Hyponatremia and Long-term Mortality in Survivors of Acute ST-Elevation Myocardial Infarction

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Background: Hyponatremia, a marker of neurohormonal activation, is a common electrolyte disorder among patients with acute ST-elevation myocardial infarction. The long-term prognostic value of hyponatremia during the acute phase of infarction is not known.

Methods: We studied 978 patients with acute ST-elevation myocardial infarction and without a history of heart failure who survived the index event. During the hospital stay, sodium levels were obtained on admission and at 24, 48, and 72 hours. The median duration of follow-up after hospital discharge was 31 months (range, 9-61 months).

Results: Hyponatremia, defined as a mean serum sodium level less than 136 mEq/L, was present during admission in 108 patients (11.0%). In a multivariable Cox proportional hazards model adjusting for other potential clinical predictors of mortality and for left ventricular ejection fraction, hyponatremia during admission remained an independent predictor of postdischarge death (hazard ratio [HR], 2.0; 95% confidence interval [CI], 1.3-3.2; \( P = .002 \)). Hyponatremia during admission was also independently associated with postdischarge readmission for heart failure (HR, 1.6; 95% CI, 1.1-2.6; \( P = .04 \)). When serum sodium level was used as a continuous variable, the adjusted HR for death or heart failure was 1.12 for every 1-mEq/L decrease (95% CI, 1.07-1.18; \( P < .001 \)).

Conclusion: Hyponatremia in the early phase of ST-elevation myocardial infarction is a predictor of long-term mortality and admission for heart failure after hospital discharge, independent of other clinical predictors of adverse outcome and left ventricular ejection fraction.

Arch Intern Med. 2006;166:781-786

Hyponatremia is the most common electrolyte disorder in hospitalized patients in diverse clinical settings. Severe hyponatremia is a potentially serious and life-threatening disorder, which can lead to grave neurological complications. Hyponatremia is frequently a marker of significant underlying disease and is therefore associated with poor short-term prognosis, even when the serum sodium level is only mildly reduced.

We have recently shown that hyponatremia commonly develops in the acute phase of ST-elevation myocardial infarction (MI) and is an independent predictor of 30-day mortality. In acute MI, the development of hyponatremia is a marker that probably incorporates different prognostic entities, including the severity of left ventricular dysfunction, hemodynamic alterations, and the extent of neurohormonal activation.

Neurohormonal activation in the acute phase of MI is similar to that occurring in heart failure (HF). We therefore hypothesized that the development of hyponatremia in the acute phase of MI reflects, at least in part, profound neurohormonal activation. Because neurohormonal activation in the acute phase of MI affects left ventricular remodeling, patients with lower sodium levels (even if transient) may be at higher long-term risk for HF and mortality. Therefore, the purpose of the present report was to test the hypothesis that early hyponatremia, a simple marker of neurohormonal activation during the acute phase of MI, may predict the long-term development of HF and death. To this end, we studied the prognostic value of hyponatremia together with left ventricular ejection fraction (LVEF) in a cohort of patients without a history of HF who survived their index MI.

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METHODS

PATIENTS

We used a prospective database consisting of all admissions of patients with acute ST-elevation MI to Rambam Medical Center, Haifa, Israel, during a 52-month period (January 1, 2000, to April 30, 2004). Myocardial infarction was diagnosed according to the criteria of the Joint European Society of Cardiology and American College of Cardiology.11 For this analysis, patients had to be without a history of HF, have an echocardiographic evaluation of LVEF, and be alive at the time of discharge. The study was approved by the investigational review committee on human research at our institution.

DEFINITION OF HYponATREMIA

Venous blood samples were obtained on admission and at 24, 48, and 72 hours thereafter.6 Based on these measurements, hyponatremia was defined as a mean serum sodium level less than 136 mEq/L during the first 72 hours of the hospital stay.

