URINARY SODIUM-GUIDED PRECISION MANAGEMENT FOR HEART FAILURE

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LIST OF ABBREVIATIONS

ACEi	Angiotensin-Converting Enzyme Inhibitor
ADHF	Acute Decompensated Heart Failure
ADVOR	Acetazolamide in Decompensated Heart Failure with Volume Overload
AHF	Acute Heart Failure
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
BB	Beta-Blocker
BHF	Belgian Heart Foundation
CABG	Coronary Artery Bypass Grafting
CHF	Chronic Heart Failure
CI	Confidence Interval
CIED	Cardiac Implantable Electronic Device
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
GDMT	Guideline-Directed Medical Therapy
HF	Heart Failure
HFA	Heart Failure Association
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ICD	Implantable Cardioverter-Defibrillator
IQR	Interquartile Range
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LV	Left Ventricle

LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonist
NT-proBNP	N-terminal pro–B-type Natriuretic Peptide
NYHA	New York Heart Association
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAP	Pulmonary Artery Pressure
PCI	Percutaneous Coronary Intervention
POC	Point-of-Care
PRA	Plasma Renin Activity
PTCA	Percutaneous Transluminal Coronary Angioplasty
RVSP	Right Ventricular Systolic Pressure
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
SOC	Standard of Care
WRF	Worsening Renal Function
ZOL	Ziekenhuis Oost-Limburg

If we knew what we were doing,
it would not be called research, would it?

- Albert Einstein -

GENERAL INTRODUCTION

Globally, it is estimated that 64.3 million patients are living with heart failure, accounting for a prevalence of 1-2% in the adult population in the developed countries. (1,2) Chronic heart failure (CHF) is characterized by episodes of acute heart failure (AHF), with signs and symptoms of congestion being the main reason to seek urgent medical attention. (3) The majority (up to 90%) of the patients with AHF experience signs of congestion and only the minority of the cases have symptoms due to hypoperfusion. (4–6) Despite the improvements in guideline-directed medical therapy (GDMT), hospitalization rates for AHF with congestion remain extremely high, illustrated by recent heart failure trials (Table 1).

In addition, the risk for rehospitalization or all cause-mortality after an AHF event is even higher, which creates a tremendous economic and social burden on the society. Rehospitalization rates count up to one-fourth within three months (also referred to as the 'vulnerable phase') and 67% within one year after AHF, especially in patients discharged with residual signs and symptoms of congestion. (6,7) In Europe, AHF hospitalizations account for 1-2% of all admissions and representing the most prevalent reason for hospitalization among the elderly patients. While the widespread use of GDMT improves life expectancy in patients with CHF, it also leads to aging of the heart failure population and an increase in the prevalence of CHF. For example, more than 250 000 citizens in Belgium have CHF, and every year up to 20.000 new patients are diagnosed which results in an annual heart failure related expenditure (mainly spent on AHF hospitalization) of more than 150 million €. This accounts for 3% of the national healthcare budget. As such, the growing HF hospital (re)admission rates are alarming and pose a heavy burden on the healthcare expenditure as well as on the quality of life of the HF patients.

Table 1

Event rate (cardiovascular death and heart failure hospitalization) in most recent trials

	PARADIGM (2014)	DAPA-HF (2019)		DELIVER (2022)		EMPEROR-Reduced (2020)			EMPEROR-Preserved (2021)	
Study	Sacubitril /valsartan	Enalapril	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo
LVEF	29.6 (± 6.3)%	29.4 (± 6.3)%	31.2 (± 6.7)%	30.9 (± 6.9)%	54.0 (± 8.6)%	54.3 (± 8.9)%	27.7 (± 6.0)%	27.2 (± 6.1)%	54.3 (± 8.8)%	54.3 (± 8.8)%
Event rate	21.8%	26.5%	16.3%	21.2%	16.4%	19.5%	19.4%	24.7%	13.8%	17.1%
Hospita-lization rate	12.8%	15.6%	9.7%	13.4%	11.8%	14.5%	13.2%	18.3%	8.6%	11.8%
Hazard Ratio	0.80 (0.73-0.87)	0.74 (0.65-0.85)		0.82 (0.73-0.92)		0.75 (0.65-0.86)			0.79 (0.69-0.90)	

Chronic heart failure

CHF is a clinical syndrome consisting of cardinal symptoms and signs (breathlessness, fatigue, leg edema, …) which is the result of structural and/or functional abnormalities of the heart. These result in elevated intracardiac pressures and/or reduced contractility with an inadequate cardiac output at rest and/or during exercise. Identification of the underlying etiology is crucial as this might direct specific therapeutic strategies. (8) Traditionally, heart failure patients are classified based on their underlying ejection fraction as either heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction or heart failure with preserved ejection fraction (HFpEF) (Table 2). (8)

Table 2

Heart failure subcategories

HFrEF	HFmrEF	HFpEF
Signs and symptoms	Signs and symptoms	Signs and symptoms
LVEF ≤40%	LVEF 41-49%	LVEF ≥50%
		Evidence of structural and/or functional cardiac abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides.

Although there is an overlap between the categories, recommendations for specific therapeutic options (devices and medication) and the strength of the recommendation differ between them. With regard to disease-specific medication, there are 4 groups of medication (beta-blockers, mineralocorticoid receptor antagonists (MRA), sodium-glucose cotransporter 2 inhibitors (SGLT2i) and angiotensin-converter enzyme-inhibitors (ACEi), angiotensin-receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitor (ARNI)) that have demonstrated to improve morbidity and mortality in these patients. These are referred to as guideline-directed medical therapy (GDMT), which have the strongest recommendation (Class I) for patients with HFrEF, with the exception for SGLT2i which have a Class I recommendation in all subcategories. (8) In patients with HFrEF, the goal is to prescribe all 4 in the highest tolerable dose.

Importantly, these medications do not treat signs of congestion, but aim to prevent AHF episodes. In that case, loop diuretics are recommended to relieve signs and symptoms of congestion (Class I). (8) However, these have never demonstrated any benefit with regard to long-term outcome and they should be aimed to be dosed at the lowest dose necessary.

Irrespective of the underlying category and cause, AHF is the main reason for hospitalization in all subcategories. The interaction between heart and kidney with neurohumoral up-regulation in patients with CHF leads to congestion due to an increased renal sodium avidity. (9) The compromised natriuresis results in a positive sodium and water balance (3,9), leading to interstitial and intravascular volume retention. (10,11) Additionally, sympathetic activation gives rise to splanchnic arterial and venous vasoconstriction with redistribution of the blood from splanchnic capacitance bed to the effective circulatory volume. (3) Both the increased plasma volume and the redistribution to the effective circulating volume result in an increased venous return with augmented cardiac filling pressures and consequently signs and symptoms of congestion. (11,12) During the CHF phase, the main aim is to maintain euvolemia and preventing AHF episodes. Unfortunately, current metrics are limited. Evaluations based on weight change, fluid balance and symptoms are not reliable to successfully predict and prevent episodes of congestion.

Implantable hemodynamic monitoring systems have demonstrated to be able to predict an AHF event due to a rise in pulmonary artery pressures which preceded the event by several days to weeks. (13) In addition, heart failure management programs with therapy adjustments based on the pulmonary artery pressures have proven to reduce the hospitalization rate. (14) Despite the beneficial effect, large-scale implementation in all HF patients is hampered by the invasive and costly nature of the device and remains therefore selected for patients at higher risk for decompensation. (15) Importantly, the gradual onset of symptoms in most patients, and the fact that monitoring of weight changes lack sensitivity to predict early onset of volume overload in HF makes prediction of episodes of acute heart failure extremely difficult. As such, a multi-parameter-based evaluation of congestion using clinical assessment at rest and during dynamic maneuvers as

well as biomarkers, supplemented with technical assessments according to local expertise, has been proposed by the Heart Failure Association of the European Society of Cardiology to evaluate congestion. (3) Unfortunately, such an approach is quite cumbersome and not feasible in the ambulatory setting to evaluate a patient, let alone predict if a patient will be admitted with AHF.

Recently, the research group from the department of Cardiology ZOL Genk were one of the many investigators to prove that ambulatory urinary sodium concentration measurements provide important prognostic information. (16–18) Long-term longitudinal analysis of urinary sodium concentration in ambulatory patients might be a very attractive tool to predict the onset of AHF as it is a direct reflection of the increased renal sodium avidity leading to such episodes. Indeed, Martens et al. demonstrated that episodes of AHF most often occurred in patients with a prolonged low urinary sodium excretion with a further drop the week before hospitalization. (17) With the exception of the drop in sodium concentration, neither changes in body weight nor dyspnea scoring were predictive for imminent decompensation. These findings illustrate that the increased sodium avidity in the kidney due to neurohormonal up-regulation and consequently the plasma volume overload contribute to the onset of AHF. A strong correlation between sodium concentration in the urinary spot analysis and 24h urine sample has been demonstrated. Additionally, long-term use of loop diuretics can lead to hypertrophy of distal tubular segments and increased distal sodium reabsorption, reducing diuretic response. Moreover, inappropriately high dosing of ambulatory loop diuretics hampers the implementation of disease modifying agents for HFrEF. (19) Finally, several observational studies have linked loop diuretic use to increased mortality, even after multivariate adjustment. (20) Therefore, dosing of loop diuretics needs to be individualized and changed over time in the individual patient. An easy-to-use bedside analysis of urinary sodium content (i.e. quantitative dipstick) by the patient would be of great benefit. If urinary sodium measurements at home would demonstrate the same benefits, this would be an aid in faster identification of high-risk patients (lower sodium excreters) and facilitate diuretic dose adjustment and GDMT up-titration, hereby possibly resulting in an earlier symptom relief and reduction in HF hospitalization.

Acute heart failure

Most patients with AHF are admitted due to signs and symptoms of congestion and only the minority due to low-output failure. (4–6) In order to treat patients with AHF, the goal is to achieve a net negative fluid and sodium balance, i.e. excreting more water and sodium than intake. In order to assess this, current clinical metrics are net fluid output and serial changes in weight. These metrics are frequently incorrectly collected and have a weak correlation with the diuretic response (i.e., urinary sodium excretion per mg diuretic). (21,22) The low accuracy urges the need for better parameters to monitor the diuretic efficacy. As impaired natriuresis leads to an insufficient plasma and extravascular volume reduction, it seems rational that guiding diuretic therapy based on natriuresis might be more efficacious. Twenty-four hours urine collections are not feasible in daily practice due to the high rate of sampling errors. A urinary spot sodium analysis has proven to reflect the natriuretic response and can be used to tailor the decongestive treatment, especially during the first days of diuretic therapy. (9,21) Importantly, the diuretic efficiency differs between and within patients, reflecting different patient characteristics. (21) This makes a 'one size fits all' therapy not feasible.

The current ESC guidelines recommend an early and repetitive evaluation of the loop diuretic response through urinary spot sodium analysis and 6-hours diuresis, which permits an early intensification in patients at risk for loop diuretic resistance with fast adaptations in diuretic therapy (dose intensification or combination therapy). A spot urinary sodium concentration less than 50-70 mmol/L after 2 hours or a diuresis < 100-150 ml/h after 6 hours in patients with acute decompensated heart failure distinguishes patients with a poor diuretic response. (8) A spot urine sample is easily obtainable and has the advantage of providing information more rapidly than a (timely) urine collection. Currently, we have two large prospective trials that evaluated such a strategy. The Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) was a single-center, prospective, randomized open-label trial of 310 acute decompensated heart failure patients. (23) The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) trial was an international, non-randomized, open-label, pragmatic study, which included 484 acute

decompensated heart failure patients. (24) Both studies compared a standard-of-care group with a natriuresis-guided diuretic uptitration protocol. They had similar findings, both demonstrating that a urinary sodium-based diuretic up-titration protocol improves natriuresis and diuresis in patients with acute decompensated heart failure. Although helpful in clinical practice, broad implementation of such a protocol might be hampered as urine samples still need to be collected, transferred to and analyzed in the lab, making this type of analysis still cumbersome, time consuming and costly. Indeed, urinary sample analyses in the laboratory frequently lead to a delay in diagnosis and therapy adjustments, because of the significant lag between sample submission and result availability. As such, an easy-to-use bedside analysis of urinary sodium content (i.e. quantitative dipstick) would be of great benefit. This would further facilitate a more rapid evaluation of the diuretic response and therapy adjustment, possibly resulting in an earlier symptom relief and shortened length of hospital stay.

Direct urinary sodium measurements

Normally, urinary sodium concentration measurements are performed in-lab and require some time to process. However, there are some methods available to achieve a direct result bedside or to be used in ambulatory settings. A semi-quantitative measurement is possible through sodium or chloride dipsticks, which allow a visual quantification of the concentration. It allows a fast screening, however not completely accurate. A more precise solution is the measurements performed by the LAQUAtwin Na-11 meter (Figure 1). This advanced liquid sensor quantitatively measures the sodium concentration in a spot urinary sample. The ion-selective membrane interacts selectively with the pre-specified sodium ion and generates a voltage that scales with concentration, a method comparable to in-lab applied techniques. However, it is applied in a miniaturized, user-friendly form with still a good accuracy. The results are readable within 30 seconds. The sensor requires daily calibration with a lower and higher calibration point (standard solutions are 150 ppm and 2000 ppm). The calibration and measuring process of the device requires approximately 2 min.

Figure 1

LAQUAtwin Na-11 meter (HORIBA)



In conclusion, there is an urgent need for better tools to titrate diuretic regimens during AHF, to assess the risk to develop AHF and to guide dose adaptations of diuretic therapy and optimize GDMT in CHF. Urinary sodium concentration measurements may provide a convenient and rapid tool that should allow guiding diuretic therapy both in acute and chronic HF.

RESEARCH OBJECTIVES

OBJECTIVE # 1

To gain a better understanding of the pathophysiology and the role of urinary sodium in heart failure patients.
(PART I – Chapter 1)

OBJECTIVE # 2

To evaluate the role of urinary sodium measurements in patients admitted with acute heart failure.
(PART II – Chapter 2-3)

OBJECTIVE # 3

To explore the role of home-measurements in patients with heart failure.
(PART III – Chapter 4-6)

OBJECTIVE # 4

To explore diuretic strategies to improve decongestion in acute heart failure.
(PART IV – Chapters 7-11)

OBJECTIVE # 5

To explore optimization strategies of guideline-directed medical therapy and loop diuretic therapy in patients with chronic heart failure.
(PART V – Chapters 12-14)

OBJECTIVE # 6

To provide different insights in the use of implantable devices in chronic heart failure.
(PART VI – Chapter 15)

PART I

ROLE OF URINARY SODIUM MEASUREMENTS IN HEART FAILURE

Research is the joy of discovering something no one knew before.

- Stephen Hawking -

CHAPTER 1

Spot urinary sodium measurements: the future direction of the treatment and follow-up of patients with heart failure

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STRUCTURED ABSTRACT

Purpose of the review: Heart failure is characterized by episodes of congestion with need for hospitalization. The current metrics lack the accuracy to predict and prevent episodes of congestions and to guide diuretic titration to reach euvolemia in case of decompensation. This article aims to provide answers to the role of urinary sodium measurements in acute and chronic heart failure.

Recent findings: In acute heart failure, urinary sodium concentrations at the moment of admission and after diuretic administration are correlated with short and long-term outcome. As this reflects the degree of sodium retention, it can be used as a guide in the diuretic titration. In chronic heart failure, it might be used to predict and consequently prevent episodes of decompensation.

Summary: Urinary sodium measurements hold great promises to be a novel diagnostic and therapeutic parameter in patients with acute and chronic heart failure. However, more research is needed.

Introduction

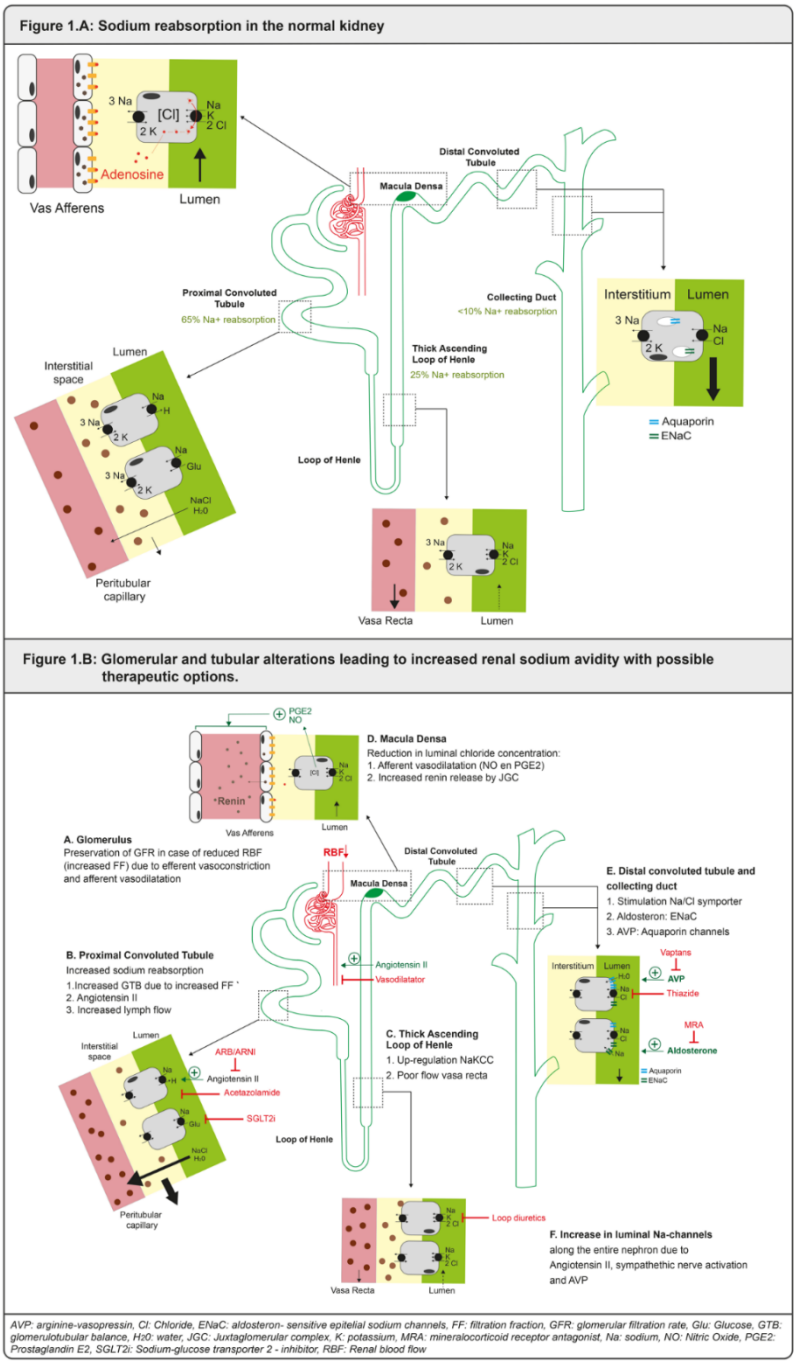
Signs and symptoms of congestion remain the main reason for hospitalization in patients with heart failure. The novel quadruple guideline-directed medical therapy has proven to reduce morbidity and mortality in heart failure with reduced ejection fraction (HFrEF) patients. (25) However, the need for hospitalization remains high with hospitalization rates up to 15% within 1 to 2 years in the latest heart failure (HF) trials, which runs up to 27% within a year in patients with more advanced heart failure. (26–29) After an acute heart failure event, the risk for rehospitalization is even higher, counting up to 25% within 3 months. (7,30) Diuretic resistance and discharge with residual signs of congestion are a major risk factor for adverse events. (6) Neurohumoral upregulation in HF increases renal sodium avidity, compromising natriuresis and resulting in a positive sodium balance. (3,31) There is growing evidence that spot urinary sodium measurements may help to guide treatment and follow-up of patients with both acute and chronic heart failure. (3,25,32,33)

Renal alterations and neurohumoral upregulation in heart failure

In normal physiological circumstances, the human body regulates the urinary sodium excretion in balance to the dietary sodium intake. The ingested salt is almost completely reabsorbed by the gastro-intestinal tract, which leads to an increase in plasma osmolality and consequently an increase in the release of arginine-vasopressin in order to reduce diuresis. The baroreceptors in the large and small vasculatures are triggered by this increase in total body water, causing an increase in sodium and water excretion in the kidney. Sodium is freely filtered in the renal glomerulus, however almost 99% is reabsorbed in the renal tubules with the largest part being reabsorbed by the proximal tubule (Figure 1.A). While the body aims to balance the sodium excretion with the sodium intake, recent insights suggest that sodium is not distributed in the body solely as a free cation, but that it is also bound to large interstitial glycosaminoglycan networks in different tissues, which have an important regulatory function. (9,11)

Figure 1

Sodium handling in the normal kidneys and in those with heart failure



In HF, hemodynamic alterations and neurohumoral upregulation give rise to an increased renal sodium avidity with a net positive sodium balance (Figure 1.B). A decreased cardiac output, increased filling pressures and elevated abdominal pressure lead to a diminished renal blood flow (RBF). (34) Increased filling pressures together with renal venous congestion result in a decreased RBF and an increase in hydrostatic capillary pressures, which are further aggravated by the neurohumoral activation. The increased glomerular pressures lead to an acceleration of nephron loss in patients with heart failure. (35) In order to maintain the glomerular filtration rate, the kidney increases the filtration fraction in case of a drop in RBF (autoregulation), which results in an increase in sodium and water reabsorption in the proximal tubule (glomerulotubular balance). As a result, the amount of sodium reaching the loop of Henle and the distal parts of the tubules is dramatically reduced. In addition, the neurohumoral upregulation in HF increases the sodium reabsorption along the ascending loop of Henle. Further down in the nephron, an increase in aldosterone levels triggers sodium reabsorption by the sodium-chloride co-symporter and by the insertion of the epithelial natrium channels (ENaC) in the distal convoluted tubules and in the collection ducts. Despite the general volume overload in patients with HF, the tubular flow in the distal part of the nephron is low due to the increased proximal sodium and water reabsorption. The decreased blood flow in the vasa recta in combination with the increased sodium reabsorption renders the interstitium of the renal medulla hypertonic. This osmotic gradient, together with the increase in arginine-vasopressin release due to angiotensin II activation, promotes free water retention in the collection ducts, and impairs the diluting capacity of the kidney. The increased sodium avidity and in parallel chloride reabsorption, in the proximal parts of the nephron, result in a reduced chloride concentration presented at the macula densa, which activates the release of renin with an ongoing activation of the renin-angiotensin-aldosterone axis (tubuloglomerular feedback). (3,36)

As impaired natriuresis is one of the key pathophysiological components leading to HF with an increase in plasma and extravascular volume, it seems rational that measuring the urinary sodium content may hold important information.

