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# The role of urine sodium in acutely decompensated heart failure

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ABSTRACT

*Background:* Diuretic resistance is common and results in poor outcome. Spot urine sodium (UrNa) is suggested as a tool to tailor diuretics and improve efficacy of therapy. We prospectively evaluate the prevalence of diuretic resistance, predictors of low spot-UrNa and the prognostic value of spot-UrNa in an unselected ADHF population.
*Methods:* Patients admitted for ADHF and treated with iv diuretics were included. Spot-UrNa was collected 2 h after administration of an IV diuretic bolus. The main endpoint was a composite of HF re-hospitalizations and all-cause mortality at 90 days follow-up.
*Results:* 143 patients were included in this study (median age 81 [75 – 85] years, 55 % male), of which 50 % were newly diagnosed with HF. Low spot-UrNa was independently associated with worse renal function, low serum sodium, and systolic blood pressure, previous loop diuretic and SGLT2i use and loop diuretic administered dose. Both absolute spot-UrNa (HR 0.87, 95 % CI 0.79 – 0.95, P=0.003 per 10 mmol/L increase) and a urinary sodium $\geq$ 100 mmol/l (HR=0.51, 95 % CI 0.27 – 0.97, P=0.04) significantly predicted the composite endpoint. This association was no longer significant after correction for confounders. Patients with low spot-UrNa attained longer IV diuretic treatment and a higher cumulative IV diuretic dose.
*Conclusions:* Spot-UrNa is prevalent and occurs more often in patients with more progressed cardio-renal disease. Spot-UrNa significantly predicts 90-day HF hospital-free survival in ADHF. Further studies are needed evaluating the effect of UrNa guided diuretic treatment on clinical endpoints.

## 1. Introduction

Acutely decompensated heart failure (ADHF) is the main indication for hospitalization in patients with heart failure (HF). It is prevalent and serious (life time risk of developing heart failure of 24 % in the United States)[1], reducing quality of life and life expectancy as well as leading to high expenditures in healthcare.[2] Treatment with intravenous (IV) diuretics remains the cornerstone therapy in ADHF to relieve congestion and associated symptoms. Relieving congestion completely is important, as persisting congestion at discharge predicts worse outcome in terms of re-hospitalization and mortality.[3,4] Nevertheless, adequate dosing of diuretics is challenging due to a varying diuretic resistance, potential side effects, and a lack of readily available and accurate markers of diuretic response to inform diuretic effectiveness.[5].

A low spot urine sodium (UrNa) yields potential as a valid biomarker for intensifying diuretic dosing in ADHF patients treated with IV diuretics according to recent European Society of Cardiology (ESC) guidelines.[6] This recommendation was based on several observational studies suggesting that lower UrNa after diuretic treatment is predictive of prolonged hospitalization, worsening renal function and potentially a worse outcome in terms of HF re-hospitalization and all-cause mortality.[7–9] However, these studies were heterogeneous in the modality and timing of the urine sample collection methods. There is still limited evidence supporting clinical improvement through usage of a spot urine sodium collection 2 h following IV diuretic administration, as recommended by the guidelines.[6] Two recent randomized controlled trials

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showed that an algorithm including a timed spot UrNa may improve cumulative sodium excretion in ADHF patients.[10,11] In PUSH-AHF, this did not impact the composite clinical endpoint of all-cause mortality and HF rehospitalizations at 180 days, although there might have been insufficient statistical power for the latter.[11] Also, only a single retrospective study of 175 ADHF patients investigated the characteristics associated with a low UrNa.[12] Therefore, there is a need for more data on the clinical use of a spot UrNa 2 h after IV diuretic administration. This prospective cohort study aimed to investigate the prognostic value of a timed spot UrNa and its associations with patient characteristics in a representative and contemporary ADHF cohort.

