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Maastricht University

Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen
master in de biomedische wetenschappen

Masterthesis

Home-based urinary sodium analysis in patients with chronic heart failure

Ruben Knevels

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

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BEGELEIDER :

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2024

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Abstract

Background – Chronic heart failure (CHF) is characterized by episodes of acute heart failure (AHF) and causes besides a high mortality and morbidity, a significant economic burden. Previous research provided evidence suggesting the role of urinary sodium concentration measurements in predicting an AHF episode. Currently, these measurements could not be performed at home, making this method less attractive. Therefore, we investigate whether it is possible to predict an AHF event in heart failure patients based on urinary sodium concentration with help of a home-based urinary sodium sensor.

Methods – Eighty stable CHF patients conducted home urinary sodium measurements twice weekly for 48 weeks. Follow-up visits were scheduled every three months to evaluate their volemic status.

Results – Preliminary data analysis of 21 CHF patients was performed in the context of a Master's thesis. Mean age was 65 ± 13 years and patients had a median NT-proBNP of 645 [286 – 2536] ng/L Analysis showed that urinary sodium excretion was highly interindividual different, but stable over time. In the duration of study follow-up, four acute heart failure events were registered. Visually, a drop in urinary sodium concentration could be witnessed, however statistically insignificant. Next to the morning sodium excretion, loop diuretic effect was assessed. All patients demonstrated an increase in sodium excretion post diuretic intake. However, magnitude varied between patients.

Conclusion – While a clear dip in urinary sodium excretion preceding AHF events was not statistically confirmed, significant insights into the loop-diuretic effect were observed. Further research is needed to validate these findings.

Introduction

Even with a rising prevalence, approximately 64.3 million people suffer from heart failure (HF) (1). This chronic condition is defined as 'clinical syndrome characterized by symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion' (2).

With an increasing age, the prevalence and incidence of HF augments. Over the years, multiple important risk factors have been elucidated. It has been established that HF is the consequence of accelerated cardiovascular aging, both affecting the vasculature and the heart. Some well-known risk factors are type 2 diabetes mellitus, obesity, arterial hypertension, coronary artery disease and valvular heart disease. In addition, in younger individuals, HF is rare and typically associated with specific causes that predominantly or exclusively affect the heart, such as genetic mutations, congenital heart disease, myocarditis, or myocardial toxicity (3).

Patient classification

In daily clinical practice, HF patients are classified in three groups according to their left ventricular ejection fraction (LVEF) (Table 1). Irrespective of the subtype of HF, all patient will show some degree of signs and symptoms of HF, as mentioned in the HF definition. These signs may not be clearly present in an early stage of the disease or in optimally treated patients (4).

Table 1: classification of HF subtypes based on LVEF (4).

Type of HF		**HFrEF**	**HFmrEF**	**HFpEF**
Criteria	1	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	2	LVEF ≤ 40%	LVEF 41% - 49%	LVEF ≥ 50%
	3	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricle diastolic dysfunction / raised LV filling pressures, including raised natriuretic peptides.

Acute heart failure

Since HF is a lifelong condition, all patients are classified as chronic heart failure (CHF) patients. The disease course is characterized by episodes of acute heart failure (AHF), which can be roughly subdivided into forward and backward failure. In forward failure, the heart struggles to pump enough blood around to oxygenate all tissues, thereby failing to meet the metabolic demands of the body (5). In backward failure, excess fluid accumulates in the body due to enhanced sodium reabsorption in the kidneys, causing signs and symptoms of congestion such as dyspnea, wheezing and peripheral oedema. These symptoms are the main reason to seek medical attention and are associated with increased morbidity and mortality (6). Despite the ongoing improvements in guideline-directed medical therapies (GDMT), hospitalization rates of HF patients due to AHF with congestion remain extremely high, as illustrated by recent HF trials (Table 2). Besides a diminished quality of life, these episodes are also the main driver for a substantial economic burden. A systematic review by Lesyuk et al. highlighted the considerable and growing economic burden of HF on the healthcare system. Approximately 1-2% of the global health budget is spent for HF each year, running up to billions of dollars in the US alone (7-9).

Table 2: Evolution event rate under new GDMT (10-13).

	PARADIGM		DAPA-HF		VICTORIA		EMPEROR	
Study	Sacubitril-Valsartan	Enalapril	Dapagliflozin	Placebo	Vericiguat	Placebo	Empagliflozin	Placebo
LVEF (%)	29.6% ± 6.1%	29.4% ± 6.3%	31.2% ± 6.7%	30.9% ± 6.9%	29.0% ± 8.3%	28.8% ± 8.3%	27.7% ± 6.0%	27.2% ± 6.1%
NT-proBNP (pg/mg)	1631	1594	1428	1446	1275	975	1887	1926
Event rate	21.8%	26.5%	16.3%	21.1%	35.5%	38.5%	19.4%	24.7%
Event rate hospitalization	12.8%	15.6%	9.7%	13.4%	27.2%	29.6%	13.2%	18.3%
Hazard ratio	0.80 (0.73 – 0.87)		0.74 (0.65 – 0.85)		0.90 (0.82-0.98)		0.75 (0.65 – 0.86)	

Renal sodium reabsorption

Elevated sodium avidity coupled with a positive sodium balance can be attributed to hemodynamic shifts and increased neurohormonal activity. The compromised contractility of the heart leads to a reduced cardiac output and heightened filling pressures, subsequently diminishing renal blood flow. This effect is partly aggravated by neurohormonal activation. To sustain the glomerular filtration rate, autoregulation enhances the filtration fraction by enhancing sodium and water reabsorption in the proximal tubule.

Despite overall volume overload in HF patients, heightened proximal sodium and water reabsorption results in reduced tubular flow in the distal nephron. Diminished blood flow in the vasa recta, combined with increased sodium reabsorption, creates a hypertonic interstitium in the renal medulla, establishing an osmotic pressure gradient. This, along with elevated arginine-vasopressin release due to angiotensin II activation, promotes free water retention in the collecting ducts and impairs the kidneys' diluting capacity.

The augmented sodium and parallel chloride reabsorption lead to decreased chloride concentration at the macula densa of the juxtaglomerular apparatus. This triggers the release of renin, perpetuating activation of the renin-angiotensin-aldosterone system (RAAS). This vicious cycle is the driving force behind congestion in HF patients. Considering that enhanced sodium reabsorption is the main driving factor for an event of AHF, measuring urinary sodium concentration holds promise as a method to predict an episode of congestion and subsequent AHF (14).

Current therapeutic approaches

Chronic Heart Failure

As mentioned before, HF treatment is based on the GDMT, which is continuously updated and published by the European Society of Cardiology (ESC). The current therapeutic approach in HFrEF and HFmrEF is based on quadruple HF therapy. This includes simultaneous treatment with an angiotensin receptor-neprilysin inhibitor (ARNI), beta blocker, mineralocorticoid receptor antagonist (MRA) and sodium-glucose cotransporter-2 (SGLT2) inhibitor.