ASSESSMENT OF RENAL FUNCTION

Glomerular filtration rate (GFR) (measured as milliliters per minute per 1.73 m2) was calculated using the following abbreviated Modification of Diet in Renal Disease Study equation12,13:

\[
GFR = \frac{186 \times \text{Serum Creatinine Level}^{1.154}}{(\text{Age})^{0.203} \times 0.742 \times \text{If Female} \times 1.210 \times \text{If Black}).
\]

This equation accurately predicts GFR from the serum creatinine concentration, in contrast to the Cockcroft-Gault equation, which estimates creatinine clearance and systematically overestimates GFR.12,13

STUDY END POINTS

The primary end points of the study were (1) all-cause mortality and (2) readmission for HF, defined as readmission to the hospital for management of HF (defined by the presence of new symptoms of dyspnea or edema with ≥1 concurrent sign, including ventricular gallop rhythm, bilateral posttussive rales in at least the lower third of the lung fields, elevated venous pressure, or pulmonary venous congestion on radiograph with interstitial or alveolar edema). The diagnosis of HF was confirmed by reviewing hospital records and discharge summaries. The secondary end point was the combined end point of death and HF. After hospital discharge, clinical endpoint information was acquired by reviewing the national death registry, contacting each patient individually, and independently reviewing the hospital course for major clinical events if the patient had been rehospitalized.

STATISTICAL ANALYSIS

Continuous data are expressed as mean ± SD. The baseline characteristics of the groups were compared by use of the unpaired t test for continuous variables and the χ2 statistic for categorical variables.

Event-free survival was estimated by the Kaplan-Meier method, and curves were compared with the log-rank test. Multivariate Cox proportional hazards analyses were performed to determine the relation between hyponatremia and mortality. After forcing age, sex, and baseline GFR into each model, backward stepwise variable selection was used to generate the final model. The following baseline clinical characteristics were considered in the multivariate procedure: history of diabetes, history of hypertension, smoking status, Killip class greater than I on admission, hypotension (systolic blood pressure <90 mm Hg) and tachycardia (heart rate >100 beats/min) on admission, anterior location of infarction, reperfusion therapy with thrombolytics or primary angioplasty, and LVEF.

Cox proportional hazards modeling was also used to determine the relationship between hyponatremia and admission for the treatment of HF. Known predictors of HF development in survivors of MI14 were considered in the model (ie, age, baseline heart rate, Killip class at admission, history of hypertension and diabetes, and LVEF).

In supporting analyses, the multivariate models were repeated after correcting sodium levels for the presence of hyperglycemia, based on the assumption that plasma sodium concentration should fall by 1.6 mEq/L for every 100-mg/dL (5.6-mmol/L) rise in plasma concentration of glucose.6,15 We also performed supplementary analyses for the combined end point of death and HF after dividing the study participants into 6 groups on the basis of the presence or absence of hyponatremia and 3 categories incorporating clinical evidence of HF during admission or reduced left ventricular systolic function, including (1) Killip class I on admission and preserved (≥45%) predischarge LVEF; (2) Killip classes II to IV on admission or reduced (<45%) predischarge LVEF; and (3) Killip classes II to IV on admission and reduced predischarge LVEF.

Differences were considered statistically significant at the 2-sided P<.05 level. All statistical analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc, Chicago, Ill).

RESULTS

SUBJECTS

During the study period, 1109 patients without a history of HF were admitted with ST-elevation MI and survived the index event. Of those, LVEF was missing in 131 (11.8%). However, LVEF data were missing at random, because the survival of the 131 nonstudy patients with missing LVEF data was similar to that of the 978 study patients with complete data (log-rank P=.59). The incidence of hyponatremia was similar in patients with missing LVEF data and those with complete data (8.4% vs 11.0%; P=.36).

Hyponatremia during hospitalization (defined as a plasma mean sodium level <136 mEq/L) was present in 108 patients (11.0%). Demographic and clinical characteristics of the study patients according to the presence and severity of hyponatremia are shown in Table 1. Patients with hyponatremia were older, had higher creatinine levels, and were more likely to have diabetes and a history of smoking. They presented more often with an anterior infarction, a higher heart rate, and a higher Killip class. Use of diuretics was greater in patients with hyponatremia. However, most patients with hyponatremia (61%) were not treated with diuretics.

