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ORIGINAL ARTICLE

Early diuretic response and outcome prediction in ambulatory worsening heart failure: Natriuresis versus diuresis

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Abstract

Aims Early diuresis and natriuresis are commonly used to assess the efficacy of decongestive therapy following an acute heart failure episode. There is limited knowledge regarding which parameter better predicts adverse clinical outcomes, especially in the outpatient setting. This study investigated the prognostic value of both metrics in predicting 30-day adverse clinical events in an ambulatory worsening heart failure (WHF) scenario.

Methods and results This is a post-hoc analysis of the SALT-HF trial involving 167 patients with ambulatory WHF randomized to receive intravenous furosemide with or without hypertonic saline solution. Early diuretic response was assessed through 3-h urine output and 3-h urinary sodium (uNa^+) levels following intravenous (IV) diuretic infusion. We analysed their association with 30-day adverse events (defined as death, heart failure hospitalization, or the need for outpatient IV diuretics) using logistic regression analysis. Both exposures were examined along the continuum and dichotomized in their median. The discriminative ability between the exposures and endpoints was assessed by receiver operating characteristic curves (AUC-ROC).

Results The median age of participants was 81 years, predominantly male (69.5%). Patients with lower 3-h urinary sodium and diuresis were older and exhibited reduced kidney function and haemoglobin levels. At 30 days, 50 (29.9%) of the sample experienced the composite endpoint. Multivariate analyses revealed that lower 3-h uNa^+ was associated with a higher risk of 30-day adverse events ($P = 0.008$). Conversely, 3-h diuresis did not significantly predict 30-day adverse outcomes ($P = 0.424$). There was a trend towards a higher AUC-ROC for the inverse of 3-h natriuresis compared with 3-h diuresis: 0.680 versus 0.601, $P = 0.092$.

Conclusions In patients with ambulatory WHF treated with IV furosemide, 3-h urinary sodium predicted 30-day outcomes whereas 3-h diuresis did not.

Keywords Ambulatory worsening heart failure; Diuresis; Natriuresis; Urinary sodium

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Introduction

Early urine output and natriuresis are common proxies to assess the efficacy of decongestive therapy in worsening heart failure (WHF). The ESC guidelines advocate using both parameters to tailor diuretic therapy in the first hours following an acute heart failure (AHF) episode.[1] However, the evidence endorsing their value for predicting adverse clinical events, particularly for diuresis, remains limited.[2, 3] Moreover, few studies have concurrently assessed diuresis and natriuresis as predictors of clinical outcomes.[2, 3] This gap in research is particularly notable in outpatient settings. To our knowledge, no prior studies have explored the clinical relevance of both parameters for evaluating diuretic response and risk stratification in ambulatory WHF.

The current study addressed this gap by assessing early diuresis and natriuresis in outpatient WHF. Specifically, we examined whether 3-h post intravenous (IV) furosemide urine output (3-h diuresis) or spot urinary sodium (3-h uNa^+) is related to 30-day adverse clinical events. By analysing these parameters together, we seek to provide a more comprehensive understanding of their predictive value for adverse outcomes, potentially enhancing the ability to personalize diuretic therapy based on patient-specific responses.

Methods

We performed a post-hoc substudy of the double-blind 1:1 randomized study SALT-HF (Efficacy of Saline Hypertonic Therapy in Ambulatory Patients with HF) trial,[4] which enrolled 167 ambulatory patients presenting an episode of WHF.

Patients were eligible if they exhibited at least two signs of volume overload (peripheral oedema, jugular enlargement, ascites or pleural effusion) and had an N-terminal pro-B-type natriuretic peptide (NT-proBNP) $>$ 1000 pg/mL or a B-type natriuretic peptide (BNP) $>$ 250 ng/mL. In addition, patients should be treated with oral loop diuretics for $\geq$1 month before inclusion at a dose of $\geq$80 mg of furosemide or $\geq$40 mg of torsemide per day. The diagnosis of HF was assessed by the treating physician based on the current HF guidelines.[1] Key exclusion criteria included cardiogenic shock, pulmonary oedema, renal replacement therapy, severe metabolic derangements or other high-risk criteria that would require hospitalization.

