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

Masterthesis

Forecasting acute heart failure hospitalizations based on home urinary sodium measurements

Marie Miseur

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

PROMOTOR :

Prof. Dr. Wilfried MULLENS

BEGELEIDER :

Mevrouw Evelyne MEEKERS

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FORECASTING ACUTE HEART FAILURE HOSPITALIZATIONS BASED ON HOME URINARY SODIUM MEASUREMENTS. *

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*Running title: *FAST-RESPONSE 2 study*

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Keywords: acute heart failure, congestion, prevention, urinary sodium excretion, natriuresis, home-based monitoring.

ABSTRACT

Background: Acute Heart Failure (AHF) is a consequence from reduced hemodynamic function triggering neurohormonal activation, leading to fluid retention and congestion. Symptoms include shortness of breath and oedema, often necessitating hospitalization. However, there is a 30% readmission risk within three months post-discharge, underscoring the urge for improved monitoring. Home-based urine samples could be a non-invasive method for monitoring sodium (Na^+) levels in patients during their vulnerable phase. The hypothesis posits that AHF patients will demonstrate a decreased natriuresis before the clinical manifestation of an AHF event due to neurohumoral upregulation with an increased Na^+ avidity.

Methods: In this single-center interventional prospective cohort study, hospitalized AHF patients collected urine samples post-discharge twice daily for two weeks. At baseline and one month follow-up, participants underwent congestion evaluation via clinical examination, transthoracic echocardiography, renal Doppler ultrasound, bio-impedance measurements, and blood sampling. The study assessed the relationship between recurrence of congestion and ambulatory urinary Na^+ concentrations.

Results: Out of 50 included subjects, 33 provided urine spot samples, and among them, 8 experienced an event (defined as increased loop-diuretics or AHF hospitalization). The data reveal a significant disparity in urinary Na^+ excretion before and after diuretic administration across all three subpopulations ($p < 0.001$), accompanied by variability in urinary Na^+ concentrations. Additionally, a dip in natriuresis can be observed four days before the occurrence of an event ($p = 0.094$).

Conclusion: These findings demonstrate that monitoring daily urinary Na^+ levels pre- and pos-loop-diuretic intake has the potential to forecast AHF events by identifying decreased natriuresis.

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1. INTRODUCTION

Acute heart failure (AHF) most often manifests as the sudden onset or exacerbation of congestive symptoms of heart failure, necessitating urgent and unscheduled hospitalization (1). These congestive symptoms, primarily responsible for the clinical manifestation of AHF and the need for hospitalization, include shortness of breath, swelling in the lower limbs, and abdominal edema (2). The clinical manifestation of acute heart failure is influenced by the site of cardiac dysfunction (**Figure 1**). Left ventricular dysfunction may be accompanied by backward failure, where pressure in the pulmonary artery increases, leading to pulmonary dysfunction and dyspnea. With forward failure, peripheral circulation of oxygenated blood decreases, causing malperfusion and renal dysfunction. Similarly, right-sided heart failure may be associated with forward and backward failure, leading to pressure and volume overload (3). Consequently, neurohormonal activation occurs as a compensatory mechanism leading to renal sodium and water retention, exacerbating edema (2).

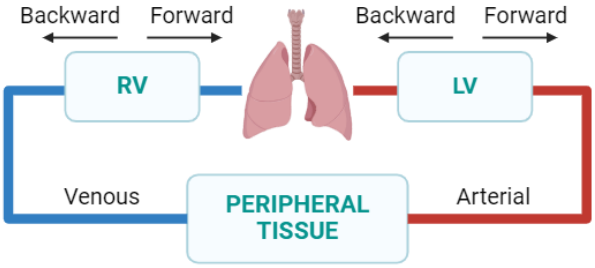

Figure 1: Schematic representation of right and left forward and backward heart failure. Depending of the site of cardiac dysfunction (left or right), heart failure can be associated with forward and backward failure. The red line represents arterial blood supply while the blue line stands for venous drainage. RV: Right Ventricle, LV: Left Ventricle.

1.1. Neurohormonal activation

In patients with heart failure, the myocardial performance is impaired, resulting in compromised blood supply to the body. The reduced cardiac output leads to a cascade of physiological responses, particularly affecting the kidneys. As highly perfused organs, the kidneys are among the first to register the hemodynamic alterations and initiate the Renin-Angiotensin-Aldosterone System (RAAS) to preserve fluid and electrolytes. The RAAS system triggers a series of reactions, including angiotensin II and aldosterone release, which instructs the kidneys to retain sodium (Na^+) and water, increasing the circulating blood volume (4).

When renal blood flow diminishes, the glomerulus compensates by increasing the filter fraction to safeguard the glomerular filtration rate (GFR). The glomerulotubular balance counteracts an increased filtration fraction by enhancing sodium reabsorption in proximal renal tubules, which accounts for approximately 65% of the total sodium reabsorption (**Figure 2**). Nevertheless, neurohormonal feedback induces greater Na^+ and water reabsorption in the proximal tubules and ascending portions of Henle's loop, prompting macula densa cells to detect a reduced Cl^- load. In response, the glomerulotubular feedback mechanism increases the secretion of renin, activating the Renin-Angiotensin II-Aldosterone axis (**Figure 3**). This cascade results in vasoconstriction of efferent arterioles and promotes the expression of active Na^+ transporters throughout the nephron. Ultimately, this neurohormonal activation intensifies Na^+ reabsorption and efferent arterioles constriction, increasing the filtration fraction and perpetuating a vicious cycle that exacerbates the pathophysiology of heart failure, i.e. AHF (5).

<u>Guideline-directed medical therapy</u>

Guideline-directed medical therapy (GDMT) serves as the fundamental pharmacological therapy for heart failure with reduced ejection fraction (HFrEF) and consists of the four main drug classes: 1) renin-angiotensin system (RAS) inhibitors, 2) β-blockers, 3) mineralocorticoid (MRA) inhibitors, and 4) sodium glucose cotransporter 2 inhibitors (SGLT2i) (6).

1. RAS-acting agents function by blocking different stages of the RAAS system, including angiotensin receptor/neprilysin inhibitors (ARNIs), Angiotensin-converting enzyme inhibitors (ACEi), and Angiotensin receptor blockers (ARBs) (**Figure 3**). ARNIs exhibit a dual action on the key regulators of the cardiovascular

system, influencing both the natriuretic peptide (NP) system and RAS system, promoting natriuresis and vasodilatation, respectively (7). ACE inhibitors block angiotensin II synthesis, reduce circulating levels of angiotensin II and aldosterone thereby mitigating vasopressor effects, lowering blood pressure, and reducing cardiac workload (8). ARBs, too, act as angiotensin II receptor antagonists. However, ARNIs are recommended as de novo treatment in hospitalized AHF patients before discharge due to its positive impact on health status, reduction in the prognostic biomarker NT-proBNP, and improvement of LV remodeling parameters when compared with ACEi/ARB (9).

2. Beta-blockers selectively bind to β1 receptors in the cardiac nodal tissue, cardiac myocytes, other heart conduction pathway tissues, and the juxtaglomerular apparatus of the kidneys. This therapy results in adverse ionotropic and chronotropic effects, while also reducing RAAS activation by decreasing renin release (10). Consequently, it contributes to enhancements in left ventricular systolic and diastolic function, alleviating heart failure symptoms, and an overall improvement in clinical status (11).

3. The renal effects of MRA involve modulating the expression and activity of sodium and potassium channels in the distal nephron and counteracting the aldosterone escape generated by neurohormonal over-activation (**Figure 2**) (12).

4. The SGLT2i inhibitors (dapagliflozin and empagliflozin) block proximal sodium absorption (12) and if combined with ACE-I/ARNI/beta-blocker/MRA, they reduce the risk of cardiovascular death and worsening HF in patients with HFrEF (**Figure 2**) (13).

The effect of the GDMTs is most beneficial when medications from the four main drug classes are combined (6).

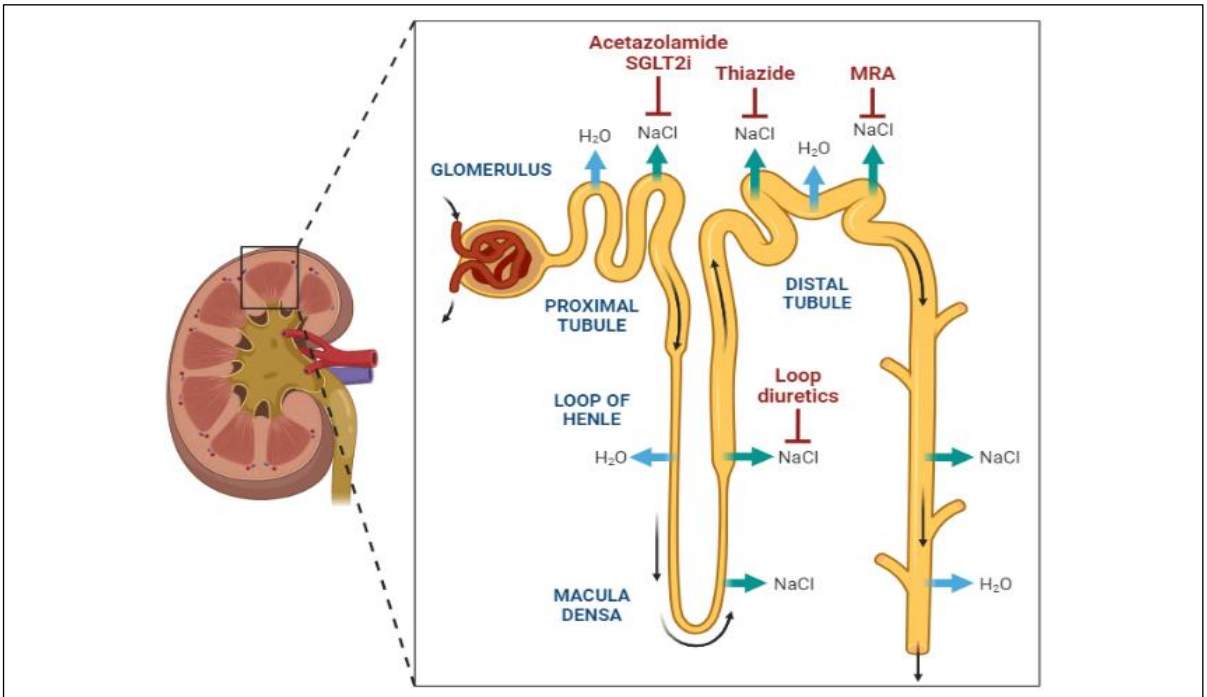

Figure 2: Nephron segments with corresponding Na^+ and water reabsorption and nephron-based therapy. Heart failure patients have a lower renal blood flow, an impaired GFR and increased filter fraction, ultimately culminating in renal sodium reabsorption along the whole tubule.