In HFpEF, therapeutic guidelines deviate. While for a long time, no intervention has conclusively demonstrated efficacy in reducing morbidity and mortality, latest trials have proven a reduced risk of cardiovascular death and HF hospitalization in patients with HFpEF when treated with an SGLT2 inhibitor. Therefore, the ESC recommends treatment with an SGLT2 inhibitor together with identifying and addressing cardiovascular and non-cardiovascular comorbidities (4, 11, 13).

Despite the subtype of HF, there is a class I recommendation for loop diuretic therapy to relieve patients from signs and symptoms of congestion (15).

Quadruple HF therapy

The fundamental approach to HFrEF treatment involves the pharmacological modulation of the RAAS and sympathetic nervous system (15). In HF patients, neurohormonal upregulation of the RAAS system leads to an increased sodium avidity, compromising natriuresis. By blocking one or multiple RAAS components, this effect is reduced (14, 15). While Angiotensin converting enzyme inhibitors (ACE-I) and Angiotensin receptor blockers (ARB) modify this system both according to their specific mechanism, ARNI's have proven to induce a 23% reduction in all-cause mortality versus ACE-I/ARB in a HFmrEF/HFrEF population (16).

While the RAAS system functions as a complex cascade with multiple molecules to interfere with, the sympathetic nervous system in HF can be modulated with selective β1-receptor antagonists to show significant improvements. These molecules have not only shown to reduce morbidity and mortality in HF patients, but also reduce symptoms (17). By exerting adverse ionotropic and chronotropic effects, they relieve the heart's oxygen demand and consequently it's workload. β1 receptors are not only present in the heart, but also in the juxtaglomerular cells of the kidney. By blocking these receptors, the release of renin is reduced, thereby indirectly inhibiting the RAAS pathway (18).

MRAs function by blocking the mineralocorticoid receptor (MR), responsible for maintaining the Na^+/K^+ balance in the nephron. By blocking the MR, Na^+ will be excreted and K^+ will be reabsorbed, thereby promoting decongestion (19).

The latest addition to the list of HF medications are SGLT2 inhibitors. While initially employed for managing diabetes, recent findings indicate that SGLT2 inhibitors can effectively decrease hospitalizations in HF patients, irrespective of their diabetes status. There are many possible mechanisms through which SGLT2 inhibitors exert their cardioprotective mechanism, such as lowering the blood pressure, inhibiting the sympathetic nervous system, improving cardiac energy metabolism, but the added value in HF therapy is most-likely, but not exclusively, due to its pro-natriuretic effect (20, 21).

Monitoring of patients

Current monitoring techniques, including keeping track of changes in weight or blood pressure, have proven to be insufficient in preventing (re)hospitalization. A staggering 15% of HF patients are rehospitalized within 1 to 2 years, running up to even 27% within a year in patients with more advanced HF. The main risk period remains the first three months after hospitalization due to event of AHF, counting 25% of this patient population (14).

Therefore, it is important to closely follow these patients in order to prevent the need for rehospitalization. Early telemonitoring techniques, which often involved telephone support, comprised combinations of weight, diuresis, vital signs (e.g. blood pressure), and HF symptoms. However, multiple studies have demonstrated that these methods do not confer any benefit in terms of reducing HF hospitalizations (22). Technologies such as pulmonary artery pressure devices to monitor volume status or cardiac implantable electronic devices offer a valid way to remotely monitor patients and enable clinicians to timely detect worsening of HF. Unfortunately, these monitoring tools are invasive and not possible in all HF patients. Hence, there is an urgent need for new non-invasive monitoring methods in CHF patients (23).

As mentioned earlier, the increased sodium avidity and reduced natriuresis due to neurohumoral upregulation in AHF might be used as a monitoring tool. The analysis of urinary sodium could serve as a viable method for non-invasive monitoring of patients at home, particularly when individuals can conduct these measurements independently. Martens et al. were the first to demonstrate that there is a drop in urinary sodium excretion one week prior to the onset of AHF, but for now the exploration of employing a home-based tool to perform these measurements remains uncharted territory (24).

A Japanese firm called HORIBA group developed an advanced liquid sensor that can quantitatively measure the sodium concentration in a spot urinary sample (Figure 1). The ion-selective membrane interacts selectively with the pre-specified ions and generates a voltage that scales with concentration. Importantly, the sensor can be attached to a small stick, which allows an accurate, fast and reliable measurement of urinary sodium. In this clinical trial, we will investigate whether urinary sodium analysis with help of this home-based urinary sodium dipstick can be a valid tool to predict episodes of AHF in previously diagnosed CHF patients.

Figure 1: urinary sodium sensor

Materials & Methods

Study design

In this single-center, interventional cohort study, the possibility of urinary sodium analysis with help of a home-base urinary dipstick to predict episodes of AHF in CHF patients was evaluated. This trial was conducted at the Ziekenhuis Oost-Limburg, Genk, Belgium. During a period of 15 months, a total of 80 patients with CHF were included. Written informed consent was obtained from all patients prior to participation. The protocol was in accordance with the GCP guidelines and was approved by the local ethics committee (i.e. Ziekenhuis Oost-Limburg). This paper only reflects a part of the total study, as the study is still ongoing at the moment.

Study population

Patients were considered eligible when they were older than 18 years old, had stable CHF (i.e. no AHF hospitalization for the last three months) and received a stable dose of guideline directed medical therapy (GDMT) for the last three months. Patients who were deemed unable to follow the study protocol or patients who were scheduled for renal replacement therapy, were not included into the study.

Procedure and clinical follow-up

Patients who signed informed consent were asked to perform urinary sodium measurements with help of a urinary sodium sensor (HORIBA) twice weekly for a total period of 48 weeks. Patients who were taking loop diuretic medication were instructed to measure the urinary sodium in the morning twice, once before intake of diuretic and once two to four hours after intake. One time a week, patients were asked to register their weight, blood pressure, VAS dyspnea score, diuretic dose and to indicate any important changes in diet (Figure 2 + Figure S1).

Upon enrollment, a comprehensive evaluation was conducted, involving a medical examination, transthoracic echocardiography (TTE), and renal doppler ultrasound. Simultaneously, a blood sample was obtained to monitor variations in multiple parameters, including NT-pro-BNP, osmolality, plasma aldosterone, and direct renin concentrations.

Patients were contacted one week after enrollment to ensure correct usage of the sensor and active participation in taking measurements. Follow-up visits were scheduled at 12-week intervals, wherein the aforementioned diagnostic procedures were reiterated.