RELATION OF HYponATREMIA TO LONG-TERM MORTALITY AFTER HOSPITAL DISCHARGE

The median duration of follow-up after hospital discharge was 31 months (range, 9-61 months). During
independent predictor of postdischarge death. LVEF, hyponatremia during admission remained an other potential clinical predictors of mortality and for able Cox proportional hazards model adjusting for other clinical risk factors, the presence of hyponatremia during admission was associated with a higher risk of death, even among patients with no evidence of HF during admission and with preserved pre-discharge LVEF, as well as in patients with clinical evidence of HF during admission or with left ventricular dysfunction.

**POSTDISCHARGE HF**

During follow-up, 114 (11.7%) of 978 study patients with complete data were admitted for the treatment of HF. Median sodium levels were significantly lower among patients who developed HF during follow-up than among those patients who did not (137 mEq/L [interquartile range, 136-139 mEq/L] vs 139 mEq/L [interquartile range, 137-140 mEq/L]; Mann-Whitney P <.001). Recurrent MI before the episode of HF occurred equally among patients with and without hyponatremia (9.8% vs 13.0%; P = .95).

Kaplan-Meier analysis showed an increased probability of death during follow-up in patients with hyponatremia during admission (Figure 1). In a multivariable Cox proportional hazards model adjusting for other potential clinical predictors of mortality and for LVEF, hyponatremia during admission remained an independent predictor of postdischarge death (Table 2).

After correcting sodium levels for hyperglycemia, 28 patients with sodium levels initially classified as hyponatremic were reclassified as nonhyponatremic. The adjusted hazard ratio for long-term mortality in patients with hyponatremia after this correction was 2.3 (95% confidence interval, 1.4-3.8; P < .001). Additional adjustments for concomitant cardiovascular medications at discharge had no discernible effect on these estimates. We found no significant interaction between hyponatremia and LVEF (P = .18) or renal function (P = .95).

We further estimated the hazard ratios for long-term mortality after dividing the study participants into 6 groups on the basis of sodium levels and clinical evi-

### Table 1. Baseline Clinical Characteristics According to Sodium Levela

<table>
<thead>
<tr>
<th>Sodium Level, mEq/L</th>
<th>≥136 (n = 870)</th>
<th>&lt;136 (n = 108)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>59 ± 12</td>
<td>62 ± 12</td>
<td>.01</td>
</tr>
<tr>
<td>Men</td>
<td>705 (81)</td>
<td>85 (79)</td>
<td>.56</td>
</tr>
<tr>
<td>Serum creatinine level, mean ± SD, mg/dL</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.5</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>177 (20)</td>
<td>47 (44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>365 (42)</td>
<td>40 (37)</td>
<td>.33</td>
</tr>
<tr>
<td>Smoking</td>
<td>419 (48)</td>
<td>41 (36)</td>
<td>.045</td>
</tr>
<tr>
<td>Systolic BP at admission, mm Hg, mean ± SD</td>
<td>132 ± 25</td>
<td>128 ± 25</td>
<td>.15</td>
</tr>
<tr>
<td>Heart rate at admission, beats/min, mean ± SD</td>
<td>78 ± 35</td>
<td>85 ± 20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class at admission, mean ± SD</td>
<td>1.2 ± 0.6</td>
<td>1.5 ± 0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>336 (39)</td>
<td>59 (55)</td>
<td>.001</td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>842 (97)</td>
<td>101 (94)</td>
<td>.06</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>759 (87)</td>
<td>92 (85)</td>
<td>.51</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>717 (82)</td>
<td>86 (80)</td>
<td>.45</td>
</tr>
<tr>
<td>Diuretics</td>
<td>187 (21)</td>
<td>42 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>276 (32)</td>
<td>30 (28)</td>
<td>.40</td>
</tr>
<tr>
<td>Primary angioplasty</td>
<td>231 (27)</td>
<td>25 (23)</td>
<td>.45</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure. SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

aUnless otherwise indicated, data are expressed as number (percentage) of patients.

