hospital length of stay is longer, prognosis is

Table 4. Predictive Value of Hyponatremia for Death at Various Time Points

<table>
<thead>
<tr>
<th>Time point</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>3.30</td>
<td>1.98 to 5.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 mo</td>
<td>2.64</td>
<td>1.78 to 3.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>1.92</td>
<td>1.37 to 2.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>1.72</td>
<td>1.22 to 2.37</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Model adjusted for NT-proBNP, troponin T, age, and estimated glomerular filtration rate.

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GFR indicates glomerular filtration rate.

![Figure 2. Rates of 1-year mortality as a function of serum sodium concentrations at presentation in ADHF. Crude mortality rates are depicted, with a least-squares quadratic fit (dotted line) illustrating a “U”-shaped association between sodium concentrations and 1-year death.](image-url)
worse, and diuretic resistance is more frequent;34 thus, this finding may have significant implications.

Although our analysis was large and demonstrated interesting associations among serum Na, NT-proBNP, and outcomes, it has limitations. Among these is the fact that this was a post-hoc analysis of a trial previously conducted for reasons other than examining the prognostic meaning of hyponatremia. Furthermore, with the exception of a small cross section of the group as a whole, we do not have serial measures of Na to evaluate the true importance of resolution of hyponatremia. Moreover, we do not have information on the doses of diuretics used by our subjects, to get a better sense of associations between intensity of loop diuretic therapy and low Na. As in any incompletely understood syndrome, although we controlled for variables associated with Na and other potential HF prognostic measures including NYHA class, signs of volume overload, serum troponin, and renal function, the potential for omitted confounders exists. Lastly, the serum Na in this study was unblinded and available to managing clinicians, which might have affected associations between hyponatremia and mortality; nonetheless, such associations remained.

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Disclosures
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References


CLINICAL PERSPECTIVE

Hyponatremia is a well-known predictor of short-term mortality in patients with acutely decompensated heart failure, however, the longer term prognostic importance of hyponatremia (serum Na ≤135 mmol/L) in this setting is not well-described, and the prognostic importance of hyponatremia in the context of results for testing with natriuretic peptides remains unknown. Among 628 subjects with acutely decompensated heart failure presenting to the emergency department, hyponatremia was diagnosed in 24%. Compared to those without hyponatremia, those affected were not generally more likely to have signs or symptoms indicative of volume overload. When examined as a function of Na deciles (ranging from Na <132 mmol/L to Na >142 mmol/L), a U-shaped association was found between Na level and 1-year mortality. In multivariate Cox proportional hazards analysis, hyponatremia was an independent predictor of 1-year mortality (HR = 1.72; 95% CI = 1.22 to 2.37; P = 0.001) as was an amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration above the median value of 4690 pg/mL (HR = 1.49; 95% CI = 1.10 to 2.00; P = 0.009). Those with hyponatremia and more elevated NT-proBNP were more likely to develop worsening renal function during their hospitalization and had highest rates of 1-year death. Notably however, hyponatremia only predicted 1-year mortality in those with an elevated NT-proBNP. In summary, among patients with acutely decompensated heart failure, hyponatremia is common, and not generally associated with most signs or symptoms of volume overload. Hyponatremia is associated with worsening renal function during index hospitalization as well as 1-year mortality in patients with acutely decompensated heart failure, however the prognostic value of low Na is mainly evident in those with more pronounced elevation of NT-proBNP concentrations.
Hyponatremia, Natriuretic Peptides, and Outcomes in Acutely Decompensated Heart Failure: Results From the International Collaborative of NT-proBNP Study
Asim A. Mohammed, Roland R.J. van Kimmenade, Mark Richards, Antoni Bayes-Genis, Yigal Pinto, Stephanie A. Moore and James L. Januzzi, Jr

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Supplemental material

**Supplemental Figure 1:** Subjects with an abnormal Na value (high or low) at presentation had higher event rates by one year, compared to those with normal Na.

**Supplemental Figure 2:** Of those with available follow-up Na data, resolution of hyponatremia by discharge was associated with lower 1-year mortality rates.
Supplemental Figure 1:

![Survival Curve](image)

- **Normal Na (N=366)**
- **Abnormal Na (N=262)**

**P < .001**
Supplemental material

Supplemental Figure 1: Subjects with an abnormal Na value (high or low) at presentation had higher event rates by one year, compared to those with normal Na.

Supplemental Figure 2: Of those with available follow-up Na data, resolution of hyponatremia by discharge was associated with lower 1-year mortality rates.
Supplemental Figure 1:

![Survival analysis graph](image)

- Normal Na (N=366)
- Abnormal Na (N=262)

$P < .001$
Supplemental Figure 2:

- Never hyponatremic (N=146)
- Baseline hyponatremia, resolved (N=35)
- Baseline hyponatremia, not resolved (N=23)