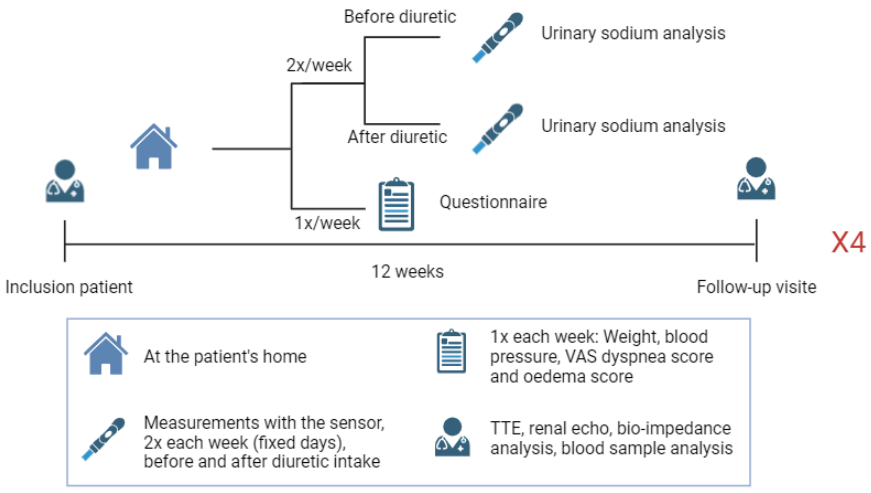

Figure 2: Study procedure and clinical follow-up

Urinary sodium dipstick

The urinary sodium sensor was developed by the HORIBA group and is capable of quantitively measuring sodium concentration in a spot urinary sample, as was previously validated by Meekers et al. (HFA, Heart Failure 2024 Lisbon, Meekers E.). The main working mechanism is based on the principle of ion-selective electrode, in which an ion-selective membrane interacts with the pre-specified ions, generating a voltage that scales with the concentration. The sensor is re-usable, but needs to be calibrated before each first measurement of the day with help of two standardized sodium concentrations. According to HORIBA, the sensor has a measuring range from 0.1-430 mmol/l (2-9900 ppm) (25).

Endpoints

The main study endpoint was described as a composite endpoint of the number of HF hospitalizations and urgent HF visits, including up-titration of chronic loop diuretic therapy. Secondary endpoint was described as number of HF hospitalizations or urgent HF visits.

Data collection

Baseline data collection consisted of demographic data, medical history and medication, obtained from the electronic patients' files of Ziekenhuis Oost-Limburg (HiX, Chipsoft, Netherlands). Together with urinary sodium measurements and data obtained from study-specific diagnostic procedures, all data was collected in the electronic case report form (Castor EDC, The Netherlands).

Statistical analysis

Statistical analysis was carried out with help of JMP Pro 17 (SAS Institute Inc., North Carolina, USA). Accompanying figures were made using Graphpad Prism version 10.2.3 for Windows. Normally distributed continuous variables were presented as mean ± standard deviation (SD), whereas not normally distributed continuous variables were presented as median [interquartile range (IQR)]. Normal distribution was checked with help of a Shapiro-Wilk test. Statistical significance of continuous baseline characteristics between unpaired groups was checked with an unpaired t-test when normally distributed, and with a Wilcoxon Rank-Sum test when not normally distributed. Paired non-parametric urinary sodium concentrations were compared using a Wilcoxon Signed-Rank test. Categorical data was presented as number (%) and checked with help of a Pearson chi-square test. Longitudinal urinary sodium concentrations over time were analyzed using linear mixed modeling for repeated measures including a fixed group (event or stable/high versus low excreter), time effect and its interaction and a random intercept. A Grubbs' test was performed to identify significant outliers. These outliers were removed from the data. Data was considered significant when $p<0.05$.

Results

Patient population

Between February 2023 and May 2024, a total of 80 patients were included in this trial. As this article forms part of a Master's internship and serves as a Master's thesis, only preliminary results are available. At the time of data analysis, 21 out of 80 patients had successfully completed at least their 3-month follow-up period. Baseline characteristics of these patients are presented in the left column of table 3. Patients had a mean age of 65 years old and were predominantly male. Most patients were diagnosed with HFrEF with an ischemic etiology. NYHA functional class together with HF symptoms showed that patients were mildly symptomatic, with the exception of one patient with NYHA functional class IV. High percentages of guideline directed HF therapy tend to reflect proper implementation of quadruple HF therapy in this HFmrEF / HFrEF patient cohort. More than half of this patient cohort was actively treated with chronic loop diuretic therapy at home (> 3 months). Congestion status at baseline was determined based on comparison of left ventricular end diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP) and vena cava inferior diameter with previous, not study-related echocardiography images, revealing that no patients had signs of congestion at baseline.

Interindividual differences in urinary sodium concentration

Data was available from at least 20 measurements per individual (2x10 weeks) since some follow-up visits were scheduled prior to the 12 week follow-up period to accommodate the patient's convenience and/or to align with another scheduled hospital visit. A total of 939 first void measurements were collected. Plotting mean first void urinary sodium measurements reveals high interindividual differences, up to 92.93 mmol/L, with a mean urinary sodium concentration of 66.6 ± 25.5 mmol/L (Figure 3a). Based on these results, a distinction could be made between naturally high and naturally low sodium excreters (Figure 3b). The low excreter group consisted of 11 individuals with a mean urinary sodium concentration of 45.71 ± 12.22 mmol/L, whereas the high excreter group consisted of 10 individuals with a mean urinary sodium excretion of 87.98 ± 15.44 mmol/L. Comparing baseline characteristics between these groups revealed a higher prevalence of individuals with HFrEF of ischemic etiology (p=0.040) and a higher proportion of individuals on chronic loop therapy (p=0.017) in the low excreters group. Furthermore, baseline characteristics did not reveal any other significant differences (Table 3).

