Clinical importance of urinary sodium excretion in acute heart failure

Kevin Damman*, Jozine M. Ter Maaten, Jenifer E. Coster, Jan A. Krikken, Vincent M. van Deursen, Hidde K. Krijnen, Mischa Hofman, Wybe Nieuwland, Dirk J. van Veldhuisen, Adriaan A. Voors, and Peter van der Meer

University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

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Aims Urinary sodium assessment has recently been proposed as a target for loop diuretic therapy in acute heart failure (AHF). We aimed to investigate the time course, clinical correlates and prognostic importance of urinary sodium excretion in AHF.

Methods and results In a prospective cohort of 175 consecutive patients with an admission for AHF we evaluated urinary sodium excretion 6 h after initiation of loop diuretic therapy. Clinical outcome was all-cause mortality or heart failure rehospitalization. Mean age was 71 ± 14 years, and 44% were female. Median urinary sodium excretion was 130 (67–229) mmol at 6 h, 347 (211–526) mmol at 24 h, and decreased from day 2 to day 4. Lower urinary sodium excretion was independently associated with male gender, younger age, renal dysfunction and pre-admission loop diuretic use. There was a strong association between urinary sodium excretion at 6 h and 24 h urine volume (beta = 0.702, P < 0.001). Urinary sodium excretion after 6 h was a strong predictor of all-cause mortality after a median follow-up of 257 days (hazard ratio 3.81, 95% confidence interval 1.92–7.57; P < 0.001 for the lowest vs. the highest tertile of urinary sodium excretion) independent of established risk factors and urinary volume. Urinary sodium excretion was not associated with heart failure rehospitalization.

Conclusion In a modern, unselected, contemporary AHF population, low urinary sodium excretion during the first 6 h after initiation of loop diuretic therapy is associated with lower urine output in the first day and independently associated with all-cause mortality.

Keywords Acute heart failure • Diuretic • Urinary sodium • Natriuresis

Introduction

The treatment of acute heart failure (AHF) has not changed over the last decades and is focused on the alleviation of congestion, volume overload, and shortening the time spent in hospital.1,2 As compared with chronic heart failure with reduced ejection fraction, prognosis of patients admitted for worsening heart failure is extremely poor, with almost 30–40% of patients dying within the first year, and a substantial number is rehospitalized for heart failure shortly after discharge. Despite current treatment with loop diuretics, vasodilators and oxygen, 25% of patients with AHF still have residual signs of congestion at discharge.3 Most of the decongestion that is achieved during hospitalization is actually achieved early after admission, with the effect of therapy decreasing in subsequent days. While loop diuretics are the most important drugs in AHF, it has also proven extremely difficult to assess its treatment effect by evaluating congestion status after start of therapy, but it is clear now that more rigorous and quick diuretic response is associated with better outcomes.4-7

*Corresponding author. University of Groningen, Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9700RB Groningen, The Netherlands. Tel: +31 50 3616161, Fax: +31 50 3614391, Email: k.damman@umcg.nl

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Recently, a consensus paper from the Heart Failure Association of the European Society of Cardiology (ESC) on diuretic therapy has proposed to investigate either spot urinary sodium and/or diuresis very early after diuretic initiation in AHF. It is proposed to intensify or expand (loop) diuretic treatment if natriuresis or diuresis are insufficient based on these metrics. However, scientific evidence for this recommendation is limited, since there are only scarce contemporary data on urinary sodium concentrations in spot urine in patients admitted for worsening heart failure. To further understand the physiology of natriuresis in AHF, and to put the consensus paper into clinical perspective in a contemporary AHF population, we investigated the clinical importance of urinary sodium excretion in AHF patients.

**Methods**

This single-centre study evaluated consecutive patients with the primary diagnosis of AHF that were prospectively included in an AHF protocol, admitted between 1 July 2017 until 31 December 2018 at the University Medical Center Groningen, a large tertiary cardiology centre in Groningen, The Netherlands. Diagnosis was based on the ESC heart failure guidelines, with patients presenting with signs and symptoms of congesting, requiring intravenous diuretic therapy. Specifically, we imposed an AHF protocol to improve and standardize AHF care at our institution. All patients admitted for AHF were treated for at least 24 h at the coronary care unit, received intravenous vasodilators when systolic blood pressure was >110 mmHg at admission, and all received bumetanide as the preferred loop diuretic. There was no protocol specifically determining the dose of bumetanide, which was entirely at the discretion of the treating physician. Furthermore, as a measure to improve calculation of fluid balance and urine output, urine collections were done the first 6 h after first intravenous diuretic (0–6 h), followed by 6 to 24 h (6–24 h), and again followed by 24 h urine collections over the next 3 days (24–48, 48–72, and 72–96 h). Measurement from these timed urine collections included urinary creatinine and urinary sodium. All information on urinary volume and urinary measurements were available to the treating physicians.