## 2. Methods

### 2.1. Study population

Eligible patients were aged ≥ 18 years and consecutively admitted to the hospital for ADHF treatment with IV diuretics, regardless of previous history of heart failure (HF) or left ventricular ejection fraction (LVEF). ADHF was defined as (1) at least two signs/symptoms of AHF with volume overload (orthopnea or paroxysmal nocturnal dyspnea, edema, pulmonary congestion or pleural fluid on chest X-ray or physical exam, ascites, and/or ultrasound evidence of dilated inferior vena-cava and dilated hepatic veins);[6] (2) New York Heart Association (NYHA) Class II-IV heart failure; and (3) NT-proBNP>300 pg/mL. Patients were excluded if they had: (1) palliative treatment intent where death was expected in the short term (≤72 h); (2) end-stage renal disease eGFR<15 mL/min/1.73 m2 with or without renal replacement therapy; (3) need for inotropic or vasopressor support therapy; and (4) ventricular assist devices, or the use of an intra-aortic balloon pump, at any time point during the study period.

### 2.2. Study design

This was a prospective, observational cohort study, conducted in a single large non-academic hospital in the Netherlands (Zuyderland Medical Center) from November of 2021 to February of 2023. Patients were enrolled following clinical assessment at the cardiology emergency department. The daily dosage of IV diuretics varied, ranging from 1 to 3 boluses, depending on preferences of the treating cardiologist. During hospitalization, UrNa spot samples were taken by a nurse 2 h after each administered bolus within the first 36 h of treatment. Patients without a urinary catheter were asked to empty their bladder before administration of the IV diuretic. In patients with a urinary catheter, the catheter was emptied just before the 2 h time point, and a sample was collected shortly thereafter. The nursing staff was extensively trained in this protocol.

The first available urine sodium of a documented administered bolus of furosemide was selected for the primary analysis. Patients who were exclusively treated with continuous IV diuretic administration (N=3) or those who did not have an available urine sodium within the first 36 h of treatment (N=22) were excluded from analysis.

During this observational study, patients were treated following usual care in our hospital. Physicians were not blinded to the UrNa concentrations. During the study – in September 2022 – an updated local ADHF treatment protocol was implemented at the cardiology department including recent developments in the treatment of HF as per the 2021 ESC HF guideline (e.g. SGLT2 inhibitors, ARNI and IV iron suppletion after initial stabilization).[6] Uptitration of diuretics based on spot urine sodium was not compulsory.

Electronic patient files were evaluated to determine baseline characteristics, treatment characteristics and occurrence of clinical endpoints. Both degree of pulmonary rales and peripheral edema were scored on a scale of 0 – 3, resulting in a combined congestion score of 0 – 6 (Table 1).

Ethics approval was obtained from the Medical Ethics Committee of the Zuyderland Medical Center. All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Guidelines for Good Clinical Practice.

**Table 1**
Clinical congestion score.

| Edema | Points | Pulmonary Crepitation | Points |
|---|---|---|---|
| None | 0 | None | 0 |
| Ankle level | 1 | Basal crepitations | 1 |
| Above ankle & below knee level | 2 | Below half thorax height | 2 |
| Knee level or higher | 3 | Above half thorax height | 3 |

### 2.3. Endpoints

The composite primary endpoint was heart failure re-hospitalizations (HFH) and all-cause mortality at 90-days follow-up. HFH was defined as a hospitalization with AHF as (or among) the primary reasons for hospitalization. Secondary endpoints were delta creatinine from admission to discharge, worsening renal function from admission to discharge (creatinine increase > 26.5 μmol/L), cumulative diuretic IV dose, days of IV diuretic treatment and length of hospitalization. Additionally, predictors of spot UrNa were explored.

### 2.4. Statistical analysis

Continuous variables are presented as means ± standard deviation when normally distributed or medians with 25th-75th percentiles when non-normally distributed. Categorical variables are presented as numbers with percentages. Patients were divided by their first available spot urine sodium – above versus below 100 mmol/L. Differences in baseline characteristics between these two groups were evaluated using the *t*-test, chi-square test or Mann-Whitney *U* test, as appropriate.

Cox regression analysis was used to analyze the association between spot urine sodium and the primary clinical outcome. In a next step, the association was adjusted for confounding characteristics – defined as variables associated both with the spot-UrNa and with the outcome.

Univariate and multivariate linear regression analyses were performed to assess the association between baseline characteristics and the first available spot urine sodium, after checking for linearity assumption. Characteristics were included in the backward stepwise multivariate analysis when P<0.1 in the univariate analysis and after checking for multicollinearity.

A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 29.