Participants were allocated to receive a 1-h infusion of IV furosemide plus hypertonic saline solution versus IV furosemide. The furosemide infusion protocol was tailored based on the patient's previous oral dose. Patients with an oral furosemide dose or equivalent $\leq$160 mg were administered 125 mg of furosemide, and those with an oral furosemide dose or equivalent $>$160 mg received 250 mg. The treatment was administered over 1 h, and the diuresis was collected for 3 h. The study design and main results were published elsewhere.[4, 5]

The endpoint of interest was 30-day adverse events, defined as a composite of death, or HF hospitalization, or need for outpatient IV diuretics. The discriminative ability and independent association between the exposures and the endpoint were assessed by area under the receiver operating curves (AUC-ROC) and logistic regression analyses. The patients were stratified into two groups based on the median of 3-h diuresis ($\leq$1000 mL vs. $>$1000 mL) and 3-h urinary sodium ($\leq$107 mmol/L vs. $>$107 mmol/L). Covariates included in the final multivariate model were chosen based on the biological plausibility and included the following covariates: age, sex, Charlson index, NYHA functional class, previous HF hospitalization, IV furosemide dose, basal urinary sodium, haemoglobin levels, estimated glomerular filtration rate and treatment allocation. Both exposures were mutually forced into the model. A second model was developed including treatment with renin angiotensin aldosterone system inhibitors (RAASi) and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Endpoint ascertainment was blinded to treatment allocation and measurements of the exposures.

Results

Baseline characteristics across the exposures

The median age of the overall population was 81 years (interquartile range [IQR] 73–87), predominantly men (69.5%), with nearly half (49.1%) presenting with a left ventricular ejection fraction (LVEF) $>$50%.

The mean 3-h uNa^+ and urine output were 103 ± 23 mmol/L and 1101 ± 602 mL, respectively, and the median 3-h uNa^+ and urine output were 107 (IQR 93–117) mmol/L and 1000 mL (IQR 700–1300), respectively. Baseline characteristics of the patients stratified by the median of the two exposures are presented in *Table 1*.

Patients with lower urinary sodium ($\leq$107 mmol/L) and diuresis ($\leq$1000 mL) were older and exhibited more pronounced kidney dysfunction and haemoglobin levels. Additionally, the group with lower urinary sodium displayed decreased systolic blood pressure, while those with lower diuresis had significantly increased natriuretic peptide values. There were no significant differences in other signs of congestion compared with those above the medians. The two groups were balanced regarding prior diuretic or neurohormonal treatment and the administered dose of IV furosemide and hypertonic saline solution infusion (*Table 1*).

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Table 1 Baseline characteristics across median of 3-h uNa and diuresis

