# Hyponatremia in Acute Heart Failure Syndromes: A Potential Therapeutic Target

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Mild hyponatremia is common in patients hospitalized for worsening heart failure, and it is a major predictor of post-discharge mortality and morbidity irrespective of left ventricular ejection fraction. Recent data also suggest that standard therapy for heart failure does not improve or normalize serum sodium concentration during hospitalization. There are conclusive data that vasopressin antagonists improve or normalize serum sodium in this patient population. However, it is not known if this improvement or normalization in serum sodium is associated with an improvement in post-discharge outcomes. Future trials with vasopressin antagonists in patients hospitalized with worsening heart failure and hyponatremia are in order.

## Introduction

Hyponatremia is frequently observed in patients hospitalized for heart failure (HF) and other medical conditions [1–4]. Although a serum sodium concentration of less than 135 mEq/L is frequently adopted as a cutoff value to define hyponatremia, a standard cutoff is not uniformly reported in the literature. Accordingly, the reported prevalence of this electrolyte disorder varies from 1% to 45% depending on the clinical setting, patient population, and serum value used [1].

Until relatively recently, HF patients with hyponatremia were poorly characterized and the prognostic value of this abnormality was not well appreciated. As a result, mild to moderate hyponatremia in HF has not been a clinical focus and is largely untreated.

This review discusses the advances in the understanding of the clinical importance of hyponatremia as an emerging predictor of outcomes in patients hospitalized with HF and describes the results of recent analyses of large-scale trials and registries in an effort to provide a rationale for its treatment.

## Epidemiology of Hyponatremia

A number of studies have shown that hyponatremia is common in patients hospitalized with HF, but these studies have frequently involved select patients enrolled in clinical trials or from a small number of centers. Recently, data from large representative populations of hospitalized HF patients have become available. The OPTIMIZE-HF registry has been developed to improve the quality of care of patients hospitalized for worsening or new-onset HF regardless of their left ventricular ejection fraction (LVEF). It represents an important source of detailed clinical information on a large number of typical HF patients ($n$ = 48,612) from 259 US hospitals with a subgroup (10% of the entire population) followed for 60 to 90 days after discharge [5].

A recent analysis of this registry showed that among 47,647 patients who had serum sodium collected at admission to the hospital, approximately 20% had hyponatremia (< 135 mEq/L serum sodium concentration) [6•]. Despite being clinically similar to the normonatremic group at admission in terms of age, sex, HF etiology, diabetes, heart rate, LVEF, symptoms of congestion, use of angiotensin-converting enzyme (ACE) inhibitors or β-blockers, and body weight loss, this patient population was more likely to be Caucasian and to have lower systolic blood pressure values and atrial arrhythmias. Intravenous inotropes, dialysis, mechanical ventilatory support, and left ventricular (LV) assist devices also were used more often in patients with low serum sodium at admission. At discharge, patients with hyponatremia were more frequently given aldosterone-blocking agents and thiazide diuretics, but they were less likely to receive ACE inhibitors, angiotensin receptor blockers (ARBs), and statins (Table 1).