## 3. Results

### 3.1. Baseline characteristics

After screening, 168 patients met the inclusion criteria and signed informed consent. 143 patients (85 %) had an available spot urine sodium < 3 h of a bolus of IV loop diuretics and were included in this analysis. The included population was slightly older (median 81 (interquartile range (IQR) 75 – 85) vs 76 (IQR 65—84 years, P=0.046) and more often male (55.2 % vs 48.0 %, P=0.003) compared to the excluded participants. Other than that, baseline characteristics were evenly distributed between in- and excluded patients.

Baseline characteristics of the study population are shown in Table 2. Median age of the study population was 81 years (IQR 75 – 85 years) and 55 % of the population was male. 50 % were newly diagnosed with heart failure during index hospitalization. Of those with pre-existing heart failure, 39 % had an ischemic etiology. Median left ventricular ejection fraction was 45 % (IQR 35 – 53 %). Prior to admission, 61 % were using loop diuretics. At admission, median NT-proBNP was 6050 ng/L (IQR

**Table 2**
Baseline characteristics.

| Characteristic | Total cohort (N=143) | UrNa < 100 mmol/L (N=59) | UrNa > 100 mmol/L (N=84) | P |
|---|---|---|---|---|
| Age (years) | 81 (75 – 85) | 81 (72 – 85) | 81 (77 – 84) | 0.815 |
| Gender (% male) | 79 (55.2) | 31 (52.5) | 48 (57.1) | 0.586 |
| Weight (kg) | 82.6 ± 29.7 | 82.4 ± 19.0 | 82.7 ± 20.4 | 0.932 |
| **Medical history** | | | | |
| Ischemic heart disease (%) | 121 (84.6) | 47 (79.7) | 74 (88.1) | 0.169 |
| Atrial fibrillation (%) | 84 (58.7) | 43 (72.9) | 41 (48.8) | **0.004** |
| COPD (%) | 116 (81.1) | 47 (79.7) | 69 (82.1) | 0.709 |
| Anemia (%) | 38 (26.6) | 19 (32.2) | 19 (22.6) | 0.201 |
| PHT (%) | 6 (4.2) | 3 (5.1) | 3 (3.6) | 0.691 |
| TIA/stroke/PAD (%) | 43 (30.1) | 19 (32.2) | 24 (28.6) | 0.641 |
| OSAS (%) | 16 (11.2) | 6 (10.2) | 10 (11.9) | 0.746 |
| Diabetes (%) | 52 (36.4) | 26 (44.1) | 26 (31.0) | 0.108 |
| **Presentation at baseline** | | | | |
| Peripheral edema (%) | | | | 0.526 |
| 0: No pheripheral edema | 31 (23.5) | 12 (22.6) | 19 (24.1) | |
| 1: Ankle level | 35 (26.5) | 11 (20.8) | 24 (30.4) | |
| 2: Above ankle below knee | 42 (31.8) | 18 (34) | 24 (30.4) | |
| 3: Above knee | 24 (18.2) | 12 (22.6) | 12 (15.2) | |
| Pulmonary rales (%) | | | | 0.846 |
| 0: No rales | 24 (25.2) | 15 (27.8) | 19 (23.5) | |
| 1: Basal rales | 90 (66.7) | 34 (63) | 56 (69.1) | |
| 2: Below half thorax height | 8 (5.9) | 4 (7.4) | 4 (4.9) | |
| 3: Above half thorax height | 3 (2.2) | 1 (1.9) | 2 (2.5) | |
| SBP (mmHg) | 137 ± 26 | 127 ± 23 | 144 ± 26 | <0.001 |
| **Treatment (before hospitalization)** | | | | |
| Loop diuretic at home (%) | 83 (60.6) | 47 (81.1) | 36 (45.5) | **<0.001** |
| Dosage (mg furosemide or equivalent) | 40 (40 – 80) | 80 (40 – 80) | 40 (40 – 40) | **0.001** |
| SGLT2i (%) | 8 (5.7) | 6 (10.3) | 2 (2.4) | **0.047** |
| ACEi/ARB (%) | 66 (47.1) | 28 (48.3) | 38 (46.3) | 0.821 |
| ARNI (%) | 5 (3.6) | 1 (1.7) | 4 (4.9) | 0.322 |
| Betablocker (%) | 79 (56.4) | 37 (63.8) | 42 (51.2) | 0.139 |
| MRA (%) | 34 (24.6) | 18 (31.6) | 16 (19.8) | 0.112 |
| DOAC (%) | 51 (36.4) | 27 (46.6) | 24 (29.3) | **0.036** |
| VKA (%) | 25 (17.9) | 12 (20.7) | 13 (15.9) | 0.462 |
| Statin (%) | 71 (50.7) | 32 (55.2) | 39 (47.6) | 0.375 |
| Ivabradine (%) | 2 (1.4) | 1 (1.7) | 1 (1.3) | 0.666 |
| Thiazide (%) | 13 (9.7) | 4 (7.3) | 9 (11.4) | 0.428 |
| Antiplatelet (%) | 41 (29.3) | 13 (22.4) | 28 (34.1) | 0.133 |
| **Treatment (during hospitalization)** | | | | |
| Dosage furosemide IV (mg) | 40 (40 – 80) | 80 (40 – 80) | 40 (40 – 80) | <0.001 |
| Acetazolamide prescribed (%) | 45 (31.5) | 20 (33.9) | 25 (29.8) | 0.600 |
| **HF history** | | | | |
| HF de novo (%) | 71 (49.7) | 20 (33.9) | 51 (60.7) | **0.002** |
| Time since first diagnosis (days) | 1162 (189 – 3347) | 1432 (292 – 3901) | 1078 (148 – 2722) | 0.649 |
| Ischemic etiology (%) | 28 (39.4) | 12 (31.6) | 16 (48.5) | 0.315 |
| LVEF (%) | 45 (35 – 53) | 42.5 (28.6 – 52.5) | 50.0 (40.0 – 52.6) | **0.017** |
| NYHA class | | | | 0.574 |
| II (%) | 19 (16.1) | 9 (19.6) | 10 (13.9) | |
| III (%) | 60 (50.8) | 24 (52.2) | 36 (50) | |
| IIII (%) | 39 (33.1) | 13 (28.3) | 26 (36.1) | |
| **Biochemistry at baseline** | | | | |
| NT-proBNP (ng/L) | 6050 (2826 – 15613) | 8729 (3338 – 18181) | 4956 (2306 – 12141) | **0.024** |
| Creatinine (μmol/L) | 111 (81 – 153) | 136 (89 – 212) | 98 (74 – 131) | **<0.001** |
| Serum sodium (mmol/L) | 138 ± 5 | 136 ± 6 | 139 ± 3 | **<0.001** |
| Serum urea (mmol/L) | 104 (72 – 157) | 138.5 (90.3 – 221.8) | 87.5 (65 – 130.5) | **<0.001** |