Variable	Total (n = 167)	uNa < median (n = 86)	uNa ≥ median (n = 81)	P-value	Diuresis < median (n = 85)	Diuresis ≥ median (n = 82)	P-value
Demographics and medical history							
Age (years)	81 (73, 87)	83 (73, 87)	80 (74, 86)	0.056	83.0 (77, 87)	79 (71, 86)	0.020
Female, *n* (%)	51 (30)	25 (29)	26 (32)	0.671	27 (32)	24 (29)	0.860
Hypertension, *n* (%)	143 (86)	73 (85)	70 (86)	0.777	73 (86)	70 (85)	1.000
Hypercholesterolemia, *n* (%)	93 (56)	46 (54)	47 (58)	0.555	49 (58)	44 (54)	0.720
Diabetes mellitus, *n* (%)	69 (41)	37 (43)	32 (39)	0.219	37 (43)	32 (39)	0.825
Atrial Fibrillation, *n* (%)	116 (69)	63 (73)	53 (65)	0.273	64 (75)	52 (63)	0.130
CKD, *n* (%)	107 (64.5)	61 (72.6)	46 (56.1)	0.051	61 (72.6)	46 (56.1)	0.008
Baseline assessment							
NYHA	3 (2, 4)	3 (2, 4)	3 (1, 4)	0.234	3 (2, 4)	3 (1, 4)	0.050
Charlson index	3 (2, 4)	3 (2, 4)	3 (1, 4)	0.234	3 (2, 4)	3 (1, 4)	0.050
Composite congestion score	4 (2)	4 (2)	4 (2)	0.868	4 (2)	4 (2)	0.215
Systolic blood pressure (mmHg)	120 (18)	117 (15)	124 (20)	0.020	118 (16)	122 (20)	0.135
Heart rate (b.p.m.)	73 (13)	73 (13)	73 (13)	0.866	74 (15)	72 (12)	0.310
BMI (kg/m^2)	27.5 (25.0, 32.0)	27.7 (25.5, 31.8)	27.4 (24.4, 32.0)	0.758	27.3 (24.5, 30, 6)	28.5 (25.0, 33.7)	0.206
LVEF (%)	50 (15)	50 (15)	50 (14)	0.740	50 (15)	49 (14)	0.837
TAPSE (mm)	17 (4)	17 (5)	17 (4)	0.805	17 (4)	17 (4)	0.526
Inferior vena cava (mm)	23 (4)	23 (4)	23 (4)	0.656	23 (4)	23 (4)	0.623
Presence of lung B-lines, *n* (%)[a]	86 (53)	40 (49)	46 (56)	0.482	40 (49)	46 (56)	0.482
Laboratory							
eGFR (mL/min/1.73 m^2)	40.2 (29.3, 53.1)	37.8 (27.5, 48.0)	44.3 (31.4, 61.4)	0.003	35.83 (28.1, 42.3)	43.64 (31.2, 61.1)	0.002
Creatinine (mg/dL)	1.5 (1.1, 1.9)	1.6 (1.3, 2.0)	1.3 (1.1, 1.8)	0.002	1.6 (1.4, 2.0)	1.4 (1.1, 1.9)	0.006
Sodium (mEq/L)	140 (4)	138 (4)	140 (4)	0.009	139 (4)	140 (4)	0.168
Potassium (mEq/L)	4.2 (0.5)	4.2 (0.5)	4.2 (0.5)	0.794	4.3 (0.5)	4.1 (0.4)	0.075
Haemoglobin (g/dL)	12.3 (11.1, 13.8)	12.0 (10.9, 13.4)	12.8 (11.7, 14.2)	0.025	12.0 (10.9, 13.4)	12.8 (11.7, 14.2)	0.025
Haematocrit (%)	38 (6)	38 (7)	37 (4)	0.628	37 (33, 42)	39 (35, 43)	0.026
NT-proBNP (pg/mL)	4969 (2508, 9328)	5136 (2607, 10 714)	4200 (2467, 8789)	0.229	6043 (2891, 11 358)	3354 (2237, 8789)	0.004
Basal urinary sodium (mEq/L)	67 (43, 88)	55 (33, 76)	84 (52, 96)	<0.001	66 (46, 84)	68 (45, 91)	0.805
Medical treatment							
Furosemide (mg)	120 (80 160)	120 (80 160)	120 (80 160)	0.688	120 (80 160)	120 (80 160)	0.751
Thiazides, *n* (%)	47 (28)	22 (26)	25 (31)	0.448	26 (31)	21 (25)	0.417
Mineral receptor antagonists, *n* (%)	81 (49)	40 (47)	41 (51)	0.596	35 (42)	46 (55)	0.075
Acetazolamide, *n* (%)	8 (5)	3 (4)	5 (6)	0.417	4 (5)	4 (5)	0.986
Beta-blockers, *n* (%)	116 (70)	61 (71)	55 (68)	0.671	55 (66)	61 (74)	0.261
RAASi, *n* (%)	91 (55)	47 (55)	44 (54)	0.966	46 (55)	45 (54)	0.944
SGLT2i, *n* (%)	61 (37)	36 (42)	25 (31)	0.140	27 (32)	34 (41)	0.237
Intervention							
IV furosemide 125 mg, *n* (%)	146 (90)	71 (90)	75 (90)	0.917	70 (89)	76 (92)	0.604
HSS therapy, *n* (%)	83 (50)	37 (45)	46 (54)	0.344	42 (49)	41 (50)	0.637