**Table 1. Patient clinical characteristics by admission serum sodium groups in the OPTIMIZE-HF registry**

| Variable | Sodium < 135 mEq/L (*n* = 9368) | Sodium ≥ 135 mEq/L (*n* = 38,279) |
|---|---|---|
| Mean age ± SD, *y* | 74.1 ± 14.0 | 73.0 ± 14.0 |
| Female, *n (%)* | 5025 (53.6) | 19,585 (51.2) |
| Caucasian, *n (%)* | 7547 (80.6) | 27,765 (72.5) |
| African American, *n (%)* | 1012 (10.8) | 7435 (19.4) |
| LVSD (LVEF, < 40% or moderate/severe LVD), *n (%)* | 4954 (52.9) | 19,854 (51.9) |
| Mean LVEF, *% (SD)* | 38.5 (18.3) | 39.1 (17.5) |
| Ischemic etiology, *n (%)* | 4310 (46.0) | 17,455 (45.6) |
| Hypertensive etiology, *n (%)* | 1924 (20.5) | 9019 (23.6) |
| No known prior HF, *n (%)* | 939 (10.0) | 4600 (12.0) |
| HF hospitalizations within 6 mo, *n (%)* | | |
| 0 | 4258 (45.5) | 1900 (49.7) |
| 1 | 1775 (18.9) | 6085 (15.9) |
| 2 | 484 (5.2) | 1519 (4.0) |
| ≥ 3 | 358 (3.8) | 1183 (3.1) |
| Unknown | 2493 (26.6) | 10,485 (27.4) |
| Atrial arrhythmias, *n (%)* | 3190 (34.1) | 11,469 (30.0) |
| ICD, *n (%)* | 552 (5.9) | 1887 (4.9) |
| Insulin-treated diabetes, *n (%)* | 1618 (17.3) | 6302 (16.5) |
| Non–insulin-treated diabetes, *n (%)* | 2363 (25.2) | 9533 (24.9) |
| Mean serum sodium, *mEq/L (SD)* | 130.6 (3.9) | 139.5 (2.9) |
| Mean BNP, *pg/mL (SD)* | 1386.7 (1385.2) | 1250.0 (1307.1) |
| Mean serum creatinine at admission, *mg/dL (SD)* | 1.86 (1.6) | 1.74 (1.5) |
| Mean serum creatinine at discharge, *mg/dL (SD)* | 1.74 (1.43) | 1.75 (1.39) |
| Mean weight change from admission to discharge, *kg (SD)* | -2.5 (4.9) | -2.6 (4.8) |
| Mean SPB at admission, *mm Hg (SD)* | 135.7 (32.6) | 144.4 (32.7) |
| Mean SPB at discharge, *mm Hg (SD)* | 122.1 (22.9) | 125.4 (22.3) |
| Mean heart rate at admission, *bpm (SD)* | 86.7 (21.6) | 86.6 (21.4) |
| Mean heart rate at discharge, *bpm (SD)* | 77.5 (14.4) | 75.6 (14.0) |
| Jugular venous distention at admission, *n (%)* | 2706 (33.1) | 10,792 (32.7) |
| Jugular venous distention at discharge, *n (%)* | 260 (5.0) | 943 (4.4) |
| Edema at admission, *n (%)* | 5937 (64.6) | 24,209 (64.7) |
| Edema at discharge, *n (%)* | 2025 (27.6) | 8145 (26.7) |
| Rales at admission, *n (%)* | 5822 (63.2) | 24,235 (64.5) |
| Rales at discharge, *n (%)* | 1276 (16.6) | 4898 (15.1) |
| Dyspnea at rest at admission, *n (%)* | 4103 (43.8) | 16,727 (43.7) |
| Dyspnea at rest at discharge, *n (%)* | 5584 (59.6) | 23,710 (61.9) |
| Orthopnea at admission, *n (%)* | 2331 (24.9) | 10,730 (28.0) |
| Paroxysmal nocturnal dyspea at admission, *n (%)* | 1235 (13.2) | 5995 (15.7) |

BNP—B-type natriuretic peptide; bpm—beats per minute; HF—heart failure; ICD—implantable cardioverter-defibrillator; LVD—left ventricular dysfunction; LVEF—LV ejection fraction; LVSD—LV systolic dysfunction; OPTIMIZE-HF–Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; SBP—systolic blood pressure.
(*Adapted from* Gheorghiade et al. [6•].)

These findings support the hypothesis that even mild hyponatremia may identify a particularly high-risk group of HF patients that has previously been largely ignored.

## An Important Predictor of Prognosis in Acute Heart Failure Syndromes

Several studies conducted in the past 15 years showed a correlation between plasma sodium concentrations at admission and increased rates of rehospitalization and mortality.

Rich et al. [7] conducted a prospective randomized trial that assessed the effects of a nurse-directed multidisciplinary intervention on readmissions at 90 days after discharge in 282 elderly patients hospitalized for worsening HF. A 3 mEq/L decrease in the concentration of plasma sodium at admission was associated with a 20% relative increase in rehospitalizations.

Similarly, hyponatremia was associated with a 50% increase in all-cause mortality at 30 days and 1 year in a retrospective analysis of 4031 patients hospitalized for HF [8].