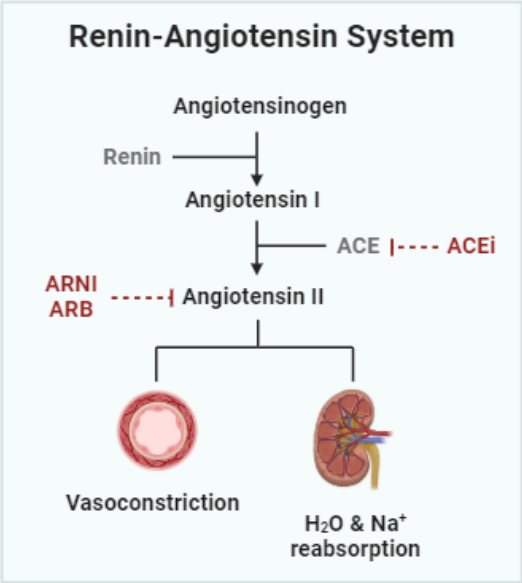

Figure 3: Operating site of Renin-Angiotensin System Acting agents in the Renin-Angiotensin axis. ACE: Angiotensin Converting Enzyme, ACEi: Angiotensin Converting Enzyme inhibitor, ARNI: Angiotensin Receptor Neprilysin Inhibitor, ARB: Angiotensin Receptor Blocker.

1.2. Acute heart failure management

The management of AHF commences with accurate identification of the condition. Diagnosis involves recognizing signs of congestion through anamnesis and clinical examination, followed by chest X-ray or lung ultrasound, observing indicators like pleural effusion. Echocardiography aids in diagnosis by assessing parameters such as the diastolic function, tricuspid regurgitation, and inferior vena cava collapsibility (13, 14). Additionally, measuring plasma levels of natriuretic peptides such as BNP or NT-proBNP can offer further insights into AHF, particularly when the diagnosis is uncertain. Natriuretic peptides have a high negative predictive value for AHF diagnosis, with specific cutoff values set at BNP ≥100 pg/mL and NT-proBNP ≥300 pg/mL (12, 13).

Diuretic therapy in AHF

Achieving an euvolemic state is the focal point of AHF treatment during hospitalization (Class I recommendation). Diuretics promote renal clearance of excess fluid and salt, by which they alleviate symptoms of congestion. Loop diuretics emerge as the golden standard, exhibiting the most potent diuretic effect (15). They inhibit the Na-K-2Cl symporter in the ascending loop of Henle and inhibit 20-30% of the Na^+ reabsorption that occurs here, thereby promoting the delivery of Na+ to distal tubule (**Figure 2**). Importantly, the Na/K/2Cl cotransporter is also located in the macula densa and blocked by loop diuretic administration. This results in reduced chloride levels, by which loop diuretics augments the neurohormonal upregulation in AHF (12). The hemodynamic changes of HF inducing increased filter fraction leads to an enhanced resorption of sodium in the proximal nephron, a process counteracted by acetazolamide and SGLT2i (16, 17). Additionally, diuretics, such as thiazide diuretics, act on the sodium-chloride cotransporter (NCC) in the distal convoluted tubule, reducing Na^+ and Cl^- reabsorption by 3-5% (12). At high doses, MRA therapy in AHF may relieve congestion through its natriuretic properties on the epithelial sodium channel (ENaC) in the distal nephron (18).

Despite their efficacy, combined diuretic therapy raises concerns about various adverse effects, including electrolyte abnormalities, renal dysfunction, hypotension, and induced cardiac arrhythmias. Loop diuretics, administered in over 90% of AHF patients, serve as the backbone of diuretic therapy (19). Their significant clinical benefits in AHF contribute to symptom improvement, solidifying their role as the primary diuretic choice for treatment.

Telemonitoring of HF

Following hospitalization due to an AHF event, there is a high risk of readmission and all-cause mortality of 30% and 15% (respectively) within three months after hospital discharge (20). During this period (called the vulnerable phase), weight change and net output are the most common monitoring tools in these patients. Nevertheless, those measurements are not accurate and insufficient in predicting an AHF episode and preventing hospitalization. This insufficiency emphasizes the urge for better monitoring of diuretic efficacy based on urinary sodium excretion during this vulnerable phase (21). One of the advancements in managing AHF was the continuous monitoring of pulmonary artery pressure by CardioMEMS or Sirona sensors, aimed at reducing the morbidity associated with

HF, as demonstrated in the COMPASS-HF study. Through a right heart catheterization, the device is directly implanted in the distal pulmonary artery and hemodynamic information from the monitor was used to guide patient management. This study revealed that an increase in cardiac filling pressures occurred several days to weeks before the onset of an AHF event, leading to a management strategy based on monitoring pulmonary artery pressures (21). Therapy adjustments based on the pulmonary artery pressures effectively lowered hospitalization rates, as evidenced by the CHAMPION study. The trial confirmed the clinical efficacy and safety of hemodynamic monitoring systems as a strategy for symptomatic HF (22). However the subsequent GUIDE-HF trial about evaluating the implementation remote pulmonary artery pressure monitoring in the United States to reduce heart failure events and mortality in a broader heart failure patients population (NYHA functional class II–IV, without a recent heart failure hospitalization), was inconclusive (23). Therefore, the MONITOR-HF trial enhanced geographical diversity by utilizing randomized trial data from patients receiving contemporary guideline-directed medical therapy within a different healthcare system, and included a control group. Results showed that hemodynamic monitoring improved quality of life and reduced heart failure hospitalizations in patients with moderate-to-severe heart failure treated according to contemporary guidelines (24). However, the invasive and costly nature of pulmonary pressure monitoring has limited its widespread implementation in AHF management.

Urinary sodium concentrations have been postulated as a possible alternative monitoring tool for patients with CHF to predict AHF onset (25). An exploratory study from Martens et al. on ambulatory monitoring involving weekly urine collection suggested that a longitudinal assessment of urinary sodium levels is feasible. Stable, chronic HF patients (n=80) with either reduced or preserved ejection fraction were included to undergo prospective collection of morning spot urinary sodium samples for 30 consecutive weeks. Patients were instructed to collect a first void morning urine sample once a week which is not representative for daily urinary sodium concentrations, especially before and after diuretic intake. Results showed that patients who developed AHF exhibited a chronically lower urinary sodium concentration and a further drop in concentration during the week preceding hospitalization (26). Subject to further validation through additional studies, urinary sodium profiling could have the potential to serve as an empowering tool for HF management by enabling the prediction of decompensation and allowing individualized diuretic therapy.

Therefore, home-based urine samples could be a simple and non-invasive method for monitoring sodium levels in patients after AHF during their vulnerable phase. The FAST-RESPONSE 2 trial is designed to observe daily changes in the urinary sodium concentrations of patients after an AHF event through the collection of daily urine samples over a two-week period preceding a potential new incident of AHF requiring hospitalization. The hypothesis posits that AHF patients will demonstrate a decrease in urinary sodium concentration before the clinical manifestation of an AHF event. This monitoring approach has the potential to facilitate future continuous tracking of urinary sodium concentrations, allowing for the anticipation of AHF events and swift assessment of diuretic response, enabling timely adjustments to diuretic therapy. Continuous monitoring would enable timely adjustments to diuretic therapy, thereby preventing exacerbation of congestive symptoms requiring hospitalization.

2. EXPERIMENTAL PROCEDURES

The FAST-RESPONSE 2 study is a single-center interventional prospective cohort study performed at the Cardiology Department of Ziekenhuis Oost-Limburg (ZOL) Genk, Belgium, from November 2023 until June 2024. The study was approved by the Medical Ethics Committee of ZOL Genk and is executed in compliance with the Declaration of Helsinki.

2.1. Study population

Patients hospitalized in the cardiac intensive/medium care unit with an AHF event were screened using the electronic patient file of ZOL Genk (HiX, Chipsoft, Netherlands). Adult patients (18 or older) were solely

included if diagnosed with heart failure[1], discharged on maintenance loop diuretics after an AHF event. Exclusion criteria were indication for renal replacement therapy or dialysis, inability to perform or store daily urinary sample collections, or pregnancy. All patients needed to provide written informed consent.

2.2. Study procedures

All included patients received study information and provided informed consent during hospitalization. After inclusion, patients were examined for signs and symptoms of congestion and underwent baseline measurements. Following hospital discharge, the patient started daily home-based urinary sample collection. Two samples were collected daily for two weeks: one morning sample (before diuretic intake) and another 1.5 hours after. Four weeks after hospital discharge, all baseline measurements were repeated at the follow-up visit (**Figure 4**).

2.2.1. Baseline

After study inclusion, baseline measurements were performed: clinical examination, transthoracic echocardiography, renal ultrasound, bioimpedance measurement, blood sample collection and completion of the EQ-5D questionnaire.