Urinary sodium was measured on a Roche Modular Analyzer as part of clinical practice. Our variable of interest was urinary sodium excretion in the first 6 h after diuretic initiation and was calculated as urinary sodium concentration × urinary volume over 6 h. This measurement represents the total excretion of sodium achieved within this time frame, which is inherently different from using spot urinary sodium at the same time point, which reflects the concentration of urinary sodium at that point for a given (small) urine void. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (mL/min/1.73 m²).

Case records of patients admitted to the department of cardiology with a diagnosis of AHF were retrospectively investigated for clinical variables, laboratory analysis and follow-up. Clinical follow-up was carried out until 31 June 2019, meaning that every patient had at least 6-month follow-up. The primary clinical endpoint was the occurrence of all-cause mortality after admission, including in-hospital mortality. Secondary endpoints included heart failure rehospitalization after discharge and the combined endpoint of a first occurrence of all-cause mortality and/or heart failure rehospitalization. The Medical Ethics Committee of the University Medical Center Groningen evaluated the research protocol and concluded that Medical Research Involving Human Subjects Act (WMO) approval was not necessary for this study.

**Results**

A total of 228 patients were admitted with a primary diagnosis of AHF during the research period. Of these, 175 patients (77%) had a 6 h urinary sodium measurement available, and these patients were included in the present analyses.

Mean age at admission was 71 ± 14 years, and 44% of patients were female. The vast majority of patients was Caucasian. De novo heart failure was present in 36% of patients, with the main cause of heart failure being ischaemic heart disease (46%). Mean left ventricular ejection fraction, if known before or when measured within hospital, was 35 ± 16%, 54% had heart failure with reduced ejection fraction (<40%), and 33% had heart failure with preserved ejection fraction (≥50%). Before admission, more than one third (39%) did not use any loop diuretic. Median plasma NT-proBNP levels at admission were 5263 (2938–10 489) pg/mL, and renal function was moderately impaired (mean eGFR 53 ± 26 mL/min/1.73 m²).

Median urinary sodium excretion during the first 6 h after intravenous diuretic initiation was 130 (67–229) mmol. After 24 h, median urinary sodium excretion was 347 (211–526) mmol (n = 150). Between 24–48 h, median sodium excretion was 181 (94–270) mmol, followed by 126 (74–194), 114 (73–160) between 48–72 h and 72–96 h, respectively. However, protocol adherence to urine collections proved to be more difficult at...
later time points. Figure 1A depicts the change in urinary sodium excretion over time during admission, showing a considerable decrease in total urinary sodium over the course of the first 4 days in patients with available urine measurements.

Median urine output after 6 h was 1400 (860–2150) mL. The total urinary volume was 3725 (2750–5000) mL, 2225 (1523–2775) mL, 1788 (1275–2400) mL and 1750 (1400–2200) mL, during consecutive days 1, 2, 3 and 4. We also calculated urinary sodium concentration based on urinary volume and sodium concentration during the first 6 h. Median urinary sodium concentration after 6 h was 94 (72–114) mmol/L.

Baseline characteristics stratified for tertiles of urinary sodium excretion in the first 6 h are reported in Table 1. Patients with lower urinary sodium excretion in the first 6 h more often had a longer history of heart failure with more diuretic use and lower blood pressure. NT-proBNP levels were higher, and renal function worse. Changes in urinary sodium excretion in these three groups are shown in Figure 1B and reveal a significant difference in total urinary sodium excretion at 6 h, 24 h and a trend at 48 h, after which no difference is observed anymore. In contrast, patients with lower urinary sodium excretion in the first 6 h, only had significant lower urinary output up to 24 h, while after 48 h, urinary output was similar (Table 2). The amount of equivalent intravenous furosemide dose given in the first 6 h was slightly higher in patients in the lower tertile of urinary sodium excretion, but the subsequent days this was similar. Online supplementary Table S1 shows the baseline characteristics when stratified above and below a urine output of 900 mL/6 h (which corresponds to 150 mL/h as deemed appropriate diuretic response). Differences in baseline characteristics between poor and adequate diuresis were remarkably similar to differences obtained when stratified for tertiles of urinary sodium.

In univariate regression analysis, variables associated with severity and duration of heart failure, and markers of renal function and loop diuretic use pre-admission were the most prominent predictors of urinary sodium excretion (Table 3). In multivariable regression analysis, only younger age, female gender, lower eGFR and loop diuretic use before admission were independently associated with lower urinary sodium excretion after 6 h (Table 3). In a subset of patients (n = 97), serum chloride was available, and in this small subset, lower serum chloride at admission was a prominent predictor of lower urinary sodium excretion (standardized beta = 0.347, P < 0.001, adjusted for age, gender, eGFR and loop diuretic use pre-admission).

There was a strong association between sodium excretion and urinary volume after 6 h (standardized beta = 0.899, P < 0.001). We observed a non-linear relationship between absolute urinary sodium excretion and urinary sodium concentration. In the lower ranges of both total excretion and concentration there was a linear association, which flattened with higher total urinary sodium excretion, with almost no patients having a urinary sodium concentration >150 mmol/L (Figure 2). This also meant that there was only a weak association between urinary sodium concentration after 6 h and urinary volume during the same time period (standardized beta = 0.297, P < 0.001).