Recent large-scale randomized trials provided similar results. OPTIME-CHF randomized 949 patients with worsening HF and systolic dysfunction to a 48- to 74-hour infusion of milrinone or placebo in addition to standard therapy [9]. A retrospective analysis of this trial revealed that patients with a serum sodium concentration below 135 mEq/L—representing 25% of the study population—had a significantly longer mean hospital stay (8 vs 6 days) and higher in-hospital (6% vs 2%) and 60-day mortality (16% vs 7%) than normonatremic patients. In addition, among the group with the lowest serum sodium concentration at baseline ($n$ = 256), patients who experienced persistent hyponatremia at discharge had a higher 60-day mortality rate (17%) than patients who had normalized serum sodium (11%) (Table 2). After adjusting for baseline variables, serum sodium on admission remained a significant predictor of the number of days hospitalized for cardiovascular causes within 60 days of randomization and a predictor of 60-day mortality: every 3 mEq/L decrease in serum sodium was associated with an 18% relative increase in the probability of death [10••].

The ESCAPE trial was a randomized, controlled, 180-day follow-up study designed to evaluate the role of the pulmonary artery catheter in addition to clinical assessment ($n$ = 215) versus clinical assessment alone ($n$ = 218) in the management of 433 patients hospitalized with severe HF due to systolic dysfunction (LVEF, < 30%) [11]. A retrospective analysis of this trial demonstrated that hyponatremia (serum sodium, < 134 mEq/L) was identified in 24% of 433 patients. Despite an "aggressive" management of HF, hyponatremia persisted in most patients during hospitalization. Patients with persistent hyponatremia were more likely than normonatremic patients to have lower baseline systolic blood pressure, to have higher baseline and last-measured serum urea nitrogen, and to have received more aldosterone-blocking agents and larger doses of diuretics. No differences were observed between the groups in terms of improvement in hemodynamics, weight loss, and signs and symptoms of HF. After covariate adjustment, serum sodium concentration was an independent predictor of 6-month mortality. No additional associations were registered between serum sodium concentration at baseline and 6-month mortality or rehospitalization. Importantly, persistent hyponatremia was associated with significantly higher risks of 6-month mortality and rehospitalization for HF [12••].

The ACTIV in CHF trial randomized 319 patients hospitalized with worsening HF and reduced systolic function to receive three different doses of tolvaptan, a selective $V_2$ vasopressin receptor antagonist, or placebo. In this study, hyponatremia was diagnosed in 22% of patients [13]. Consistent with the data previously presented, a recent retrospective analysis of this study revealed that, after covariate adjustment, baseline hyponatremia and change in serum sodium at hospital discharge were statistically significant predictors of 60-day mortality [14].

Similar findings were observed in the large group of unselected patients in the OPTIMIZE-HF registry, which also included patients with HF and preserved systolic function. A multivariate analysis showed that the risk of in-hospital death increased by 20%, the risk of follow-up mortality by 10%, and the risk of death or rehospitalization by 8% for each 3 mEq/L decrease in admission serum sodium below 140 mEq/L in patients with hyponatremia, irrespective of the systolic function [5].

These results suggest that hyponatremia in patients hospitalized with worsening HF 1) is relatively common in patients with reduced or preserved systolic function, 2) does not improve during hospitalization despite standard therapy, 3) persists despite significant clinical and hemodynamic improvement that is similar in normonatremic patients, and 4) is an independent predictor of increased mortality and morbidity after discharge.

## A Potential Target for Therapy

Patients with HF often develop hypervolemic hyponatremia, possibly as a result of further increased neurohormonal activity (increased sympathetic tone, activation of the renin-angiotensin-aldosterone system and other substances such as vasopressin secreted from the pituitary gland) that leads to fluid overload and consequently dilutional hyponatremia. It is also possible that hyponatremia per se may play a pathogenic role in HF. Whether this electrolyte disorder is a pathogenic factor or only a marker of disease severity remains unclear and requires further investigation. Hyponatremia may also occur as a consequence of the administration of therapies such as loop diuretics and spironolactone [15].