Clinical intake – During clinical examination, baseline demographics, medication, and medical history were assessed through the case report form and electronic patient file (HiX, Chipsoft). Blood pressure and pulse rate were measured using a blood pressure monitor. Dyspnea status was determined based on New York Heart association (NYHA) classification and the presence of orthopnea, bendopnea, and paroxysmal nocturnal dyspnea. Additionally, patients were asked to rate their breathlessness on a scale from 0 to 100, where 0 indicated no issues and 100 indicated severe shortness of breath. The degree of fluid accumulation in lower limbs was determined using an oedema Likert scale with a score ranging from 0 (no fluid) to +4 (massive oedema above the knee).

Blood sample – A blood sample was taken to determine hemoglobin, hematocrit, sodium, potassium, chlorine, bicarbonate, creatinine, total protein, albumin, bilirubin, GPT, GOT, LDH, troponine T, NT-proBNP, plasma aldosterone, plasma renin activity and osmolality.

EQ-5D – The EuroQol - 5 Dimension (EQ-5D) is a validated questionnaire comprising five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) that evaluate the patient's well-being. Each item can be answered on a 5-

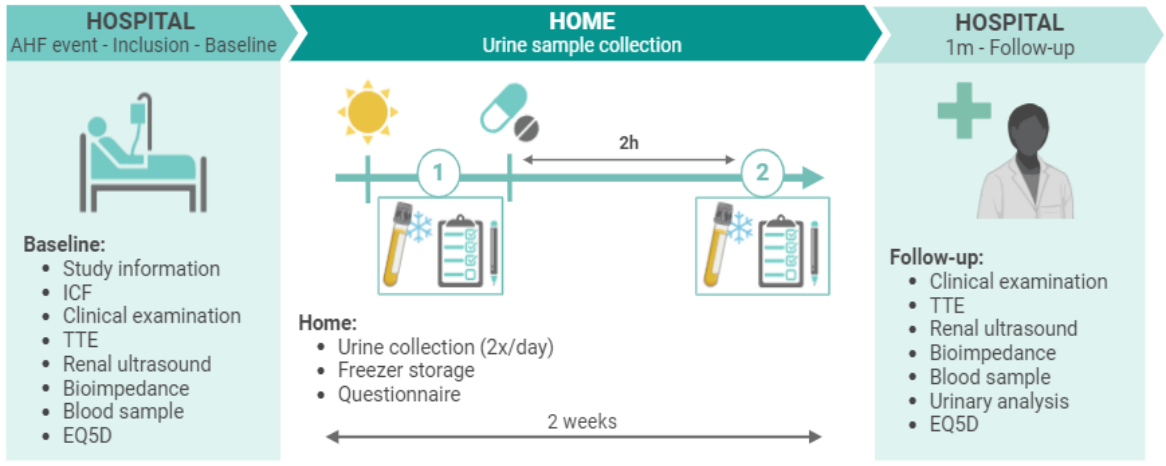

Figure 4: Study procedures at baseline, home, and follow-up. Study participants received study information during their hospitalization. Baseline and follow-up measurements were performed at the hospital. The patient performed urine collection twice daily at home for two weeks. AHF: Acute Heart Failure, ICF: Informed Consent Form, TTE: Transthoracic Echocardiogram, EQ5D: EuroQol – 5 Dimension.

[1] with HFrEF or HFpEF and, N terminal pro-B type natriuretic peptide concentration of > 1,000 ng/l and, echocardiographic signs of diastolic dysfunction.

point scale (no/slight/moderate/severe/extreme problems) (27).

Transthoracic echocardiogram – The transthoracic echocardiogram (TTE) was used to measure the cardiac hemodynamic function and pump function.

Renal ultrasound – Renal congestion was imaged by transmission of pulsed waves to vascular flow patterns. Depending on the pattern, it can be determined whether the flow is continuous or discontinuous/congested.

Bio-impedance – The bioimpedance technique measures the human body's electrical resistance, quantifying body water and enabling assessment of fluid accumulation (28). Measurements are performed with the Maltron Bioscan 920 by placing two electrodes on the right hand and two electrodes on the bare right foot of the patient.

2.2.2. Urine sample collection

On the morning following discharge from the hospital, the patient initiates a 14-day routine of daily urine sample collection (Figure X). Upon awakening, the initial urine sample is gathered using a plastic jar with a blue lid. The process involves removing the blue lid, urinating into the jar, replacing the blue lid, and extracting the sample by peeling off the white sticker from the lid. Subsequently, the urine tube marked "sample 1" and the relevant day is inserted into the opening of the blue lid. Utilizing vacuum suction, the urine tube draws in the urine, filling up to the specified line. Once filled, the tube is detached from the lid, and all samples are stored in the freezer until the scheduled study visit. The patient marks on the checklist that the sample has been collected and proceeds to complete the corresponding questionnaire for the day. Following the first urine sample, diuretic medication (either Furosemide or Bumetanide) may be taken. After two hours the process repeats with the second urine sample labeled "sample 2" and the corresponding day, following the same steps.

2.2.3. Follow-up

Within the first week of urine sample collection, patients were contacted to monitor their progress, ensure everything was proceeding smoothly, and address any questions or concerns they had. One month after inclusion, patients returned to the hospital for a follow-up study visit during which urine sample analysis is performed and baseline measurements are repeated (clinical examination, TTE, renal ultrasound, bioimpedance, EQ-5D).

2.3. Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences release 29 (IBM® SPSS ® Inc., Chicago, IL, United States). Normality of continuous data was assessed using a Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (std). If normality failed, continuous data are presented as median and interquartile range (IQR). Normally distributed dependent and independent data were analyzed using the paired t-test and unpaired t-test, respectively. Non-normally distributed continuous data were analyzed with the Mann-Whitney U test for independent samples and the Wilcoxon signed-rank test for paired samples. Categorical variables were analyzed using Fisher's exact test for small sample sizes ($n < 50$). Due to insufficient and missing data, urinary sodium concentrations from day 1 to day 6 were excluded from the analysis, which therefore focuses on data from day 7 to day 14. Longitudinal urinary Na^+ concentrations were analyzed using linear mixed models for repeated measures. The p-value for the dip in natriuresis on day -4 was quantified using a one-sided Wilcoxon signed-rank test for paired data. The difference in urinary Na+ excretion between the first void and after diuretic intake was assessed using the Wilcoxon signed-rank test for paired samples. The EQ-5D questionnaire was analyzed with the Wilcoxon signed-rank test by comparing the mean score of each topic individually at baseline and follow-up, rather than utilizing the EQ-5D summary index. A p-value < 0.05 was considered significant.

3. RESULTS

Between November 2023 and June 2024, a total of 287 patients were admitted to the hospital following an AHF episode. Among them, 180 individuals were ineligible for study participation, primarily due to their discharge

without maintenance of oral loop diuretics (n=85). Moreover, 65 patients declined to partake, resulting in 50 enrollments in the FAST-RESPONSE 2 study. Among these, 14 participants dropped out, and three were excluded from data analysis due to uncompleted study visits (scheduled later than deadline manuscript). Data analysis was conducted on 33 patients who adhered to urine sample collection protocols and attended the follow-up visit (**Figure 5).**

3.1. Demographics

The study population comprised 50 patients, categorized into two subgroups based on the occurrence of a clinical event. The mean ages of the stable and event groups were 76.8 ± 8.0 years and 75.3 ± 9.8 years, respectively, with a predominance of male patients (63.4% and 75.0%). No significant association was observed between heart failure type or etiology and the clinical outcome. However, a significant difference in diastolic blood pressure was detected between the two groups (p=0.041). Although not statistically significant, the BMI (28.4 ± 8.3 vs. 33.3 ± 6.8) appeared higher in subjects with acute heart failure (AHF) relapse. A history of atrial fibrillation and atrial hypertension were frequent comorbidities in both groups (78.6% vs 62.5% and 66.7% vs 62.5%). There was a non-significant trend towards higher prevalence of COPD in subjects with AHF relapse. Most patients were mildly symptomatic, with the majority classified as NYHA class I-II. There was no difference in guideline-directed medical therapy (GDMT) administration between the groups. In stable patients, the median NT-pro BNP level was 2509.0 ng/L, whereas AHF relapse patients had a median NT-pro BNP of 1957.0 ng/L; however, this difference was not statistically significant. Notably, the incidence of pacemaker implantation was significantly lower in the AHF relapse group, with no patients in this group receiving pacemakers (p=0.043).

3.2. Baseline vs follow up

Body weight significantly decreased from baseline to follow-up (p = 0.014), paired with reduced prevalence of orthopnea (37% vs 10%) and oedema (≥ Grade 1). The median visual analogue scale (VAS) score for dyspnea also decreased significantly at follow-up. Laboratory analysis indicated significant increases in potassium, bicarbonate, and albumin levels (p<0.001, p = 0.002, p = 0.014). Additionally, levels of plasma aldosterone and Plasma Renin Activity (PRA), which are markers for RAAS activation, approximatively doubled by the one-month follow-up visit. Other blood parameters remained stable throughout the study. Furthermore, over 50% of the patients exhibited continuous renal blood flow at both baseline and follow-up (52.2% vs 58.3%). Bio-impedance analysis suggest an increasing trend in the amount of excess body fluid compared to baseline (p = 0.084). Echocardiographic evaluation showed that left ventricular end-diastolic diameter (LVEDD) remained constant with no significant worsening of mitral insufficiency. However, right ventricular systolic pressure (RVSP) decreased significantly at follow-up with a p-value of 0.036.