Role in acute heart failure

The main goal in the treatment of AHF is to achieve decongestion (Class I recommendation), as this is linked to improved survival and a reduction in rehospitalization rate. (25,37) Recently, the Acetazolamide in Acute Decompensated Heart Failure with Volume OveRload (ADVOR) trial demonstrated that it is necessary to target congestion early during hospitalization with combination diuretic therapy of acetazolamide and loop diuretics as a delay in decongestive therapy cannot fully be corrected during the further hospital stay. (38) This is also reflected in the fact that an early initiation of diuretic therapy in patients with AHF is associated with a lower in-hospital mortality. (39) Additionally, achieving euvolemia is associated with better long term results with an improvement in survival and a lower risk for rehospitalization. (6,40) However, there is no 'one-size fits all' model in treating patients with AHF and optimization of diuretic therapy requires an individualized approach. In current daily practice, diuretic titration is based upon clinical, hemodynamic, biochemical and echocardiographic parameters. However, most of these parameters are rather inaccurate in evaluating adequate decongestion and do not allow an early adaptation of diuretic therapy as these metrics require some time to change after loop diuretic administration. (22) Urinary sodium measurement may be a valid and more importantly a fast and easily accessible tool in guiding diuretic therapy in patients with AHF. (31,33)

Loop diuretics are the cornerstone of the treatment of patients with acute heart failure, promoting sodium excretion in the ascending part of the loop of Henle by blocking the sodium/potassium/2chloride (NKCC2) cotransporter. Renal adaptations increase sodium reabsorption in proximal and distal parts of the nephron, which is defined as loop diuretic resistance. (41) Loop diuretics not only block the NKCC2-cotransporter at the ascending part of the loop of Henle, but also the apical NKCC2 in the macula densa. By inhibiting the NKCC2 cotransporter, the chloride concentration delivered at the macula densa is decreased, which leads to a release of prostaglandin E2 (PGE2) and nitric oxide (NO). The increased levels of PGE2 and NO cause vasodilatation of the afferent arteriole and trigger the juxtaglomerular cells to release renin, which further increases neurohormonal activation (Figure 1.B). (42) Therefore, optimizing diuretic therapy in patients with

volume overload requires an individualized approach. The dosage of loop diuretics and need for combination therapy varies between and within patients over time. (21,43) The urinary sodium excretion is a marker of their efficacy as it directly reflects its mechanism of action. In order to make a judgement about the sodium balance, the total natriuresis should be interpreted in the light of the dietary sodium intake. (44)

The level of sodium excretion can be measured in a 24-hour urine collection, a 6-hour urine collection or a urinary sample spot. A spot sample has the advantage of being simpler and easier to obtain and to make an immediate assessment regarding diuretic response. However, bear in mind that this only gives the sodium concentration (mmol/L) and does not determine the daily total urinary sodium excretion (mmol).

- ***To guide diuretic therapy in AHF***

Singh et al. were the first to demonstrate in 52 patients with AHF that a diminished urinary sodium excretion on spot samples measurements was associated with a low net 24-hour volume output. (45) A poor diuretic response was later defined by Testani et al. as a cumulative urinary sodium output below 50 mmol in a 6 hours urinary collection after diuretic administration. (21) This threshold was chosen based on the pharmacodynamic principle that loop diuretics have a half-life of 1.5-2 hours and that their natriuretic effect is completed within 6 hours. (46) A suboptimal diuretic efficiency was defined as a urinary sodium excretion below 100 mmol in the first 6 hours after diuretic administration. Damman et al. confirmed the association between a 6-hour sodium excretion and the total 24-hour urine output. (47) However, this definition of poor diuretic response requires timed urinary collections in hospital, which is known to be difficult and is associated with a high level of sampling errors. Therefore, spot urinary sodium samples are suggested as an alternative method. Testani et al. demonstrated that a highly accurate prediction of sodium content of a timed 6-hour urine collection was achievable with a physiology-derived equation using the sodium concentration in a spot urine sample collected 2 hours after diuretic administration (area under the curve (AUC) 0.90-0.92). (44,48) The natriuretic response prediction equation (NRPE) calculates the six-hours urinary sodium excretion by

estimating the instantaneous rate of urine production, multiplied by the urinary sodium concentration on a spot sample two hours after diuretic administration. The rate of urine production can be calculated from the estimated glomerular filtration rate and the serum to urine creatinine ratio as creatinine is limited reabsorbed or secreted in the tubules. This suggests that an early evaluation of the diuretic response with timely therapy alterations is possible in patients with AHF. (21) However, NRPE is still complex and requires not only urinary sodium content, but also the blood and urinary creatinine levels together with body weight and length.

Na^+ output (mmol) =

eGFR x (BSA/1.73m²) x (Serum Cr/ Urine Cr) x 60min x 3.25h x (Urine Na/1000 mL)

BSA: body surface area, Cr: creatinine, eGFR: estimated glomerular filtration rate, Na^+: sodium

A urine spot sample sodium concentration is a simplified strategy and still holds an AUC of 0.89 to predict a poor loop diuretic response. (48) In order to simplify the recommendations, a post hoc analysis showed that a spot urinary sodium concentration below 50-70 mmol/L identifies patients with a poor loop diuretic response and patients who may benefit from early diuretic up-titration. A protocol for decongestive therapy based upon urinary sodium concentration measurement and volume output has been suggested by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) position paper, which was more recently incorporated in the latest ESC heart failure guidelines. (25,31) The usefulness of the natriuretic concentration threshold was confirmed in a monocentric observational trial in which patients with a urinary sodium concentration below 50mEq/L had a higher risk for developing diuretic resistance during hospital stay (risk ratio 5.0, 95% confidence interval 2.4-10). Neither weight change, nor initial diuresis were able to predict diuretic resistance. (32) Brinkley et al. conducted a prospective trial in 176 patients with AHF receiving intravenous loop diuretics in an outpatient clinic. They demonstrated that a spot urinary sodium measurement on the first void after diuretic administration correlated well with the urinary output after three hours and higher sodium concentrations were associated with a lower risk for hospitalization or emergency visits within 30 days. (49)

Importantly, the urinary sodium composition during decongestive therapy changes significantly over time when using loop diuretic mono therapy. Although urinary volume output remains stable (diuresis), a drop in natriuresis is expected during the consecutive days of loop diuretic therapy. (47) The diagnostic and prognostic value of a urinary sodium measurement after the first administration of loop diuretics has been demonstrated in several studies, however its diagnostic value during the consecutive days remains unanswered.

Importantly, as suggested by the ESC heart failure guidelines, urinary sodium concentration early during decongestive therapy may help identify patients who are in need of diuretic intensification in order to maximize diuretic efficacy. Observational studies demonstrated that up to 40% of patients presenting with AHF met criteria for diuretic resistance, which highlights the importance of this strategy. (21,50–52) Patients with diuretic resistance are more likely to have a worse glomerular filtration rate, a higher dose of home maintenance therapy with loop diuretics, a higher NYHA class, a lower blood pressure, higher natriuretic peptides and lower hemoglobin levels at presentation. (32,47,53–55) Urinary spot sodium measurement may be the new kid in the block, leading to early optimization of diuretic treatment in patients with AHF. Beside the evaluation of diuretic response, urinary sodium concentration measurements also have a role as a prognostic marker in AHF (Table 1).

Table 1

*Studies involving sodium measurement in patients with acute heart failure (integrated from Tersalvi et. al) (33). Considered important literature in bold with * or ** (extra important).*

Author (year)	N	Study type	Sample	Follow-up	Threshold	Outcome
*** Singh et al. (2014)** (45)	52	Prospective, single-center, observational	Spot sample at steady-state of continuous intravenous furosemide	5 months	U_{Na} <50 mmol U_{Na}:$U_{Furosemide}$ ratio < 2 mmol/mg	Diminished urine output, net fluid output and weight loss over 24h Increased risk of death, cardiac transplantation or HF hospitalization.
*** Verbrugge et al. (2014)** (56)	50	Prospective, single-center, observational	Total sodium excretion during 72-hour urine collection	284 days	U_{Na} 127 mmol/mg bumetanide	Greater likelihood of all-cause mortality an AHF re-hospitalization.
Verbrugge et al. (2015) (57)	54	Prospective, single-center, observational	Total sodium excretion at 0-24, 25-48 and 49-72 hours	188 days	A stronger natriuretic response to diuretics is associated with a larger decrease in plasma NT-proBNP levels, less neurohumoral activation and better clinical outcome.	
**** Testani et al. (2016)** (21)	50	Prospective, single-center, observational	Spot sample 1-2 hours after loop diuretic	/	U_{Na} <60 mmol/L cumulative in a 6h collection	Poor diuretic response at 6 hours can be predicted 1-2 hours after diuretic administration using a spot sample.
Ferreira et al. (2016) (58)	100	Single-center, non-randomized, open-label case-control trial	Spot sample collected at day 3 of loop diuretics	180 days	U_{Na} <60 mmol/L	Higher rate of cardiovascular mortality and AHF hospitalizations.
Doering et al. (2017) (59)	187	Post hoc analysis (STRATIFY and DECIDE trials)	Spot sample in the first 24h	30 days	U_{Na} <50 mmol/L	Higher readmission rates for AHF.

Luk et al. (2018) (60)	103	Prospective, single-center, observational	Spot sample collected at 1st urine void after loop diuretics	90 days	U_{Na} <60 mmol/L	Greater risk for composited primary endpoint (death at 90 days, mechanical or inotropic support).
*** Honda et al. (2018**) (61)	669	Posthoc analysis (NaDEF registry)	Spot sample at admission	560 days	U_{Na} <74 mg/dL (32 mmol/L)	Greater likelihood of all-cause mortality and worsening heart failure.
*** Brinkley et al. (2018)** (49)	176	Prospective, single-center, observational	Spot sample collected at first urine void after loop diuretic	30 days	U_{Na} <65 mmol/L Urine output <1200 ml	Higher hospitalization rate.
Collins et al. (2018) (62)	61	Prospective, single-center, observational	Spot sample collected 1 hour after loop diuretic	Hospital duration	U_{Na} <48 mmol/L	Increased risk for worsening heart failure.
Biegus et al. (2019) (63)	111	Prospective, single-center, observational	Spot sample collected at admission, 6, 24, 48 hours after loop diuretics	1 year	Low spot U_{Na} and lack to increase U_{Na} in response to loop diuretics are associated with poor diuretic response, markers of tubular injury and 1-year mortality.	
Hodson et al. (2019) (64)	316	Post hoc analysis (ROSE-AHF trial)	Sodium excretion on the first 24hour urine collection	6 months	Sodium excretion <2 g/day	Increased 6-month mortality.
Cunningham et al. (2019) (65)	298	Post hoc analysis (ROSE-AHF)	Sodium excretion on the first 24hour urine collection	Hospital duration	$U_{Na} \leq 60$ mmol/L	Longer hospital duration. Lower 72-hour weight loss.
Galluzzo et al (2020) (50)	80	Post hoc analysis (DRAIN trial)	Spot sample collected 2 hours after loop diuretics	Hospital duration	$U_{Na} \leq 50$ mmol/L	Lower daily urinary output, lower body weight loos, increased NT-proBNP levels at 72 hours.
*** Damman et al. (2020)** (47)	175	Prospective, single-center, observational	Total sodium excretion in the first 6 hours after loop diuretics	257 days	$U_{Na} \leq 89$ mmol/L	Lower urinary output in the first 24 hours. Higher mortality rate.

**** Cox et al. (2021)** (66)	285	Prospective, single-center, observational	Spot urine sample prior to loop diuretic followed by timed 6-hour and 18-hour collection	/	Basal sodium avidity rather than post-diuretic sodium retention determines diuretic and post-diuretic natriuresis in AHF.	
de la Espriella et al. (2021) (67)	160	Post hoc analysis (IMPROVE-HF)	Spot urine sample at randomization and 24 hours	1.73 year (median)	U_{Na} ≤50 mmol/L Delta $U_{Na.}$ after 24h	Higher risk all-cause mortality and re-hospitalization.
Biegus et al. (2021) (68)	172	Prospective, single-center, observational	Spot sample on admission, 24, 48 hours and discharge	1 year	Early urine sodium measurement, during active decongestive phase, was associated with 1-year mortality and HF rehospitalization. No association for U_{Na} at discharge.	
Perez et al. (2021) (69)	65	Prospective, single-center, observational	Spot sample collected 2 hours after loop diuretic	6 months	U_{Na} <83 mmol/L	Less reduction NT-proBNP levels, more signs of congestion at day 5, lower diuresis and weight loss. Longer length of hospital stay, worsening heart failure, more HF readmissions or death.
*** Biegus et al. (2021)** (52)	219	Prospective, single-center, observational	Spot urine sample and eGFR on admission, day 1 and day 2.	1 year	U_{Na} <60 mmol/L eGFR <60 ml/min/1.73m^2	Increased risk in-hospital worsening heart failure, inotropic support, rehospitalization and 1-year mortality.
* Martens et al (2022) (70)	339	Post-hoc analysis of the ROSE-AHF	A random spot urinary sample before randomization.	72h	U_{Na} 19-40 mmol/L U_{Na} 41-68 mmol/L U_{Na} 69-139 mmol/L	Low urinary sodium excretion is associated with less improvement in decongestive metrics with a lower total natriuresis and diuresis.

AHF: acute heart failure, eGFR: estimated glomerular filtration rate, UNa: urinary sodium

- ***Prognostic marker in AHF***

As mentioned above, the urinary sodium concentration after diuretic administration is useful in predicting the diuretic response and may guide the decongestive therapy. However, a measurement of the urinary sodium concentration *prior* to loop diuretic administration may also hold information regarding the intrinsic renal sodium avidity. A large retrospective analysis of a Japanese registry divided a total of 669 patients into tertiles based upon the urinary sodium result at the moment of hospital admission before diuretic therapy was administered. Patients with a lower baseline urinary sodium concentration tended to have higher plasma renin, aldosterone, cortisol and dopamine levels, indicating that these patients had a higher neurohumoral upregulation which resulted in an increased renal sodium avidity with lower renal sodium excretion. These patients required higher diuretic dosages during hospital stay and in the long-term had an increased risk for all-cause mortality and worsening renal failure. (61) Cox et al. demonstrated that in patients with AHF and volume overload compensatory post-diuretic sodium reabsorption is not a major driver of diuretic resistance. On the contrary, patients with a higher natriuretic response after loop diuretics also tended to have a higher post-diuretic spontaneous natriuresis. The diuretic response itself was largely determined by the basal sodium avidity, enhancing the prognostic importance of a baseline urinary sodium measurement. (66) A post hoc analysis of the IMPROVE-trial demonstrated that for every 20 mmol/L increase in baseline urine sodium concentration, there was a 25% decrease in all-cause mortality and an 8% decrease in all-cause readmissions. The inability to increase the urinary sodium excretion after 24 hours was associated with an increase in mortality rates. However, the ability to increase natriuresis after diuretic administration seemed only of importance in patients with a baseline low urinary sodium excretion as there was no effect found in the group with a urinary sodium excretion above 50 mmol/L. (67) It should be noted that this was a retrospective analysis of a relatively small sample size (n = 160) and patients could have received intravenous loop diuretics prior to randomization, i.e. prior to urine sample collection. A prospective, observational trial performing serial urinary sodium measurements in patients with AHF was not able to confirm a correlation between the baseline urinary sodium concentration and clinical outcome. However, a low urinary sodium at 6 hours or the inability to

increase the urinary sodium concentration after diuretic administration was associated with a higher one-year mortality risk compared to patients with an increase in sodium concentration. There was no difference in baseline glomerular filtration rate between the two groups, highlighting the different role and the disconnection of the tubular and glomerular function of the kidney. (63) Other small observational studies confirmed these results, stating that a stronger natriuretic response was associated with a better long-term outcome, a lower risk for all-cause mortality and heart failure rehospitalizations, independently from baseline glomerular filtration rate. (47,52,56,57,59) A retrospective analysis of the ROSE-AHF demonstrated in almost 30% of the patients a poor natriuretic response after 24-hours, which was associated with an increased risk for all-cause mortality at 6 months, even in the context of a negative fluid balance. (64) Damman et al. performed a prospective, single-center, open-label study and were able to demonstrate in a cohort of 175 AHF patients that a six-hour sodium output below 89 mmol was a strong predictor of a higher all-cause mortality with a median follow-up of 257 days (hazard ratio of 3.81 (CI 1.92-7.57)). (47)

Another approach is measuring the urinary sodium concentration on the first void *after* diuretic administration. A trial conducted in 103 patients with AHF compared clinical outcome between patients with a urinary sodium concentration below and above 60 mmol/L. The time to first void did not differ between the two groups. Patients with a urinary sodium concentration below the predefined cut-off point were more than twice as likely to need mechanical circulatory or inotropic support during admission or to die during the next 90 days. (60) Despite the limitations of the small sample size and the arbitrary cut-off, the main message remains that an early urinary sodium measurement may identify patients at risk for poor outcome. The median time to first void was 157 minutes (86-244 minutes) and could be compared to a urine sample after two hours as was proposed by Testani. The same cut-off value was used in a post-hoc analysis of the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial, which showed that patients with a urinary sodium concentration below 60 mmol/L had a longer length of hospital stay and a lower weight loss after 72 hours. (65) Collins et al. demonstrated that an early assessment of urinary sodium excretion after loop diuretic therapy was not only useful to determine diuretic response, but was also

a predictor of worsening heart failure (WHF). Patients who developed WHF during hospitalization had a diminished urinary sodium concentration 1-hour after diuretic administration, with a 100% sensitivity for predicting WHF in patients with a urinary sodium content below 35.4 mmol. (62) A poor natriuretic response had a stronger association with short-term and long-term outcome than historically used parameters such as weight change, urinary output or fluid balance. Perez et al. confirmed these results and a low natriuresis on a spot sample 2-hours after diuretic administration was association with a higher risk for diuretic resistance, longer hospital stay and worse clinical outcome (rehospitalization and death) at 6 months. (69)

Biegus et al. investigated whether the prognostic information of the urinary sodium concentration depended on the time course of the AHF hospitalization. The urine sodium concentration after diuretic intake at the moment of admission, at 24 hours and 48 hours all entailed significant prognostic information regarding a composite end point of 1-year all-cause mortality or heart failure hospitalization. However, the urinary sodium concentration at discharge was not able to predict clinical outcome. (68) This emphasizes the importance of knowing the timing and volume status at the moment of sodium measurement in order to make an adequate assumption regarding prognosis.

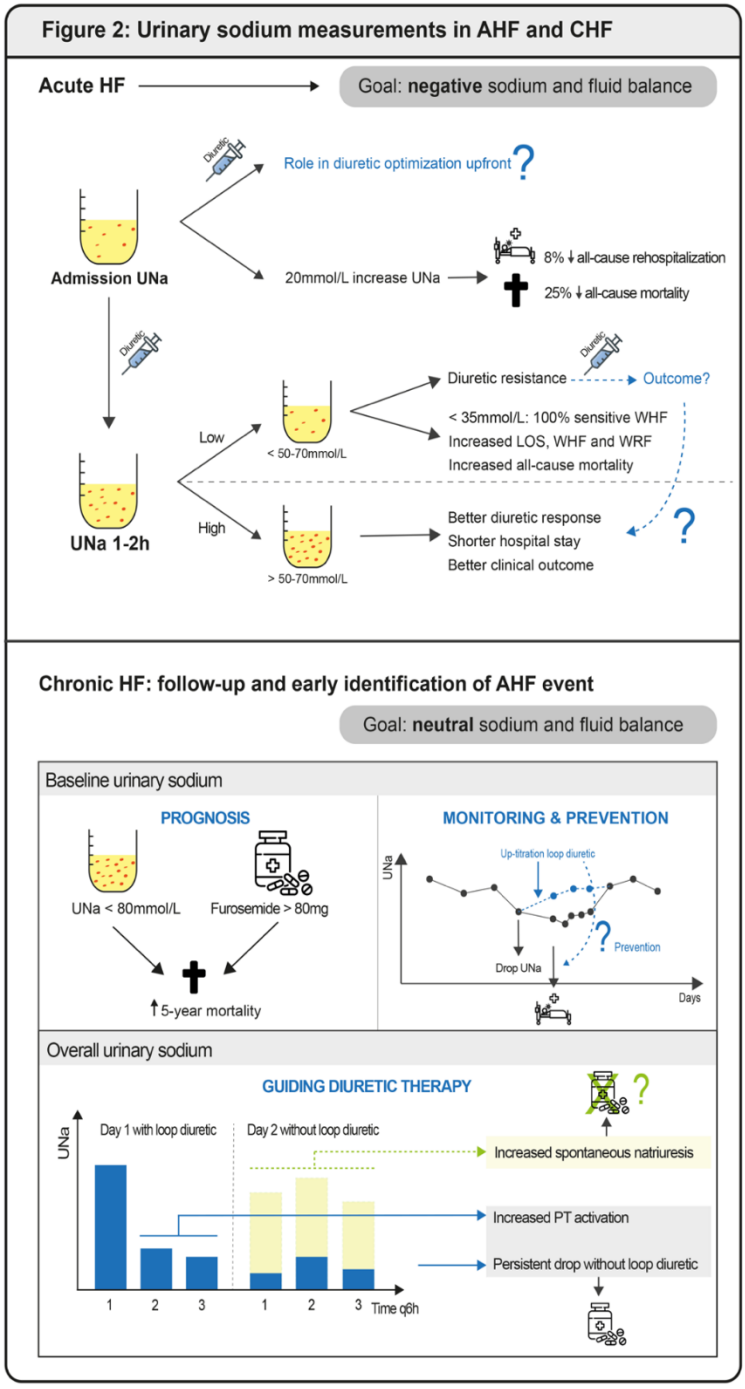
- ***Ongoing trials assessing the value of spot urinary sodium in AHF***

It should be noted that all these data are collected from retrospective or observational studies with a relatively small sample size (Table 1). Currently, three prospective trials are investigating the importance of a urinary sodium guided diuretic approach. The Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF, NCT04606927) is a single-center, randomized, open-label trial in the Netherlands. It aims to randomize 310 patients towards an intervention group or a standard of care group. In the intervention arm, diuretic therapy is titrated based upon the urinary sodium concentration with a stepwise approach of increasing dose and starting combination therapy. The co-primary end point is the total natriuresis after 24 hours and the combined end point of mortality or first heart failure rehospitalization within 6 months. (71) The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) trial

is an international, non-randomized, open-label, pragmatic study, aiming to enroll 500 patients. In order to be eligible for inclusion, patients should be treated with a maintenance dose of loop diuretics of at least 40 mg of furosemide or equivalents. Participating study centers will first include patients in phase 1 of the study, i.e. standard of care, and afterwards in the phase 2 of the study. In phase 2, patients will receive diuretic up-titration based upon the protocol suggested by the HFA algorithm and the result of the urinary sodium measurement. The primary end point is the total urinary sodium excretion after 24 hours. (72) A large, randomized, triple-blinded study aims to include 484 AHF patients in the emergency department, with a stratification in a 1:1 ratio towards standard of care or intervention group. In the intervention group, results of urine and serum creatinine will be entered in a diuretic calculator three times daily after which a diuretic dose will be chosen based on daily urine output goals. The primary endpoint is the days of clinical benefit from randomization through day 14, which includes global clinical status and hospital days (NCT04481919). These trials will provide important insights whether an improvement in natriuresis will also lead to changes in morbidity and mortality, or whether it is just a reflection of a more advanced disease stage without any influence on outcome (Figure 2).