Urinary sodium excretion after 6 h was a strong predictor of total urinary volume after 24 h (standardized beta = 0.702, P < 0.001) (Figure 3), whereas urinary sodium concentration showed only a weak association (standardized beta = 0.252, P = 0.002). As compared with the lowest tertile of urinary sodium excretion at 6 h, patients in the middle and highest tertile were more likely to achieve <3 L of diuresis in the first 24 h [odds ratio 6.1 (1.6–22.7), and 44.9 (11.9–169), P = 0.008 and P < 0.001, respectively]. In absolute numbers, only 27% of patients achieved >3 L diuresis after 24 h in the lowest tertile, vs. 73% and 94% in the middle and highest tertile. Online supplementary Table S2 summarizes correlations between different cardiorenal variables of interest.

After a median follow-up of 257 (152–427) days, a total of 57 patients (33%) died, and 41 (23%) were rehospitalized for heart
Table 1 Baseline characteristics stratified by tertiles of urinary sodium excretion at 6 h

| Variable                        | Total cohort | Tertiles of 6 h urinary sodium | P-value |
|---------------------------------|--------------|--------------------------------|---------|
|                                 |              | < 89 mmol | 89–187 mmol | > 187 mmol |
| **Patients, n**                 | 175          | 59 (34)   | 58 (33)     | 58 (33)     | 0.09    |
| Age (years)                     | 71 ± 14      | 69 ± 13   | 74 ± 12     | 70 ± 15     | 0.37    |
| Females, n (%)                  | 77 (44)      | 30 (51)   | 25 (43)     | 22 (38)     | 0.61    |
| Caucasian race (%)              | 99           | 98        | 98          | 100         | 0.61    |
| SBP (mmHg)                      | 133 ± 31     | 123 ± 36  | 140 ± 28    | 136 ± 28    | 0.112   |
| DBP (mmHg)                      | 82 ± 22      | 77 ± 22   | 81 ± 17     | 88 ± 25     | 0.023   |
| HR (mmHg)                       | 96 ± 29      | 90 ± 22   | 92 ± 26     | 105 ± 36    | 0.014   |
| NYHA class III/IV (%)           | 84           | 79        | 83          | 81          | 0.41    |
| NYHA (%)                        | 36 ± 15      | 36 ± 15   | 36 ± 15     | 36 ± 16     | 0.99    |
| Categorical                     |              |           |             |             | 0.61    |
| >40%                            | 54           | 46        | 57          | 59          |         |
| 40–50%                          | 13           | 17        | 10          | 12          |         |
| ≥50%                            | 33           | 37        | 33          | 29          |         |
| De novo HF (%)                  | 36           | 25        | 34          | 48          | 0.035   |
| Main cause (%)                  |              |           |             |             | 0.94    |
| Ischaemic heart disease (%)     | 46           | 43        | 50          | 45          |         |
| Dilated cardiomyopathy (%)      | 12           | 16        | 10          | 12          |         |
| Hypertrophic cardiomyopathy (%) | 1            | 2         | –           | –           |         |
| Congenital heart disease (%)    | 1            | –         | 2           | 2           |         |
| Valvular heart disease (%)      | 12           | 12        | 10          | 14          |         |
| Hypertension (%)                | 17           | 14        | 19          | 17          |         |
| Other/unknown (%)               | 11           | 14        | 9           | 10          |         |
| Medical history (%)             |              |           |             |             |         |
| Myocardial infarction (%)       | 38           | 42        | 34          | 36          | 0.66    |
| Hypertension (%)                | 59           | 48        | 66          | 64          | 0.11    |
| Diabetes mellitus (%)           | 41           | 46        | 43          | 33          | 0.32    |
| Cerebrovascular accident (%)    | 15           | 14        | 14          | 17          | 0.82    |
| COPD (%)                        | 17           | 19        | 16          | 17          | 0.90    |
| Cancer (%)                      | 30           | 34        | 34          | 22          | 0.28    |
| Medical therapy (%)             |              |           |             |             |         |
| ACEI (%)                        | 42           | 45        | 41          | 39          | 0.81    |
| ARB (%)                         | 18           | 18        | 14          | 21          | 0.59    |
| Beta-blocker (%)                | 66           | 68        | 71          | 60          | 0.43    |
| MRA (%)                         | 31           | 39        | 31          | 25          | 0.27    |
| Loop diuretic (%)               | 61           | 80        | 60          | 44          | 0.002   |
| Daily dose loop diuretic (%)    |              |           |             |             | <0.001  |
| Overall (mg)                    | 40 (0–80)    | 80 (40–120)| 40 (0–80)  | 40 (0–40)  |         |
| >0–40 mg (%)                    | 46           | 34        | 52          | 63          |         |
| >40–80 mg (%)                   | 25           | 32        | 21          | 17          |         |
| >80 mg (%)                      | 29           | 34        | 27          | 21          |         |
| ICD (%)                         | 25           | 29        | 24          | 21          | 0.59    |
| CRT (%)                         | 11           | 15        | 12          | 5           | 0.21    |
| Inotropes during admission (%)  | 14           | 29        | 4           | 6           | <0.001  |
| Vasopressors during admission   | 12           | 25        | 6           | 4           | 0.002   |
| Length of stay (days)           | 7 (5–13)     | 8 (5–16)  | 7 (5–10)    | 7 (5–9)     | 0.21    |
| Laboratory at baseline         |              |           |             |             |         |
| NT-proBNP (pg/mL)               | 5263 (2938–10 489) | 8955 (3255–16 789) | 4275 (2807–8205) | 4422 (2970–7853) | 0.007 |
| Serum creatinine (μmol/L)       | 112 (86–148) | 144 (97–211) | 114 (88–136) | 91 (74–113) | <0.001 |
| eGFR (mL/min/1.73 m²)           | 53 ± 26      | 44 ± 30   | 51 ± 20     | 65 ± 23     | <0.001 |
| Sodium (mmol/L)                 | 135 ± 15     | 136 ± 5   | 135 ± 18    | 136 ± 18    | 0.82    |
| Potassium (mmol/L)              | 4.4 ± 0.8    | 4.5 ± 1.0 | 4.3 ± 0.9   | 4.3 ± 0.6   | 0.37    |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-debrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