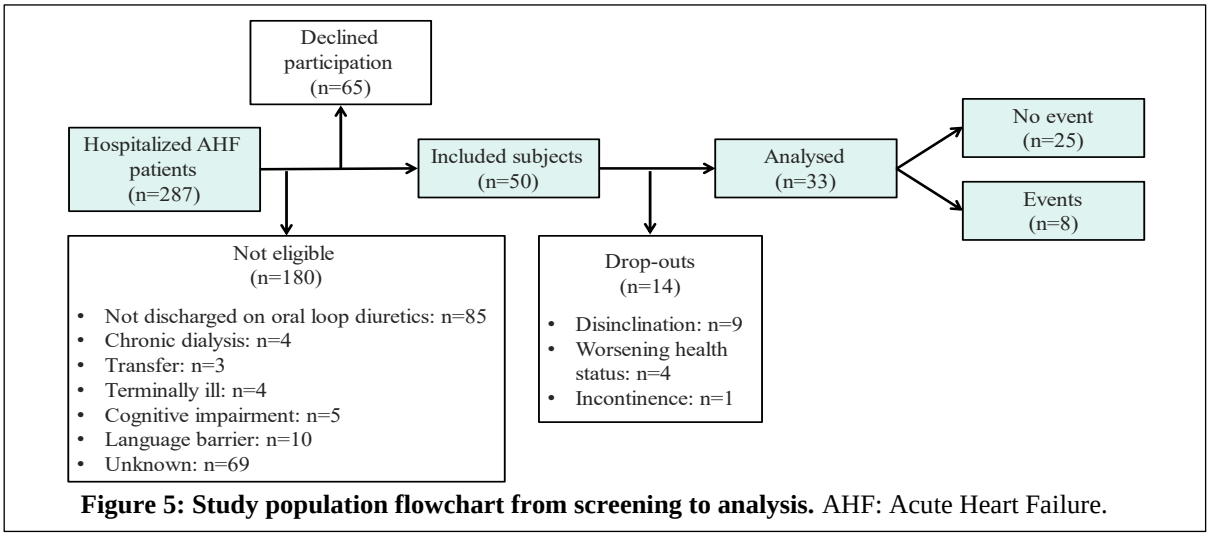

Figure 5: Study population flowchart from screening to analysis. AHF: Acute Heart Failure.

Table 1: Demographics of the FAST-RESPONSE 2 study population (n=50).

Variables	Stable group (n=42)	AHF relapse (n= 8)	p-value
Demographics			
Age	76.1 ± 8.5	75.3 ± 9.8	0.802
Male, n(%)	26.0 (63.4)	6.0 (75.0)	1.000
Active smokers, n(%)	6 (14.63)	0.0 (0.0)	0.522
Heart failure type, n(%)			0.718
HFpEF	18.0 (42.9)	4.0 (50.0)	
HFrEF	24.0 (57.1)	4.0 (50.0)	
Heart failure etiology, n(%)			1.000
Ischemic	20.0 (47.6)	4.0 (50.0)	
Non-ischemic	22.0 (52.4)	4.0 (50.0)	
Physical features			
Heartrate, bpm	68.2 ± 12.1	68.4 ± 15.7	0.967
SBP, mmHg	117.6 ± 18.4	114.4 ± 14.4	0.644
DBP, mmHg	68.2 ± 9.9	60.4 ± 7.6	**0.041***
Weight, kg	80.3 ± 21.9	95.1 ± 15.7	0.075
BMI, kg/m²	28.3 [23.6 – 32.0]	32.0 [28.1 – 38.9]	0.099
VAS score	36.5 ± 19.8	25.8 ± 22.9	0.257
Comorbidities, n(%)			
Atrial fibrillation	33.0 (78.6)	5.0 (62.5)	0.379
COPD	8.0 (19.0)	4.0 (50.0)	0.082
Arterial Hypertension	28.0 (66.7)	5.0 (62.5)	1.000
Diabetes	16.0 (38.1)	5.0 (62.5)	0.255
NYHA class, n(%)			0.284
Class I	6.0 (14.3)	3.0 (37.5)	
Class II	28.0 (66.7)	3.0 (37.5)	
Class III	6.0 (14.3)	2.0 (25.0)	
Class IV	2.0 (4.8)	0.0 (0.0)	
GDMT, n(%)			
ACE-I /ARB	16.0 (38.1)	2.0 (25.0)	0.694
ARNI	14.0 (33.3)	3.0 (37.5)	1.000
MRA	32.0 (76.2)	6.0 (75.0)	1.000
SGLT2-I	15.0 (35.7)	5.0 (62.5)	0.240
Beta-blocker	37.0 (88.1)	6.0 (75.0)	0.310
Laboratory analysis			
Hemoglobin, g/dL	12.6 [11.7 – 14.0]	12.1 [10.8 – 13.6]	0.426
Sodium, mmol/L	138.6 ± 3.0	139.9 ± 5.3	0.378
Serum creatinine, mg/dL	1.5 [1.2 – 1.8]	1.6 [1.2 – 2.1]	0.830
Albumin, g/L	40.8 [33.0 – 43.0]	36.2 [32.0 – 39.0]	0.305
Troponin T, ng/L	35.0 [22.8 – 59.0]	41.0 [28.75 – 45.5]	0.758
NT-pro BNP, ng/L	2509.0 [1188.0 – 5526.0]	1957.0 [1013.00 – 5296.0]	0.677
Plasma Aldosterone, ng/g	87.0 [49.0 – 145.3]	70.0 [57.0 – 118.0]	0.858
PRA, ng/mL/h	121.8 [26.3 – 392.5]	163.1 [45.1 – 374.2]	0.324
Osmolality, mOsm/L	305.1 ± 17.7	310.2 ± 18.3	0.550
Implantable device, n(%)			
Pacemaker	16.0 (38.1)	0.0 (0.0)	**0.043***
CRT	6.0 (14.3)	1.0 (12.5)	1.000
ICD	16.0 (38.1)	2.0 (25.0)	0.694

Data is presented as mean ± standard deviation (std.d) if normally distributed or as median and interquartile range (IQR) if normal distribution was not achieved. Discrete and continuous variables are presented as count (n) and percentage. A p-value of p<0.05 was considered as statistically significant (*). AHF: Acute Heart Failure, HFpEF: Heart failure with preserved Ejection Fraction, HFrEF: Heart Failure with reduced Ejection Fraction, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, COPD: Chronic Obstructive Pulmonary Disease, NYHA: New York Heart Association, ACE-I: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker, MRA: Mineralocorticoid Receptor Antagonist, SGLT2-I: Sodium-Glucose Transport Protein Inhibitor, PRA: Plasma Renin Activity, CRT: Cardiac Resynchronization Therapy, ICD: Implantable Cardioverter-Defibrillator.

Table 2: Characteristics at baseline and follow-up without drop-outs.

Variable	Baseline characteristics (n= 30)	Follow-up characteristics (n= 30)	p-value
Clinical characteristics, n(%)			
Orthopnea	11.0 (36.7)	3.0 (10.0)	**0.041***
Bendopnea	9.0 (30.0)	5.0 (16.7)	0.143
Paroxysmal nocturnal dyspnea	2.0 (6.7)	1.0 (3.3)	1.000
VAS score dyspnea	30.0 [20.0 – 50.0]	20.0 [7.8 – 40.0]	**0.030***
Oedema			**0.026***
Grade 0	13.0 (43.3)	16.0 (53.3)	
Grade 1	11.0 (36.7)	8.0 (26.7)	
Grade 2	3.0 (10.0)	3.0 (10.0)	
Grade 3	3.0 (10.0)	2.0 (6.7)	
Grade 4	0.0 (0.0)	1.0 (3.3)	
Weight, kg	85.7 ± 22.7	83.7 ± 21.2	**0.014***
Laboratory analysis			
Hemoglobin, g/dL	12.6 [11.6 – 13.9]	12.9 [11.6 – 14.0]	0.523
Sodium, mmol/L	138.5 [135.0 – 141.3]	138.0 [136.0 – 141.0]	0.276
Potassium, mmol/L	3.9 [3.6 – 4.3]	4.7 [4.2 – 5.0]	< **0.001***
Chloride, mmol/L	101.7 ± 5.5	100.2 ± 4.8	0.050
Bicarbonate, mmol/L	25.5 ± 3.7	25.9 ± 3.7	**0.002***
Serum creatinine, mg/dL	1.6 [1.3 – 1.9]	1.7 [1.4 – 2.0]	0.141
Total protein, g/dL	69.2 [63.0 – 74.7]	73.5 [70.4 – 76.9]	0.063
Albumin, g/L	39.9 [33.0 – 42.5]	41.9 [38.6 – 44.1]	**0.014***
Troponin T, ng/L	36.5 [25.8 – 51.0]	37.5 [22.8 – 51.0]	0.682
NT-pro BNP, ng/L	2509.0 [1160.5 – 5481.0]	2172.0 [1318.5 – 3146.8]	0.206
Plasma Aldosterone, ng/g	70.0 [49.0 – 137.0]	180.0 [83.0 – 314.0]	**0.007***
PRA, ng/mL/h	131.1 [30.0 – 374.2]	225.1 [87.9 – 550.0]	**0.039***
Osmolality, mOsm/L	306.0 [296.3 -312.0]	302.0 [297.0 – 308.0]	0.477
Renal Doppler Ultrasonography, n(%)			
Continuous flow	12.0 (52.2)	14.0 (58.3)	0.342
Not done	7.0 (23.3)	6.0 (20.0)	
Bio-impedance			
Excess fluid, L	2.1 [0.0 – 4.7]	3.5 [0.0 – 7.6]	0.084
Echocardiography			
LVEDD, mm	48.5 [44.0 – 58.5]	48.5 [42.5 – 55.8]	0.416
RVSP, mmHg	34.6 [26.5 – 44.5]	35.0 [23.9 – 41.3]	**0.036***
MI grade	1.0 [1.0 – 1.5]	1.0 [0.0 – 1.0]	0.205

Data is presented as mean ± standard deviation (std.d) if normally distributed or as median and interquartile range (IQR) if normal distribution was not achieved. Discrete and continuous variables are presented as count (n) and percentage. A p-value of p<0.05 was considered as statistically significant (*). VAS: Visual Analogue Score, NT-pro BNP: N-terminal pro B-type natriuretic peptide, PRA: Plasma Renin Activity, LVEDD: Left Ventricle End Diastolic Diameter, RVSP: Right Ventricular Systolic Pressure, MI: Mitral Insufficiency.