Continuous variables are presented as means ± standard deviations or median values with interquartile ranges, depending on the distribution of the data.
CA125, antigen carbohydrate 125; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HSS, hypertonic saline therapy; IV, intravenous; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose co-transporter-2 inhibitors.
[a]Considered positive when ≥3 B-lines were bilaterally observed in ≥2 lung fields.

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Association between 3-h uNa and 3-h diuresis with 30-day adverse clinical events

At 30 days, 50 (29.9%) of the patients experienced the composite endpoint (3 deaths, 11 HF hospitalizations, and 44 new requirements of IV furosemide for WHF). Mean 3-h uNa^+ and diuresis were higher in those without adverse events (106.7 ± 21.9 vs. 93.8 ± 24.5, $P < 0.001$ and 1165 ± 649 vs. 954 ± 447, $P = 0.038$).

Univariate logistic regression showed that both exposures were inversely related to the composite endpoint (3-h uNa+: OR = 1.29, 95% CI: 1.10 to 1.51, $P = 0.001$ per decrease in 10 mmol/L and 3-h diuresis: OR = 1.08, 95% CI: 1.01 to 1.15, $P = 0.023$ per decrease in 100 mL). The associations between 3-h uNa were significant for 30-day HF hospitalization and ambulatory WHF when evaluated as isolated endpoints. They were not for 3-h diuresis (*Table S1*).

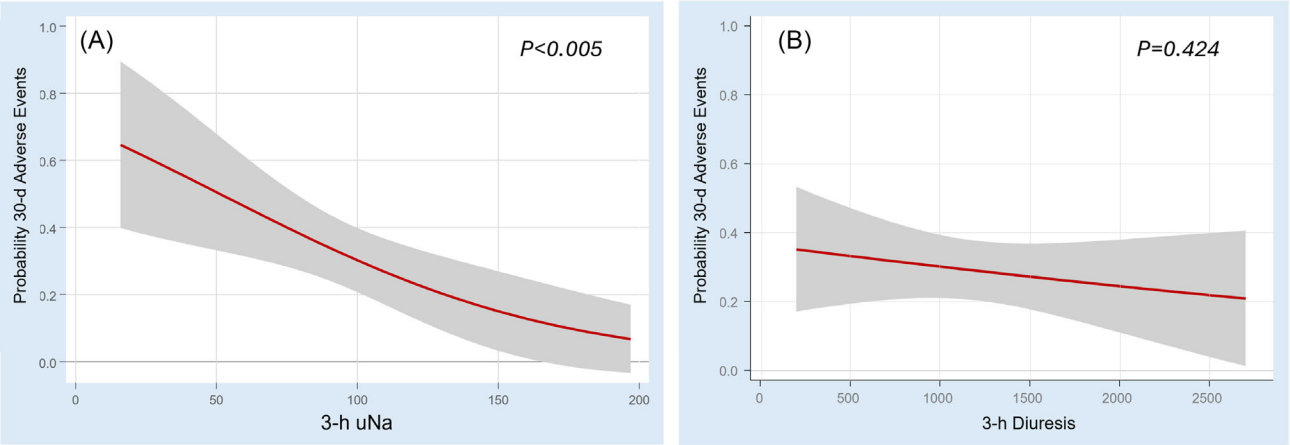
Multivariate regression analysis confirmed that lower 3-h uNa^+ was inverse and linearly associated with an increased risk of adverse clinical events (OR = 1.23, 95% CI: 1.06 to 1.44, $P = 0.008$, per decrease in 10 mmol/L of uNa^+), as is shown in *Figure 1A*. Compared with patients above the median (3-h $uNa^+ > 107$ mmol/L), those below or equal to the median showed a threefold increased risk of adverse clinical events (OR = 3.01, 95% CI: 1.79 to 5.04, $P < 0.001$). On the contrary, under the same multivariate setting (including 3-h uNa^+ as covariate), 3-h diuresis was no longer related to the endpoint (OR = 1.04, 95% CI: 0.95 to 1.13, $P = 0.424$ per decrease in 100 mL), as depicted in *Figure 1B*. Likewise, 3-h diuresis below or equal to the median was not associated with the endpoint (OR = 1.55, 95% CI: 0.79 to 3.07, $P = 0.202$). The AUC of the multivariate full model was 0.777. After forcing in the multivariate model treatment with RAASi and SGLT2i, risk estimates remain showing a significant association between 3-h uNa+ and clinical endpoint but not for 3-h diuresis (*Figure* S1a,b).

