ESC European Society of Cardiology

European Journal of Heart Failure (2020) **22**, 1438–1447
doi:10.1002/ejhf.1753

RESEARCH ARTICLE

Clinical importance of urinary sodium excretion in acute heart failure

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Received 12 September 2019; revised 22 December 2019; accepted 12 January 2020; online publish-ahead-of-print 22 February 2020

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]

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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.[8] 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 congestion, requiring intravenous diuretic therapy.[1] 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 m^2).[9]

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.

Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation, non-normally distributed variables as median and 25th–75th percentile. Categorical variables are presented as numbers (percentage). Differences in baseline characteristics based on high or low urinary sodium at 6 h was evaluated using either *t*-test, chi-square or Mann–Whitney U test, as appropriate. Baseline characteristics were split based on tertiles of urinary sodium levels at 6 h. Univariate and multivariable linear regression analysis was carried out for the association between urinary sodium at 6 h and baseline characteristics at admission. Multivariable stepwise linear regression analysis was carried out including all variables with $P < 0.1$ in univariate analysis. The association between urinary sodium concentration and absolute sodium excretion at 6 h was evaluated using fractional polynomial regression. The association between urinary sodium excretion and achieving 3 L of diuresis in the first 24 h was evaluated using logistic regression. The association between urinary sodium excretion at 6 h and clinical outcome was analysed using Cox proportional hazard analysis, on a continuous scale and stratified within tertiles with the highest tertile being the reference category. In multivariable Cox regression analysis, the variable of interest (urinary sodium excretion) was adjusted for age, gender and clinical variables associated with all-cause mortality in this dataset, including eGFR, N-terminal pro-brain natriuretic peptide (NT-proBNP), heart rate, QRS width, *de novo* vs. known heart failure, history of chronic obstructive pulmonary disease or coronary artery disease. The proportional hazard assumption was checked using Schoenfeld residuals. First-degree interactions between variables of interest were evaluated. Visual depiction of the interaction between urinary sodium excretion and volume was established using marginal effects. Two-tailed *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using STATA SE 12.0 (Stata Corp., College Station, TX, USA).

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 m^2).

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 proofed to be more difficult at

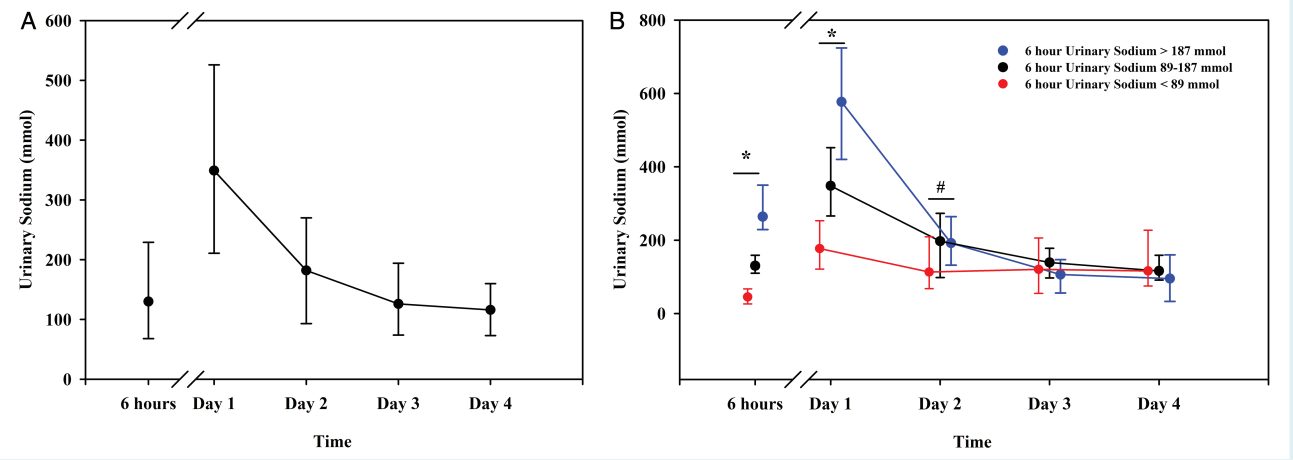

Figure 1 (*A*) Change in urinary sodium excretion in the first 4 days after admission. (*B*) Change in urinary sodium excretion in the first 4 days after admission stratified for tertiles of urinary sodium excretion at 6 h. *$P < 0.001$, #$P = 0.088$.

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)	
Age (years)	71 ± 14	69 ± 13	74 ± 12	70 ± 15	0.09
Females, *n* (%)	77 (44)	30 (51)	25 (43)	22 (38)	0.37
Caucasian race (%)	99	98	98	100	0.61
SBP (mmHg)	133 ± 31	123 ± 36	140 ± 28	136 ± 28	0.012
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
LVEF (%)[a]	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 (furosemide equivalents)					< 0.001
Overall	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[b]	14	29	4	6	< 0.001
Vasopressors during admission[b]	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 m^2)	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-defibrillator; 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.

[a]LVEF was either known before hospitalization or measured during hospitalization (n = 157).

[b]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)[a]				
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

[a]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.

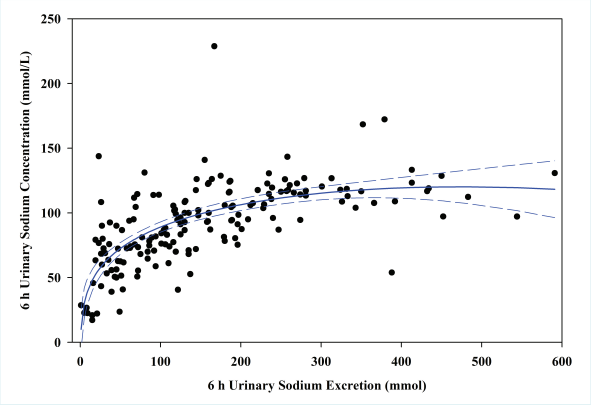

Figure 2 Non-linear association between total urinary sodium excretion and sodium concentration.