3.3. Longitudinal urinary sodium measurements

A total of 33 participants collected urine samples twice daily. Among these participants, eight experienced an event characterized by an increased dose of loop-diuretics or hospitalization due to an AHF episode. This allowed for the analysis of longitudinal urinary sodium concentration analysis across three subpopulations: the entire study population, stable patients, and those who experienced an AHF event.

Figure 6a depicts the longitudinal daily natriuresis before and after diuretic intake for the entire study population. Mean urinary Na^+ concentration measured at first void ranges from a minimum of 29.0 mmol/L to a maximum of 44.0 mmol/L (at day 14 and 12, respectively). Post-diuretic intake natriuresis showed significantly higher Na^+ concentrations

compared to first void measurements, with mean values ranging from 50.5 mmol/L to 62.0 mmol/L ($p < 0.001$). The pattern of change in urinary Na^+ concentrations over time is borderline significantly different between the pre- and post-diuretic measurements ($p = 0.05$).

In stable AHF patients, first void and post-diuretic natriuresis showed no consistent pattern and exhibited a wider range of values. Baseline mean Na^+ concentrations ranged from 12.5 mmol/L to 43.5 mmol/L, while post-diuretic intake concentrations varied from 37.0 mmol/L to 63.5 mmol/L (**Figure 6b)**. Despite the absence of a clear pattern, post-diuretic Na^+ concentrations remained significantly higher than first void measurements ($p < 0.001$), with similar trends observed over time before and after diuretic intake ($p = 0.488$).

In contrast to stable patients, AHF event patients exhibited a tendency for a reduction in post-diuretic natriuresis four days before the occurrence of an event ($p = 0.094$), when Na^+ concentrations were aligned to the event day (**Figure 6c)**. Furthermore, the difference between pre- and post-diuretic natriuresis remained distinct in patients experiencing an event ($p < 0.001$). Although not statistically significant, there is a trend suggesting that the patterns over time differ before and after diuretic intake in the event group ($p = 0.060$).

Figure 7 illustrates the mean longitudinal urinary Na^+ concentrations for two groups: patients who experienced an AHF event and stable patients. The top panel (**Figure 7a**) presents mean urinary Na^+ concentrations measured at first void. Both groups display similar fluctuations in mean Na^+ concentrations ($p = 0.236$), varying from 12.5 mmol/L to 43.5 mmol/L in the stable group and from 28.0 mmol/L to 44.0 mmol/L in the event group. The interaction between the groups over time was not statistically significant (interaction $p = 0.801$). The bottom panel (**Figure 7b**) shows urinary Na^+ concentrations after loop diuretic intake. In contrast to the stable group, the event group exhibits more variability in mean Na^+ concentrations throughout the last week. However, there is no significant difference in between the means of the stable and event group ($p = 0.667$). Natriuresis exhibited a marked decrease, declining from a mean of 67.0 mmol/L on day -8 to 30.0 mmol/L by day -4 prior to the acute heart failure episode. However, the interaction between the groups over time was also not statistically significant (interaction $p = 0.762$).

Additionally, the median delta was assessed to identify high and low responders to diuretic therapy. The difference between pre- and post-diuretic urinary Na^+ concentrations was calculated for each participant, with a general median of 11.0 mmol/L. Among the 25 stable patients and 8 event patients, 48.0% and 37.5% were classified as low responders (median $\Delta_{post\text{-}pre} < 11.0$ mmol/L), respectively. Similarly, the median of urinary Na^+ was assessed for pre-diuretic natriuresis, with 48.0% of the stable group and 37.5% event group as low excreters.

Overall, these data demonstrate a difference ($p < 0.001$) in mean urinary Na^+ excretion between pre- and post-diuretic in all three subpopulations along with a variability in urinary Na^+ concentrations. Additionally, a dip in natriuresis can be observed four days before the occurrence of an event, followed by a subsequent increase.

3.4. EQ-5D

EQ-5D questionnaire was taken at baseline and after one month at the study visit. The calculated mean baseline scores for each of the five topics assessed by EQ5D were compared to the follow-up means to analyze any changes over time. There was no significant difference ($p > 0.05$) between each topic (mobility, selfcare, daily activities, pain/discomfort, fear/depression). The mean health score was constant between the two time points with a value of 63.9 ± 15.7 at baseline and 63.3 ± 23.0 at follow-up.

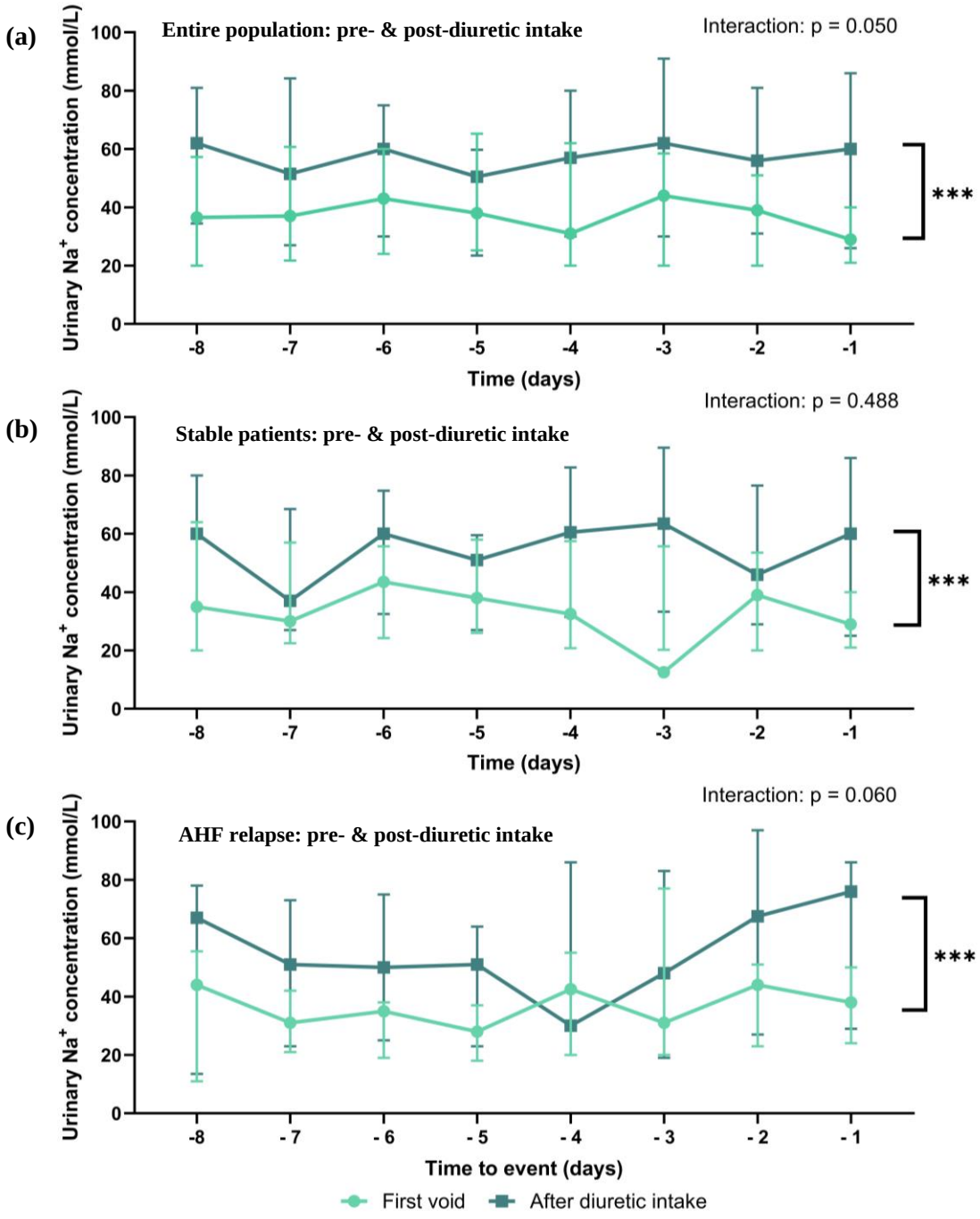

Figure 6: Longitudinal urinary Na^+ concentrations at first void and after diuretic intake. Timeline of sample collection is depicted counting days backward, with day -1 representing the final day of sample collection, day -2 as the second-to-last day, and so forth. **(a)** Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake plotted for the entire study population (n=33). **(b)** Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake plotted for the stable subpopulation (n = 25). **(c)** Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake preceding the event occurrence. Data is presented as median and IQR. *** $p < 0.001$