Figure 2

Urinary sodium measurement in acute and chronic heart failure



Role of urinary sodium assessment in patients with chronic heart failure

In contrast to AHF where the goal is to achieve decongestion with a net negative sodium and fluid balance, the goal in patients with chronic heart failure (CHF) is to maintain euvolemia with a neutral sodium and fluid balance. The assessment of urinary sodium concentrations might be helpful to monitor changes in volemic state. (Table 2)

- ***Urinary sodium and prognosis***

Multiple trials have demonstrated a strong correlation between the sodium concentration on a morning spot urinary sample prior to diuretic intake and the total 24-hour urinary sodium excretion. (17,55) A retrospective cohort study examined the long-term outcome in ambulatory chronic heart failure patients in relationship to the morning spot urinary sodium concentration. Patients with a furosemide dosage to urinary sodium concentration ratio above 0.8 (i.e. higher maintenance loop diuretic or lower baseline urinary sodium excretion) would have a three-times higher risk of dying within the next 5 years. Patients with a baseline high urinary sodium excretion (> 80 mmol/L) and concomitantly a low dosage of maintenance loop diuretic therapy (furosemide < 80 mg per day) had the best survival rate, suggesting that patients with the least neurohormonal activation and consequently lowest diuretic resistance had the best long-term outcome. In line with this cohort, Elias et al. demonstrated that patients with more advanced disease reflected by a low baseline urinary sodium concentration (< 80 mmol/L) despite high maintenance diuretic therapy (furosemide > 80 mg per day) had a five-times higher mortality risk in the next 5 years. (55) The prognostic role of urinary sodium excretion in stable, chronic heart failure patients is confirmed in a prospective cohort study with a median follow-up time of 10-14 years, including 180 men from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The study lacked to demonstrate an association with major adverse coronary events (MACE), but was able to demonstrate an inverse association between the total 24-hour urinary sodium excretion and all-cause mortality risk. (73)

Table 2

*Studies involving urinary measurements in patients with chronic heart failure. Considered important literature in bold with * or ** (extra important)*

Author (year)	N	Study type	Sample	Follow-up	Threshold	Outcome
Verbrugge et al. (2018) (16)	50	Single-center prospective, observational study	Spot urine sample after loop diuretic intake	30 days	Loop diuretic down-titration was feasible in 3 out of 4 patients. Tendency towards easier down-titration in patients with low urinary chloride content.	
**** Martens et al. (2019)** (17)	80	Single-center, prospective observational study	Morning spot urine sample	587 ± 54 days	Chronic lower U_{Na} profile in patients with AHF event. Drop in U_{Na} during the week preceding an AHF event.	
Dauw et al. (2021) (74)	40	Single-center, prospective observational study	Two 24-hour urine collections with three phases (first 6 hours, day, night)	/	Persistent diuretic response in CHF. Drop in diuresis and natriuresis after diuretic omission.	
*** Elias et al. (2021)** (55)	283	Post hoc analysis of a single-center observational cohort	Morning spot urine sample and 24-hour urine collection	5 years	U_{Na} <80 mmol/L Furosemide/ U_{Na} >0.8	3-5 times higher mortality rate
Ganes et al. (2022) (73)	180	Post hoc analysis of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)	24-hour urine collection	10-14 years	Tertiles <173 mmol 173-229 mmol >229 mmol	No association with MACE outcome. U-shaped association with all-cause mortality.

MACE: major adverse cardiovascular events, UNa: urinary sodium

Martens et al. anticipated a role of home urinary sodium measurements in telemonitoring patients with CHF. This single-center, observational trial prospectively followed 80 patients with chronic, stable heart failure. Patients were asked to collect a first morning void once-weekly for 30 consecutive weeks. During a mean follow-up of 587 ± 54 days, 21 patients developed an AHF event and 16 of these events were during active measurements of the urinary sodium. The longitudinal urinary sodium profile of patients with an AHF event was in general lower than the profile of patients with stable CHF. Moreover, there was a clear drop in urinary sodium concentration in the week preceding an AHF event and the urinary sodium concentration returned to baseline after decongestion. (17) Despite the study limitations (small sample size, single-center, observational study), these results hold great promise for novel telemonitoring possibilities in the future (Figure 2). Albeit more data with multicentric, randomized trials are necessary for urinary sodium measurements in patients with chronic heart failure, there is already a trend that this may pay an important role in the prediction of AHF events, maintenance loop diuretic titration and prognostication (Table 2).

- ***Urinary sodium to guide loop diuretic withdrawal***

Cox et al. demonstrated in patients with AHF that compensatory post-diuretic sodium retention is not an important driver of diuretic resistance, as patients with a higher natriuretic response on diuretic therapy also have a larger spontaneous natriuresis afterwards. Chronic loop diuretic therapy is associated with an increase in morbidity and mortality and may hamper up-titration of guideline-directed medical therapy. Therefore, Dauw et al. investigated whether cessation of maintenance loop diuretic therapy was possible in patients with stable chronic heart failure in whom the investigators felt there was a need to continue loop diuretic therapy. A 24-hour urine collection was collected after diuretic intake and repeated the next day after cessation of diuretic therapy. On the day of diuretic omission, there was a tremendous drop in natriuresis (50 ± 23%) and urine output (30 ± 20%) in comparison with the 24-hour urine collection the day before on diuretic therapy. Despite the small study sample, the study demonstrated that stable, CHF patients necessitating chronic maintenance loop diuretic therapy still have a clear loop diuretic response. The natriuresis and urine output on the day of diuretic intake was comparable to patients without the need for maintenance

therapy, however with a distinct time pattern. After diuretic omission, a drop in urinary sodium excretion and volume production remained during the day and night. As demonstrated in AHF, the drop in natriuresis and urine output after diuretic cessation is most likely the result of an increased intrinsic renal sodium avidity reflecting the need for diuretic therapy in this patient cohort rather than a pure effect of diuretic omission. (74)

In contrast, the ReBIC1-trial was a randomized, double blind, placebo-controlled trial investigating whether diuretic cessation was achievable in CHF patients (n = 188) on stable diuretic maintenance dose, without signs and symptoms of volume overload, without a heart failure hospitalization during the last six months and with optimized and stable HF treatment. After diuretic withdrawal, there was no significant difference in patient-reported dyspnea score after 90 days with an excellent short-term prognosis. (75) An observational study examined down-titration of loop diuretic therapy in 50 patients with stable, chronic heart failure. After 30 and 180 days, down-titration was feasible in 62% of the patients and down-titration failure was always notable within 30 days. (76) Therefore, it should be feasible to down-titrate diuretic maintenance therapy in a pre-selected subgroup of CHF patients. A correct identification of these patients may still hamper down-titration efforts in clinical practice.

A small, observational study demonstrated a tendency towards easier down-titration in patients with low urinary chloride concentration post-diuretic therapy. Lower urinary chloride (and sodium) concentrations were reflective of better decongested state without the need for loop diuretics. The urinary chloride concentration correlated strongly with the urinary sodium concentration. (16)

As such, urinary sodium (and chloride) measurement may play an important role in guiding diuretic needs in the outpatient setting but it is clear that this depends on the timing of the sample in relation with the loop diuretic intake (and dosing).

CONCLUSION

Neurohumoral upregulation is the driving mechanism leading to excessive renal sodium avidity in patients with heart failure, resulting in extracellular volume overload with signs and symptoms of congestion. As natriuresis is a direct marker of neurohumoral activation, it seems logical that this may be a useful parameter in patients with HF. In AHF, the role of early urinary sodium measurements is well established with its recommendation in the novel ESC guidelines. It allows early identification of patients with diuretic resistance with prompt adaptation of diuretic therapy. As patients with diuretic resistance have a more advanced disease process, the urinary sodium measurement also correlates with long-term outcomes. Data in patients with CHF are less robust, however, there are some data that urinary sodium measurements also hold a prognostic and therapeutic role but more research is necessary.

PART II

URINARY SODIUM IN ACUTE HEART FAILURE

The question you should ask is "Why?"

- Frank Ruschitzka -

CHAPTER 2

Nurse-Led Diuretic Titration via a Point of Care Urinary Sodium Sensor in Patients with Acute Decompensated Heart Failure (EASY-HF): a single-center, randomized, open label study

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Eur J Heart Fail. 2024;26(10):2129-2139

ABSTRACT

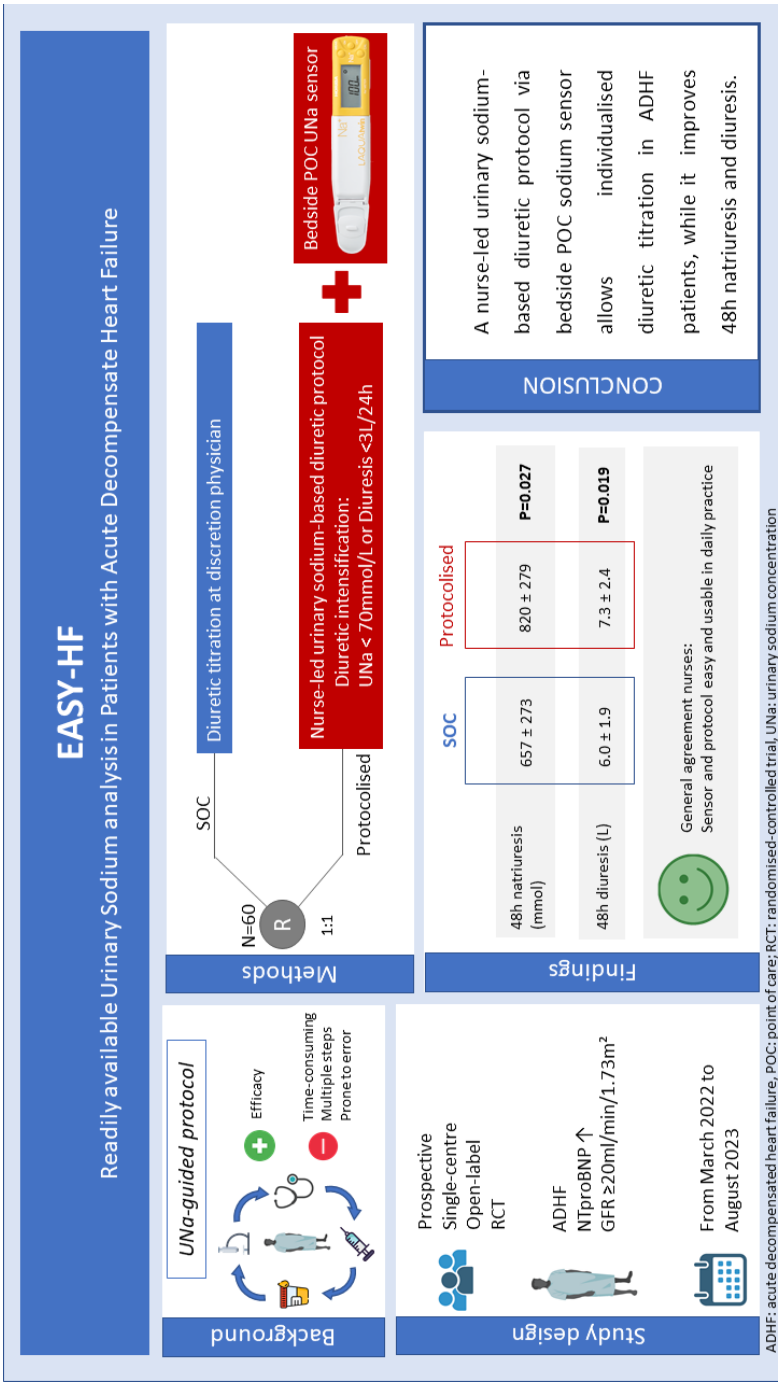
Background: Early evaluation of the natriuretic response is recommended to guide diuretic therapy in acute decompensated heart failure (ADHF). However, its implementation in daily practice is hampered by implementation barriers and increased time constraints. The 'Readily available Urinary Sodium Analysis in Patients with acute decompensated Heart Failure' (EASY-HF) study assessed the feasibility, efficacy and safety of a nurse-led urinary sodium-based diuretic titration protocol with the use of a point-of-care urinary sodium sensor.

Methods: The EASY-HF study was a single-centre, randomized, open-label study comparing diuretic management at the treating physician's discretion as standard of care (SOC) with a nurse-led natriuresis-guided protocol in patients with ADHF. The LAQUAtwin Sodium Meter (HORIBA) was used as point-of-care sensor to measure urine sodium concentration. The primary endpoint was natriuresis after 48 hours. Secondary endpoints included safety profile and user-friendliness of both the protocol and the point-of-care sensor.

Results: Sixty patients were randomized towards SOC (n=30) versus protocolized care (n=30). The mean age was 80 ± 8 years, 25% were women and the median NT-proBNP was 4,667 (2,667-7,709) ng/L. Natriuresis after 48 hours was significantly higher in the protocolized versus SOC group (820±279 versus 657 ± 273 mmol; p-value=0.027). Predefined safety endpoints were similar among both groups. The sensor-based protocol was evaluated as easy to use by the nursing staff, and preferred over urinary collections.

Conclusion: A nurse-led diuretic titration protocol via a point-of-care urinary sodium sensor was feasible, safe and resulted in an increased natriuresis in ADHF compared to SOC.

GRAPHICAL ABSTRACT



INTRODUCTION

Episodes of acute decompensated heart failure (ADHF) characterize the disease course of patients with heart failure and are associated with a high morbidity and mortality rate. (1,77) According to current guidelines, intravenous (IV) loop diuretics remain the cornerstone in the treatment of ADHF, in order to relieve signs and symptoms of congestion. (25,37) Several expert position papers as well as the European Society of Cardiology (ESC) guidelines advise early assessment of the diuretic response based on a spot urinary sodium concentration within 2 h after diuretic initiation to monitor urinary sodium concentrations, targeted above >50-70 mmol/L. (3,25,78) Recently, the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) study and the Pragmatic Urinary Sodium-based algorithm in Acute Heart Failure (PUSH-AHF) study, have both demonstrated that such a urinary sodium-based diuretic up-titration protocol improves natriuresis and diuresis in patients with ADHF. (23,24,79) However, the implementation in daily clinical practice is perceived to be cumbersome as this strategy requires frequent timely collections of urine samples, synchronized with diuretic prescriptions by the cardiologist, and laboratory assessments. Additionally, laboratory derived urinary sodium values might not always be timely available due to time-delays in the laboratory not allowing for convenient dose adjustments. Therefore, the 'REadily available UrinAry Sodium analYsis in Patients with Acute Decompensate Heart Failure' (EASY-HF) study was designed to assess the feasibility, safety, and efficacy of a nurse-led urinary sodium-based diuretic up-titration protocol with the use of a point-of-care (POC) urinary sodium sensor.

METHODS

Trial design

This is a single-center (Ziekenhuis Oost-Limburg, Genk, Belgium), prospective, open-label, randomized, controlled trial. The trial protocol was approved by the local ethical committee and the Belgian Federal Agency for Medicines and Health Products (IVDPS202118) and registered at ClinicalTrials.gov (NCT06278792). All patients provided written informed consent prior to randomization.

Patients

Patients with a hospital admission due to acute decompensated heart failure (ADHF) and at least one clinical sign of volume overload (i.e., edema, pleural effusion, or ascites) were eligible for inclusion if they had N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels >500 ng/L (or >800 ng/L in case of atrial fibrillation). (25,80) Main exclusion criteria were the inability to collect a 48-hour urine collection; or an estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m^2. Patients who received IV loop diuretics at a cumulative dose exceeding 80 mg of furosemide equivalents (conversion factor 1 mg bumetanide = 40 mg furosemide) during the index hospitalization prior to randomization were excluded, to ensure capturing the full decongestive treatment period in-hospital. A full list of the in- and exclusion criteria can be found in the supplemental materials (Supplemental table 1).

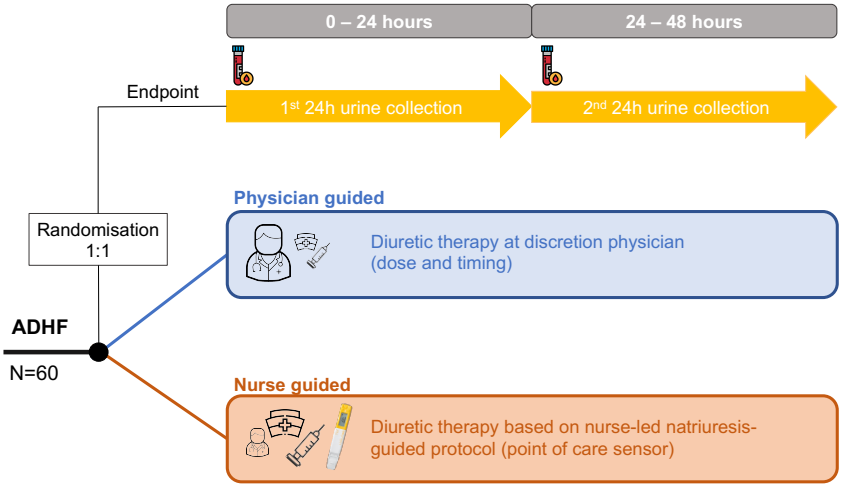
Trial procedures

Patients hospitalized with ADHF were randomized (through CASTOR EDC) in a 1:1 ratio to standard of care (SOC) or the study intervention with stratification based on renal function (eGFR above or below 50ml/min/1.73m^2) and the presence of home maintenance loop diuretic therapy, Figure 1. To prevent bias as this was an open-label study, all physicians were blinded for the spot urinary sodium measurements. Additionally, while urine was collected for the first 48 h in both groups, the urinary analysis was only performed after completion of the study period to avoid contamination of knowledge by the cumulative natriuresis. A training session of 30 min was provided to the entire cardiac nursing staff at forehand to familiarize with protocol implementation and the use of the POC sensor. In both groups, all oral diuretics were stopped and patients were asked to empty their bladder prior to diuretic administration. Patients were examined at least once daily by the attending cardiologist to assess the need for ongoing IV diuretic therapy. A congestion score based on the Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial (Supplemental figure 1) was assessed on a daily base. (38,81) Patients were considered to have persistent volume overload if they had a clinical congestion score of at least 2 (i.e., more than trace oedema or ascites or pleural effusion). A daily blood analysis

was performed during the first 3 days after randomization. Two consecutive 24-hour urine collections were collected during the first 2 days of hospitalization, starting from the moment of the first IV bolus of loop diuretics. Potassium supplements were left at the discretion of the physician. All patients received fluid and salt restrictions with a maximum of 1.5 L of fluids and 1.5-2 g of sodium per day. Patients were asked to give a dyspnea score at the moment of screening, after 24 h and after 48 h of treatment on a visual analogue scale (1=extreme shortness of breath, 5=no shortness of breath).

Figure 1

Study design



Diuretic administration in the SOC group was completely at the discretion of the attending physician, with the exception that the first diuretic administration had to be monotherapy with IV loop diuretics according to the current ESC heart failure guidelines. (25) As such, upfront use of acetazolamide or thiazides was not allowed, however intensification with any agent was allowed afterwards. Physicians had access to all patient data throughout the study duration and were allowed to perform testing as indicated.

For the intervention group, a protocol (Supplemental figure 2) was developed for diuretic up-titration during the first 48-hours based on the most recent guidelines

of the ESC. (3,25) The diuretic schedule was pre-specified by the protocol and implemented by the nurses. Treating physicians only decided on the indication for continuation of IV diuretic therapy based on signs of persistent congestion. The starting IV loop diuretic dose was equal to the oral home maintenance dose. In case of an eGFR <50 ml/min/1.73m^2, the starting dose was twice the home maintenance dose. If patients were diuretic naive, the starting dose was bumetanide 1 mg (or equivalents), or 2 mg in case of an eGFR below 50 ml/min/1.73m². A urinary sample was analyzed with the POC sodium sensor 2-4 h after every loop diuretic dose during the first 48 h of diuretic therapy. Up to 3 diuretic up-titrations were allowed in case of a low urinary sodium concentration (defined as <70 mmol/L) during the first 24 h. If the spot urinary sodium concentration was ≥70 mmol/L, the loop diuretic dose was deemed adequate and repeated after 12 h. In case of a urinary sodium excretion <70 mmol/L, the loop diuretic dose was doubled with a new administration after 6 h. After each dose increasement, a novel assessment 2 h after administration was performed with again doubling of the diuretic dose 6 h later (after the last dose) if urinary sodium excretion was inadequate. After 24 h of treatment, the urinary volume was assessed. If the total urinary volume was less than 3 L during the first 24 h, the dose of the IV bolus of loop diuretics was doubled for the next administration. This dose was administered twice on the second day (at 24h and 36h). Loop diuretics were up-titrated to a maximum of 5 mg of bumetanide (i.e., 200 mg of furosemide) per bolus. If this was insufficient, the second and third step were the addition of acetazolamide 500 mg intravenously and an oral thiazide (chlortalidone 50 mg), respectively. During the study period, the nursing team was advised to contact the treating physician prior to diuretic administration in case of symptomatic hypotension with a systolic blood pressure below 85mmHg. After the trial termination, the nurses were asked to fill out a questionnaire regarding the user-friendliness of the device and the protocols.

Direct sodium measurement

Urinary sodium concentration measurements during the study were performed bedside by the nurses via the LAQUAtwin Na-11 meter (HORIBA) (Figure 2). (82) This advanced liquid sensor quantitatively measures the sodium concentration in a spot urinary sample (Figure 2). The sensor requires daily calibration with a lower

and higher calibration point. The ion-selective membrane interacts selectively with the pre-specified ions and generates a voltage that scales with concentration. The result is immediately readable and therefore also immediately usable after the measurement. Results are given in parts per million (PPM) and a conversion factor can be programmed so the value in PPM equals mmol/L. The calibration and measuring process of the device requires approximately 2 min. The accuracy of the sensor has been tested prior to this study (Supplemental material 1). There was a very strong positive correlation to in-lab measurement ($R^2(48)=0.97$, p-value<0.001) with an excellent reproducibility (intraclass correlation 0.998).

Endpoints

The primary endpoint of the trial was natriuresis after 48 h. Secondary endpoints were 24-hour natriuresis, 24-hour diuresis, 48-hour diuresis and the achievement of complete decongestion (i.e., not more than trace oedema and no ascites or pleural effusion) after 48 h, and length of hospital stay. Changes in weight, congestion and dyspnea score, and the dose of loop diuretics administered with the loop diuretic responsiveness were also collected. Predefined safety endpoints included symptomatic hypotension (defined as a systolic blood pressure <85 mmHg), hypokalemia (defined as a serum potassium concentration <3 mmol/L) and renal impairment (defined as doubling of the serum creatinine or a decrease of at least 50 % in eGFR) during the first 4 days. Additional endpoints were the combined and individual events of heart failure rehospitalization and all-cause mortality during a subsequent 180-day follow-up. The user-friendliness of the device and the flowcharts used in the study were evaluated using a questionnaire (Likert scale 1-10, 1 = do not agree, 10 = completely agree, Supplemental figure 3).