*LVEF was either known before hospitalization or measured during hospitalization (n = 157).

*Only available in 146 patients.
### Table 2: Urinary measurements in the first 96 h according to urinary sodium excretion after 6 h

| Urinary measurements                  | Tertiles of 6 h urinary sodium | P-value |
|---------------------------------------|--------------------------------|---------|
|                                       | < 89 mmol                      | 89–187 mmol | > 187 mmol |
| Urinary sodium (mmol)                 |                                |          |          |
| First 6 h                             | 45 (26–67)                     | 130 (110–159) | 264 (229–350) | < 0.001 |
| 6–24 h (n = 161)                      | 133 (76–205)                   | 212 (156–333) | 256 (135–396) | < 0.001 |
| 24–48 h (n = 105)                     | 113 (68–209)                   | 197 (98–273)  | 192 (132–264) | 0.088  |
| 48–72 h (n = 87)                      | 120 (55–206)                   | 139 (97–178)  | 106 (56–147)  | 0.31   |
| 72–96 h (n = 46)                      | 116 (75–227)                   | 116 (91–159)  | 95 (33–160)   | 0.59   |
| Urinary volume (mL)                   |                                |          |          |
| First 6 h                             | 650 (400–900)                  | 1365 (1200–1600) | 2300 (2050–3000) | < 0.001 |
| 6–24 h (n = 161)                      | 1900 (1450–2250)              | 2200 (1700–3050) | 2740 (1700–3300) | 0.011  |
| 24–48 h (n = 105)                     | 2275 (1313–2725)              | 2285 (1600–2925) | 2175 (1700–2675) | 0.72   |
| 48–72 h (n = 87)                      | 2225 (1300–2850)              | 2010 (1520–2400) | 1550 (1000–2100) | 0.035  |
| 72–96 h (n = 46)                      | 1750 (1300–2200)              | 1720 (1400–2400) | 1840 (1500–2100) | 0.99   |
| Total dose i.v. furosemide (mg)*      |                                |          |          |
| Furosemide equivalent in first 6 h    | 100 (60–130)                   | 90 (50–123)  | 108 (65–130)  | 0.74   |
| First 24 h                            | 268 (171–400)                 | 212 (167–282) | 220 (138–280) | 0.042  |
| 24–48 h                               | 120 (0–300)                   | 80 (20–188)  | 80 (20–160)   | 0.19   |
| 48–72 h                               | 57 (0–240)                    | 40 (0–120)   | 40 (0–100)    | 0.59   |
| 72–96 h                               | 80 (0–200)                    | 40 (0–120)   | 20 (0–80)     | 0.18   |

*Recalculated according to: [total i.v. dose/40 mg + (total oral dose)/80 mg] [recalculated to furosemide (bumetanide 1 mg – 40 mg furosemide, no torsemide use in our cohort].

### Table 3: Univariate and multivariable regression analysis for 6 h urinary sodium excretion

|                        | Univariate                      | Multivariable                   |
|------------------------|---------------------------------|---------------------------------|
|                        | Standardized beta | P-value | Standardized beta | P-value |
| Age                    | −0.003 | 0.97 | 0.163 | 0.023 |
| Female                 | −0.144 | 0.058 | −0.169 | 0.013 |
| Length of stay         | 0.159 | 0.037 |                      |
| Admission SBP          | 0.178 | 0.021 |                      |
| Admission DBP          | 0.205 | 0.007 |                      |
| Admission HR           | 0.220 | 0.003 |                      |
| History of heart failure | −0.263 | < 0.001 |                      |
| Time since diagnosis   | −0.280 | < 0.001 |                      |
| History of diabetes    | −0.132 | 0.082 |                      |
| History of cancer      | −0.135 | 0.074 |                      |
| Serum creatinine at admission | −0.322 | < 0.001 |                      |
| eGFR at admission      | 0.394 | < 0.001 | 0.339 | < 0.001 |
| BUN at admission       | −0.347 | < 0.001 |                      |
| Chloride at admission  | 0.304 | 0.002 |                      |
| Log NT-proBNP          | −0.184 | 0.016 |                      |
| Nitrate use first 24 h | 0.200 | 0.017 |                      |
| Loop diuretic use before admission | −0.386 | < 0.001 | −0.319 | < 0.001 |
| MRA use before admission | −0.172 | 0.024 |                      |
| BB use before admission | −0.134 | 0.081 |                      |

BB, beta-blocker; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.