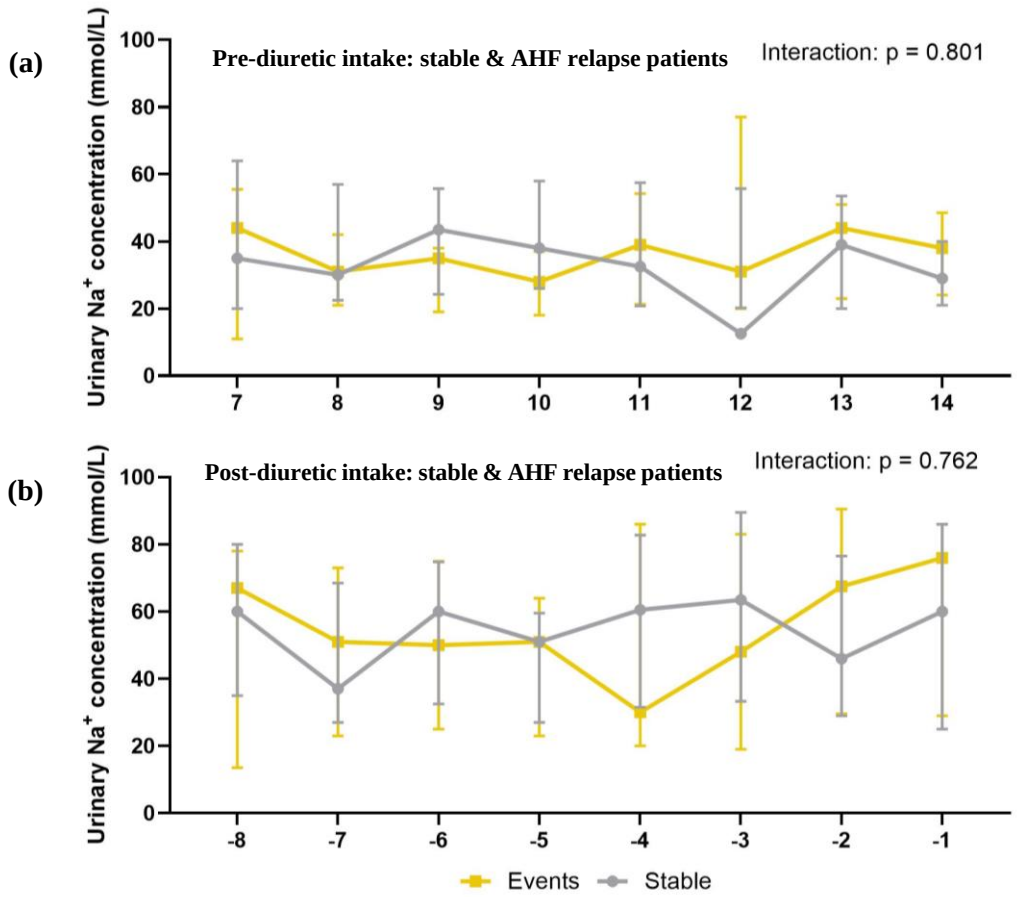

Figure 7: Longitudinal urinary Na^+ concentrations in the stable and event subpopulation. (a) Urinary Na^+ concentrations (mmol/L) at first void plotted for the stable and event subpopulation. **(b)** Urinary Na^+ concentrations (mmol/L) post-diuretic intake plotted for the stable and event subpopulation. Events are aligned for the AHF relapse subpopulation, where the x-axis represents the days leading up to the event, or the days counted backward from the end of sample collection for the stable group. Data presented as median and IQR.

4. DISCUSSION

This single-center interventional prospective cohort study aimed to observe daily changes in urinary sodium concentrations in patients post-AHF hospitalization. The hypothesis posited that AHF patients would show a decrease in urinary sodium concentration before the clinical manifestation of an AHF event. The main findings of this study are: (1) there was a drop in natriuresis four days prior to an event in AHF patients followed by an increase in urinary sodium excretion. (2) Baseline natriuresis is significantly different from post-diuretic intake urinary Na^+ levels in all patients.

The study population could be divided into two groups based on the occurrence of a clinical event (increased loop-diuretic dose/AHF rehospitalization). Both groups were predominantly males around 75 years old. There was no association between heart failure type or etiology and clinical outcome. Most patients were mildly symptomatic and classified as NYHA class I-II. Guideline-directed medical therapy was similarly administered in both groups. Although not statistically significant, participants with an AHF relapse tended to have a higher BMI compared to the stable group. The higher weight in the AHF relapse group might imply residual fluid accumulation at the moment of discharge, however no other parameters (no difference in VAS dyspnea score, NYHA class or NT-pro BNP) indicating fluid excess were present. Heart failure patients with a higher body weight exhibit several pathophysiologic

features, such as greater right ventricular remodeling, plasma volume expansion and pericardial restraint, which make them more vulnerable to new AHF episodes due to the negative effect of decongestion on renal function (29).

Both at baseline (i.e., at the end of the AHF hospitalization) and at the one-month follow-up visit, participants underwent clinical assessments to evaluate signs and symptoms of congestion. Despite overall good decongestion at discharge, there was an even further decrease in body weight, congestion parameters and dyspnea score. This might be attributable to the optimization of GDMT during hospitalization. At the moment of discharge 69.4% were taking quadruple or triple heart failure therapy. The STRONG-HF (acronym lang) evaluated rapid up-titration of GDMT after an acute heart failure hospitalization and demonstrated a reduction in heart failure symptoms, improvement in QoL and reduced 180-day mortality and rehospitalization risk. In addition, there was a decrease in blood pressure, pulse, NYHA class and body weight after 90 days. These results are confirmed in our study. Despite the limited sample size, there was a general high prescription rate of GDMT, which might be the reason for the continued improvement at home (30).

The lower potassium levels predischarge are likely due to the use of intravenous diuretics, which are not potassium-sparing. However, the administration of spironolactone or eplerenone in the ambulatory setting leads to a restoration of potassium levels at follow-up (18). The apparent elevation of albumin levels from 39.9 g/L at baseline to 41.9 g/L at follow-up is attributed to the fact that, at baseline, some patients were still experiencing mild congestion, thereby diluting the albumin levels. This dilution effect is resolved at follow-up when patients are no longer experiencing fluid overload (31). The observed twofold increase in Plasma Renin Activity (PRA) levels can be elucidated by the well-known disparity in PRA levels between ambulatory patients and those with acute decompensated heart failure. Nijst *et al.* showed that ambulatory chronic patients, devoid of signs and symptoms of congestion, exhibit elevated PRA levels due to optimal treatment with ACE inhibitors (ACE-i), angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs). These medications effectively antagonize the renin-angiotensin system (RAS) downstream of the renin cascade at the levels of ACE and Angiotensin II (Ang II), thereby attenuating the effects of renin activation without directly suppressing renin secretion itself (32). The surplus fluid quantified via bioimpedance analysis suggests patients accumulate a greater volume of fluid at follow-up compared to baseline. However, this observation is not consistent with the reduction in weight (-2kg) and laboratory blood measurements. It is imperative to acknowledge that deviations from this observation may arise due to potential limitations or inaccuracies inherent to the bioimpedance device itself.

According to ESC guidelines, a satisfactory diuretic response is defined as a urine Na^+ concentration exceeding 50-70 mEq/L two hours after intravenous diuretic administration. Natriuresis below this treshold identifies a poor loop-diuretic response and suggests that such patients may benefit from early diuretic up-titration (12). In this study however, the mean post-diuretic natriuresis in a stable outpatient population ranged from 37.0 mmol/L to 63.5 mmol/L with a median of 60.0 mmol/L, not reaching the 70 mEq/L cutoff. Additionally, individual patient urinary Na^+ levels frequently fluctuated, often falling below the 50-70 mmol/L range, despite patients maintaining clinical stability and exhibiting no AHF symptoms in the ambulatory setting. These findings suggest that the natriuresis cutoff may require adjustment for applicability in an ambulatory setting. A lower threshold may be valid for this stable outpatient population as the goal is to maintain a neutral Na^+ balance (Na^+-in equals Na^+-out), while during an AHF episode the goal is to achieve a negative Na^+ balance (Na^+-out is higher than Na^+-in) to get rid of the excess Na^+. To our knowledge, this study is the first to utilize daily post-diuretic urinary Na^+ spot measurements in a home-based context , potentially enabling the adaptation of a diuretic response cutoff to an ambulatory setting. However, the limited dataset requires further validation. Larger studies with diverse populations and extended follow-up are needed to establish the optimal natriuresis cutoff for ambulatory settings.

In this study, 33 participants collected urine samples twice daily for 14 days, providing

insights into urinary sodium concentration dynamics among different heart failure (HF) subpopulations. Eight participants, or 22.2%, experienced HF events within the first month after discharge, aligning with findings in the literature where rehospitalization rates were up to 18.2% within 30 days (17, 33). Owing to insufficient data and a substantial dropout rate, urine collections spanning from day 1 to day 6 were excluded. This decision was made to ensure data equilibrium, as including these collections would have resulted in skewed means due to disparate data points.

Pre- and post-diuretic urinary sodium concentrations were significantly different across all subpopulations, with notable variability observed. This emphasizes the remarkable fact that even after AHF hospitalization with high-dose IV diuretics, patients remain responsive to a small dose (1 mg) of diuretics.

Stable HF patients exhibited similar trends in sodium excretion before and after diuretic intake, while event patients showed a decline in post-diuretic natriuresis four days preceding HF events. These findings align with an explorative study by Martens *et al.*, which investigated the relationship between urinary sodium concentrations and the development of AHF hospitalization in, stable, chronic patients over a 30-week period of first-void urine collection. The results showed a relatively stable urinary Na^+ concentration over time, yet significant interindividual variations were observed. Nonetheless, the study indicated that stable, chronic heart failure experiencing an AHF event consistently exhibited lower natriuresis at first-void, with a further decline in the week preceding hospitalization (26). However, the FAST-RESPONSE 2 study revealed a sudden declining trend in post-diuretic natriuresis of AHF patients the fourth day before hospitalization with no difference between baseline urinary sodium concentrations.

These findings confirm the hypothesis that the natriuresis of AHF patients decreases prior to the onset of physical symptoms, emphasizing its significant impact on home-based monitoring and the prevention of hospitalization. Additionally, they underscore the complexity of sodium excretion dynamics in HF patients and highlight the potential utility of monitoring urinary sodium concentrations in predicting HF exacerbations.