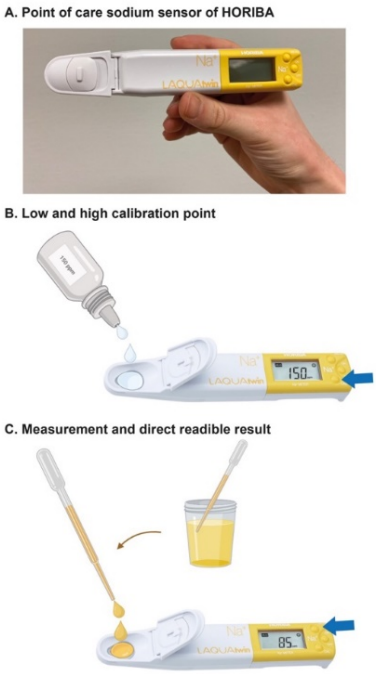
Statistical analysis

Variables are summarized as means with standard deviations, medians with 25-75th percentile, or numbers with percentages and evaluated using ANOVA, Kruskal-Wallis and chi-square tests as appropriate. The primary and secondary endpoints of difference in natriuresis and diuresis were evaluated using a generalized linear mixed model which included a fixed treatment effect and random intercept to calculate a mean difference with 95% confidence intervals.

The difference in loop diuretic dosing was evaluated with a linear mixed-model with repeated measurements over time, including a fixed effect of treatment arm, baseline loop diuretic dose, time and a random intercept. The duration of the index hospitalization was compared with the use of a linear mixed model after logarithmic transformed (fixed treatment effect and random intercept). Results were exponentially transformed to report length of stay as geometric means with a 95% confidence interval. Longitudinal changes in weight change, scoring, serum potassium, creatinine level and eGFR according to treatment allocation were assessed using a linear mixed-effects models with repeated measurements over time including fixed effect of treatment arm, time, its interaction and including a random intercept. The combined endpoint of all-cause mortality and heart failure rehospitalization after 180 days was assessed in a time-to-event analysis using a Cox proportional hazard model. All the hypotheses testing was 2-sided with a significance level of α = 0.05. All statistical analyses were done using SPSS version 29.

Figure 2

Point of care urinary sodium sensor (LAQUATwin HORIBA)



RESULTS

Baseline characteristics

Between March 7th, 2022 and August 7th, 2023, 60 patients were randomized towards either the control (N=30) or intervention group (N=30) (Table 1), and the mean age of the patients was 80 ± 8 years with a mean left ventricular ejection fraction of 43 ± 16 %. Patients had significant signs and symptoms of congestion, a median NT-proBNP of 4,667 (2,667-7,709) ng/L and most patients were functioning in New York Heart Association (NYHA) class III or IV upon admission. Mean serum creatinine was 1.4 ± 0.5 mg/dL and 58% of the patients had an eGFR below 50 ml/min/1.73m². Approximately 50% of the patients already had maintenance therapy with loop diuretics at home with a median dose of 40 (40-80) mg of furosemide equivalents.

Table 1

Baseline characteristics

	Total (n=60)	Control (n=30)	Intervention (n=30)
Age	79.6 ± 7.8	78.9 ± 7.2	80.4 ± 8.4
Female gender (%)	15 (25.0%)	5 (16.7%)	10 (33.3%)
Heart rate (bpm)	86.6 ± 21.5	83.8 ± 18.7	89.5 ± 24.0
Blood pressure			
Systolic (mmHg)	129 ± 24	133 ± 29	125 ± 18
Diastolic (mmHg)	73 ± 18	74 ± 21	72 ± 15
BMI (kg/m²)	28.5 (24.8-33.7)	27.5 (24.3-33.8)	28.7 (24.9-33.5)
Congestion score	5.00 (4.25-6.00)	5.00 (3.75-6.00)	5.5 (5.0-6.25)
Components of congestion			
Edema			
0	1 (1.7%)	1 (3.3%)	0 (0.0%)
1	0 (0%)	0 (0.0%)	0 (0.0%)
2	1 (1.7%)	1 (3.3%)	0 (0.0%)
3	37 (61.7%)	18 (60.0%)	19 (63.3%)
4	21 (35.0%)	10 (33.3%)	11 (36.7%)
Pleural effusion			
0	11 (18.3%)	8 (26.7%)	3 (10.0%)
2	29 (48.3%)	11 (36.7%)	18 (60.0%)
3	20 (33.3%)	11 (36.7%)	9 (30.0%)
Ascites			
0	55 (91.7%)	28 (93.3%)	27 (90.0%)
2	5 (8.3%)	2 (6.7%)	3 (10.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)

LVEF (%)	43.0 ± 15.5	46.8 ± 14.3	39.1 ± 15.9
De novo heart failure (%)	22 (37%)	9 (30%)	13 (43%)
LVEF Class			
HFrEF	24 (40.0%)	8 (26.7%)	16 (53.3%)
HFmrEF	2 (3.3%)	2 (6.7%)	0 (0.0%)
HFpEF	34 (56.7%)	20 (66.7%)	14 (46.7%)
NYHA functional class			
II	4 (6.7%)	3 (10.0%)	1 (3.3%)
III	27 (45.0%)	11 (36.7%)	16 (53.3%)
IV	29 (48.3%)	16 (53.3%)	13 (43.3%)
Laboratory values			
Hemoglobin (g/dL)	11.7 ±2.3	11.9 ± 2.2	11.6 ± 2.5
Sodium (mmol/L)	139.6 ± 3.7	139.3 ± 3.6	139.8 ± 3.9
Potassium (mmol/L)	4.1 ± 0.6	4.1 ± 0.7	4.1± 0.6
Urea (mg/dL)	54 (43-69)	53 (45-68)	57 (37-69)
Creatinine (mg/dL)	1.38 ± 0.45	1.37 ± 0.41	1.39 ± 0.48
eGFR (ml/min/1.73m^2)	50.4 ± 18.3	51.0 ± 17.7	49.8 ± 19.2
eGFR<50ml/min/1.73m²	35 (58.3%)	17 (56.7%)	18 (60.0%)
NT-proBNP (ng/L)	4667 (2667-7709)	4532 (2651–7333)	5077 (2654-12150)
Coexisting conditions			
History of atrial fibrillation	45 (75.0%)	24 (80.0%)	21 (70.0%)
Stroke	7 (11.7%)	5 (16.7%)	2 (6.7%)
Diabetes	23 (38.3%)	9 (30.0%)	14 (46.7%)
Hypertension	44 (73.3%)	22 (73.3%)	22 (73.3%)
CABG/PCI	23 (38.3%)	12 (40.0%)	11 (36.7%)
Valve surgery	9 (15.0%)	4 (13.3%)	5 (16.7%)
PAD	12 (20.0%)	8 (26.7%)	4 (13.3%)
COPD	14 (23.3%)	8 (26.7%)	6 (20.0%)
Baseline treatment			
% Loop diuretics at home	31 (51.7%)	16 (53.3%)	15 (50.0%)
Home maintenance dose of furosemide equivalents (mg)	40 (40-80)	40 (40-80)	40 (40-80)
ACE-I, ARB	19 (31.7%)	14 (46.7%)	5 (16.7%)
ARNI	4 (6.7%)	1 (3.3%)	3 (10.0%)
Beta-blocker	39 (65.0%)	19 (63.3%)	20 (66.7%)
MRA	15 (25.0%)	8 (26.7%)	7 (23.3%)
SGLT2i	13 (21.7%)	5 (16.7%)	8 (26.7%)
Pacemaker	9 (15.0%)	5 (16.7%)	4 (13.3%)
ICD	3 (5.0%)	1 (3.3%)	2 (6.7%)
CRT	6 (10.0%)	2 (6.7%)	4 (13.3%)

Diuretic therapy

Median starting dose of loop diuretics was 80 (40-80) mg of furosemide equivalents, which did not differ between both treatment groups (p-value=0.729). The median dose of loop diuretics administered during first 48 hours was 240 (200-320) mg in the SOC versus 320 (160-480) mg in the intervention group (Supplemental figure 4). There was only 1 protocol deviation in 1 patient in the intervention group with the administration of an additional diuretic dose after 6 h despite a good natriuretic response. In all other cases, the protocol was followed by the nurses as intended. In the intervention arm, 9 patients (30%) received a protocol-based up-titration of diuretic therapy (6 based on a low urinary sodium concentration after 2-4 h and 3 based on a low urinary output after 24 h). None of the patient in the intervention arm needed up-titration with acetazolamide or hydrochlorothiazide. In the control arm, 5 patients (17%) received IV acetazolamide on top of loop diuretics.

Natriuresis and diuresis

The mean total natriuresis after 48 h was significantly higher in the intervention group (820 ± 279 mmol) compared with the placebo group (657 ± 273 mmol) (p-value = 0.027) (Figure 3 and Table 2). This difference was mostly explained by a higher natriuresis during the second 24 h of treatment (p-value = 0.009). The higher degree of natriuresis in the intervention group was reflected by a higher diuresis (7.3 ± 2.4 L versus 6.0 ± 1.9 L, p-value = 0.019). Although numerically higher in the intervention group, there was no significant difference in the degree of natriuresis after correction for furosemide equivalents between both groups. However, the overall natriuretic and diuretic response was substantially higher in diuretic naive patients compared to patients with home maintenance loop diuretic therapy (Supplemental table 2).

Evolution in weight, congestion score, dyspnea score and length of stay

After two days of treatment, patients lost approximately 4.2 (± 2.4) kg and had a significant improvement in their congestion score (Table 2). Overall, the magnitude of improvements tended to be higher in the intervention arm. The overall percentage of patients decongested after 2 days of treatment was 40% and did not differ between both treatment groups (11 versus 13 patients; p-value=0.589). Despite slightly more dyspnea relieve in the intervention arm, there was no significant difference in the score after 2 days of treatment (p-value = 0.182) (Table 2). The duration of the index hospitalization was 7.4 days (95% CI, 3.6 to 16.0) in the intervention group and 8.0 days (95% CI, 3.7 to 17.2) in the control group (p-value=0.601).

Safety with regard to hypotension, hypokalemia and renal function

Adverse events and safety of the protocol are depicted in Table 3. In one intervention patient, diuretic therapy was temporarily paused due to symptomatic hypotension. During the study period, the change in blood pressure did not differ between both treatment groups for both systolic blood pressure (p-value=0.283) and diastolic blood pressure (p=0.875). Hypokalemia, defined as a serum potassium <3 mmol/L, occurred in 6 patients (10%) during a 3-day follow-up period which was comparable between both treatment groups. No patients experienced a doubling in their serum creatinine or a 50% decrease in eGFR. A rise in serum creatinine, defined as an increase >0.3 mg/dL, was noted in 4 patients in the control group and 9 patients in the intervention group (13% versus 30% respectively, p-value=0.209). There was no need for renal replacement therapy during the index hospitalization. The change in serum potassium, creatinine and eGFR did not differ between both treatment groups (p for interaction 0.363, 0.061 and 0.235, respectively, Supplemental table 3).

Heart failure rehospitalizations and mortality

Rehospitalization for heart failure and/or all-cause mortality occurred in 10 patients (33%) in the intervention group and 10 patients (33%) in the control group during a follow-up of 180 days (HR 0.99; 95% CI 0.41 to 2.37; p-value = 0.978) (Table 3, Supplemental figure 5). The individual events of all-cause

mortality (HR 1.26; 95% CI 0.34 to 4.69; p-value = 0.731) and heart failure rehospitalization (HR 0.62; 95% CI 0.20 to 1.89; p-value = 0.401) were also not significantly different between both groups.

Figure 3

Natriuresis and diuresis after 24 and 48 hours

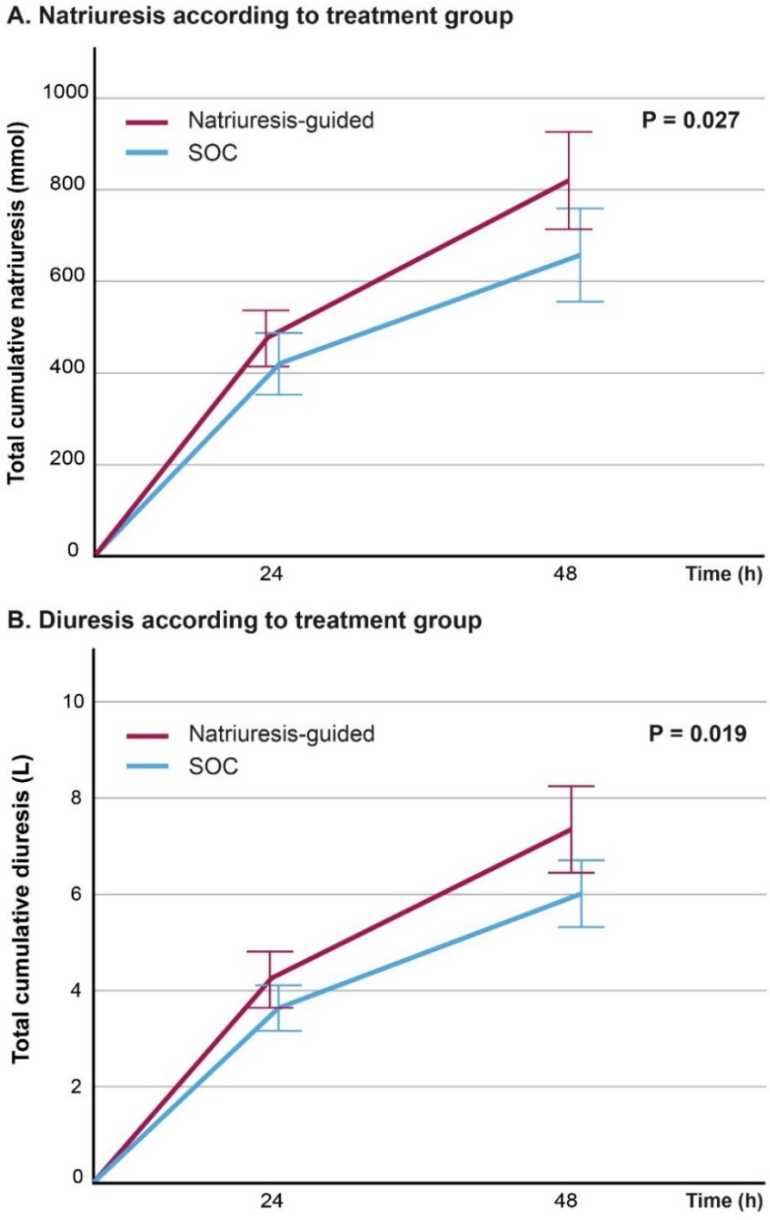


Table 2

Primary, secondary and exploratory endpoints

	Control	Intervention	Absolute difference/ Odds ratio/ Mean ratio (95% CI)	P-value
Primary endpoint				
Natriuresis after 48h (mmol)	657.4 ± 272.7	820.0 ± 279.0	162.6 (18.7 to 306.4)	**0.027**
Secondary endpoint				
Diuresis after 48h (L)	6.0 ± 1.9	7.3 ± 2.4	1.3 (0.2 to 2.4)	**0.019**
Natriuresis 0-24h (mmol)	420.2 ± 180.6	475.4 ± 160.7	55.2 (-34.0 to 144.4)	0.220
Natriuresis 24-48h (mmol)	237.2 ± 127.1	344.6 ± 175.9	107 (28 to 187)	**0.009**
Diuresis 0-24h (L)	3.6 ± 1.3	4.2 ± 1.5	0.6 (-0.1 to 1.3)	0.112
Diuresis 24-48h (L)	2.4 ± 0.9	3.1 ± 1.3	0.7 (0.2 to 1.3)	**0.015**
Loop diuretic responsiveness				
Natriuresis/40mg furosemide (mmol)	107.1 ± 54.0	121.7 ± 79.3	14.6 (-20.6 to 50.0)	0.410
Diuresis/40mg furosemide (L)	1.0 ± 0.4	1.1 ± 0.6	0.09 (-0.2 to 0.4)	0.518
Successful decongestion after 48 h	11 (37%)	13 (43%)	1.38 (0.42 to 4.56)	0.589
Length of hospital stay (days)	8.0 (3.7-17.2)	7.4 (3.4-16.0)	0.03 (-0.09 to 0.15)	0.601
Exploratory endpoints				
Weight change (kg)				
Delta Day 2	-2.1 (± 2.5)	-2.5 (± 2.3)	0.4 (-1.0 to 1.8)	0.603
Delta Day 3	-4.0 (± 2.5)	-4.4 (± 2.3)	0.4 (-1.1 to 1.9)	0.604
Dyspnea score				
Delta Day 2	+ 1.1 (± 0.8)	+ 1.4 (± 1.0)	0.4 (-0.1 to 0.8)	0.105
Delta Day 3	+ 1.6 (± 0.9)	+ 1.9 (± 1.0)	0.3 (-0.2 to 0.9)	0.182
Congestion score				
Delta Day 2	-1.0 (± 1.5)	-1.5 (± 1.5)	0.6 (-0.2 to 1.3)	0.154
Delta Day 3	-2.8 (± 1.6)	-3.6 (± 1.5)	0.8 (-0.02 to 1.6)	0.057

Table 3

Safety endpoints and long-term follow-up

	Control	Intervention	P-value
Adverse events			
Hypotension*	0 (0%)	1 (3%)	1.000
Hypokalemia#	3 (10%)	3 (10%)	1.000
Doubling of serum creatinine	0 (0%)	0 (0%)	/
≥50% decrease in eGFR	0 (0%)	0 (0%)	/
Rise in serum creatinine °	4 (13%)	9 (30%)	0.209
Long-term follow-up			
Combined endpoint of heart failure hospitalizations and all-cause mortality	10 (33%)	10 (33%)	1.000
All-cause mortality	4 (13%)	5 (17%)	1.000
Number of heart failure hospitalizations	8 (30%)	5 (21%)	0.532

** Hypotension was defined as a systolic blood pressure below 85 mmHg.*

Hypokalemia was defined as a serum potassium below 3 mmol/L.

° Rise in serum creatinine was defined as an increase of at least 0.3 mg/dL.

User-friendliness of the protocol and the urinary sensor

A total of 25 nurses were involved in the study protocol and filled out the questionnaire (Supplemental figure 3). The urinary sensor was assessed as very easy in use (median score of 9 out of 10, 25th-75th percentile 8 to 10), fast (entire measurement process requires approximately 2 minutes) and very easy to calibrate (median score of 8 out of 10, 25th-75th percentile 7 to 9) (Figure 4). Almost all preferred the use of the sensor over daily urinary collections (median score of 9 out of 10, 25th-75th percentile 7.5 to 10). Overall, the nurses agreed that the flowchart was easy implementable in their daily practice (median score of 9 out of 10, 25th-75th percentile 8 to 9.75) and that a nurse-led urinary sodium concentration-based program with the sensor and protocol during the first 48 hours is achievable in daily practice (median score of 9 out of 10, 25th-75th percentile 7.5 to 9) without significant time involvement.

DISCUSSION

This single-center, randomized, open-label study demonstrated the feasibility and safety of a nurse-led urinary sodium-based protocol via the use of a POC urinary sodium sensor to titrate diuretic therapy in patients with ADHF. Moreover, natriuresis and diuresis after 48 h were significantly higher in the nurse-led POC urinary sodium-guided group compared to SOC, without an increased incidence of adverse events. As such, the a POC urinary sodium sensor allowed for a fast, easy, user-friendly, and reliable interpretation of urinary sodium, enabling frequent and adequate changes in diuretics through a nurse-led protocol, which can be readily implemented in daily clinical practice.

The diuretic protocol used in the EASY-HF study was based on the recommendations of several expert position papers and the most recent heart failure guidelines of the ESC (3,8,78). Early follow-up of urinary sodium excretion after loop diuretic administration is of utmost relevance as this is a marker of their efficacy, directly reflecting their mechanism of action. (83) A poor natriuretic response during decongestive efforts in ADHF has been associated with worsening heart failure, longer length of stay, heart failure rehospitalization and mortality. (60,62,65,69) Recently, both the single-center PUSH-AHF and international multi-center ENACT-HF study demonstrated the feasibility and efficiency of a natriuresis-guided diuretic protocol. (23,24,79,84) Both trials clearly demonstrated significant increases in natriuresis and diuresis at 48 h. However, this benefit was at the expense of intense physician, nursing, logistic and laboratory staff efforts, which was required to perform frequent urinary sodium tests via traditional laboratory analyses, alongside adjustments to diuretic changes. The EASY-HF confirms the results of the ENACT-HF and PUSH-AHF studies, with a significantly higher natriuresis (820 [± 279] mmol versus 657 [± 273] mmol) in the intervention group. Of note, this was achieved by the standard nursing staff with no or minimal involvement of any other health care provider or resource. Such nurse-led protocols are common practice in many health-care systems including sliding scales for insulin adjustment or potassium supplementation, in which an easy interpretable value (POC glucose levels or blood gas analysis potassium values) lead to a protocolized dose adjustment. The

current study suggest that a similar approach could be applied in the setting of acute heart failure.

Dosages of loop diuretics administered in the intervention and standard of care group in both the ENACT-HF and PUSH-AHF were considerably higher than in the EASY-HF, which is probably reflected by the fact that half of the patients in EASY-HF were diuretic naive, as well as other baseline differences amongst included patients and less stringent changes in response to the urinary sodium result. Despite the higher total dose of loop diuretics, the diuretic response (expressed as degree of natriuresis per 40mg furosemide equivalents) was lower in the PUSH-AHF and the ENACT-HF trial. This indicates a more diuretic-responsive patient population in the EASY-HF, with less intrinsic renal sodium avidity by the nature of randomization of numerous patients that were diuretic naïve at baseline. This also extends the concept of improved decongestion through measuring diuretic responsiveness to a diuretic naïve patient population, a population that is often thought to achieve easy decongestion. The beneficial effects on natriuresis and diuresis were associated with only a trend towards a higher degree of weight loss, dyspnea relieve and improvement in congestion score in the intervention group. This might relate to the small sample size, the challenging nature of accurate daily weight measurements, the fact that weight changes might take longer to be apparent, and that both groups are relatively well decongested with a good natriuresis and diuresis already during the first 2 days, rendering the difference in weight loss too small to be significant. (24) The largest benefit in natriuresis and diuresis was achieved during the second day of treatment. This might reflect better patient selection for diuretic up-titration and possibly a factor physician inertia (also because of lack of insights into detailed urine dynamics), which both can be solved by a nurse-led urinary sodium-guided diuretic protocol.

Despite the more intense protocol leading to higher dosages and more combinational diuretic therapy, both the PUSH-AHF and ENACT-HF studies have proven to be safe with regard to worsening renal function and electrolyte disturbances, which is corroborated by the current EASY-HF study. Importantly, safety was confirmed even though physician involvement in the nurse-led diuretic protocol arm was very limited. Previously, the Yale Diuretic Pathway (YDP) already

demonstrated the safety of a nurse-led, sodium-based diuretic protocol with a modestly increased use of potassium supplements as the only significant finding. (85,86) However, as that protocol was initiated only after 3 days of standard diuretic therapy, the trial did not reflect applicability and safety during the first and most crucial days of treatment. On top, the laboratory analysis of the urinary spot sample is an additional cumbersome step in the cycle, prone to errors and delays in the protocol implementation.

