EDITORIAL

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# Hyponatremia in acute heart failure: a marker of poor condition or a mediator of poor outcome?

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See Article on Page 460-470

Heart failure is a growing issue around the world; there are currently more than 20 million affected patients. Hospitalization for acute heart failure (AHF) is associated with poor prognosis; the 1-year mortality rate for AHF patients is roughly 10 times that for healthy individuals [1].

Among various predictors known to correlate with clinical outcomes, hyponatremia is a common electrolyte disturbance that has been associated with high mortality and rehospitalization in Western AHF studies [2-4]. However, little is known about the prognostic value of hyponatremia in Asian AHF patients. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), low sodium levels were associated with high in-hospital mortality [3], and the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) showed that low serum sodium levels were an independent predictor of prolonged hospitalization and increased mortality 60 days after discharge [4]. In the Korean Heart Failure (KorHF) registry, hyponatremia was associated with a poor clinical outcome [5].

There are several explanations for the association between hyponatremia and prognosis in patients with AHF. However, whether hyponatremia is a "marker" of poor patient condition or a "mediator" of poor patient outcome has yet to be determined. Low cardiac output due to reduced left ventricular systolic function activates several neurohormonal systems to preserve blood volume and pressure. Activation of the renin-angiotensin-aldosterone pathway and the non-osmotic release of arginine vasopressin (AVP) result in decreased water and sodium delivery to the kidneys, decreased water excretion, water retention by the kidneys, and, ultimately, hyponatremia [6,7]. Due to these factors, hyponatremia may be a marker of neurohormonal activation.

A recent study reported that low serum sodium levels were associated with increased mortality in oligoanuric patients receiving maintenance hemodialysis [8]. Patients with end-stage renal disease do not have the ability to concentrate urine in response to circulating AVP, and the removal of water and sodium is determined by dialysis. This suggests that hyponatremia itself can be seen as directly toxic rather than as a result of neurohormonal activation caused by low cardiac output.

Few studies have examined the prognostic impact of hyponatremia correction during hospitalization, and the results are conflicting. In a single-center

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study by Madan et al. [9], serum sodium levels increased in 68.9% of patients during hospitalization, and patients with increased serum sodium concentrations had markedly improved long-term outcomes. This suggests that optimal treatment can be effective in increasing serum sodium levels, and that patients who respond to optimizing therapy have better outcomes than those who do not. However, in the KorHF registry [5], improved hyponatremia during hospitalization was not associated with better outcomes.

In a multinational, multicenter study published in the current issue of this journal, 1,470 patients hospitalized for AHF at eight centers in South Korea, Taiwan, and China were analyzed [10]. Hyponatremia at admission was defined as a serum sodium level < 135 mmol/L, and was present in 247 patients (16.8%). Patients with hyponatremia had poor baseline characteristics such as older age, higher frequency of chronic kidney disease, lower systolic blood pressure, and a lower prescription rate of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and/or spironolactone. Hyponatremia was an independent predictor of 12-month mortality after adjusting for these confounding variables by a multivariate analysis and propensity score matching. Moreover, the postdischarge clinical outcomes of the patients with hyponatremia at admission were not improved by hyponatremia correction.

This study shows that hyponatremia at hospital admission is common, and that it is an independent predictor of a worse clinical outcome in hospitalized Asian heart failure patients. However, there are several limitations to this study. First, this was not a prospective study. As discussed by the authors, unmeasured confounding variables could have affected the results even though propensity score matching for unbalanced variables was performed. Second, the distribution of the patients' serum sodium concentrations and the technical details of sodium measurement at each center or in each nation were not presented. This study included eight centers from three nations. Although the measurement of serum sodium is standardized, we do not know the systems, calibration data, and normal values used at each center. Third, although hyponatremia was defined as a serum sodium level < 135 mmol/L, the optimal cut-off level for predicting a poor clinical outcome in AHF patients may differ for each study population, center, or country. If 140 mmol/L, the level at which mortality was the lowest, was used as the cut-off level, the authors may have obtained different, and probably better, results. Finally, differences in socioeconomic status, medical resources, and treatment patterns at each center were not controlled in this study.

However, since this study demonstrates an association between hyponatremia and poor prognosis in Asian AHF patients, it is worth considering, despite the limitations.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

## REFERENCES


1. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. J Card Fail 2004;10:374-379.
2. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119(7 Suppl 1):S30-S35.
3. Abraham WT, Fonarow GC, Albert NM, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 2008;52:347-356.
4. Klein L, O'Connor CM, Leimberger JD, et al. 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. Circulation 2005;111:2454-2460.
5. Lee SE, Choi DJ, Yoon CH, et al. Improvement of hyponatraemia during hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry. Heart 2012;98:1798-1804.
6. Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med 1981;305:263-266.
7. Hoorn EJ, Zietse R. Hyponatremia and mortality: mov-

ing beyond associations. Am J Kidney Dis 2013;62:139-149.
8. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance hemodialysis. Am J Med 2011;124:77-84.
9. Madan VD, Novak E, Rich MW. Impact of change in serum sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia. Circ Heart Fail 2011;4:637-643.
10. Yoo BS, Park JJ, Choi DJ, et al. Prognostic value of hyponatremia in heart failure patients: an analysis of the Clinical Characteristics and Outcomes in the Relation with Serum Sodium Level in Asian Patients Hospitalized for Heart Failure (COAST) study. Korean J Intern Med 2015;30:460-470.


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