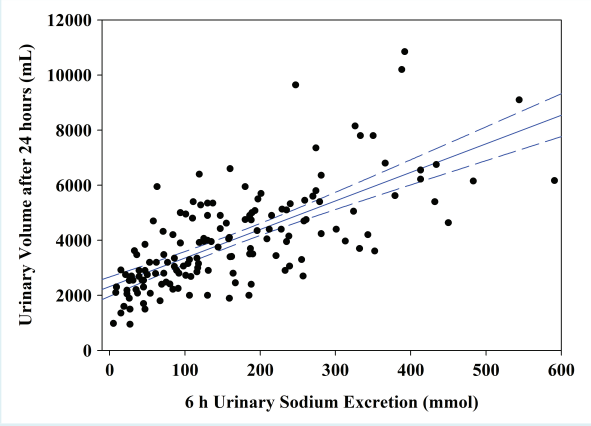

Figure 3 Association between 6 h urinary sodium excretion and total urinary volume after 24 h.

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 strong 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 S1*). 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.[1,2,8] 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

Table 4 Cox regression analysis

Variable	All-cause mortality		HF rehospitalization	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Univariate				
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 age, gender, eGFR, admission log NT-proBNP, admission HR, history of COPD, coronary artery disease, heart failure, QRS width				
6 h urinary sodium excretion (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)				
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
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)	1.09 (1.03–1.16)	0.005	1.04 (0.96–1.11)	0.34
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)	1.82 (0.67–4.90)	0.24	1.59 (0.73–3.45)	0.24
Lowest tertile (<89 mmol)	6.24 (1.94–20.0)	0.002	3.62 (1.38–9.49)	0.009
6 h urinary sodium concentration - adjusted for 6 h urinary volume (per 10 mmol/L decrease)	1.11 (1.01–1.22)	0.024	1.03 (0.92–1.14)	0.64
6 h urinary volume - adjusted for 6 h urinary sodium excretion (per 100 mL decrease)	1.05 (0.98–1.11)	0.16	1.00 (0.92–1.09)	0.98

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.

where cholesterol and blood pressure are easy and cheap response variables to guide treatment.[8] 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.[8] 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.*[14] 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.[15] 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.[16] 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.[17] In data from ROSE-AHF, urinary sodium excretion

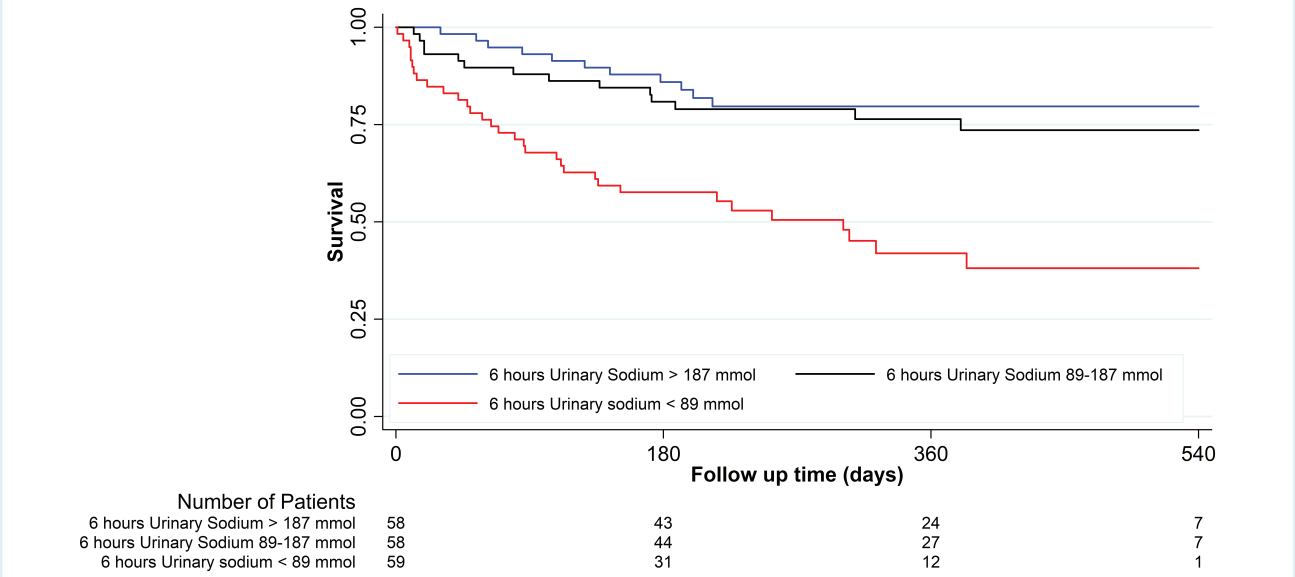

Figure 4 Kaplan–Meier curves for all-cause mortality stratified for tertiles of urinary sodium excretion at 6 h.

after 24 h was associated with mortality, even in the setting of a negative fluid balance.[18] Finally, Biegus *et al.*[19] 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.*[21] 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.[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 *et al.*,[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 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 </≥ 900 mL at 6 h.

Table S2. Correlation between cardiorenal markers.

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 (</≥900 mL after 6 h).

Conflict of interest: none declared.

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