COPD, chronic obstructive pulmonary disease; PHT, pulmonary hypertension; TIA, transient ischemic attack; PHD, peripheral artery disease; OSAS, obstructive sleep apnea syndrome; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitors; ACEi, angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; ARNI, angiotensine-receptor neprilysine-inhibitor; MRA, mineralocorticoid receptor antagonist; DOAC, direct oral anticoagulants; VKA, vitamin K antagonist; IV, intravenous; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide.

2826 – 15613).

Fifty-nine patients (41 %) had a first available spot urine sodium of < 100 mmol/L. They had a significantly lower systolic blood pressure, serum sodium and LVEF at admission and were less often diagnosed with heart failure de novo. Furthermore, they had a significantly higher NT-proBNP, creatinine and serum urea at admission and more often had a history of atrial fibrillation (Table 2).

### 3.2. Prognostic value of timed urinary spot sodium

In the univariate Cox proportional hazard analysis both absolute spot urine sodium (HR 0.87, 95 % CI 0.79 – 0.95, P=0.003 per 10 mmol/L increase) and a urine sodium ≥ 100 mmol/L (HR=0.51, 95 % CI 0.27 – 0.97, P=0.04) (Fig. 1) were significant predictors of a better outcome on a composite of heart failure re-hospitalization and all-cause mortality after 90 days (event rate was 20 % (N=17) in high UrNa group and 36 % (N=21) in low UrNa group). After correction for significant confounders – being serum creatinine and systolic blood pressure at admission – the association was no longer significant (respectively P=0.27 and P=0.92 for absolute spot urine sodium and urine sodium ≥ 100 mmol/L). Change of NT-proBNP from admission to discharge > 30 % did not significantly predict the composite endpoint (HR 0.54, 95 % CI 0.24 – 1.22, P=0.137) and was therefore not included in the multivariable regression analysis. Hydrochlorothiazide was administered additionally to loop diuretic therapy during hospitalization happened in 4 subjects during hospitalization. These subjects did not have a significantly worse outcome (HR 0.96, 95 % CI 0.13 – 7.00, P=0.968). Subgroup analysis for LVEF phenotypes showed a similar prognostic value of urine sodium across the LVEF spectrum (Table 3). There was no significant interaction between LVEF and spot urine sodium (P=0.490).