In addition, we examined the relationship between natriuresis and diuresis and their impact on adverse events. We categorized both exposures based on their median values, creating a four-level variable [1: low diuresis/low natriuresis ($n = 52$); 2: high diuresis-low natriuresis ($n = 31$); 3: low diuresis/high natriuresis ($n = 31$); and 4: high diuresis/high natriuresis ($n = 53$)], we found a stepwise decreased rates of the endpoint rates when moving from category 1 to 4. Indeed, the rates of 30-day adverse events were 50%, 32.3%, 19.4%, and 15.1% for 1, 2, 3 and 4 categories. Under multivariate setting, compared with patients with high diuretic and natriuretic response (category 4), patients with low diuretic/low natriuresis and high diuresis/low natriuresis showed higher risk (OR: 4.80, 95% CI = 1.58 to 14.75, $P = 0.006$ and OR: 2.76, 95% CI = 1.05 to 7.24, $P = 0.039$). Those with low diuresis/high natriuresis were not at increased risk (OR: 1.30, 95% CI = 0.40 to 4.25, $P = 0.655$).

Discriminative ability 3-h uNa versus 3-h diuresis for 30-day adverse clinical events

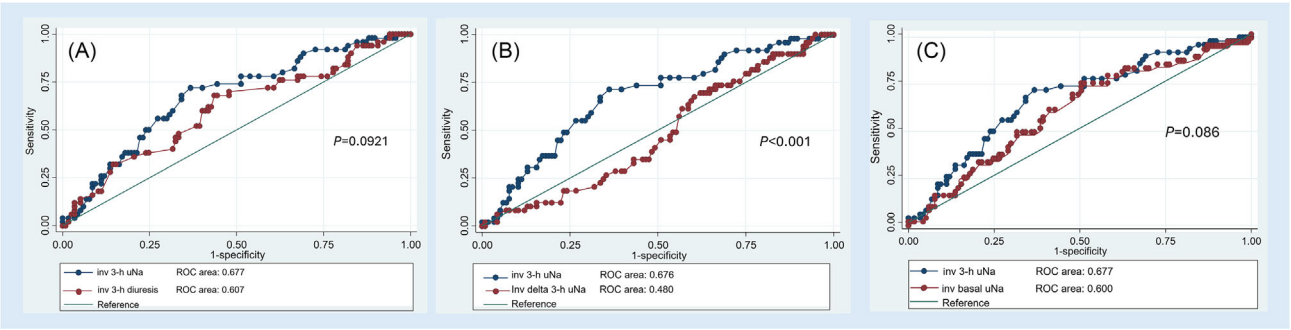
There was a trend towards a higher AUC-ROC for the inverse of 3-h natriuresis compared with 3-h diuresis: 0.680 versus 0.601, $P = 0.092$, as shown in *Figure 2A*. Likewise, the inverse of 3-h uNa^+ showed a better discriminative ability than the inverse of 3-h changes in uNa^+ (*Figure 2B*) and a statistical trend to best performance than baseline uNa^+ (*Figure 2C*).

Figure 1 Association of 3-h urinary sodium and 3-h diuresis with 30-day adverse events. Logistic regression analysis showing an increased risk of adverse events associated with lower 3-h urinary sodium levels (A) and no significant association between 3-h diuresis (B) and 30-day adverse outcomes.