The EASY-HF study is the first study with the use of a point of care urinary sodium sensor to provide an immediate, easy to interpret, reliable, bedside result. The goal of the sensor was to close the circle with timely and adequate diuretic alterations by the nurse. The direct measurement overcomes the additional costs as well as time delay inherent to laboratory measurements further simplifying the protocol in order to be achievable in daily practice. The sensor has demonstrated to be easy in use, accurate and reliable if calibrated once daily. The protocol in the EASY-HF study has been carried out in the cardiac care unit with regular nursing staff, which only needed minimal training in the protocol and use of the sensor. There was a general agreement amongst the nurses that both the protocol and the sensor were easily applicable in daily practice. While the sensor requires daily calibration, the process is comparable and as easy as the calibration of a glucometer. The EASY-HF study has therefore great additional value to the ENACT-HF and PUSH-AHF study, as this is the first study which uses a nurse-led protocol based on the urinary sodium concentration to provide individualized titration of diuretic therapy in ADHF patients. These results suggest that a more aggressive diuretic strategy based on spot urine sodium measurements can now effectively be implemented across a broad array of clinical sites in different countries, with improved natriuresis and without identified safety concerns, at very low cost.

The EASY-HF study has some limitations that should be addressed. The study was an open-label, single-centre feasibility study with a small sample size. Also, the study might be underpowered to demonstrate differences in congestion score, weight change, health scores or length of stay. Although the chosen NT-proBNP cut-offs were higher than those proposed by the ESC guidelines (25) and patients

had clear signs of congestion at the moment of admission, it might have been more appropriate to choose age-dependent cut-offs. (87) In addition, the study assessed the role of a urinary sodium concentration-guided protocol. However, similarly to the guidelines and other trials, there was also an evaluation of the urinary output after 24-hours. Finally, although patients were hospitalized and received standardized dietary salt and water intake, some fluctuations in salt intake could have influenced urinary sodium measurements.

CONCLUSION

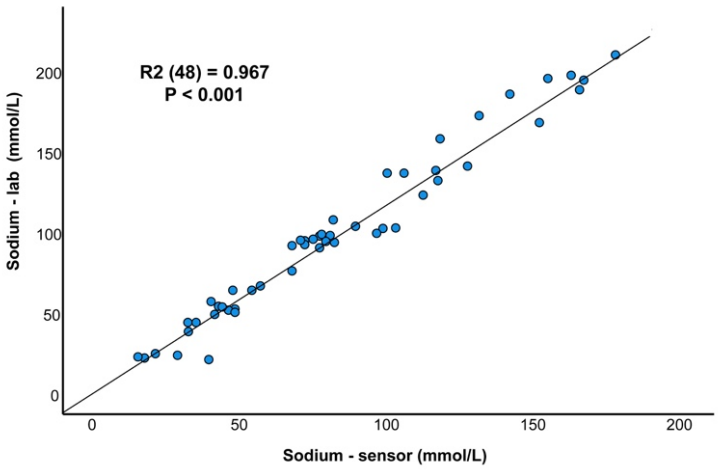
The EASY-HF study demonstrates that a nurse-led natriuresis-guided diuretic protocol with the use of a point of care sodium-sensor is feasible and safe, resulting in an improved natriuresis and diuresis in patients with ADHF.

SUPPLEMENTAL MATERIAL

Supplemental material 1

Accuracy of the LAQUAtwin Na-11 sensor (Horiba®)

The accuracy of the sensor was tested prior to the EASY-HF study. Before collecting urinary samples, the sensor was tested for known sodium content solutions (44ppm and 3550ppm), demonstrating good accuracy for low and high sodium values. Urinary samples were collected and urinary sodium concentrations were measured in laboratory (Cobas 8000 ISE) and with the urinary sensor. Measurements were repeated three times with both methods. The sensor was calibrated on a daily base with a low and high calibration point (150ppm and 2000ppm respectively). The goal of this study was to demonstrate the accuracy of the urinary sensor in comparison with the standard laboratory test, as well as to demonstrate a low intra-test variability. Horiba claims a good accuracy with their result within +/- 10% of the actual value. With a two-tailed alpha, a power of 80% and an expected correlation coefficient of 0.8, we would need only 10 participants. As this was easily obtainable, the sample size was augmented to 50 participants. For this study, healthy volunteers older than 18 years were included. This study demonstrated a very strong correlation between the measurements performed with both methods ($R(48)=0.983$; $R^2(48)=0.967$; p-value=<0.001). The intraclass correlation for both the laboratory measurements (correlation = 1.000) and the sensor (correlation = 0.998) were excellent.



Supplemental table 1

Full list of in- and exclusion criteria

INCLUSION CRITERIA
- Participants should be older than 18 years and should be able to give written informed consent. - hospital admission with signs and symptoms of congestion warranting intravenous decongestive therapy - A clinical congestion score of at least 2 based upon the presence of edema, pleural effusion, or ascites - N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of at least 500 ng per liter (800 ng per liter in case of atrial fibrillation)
EXCLUSION CRITERIA
- Patients unable to collect a 48h-urine collection - Estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m^2 - Concomitant diagnosis of an acute coronary syndrome - Need for inotropic or vasopressor support - Ventricular assist device - Renal replacement therapy (acute or chronic). - Treatment with intravenous loop diuretics > 80 mg furosemide or an equivalence of another loop diuretic (40 mg furosemide = 1 mg bumetanide) during the index hospitalization and prior to randomization

Supplemental table 2

Natriuresis and diuresis according to maintenance diuretic therapy

Parameter	Control	Intervention	Absolute difference	P-value	*P-interaction
Natriuresis (mmol)	657.4 ± 272.7	820.0 ± 279.0	162.6 (18.7 to 306.4)	**0.027**	
Diuretic naive	722.7 ± 325.9	833.4 ± 289.5	110.7 (-115.3 to 336.8)		0.422
Home diuretics	592.2 ± 196.8	803.5 ± 276.4	211.3 (26.8 to 395.8)		
Natriuresis/40 mg furosemide (mmol)	107.1 ± 54.0	121.7 ± 79.3	14.6 (-20.6 to 49.9)	0.410	
Diuretic naive	128.0 ± 60	160.8 ± 82.4	32.9 (-20.5 to 86.2)		**<0.001**
Home diuretics	86.2 ± 38.1	73.5 ± 40.2	-12.7 (-43.1 to 17.8)		
Diuresis (L)	6.0 ± 1.9	7.3 ± 2.4	1.3 (0.2 to 2.4)	**0.019**	
Diuretic naive	6.2 ± 2.2	7.0 ± 2.1	0.7 (-0.8 to 2.3)		0.467
Home diuretics	5.8 ± 1.5	7.8 ± 2.7	2.0 (0.4 to 3.7)		
Diuresis/40 mg furosemide (L)	1.0 ± 0.4	1.1 ± 0.6	0.09 (-0.18 to 0.35)	0.521	
Diuretic naive	1.1 ± 0.4	1.3 ± 0.6	0.2 (-0.2 to 0.6)		**<0.001**
Home diuretics	0.8 ± 0.3	0.7 ± 0.332	-0.1 (-0.4 to 0.1)		

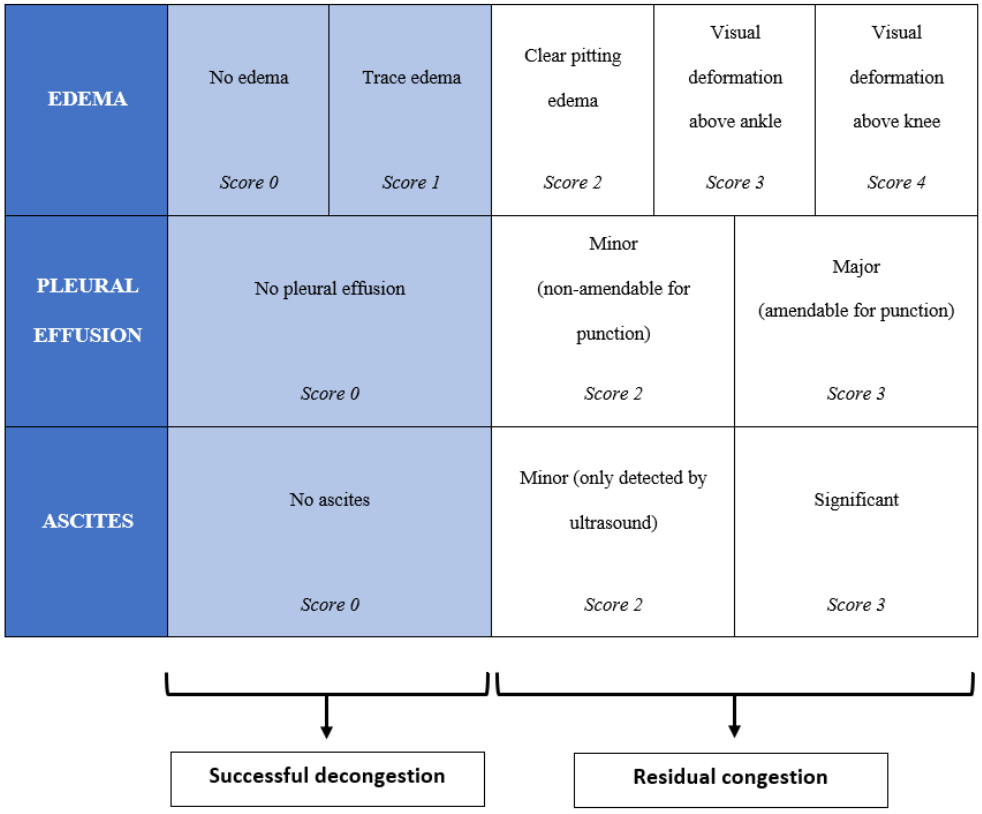
Supplemental table 3

Serum potassium, creatinine and eGFR

	Total	Control	Intervention	P-value	P*
Serum Potassium (mmol/L)					0.363
Day 1	4.1 ± 0.6	4.1 ± 0.7	4.1± 0.6	0.633	
Day 2	3.7 ± 0.5	3.7 ± 0.4	3.7 ± 0.6	0.997	
Day 3	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.5	0.934	
Day 4	3.9 ± 0.5	3.8 ± 0.5	4.0 ± 0.5	0.117	
Serum Creatinine (mg/dL)					0.061
Day 1	1.38 ± 0.45	1.37 ± 0.41	1.39 ± 0.48	0.891	
Day 2	1.35 ± 0.43	1.36 ± 0.42	1.35 ± 0.44	0.951	
Day 3	1.43 ± 0.47	1.39 ± 0.45	1.48 ± 0.49	0.464	
Day 4	1.47 ± 0.50	1.39 ± 0.43	1.54 ± 0.56	0.268	
Serum eGFR (ml/min/1.73m^2)					0.235
Day 1	50.4 ± 18.3	51.0 ± 17.7	49.8 ± 19.2	0.791	
Day 2	51.2 ± 18.8	51.2 ± 17.8	51.2 ± 20.1	0.996	
Day 3	48.6 ± 18.3	50.3 ± 18.1	46.9 ± 18.8	0.472	
Day 4	47.5 ± 19.7	49.7 ± 18.1	45.3 ± 19.4	0.374	

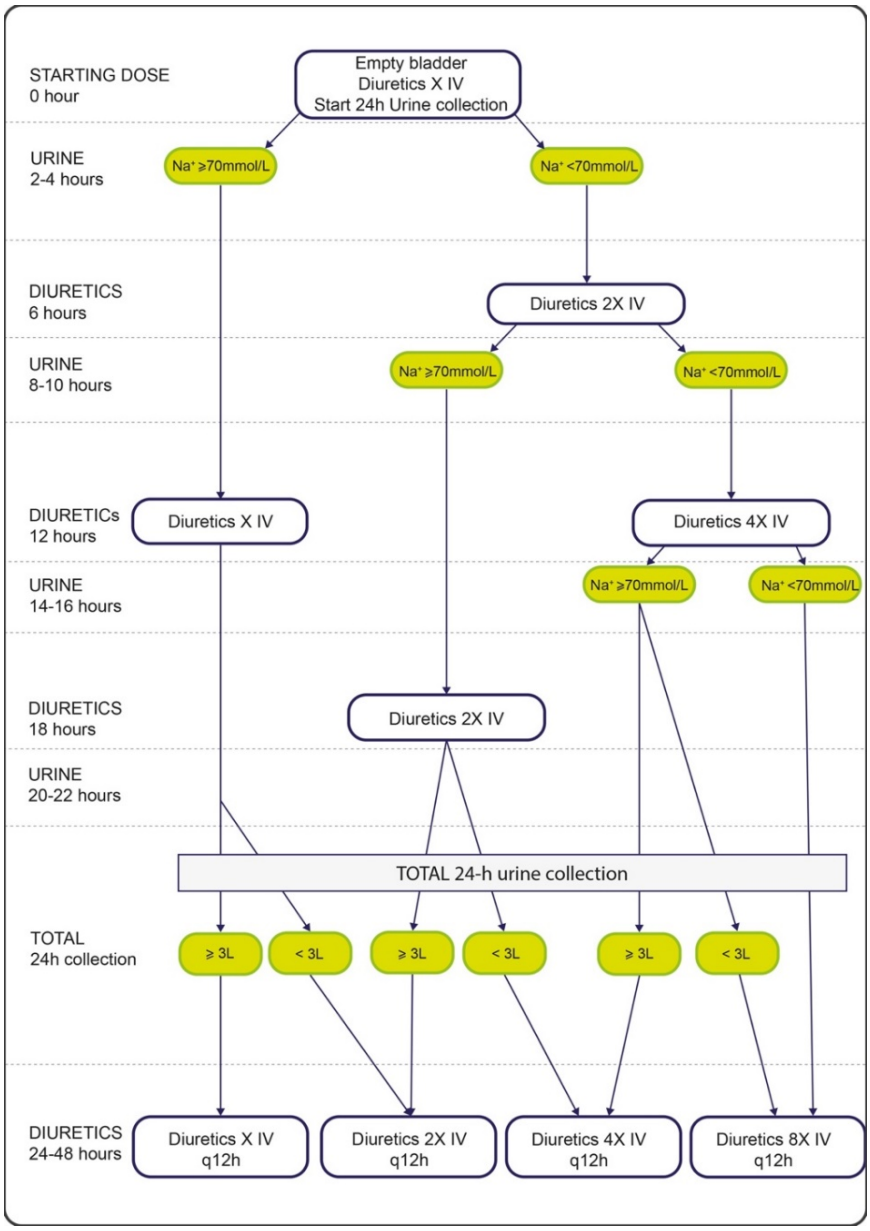
Supplemental figure 1

Congestion score



Supplemental figure 2

Flowchart natriuresis-guided protocol



IV: intravenous

Flowchart provided to the nursing team of the cardiac care unit. Diuretics were doubled every 6 hours until an adequate natriuresis (≥ 70 mmol/L) was achieved. Loop diuretics were titrated up to 5mg of bumetanide equivalents. Subsequently, acetazolamide and thiazide were added as a second and third step to the protocol.

Supplemental figure 3

Questionnaire for the nursing team

Please score from 1 (totally disagree) to 10 (completely agree)

1. The point of care urinary sodium sensor was easy to use:

1	2	3	4	5	6	7	8	9	10

2. The point of care urinary sodium sensor was easy to calibrate:

1	2	3	4	5	6	7	8	9	10

3. The flowchart used in the intervention group was easy to use and applicable in daily practice:

1	2	3	4	5	6	7	8	9	10

4. A nurse-led diuretic protocol during the first 48-hours of a hospital admission for patients with acute decompensated heart failure is achievable in daily clinical practice:

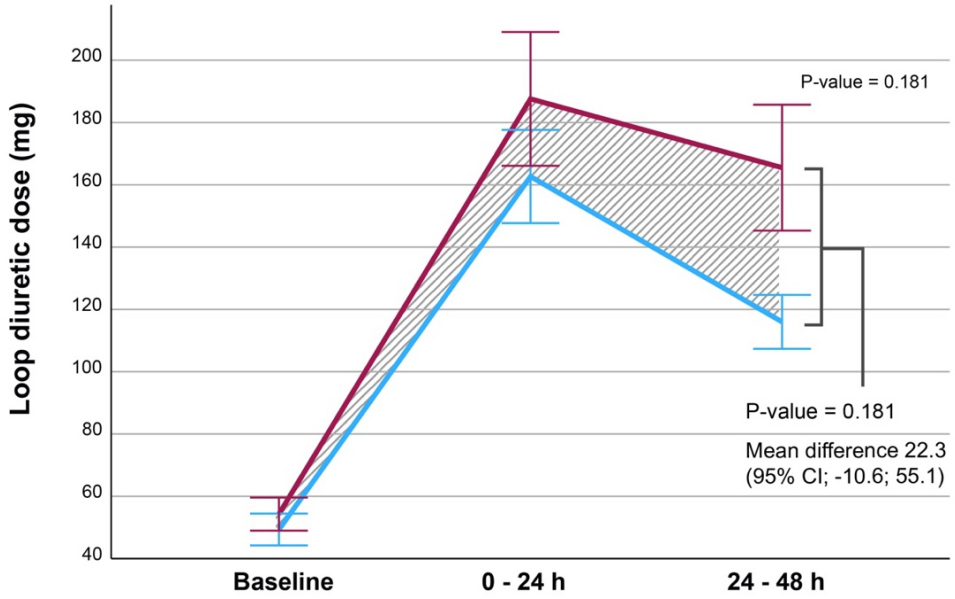
1	2	3	4	5	6	7	8	9	10

5. In the future, I prefer the point of care sensor over 24-hour urinary collections:

1	2	3	4	5	6	7	8	9	10

Supplemental figure 4

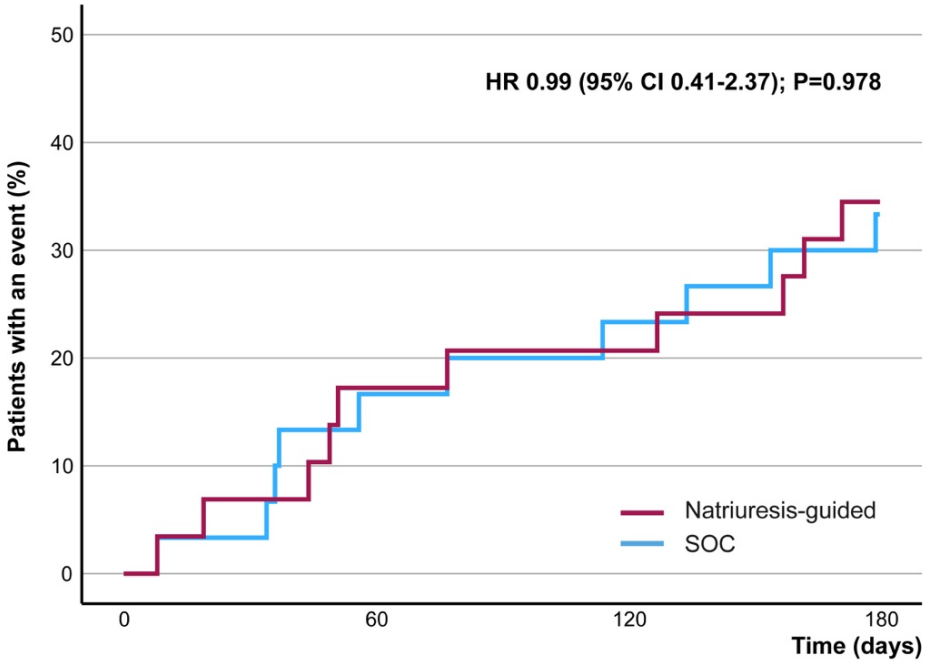
Loop diuretic dosages



Control	40 (40-80)	140 (120-170)	120 (80-160)
Intervention	40 (40-80)	160 (80-240)	160 (80-320)

Supplemental figure 5

Kaplan-Meier for the combined endpoint of all-cause mortality and heart failure hospitalizations



CHAPTER 3

Urinary sodium analysis: The key to effective diuretic titration? European Journal of Heart Failure expert consensus document

Evelyne Meekers, Jeroen Dauw, Jozine ter Maaten, Pieter Martens, Petra Nijst, Frederik Verbrugge, Marnicq Van Es, Jonas Erzeel, Kevin Damman, Joan Carles Trullàs, Matthias Dupont, Wilfried Mullens

Eur J Heart Fail. 2025, Online ahead of print.

ABSTRACT

In patients with heart failure, neurohumoral activation leads to increased renal sodium avidity across the entire renal tubules, resulting in a positive sodium and water balance, leading to decompensated heart failure requiring intravenous diuretics. As the dose of diuretic therapy required to achieve euvolemia is difficult to estimate due to considerable intra- and interindividual differences, the European Society of Cardiology recommends assessment of the diuretic response within hours either via evaluation of the urinary sodium concentration or via urinary volume after initial diuretic administration. All diuretic agents enhance sodium excretion to a different extent depending on their side of action across the renal tubules, and renal adaptation mechanisms due to neurohumoral stimulation. Impaired sodium excretion, even in the presence of fluid loss, is associated with worse clinical outcomes. Therefore, assessing urinary sodium excretion is considered a good and direct marker of the diuretic efficacy. Such natriuresis-guided protocols have been tested prospectively by the Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure and the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure study, both demonstrating increased natriuresis and diuresis. Moreover, the Readily Available Urinary Sodium Analysis in Patients with Acute Decompensated Heart Failure study has demonstrated that a nurse-led natriuresis-guided protocol is feasible through the use of a point-of-care urinary sodium sensor, allowing an immediately readable urinary sodium result, enabling fast changes in diuretic therapy. This review summarizes the rationale, current evidence and gaps supporting the role of the urinary sodium concentration in patients with acute decompensated heart failure.