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failure. Urinary sodium excretion after 6 h was a strong predictor of all-cause mortality [hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.02–1.08, \( P = 0.001 \) per 10 mmol decrease in urinary sodium excretion]. Also urinary volume after 6 h (HR 1.05, 95% CI 1.01–1.08, \( P = 0.007 \) per 100 mL decrease in urine output) and urinary sodium concentration (HR 1.16, 95% CI 1.06–1.26, \( P = 0.001 \) per 10 mmol/L decrease in urinary sodium excretion) were strong predictors of mortality. The association with heart failure rehospitalization was less strong for urinary sodium excretion (HR 1.03, 95% CI 1.00–1.07 per 10 mmol decrease), and was not statistically significant for both urinary volume and urinary sodium concentration. Table 4 shows the univariate and multivariable Cox regression for the variables of interest. Both indices of urinary sodium excretion (absolute and concentration) were independent predictors of all-cause mortality, but not heart failure rehospitalization. After correction for either urinary volume or urinary sodium excretion (depending on the variable of interest), only indices of urinary sodium excretion remained independent predictors of outcome (Table 4). In univariate (but not multivariable) analysis, there was a significant, but weak interaction between urinary sodium excretion and urinary volume after 6 h. The association between urinary sodium excretion and death was stronger when urinary volume after 6 h was lower (online supplementary Figure S7). Urinary sodium excretion also predicted the combined endpoint of all-cause mortality and heart failure rehospitalization (HR 1.04, 95% CI 1.01–1.07 per 10 mmol decrease, \( P = 0.005 \)) (online supplementary Figure S2).

When stratified for tertiles of urinary sodium excretion at 6 h, this resulted in a HR 3.81 (95% CI 1.92–7.57, \( P < 0.001 \)) for the lowest vs. the highest tertile, while the middle tertile did not show a significant difference with the highest tertile, and this is visually depicted in Figure 4. After multivariable adjustment, this association remained significant (adjusted HR 4.66, 95% CI 2.07–10.5, \( P < 0.001 \)) (Table 4). Patients with missing urinary sodium measurement had similar outcome to those patients with sodium excretion in the middle or highest tertile (online supplementary Figure S3). Online supplementary Figure S4 shows the association between poor vs. adequate diuresis at 6 h and mortality.

Discussion

We showed that total lower urinary sodium excretion during the first 6 h after the initiation of intravenous loop diuretic therapy in patients admitted for AHF was associated with lower urine output after 24 h and with a higher risk of mortality during follow-up. Lower urinary sodium excretion, a marker of poor diuretic response, was especially found in younger patients, preferably males with evidence of renal dysfunction and already on loop diuretic therapy before hospital admission. Finally, we found that excretion of sodium (and water) is greatest during the first 24–48 h and declines afterwards.

The main treatment goals in AHF are early, safe and effective decongestion, and prevention of early rehospitalization and mortality.\(^2\)\(^3\)\(^6\) Many treatments have been investigated to improve clinical outcome, but to date the primary choice of decongestive therapy is still loop diuretics. However, there is a lack of consensus on the guidance of loop diuretic treatment, which may be one reason why residual congestion at discharge is still frequent, and associated with worse clinical outcome.\(^3\)\(^10\) The paucity of data that are available on loop diuretic strategies mainly focus on route and dose of loop diuretic therapy, suggesting only minor differences between treatment strategies.\(^11\) Also, there have been no novel easy, reliable, cheap and stable biomarkers that can serve as response variable in AHF (with or without renal dysfunction), either in plasma or urine, although urinary markers may be better as response variable of diuretic therapy.\(^12\)\(^13\)

Effective decongestion achieved by a good diuretic response is associated with favourable outcomes.\(^5\)\(^7\) Diuretic response may be assessed by many different measurements, but generally takes a few days to calculate (i.e. weight change, diuresis or natriuresis per amount of furosemide used over a few days).\(^6\) How to guide effective diuretic treatment to achieve a favourable diuretic response, resulting possibly in improved clinical outcomes, is largely unknown. It is remarkable that no reliable, scientifically validated response variable is available for loop diuretic treatment, in the light of other treatments such as statins and anti-hypertensives.
where cholesterol and blood pressure are easy and cheap response variables to guide treatment. Historically, adjustment of diuretic therapy in AHF is mostly based on changes in symptoms and signs, vital signs, diuresis, weight changes and sometimes electrolytes and renal function. However, these estimates are notoriously inaccurate and do not capture the pharmacological effect loop diuretics exert when they are used.