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Figure 2 Comparison of the discriminative ability of 3-h inverse urinary sodium to predict 30-day adverse events. (A) Comparative ROC analysis of 3-h Inv uNa^+ versus 3-h Inv diuresis. (B) Comparative ROC analysis of 3-h Inv uNa^+ versus 3-h change in Inv uNa^+. (C) Comparative ROC Analysis of 3-h Inv uNa^+ versus baseline Inv uNa^+. Inv uNa^+: inverse urinary sodium.



Discussion

In ambulatory patients with WHF treated with a single infusion of IV furosemide, this post-hoc analysis of the SALT-HF trial showed that 3-h urinary sodium better predicted 30-day adverse clinical outcomes than 3-h diuresis.

Predictive value of natriuresis and diuresis in clinical outcomes

The current analysis is aligned with prior studies that identify early natriuresis not only as a useful indicator of early diuretic response but also as a risk factor for predicting adverse clinical events in patients with WHF.[2, 3, 6–11]

To date, most existing data derive from hospitalized patients with AHF, where low urinary sodium levels have been consistently associated with worse long-term clinical outcomes along with increased neurohormonal activation, diuretic resistance and higher odds of worsening renal function.[2, 3, 6–14]

In contrast, our study focuses on the ambulatory setting, where the evidence is more limited. An observational single-center study in an outpatient HF clinic involving 176 patients found an association between urinary sodium levels, 3-h diuresis, and 30-day heart failure outcomes (hospitalization or emergency department visits).[15] While this study identified an increased risk of events in patients with urinary sodium $<$65 mmol/L and urine output $<$1200 mL, it did not evaluate 3-h diuresis as an independent predictor.

Indeed, the prognostic role of diuresis in medium and long-term outcomes remains uncertain. Damman et al. evaluated the association between urinary sodium excretion and diuresis 6 h after loop diuretic administration with all-cause mortality or HF hospitalization.[3] The authors found that urinary sodium, but not urinary output, independently predicted mortality but not HF rehospitalization. The association between urinary sodium excretion and mortality was particularly pronounced in patients with lower urinary volumes.[3] Likewise, a subanalysis of the ROSE AHF (Renal Optimization Strategies Evaluation-Acute Heart Failure) trial in patients with acute HF indicated that neither fluid balance nor urine output correlated with clinical outcomes.[2] Conversely, sodium excretion was strongly associated with 6-month survival even in patients who achieved a net fluid loss.[2]

Our analysis further highlights the complex interplay between natriuresis and diuresis in predicting outcomes among ambulatory patients with WHF. By categorizing patients into four groups based on their natriuretic and diuretic response, we observed a stepwise decrease in 30-day adverse events from those with low diuresis/low natriuresis to those with high diuresis/high natriuresis. Notably, patients with high diuresis but low natriuresis exhibited a significantly increased risk of adverse events, suggesting that a high urine output alone may not necessarily reflect effective decongestion.

This finding aligns with prior studies indicating that diuresis without adequate natriuresis could reflect a state of impaired sodium excretion, potentially driven by excessive free water clearance, neurohormonal activation or underlying renal dysfunction.[2, 3, 6–12] In contrast, patients with low diuresis but high natriuresis did not demonstrate a significantly higher risk, reinforcing the notion that sodium excretion, rather than fluid loss per se, may be a more relevant indicator of effective decongestion and improved outcomes.

The central role of sodium handling in worsening heart failure

Congestion in HF is characterized by increased sodium avidity and extracellular volume overload.[13, 14] Renal tubules normally reabsorb over 99% of filtered sodium, excreting only a small fraction in the urine, a process tightly regulated to maintain extracellular volume homeostasis.[16] Persistent

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congestion reflects the inability of the kidneys to preserve this sodium balance, a condition exacerbated by neurohormonal activation and venous congestion.