INTRODUCTION

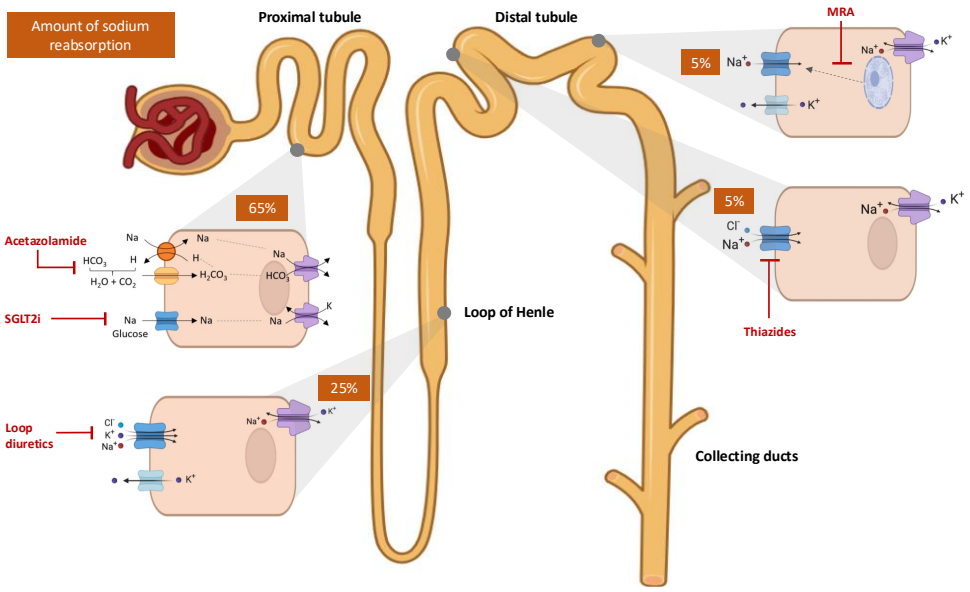
Acute decompensated heart failure (ADHF) significantly impacts patients with heart failure, contributing to high morbidity, mortality, and healthcare costs. (1,8,77) Despite advancements in chronic heart failure treatment, ADHF episodes remain prevalent, severely affecting patients' quality of life. Congestion is the primary reason for seeking urgent medical attention. Therefore, the primary goal during hospitalization is to achieve and maintain euvolemia in addition to optimizing guideline directed medical therapy and treating comorbid conditions. According to current guidelines, judicious use of intravenous (IV) loop diuretics remains the cornerstone in treating ADHF, to relieve signs and symptoms of congestion. (8,37) Nevertheless, only 11-18% of the patients achieved decongestion after 72 hours of treatment in the Diuretic Optimization Strategies Evaluation (DOSE) trial. (88) In addition, in the recent Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial, not all patients were fully decongested at the moment of discharge, despite the fact that upfront combination therapy with acetazolamide improves decongestion rate considerably. (38) Therefore, there is a pressing need for effective and pragmatic metrics to optimize diuretic therapy, tailored to each patient's need. Several expert position papers, as well as the 2021 heart failure guidelines of the European Society of Cardiology (ESC) advise early assessment of the diuretic response using spot urinary sodium concentrations within two hours of diuretic administration, with levels >50–70 mmol/L targeted. (3,25,78) Recent trials have tested various diuretic protocols guided by urinary sodium concentrations in patients with ADHF. This review summarizes the physiological basis and current evidence supporting urinary sodium concentration as a tool to guide diuretic therapy. It proposes practical approaches to titration in daily practice and highlights gaps in evidence, emphasizing its potential role in improving outcomes for ADHF patients.

IMPAIRED NATRIURESIS AND DIURESIS IN HEART FAILURE

Although sodium is freely filtered across the renal glomerulus, more than 99% is reabsorbed in the renal tubules, primarily in the proximal tubules (Figure 1). In heart failure, hemodynamic alterations and neurohumoral stimulation enhance renal sodium avidity. Importantly, heart failure is characterized by disproportionate sodium retention relative to water retention. (89,90) Decreased cardiac output, elevated filling pressures and renal venous congestion lead to reduced renal blood flow (RBF), requiring an increase in single-nephron glomerular filtration rate (GFR) to maintain overall GFR (34). This compensatory increase in single-nephron filtration accelerates nephron loss in heart failure patients. (35) Thus, as RBF decreases, the kidneys autoregulate by increasing the filtration fraction to maintain the GFR. This heightened filtration fraction raises sodium and water reabsorption across the proximal tubule (glomerulotubular balance) due to higher oncotic pressures in the peritubular capillaries. Consequently, the amount of sodium and chloride reaching the loop of Henle and the more distal parts of the tubules is considerably reduced. Neurohumoral upregulation further amplifies sodium and water reabsorption across the nephron. Additionally, reduced chloride delivery to the macula densa triggers renin release, activating the renin-angiotensin-aldosterone axis (tubuloglomerular feedback).

Figure 1

Renal tubules and different diuretic target sides



In the distal nephron, aldosterone increases sodium reabsorption by the sodium-chloride co-symporter and by the insertion of the epithelial natrium channels (ENaC) in the distal convoluted tubules and in the collecting ducts. Chronic high-dose loop diuretics use promotes distal tubular hypertrophy, further enhancing sodium retention. Reduced tubular flow in the distal nephron segments, combined with decreased blood flow in the vasa recta and increased sodium reabsorption, creates a hypertonic medullary interstitium. This osmotic gradient, along with arginine-vasopressin release stimulated by angiotensin II, promotes free water retention in the collection ducts, impairing the diluting capacity of the kidney. (3,36) This highlights that plasma volume regulation is primarily mediated by renal sodium handling. Sodium serves as the primary determinant of extracellular fluid volume, and plasma sodium concentration reflects plasma volume regulation rather than osmoregulation. (91)

DIURETICS IN HEART FAILURE

Under conditions of forced sodium intake of 540 mEq (>12 g) with unrestricted access to water, maximal urinary sodium concentration can reach 280 mEq/L (92) In contrast, during decongestion therapy with diuretics in the management of heart failure, urinary sodium concentration typically remains lower than serum sodium levels (~140 mEq/L). Therefore, a significant volume of water is required to promote the effective excretion of excess sodium in heart failure. Loop diuretics are strongly recommended (Class I) for alleviating signs and symptoms of congestion in patients with ADHF. In patients with diuretic resistance, combination diuretic therapy might be indicated, as it enhances natriuresis and diuresis, although the comparison was not to a higher dose of loop diuretics, but against placebo. Given the varying mechanisms of action of different diuretics along the renal tubules, combination diuretic therapy blocks sodium reabsorption at multiple sites, augmenting the diuretic response (Figure 1).

Targeting the Loop of Henle

Loop diuretic therapy blocks the $Na^+/K^+/2Cl^-$-symporter at the luminal membrane of the ascending loop of Henle, where 25% of sodium reabsorption occurs. This produces potent diuretic effects as the distal tubules have limited compensatory capacity (Figure 1). However, loop diuretics reduce the intracellular chloride load in the macula densa, triggering renin release and consequently higher renin-angiotensin-aldosterone system (RAAS) activation. Importantly, chronic use of loop diuretics may induce distal tubular hypertrophy and increased sodium reabsorption, resulting in diuretic resistance. (3) This effect may be countered by adding thiazides, which block the sodium-chloride cotransporter (NCC) in the early part of the distal convoluted tubules (Figure 1). (3) The Safety and Efficacy of Combination of Loop with Thiazide-type Diuretics in patients with Decompensated Heart Failure (CLOROTIC) trial demonstrated that combining hydrochlorothiazide with intravenous furosemide was safe and effective in patients with ADHF, improving diuresis, natriuresis and weight loss in patients with chronic high-dose loop diuretics (maintenance therapy of more than 80mg of furosemide daily), i.e. patients often classified as having diuretic resistance. (93) Similarly, the Diuresis Efficacy in Ambulatory Congested Heart Failure Patients (DEA-HF) trial showed

that patients with intermittent long-term very high-dose intravenous loop diuretic therapy have a beneficial effect of the addition of thiazides to overcome the distal tubular hypertrophy. (94) With regard to different types of loop diuretics, torsemide has a longer half-life than bumetanide and furosemide. (95) Despite this, the Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) study was not able to demonstrate a significant difference in all-cause mortality over 12 months between ambulatory heart failure patients treated with torsemide and those with furosemide. (96)

Targeting the proximal tubule

Proximal diuretic agents are acetazolamide and sodium-glucose cotransporter 2-inhibitors (SGLT2i). Acetazolamide, a carbonic anhydrase inhibitor, blocks sodium reabsorption in the proximal tubules (Figure 1). (3,81,97) The ADVOR trial revealed that upfront use of intravenous acetazolamide in addition to intravenous loop diuretics in patients with ADHF resulted in a greater incidence of successful decongestion within 3 days and at discharge, attributed to higher cumulative urine output and natriuresis. (38) SGLT2i block the sodium and glucose reabsorption at the proximal tubules (Figure 1), promoting osmotic diuresis through glucosuria. However, this effect is rather small with only a transient increase in natriuresis. (98) Indeed, the association of an SGLT2i to loop diuretic therapy led to a significant increase in 24-hour diuresis, without an increase in urinary sodium excretion at both 3 days and 6 weeks treatment. (99) The increase in urinary volume due to the osmotic diuretic effect of SGLT2i even weans off 24-48hours after the initiation due to the parallel release of vasopressin, resulting in renal water reabsorption. (100) Furthermore, in patients with diuretic resistance, the addition of dapagliflozin to loop diuretics did not lead to an increase in weight loss after 96 hours compared with the addition of metolazone (DAPA-RESIST). (101) Thus, while SGLT2i have limited utility in achieving acute euvolemia, they are essential in chronic heart failure therapy for their disease-modifying benefits.

Targeting the Distal Nephron

Mineralocorticoid receptor antagonists (MRA) also theoretically induce natriuresis by modulating sodium and potassium channel activity in the distal nephron. (3) However, as they work as a prodrug, they have a slow onset and only work 48-

72 hours after oral intake. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial confirmed that their diuretic properties are limited as high dose (100 mg) spironolactone was not superior to low dose (25 mg) with regard to 96-h diuresis in patients with ADHF. (102) Importantly, like SGLT2i, they are also part of the chronic therapy in all patients with symptomatic heart failure. An auxiliary benefit of early addition of a MRA is the protection against hypokalemia during aggressive decongestion. (103)

NATRIURESIS GUIDED DIURETIC STRATEGIES

The disproportionate increase in sodium retention relative to water avidity in ADHF represents a key pathophysiological mechanism. Therefore, it is logical that assessing urinary sodium content could offer valuable clinical insights. Strategies that enhance natriuresis are prognostically significant in patients hospitalized with ADHF. Among patients receiving high-dose loop diuretics, sodium concentration and excretion demonstrate substantial variability. Notably, sodium excretion is strongly correlated with 6-month mortality, whereas traditional fluid-based metrics including diuresis (aquaresis) show limited prognostic value. Impaired sodium excretion, even in the presence of fluid loss, is associated with worse clinical outcomes. (64,70)

Testani et al. defined a poor diuretic response as a cumulative urinary sodium output below 50 mmol in a 6-hours urinary collection post-diuretic administration. (21) This threshold reflects the pharmacodynamic principle that loop diuretics have a half-life of 1.5-2 hours and that their natriuretic effect is completed within 6 hours. (46) If diuretics are given twice a day, this would lead to a total sodium excretion below 100 mmol. As the recommended daily sodium intake is limited to 3 grams a day, which equals 130 mmol, there would still be a positive sodium balance, leading to salt and fluid retention. While 6-hour sodium excretion correlates well with total 24-hour urine output (47), this requires timed urinary collections, prone to sampling errors. Therefore, spot urinary sodium samples offers an alternative, simplified and pragmatic strategy to predict a poor loop diuretic response with a good accuracy. (21,48) This method provides an early diuretic response evaluation within 2 hours, enabling rapid adjustments to the

diuretic regimen. (104) Biegus et al. demonstrated in a small, single-center study (n=50) that urinary sodium concentration during the first six hours exhibits an exponential relationship with urinary output, particularly in diuretic-naive patients. (105) This suggests that urinary output might be simplified to once after 24 hours rather than every 6 hours. However, beyond this initial period, the relationship between urinary sodium concentration and output is less consistent.

NATRIURESIS-GUIDED PROTOCOLS

As illustrated, all diuretic agents (except vaptans) block sodium reabsorption along distinct sites along the renal tubule. Measuring urinary sodium concentrations early during decongestive therapy can identify patients requiring diuretic intensification to enhance diuretic efficacy. Observational studies show up to 40% of ADHF patients meet criteria for diuretic resistance, emphasizing the need for early evaluation strategies. (21,50–52) Given the good accuracy of spot urinary sodium concentrations for predicting diuretic resistance, the ESC guidelines recommend natriuresis-guided decongestive protocols. These protocols suggest diuretic up-titration if urinary sodium concentration falls below 50-70 mmol/L or urinary output is less than 100-150 ml/u, measured at 2 and 6 hours post-diuretic administration, respectively. (8) As previously used metrics (such as weight change or initial diuresis) were not good predictors for diuretic resistance (32), urinary spot sodium measurement may be the new kid in the block, leading to early optimization of diuretic treatment in patients with ADHF.

As present, 2 large trials and one small feasibility trial have tested the protocol prospectively (Table 1). The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) study was a multicenter, international, open-label, non-randomized, two-phase study (n=401), in which a natriuresis-guided protocol (n=147) improved natriuresis after 1 and 2 days (respectively, 174 versus 282 mmol, $p<0.001$; and 365 versus 538 mmol, $p<0.001$), diuresis after 2 days (5.8 L versus 4.4 L, $p<0.001$), with a reduction in length of stay (5.8 versus 7.0 day; $p=0.036$) compared to the standard of care (n=254). (24,79) Similarly, the Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure (PUSH-AHF) trial was a single-center, open-label, randomized-controlled study (n=310), which

confirmed that a natriuresis-guided therapy resulted in a significant improvement in 24-hour and 48-hour natriuresis (respectively 345 versus 409 mmol, and 575 versus 653 mmol) and diuresis (respectively 3.3 versus 3.9 L, and 5.9 versus 6.7 L) compared to the standard-of-care. (23,84)

There are some discrepancies between the study designs that should be addressed. The ENACT-HF protocol required a minimum home maintenance loop diuretic dose of 40 mg, while 45% of patients in the PUSH-AHF trial were diuretic-naive. The first loop diuretic bolus was double of the oral maintenance dose in all patients in the intervention arm. Up-titration was performed in case of a urinary sodium concentration below 50 mmol/L after 2 hours or a urine output below 100mL/h after 6 hours, and doubling of the diuretic dose occurred 6 to 12 hours after the first one. If these measurements were adequate, the same dose was repeated 6 to 12 hours after the first administration. In case of a urine output below 3 L the next morning (i.e., not per definition after 24h), diuretic dosage was doubled during the second day of treatment. In the standard of care arm, intravenous diuretic therapy was left at the discretion of the treating physician. (79)

In the PUSH-AHF study, the cut-off for the urinary sodium concentration was set higher at 70 mmol/L in the intervention arm. (84) The starting dose was equal to the oral home maintenance loop diuretic dose (or 40 mg of furosemide equivalents in loop diuretic naive patients) with a doubling of the dose in patients with an impaired kidney function (eGFR < 60 ml/min/1.73m^2). During the treatment phase in the PUSH-AHF, doubling of the diuretic dose was possible in case of a low urine output (< 150 ml/L) or sodium concentration (< 70 mmol/L) at any set timepoint (2, 6, 12, 18, 24 and 36 hours).

Figure 2

Diuretic titration in patients with ADHF with volume overload

	PUSH-AHF	ENACT-HF	EASY-HF
Methods			
Study design	Single-center, open-label	Multicenter, open-label	Single-center, open-label
Randomized	+	-	+
Sample size	310	401	60
Patient population	ADHF	ADHF with maintenance loop diuretic therapy at home	ADHF
Exclusion criteria	Severe renal impairment receiving dialysis or requiring ultrafiltration	- cardiogenic shock or systolic blood pressure <90 mmHg - use of renal replacement therapy or ultrafiltration - use or anticipated use of intravenous inotropes.	- eGFR < 20 ml/min/1.73m^2 - patients currently undergoing or with a history of renal replacement therapy
Intervention	Diuretic intensification if - U_{Na+} < 70 mmol/L 2, 6, 12, 18, 24 and 36 h - U_{out} <150ml/h at 6, 12, 18, 24 and 36 h	Diuretic intensification if - U_{Na+} < 50 mmol/L after 2h - U_{out} < 100 ml/h after 6h - U_{out} < 3L after 1 day	Diuretic intensification if - U_{Na+} < 70 mmol/L after 2h - U_{out} < 3 L after 24h
Primary endpoint	- 24 h urinary sodium excretion - combined endpoint of time to all-cause mortality or adjudicated heart failure rehospitalization at 180 days	Natriuresis after 1 day (first diuretic administration until next morning 8 – 10 AM)	48h natriuresis
Patient characteristics			
Age (years)	74 (65-82)	70 ± 14	80 ± 8
Male gender (%)	55%	250 (62%)	45 (75%)
EF (%)	38 ± 14	39 ± 15	43 ± 16
EF <40 (%)	124 (54%)	223 (56%)	24 (40%)

Baseline therapy						
Loop diuretics at home	114 (37%)		401 (100%)		31 (52%)	
Dose of oral furosemide or equivalents (mg/day)	80 (40-160)		60 (40–90)		40 (40-80)	
ACEi/ARB/ARNI	109 (35%)		270 (67.3%)		23 (38%)	
BB	139 (45%)		317 (79.1%)		39 (65%)	
MRA	69 (22%)		207 (51.6%)		15 (25%)	
SGLT2i	13 (17%)		68 (17.0%)		13 (22%)	
Laboratory						
eGFR (ml/min/1.73m^2)	53 (35-73)		49 (32–74)		51 ± 18	
NT-proBNP (ng/L)	4,710 (2,553–8,750)		5,888 (3,200–11,934)		4,667 (2,667-7,709)	
Diuretics	Intervention	Control	Intervention	Control	Intervention	Control
Loop diuretics after 2 days (furosemide equivalents)	640 (400-960)	320 (200-560)	640 (320-760)	240 (195-391)	320 (160-480)	240 (200-320)
Use of thiazides (%)	24%	3%	18.9%	5.7%	0%	0%
Acetazolamide	0.4%	1%	0.7%	1.6%	0%	17%
Number of up-titration	85%		35%		30%	
Outcome	Intervention	Control	Intervention	Control	Intervention	Control
Natriuresis after 1 day (mmol)	409 ± 178	345 ± 202	282 (254-312)	174 (154–196)	475 ± 161	420 ± 181
Natriuresis after 2 days (mmol)	653 ± 249	575 ± 290	538 (493–587)	365 (330–403)	820 ± 279	657 ± 273
Diuresis after 1 day (L)	3.9 (3.2–4.9)	3.3 (2.5–4.5)	3.1 (2.3-4.0)	2.2 (1.5-3.1)	4.2 ± 1.5	3.6 ± 1.3
Diuresis after 2 day (L)	6.7 (5.4–7.8)	5.9 (4.6–7.4)	5.8 (5.4–6.2)	4.4 (4.1–4.7)	7.3 ± 2.4	6.0 ± 1.9
Length-of-stay (days)	6 (5–9)	7 (5–10)	6 (5–7)	7 (6–8)	7 (3–16)	8 (4–17)

Although the initial diuretic administration was more cautious with loop diuretic titration based on the renal function, the PUSH-AHF study employed a more aggressive diuretic protocol with intensification of the therapy at any of the previously mentioned time points. The ENACT-HF study used the lower range of the values proposed by the ESC for both the urinary sodium concentration and urinary output, in contrast to the PUSH-AHF which used the upper range. Although the study designs were somewhat different, both protocols seemed to be effective with regard to improving decongestive therapy (i.e. natriuresis and diuresis) in patients with ADHF compared to our current practice. A comparable protocol has been tested through a nurse-led diuretic protocol in the Readily Available Urinary Sodium Analysis in Patients with Acute Decompensated Heart Failure (EASY-HF) study. (106) This open-label, single-center study randomized 60 patients to a standard-of-care arm or a nurse-led urinary sodium-guided diuretic up-titration protocol. Urinary sodium concentrations were measured bedside through a urinary sodium sensor (Horiba, LaquaTwin Na-11, Japan), providing an immediately readable result which allowed direct adjustments to the diuretic protocol in case of an insufficient diuretic efficiency (defined as urinary sodium concentration below 70 mmol/L 2 hours after diuretic administration or urinary output below 3 L after 24 hours). This trial demonstrated that individualized titration significantly improved natriuresis (657 ± 273 mmol versus 820 ± 279 mmol, $p<0.05$) and diuresis (6.0 ± 1.9 L versus 7.3 ± 2.4 L, $p<0.05$) within 48 hours (without physician intervention). The incorporation of a point-of-care urinary sodium sensor into the existing protocol enables nurse-led (or other health care providers) individualized diuretic titration, potentially establishing it as a standard procedure applicable across various departments beyond cardiology, which could significantly enhance the success of decongestion.

The dosage of loop diuretic therapy administered after two days of treatment in both arms in the ENACT-HF (640 [320-760] mg and 240 [195-391] mg) and PUSH-AHF (640 [400-960] mg and 320 [200-560] mg) trials were considerably higher than in the EASY-HF study (320 [160-480] mg and 240 [200-320] mg). The higher loop diuretic dosages in the PUSH-AHF and the ENACT-HF are related to the fact that the diuretic protocol was more intensive (i.e. the combination of the hourly urine output or the urinary sodium concentration criteria, the lower

urine output requirements in the ENACT-HF study and the doubling at any set timepoint irrespective of previous diuretic responses in the PUSH-AHF study) and the more diuretic resistant study population of the ENACT-HF. This was also reflected by the proportion of patients requiring up-titration according to the protocol, i.e. 30% in the EASY-HF study, 35% in the ENACT-HF study and 85% in the PUSH-AHF study. Notably, diuretic response, measured as natriuresis per 40 mg furosemide equivalents, was lower in PUSH-AHF and ENACT-HF than EASY-HF, highlighting greater diuretic responsiveness in the latter population. Therefore, by taking all differences between the trial protocols in account, it can be postulated that urinary sodium guided diuretic protocols have demonstrated to be efficient and safe across a broad spectrum of heart failure patients (de novo to more diuretic resistant heart failure patients).