Vasopressin attracted the attention of the scientific community because it appears to play an important role in the regulation of water and electrolyte balance and is

**Table 2. Outcomes by serum sodium quartiles (unadjusted analysis) in the OPTIME-CHF trial**

| | 1st quartile (*n* = 256) | 2nd quartile (*n* = 207) | 3rd quartile (*n* = 220) | 4th quartile (*n* = 260) |
|---|---|---|---|---|
| Primary end point, *d (IQR)** | 8 (4.5–18.5) | 6 (4–13) | 6 (4–11.5) | 6 (4–12) |
| In-hospital mortality, *n (%)* | 15 (5.9) | 2 (1) | 5 (2.3) | 6 (2.3) |
| OR (95% CI) | Referent | 0.16 (0.035–0.69) | 0.37 (0.13–1.05) | 0.38 (0.15–0.99) |
| 60-d mortality, *n (%)*† | 40 (15.9) | 13 (6.4) | 17 (7.8) | 18 (7) |
| OR (95% CI) | Referent | 0.38 (0.2–0.72) | 0.47 (0.27–0.82) | 0.42 (0.24–0.74) |
| Rehospitalization/death within 60 d, *n (%)*† | 103 (41) | 62 (30.4) | 73 (33.5) | 87 (33.6) |
| OR (95% CI) | Referent | 0.63 (0.43–0.9) | 0.72 (0.5–1.06) | 0.73 (0.51–1.04) |
| Treatment failures (during infusion), % | 17.9 | 13.2 | 13.8 | 13.1 |
| In-hospital complications (any), % | 14.8 | 9.2 | 9.1 | 16.9 |
| Sustained hypotension, % | 10.5 | 3.9 | 5 | 6.9 |
| New atrial arrhythmias, % | 4.3 | 3.4 | 0.9 | 3.5 |
| Sustained ventricular tachycardia, % | 0.8 | 1.5 | 1.8 | 3.8 |
| Ventricular fibrillation, % | 1.2 | 1.9 | 0.9 | 0.8 |
| Reached target ACE dosing by discharge, % | 39.1 | 41.1 | 42.3 | 46.9 |
| Visual analogue QOL score (100-point scale) | | | | |
| Baseline score (IQR) | 40 (25–50) | 40 (25–55) | 40 (25–50) | 50 (30–60) |
| Change in score at discharge (IQR) | 25 (10–40) | 26.5 (10–50) | 30 (15–45) | 25 (10–40) |
| Change at 30 d (IQR) | 20 (2.5–40) | 25 (5–40) | 23.5 (5–40) | 20 (0–38) |
| Change at 60 d (IQR) | 21 (5–45) | 30 (7–45) | 25 (5–40) | 25 (5–40) |
| Subjective health questionnaire (better/same) | | | | |
| Change at discharge, % | 99 | 99 | 100 | 99 |
| Change at 30 d, % | 85 | 88 | 90 | 88 |
| Change at 60 d, % | 87 | 84 | 88 | 88 |

*Continuous variables are presented as median (interquartile range [IQR]). Analysis of variance (ANOVA) or the Kruskal-Wallis test was used to test for overall differences between continuous variables. Cox proportional hazards regression with indicator variables was used to analyze 60-day mortality. Categorical variables were analyzed with logistic regression.
†Raw percentages of patients followed to 60-day visit.
ACE—angiotensin-converting enzyme; OPTIME-CHF—Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; QOL—quality of life.
(*Adapted from* Klein et al. [10••].)

inappropriately elevated in patients with HF and hyponatremia [16]. This nonapeptide hormone regulates vascular tone through $V_{1a}$ receptors in the peripheral vasculature and plasma osmolality via $V_2$ receptors in the kidney that promote water retention [17].

Thus, reducing the effects of vasopressin appears to be an attractive therapeutic strategy to promote diuresis (which is indeed "aquaresis" given that electrolytes such as potassium do not follow this free water clearance) and correct hyponatremia; other options, such as strict fluid restriction or combinations of hypertonic saline and loop diuretics, are usually poor tolerated and/or potentially harmful [18].