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Figure 1. Kaplan-Meier plot showing the crude cumulative incidence of death according to sodium level.

Mortality and HF increased linearly throughout the entire spectrum of serum sodium levels. Death or HF
occurred in 36.2% of patients in the lowest sodium decile (<135 mEq/L) and 9.7% of patients in the highest sodium decile (≥143 mEq/L) (Figure 4). When serum sodium level was used as a continuous variable in a Cox proportional hazards model, the adjusted hazards ratio for every 1-mEq/L decrease in sodium level was 1.12 (95% confidence interval, 1.07-1.18; \( P < .001 \)).

The present study demonstrates a strong association between hyponatremia in the early phase of MI and long-term mortality in survivors of acute MI. Hyponatremia remained a strong and independent predictor of mortality after adjustment for established clinical predictors of adverse outcome, including LVEF. Furthermore, the relationship between hyponatremia and adverse outcome remained robust when assessed in low-risk patients (preserved LVEF and Killip class I during admission), as well as in high-risk patients (reduced LVEF and Killip class II-IV admission). Our results also show that hyponatremia in the acute phase of MI predicts future admissions for the treatment of HF, supporting the underlying pathophysiological relationship between hyponatremia and neurohormonal activation. Readmission for late HF in patients after MI is particularly ominous because these patients have a severalfold increase in the risk of death when compared with other MI survivors. In a recent study, MI survivors who were readmitted for HF had a 10-fold risk of death compared with patients who did not develop HF. Several clinical predictors for the development of HF after MI have been identified, with advanced age, diabetes, and reduced LVEF being the most consistent. One of the most important mechanisms that leads to late development of HF in MI survivors is progressive remodeling, which is closely linked to the degree of neurohormonal activation. Our data indicate that hyponatremia in the early course of MI, a marker of excessive neurohormonal activation, may identify patients at high risk for HF even after hospital discharge.

In cardiovascular diseases, hyponatremia is frequently encountered in patients with advanced HF. In this setting, hyponatremia is an established indicator of HF progression and death. Hypotensive patients with HF have greater activation of the renin-angiotensin-aldosterone system, higher norepinephrine and epinephrine levels, and more severe impairment of renal and hepatic blood flow. The relationship between hyponatremia and poor outcome in HF is therefore explained, in part, by the marked neurohormonal activation that characterizes hyponatremia.

### Table 2. Unadjusted and Adjusted Cox Proportional Hazards Model for Postdischarge All-Cause Mortality*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted OR (95% CI)</th>
<th>( P ) Value</th>
<th>Adjusted OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>4.2 (2.8-6.4)</td>
<td>&lt;.001</td>
<td>2.6 (1.7-4.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.3 (1.5-3.4)</td>
<td>&lt;.001</td>
<td>1.6 (1.2-2.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Baseline GFR per 10-mL/min decrease</td>
<td>1.4 (1.3-1.5)</td>
<td>&lt;.001</td>
<td>1.2 (1.1-1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min at admission</td>
<td>3.5 (2.2-5.6)</td>
<td>&lt;.001</td>
<td>2.8 (1.8-4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class &gt;1 at admission</td>
<td>3.6 (2.4-5.3)</td>
<td>&lt;.001</td>
<td>1.6 (1.1-2.5)</td>
<td>.02</td>
</tr>
<tr>
<td>LVEF ≤45%</td>
<td>3.0 (2.0-4.4)</td>
<td>&lt;.001</td>
<td>2.0 (1.3-3.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Mean sodium level &lt;136 mEq/L</td>
<td>3.2 (2.1-4.9)</td>
<td>&lt;.001</td>
<td>2.0 (1.3-3.2)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio.

*Adjusted for age, sex, baseline GFR, history of hypertension and diabetes, smoking status, presence of anterior infarction, Killip class at admission, heart rate and blood pressure on admission, use of reperfusion therapy, and LVEF.