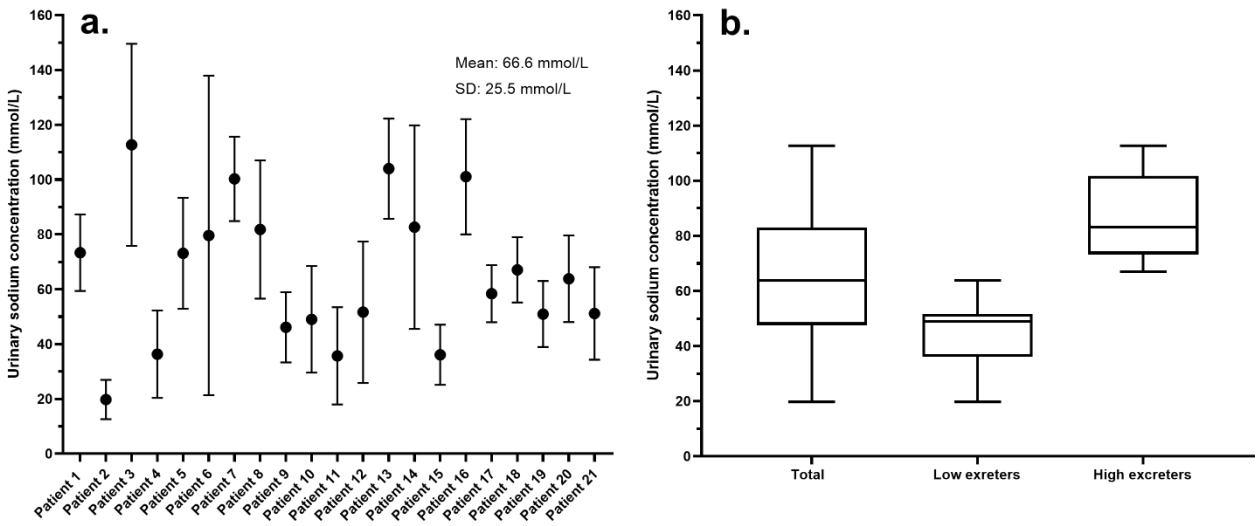

Figure 3: Urinary sodium concentrations displayed for each individual (a) and subdivided in low- and high excreter groups (b). Data presented as mean ± SD (a) or as boxplot in which the mean of each individual was used (b).

Table 3: Baseline patient characteristics divided in low and high sodium excreters				
	Total population (n=21)	**Low sodium excreters (n=11)**	**High sodium excreters (n=10)**	**P value**
Demographics				
Age (years)	65 ± 13	69 ± 10	62 ± 15	0.230
Males	17 (81%)	8 (73%)	9 (90%)	0.314
HF type				0.197
HFpEF	7 (33%)	5 (45%)	2 (20%)	
HFmrEF	2 (10%)	0 (0%)	2 (20%)	
HFrEF	12 (57%)	6 (55%)	6 (60%)	
HF cause [HFmrEF or HFrEF]				**0.040**
Ischemic	10 (71%)	6 (100%)	4 (50%)	
Non-ischemic	4 (29%)	0 (0%)	4 (50%)	
Physical features				
Systolic blood pressure (mmHg)	115 ± 17	114 ± 11	115 ± 22	0.948
Diastolic blood pressure (mmHg)	72 ± 14	71 ± 17	73 ± 10	0.719
Weight (kg)	84 ± 17	80 ± 16	89 ± 19	0.272
BMI (kg/m²)	27 ± 5	27 ± 4	28 ± 5	0.534
Comorbidities				
Atrial fibrillation	16 (76%)	8 (73%)	8 (80%)	0.696
Arterial hypertension	10 (48%)	6 (55%)	4 (40%)	0.505
Diabetes	6 (29%)	3 (27%)	3 (30%)	0.890
Dyslipidemia	7 (33%)	5 (45%)	2 (20%)	0.217
Baseline laboratory analysis				
Hemoglobin (g/dL)	14.6 [12.1 – 15.7]	14.1 [10.9 – 15.6]	15.3 [13.5 – 15.8]	0.213
Sodium (mmol/L)	139 ± 2	139 ± 2.9	139 ± 1.9	0.921
Potassium (mmol/L)	4.5 ± 0.5	4.3 ± 0.5	4.7 ± 0.4	0.073
Serum creatinine (mg/dL)	1.1 [1 – 1.5]	1.1 [0.9 – 1.5]	1.3 [1.0 – 1.9]	0.398
NT-proBNP (ng/L)	645 [286 – 2536]	1339 [535 – 2681]	443 [110 – 1345]	0.129
Plasma renin activity (µU/mL)	404 [158 – 550]	550 [187 – 550]	217 [134 – 550]	0.347
Plasma aldosterone (ng/L)	237 ± 146	314 ± 136	170 ± 126	0.054
Plasma osmolality (mOsmol/kg H_2O)	302 ± 9	302 ± 11	302 ± 7	0.821
NYHA functional class				0.547
I	8 (37%)	3 (27%)	5 (50%)	
II	6 (29%)	3 (27%)	3 (30%)	
III	6 (29%)	4 (36%)	2 (20%)	
IV	1 (5%)	1 (9%)	0 (0%)	
Orthopnea	5 (24%)	4 (36%)	1 (10%)	0.157
Bendopnea	3 (14%)	2 (18%)	1 (10%)	0.593
Paroxysmal nocturnal dyspnea	1 (5%)	0 (0%)	1 (10%)	0.283
VAS dyspnea score (0-100)	74 ± 15	72 ± 14	76 ± 18	0.576
Baseline echocardiography				
LVEF (%) [HFmrEF or HFrEF]	32 ± 8	33 ± 8	31 ± 9	0.779
LVEDD (mm)	51.7 ± 5.0	50.8 ± 6.1	52.7 ± 3.4	0.407
MI (grade)				0.693
0 – 2	21	11	10	
RVSP (mmHg)	27 [25 – 41]	28 [25 – 44]	26 [23 – 38]	0.624
Baseline renal echo **				0.377
Continuous	11 (92%)	6 (86%)	5 (100%)	
Discontinuous	1 (8%)	1 (14%)	0 (0%)	
Guideline directed HF therapy				
ACE inhibitor or ARB [HFmrEF or HFrEF]	3 (21%)	2 (33%)	1 (13%)	0.347
ARNI [HFmrEF or HFrEF]	10 (71%)	4 (67%)	6 (75%)	0.731
Beta-blocker [HFmrEF or HFrEF]	12 (86%)	5 (83%)	7 (88%)	0.826
SGLT2 inhibitor	18 (86%)	9 (82%)	9 (90%)	0.593
Aldosteron antagonist	19 (90%)	10 (91%)	9 (90%)	0.944
Loop diuretics	12 (57%)	9 (82%)	3 (30%)	**0.017**

Table 3 continued: Baseline patient characteristics divided in low and high sodium excreters				
	Total population (n=21)	**Low sodium excreters (n=11)**	**High sodium excreters (n=10)**	**P value**
CRT	9 (43%)	4 (36%)	5 (50%)	0.538
PM	1 (5%)	1 (9%)	0 (0%)	0.329
ICD	8 (38%)	5 (45%)	3 (30%)	0.466

Values are mean ± SD, median [IQR] or n (%). HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association, VAS = visual analog scale, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, RVSP = right ventricular systolic pressure, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprylisin inhibitor, SGLT2 = sodium glucose transporter 2, CRT = cardiac resynchronization therapy, PM = pacemaker, ICD = implantable cardiac defibrillator. ** Baseline renal echo was only performed in 12 out of 21 patients.

