CLINICAL RESEARCH STUDY

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Transient Hyponatremia During Hospitalization for Acute Heart Failure

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ABSTRACT

OBJECTIVE: The objective was to study whether the temporal pattern of transient hyponatremia development in acute heart failure might provide insight into its pathophysiology and prognostic relevance.

METHODS: A post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) and Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF) studies was performed (n = 716). Patients were stratified according to the temporal pattern of hyponatremia development: (1) no hyponatremia, (2) persistent hyponatremia, (3) decompensation hyponatremia disappearing with decongestive treatment, and (4) treatment-induced hyponatremia.

RESULTS: Transient decompensation versus no hyponatremia was associated with significantly elevated blood urea nitrogen/creatinine ratio ($P < .001$), plasma renin activity ($P < .001$), and plasma aldosterone levels ($P < .001$) at baseline. Disease severity characteristics of such patients were intermediate between no and persistent hyponatremia. In contrast, patients with treatment-induced versus no hyponatremia had similar baseline characteristics and comparable natriuretic peptide levels, and both groups had little neurohumoral activation at baseline. Diuretic efficacy, defined as net fluid balance (milliliters) per 40 mg furosemide-equivalent dose administered, was lower in patients with persistent or treatment-induced hyponatremia versus decompensation hyponatremia or no hyponatremia, respectively. The former versus latter groups also had more pronounced neurohumoral activation with decongestive treatment. The risk for all-cause mortality (hazard ratio, 2.50; 95% confidence interval, 1.50-4.19; $P < .001$) and death or heart failure readmission (hazard ratio, 2.18; 95% confidence interval, 1.60-2.97; $P < .001$) was significantly elevated in patients with persistent versus no hyponatremia, with the risk of decompensation and treatment hyponatremia situated in between.

CONCLUSIONS: Transient hyponatremia is prognostically relevant, but it has a heterogeneous cause according to its temporal pattern of development.

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Hyponatremia, defined as a serum sodium level <135 mmol/L, is common in heart failure. It is present in approximately 20% of patients admitted with acute heart failure and develops during decongestive treatment in an additional approximately 15% to 25%.[1-3] Hyponatremia in heart failure is associated with worse outcomes and increased mortality, especially when persistent.[4,5] However, it remains unclear whether this relationship is causal or hyponatremia just represents a marker of more advanced disease. Studies assessing the prognostic impact of correcting hyponatremia during decongestive treatment in acute

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heart failure have yielded conflicting results.[6,7] This should not be surprising because the underlying pathophysiologic mechanisms of hyponatremia in heart failure are complex and diverse, warranting an individualized approach.[8] The temporal pattern of hyponatremia development might help to assess its cause and could portend prognostic significance. The aim of the current analysis was to characterize 2 distinct patterns of transient hyponatremia development in patients with acute heart failure undergoing decongestive treatment: (1) *decompensation hyponatremia*, present on admission but disappearing with decongestive treatment, versus (2) *treatment-induced hyponatremia*, not present at admission but developed during decongestive treatment and present at discharge. Baseline and treatment characteristics, and prognostic significance of those patterns were compared with both persistent and no hyponatremia development in patient populations from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) and Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF) studies.

CLINICAL SIGNIFICANCE

- The temporal pattern of hyponatremia development in patients with acute heart failure provides differential prognostic information and characterizes different phenotypes of patients regarding efficacy of decongestion and associated neurohumoral activation.
- In transient decompensation hyponatremia, decongestion was inadequate despite good diuretic efficacy.
- In contrast, treatment-induced hyponatremia was associated with good decongestion, marked neurohumoral activation, and poor diuretic efficacy.
- Overdiuresis with marked neurohumoral activation and treatment-induced hyponatremia should be avoided because it is associated with worse outcomes.

MATERIAL AND METHODS

Study Design

This study is a post hoc analysis from the ESCAPE and DOSE AHF studies. Detailed methods of those studies have been reported.[9,10] For the purpose of the current analysis, patients were selected who had serum sodium levels available at baseline and at least at 1 other moment during their index hospitalization. Patients not discharged alive were excluded. All-cause mortality, orthotopic heart transplantation, left ventricular assist device implantation, and heart failure readmissions were adjudicated end points in both trials.

Hyponatremia Patterns

Persistent hyponatremia was defined as hyponatremia (ie, serum sodium levels <135 mmol/L) present on admission and persisting until discharge. *Decompensation hyponatremia* was specified as admission hyponatremia that disappeared with decongestive treatment at discharge. *Treatment-induced hyponatremia* was defined by normal admission serum sodium levels (ie, ≥ 135 mmol/L) with a subsequent decrease <135 mmol/L at discharge. Baseline and treatment characteristics were compared according to the pattern of hyponatremia development. Plasma N-terminal of the prohormone of B-type natriuretic peptide (NT-proBNP) levels, plasma renin activity, and plasma aldosterone levels were assessed only in DOSE AHF patients with a full set of biomarkers available at baseline and after 72 hours ($n = 308$). For the same group, diuretic efficacy was defined as net fluid balance after 72 hours per 40 mg of furosemide-equivalent dose administered. Net fluid balance was not consistently reported in ESCAPE.

Study End Points

The primary end point for this analysis was all-cause mortality. The secondary end point constituted the combination of all-cause mortality or unscheduled heart failure hospitalization. Data were censored in case of orthotopic heart transplantation or implantation of a left ventricular assist device or at the end of follow-up after 180 days in the ESCAPE study and 60 days in the DOSE AHF study.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation if normally distributed or otherwise as median (interquartile range) and compared using the independent-samples Student t test, 1-way analysis of variance, Mann-Whitney U test, or Kruskal-Wallis H test, as appropriate. Normality was assessed by the Shapiro-Wilk statistic. Categorical data are expressed as percentages and compared by Pearson's chi-square test. Cumulative, actuarial survival rates were calculated according to the Kaplan-Meier method with the log-rank test used for comparison among groups. Cox proportional hazards models were used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (CI) for occurrence of the primary and secondary study end points associated with each pattern of hyponatremia development. Statistical significance was always set at a 2-tailed probability level of <0.05. All statistics were performed using IBM SPSS (version 22.0 for Windows; IBM, New York, NY).

RESULTS

Study Population Characteristics

A study flowchart is presented in **Figure 1**. A total of 716 patients from the original ESCAPE and DOSE AHF