4.1. Limitations

The primary limitations of this study include a small sample size and a high dropout rate. Patients found the sample collection protocol burdensome and impractical, particularly given their post-hospitalization state, which adversely affected their motivation. Furthermore, due to constraints related to the measuring equipment in the clinical laboratory, urinary sodium concentrations below 20 mmol/l and plasma renin activation above 550 ng/mL/h could not be measured. This limitation has significant implications for monitoring urinary Na+ concentrations, as very low excretion rates, particularly preceding an event, could not be quantified, thereby impacting the data's significance during analysis. Subsequent steps should involve extending sample collection over a three-month period during the vulnerable phase to validate these findings over a longer duration. Additionally, developing a home-based tool for measuring these values would circumvent the need for clinical laboratory testing and enable timely intervention, potentially preventing hospitalization by adjusting diuretic therapy as needed.

5. CONCLUSION

In conclusion, our study demonstrates that monitoring daily urinary Na^+ levels before and after loop-diuretic intake holds promise in predicting acute heart failure (AHF) events by identifying a decline in natriuresis. This finding carries significant implications for heart failure management, as it suggests the potential to customize diuretic dosages based on urinary sodium concentrations, ultimately leading to a reduction in AHF events and associated hospitalizations and mortality rates. However, further data and a larger sample size are required to solidify these findings before implementation in routine clinical practice.

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Author contributions – Prof. Dr. W. Mullens, Dr. E. Meekers and Dr. P. Martens conceived and designed the research. M. Miseur, R. Knevels and Dr. E. Meekers performed experiments and data analysis. M. Miseur designed the figures. M. Miseur and E. Meekers wrote the paper. All authors carefully edited the manuscript.

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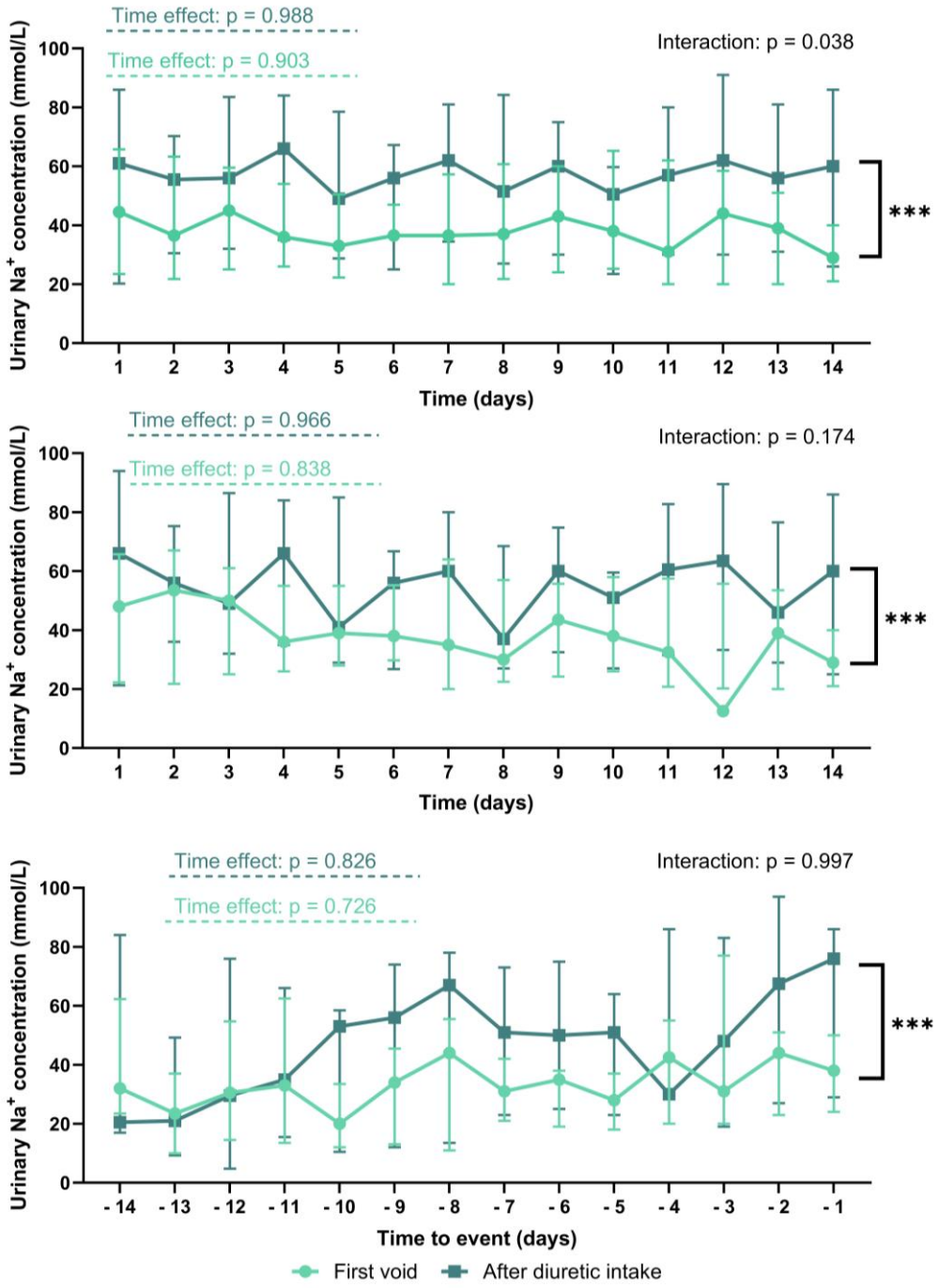
Supplementary Table 1: Characteristics at baseline and follow-up.

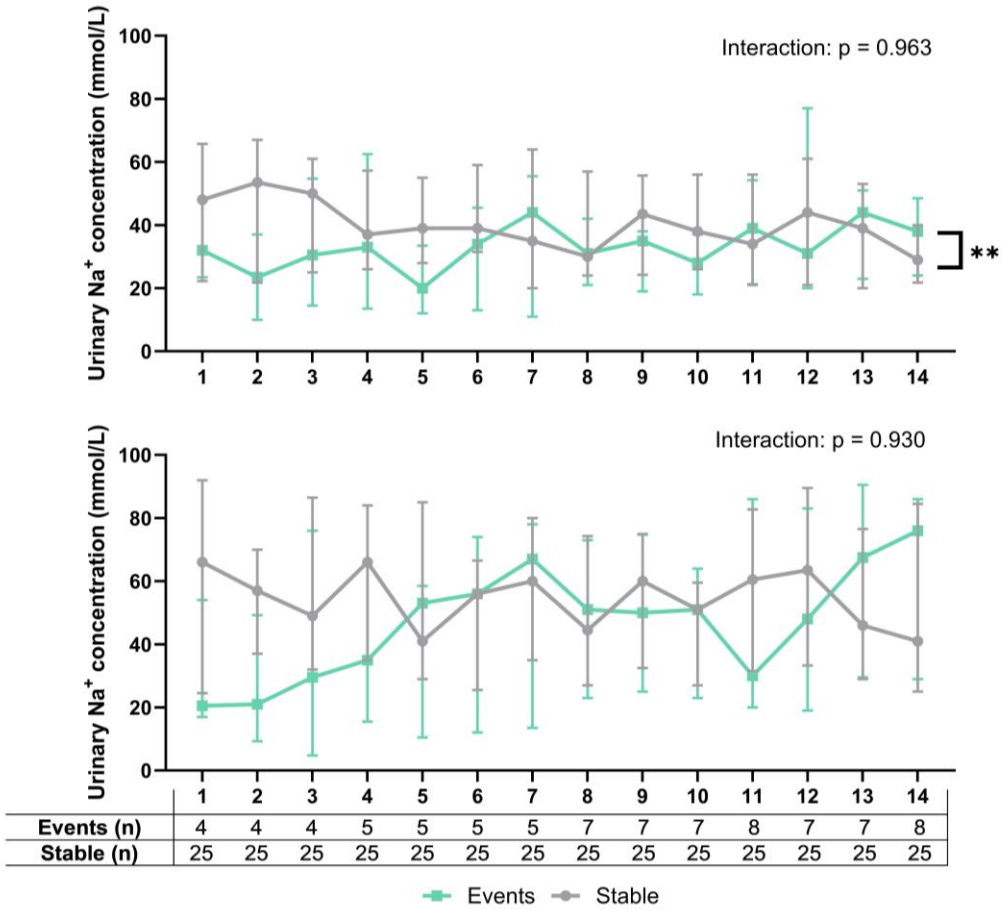
Variable	Baseline characteristics	Follow-up characteristics	p-value
Clinical characteristics, n(%)			
Orthopnea	22.0 (44.0)	3.0 (8.8)	**0.048**
Bendopnea	17.0 (34.0)	5.0 (14.7)	0.300
Paroxysmal nocturnal dyspnea	7.0 (14.0)	1.0 (2.9)	1.000
VAS score dyspnea	35.3 ± 19.6	20.0 [6.5 – 36.25]	**0.009**
Oedema			**0.016**
Grade 0	25.0 (50.0)	19.0 (55.9)	
Grade 1	16.0 (32.0)	8.0 (23.5)	
Grade 2	6.0 (12.0)	3.0 (8.8)	
Grade 3	3.0 (6.0)	2.0 (5.9)	
Grade 4	0.0 (0.0)	2.0 (5.9)	
Weight, kg	82.7 ± 21.6	81.8 ± 20.8	**0.015**
Laboratory analysis			
Hemoglobin, g/dL	12.7 [11.3 – 13.9]	13.1 [11.6 – 14.1]	0.620
Sodium, mmol/L	138.8 ± 3.6	138.5 [136 – 141]	0.246
Potassium, mmol/L	4.0 ± 0.5	4.8 [4.2 – 5.0]	**<0.001**
Chlorine, mmol/L	100.8 ± 5.1	100.6 ± 4.7	0.193
Bicarbonate, mmol/L	22.3 [21.3 – 28.9]	26.2 ± 3.6	0.204
Serum creatinine, mg/dL	1.5 [1.1 – 1.7]	1.6 [1.3 – 1.9]	0.073
Total protein, g/Dl	70.1 [63.5 – 74.6]	73.1 [68.9 – 76.9]	**0.025**
Albumin, g/L	38.3 [34.5 – 41.9]	41.5 ± 4.1	**0.004**
Troponin T, ng/L	36.5 [25.8 – 50.0]	35.0 [22.8 – 49.3]	0.438
NT-pro BNP, ng/L	2828.0 [1328.0 – 5526.0]	2172 [1318.5 – 3146.8]	0.166
Plasma Aldosterone, ng/g	67.5 [46.8 – 160.8]	180.0 [80.0 – 300.5]	**0.017**
PRA, ng/mL/h	82.8 [21.1 – 178.6]	196.4 [50.2 – 550.0]	**0.011**
Osmolality, mOsm/L	303.1 ± 15.7	302.0 [297.0 – 307]	0.709
Renal Doppler Ultrasonography, n(%)			
Continuous flow	19.0 (38.0)	18.0 (58.1)	0.414
Not done	11.0 (22.0)	19.0 (38)	
Bio-impedance			
Excess fluid, L	2.5 [0.0 – 4.7]	2.9 [0.0 – 7.0]	0.058
Echocardiography			
LVEDD, mm	50.0 [44.2 – 60.6]	50.4 ± 9.2	0.467
RVSP	36.0 [27.0 – 46.0]	33.3 ± 11.8	0.294
MI grade	1.0 [1.0 – 2.0]	1.0 [0.0 – 1.75]	**0.021**