Urinary sodium concentration over time

It was only possible to plot mean urinary sodium concentration measurements over a 10-week period due to a decline in the number of available samples after that point. Overall, mean urinary sodium concentration stayed relatively stable over time (p-value for time effect=0.919) (Figure 4a). This effect continued when looking at both the low excreter (p=0.870) and high excreter group (p=0.861) separately. There was no difference in the evolution over time between both groups (P for time effect between groups:0.998). There was a significant difference between both groups (p<0.01) (Figure 4b).

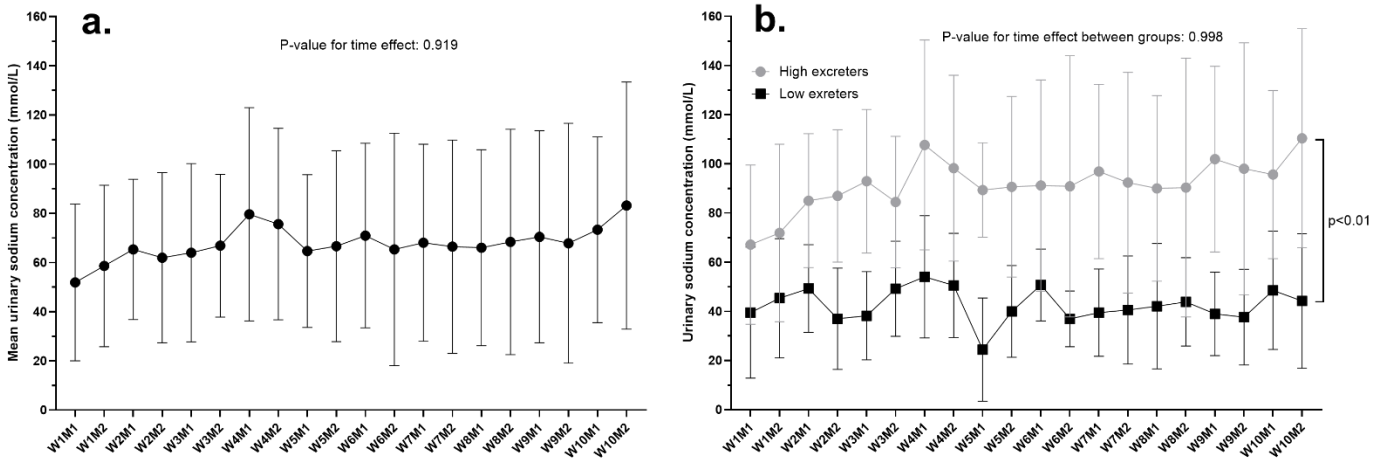

Figure 4: Longitudinal urinary sodium concentrations over a time-span of 10 weeks for the whole population,(a) and high and low sodium excreters (b). Data presented as mean ± SD. P-value for time effect was assessed using linear mixed modeling. P-value between groups was assessed using a Wilcoxon Rank-Sum test.

Predicting value of urinary sodium concentration

The overarching aim of this paper was to assess the predictive value of urinary sodium concentration. Over the period February 2023 to May 2024, a total of four AHF events occurred within the included patient cohort. Out of these four events, two events occurred in the same patient. These events comprised one mild AHF hospitalization and three instances of up-titrating loop diuretic therapy (doubling the maintenance dose). Two out of three patients who experienced an AHF event were classified in the low excreter group whereas the third one had a mean urinary sodium excretion of 67.1 mmol/L (cutoff 66.6 mmol/L). Analysis of the mean urinary sodium concentrations spanning four weeks before to four weeks after the AHF events indicates a decline of 17.81 mmol/L in mean urinary sodium concentration in the second measurement of the week preceding the event. However, this drop does not differ significantly when compared to the preceding measurement (P=0.458). Urinary sodium concentration slightly rises the measurement directly before the event, but is still lower than the mean of the preceding measurements. Linear mixed modeling indicates stability of urinary sodium excretion in this time span (p=0.996) (Figure 5). Tabel S1 compares baseline characteristics between individuals who experienced an event of AHF vs individuals who remained stable. In the event group, mean age was 53 ± 17 years

old, remarkable lower compared to the no event group (68 ± 12 years old), however insignificant (p=0.089). Median NT-proBNP in the event group was 2100 [516 – 3448] compared to the no event group (628 [225 – 2350]) (p=0.397). Despite the small number of individuals in the event group (n=3), significant differences were found when comparing the baseline systolic (p<0.001) and diastolic (p=0.047) blood pressure. Other baseline characteristics revealed no significant differences.