The SALT-1 and SALT-2 trials, which had identical protocols, enrolled 448 patients with euvolemia or hypervolemia attributable to HF, liver disease, or syndrome of inappropriate secretion of antidiuretic hormone. The patients were randomized to receive 15 mg of tolvaptan (up-titrated to 60 mg according to serum sodium levels) or placebo in addition to standard therapy. Serum sodium concentrations increased more in the tolvaptan group than the placebo group during the first 4 days and after the full 30 days of therapy. Importantly, when tolvaptan was discontinued there was a significant decrease in serum sodium in both trials to a level similar to the serum sodium concentration noted in the placebo group. Furthermore, a prespecified analysis combining the two trials showed significant improvement from baseline to day 30 in the tolvaptan group according to scores on the Mental Component of the Medical Outcomes Study 12-item Short-Form General Health Survey [19].

A small, prospective, multicenter, randomized, active-controlled, open-label trial designed to determine the effect of tolvaptan (10 mg/d up-titrated to 60 mg if needed) versus

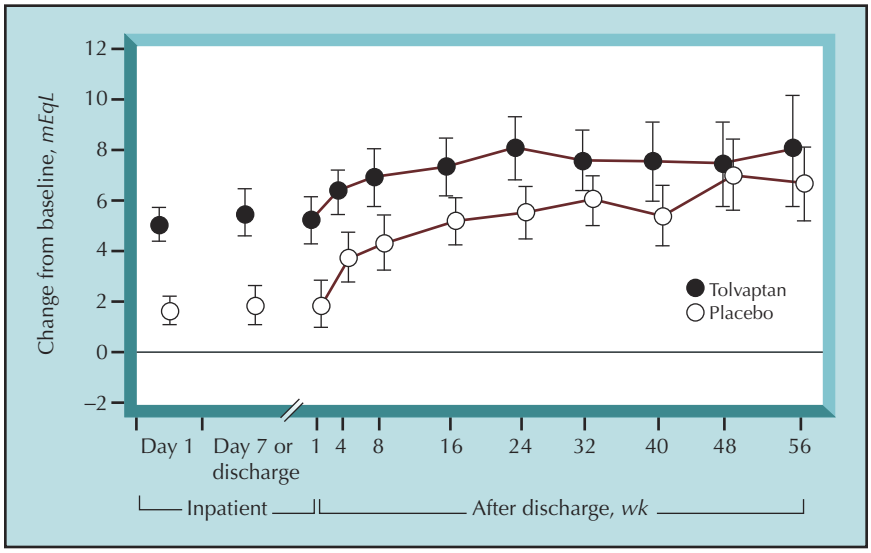


**Figure 1.** Changes from baseline in serum sodium concentrations in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trials. (*Adapted from* Konstam et al. [22••].)

fluid restriction (1200 mL/d) and placebo on serum sodium concentration of 28 hospitalized subjects with hyponatremia (serum sodium, < 135 mEq/L) showed that at the last inpatient visit the tolvaptan group experienced a higher increase in serum sodium concentration than the fluid restriction group (5.7 ± 3.2 vs 1.0 ± 4.7 mEq/L, respectively). However, no differences in adverse events were observed between the groups at the end of the 65-day follow-up period [20].

A randomized placebo-controlled study investigated the effects of three different doses of tolvaptan in 254 patients with chronic HF. Patients in the tolvaptan arm experienced a significant decrease in body weight and an increase in urine volume at day 1 compared with a slight increase in body weight and lower urine output in the placebo arm. Patients in the tolvaptan group with hyponatremia also normalized their serum sodium and had a decrease in signs of congestion without significant changes in heart rate, blood pressure, serum potassium, or renal function. However, no further effects were recorded beyond day 1 of administration, and no changes in the assessment of quality of life were observed between the tolvaptan and placebo group [21].

ACTIV in CHF was a double-blind, parallel-group, dose-ranging, multicenter, phase 2 trial that randomized 319 patients with LVEFs below 40% who were hospitalized for worsening HF to 30, 60, and 90 mg of oral tolvaptan in addition to standard therapy or placebo. At 24 hours the tolvaptan groups experienced a significant decrease in body weight (mean, -1.80, -2.10, and -2.05 kg in the 30, 60, and 90 mg tolvaptan groups, respectively, vs -0.60 kg in the placebo group) without significant changes in heart rate, blood pressure, serum potassium, or renal function. Patients who were hyponatremic in the tolvaptan group also experienced a rapid increase and often normalization in plasma serum sodium concentration that was sustained throughout the study. Although there were no differences in worsening HF at 60 days between the tolvaptan and placebo group, a post hoc analysis revealed a reduction in 60-day mortality in patients receiving tolvaptan who had renal dysfunction or severe systemic congestion. However, this study was underpowered and not designed to evaluate mortality as an end point [13]. A further ACTIV in CHF trial analysis conducted by Rossi et al. [14] suggested that improved serum sodium during hospitalization for worsening HF was associated with an improved postdischarge survival. In this analysis, of the 22% of patients presenting with hyponatremia, 66% improved (≥ 2 mEq/L). Sixty days after discharge, mortality was 11% in patients who improved and 22% in those showing no improvement [14].