Lower spot urine sodium was strongly associated with a higher cumulative diuretic dosage during hospitalization (standardized beta = -0.41, P<0.001) and longer duration of IV diuretic treatment in days (standardized beta = -0.26, P=0.002) (Fig. 2). Lower spot urine sodium was also associated with a longer total hospitalization (standardized beta = -0.22, P=0.01).

Finally, lower spot urine sodium was associated with a lower increase of creatinine from baseline to hospital discharge (standardized beta 0.27, P=0.001). However, the incidence of worsening renal function (WRF) during hospitalization was not related to the spot UrNa (standardized beta 0.11, P=0.19).

### 3.3. Predictors of a poor natriuretic response

Univariate linear regression analysis showed that serum creatinine and urea at admission, history of heart failure, history of atrial fibrillation, loop diuretic use at home, SGLT2i use at home, and IV loop diuretic bolus dosage before urinary collection were significant predictors of a lower spot urine sodium. Serum sodium at admission, systolic blood pressure, and left ventricular ejection fraction were significantly associated with a higher spot urine sodium (Table 4). In the multivariate analysis, serum sodium, creatinine, systolic blood pressure, loop diuretic usage at home, SGLT2i usage at home, and dosage (in mg) of bolus IV loop diuretic before urine collection were independent predictors of the first available spot urine sodium concentration.

## 4. Discussion

This study showed that a reduced spot urine sodium in response to a

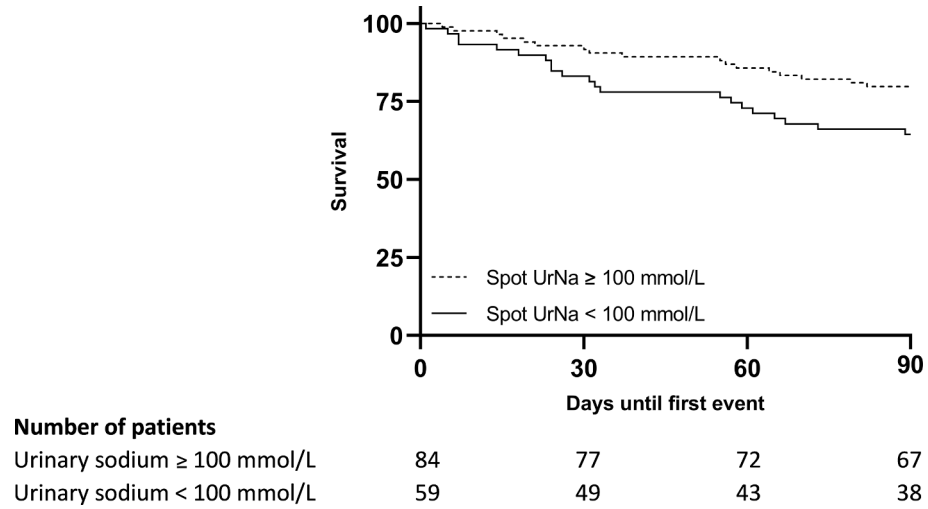


**Fig. 1.** Kaplan Meier curves for a combined endpoint of all-cause mortality and heart failure re-hospitalization stratified by spot urine sodium.

**Table 3**
Subgroup analysis for the effect of absolute spot urine sodium on the combined endpoint of all-cause mortality and heart failure re-hospitalizationVariable.

| | *Heart failure re-hospitalizations and all-cause mortality* | |
|---|---|---|
| | HR (95 % CI)* | P-value |
| HFpEF (N=52) | 0.80 (0.67 – 0.95) | 0.012 |
| HFmrEF (N=31) | 0.85 (0.67 – 1.09) | 0.202 |
| HFrEF (N=27) | 0.86 (0.70 – 1.05) | 0.142 |
| LVEF subgroup and spot urine sodium interaction | – | 0.490 |

HFpEF, Heart Failure with preserved Ejection fracture; HFmrEF, Heart Failure with midrange Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction.