Evaluating natriuresis following diuretic administration provides insights into volume status and diuretic response. Lower uNa^+ values may indicate increased renal sodium retention, diuretic resistance, or a more severe decompensation. Furthermore, sodium handling offers a comprehensive measure of both glomerular and tubular function, making it a valuable metric for assessing tubular response and diuretic efficacy.[13, 14]

While the majority of prognostic evidence on urinary sodium is derived from measurements obtained after diuretic administration, both baseline urinary sodium levels and the natriuretic response to diuretic therapy have been proposed as valuable parameters for guiding individualized diuretic management in patients with heart failure.[2, 3, 6–12, 17] The NaDEF registry found that lower admission uNa^+ was associated with chronic kidney disease, prior HF hospitalizations, higher neurohormonal activation, reduced weight loss, greater diuretic needs and worse long-term outcomes.[7]

In contrast, a study by Biegus et al. showed that while baseline UNa did not predict outcomes, failure to increase uNa^+ at 6 and 48 h post-diuretic treatment was linked to higher 1-year mortality, poorer diuretic response and increased tubular injury biomarkers.[8]

In this subanalysis of the SALT-HF trial, we also found that the absolute 3-h natriuresis value demonstrated superior discriminative ability in predicting 30-day adverse clinical events compared with baseline urinary sodium. Additionally, absolute 3-h uNa outperformed the change in natriuresis over the same period. However, a longer observation period may have been necessary to fully assess the impact of dynamic natriuretic changes.

It should be noted that there is a progressive decline in uNa^+ during diuretic therapy in WHF.[18, 19] As the extracellular volume overload diminishes, natriuresis similarly declines, balancing sodium excretion with intake.[17, 18] Determining whether a reduction in uNa^+ along the course of the decompensation implies diuretic resistance or, alternatively, a physiological adaptation to reduced extracellular volume is difficult to ascertain.

Clinical implications

In contrast to prior investigations, our study tried to evaluate which parameter of diuretic response better predicted adverse events in WHF, highlighting the role of urinary sodium in refining risk stratification. In addition, our study focused on outpatient WHF, a context that has been largely underexplored. This approach underscores the utility of routine assessment of the natriuretic response in patients presenting with ambulatory WHF. According to the current findings, early natriuretic response may be useful for clinical decision-making, tailoring the intensity of diuretic strategy and monitoring.

Limitations

Several limitations of this study should be acknowledged. First, this was a post-hoc analysis of the SALT-HF trial, which was not designed to evaluate the prognostic value of natriuresis and diuresis in ambulatory WHF. Therefore, all of the results should be considered exploratory and hypothesis-generating. Second, due to the limited sample size, some negative results could be explained by type II error (insufficient statistical power). Third, given the limited number of adverse outcomes, we cannot robustly evaluate the association between the exposures and isolated components of the combined endpoint. Fourth, we did not comprehensively record all diuretic adjustments made in the subsequent days after the study treatment intervention. This lack of detailed follow-up data introduces uncertainty regarding the 30-day outcomes. Fifth, we cannot definitively elucidate the mechanisms underlying these findings, as this is a hypothesis-generating analysis.

Conclusions

In summary, our research shows that early urinary sodium excretion following IV loop diuretic therapy significantly predicted 30-day adverse clinical events in patients with ambulatory WHF. Conversely, early urinary output was not associated with the endpoint. These findings emphasize the central role of sodium handling in the pathophysiology of congestion in WHF and reinforce natriuresis as an essential prognostic marker across different WHF scenarios.

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Conflict of interest

None. All the authors have approved the manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Association of 3-hour Natriuresis and 3-hour Diuresis with 30-day Heart Failure Hospitalizations and Ambulatory Worsening Heart Failure.

Figure S1. Association of 3-hour urinary sodium and 3-hour diuresis with 30-day adverse events after adjusting for age, sex, Charlson index, NYHA functional class, previous HF hospitalization, intravenous furosemide dose, basal urinary sodium, haemoglobin levels, estimated glomerular filtration rate, treatment allocation and treatment with renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors and mineral receptor antagonists.

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