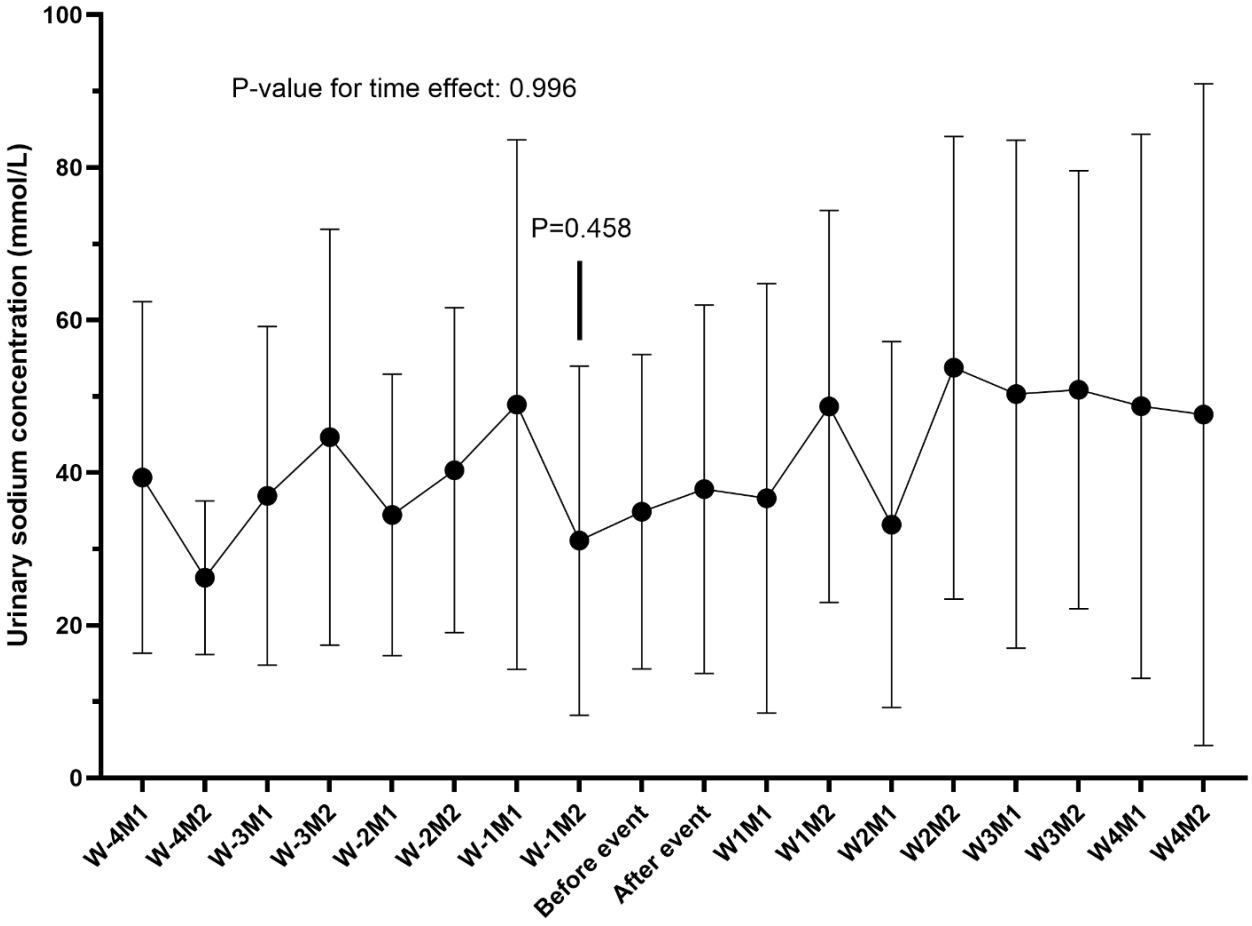

Figure 5: Longitudinal mean urinary sodium concentration spanning from four weeks before the AHF event until four weeks after the AHF event. Data presented as mean ± SD. P-value for time effect was assessed using linear mixed modeling. P-value at the drop was assessed using a Wilcoxon Signed-Rank test comparing the urinary sodium concentration with the value of the preceding measurement.

Conventional follow-up

The current follow-up methods involve monitoring patients' weight and blood pressure. Patients were instructed to record these measurements weekly. However, in the event group, only 1 out of 3 individuals provided this information. Consequently, there is insufficient data in this trial to confirm any changes in weight or blood pressure prior to AHF events.

Loop-diuretic effect

Out of 21 patients, 12 patients received chronic loop-diuretic therapy. Doses are displayed in furosemide equivalents (40mg of furosemide = 1mg of bumetanide). In total, 5 patients received 20mg/day, 3 patients received 40mg/day, 3 patients received 80mg/day and 1 patient received 100mg/day. Regardless of diuretic dose, median delta diuretic effect was + 32.10 [19.31 – 54.44] mmol/L after diuretic intake. All patients remained response with an increase in their urinary sodium concentration after diuretic administration. Individual diuretic effect ranged from +9.24 mmol/L to +129.88 mmol/L, regardless of diuretic dose.

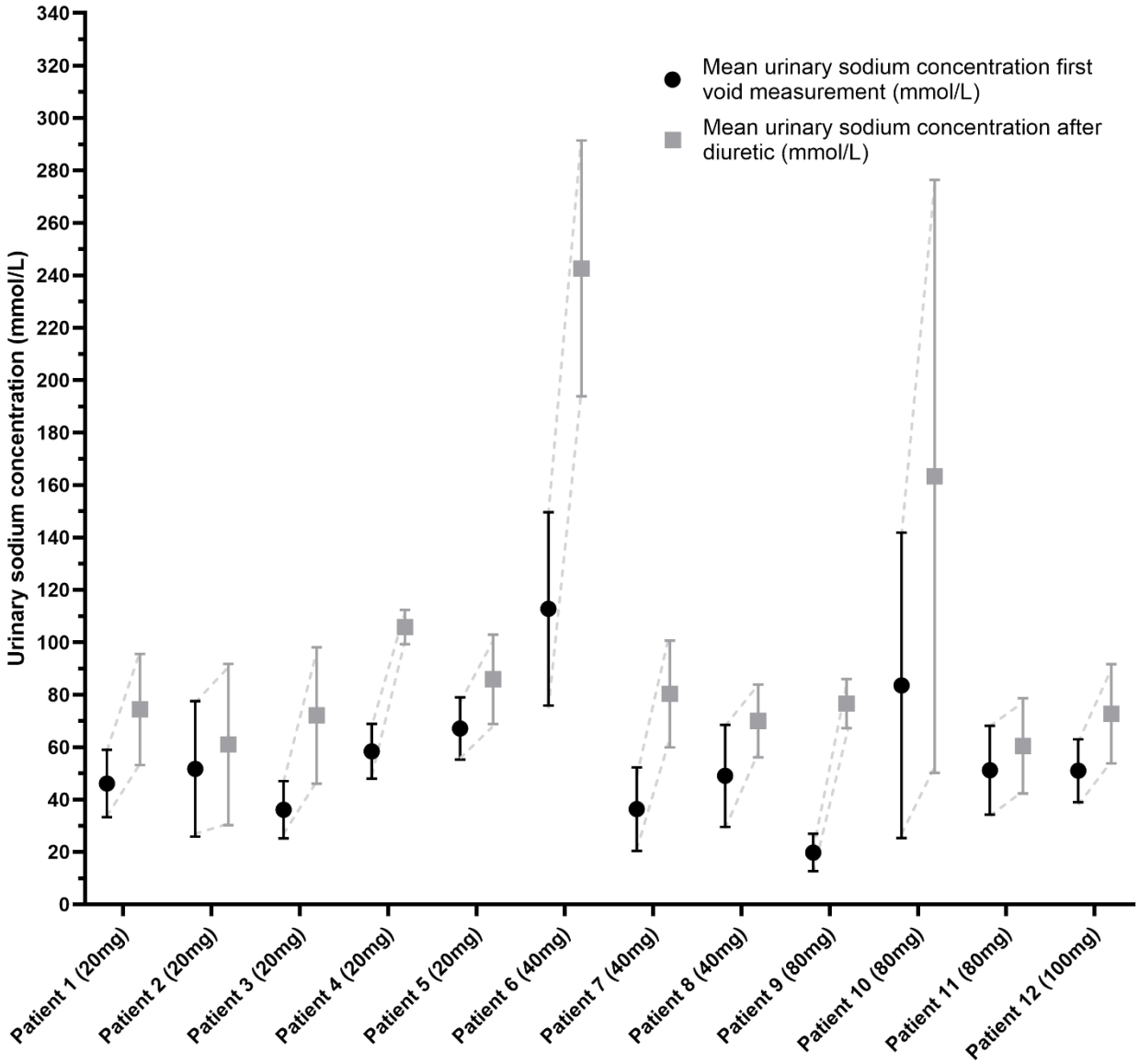

Figure 6: Assessment of loop-diuretic effect for each individual patient. Patients are ordered based on daily loop diuretic dose, ranging from 20mg to 100mg. Data presented as mean ± SD.