Recently, a position paper on diuretic therapy has proposed to use a biologically plausible response variable early after diuretic initiation, which could be either urinary sodium concentration and/or urinary volume. There are, however, only limited data on urinary sodium excretion in (acute) heart failure to provide scientific back up for the proposed algorithm. Singh et al. showed in 52 patients with AHF that urinary sodium was associated with diuretic response, and together with urinary furosemide concentrations was also associated with clinical outcome. In a larger study, lower urinary sodium concentration at admission was associated with more evidence of neurohormonal activation, poorer diuretic response, and also worse clinical outcome. In another study including over 170 advanced heart failure patients admitted to an ambulatory heart failure clinic, urinary sodium was associated with 3 h diuresis, and with subsequent heart failure events. In a recent paper, the importance of lower urinary sodium excretion in the week before a heart failure readmission has been shown, highlighting the pathophysiological importance of urinary sodium excretion. In data from ROSE-AHF, urinary sodium excretion was also associated with clinical outcome.

### Table 4 Cox regression analysis

| Variable | All-cause mortality | HF rehospitalization |
|----------|---------------------|----------------------|
|          | HR (95% CI) | P-value | HR (95% CI) | P-value |
| 6 h urinary sodium excretion (per 10 mmol decrease) | 1.05 (1.02–1.08) | 0.001 | 1.03 (1.00–1.07) | 0.033 |
| 6 h urinary sodium excretion (tertiles) | | | | |
| Highest tertile (>187 mmol) | 1.00 (ref) | – | 1.00 (ref) | – |
| Middle tertile (89–187 mmol) | 1.29 (0.59–2.84) | 0.53 | 1.39 (0.75–2.56) | 0.29 |
| Lowest tertile (<89 mmol) | 3.81 (1.92–7.57) | <0.001 | 3.11 (1.79–5.42) | <0.001 |
| 6 h urinary sodium concentration (per 10 mmol/L decrease) | 1.16 (1.06–1.26) | 0.001 | 1.07 (0.96–1.18) | 0.23 |
| 6 h urinary volume (per 100 mL decrease) | 1.05 (1.01–1.08) | 0.007 | 1.04 (1.00–1.07) | 0.056 |
| Adjusted for age, gender and eGFR | | | | |
| 6 h urinary sodium excretion (per 10 mmol decrease) | 1.06 (1.02–1.10) | 0.002 | 1.03 (0.99–1.06) | 0.15 |
| 6 h urinary sodium excretion (tertiles) | | | | |
| Highest tertile (>187 mmol) | 1.00 (ref) | – | 1.00 (ref) | – |
| Middle tertile (89–187 mmol) | 1.18 (0.52–2.68) | 0.69 | 1.27 (0.68–2.37) | 0.46 |
| Lowest tertile (<89 mmol) | 4.41 (2.06–9.43) | <0.001 | 3.15 (1.72–5.79) | <0.001 |
| 6 h urinary sodium concentration (per 10 mmol/L decrease) | 1.22 (1.10–1.35) | <0.001 | 1.05 (0.94–1.18) | 0.37 |
| 6 h urinary volume (per 100 mL decrease) | 1.04 (1.00–1.08) | 0.035 | 1.02 (0.98–1.07) | 0.24 |
| Adjusted for sodium or volume excretion (depending on the variable of interest) | | | | |
| 6 h Urinary sodium excretion – adjusted for 6 h urinary volume (per 10 mmol decrease) | 1.06 (1.02–1.10) | 0.002 | 1.01 (0.98–1.05) | 0.50 |
| 6 h urinary sodium excretion (tertiles) – adjusted for 6 h urinary volume | | | | |
| Highest tertile (>187 mmol) | 1.00 (ref) | – | 1.00 (ref) | – |
| Middle tertile (89–187 mmol) | 1.36 (0.58–3.19) | 0.48 | 1.25 (0.65–2.41) | 0.51 |
| Lowest tertile (<89 mmol) | 4.66 (2.07–10.5) | <0.001 | 2.92 (1.54–5.53) | 0.001 |
| 6 h urinary sodium concentration (per 10 mmol/L decrease) | 1.25 (1.11–1.41) | <0.001 | 1.01 (0.89–1.14) | 0.91 |
| 6 h urinary volume (per 100 mL decrease) | 1.04 (1.00–1.08) | 0.036 | 1.01 (0.97–1.05) | 0.64 |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.
after 24 h was associated with mortality, even in the setting of a negative fluid balance. Finally, Biegus et al. recently reported on spot urinary sodium concentration in little over 100, mostly male, AHF patients. In this prospective cohort, they found a small increase in spot urinary sodium concentration after admission (and start of intravenous diuretic), followed by a decrease. They also showed that lower urinary sodium concentration was associated with increased 1-year mortality rates, independent of covariates, and that a decrease in urinary sodium concentration was also associated with all-cause mortality. However, none of these studies investigated absolute sodium excretion as early as 6 h after start of diuretic therapy.