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Although hyponatremia has been traditionally investigated in the context of chronic HF, it may be as important during acute cardiac injury. In patients with acute MI, hyponatremia develops primarily owing to excessive or inappropriate vasopressin secretion that occurs in response to nonosmotic stimuli. These include the acute development of left ventricular dysfunction, pain, and nausea and administration of analgesics and diuretics. Elevated vasopressin concentrations lead to the insertion of aquaporin-2 water channels into cell membranes of the collecting duct of the kidney and result in increased free-water reabsorption.

Acute MI also results in marked activation of the renin-angiotensin system and increased catecholamine production. These factors promote renal vasoconstriction, leading to diminished GFR and subsequent delivery of tubular fluid to the diluting segment of the nephron, further contributing to the reduction of renal water excretion. Thus, neurohormonal activation in the acute phase of MI bears a striking resemblance to that seen in chronic HF. Consequently, patients with acute MI are predisposed to hyponatremia, especially if marked neurohormonal activation has occurred.

Despite the potential pathophysiological link between hyponatremia and neurohormonal activation, our previous study addressed the short-term prognostic implication of hyponatremia. Therefore, most of the prognostic information was contributed by early events occurring in the intensive care setting. Such events are often associated with prolonged hemodynamic deterioration and shock and with complications such as acute renal failure and infection, all potentially contributing to the development of hyponatremia.

The results of the present analysis demonstrate that the prognostic implications of hyponatremia extend beyond the early phase of MI and are not related to the associated in-hospital complications. Hyponatremia in the early phase of MI provided prognostic information with regard to long-term mortality and subsequent development of HF in patients who survived the acute event. The effect of hyponatremia was also independent of renal function and left ventricular systolic function.

Previous studies of patients with chronic HF have evaluated the relationship between sodium level and prognosis using dichotomous groupings (eg, those above and below an arbitrary cut point for hyponatremia). In those studies, cutoff values for the definition of hyponatremia varied greatly, from less than 125 to 140 mEq/L. In the present study we used a similar approach for our main analyses, with a recently recommended cutoff for hyponatremia. However, when sodium level was used as a continuous variable, we found no clear cutoff value for the association between sodium level and adverse outcome. Indeed, the inverse association between sodium level and mortality or admission for HF was present across the entire range of its values.

Our study has several important limitations. The study was prospective in patient enrollment but observational in nature. Information on neurohormonal activation was not available in the study patients. Thus, we have no supporting evidence that hyponatremia in the setting of acute MI reflects profound neurohormonal activation. In addition, we collected no information on sodium levels after hospital discharge. Thus, the prognostic implications of transient vs persistent hyponatremia could not be analyzed.

We conclude that hyponatremia in the early phase of ST-elevation MI is a predictor of long-term mortality and admission for HF after hospital discharge, independent of other clinical predictors of adverse outcome and LVEF. Serum sodium level appears to be a simple marker of excessive neurohormonal activation.

**Table 3. Unadjusted and Adjusted Cox Proportional Hazards Model for Postdischarge Admission for the Treatment of Heart Failure**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>3.0 (2.1-4.3)</td>
<td>&lt;.001</td>
<td>1.9 (1.3-2.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.1 (1.4-3.1)</td>
<td>&lt;.001</td>
<td>1.6 (1.1-2.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Killip class &gt;1 at admission</td>
<td>4.1 (2.8-5.9)</td>
<td>&lt;.001</td>
<td>2.4 (1.6-3.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVEF ≤45%</td>
<td>3.5 (2.8-5.9)</td>
<td>&lt;.001</td>
<td>2.5 (1.7-3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean sodium level &lt;136 mEq/L</td>
<td>2.2 (1.4-3.5)</td>
<td>.006</td>
<td>1.6 (1.1-2.6)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

*The final model adjusted for age, sex, baseline glomerular filtration rate, history of hypertension and diabetes, presence of anterior infarction, Killip class at admission, heart rate on admission, and LVEF.

**Figure 4. Long-term mortality or admission for the treatment of heart failure (HF) among strata of patients, according to deciles of sodium levels.**
the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None.

REFERENCES