Feasibility of clinical implementation

As previously mentioned, data was available from 21 individuals who performed urinary sodium number of measurements each individual should have performed, a total of 994 first void measurements and 552 after diuretic measurements should have collected. In reality, 94.5% of the total expected number of first void measurements were performed and 89.5% of the total expected after diuretic measurements were performed. Missing data was mostly localized in the same individuals, with 1 individual who only performed half of the expected number of measurements. Out of 21 individuals, 9 individuals performed 100% of the expected number of measurements.

Figure 7: Visual representation of the amount of performed vs not-performed urinary sodium measurements. For the 'first void measurement' group n=21, for the 'after diuretic' group n=12.

Discussion

To the best of our knowledge, this clinical trial was the first to test a home-based tool for monitoring urinary sodium levels over time in patients with heart failure. The main goal of this study was to confirm a decrease in urinary sodium output with help of a home-based urinary sodium sensor the week running up to an event of AHF in CHF patients, as previously established by Martens et al. (24). While it was not possible to confirm this drop in this preliminary analysis due to the limited event rate, there was an interesting find about the effect of loop diuretics in CHF patients.

Natural urinary sodium excretion

First of all, this article does not represent the full study, but is only a preliminary analysis of readily obtained data. Analysis of spot urinary sodium concentration measurements shows high interindividual differences as big as 93 mmol/L between individuals. These differences allowed us to differentiate between individuals with a naturally low sodium excretion and individuals with a naturally high sodium excretion. Whereas Martens et al. defined groups as high with a mean urinary sodium concentration of 88 mmol/L or low with mean urinary sodium concentration of 73 mmol/L, we were able to pull these groups further apart and draw the line at a mean urinary sodium concentration of 88 mmol/L for the high excreter group and at 46 mmol/L for the low excreter group (24). These differences may be explained due to the fact that the sensor that was used in this clinical trial has a measuring range that can detect a sodium concentration down to 0.3 mmol/L, whereas the clinical laboratory does not report exact values below 20 mmol/L. Baseline characteristics are grossly in line with findings from previous related studies, with the exception of PRA, which was reported approximately 2.7x higher (404 vs 1086 µU/mL) by Nijst et al. in ambulatory chronic HFrEF patients (26). This difference is most likely due to the fact that the clinical laboratory analyzing our samples did not report values above 550 µU/mL. When comparing between groups, multiple differences were visible . A higher median NT-proBNP, PRA and mean plasma aldosterone in the low excreter group may indicate a higher driving force for fluid accumulation in this group. Statistical analysis showing a higher incidence of ischemia in the low excreter group is most likely due to low sample size. However, a higher percentage of chronic loop-diuretic users in the low excreter group might can be explained by multiple hypotheses. be the driving force for low sodium excretion as loop-diuretics cause more sodium to leave the body. First of all, patients in this group could be more severely ill and therefore have a higher RAAS activity. This heightened RAAS activity necessitates the maintenance of diuretic therapy to facilitate sodium excretion. These patients may exhibit low sodium excretion due to an inherently higher sodium avidity. Secondly, low sodium levels might primarily result from the use of diuretics, as patients initially excrete more sodium when taking the medication. However, this is followed by a rebound sodium retention until the next dose is administered, necessitating the continued use of diuretics to maintain sodium excretion. Lastly, patients in this group could be more severely ill and are may therefore adhere more strictly to dietary guidelines, resulting in reduced sodium excretion. This adherence leads to stable sodium levels over time without significant fluctuations or events. Unfortunately, as of today, there is no literature available to support these assumptions and further research is necessary.

Previous research already found that urinary sodium concentrations have proven to be relatively stable over time when the individual itself is stable (24). Whilst it would have been better to confirm this finding over the whole follow-up period of this study, at the moment of the manuscript draft there was not enough data available to perform this analysis. Therefore, a time interval with all available measurements of the included participants was chosen (i.e. 10 weeks). This research again confirmed stability of longitudinal urinary sodium concentration measurements over a time period of 10 weeks in stable CHF patients.

Prognostic value

Since this is only the second trial investigating the predictive value of spot-sample urinary sodium concentration as a CHF patient progresses towards an AHF event, there is limited data available for comparison. AHF events were defined as either hospitalization due to AHF, an urgent heart failure visit, or ambulatory diuretic up-titration as specified in the study endpoints. In total, 4 AHF events took place in 3 individuals during study follow-up. At eyesight, a drop in urinary sodium concentration is visible the week preceding the AHF event, with the concentration slightly rising just before the event, which could indicate that the body tries to get rid of excess sodium itself, however unsuccessfully. Analysis of the time effect tells us that the measurements stay stable over time and comparing the dip of 17.81 mmol/L with the measurements directly preceding the event reveals no significant difference ($p=0.458$). Therefore, these results are unable to confirm a clear dip in urinary sodium concentration preceding the AHF event. This does not correlate to previous findings, but may most likely be due to the small sample size (24).

Diuretic response

Identifying patients with poor diuretic response is a critical challenge in the field of HF, as a poor response to diuretics is linked to a higher risk of rehospitalization and increased mortality in the acute setting (27, 28). In the acute setting, insufficient diuretic response was previously determined at <70mmol/L, but supporting evidence seems to be missing (29). Out of 21 included patients, 12 patients were active on chronic loop diuretic therapy. This small number of patients made it possible to evaluate the diuretic response for each individual separately. Most patients had at first void a low urinary sodium excretion, but have a mean urinary sodium excretion well above 70mmol/L after diuretic intake, with only 2 exceptions (patient 2 and patient 11 (Fig. 6), 61.05 and 60.43 mmol/L respectively). Minimal diuretic response may be due to the fact that the individual is already in an euvolemic state, generating the hypothesis that in these individuals discontinuation of loop diuretic may be possible. Enormous diuretic response (delta > first void measurement), might indicate poor compliance to the salt and fluid intake restrictions or inherent high sodium avidity with the need for loop diuretics to achieve a neutral sodium balance.

Feasibility

Although outside the scope of this trial, we explored the feasibility of using a urinary sodium sensor to monitor patients at home. Our data suggests that implementing this technique is both feasible and straightforward in an elderly CHF population. However, there may be at least 5% missing data for the first void measurement over a period of 48 weeks. Patients were contacted by telephone one week after inclusion to validate study compliance and motivated in case no measurement was performed yet. Out of a total of 80 included participants, 10 patients dropped-out of the study without performing a single measurement. This lays in line with similar clinical trials (24). Measurements taken after diuretic intake had twice the amount of missing data, likely because these measurements needed to be done around noon, a more challenging time for patients as this interferes with their daily activities. Whether this could provide a new method to successfully monitor CHF patients over a long period of time, needs to be explored in further research.