* per 10 mmol/L increase.

bolus of IV loop diuretics is associated with worse outcome in terms of HF hospitalization and mortality, attributed to a more advanced heart failure. This results in a more challenging decongestion process with a higher cumulative diuretic dose and longer duration of IV diuretic treatment during hospitalization. High spot urine sodium was not associated with occurrence of WRF. A lower spot urine sodium was independently predicted by lower serum sodium, increased creatinine, lower systolic blood pressure, loop diuretic usage at home, SGLT2i usage at home, and lower dosage of loop diuretic administered prior to collection of spot urine sodium.

Despite the global use of loop diuretics in ADHF management, there is no robust parameter to assess adequate treatment response. Currently used metrics may take days to identify impaired diuretic response (e.g. urine output, weight change, reducing edema) and may present technical and practical challenges due to, for example, invalid report of urine output and the use of non-calibrated and different scales.[5] This results in a common discrepancy between fluid balance and weight loss in patients with ADHF.[13] Moreover, impaired diuretic response, i.e. diuretic resistance, is prevalent in patients with ADHF, indicating failure to increase salt and fluid output to relieve volume overload. Early diuretic response assessment is crucial, as diminished response predicts poor prognosis in terms of mortality and heart failure rehospitalization.[4] Therefore, a reliable parameter for the assessment of diuretic response is strongly needed. The suggestion of using spot urine sodium 2 h after diuretic administration offers a potential solution.[5].

In this study, both increase in absolute spot urine sodium and a urine sodium $\geq$ 100 mmol/L predicted a better outcome on a composite of heart failure re-hospitalization and all-cause mortality at 90 days follow up, with a similar prognostic effect across the LVEF subgroups. This is in line with the findings of earlier studies.[8,9,12,14] However, the effect did not remain statistically significant after correction for confounding factors. This could be attributed to the higher age (median age of 81 years) and apparent signs of more progressed cardio-renal failure (higher NT-proBNP and creatinine) in our study population. Consequently, it is more challenging to indicate patients at risk for early events. As in recent literature, our data confirms that a high spot urine

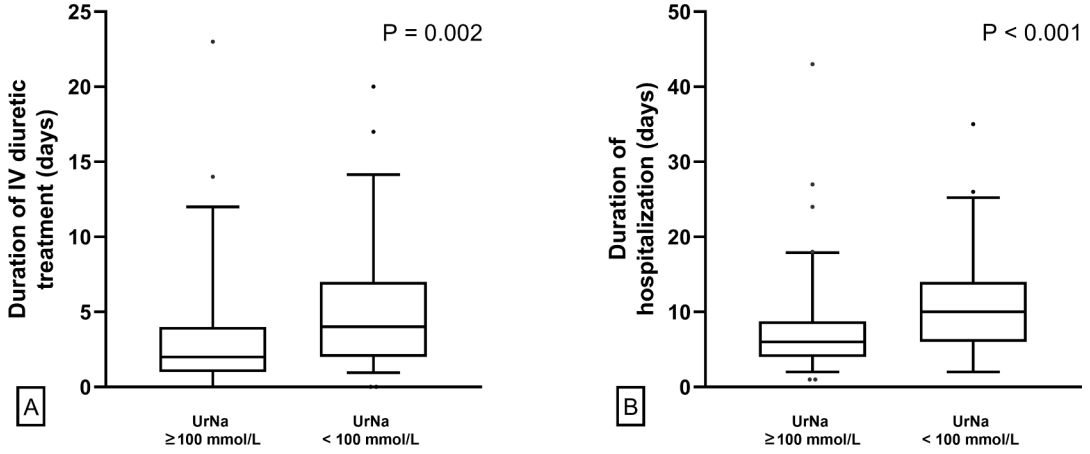


**Fig. 2.** Association between urine sodium > 100 mmol/L and duration of IV diuretic treatment (A) and total hospitalization (B).