PRACTICAL APPROACH

Since the release of the ESC guidelines and position statement, significant new data has emerged regarding diuretic titration in ADHF. These recommendations may seem less practical in daily use due to their broad urinary sodium concentration range (50–70 mmol/L) with the need for hourly urinary volume assessments. The ESC flowchart may be too abstract, while the position statement's detailed recommendations could limit clinical applicability. (3,8) Therefore, based on recent trial data and real-world use of natriuresis-guided diuretic protocols, a novel more pragmatic algorithm is proposed to optimize diuretic therapy in patients with ADHF (Figure 2). For diuretic-naive patients, treatment starts with 40 mg IV furosemide (equivalent to 1 mg bumetanide or 10 mg torsemide), doubled for eGFR <60 ml/min/1.73m². Patients on maintenance loop diuretics begin with double their oral dose intravenously, and the upfront addition of intravenously acetazolamide (500 mg IV once daily) or an oral thiazide (e.g., hydrochlorothiazide, dose adjusted by eGFR) should already be considered. Acetazolamide is the preferred first line agent for most maintenance patients, while upfront thiazides are reserved for high-dose loop diuretic users. If urinary spot sodium concentration is <70 mmol/L two hours after administration or a urinary volume <150ml/h, diuretic therapy should be doubled. Loop diuretics should be titrated to a maximum bolus dose of 200 mg of furosemide (daily

maximum 600 mg, with higher doses cautiously considered for patients with impaired renal function, though this increases the risk of ototoxicity). In patients with poor natriuretic or diuretic response, early combination therapy with acetazolamide or thiazides should be considered in diuretic naive patients. Both acetazolamide (500 mg IV once daily) or a thiazide (hydrochlorothiazide if eGFR >50 ml/min: 25 mg daily; GFR 20–50 ml/min: 50 mg daily; and GFR <20 ml/min: 100 mg daily) are administered in a once daily regimen. Diuretic therapy should be optimized during the first day until natriuretic response is sufficient (i.e., ≥70 mmol/L and output ≥150ml/h). Once achieved, this dose should be repeated every 12 hours until decongestion is accomplished. After 24h of treatment, total diuresis should be taken in consideration. If diuresis remains <3 L and congestion persists, further diuretic escalation should be considered during the second day of treatment. Importantly, other options like ultrafiltration in case of overt diuretic resistant volume overload, IV vasodilator therapy like nitroprusside (or inotropes in low-output states) in case of advanced low-output left ventricular failure with reduced ejection fraction or performing paracentesis in case of ascites should be considered. (107–109) Diuretic therapy should be given at least twice daily to limit the amount of post-diuretic sodium retention. Bolus intravenous loop therapy is preferred as it allows easier changes. However, when continuous infusions are chosen, an initial bolus should be administered to reach the diuretic threshold. During decongestive treatment, some degree of worsening renal function (WRF) may be anticipated due to hemodynamic alterations. (31) However, in case of adequate diuresis and no signs of hypoperfusion/hypotension, this should be interpreted as pseudo-WRF. Pseudo-WRF generally does not worsen prognosis if effective decongestion is achieved. So, in case of residual signs of congestion, continuation of decongestive therapy is advised under monitoring of electrolytes and serum creatinine. In contrast, if true WRF occurs in the face of a poor diuretic response, diuretic escalation is often necessary and signs of hypoperfusion should be ruled out (Figure 2). Consequently, changes in renal markers should be interpreted within the clinical context, focusing on achieving complete decongestion without overly reducing essential therapies based solely on transient increases in serum creatinine.(31) In the process of assessing changes in creatinine with diuresis, urinary sodium is also useful as patients with true WRF will have low urinary sodium concentration. These recommendations differ from

the current ESC guidelines as patients with maintenance loop diuretic therapy receive already a different initial diuretic approach as they are considered to be more diuretic resistance (Table 2). In addition, the upper value of the target urinary sodium concentration and urine output has been chosen (i.e., ≥ 70 mmol/L and 150ml/h). Most importantly, the urinary sodium concentration assessment is limited to the first day of treatment as the composition of the urinary sodium concentration during decongestive therapy changes significantly over time. Although urinary volume output remains relatively stable (diuresis), a drop in natriuresis is expected during the consecutive days of loop diuretic therapy. (47) The role of urinary sodium-guided diuretic therapy during the first 24 to 48 hours of treatment has been firmly established, however it is rather unsure how it may aid in diuretic titration afterwards as the urine becomes more hypotonic as a result of both hemodynamic and neurohumoral changes. (47,74,104) Most importantly, if decongestive therapy is optimized early, most of the patients are assessed decongested after a short treatment period. (38,106)

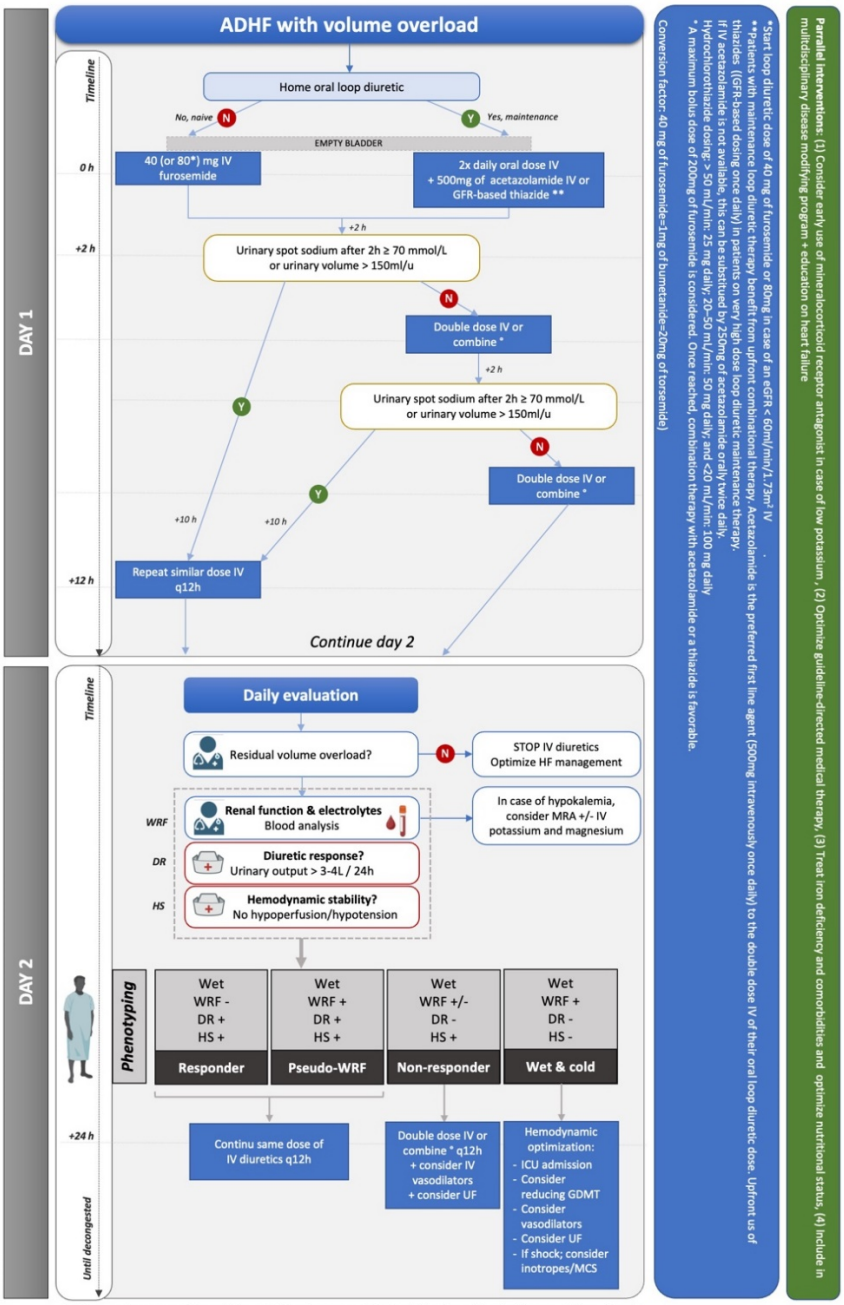
Table 2

Novelties of the proposed flowchart

What is new?
- Upfront combination therapy in patients who receive oral loop diuretic maintenance therapy at home. - Urinary sodium concentration assessment after 2 hours, possible through a nurse-led protocol. A urinary sodium concentration above 70 mmol/L (not 50 mmol/L) is considered as adequate. - Use of point-of-care urinary sodium concentration tests or rapid laboratory testing in order to timely optimize diuretic titration.

Figure 2

Diuretic titration in patients with ADHF with volume overload



ADHF: acute decompensated heart failure; DR: diuretic response; GDMT: guideline-directed medical therapy; HS: hemodynamic stability; IV: intravenously; MCS: mechanical circulatory support; MRA: mineralocorticoid receptor antagonist; UF: ultrafiltration; WRF: worsening renal function

WRF defined as a rise in serum creatinine of >0.3mg/dL and/or an increase >25%.

Future directions

Some gaps in the current evidence with regard to urinary sodium guided diuretic titration remain. The ongoing 'Urine Chemistry Guided Acute Heart Failure Treatment' (ESCALATE) trial may aid to provide an answer to the role of the urinary sodium concentration during the later phases of decongestion (i.e., after 48 hours). The study randomizes 450 patients with ADHF to standard-of-care or urinary sodium-guided diuretic titration until euvolemia is reached (NCT04481919). (110) Such a strategy is also tested in the Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) trial, which randomizes 107 ADHF and evaluates whether a diuretic sodium-guided regimen with low-threshold use of combination diuretic therapy improves decongestion and outcome compared to usual care (NCT05411991). Given the results of the ADVOR and the CLOROTIC trial, early combination of diuretic agents might be indicated in a subpopulation of ADHF patients. The DECONGEST trial will evaluate how this might have an impact on the urinary sodium concentration during decongestion. It is important to note that a clinical evaluation of the congestion state remains necessary as a drop in urinary sodium excretion may implicate that euvolemia is reached. However, it could also imply growing diuretic resistance in case of remaining signs and symptoms of congestion. In addition, the target urinary spot sodium concentration of 50-70 mmol/L is derived from the equation of Testani and showed to have a good accuracy, but not excellent. The chosen threshold of 70 mmol/L is therefore somewhat arbitrary and reflects the guidelines, but any value below 100 mmol/L may represent some kind of diuretic resistance. (111) Finally, although most ADHF patients receive dietary restrictions during hospitalizations, these might differ between centers. Dietary salt intake and total volume intake might have an influence on the urinary sodium concentration measured during decongestive treatment.

Beyond its role in the titration of diuretic therapy in ADHF patients, urinary sodium concentration measurements may also provide valuable prognostic and therapeutic insights for patients with chronic heart failure (CHF). Studies have shown that CHF patients with a low baseline urinary sodium excretion (i.e. <80 mmol/L), who are concurrently on high dose of maintenance loop diuretic therapy

(furosemide >80 mg per day) exhibit a higher mortality risk (55). Martens et al. have explored the longitudinal significance of urinary sodium measurements in CHF patients. Their findings indicate that patients who experienced ADHF events generally presented with lower urinary sodium concentration compared to those with stable CHF. Furthermore, in these patients, episodes of congestion were preceded by a drop in urinary sodium concentration, likely due to increased neurohumoral activation (17). Sodium retention and congestion are inherently dynamic processes, resulting in frequent changes in home loop diuretic therapy. In addition to its potential role in prognostication, evidence suggests that urinary sodium concentration may assist in optimizing loop diuretic maintenance therapy (16,74–76). However, further research is required to determine whether individual diuretic adjustments based on urinary sodium measurements are feasible and improve outcomes in CHF management, as well as to assess the impact of dietary sodium and fluid intake on these adjustments.

CONCLUSION

Until recently, no good metrics and lack of interest to guide diuretic therapy in patients with acute decompensated heart failure, often lead to relatively late change in dose escalation and initiation of combination therapy, contributing to diuretic resistance. As urinary sodium excretion is a direct reflection of the action of diuretic agents, regular assessment of urinary sodium concentrations holds great promises. The benefit of a natriuresis-guided diuretic protocol, especially during the first 24 to 48 hours, has consistently demonstrated to improve diuresis and natriuresis, with a possible reduction in length of hospital stay. Incorporating a point-of-care sensor to the protocol allows individualized (nurse-led) diuretic titration, enhancing heart failure care. Despite the growing evidence, there are still some gaps, which might be answered by the current ongoing trials (DECONGEST, ESCALATE).

PART III

URINARY SODIUM IN CHRONIC HEART FAILURE

Somewhere, something incredible
is waiting to be known.

- Carl Sagan -

CHAPTER 4

Home Urinary Sodium Measurements as a Predictor of Heart Failure Stability After Acute Heart Failure Hospitalization: Results of the FAST-RESPONSE Study

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ABSTRACT

Background: Acute decompensated heart failure (ADHF) frequently results in rehospitalization, and although early post-discharge follow-up may mitigate this risk, implementation remains challenging. Ambulatory urinary sodium profiling, reflecting neurohumoral activation and diuretic response, may predict congestion during this high-risk phase.

Methods and Aims: This single-center study included 50 ADHF patients post-discharge, who collected daily urine samples (first-void and post-diuretic) for two weeks. Urinary sodium concentrations were analyzed to assess feasibility and predictive value for recurrent ADHF events (rehospitalization or diuretic escalation), congestion (composite; ADHF, >2 kg weight gain, or >10 mmHg increase in right ventricular systolic pressure) at 4 weeks and outcome (death or heart failure hospitalization) at 6 months.

Results: Of the 50 patients, 36 (72%) patients completed the study. Mean age was 76.1±8.7 years, 68% were male, 70% had chronic kidney disease (eGFR <60 mL/min/1.73m²), and NT-proBNP was 2,719 ng/L (1,358–5,460). Adherence rates were 92% (morning) and 89% (post-diuretic) for 913 collected samples. Median urinary sodium concentration was 37(25-56) mmol/L pre-diuretic and 56(29-81) mmol/L post-diuretic (p<0.001). Among 36 patients with follow-up, 7 (19%) and 13 (36%) patients experienced ADHF and congestion, respectively. These patients exhibited significantly lower morning urinary sodium concentrations (36[23–46] versus 44[31–59] mmol/L, p<0.001) and lower post-diuretic urinary sodium concentrations (51[29–63] mmol/L versus 58[33–74], p=0.011). The composite long-term endpoint occurred in 56% and this group exhibited significantly lower urinary sodium concentrations than stable patients (both, p-value<0.001).

Conclusion: Urinary sodium profiling is a promising, non-invasive tool to identify high-risk patients after ADHF hospitalization. Further studies are needed to explore its role to guide therapies after ADHF hospitalization.

CONDENSED ABSTRACT

Background: Acute decompensated heart failure (ADHF) often leads to rehospitalization. Ambulatory urinary sodium profiling may predict congestion and clinical stability post-discharge.

Methods: In this single-center study, 50 ADHF patients collected urine samples twice daily for 14 days. Urinary sodium was analyzed for feasibility and predictive value regarding ADHF events, congestion at 4 weeks, and outcomes at 6 months.

Results: Among 36 patients completing follow-up, lower first-void urinary sodium correlated with ADHF events ($p<0.001$), congestion ($p<0.001$), and poor long-term outcomes ($p<0.001$).

Conclusion: Urinary sodium profiling is a feasible, non-invasive tool to identify high-risk ADHF patients needing closer follow-up.

INTRODUCTION

Episodes of acute decompensated heart failure (ADHF) represent a significant clinical challenge and burden for our healthcare system, as they are the main reason for hospitalization in patients with heart failure. (25) Despite advancements in therapy, the post-discharge period following an ADHF event is often referred to as the 'vulnerable phase' due to the high risk for rehospitalization. Nearly 20–30% of the patients experience a rehospitalization within the first 30 days and up to 50% within six months. (13,20,22) These recurrent episodes are often driven by unresolved or recurrent congestion, underscoring the critical need for early identification of patients at risk for deterioration. (22) Early follow-up after ADHF is recommended to evaluate patients for signs and symptoms of congestion; however, it is time-consuming, challenging to coordinate, and logistically burdensome. (25) Neurohumoral activation, a hallmark of heart failure pathophysiology, leads to alterations in sodium handling and fluid retention. (3) Urinary sodium profiling provides a direct insight into these pathophysiological processes, reflecting the dynamic interplay of diuretic response and neurohormonal regulation. Serial assessments of urinary sodium concentration are already well-established as a marker for evaluating diuretic efficacy and guiding therapy adjustments in ADHF endorsed by the guidelines. (23,74,106) In addition, chronic stable HF patients at highest risk for acute decompensated heart failure (ADHF), exhibit lower urinary sodium concentrations, with a noticeable decline in the week preceding hospitalization. (17) However, the feasibility and value of urinary sodium measurements in patients immediately after an ADHF event remains unexplored. In the Forecasting Acute Heart Failure Hospitalizations Based on Home Urinary Sodium Measurements (FAST-RESPONSE) study, the role of urinary sodium concentrations in patients discharged after an ADHF event is evaluated as a predictive tool to identify individuals at risk of future episodes of congestion. The aim is to assess the feasibility and utility of longitudinal urinary sodium measurements as a marker of clinical stability and early congestion in this vulnerable population.

METHODS

Trial design

This is a single-center (Ziekenhuis Oost-Limburg, Genk, Belgium), interventional, prospective study. The trial protocol was approved by the local ethical committee and executed in compliance with the Declaration of Helsinki. All patients provided written informed consent.

Study population

Patients (older than 18 years) were screened for inclusion from the cardiology department. They were eligible for inclusion if they were hospitalized at the cardiology department with an ADHF event (signs and symptoms of congestion, NTproBNP > 1000 pg/ml warranting hospitalization and therapy with IV diuretics) and received loop diuretic as a maintenance therapy after discharge. Main exclusion criteria were patients undergoing renal replacement therapy or patients deemed to be unable to collect daily urinary sample collections. A full list of in- and exclusion criteria is provided in Supplemental table 1.

Baseline visit

Patients were enrolled either on the day prior to discharge or on the day of discharge. After inclusion, baseline measurements were collected prior to the day of discharge (Figure 1). Patients were examined for residual signs and symptoms of congestion and underwent a transthoracic echocardiography and blood sample collection. Patients were instructed about a healthy balanced diet according to ESC HF guidelines avoiding excess sodium intake. (25) The discharge home dose of loop diuretics was at the discretion of the treating heart failure physician at the time of discharge.

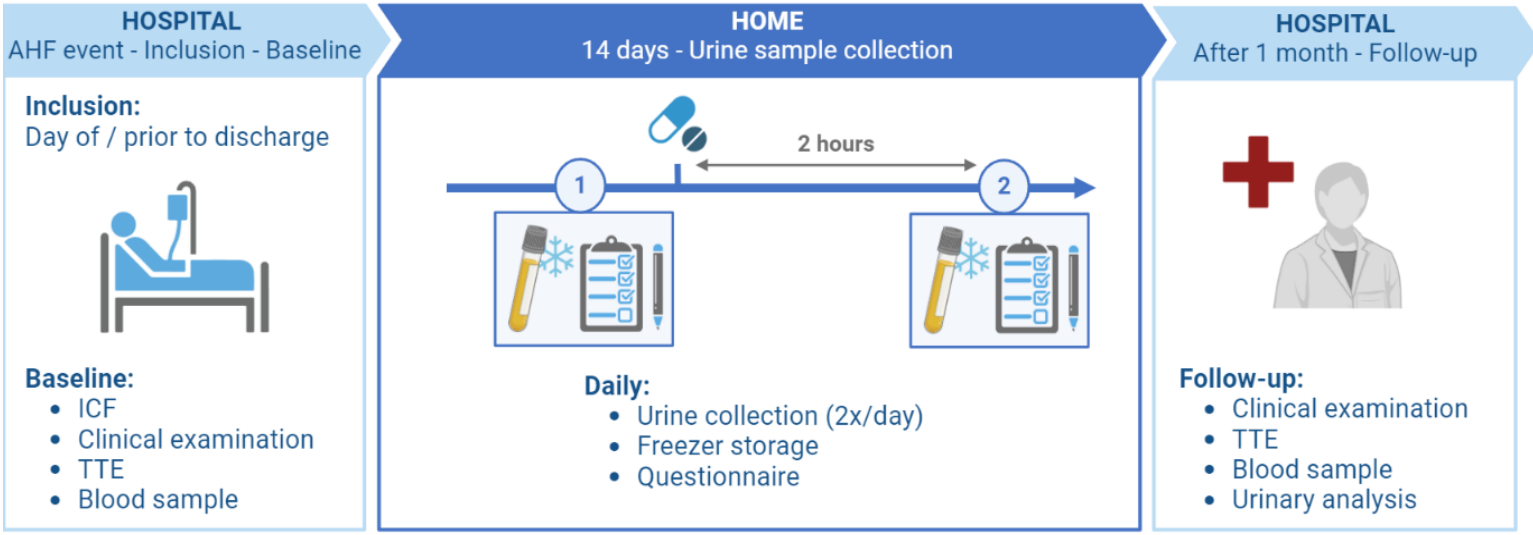
Daily urinary sampling and storage

Following hospital discharge, patients were asked to start collecting daily urinary samples at home. Two samples were collected on a daily base for two weeks: one morning sample (first void, prior to medication intake) and another 1.5-2 hours after loop diuretic intake. At the baseline visit, methods for collection and storage

were thoroughly discussed with the patient and/or care giver. Urine collection was performed in a disposable urine cup and patients were instructed to consequently obtain a urine spot sample through aspiration from the sealed collection cup by a vacuum tube (Supplemental figure 1). Patients were asked to freeze the samples immediately in their freezer (approximately -18°C). Together with the sample collections, patients needed to report daily their weight, blood pressure, dyspnea score (VAS; 0 = no dyspnea at all, 100 = extreme shortness of breath), presence of edema (Likert scale with a score ranging from 0 (no fluid) to +4 (massive edema above the knee) and loop diuretic dose. Patients were instructed to document any significant dietary changes that occurred during that day. Both the vacuum tube and the daily questionnaire were labeled according to the day and moment of sampling (e.g., day 1 – sample 1, day 1 – sample 2, day 2 – sample 1, …). Prior to freezing the urine sample, the patient completed a safety check verifying that the sample had been collected and that both the urine sample and the questionnaire were correctly labeled. After one week, patients were contacted by phone by the study team to enhance compliance.

Figure 1

Trial design



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

Follow-up visit

An ambulatory follow-up visit was scheduled after 4 weeks, at which the patients brought their frozen samples and the questionnaires. Samples were brought immediately to the laboratory for analysis (Cobas-8000 analyzer, Roche Diagnostics, Basel, Switzerland). Additionally, during the follow-up visit, patients underwent physical examination, laboratory assessments, transthoracic echocardiography, and blood sample collection.

Events

All patients' electronic health records were tagged to prospectively assess development of ADHF hospitalizations and all-cause mortality. Three different endpoints were assessed during the study. First, development of ADHF, defined as either (1) a hospitalization due to signs or symptoms of congestion necessitating the use of intravenous diuretics or (2) an urgent outpatient visit with the need for increasing home loop diuretic maintenance therapy due to signs of congestion, during the measurement period of 2 weeks. In addition, congestion events were prospectively defined as either ADHF, weight gain > 2kg or increase in right ventricular systolic pressure > 10 mmHg at 4 weeks of follow-up. Finally, six months all-cause death and heart failure hospitalization was collected.

Statistical analysis

Normality of continuous data was assessed using a Shapiro-Wilk test. Variables are summarized as means with standard deviations, medians with 25-75th percentile, or numbers with percentages and evaluated using ANOVA, Kruskal-Wallis and chi-square tests as appropriate. 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 or in case of dependent data with the McNemar test.

Longitudinal urinary sodium concentrations were analyzed using linear mixed models for repeated measures. Due to the anticipated occurrence of missing values in the repeated-measures design, mixed modeling was selected over

repeated-measures analysis of variance. A first-order autoregressive structure was applied to model the time effect, as measurements of sodium taken closer in time were assumed to exhibit higher correlations. The models were designed to assess the fixed effects of time, group (ADHF, occurrence of congestion or heart failure hospitalization or death during 180days follow-up), and the interaction between group and time ([group × time] effect). The fixed effects were assessed using Type III sum of squares. Given the tendency of non-normal distribution of urinary sodium, the residuals of the longitudinal models were checked to determine the violation of the normal distribution assumption. For patients experienced an ADHF hospitalization, the urinary sodium concentrations were censored to the day of the event and the last 7 days prior to the event were analyzed by using a paired t-test.