Our results further extend the above-mentioned findings, in a somewhat larger more contemporary AHF cohort. Furthermore, we used sequential, timed urine collections, and a population that includes almost 50% females, as well as patients with both reduced and preserved ejection fraction, and with more advanced age. We also found a decrease in urinary sodium excretion after 24 h, which could be due to multiple causes. First, it could be that this a true biological effect; diuretic response might be more effective when congestion is still more severe, although also the opposite might be true as well. Second, after an initial favourable response, clinicians might be tempted to decrease the diuretic dose after the initial 24 h, thereby limiting natriuresis after 24 h. Third, neurohormonal activation and the braking phenomenon may play a role after (high-dose) loop diuretic initiation.20

We also found that patients with the poorest sodium excretion ([arbitrary <87 mmol (lowest tertile)] did not improve their sodium excretion at 24 h or 48 h, which might be due to intrinsic diuretic resistance, underdosing of diuretics, more severe congestion, or lower eGFR in this patient group. Since this group also comprised patients with more frequent long-term loop diuretic therapy, also intrarenal alterations such as tubular hypertrophy might limit the response to intravenous diuretics.20 It is important to note that our study is unique as we evaluated total urinary sodium over 6 h, rather than spot urinary sodium concentration. The latter is a very early and good representation of diuretic and natriuretic response when it is evaluated quickly after initiation (1–2 h), but after more than 5–6 h, the initial peak plasma concentration after a bolus of intravenous diuretic therapy will have subsided. What remains after 6 h in spot urine sodium concentration is still too some extent a measurement of natriuretic response, and associated with clinical outcome, but does not really capture the overall response to initial diuretic therapy. Both entities track well in the lower ranges of urinary sodium, but with more diuresis and more sodium excretion, the limit of urinary sodium concentration (and dilution) is reached at around 150 mmol/L, rarely exceeding this. Sodium excretion beyond this figure is solely dependent on more diuresis (free water excretion/clearance), rather than further increase in sodium concentration of urine. Therefore, on a continuous scale over the entire spectrum, assessment of total urinary sodium excretion might be preferred over urinary sodium concentration. One additional reason might also be the strong association between urinary sodium excretion and subsequent urinary output, in our study after 24 h. The odds of achieving more than 3 L of diuresis in the first 24 h was much higher in patients in the highest tertile of urinary sodium excretion compared with the lowest (94% vs. 27%). Testani et al.1 already established a formula to estimate 6 h urine output based on a spot urine sodium measurement after 1–2 h in a small number of patients, and our current analysis further support this finding. In contrast to measurement of urinary volume, indices of urinary sodium were independently associated with worse outcome, which may be a reason to use natriuresis rather than diuresis. It has to be acknowledged, however, that to calculate total urinary sodium excretion,
measurement of urinary volume is also necessary. In the end, effective natriuresis coupled with effective diuresis with subsequent decongestion is the treatment goal with loop diuretic therapy.

Finally, as also found by earlier, smaller studies, we found that lower urinary sodium (either absolute or concentration) was associated with all-cause mortality.\textsuperscript{14,19} This association was found, independent of urinary volume in the same time frame, and the risk associated with lower urinary sodium excretion was stronger when urinary volume was lower. Surprisingly, we did not find such a strong association with heart failure rehospitalization, but this might be due to competing risk, since the patients with very low urinary sodium excretion had a very high risk of mortality. Overall, together with the recent findings by Biegus \textit{et al.},\textsuperscript{19} our findings establish early urinary sodium excretion after initiation of loop diuretic therapy in AHF as an important prognostic marker, on top of established markers of prognosis. We have to realize that all studies, including our current analyses, found associations and claim a causal relationship between targeting higher urinary sodium excretion and better outcomes. Even if this is plausible from pathophysiology and findings from our and previous studies, interventional studies should be conducted to proof causality.

Limitations

This was a single-centre study in a tertiary heart failure centre, which means our AHF population might be slightly younger and have more advanced heart failure compared with the more general heart failure population. This may also be the reason by which we found a lower urinary sodium excretion associated with lower age; probably these patients had more advanced heart failure. Urinary sodium measurements and volume assessment were carried out as part of clinical care, which also meant treating physicians were unblinded to these results and may have adapted their therapy on the basis of both urinary volume and sodium excretion. There was, however, no protocol that reported a pre-specified loop diuretic dose or dose adjustment based on urinary sodium levels. Because this is also a reflection of the real-world situation, we unfortunately had a lot of missing urinary data after day 2, where it seemed that protocol adherence by the medical staff to evaluate diuresis and natriuresis was suboptimal. Our results need validation in a prospective, perhaps even interventional study.

Conclusions

Low urinary sodium excretion, during the first 6 h after initiation of loop diuretic therapy in AHF, is associated with lower urine output in the first day and with all-cause mortality independent of urinary volume.