**Table 4**
Univariate and multivariable regression analysis for first available spot urine sodium.

| Univariate | | | Multivariate | | |
|---|---|---|---|---|---|
| Variable | Standardized beta (SD) | P | | Standardized beta (SD) | P |
| Age | 0.123 (0.282) | 0.124 | | | |
| Gender | 0.047 (5.094) | 0.581 | | | |
| Weight | 0.033 (0.132) | 0.699 | | | |
| Creatinine (admission) | −0.301 (0.035) | <0.001 | Creatinine (admission) | −0.212 (0.033) | 0.006 |
| NT-proBNP | −0.213 (0.000) | 0.12 | | | |
| Serum sodium | 0.381 (0.512) | <0.001 | Serum sodium | 0.347 (0.464) | <0.001 |
| Serum urea | −0.398 (0.032) | <0.001 | – | | |
| Congestion score | −0.097 (2.165) | 0.271 | | | |
| Peripheral edema | −0.131 (2.523) | 0.134 | | | |
| SBP | 0.323 (0.094) | <0.001 | SBP | 2.102 (0.157) | 0.038 |
| HF history | −0.266 (4.889) | 0.001 | * | | |
| Duration of HF | −0.160 (0.002) | 0.192 | | | |
| AF history | −0.200 (5.047) | 0.017 | * | | |
| First dose loop diuretic | −0.266 (0.077) | 0.002 | – | | |
| Loop diuretic home (y/n) | −0.324 (4.873) | <0.001 | Loop diuretic Home | −0.168 (4.644) | 0.027 |
| Loop diuretic home dosage | −0.301 (0.031) | 0.005 | – | | |
| Thiazide diuretic home | 0.099 (8.233) | 0.238 | | | |
| RAASi home | 0.040 (5.170) | 0.639 | | | |
| SGLT2 home | −0.277 (10.708) | <0.001 | SGLT2 home | −0.144 (9.346) | 0.048 |
| LVEF | 0.178 (0.218) | 0.036 | * | | |
| NYHA | 0.018 (3.598) | 0.843 | | | |
| Loop diuretic administered before UrNa | −0.275 (0.076) | <0.001 | Loop diuretic administered before UrNa | −0.158 (0.092) | 0.043 |

NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure; HF, heart failure; AF, atrial fibrillation; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitors; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

sodium following diuretic treatment predicts a lower cumulative diuretic dosage and shorter hospitalization.[15] This confirms the value of low spot urine sodium in predicting poor diuretic response, and reflects advanced disease, therefore requiring prolonged therapy. In contrast to earlier findings, this study showed that a higher spot urine sodium predicted a higher increase in creatinine from admission to discharge. However, there was no significant difference in the occurrence of WRF. We hypothesize that the change in creatinine in this acute treatment phase are predominantly hemodynamic effects and thus, the association did not translate into a clinically relevant increase in WRF.[16] In other words, increase of creatinine in the light of decongestive treatment is often not an indication of actual tubular damage. Especially when there is a satisfactory diuretic response, it could reflect the kidney undergoing hemodynamic changes due to the treatment effect of the diuretics. In support of this notion, several studies showed that the presence of WRF in the context of a good diuretic response had similar prognosis on both cardiovascular and renal endpoints compared to the group with a good diuretic response without WRF. Patients with a poor diuretic response and WRF had the worst prognosis.[17,18].

Additionally, our data indicated that factors associated with more progressed or long-standing HF, i.e. diminished renal function and previous use of loop diuretics, are predictive of poorer natriuresis. This is in line with findings from recent literature.[12] Both factors have a well-known role in the development of diuretic resistance. Although the pathophysiological mechanisms are not entirely clear, diminished renal blood flow, resulting in diminished renal function, leads to decreased diuretic delivery to the kidney's tubules. Additionally, prior loop diuretics use contributes to nephron remodeling, favoring pathways for salt reabsorption, and ultimately resulting in sodium retention.[19,20] Beyond recent studies, additional predictors of inadequate natriuresis include lower serum sodium, lower systolic blood pressure, and the use of SGLT2i prior to admission. SGLT2i use was not included in most of the analyses on natriuretic response of available literature since it has only recently gotten a prominent role in the treatment of heart failure. A potential explanation of SGLT2i use as a predictor for poor natriuresis is the higher likelihood of more advanced HF, which might lead to initiation of SGLT2i pre-hospitalization. The management of diuretics becomes more challenging with advanced HF, whereas SGLT2i use intrinsically does not enhance natriuresis.[21] Lower serum sodium levels are often a result of free water retention due to vasopressin release, induced by advanced heart failure resulting in diminished renal perfusion.[20] Age was shown not to be a significant predictor of spot urine sodium, contrary to expectations based on the more active RAAS system in younger patients.[12] However, age may be less relevant in the light of other factors in our analysis and median age was overall higher compared to previous studies, but therefore more reflective of the real-world population.