Data is presented as mean ± standard deviation (std.d) if normally distributed or as median and interquartile range (IQR) if normal distribution was not achieved. Discrete and continuous variables are presented as count (n) and percentage. A p-value of $p<0.05$ was considered as statistically significant (*). VAS: Visual Analogue Score, NT-pro BNP: N-terminal pro B-type natriuretic peptide, PRA: Plasma Renin Activity, LVEDD: Left Ventricle End Diastolic Diameter, RVSP: Right Ventricular Systolic Pressure, MI: Mitral Insufficiency.

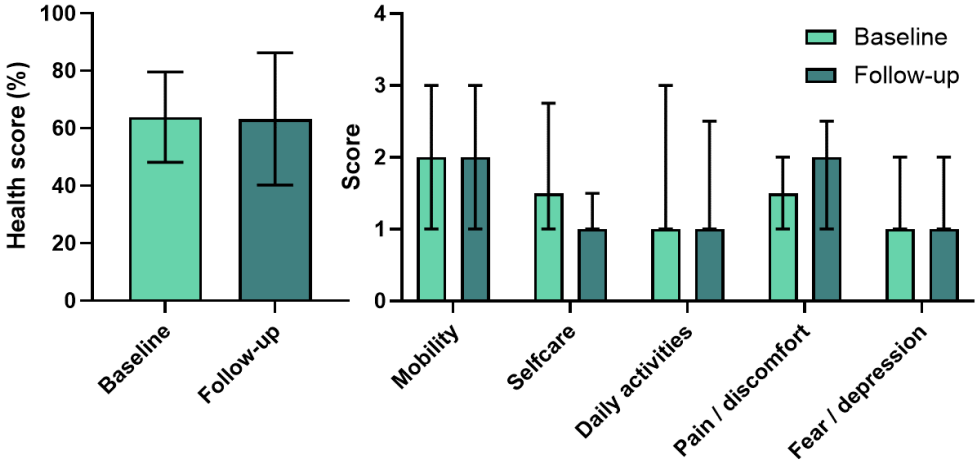


	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
First void (n)	4	4	4	5	5	5	5	7	7	7	8	7	7	8
After diuretic intake (n)	4	4	4	5	5	5	5	7	7	7	7	7	8	7

Supplementary Figure 1: Longitudinal urinary Na^+ concentrations at first void and after diuretic intake over 14 days. (a) Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake plotted over 14 days for the entire study population (n=33). **(b)** Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake plotted over 14 days for the stable subpopulation (n = 25). **(c)** Urinary Na^+ concentrations (mmol/L) pre- and post-diuretic intake plotted over 14 days preceding the event occurrence. Data is presented as median and IQR. *** $p < 0.001$



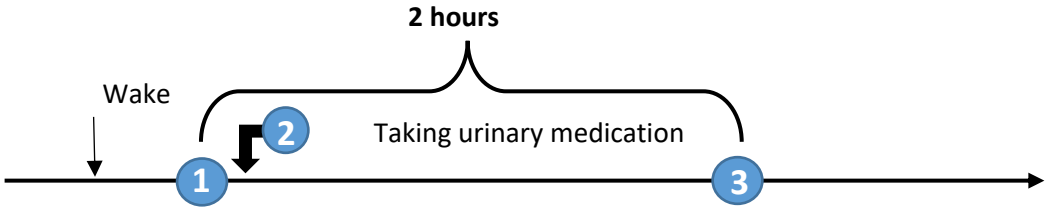
Supplementary Figure 3: Longitudinal urinary Na^+ concentrations in the stable and event subpopulation. (a) Urinary Na^+ concentrations (mmol/L) at first void plotted over 14 days for the stable and event subpopulation. (b) Urinary Na^+ concentrations (mmol/L) post-diuretic intake plotted over 14 days for the stable and event subpopulation. Events are aligned after day 14, meaning that the x-axis are the days preceding the event. The number of collected urine samples are displayed in the table. Data presented as median and IQR. ** $p < 0.01$



Supplementary Figure 2: Median scores on EuroQuol-5 Dimension questionnaire. p-values EQ-5D score mobility, selfcare, daily activities, pain/discomfort, fear/depression p = 0.827, p = 0.090, p= 0.971, p=0.408, p=0.625

Procedure for taking urine samples

You will take urine samples during 14 days. The following steps describe the actions you need to perform each day. These actions are shown graphically in the diagram below.



- Collect urine sample 1 (before diuretic medication)
- Store urine sample in freezer
- Fill out the checklist
- Install reminder alarm (1h30min later)
- Fill out the questionnaire

- Collect urine sample 2 (after diuretic medication)
- Store urine samples in freezer
- Fill out the checklist

Step 1: Sample 1 collection

- After waking up in the morning, the first urine sample is taken.
  - You remove the blue lid from the plastic jar and urinate in the jar.
  - Then put the blue lid back on the jar.
  - Remove the white sticker on top of the blue lid.
  - You take the tube marked 'sample 1 and the corresponding day'.
  - You insert the tube into the hole of the lid.
  - You fill the tube up to the mark and then remove the urethra.
- Storage of urine sample.
  - You place the urine sample in the freezer for further storage.
- Fill in checklist.
  - In the checklist, tick the box that you have taken the first urine sample.
- Install reminder alarm.
  - You set an alarm for 1 hour and 30 minutes later.
- Filling out the questionnaire
  - You fill in the questionnaire of that day.

Step 2: Taking urine medication

- After taking the first urine sample, you may take your diuretic medication.

Step 3: Sample 2 collection

- After 1 hour and 30 minutes, the alarm you set in **step 1** will sound.
- At this point, you will take another urine sample.
  - You urinate in the jar again as described in **step 1**.
  - You take the tube marked 'sample 2 and the corresponding day'.
- Fill in checklist.
  - You tick the box in the checklist that you have taken the second urine sample.
- Storage of urine sample.
  - In the checklist, tick the box that you have taken the first urine sample.

Daily questionnaire

(fill in in the morning)

Blood pressure ☐☐☐☐☐ mmHg	Weight ☐☐☐☐☐ kg

VAS score dyspnee *Score shortness of breath 0 – 100.* *0: No complaints – no shorteness of breath.* *100: Very severe shortness of breath.* ☐☐☐	Medication dose *(Lasix/Burinex)* Dose of diuretic medication ..... mg

Edema – fluid accumulation in 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 present)
- ❑ 3+ (Obvious swelling/fluid accumulation of lower leg)
- ❑ 4+ (Fluid accumulation above the knee)

Diet

Have there been any changes to your diet today?

- ❑ No
- ❑ Yes, which

.....

.....

.....

EQ5D questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking about ☐

I have slight problems walking about ☐

I have moderate problems walking about ☐

I have serious problems walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have serious problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

DAILY ACTIVITIES (e.g. work, housekeeping, family and leisure activities)

I have no problems with my daily activities ☐

I have slight problems with my daily activities ☐

I have moderate problems with my daily activities ☐

I have serious problems with my daily activities ☐

I am unable to carry out my daily activities ☐

PAIN/DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY/DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

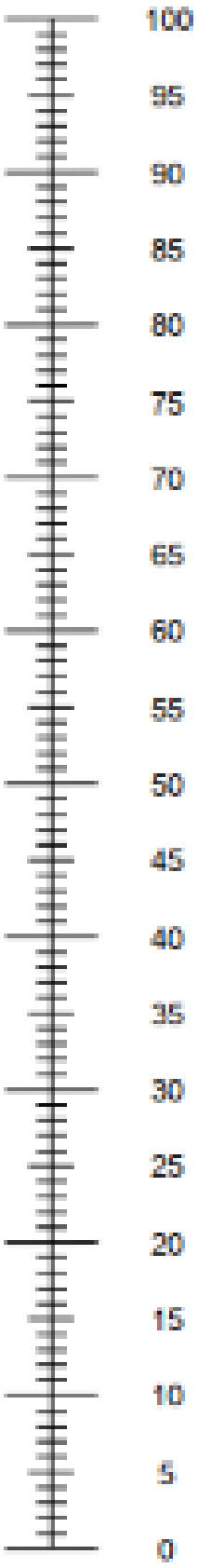
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Please write the number you marked in the scale in the box below.

The best health you can imagine



The worst health you can imagine