Supplementary Information

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

Table S1. Baseline characteristics stratified by urinary volume \(<\geq 900\text{mL} \text{ at } 6\text{ h})$. 

| Table S2. Correlation between cardioiuremarkerallost. | Figure S1. Interaction between 6 h urinary sodium excretion and urinary volume with respect to hazard for all cause mortality. | Figure S2. Relationship between tertiles of urinary sodium excretion and the combined endpoint of all-cause mortality and heart failure rehospitalization. | Figure S3. Kaplan–Meier curve including patients with missing urinary sodium measurements. | Figure S4. Kaplan–Meier curve for all-cause mortality according to poor vs. adequate diuresis \(<\geq 900\text{mL} \text{ at } 6\text{ h})$. |

Conflict of interest: none declared.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Comin-Colet J, Cyrys J, De Caterina R, Galie N, Hindricks G, Janicki S, Joyner M, Lancellotti P, Lip GYH, Lindorf L, Nt大量cella V, van Domburg RT, Humbert M, Voors AA, European Society of Cardiology. ESC guidelines for the diagnosis \& treatment of acute and chronic heart failure: the Task Force for the diagnosis \& treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. \textit{Eur J Heart Fail} 2016;18:891–975.

2. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Lanbi S, Ristic AD, Lambriou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital \& early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. \textit{Eur J Heart Fail} 2015;17:544–558.

3. Rubio-Gracia J, Demissie BG, Ter Maaten JM, Cleden GJ, O’Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, Givertz MM, Bloomfield DM, Districh H, Damman K, Perez-Calvo JL, Voors AA. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. \textit{Int J Cardiol} 2018;258:185–191.

4. ter Maaten JH, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure – pathophysiology, evaluation, and therapy. \textit{Nat Rev Cardiol} 2015;12:184–192.

5. Valente MA, Voors AA, Damman K, van Veldhuisen DJ, Massie BM, O’Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleden GJ, Givertz MM, Bloomfield DM, Fuziat M, Districh HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. \textit{Eur Heart J} 2014;35:1284–1293.

6. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH, Mullens W. The kidney in congestive heart failure: ‘are natriuresis, sodium, and diuretics really the good, the bad and the ugly?’. \textit{Eur J Heart Fail} 2014;16:133–142.

7. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. \textit{Circ Heart Fail} 2014;7:261–270.

8. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. \textit{Eur J Heart Fail} 2019;21:137–155.

9. Valente MA, Hillege HL, Navis G, Voors AA, Dunseldham PH, van Veldhuisen DJ, Damman K. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. \textit{Eur J Heart Fail} 2014;16:86–94.

10. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovaneli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. \textit{Circ Heart Fail} 2012;5:54–62.
11. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascetti AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797–805.

12. van Veldhuisen DJ, Ruilope LM, Maisel AS, Damman K. Biomarkers of renal injury and function: diagnostic, prognostic and therapeutic implications in heart failure. *Eur Heart J* 2016;37:2577–2585.

13. Damman K, Ng Kam Chuen MJ, MacFadyen RJ, Lip GY, Gaze D, Collinson PO, Hillege HL, van OW, Voors AA, Van Veldhuisen DJ. Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. *J Am Coll Cardiol* 2011;57:2233–2241.

14. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail* 2014;20:392–399.

15. Honda S, Nogi T, Nishimura K, Nakai M, Honda Y, Nakano H, Iwakami N, Sugano Y, Asaumi Y, Aiba T, Noguchi T, Kusano K, Yokoyama H, Ogawa H, Yasuda S, Anzai T; NaDEF Investigators. Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure. *Int J Cardiol* 2018;254:189–194.

16. Brinkley DM Jr, Burpee Lj, Chaudhry SP, Smallwood JA, Lindenfeld J, Lakdawala NK, Desai AS, Stevenson LW. Spot urine sodium as triage for effective diuretic infusion in an ambulatory heart failure unit. *J Card Fail* 2018;24:349–354.

17. Martens P, Dupont M, Verbrugge FH, Damman K, Degryse N, Nijst P, Rengers C, Penders J, Tang WH, Testani J, Mullens W. Urinary sodium profiling in chronic heart failure to detect development of acute decompensated heart failure. *JACC Heart Fail* 2019;7:404–414.

18. Hodson DZ, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J, Wilson FP, Tang WH, Rao VS, Collins SP, Mullens W, Testani JM. Natriuretic response is highly variable and associated with 6-month survival: insights from the ROSE-AHF trial. *JACC Heart Fail* 2019;7:383–391.

19. Biegus J, Zymlinski R, Sokolski M, Todd J, Cotter G, Metra M, Jankowska EA, Banasiak W, Ponikowski P. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. *Eur J Heart Fail* 2019;21:624–633.

20. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2017;377:1964–1975.

21. Testani JM, Hanberg JS, Cheng S, Rao V, Onyebake C, Laur O, Kula A, Chen M, Wilson FP, Darlington A, Bellumkonda L, Jacoby D, Tang WH, Parikh CR. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. *Circ Heart Fail* 2016;9:e002370.