The integration of spot urine sodium could be used in guiding diuretic therapy and could provide more targeted and personalized care for patients requiring additional decongestive therapy based on a low spot urine sodium. A recent single center randomized controlled trial (PUSH-AHF) showed that a urine sodium guided, intensified diuretic protocol could increase 24-hour sodium excretion, while there was no significant effect on the combined endpoint of all-cause mortality and heart failure rehospitalization (although it might have been underpowered on the latter).[11] Likewise, the multicenter ENACT-HF study showed that a natriuresis guided diuretic strategy resulted in increased diuresis and natriuresis and decreased length of stay.[10] Similarly, the recent CLOROTIC and ADVOR trials showed that intensified diuretic treatment (by adding acetazolamide or hydrochlorothiazide, respectively, to loop diuretic treatment) resulted in faster/improved decongestion, but did not result in reduction of hard clinical endpoints.[22,23] Therefore, as of yet, the value of increased natriuresis on the prevention of re-hospitalizations and mortality remains unclear. The data from this study supports the hypothesis that urine sodium might have an important role in the guidance of diuretic treatment. Still, more randomized controlled trials are needed and currently ongoing (clinicaltrials.gov: NCT06092437; NCT05411991; NCT04481919) to better define the clinical value of using spot urine sodium to guide diuretic therapy.

## 5. Limitations

The relatively small sample size of our cohort could potentially underpower our results. This study is a single center study, which may reduce applicability of results to others, yet our included population is a very elderly and representative AHF population. Nevertheless, it is the first study to assess clinical predictors of low urine sodium at 2 h after IV diuretic administration as suggested in recent ESC guidelines, in a

contemporary heart failure cohort.[6] The elderly nature of the participants, along with their advanced heart failure and frequent co-morbidities, make them representative of the real-life HF population, despite being from a single center study.

The collection of the timed urine samples integrated in the clinical routine in this observational study led to missing or invalid (i.e. not timed correctly at 2 h after loop diuretic bolus) urine sampling in some patients. In order to maintain sufficient sample size, we used the first available, validly timed urine sample within 36 h of admission, thus introducing some heterogeneity in the moment of the sample. However, this reflects a real-life cohort as these bottlenecks appear daily in clinical practice. As the value of urine sodium in predicting net natriuresis and diuresis is known to decrease over time during admission, this may reduce the predictive value of our study.[24].

## 6. Conclusion

This study showed that a low spot urine sodium, obtained two hours after the administering of a bolus of IV loop diuretics, in ADHF is associated with a higher cumulative diuretic dose, longer IV diuretic treatment, and a longer hospitalization. It also predicts worse prognosis in terms of HF rehospitalization and mortality. Factors associated with a diminished urine sodium are lower serum sodium levels, reduced renal function, previous use of loop diuretics and SGLT2i, and lower systolic blood pressure. These results strengthen the hypothesis that urine sodium could be useful in identifying ADHF patients who are diuretic resistant and could have an important role in guiding and personalizing diuretic treatment. Still, the real clinical value for patients with ADHF remains to be investigated and more randomized clinical trials are required to prove clinical value and safety of implementing a urine sodium-guided algorithm.

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## CRediT authorship contribution statement

**Mick Hoen:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Delian E Hofman:** Writing – original draft, Investigation, Formal analysis. **Bjorn H.A. Hompes:** Writing – review & editing, Investigation, Conceptualization. **Lukas E.E. Peeters:** Writing – review & editing, Investigation. **Bart Langenveld:** Writing – review & editing, Investigation, Conceptualization. **Roland R.J. van Kimmenade:** Writing – review & editing. **Leon A.M. Frenken:** Writing – review & editing. **Timo Lenderink:** Writing – review & editing, Conceptualization. **Hans-Peter Brunner-La Rocca:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Sandra Sanders-Van Wijk:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

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## Data availability

Data will be made available on request.

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