Study limitations

Since this article was preliminary written as a Master's thesis, not enough data was available to have enough power to confirm a drop in urinary sodium concentration preceding an AHF event. Due to multiple changes in GDMT, patients are treated better comparing to in previous literature, making them more stable and possible events of AHF 'softer'. Another limitation is that the total duration of the study (48 weeks) may be the reason for early drop-outs and missing data, but this could be expected. While patients were precise in the beginning, there was more lacking of data towards the end of the follow-up period, potentially negative influencing study results towards the end.

Conclusion

Previously findings about predicting an event of AHF based on urinary sodium analysis could not be validated. Comparing the effect of loop-diuretics on the urinary sodium concentration between individuals provides more information about potential diuretic resistance and might uncover individuals in which stopping of chronic loop diuretic therapy is safe. Further research is necessary to provide better insights into this topic.

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Author contributions

Mullens W. and Meekers E. are responsible for designing the protocol. Knevels R. is responsible for designing the electronic case report form. Meekers E., Miseur M. and Knevels R. are responsible for gathering data. Knevels R. and Meekers E. are responsible for statistical analysis and writing.

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Supplements

Weekly questionnaire *(To be completed in the morning)* Week X

Bloodpressure ☐☐☐☐☐ mmHg	Weight ☐☐☐☐☐ kg

Date	Sample 1 (before diuretic)	Sample 2 (after diuretic)
Day 1 **…/…/…**	❑ Sample 1 collected ❑ Sample 1 **not** collected Result:……	❑ Sample 2 collected ❑ Sample 2 **not** collected Result:……
Day 2 **…/…/…**	❑ Sample 1 collected ❑ Sample 1 **not** collected Result:……	❑ Sample 2 collected ❑ Sample 2 **not** collected Result:……

VAS dyspnea score

1	2	3	4	5

Bad *Good*

Medication dose *(Lasix/Burinex)*

Dose diuretic: …… mg

Oedema – fluid accumulation in the legs

- ❑ 0 (No fluid in the legs)
- ❑ 1+ (Dimple in leg after pushing with finger, disappears quickly)
- ❑ 2+ (Dimple in leg after pushing with finger, remains longer)
- ❑ 3+ (Clear swelling / fluid accumulation of the lower leg)
- ❑ 4+ (Fluid accumulation above the knee)

Diet

Were there any important changes in your diet this week?

❑ No

❑ Yes, specifically:

……
……

Figure S1: weekly questionnaire patients were asked to fill in for a total period of 48 weeks.

Table S1: Baseline patient characteristics divided in a no event and an event group.			
	No event (n=18)	**Event (n=3)**	**P value**
Demographics			
Age (years)	68 ± 12	53 ± 17	0.089
Males	15 (83%)	2 (67%)	0.496
HF type			0.823
HFpEF	6 (33%)	1 (33%)	
HFmrEF	2 (11%)	0 (0%)	
HFrEF	10 (56%)	2 (67%)	
HF cause [HFmrEF or HFrEF]			0.469
Ischemic	8 (67%)	2 (100%)	
Non-ischemic	4 (33%)	0 (0%)	
Physical features			
Systolic blood pressure (mmHg)	120 ± 13	86 ± 9	**<0.001**
Diastolic blood pressure (mmHg)	75 ± 14	57 ± 2	**0.047**
Weight (kg)	86 ± 18	71 ± 8	0.156
BMI (kg/m²)	28 ± 5	24 ± 2	0.216
Comorbidities			
Atrial fibrillation	15 (83%)	1 (33%)	0.060
Arterial hypertension	8 (44%)	2 (67%)	0.476
Diabetes	6 (33%)	0 (0%)	0.237
Dyslipidemia	5 (28%)	2 (67%)	0.186
Baseline laboratory analysis			
Hemoglobin (g/dL)	14.7 [11.8 – 15.7]	14.1 [13.6 – 16.3]	0.763
Sodium (mmol/L)	139 [138 – 141]	138 [138 – 142]	0.920
Potassium (mmol/L)	4.5 ± 0.5	4.6 ± 0.6	0.630
Serum creatinine (mg/dL)	1.13 [1.00 – 1.65]	1.33 [0.81 – 1.41]	0.725
NT-proBNP (ng/L)	628 [225 – 2350]	2100 [516 – 3448]	0.397
Plasma renin activity (µU/mL)	260 [152 – 260]	550 [550 – 550]	0.440
Plasma aldosterone (ng/L)	239 ± 147	225 ± 202	0.900
Plasma osmolality (mOsmol/kg H_2O)	303 ± 8	297 ± 18	0.422
NYHA functional class			0.970
I	7 (39%)	1 (33%)	
II	5 (28%)	1 (33%)	
III	5 (28%)	1 (33%)	
IV	1 (6%)	0 (0%)	
HF symptoms			
Orthopnea	4 (22%)	1 (33%)	0.676
Bendopnea	3 (17%)	0 (0%)	0.445
Paroxysmal nocturnal dyspnea	1 (1%)	0 (0%)	0.676
VAS dyspnea score (0-100)	73 ± 16	78 ± 4	0.731
Baseline echocardiography			
LVEF (%) [HFmrEF or HFrEF]	33 ± 8	25 ± 7	0.205
LVEDD (mm)	51.2 ± 4.2	54.6 ± 8.7	0.293
MI (grade)			0.128
0 – 2	18	3	
RVSP (mmHg)	27 [25 – 39]	26 [20 – 48]	0.839
Baseline renal echo **			0.547
Continuous	8 (89%)	3 (100%)	
Discontinuous	1 (11%)	0 (0%)	
Guideline directed HF therapy			
ACE inhibitor or ARB [HFmrEF or HFrEF]	3 (25%)	0 (0%)	0.425
ARNI [HFmrEF or HFrEF]	8 (67%)	2 (100%)	0.334
Beta-blocker [HFmrEF or HFrEF]	10 (83%)	2 (100%)	0.533
SGLT2 inhibitor	16 (89%)	2 (67%)	0.309
Aldosteron antagonist	16 (89%)	3 (100%)	0.544
Loop diuretics	9 (50%)	3 (100%)	0.105
Device therapy			
CRT	7 (39%)	2 (67%)	0.368
PM	1 (6%)	0 (0%)	0.677
ICD	7 (39%)	1 (33%)	0.854

Values are mean ± SD, median [IQR] or n (%). HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association, VAS = visual analog scale, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, RVSP = right ventricular systolic pressure, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprylisin inhibitor, SGLT2 = sodium glucose transporter 2, CRT = cardiac resynchronization therapy, PM = pacemaker, ICD = implantable cardiac defibrillator. ** Baseline renal echo was only performed in 12 out of 21 patients.