The EVEREST trials were randomized, double-blind, placebo-controlled programs that evaluated the short-term effects of tolvaptan when added to standard therapy in patients hospitalized with worsening HF. The EVEREST trials included two identical short-term trials that took place during the inpatient period and a long-term outcome study examining the postdischarge mortality and hospitalizations of the patients from the short-term trials. A total of 4133 patients with reduced systolic function were randomized within an average of 24 hours after admission to receive 30 mg of tolvaptan or placebo; the dosing was continued after discharge for approximately 10 months. All patients were well treated with diuretics (97%), ACE inhibitors or ARBs (84%), and β-blockers (70%). During the hospital phase of the trials, the addition of tolvaptan to standard therapy resulted in a significant decrease in body weight that was associated with improvement in signs and symptoms of HF throughout hospitalization without adversely affecting heart rate, blood pressure, or renal function. However, despite a sustained reduction in body weight in response to tolvaptan after discharge, no differences were noted in outcomes (mortality and hospitalizations) between the tolvaptan and the placebo groups. As expected, hyponatremic patients improved or normalized their serum sodium in response to tolvaptan throughout the study (Fig. 1). However, this improvement did not translate into improved clinical outcomes. Nota-

bly, only 8% of EVEREST patients had hyponatremia (in this study defined as serum sodium < 134 mEq/L), versus about 25% of patients that had hyponatremia at the time of admission in prior registries and studies. Accordingly, the hypothesis that improvement in hyponatremia with tolvaptan results in an outcome benefit remains to be tested. However, EVEREST confirmed that even mild hyponatremia was an important predictor of postdischarge outcomes. Ten-month postdischarge mortality was 38% in patients with serum sodium below 137 mEq/L and 22% in normonatremic patients [22••,23••].

Other vasopressin-blocking agents have been developed, including conivaptan, a nonselective $V_{1a}$-$V_2$ vasopressin antagonist that has been recently tested in a randomized trial enrolling 84 patients hospitalized with euvolemic or hypervolemic hyponatremia. HF was diagnosed in only 25 patients (22%). After 4 days of intravenous infusion of 40 mg/d, the drug significantly increased serum sodium concentrations and was well tolerated overall. However, given the relatively small number of patients, no mortality data could be retrieved from this experience [24]. Similar results with conivaptan were reported by Ghali et al. [25]. Short-term intravenous conivaptan has been approved by the US Food and Drug Administration for the short-term treatment of hypervolemic and normovolemic hyponatremia.

## Conclusions

Hyponatremic HF patients are a high-risk population with longer hospital stay, lower systolic blood pressure, and a higher incidence of atrial arrhythmias and renal abnormalities, resulting in a more frequent use of intravenous inotropes, dialysis, mechanical ventilatory support, and LV assist devices.

Importantly, several recent retrospective analyses of trials and registries have demonstrated that about 25% of patients admitted with HF irrespective of their systolic function have hyponatremia. Standard therapy, including fluid restriction, does not appear to correct this abnormality during hospitalization. Even though patients with hyponatremia have a substantial clinical and hemodynamic improvement during hospitalization that is similar to that observed in normonatremic patients, persistent hyponatremia during hospitalization is an independent predictor of rehospitalization and postdischarge mortality. Although vasopressin antagonists are extremely effective in normalizing serum sodium without significant side effects, their impact on clinical outcomes in patients with hyponatremia remains to be determined.

## Clinical Trial Acronyms

ACTIV in CHF—Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure; ESCAPE—Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EVEREST—Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan; OPTIME-CHF—Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; OPTIMIZE-HF–Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; SALT—Study of Ascending Levels of Tolvaptan in Hyponatremia.

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