No adjustments for multiplicity were performed, so all reported p-values are exploratory. All the hypotheses testing was 2-sided with a significance level of α = 0.05. All statistical analyses were done using SPSS version 29 (IBM® SPSS ® Inc., Chicago, IL, United States).

RESULTS

Baseline demographics

Patients were screened between November 2023 and June 2024, 50 patients consented to participate (Table 1 and Figure 2). Mean age of the patients was 76.1 (± 8.7) years old, with the majority of the patients being male (68%). Most patient were functioning in New York Heart Association (NYHA) class II (Supplemental table 2) with few signs of residual clinical congestion at the moment of discharge despite a n-terminal pro-brain natriuretic peptide (NT-proBNP) level of 2,719 (1,358-5,460) ng/L at discharge. Most of the patients were known with chronic kidney disease, i.e. 70% had an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m². The median dosage of loop diuretic maintenance therapy at the moment of discharge was 40 (40-80) mg of furosemide equivalents, median ejection fraction was 44 (25-55) %, with approximately half of the patients known with heart failure with reduced ejection fraction. Patients with heart failure with reduced ejection fraction (HFrEF) were well treated with guideline-directed medical therapy (GDMT) (Supplemental table 3). Importantly, 14 of the 50 patients (28%) completed the baseline evaluation, however, did not collect their urinary samples or did not return for follow-up visit. The primary reason was logistical challenges, as they found it too difficult to collect samples twice daily at home for 2 weeks. Overall, baseline characteristics were comparable between the analyzed patients and drop-outs (Table 1).

Follow-up visit

At the 4 weeks follow-up visit, body weight decreased significantly compared to baseline ($p = 0.014$), accompanied by a reduction in the prevalence of orthopnea (36.7% vs 8%) and dyspnea score (Table 2). Laboratory analysis indicated increased levels of plasma aldosterone and plasma renin activity (PRA). Other blood parameters remained stable throughout the study. Echocardiographic evaluation showed stable values of left ventricular end-diastolic diameter (LVEDD) and right ventricular systolic pressure.

Table 1

Baseline demographics

	Total (n=50)	Drop out (n=14)	Analysed (n=36)	P-value
Age	76.1 ± 8.7	79.3 ± 6.1	74.8 ± 9.3	0.056
Male %	34 (68%)	7 (50%)	27 (75%)	0.105
LVEF (%)	44 (25-55)	48 (20-55)	38 (25-55)	0.983
LVEF Class				
HFrEF	24 (48%)	5 (36%)	19 (53%)	0.531
HFmrEF	5 (10%)	2 (14%)	3 (8%)	
HFpEF	21 (42%)	7 (50%)	14 (39%)	
RVSP	35 (27-46)	35 (27-51)	35 (26-45)	0.712
Ischemic	23 (46%)	5 (36%)	18 (50%)	0.529
Heart rate	68 ± 13	70 ± 10	68 ± 14	0.594
Blood pressure				
Systolic	116 ± 18	115 ± 23	116 ± 16	0.819
Diastolic	66 ± 10	69 ± 12	65 ± 9	0.381
BMI (kg/m²)	28.3 (24.1-34.0)	27.2 (22.8-31.7)	28.6 (24.5-34.6)	0.100
Comorbidities				
AF	39 (78%)	12 (86%)	27 (75%)	0.705
Stroke	11 (22%)	4 (29%)	7 (19%)	0.476
COPD	11 (22%)	2 (14%)	9 (25%)	0.705
Dyslipidemia	13 (26%)	2 (14%)	11 (31%)	0.303
Arterial hypertension	35 (70%)	11 (79%)	24 (67%)	0.507
Diabetes Mellitus	21 (42%)	3 (21%)	18 (50%)	0.110
Medication				
ACEi/ARB/ARNI	34 (68%)	11 (79%)	23 (64%)	0.501
Beta-blocker	43 (86%)	13 (93%)	30 (83%)	0.657
MRA	38 (76%)	10 (71%)	28 (78%)	0.718
SGLT2i	22 (44%)	3 (21%)	19 (53%)	0.061
Dose LD (mg, furosemide eq)	40 (40-80)	40 (40-80)	40 (40-80)	0.604
Devices				
PM	7 (14%)	3 (21%)	4 (11%)	0.384
CRT	7 (14%)	3 (21%)	4 (11%)	0.384
ICD	18 (36%)	5 (36%)	13 (36%)	1.000
Laboratory				
CKD (<60)	35 (70%)	6 (43%)	29 (81%)	**0.016**
Creatinine (mg/dL)	1.47 (1.11-1.70)	1.10 (0.90-1.46)	1.56 (1.20-1.82)	**0.010**
NTproBNP (ng/L)	2719 (1358-5460)	3382 (2280-7142)	2142 (1039-5459)	0.147

ACEi: Angiotensin-Converting Enzyme Inhibitor, AHF: Acute Heart Failure, ARB: Angiotensin Receptor Blocker, COPD: Chronic Obstructive Pulmonary Disease, CRT: Cardiac Resynchronization Therapy, HFmrEF: Heart Failure with mildly reduced Ejection Fraction, HFpEF: Heart failure with preserved Ejection Fraction, HFrEF: Heart Failure with reduced Ejection Fraction, ICD: Implantable Cardioverter-Defibrillator, MRA: Mineralocorticoid Receptor Antagonist, NYHA: New York Heart Association, SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor

Figure 2

Patient flowchart from screening to analysis

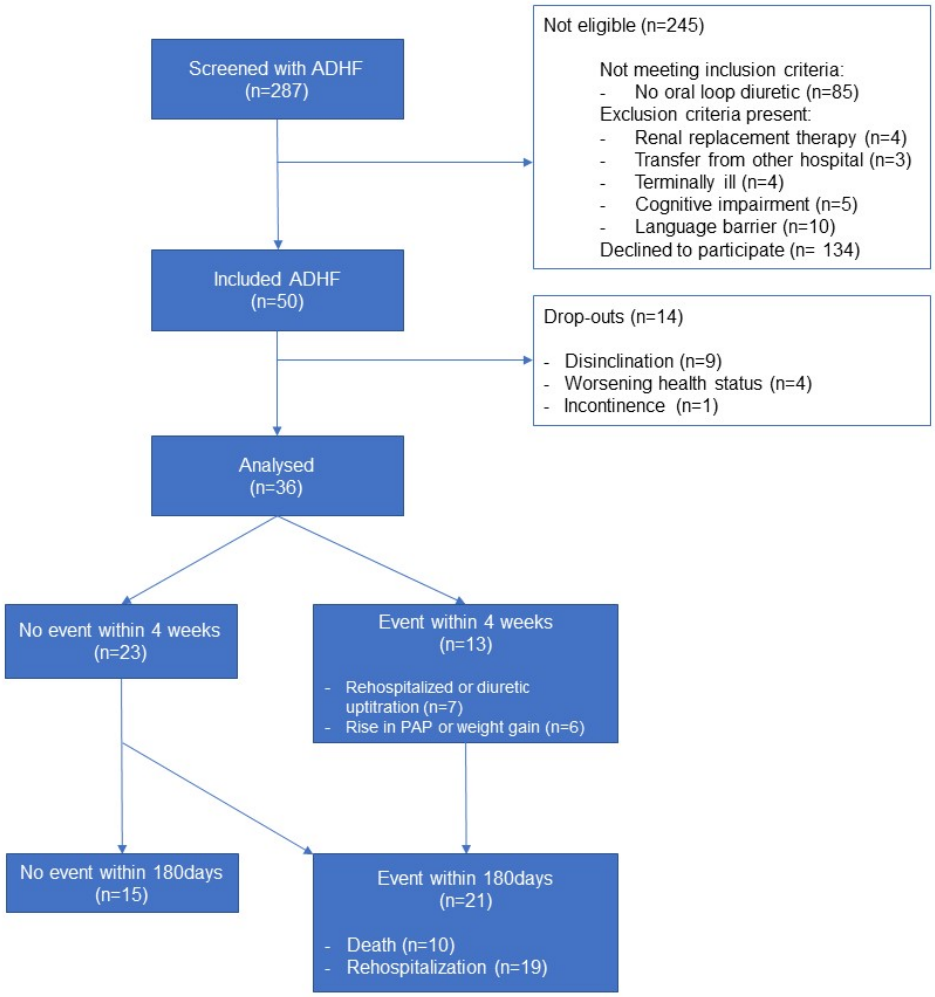


Table 2

Characteristics at baseline and follow-up visit (4 weeks)

	Baseline (n=36)	Follow-up (n=36)	P-value
Clinical			
Orthopnea	13 (36%)	3 (8%)	**<0.001**
Bendopnea	10 (28%)	6 (17%)	0.109
Paroxysmal nocturnal dyspnea	2 (6%)	1 (3%)	0.625
VAS dyspnea score	30 (20-50)	20 (8-38)	**0.014**
Oedema			0.873
Grade 0	16 (44%)	21 (58%)	
Grade 1	14 (39%)	8 (22%)	
Grade 2	3 (8%)	4 (11%)	
Grade 3	3 (8%)	2 (6%)	
Grade 4	0 (0%)	1 (3%)	
Weight (kg)	86.2 ± 22.7	84.1 ± 22.3	**0.035**
Heart rate (bpm)	68 ± 14	71 ± 14	0.238
Systolic blood pressure	116 ± 16	116 ± 19	0.835
Diastolic blood pressure	65 ± 9	67 ± 11	0.830
Laboratory			
Hemoglobin (g/dL)	12.7 ± 2.0	13.0 ± 1.9	0.607
Serum creatinine (mg/dL)	1.56 (1.20-1.82)	1.67 (1.35-1.96)	0.110
Troponin (ng/L)	36 (25-47)	35 (23-50)	0.543
NT-pro BNP (ng/L)	2142 (1039-5459)	2123 (1365-3239)	0.217
Plasma Aldosterone (ng/g)	90 (50-145)	167 (71-314)	**0.014**
PRA (ng/mL/h)	134 (34-409)	239 (88-550)	0.102
Osmolality (mOsm/L)	306 (295-317)	302 (298-309)	0.902
Echocardiography			
LVEDD, mm	50 (44-60)	50 (44-56)	0.208
RVSP, mmHg	35 (26-45)	35 (25-41)	0.218
MR grade	1 (1-2)	1 (0-1)	0.016

Longitudinal urinary sodium measurements

A total of 36 participants collected urine samples twice daily over a period of 14 days. In total, 462 first void samples and 451 samples 2 hours after diuretic intake were collected, which corresponds to a sample compliance of 92% and 89% respectively in those patients who started sample collection post-discharge. Overall, median morning urinary sodium concentration was 37 (23-56) mmol/L, which significantly increased to 56 (29-81) mmol/L post diuretic therapy ($p<0.001$). There was a strong correlation between the first-void and post-diuretic urinary sodium measurement ($r=0.582$, $p<0.001$). There was no significant difference between both measurements over time ($p=0.898$). Urinary chloride levels exhibited a similar increase 20 (18-32) mmol/L to 52 (24-80) mmol/L) post diuretic therapy ($p<0.001$). Histograms of the spot urinary sodium concentrations (first void and two hours after diuretic intake) are depicted in Supplemental figure 2. Over a follow-up of 14 days, urinary sodium and chloride excretion remained relatively stable, with a higher excretion of both electrolytes post-diuretic therapy (Figure 3 and 4).

Figure 3

Mean first void and post-diuretic urinary sodium excretion; compared between A) stable heart failure and patients experiencing an ADHF event at 14 days; B) stable heart failure and those experiencing congestion event at one month follow-up; C) stable heart failure and those experiencing heart failure rehospitalization or death during 180 days follow-up.

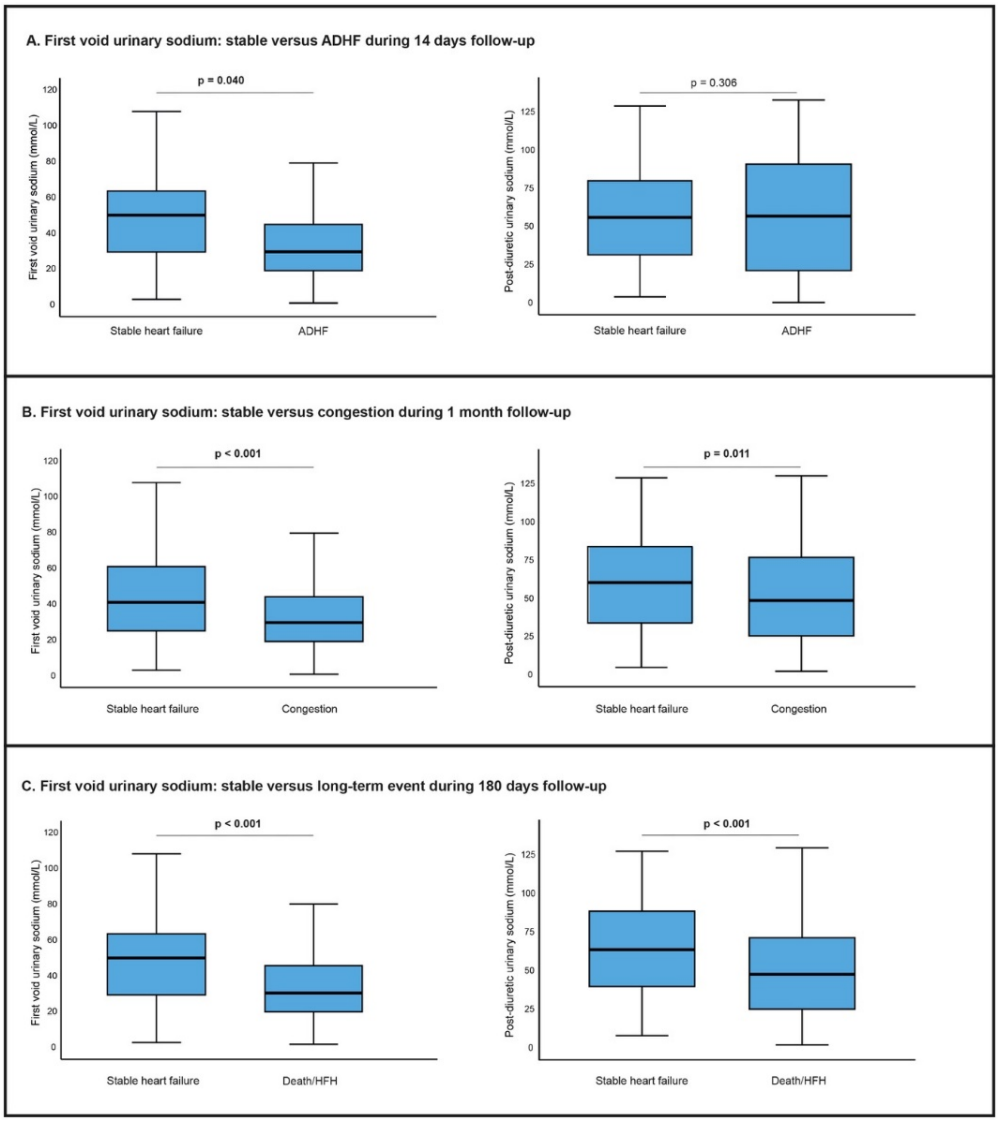
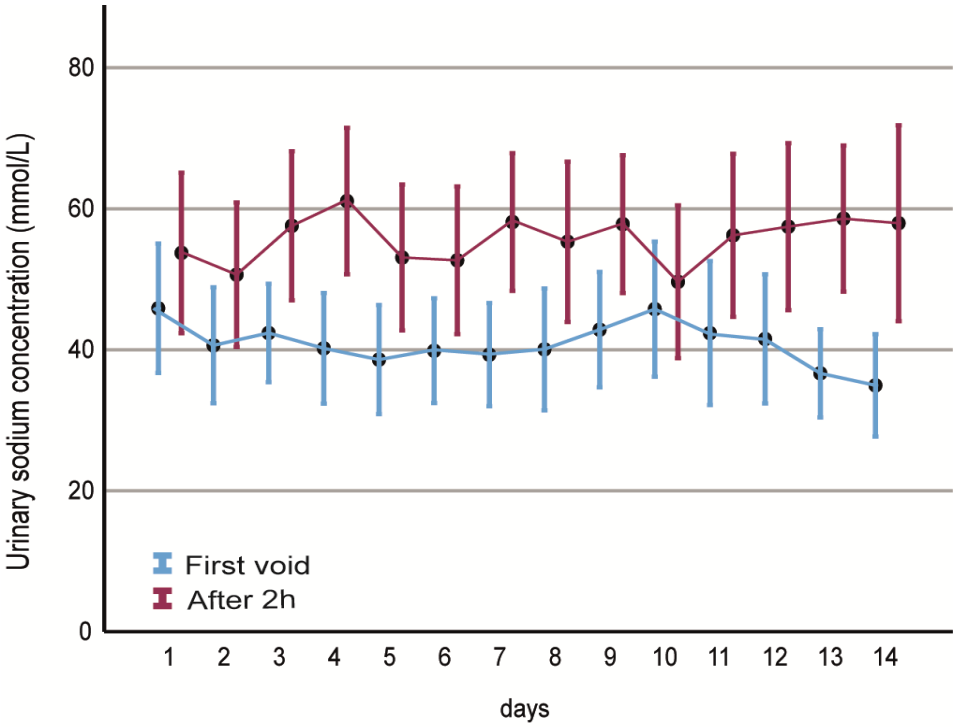


Figure 4

Longitudinal urinary sodium concentration over 14 consecutive days



Short term follow-up (4 weeks)

Seven patients (19%) experienced an event characterized by an increased dose of loop-diuretics or hospitalization due to an ADHF episode within 2 weeks follow-up. In addition, six patients had a weight gain of more than 2 kilograms and four patients experienced an increase in right ventricular systolic pressures of more than 10mmHg within 4 weeks follow-up compared to discharge. As such, 13 out of the 36 patients (36%) experienced either the combined endpoint of a congestion event defined as ADHF event (rehospitalization or increase in oral loop diuretic dose), a rise in PAP pressures or weight gain within 4 weeks follow-up. With the exception of a higher ejection fraction in patients experiencing some degree of congestion during follow-up, baseline characteristics were not significantly different between the two groups (Supplemental Table 4). Urinary sodium concentration in the first void urinary spot were significantly higher in patients with stable heart failure compared to patients with ADHF (42 ± 23 mmol/L

versus 37 ± 22 mmol/L, p=0.040) and between patient with stable heart failure and those experiencing congestion (44 ± 23 mmol/L versus 36 ± 22 mmol/L, p<0.001) (Figure 3.A and 3.B). With regard to the post-diuretic void, this was not-significantly higher in patients with stable heart failure compared to those with ADHF (56 ± 29 mmol/L versus 53 ± 33 mmol/L, p=0.306), but significantly higher in patients with stable heart failure compared to those with congestion (58 ± 29 mmol/L versus 51 ± 30 mmol/L, p=0.011). Importantly, measurements performed on the first day after discharge were not significantly different from the mean measurements performed over the study period (overall for first-void p=0.345, post-diuretic void p=0.387). The evolution of the morning spot urinary sodium concentration over time differed significantly between patients experiencing an ADHF event and patients with stable CHF (p=0.033), as well between patients with stable CHF and patients with signs of congestion (p=0.037) (Supplemental figure 3).

After censoring urinary samples to the day of the ADHF event, no apparent difference was noted in the urinary sodium excretion during the last seven days prior to the event.

Long-term follow-up (180 days)

After a follow-up period of 180 days, 28 out of the 50 patients (56%) experienced a combined endpoint of all-cause mortality (15 out of 50, 30%) or heart failure rehospitalization (23 out of 50, 46%). After the exclusion of the drop-outs, 21 out of 36 (58.3%) experienced a combined endpoint after 180 days (10 patients died (27.8%) and 19 were rehospitalized due to ADHF (52.8%)). This group exhibited significantly lower first-void (37 ± 22 mmol/L versus 48 ± 22 mmol/L, p<0.001) and post-diuretic (64 ± 29 mmol/L versus 50 ± 29 mmol/L, p<0.001) urinary sodium concentrations compared to stable patients throughout the follow-up period (Figure 3.C).

DISCUSSION

The FAST-RESPONSE study was the first to evaluate urinary sodium excretion (i.e., natriuresis) profiles at home twice daily over a 14-day period following hospitalization for an ADHF event. Key findings from the study include: 1) home measurements were feasible, with a compliance rate of 91% (92% first-void and 89% post-diuretic void); 2) first-void natriuresis was consistently lower than the post-diuretic natriuresis in all patients with a good correlation between both measurements over time, indicating persistent diuretic responsiveness; 3) urinary sodium concentration measured on the first day after discharge did not differ from the mean urinary sodium concentration over time, 4) patients experiencing congestion the first month after discharge had significantly lower first-void and post-diuretic natriuresis; and 5) patients experiencing death or heart failure rehospitalization at 6 months exhibited significantly lower urinary sodium excretion compared to stable patients. These findings underscore the potential of spot urinary natriuresis as a valuable, practical tool not only for evaluating diuretic efficacy, but also for predicting clinical stability in patients discharged after ADHF.

Episodes of congestion are the main reason for patients with heart failure to seek medical attention with hospitalization rates around 10-20% within a year. (112) Following hospitalization, the risk for rehospitalization rises sharply, counting up to 30% within the first month and 50% within the first 6-months. (13,20,22,113) Therefore, this critical timeframe is often referred to as the vulnerable phase. (114) ESC guidelines recommend an early follow-up visit at 1-2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy. (25) Logistical restraints make the implementation of this guideline challenging. Therefore, there is a pressing need for better metrics to monitor patients and guide interventions during this vulnerable period, and to potentially identify HF patients at higher risk for adverse outcomes.

The measurement of natriuresis has emerged as a promising tool, reflecting the degree of neurohumoral activation. Lower urinary sodium concentrations are associated with a poorer prognosis both during decongestion as well as during follow-up. (115) Despite this, data on the utility of urinary sodium measurements in ambulatory heart failure patients remain limited. It has been demonstrated that

stable ambulatory chronic heart failure patients exhibit higher sodium excretion over long-term compared to those experiencing ADHF events. (17) The FAST-RESPONSE study, was the first to assess longitudinal natriuresis profiles in patients discharged after ADHF and confirmed that patients who developed signs of congestion had significantly lower natriuresis profiles, both pre- as well as post-diuretic intake. Additional studies with larger samples sizes are needed to determine the cut-off value with the best predictive value. Moreover, the FAST-RESPONSE study supports the physiological basis of increased sodium retention in unstable heart failure. (3,9,17,36,83) A lower urinary sodium excretion following ADHF was also predictive for poor long-term outcomes, including death or heart failure rehospitalization. This reinforces the role of natriuresis as a surrogate marker for clinical stability both short as well as long-term. (115) Incorporating this parameter into post-discharge monitoring might facilitate timely therapeutic adjustments and should help to identify high-risk patients in need for closer follow-up. A one-time post-discharge measurement held the same predictive value as longitudinal daily measurements during this vulnerable phase. This might indicate that a more high-risk subgroup should be easily identifiable based on first-void urinary sodium excretion. Future research targeted at therapeutic strategies that enhance urinary sodium excretion with prognostic benefits would further solidify the role of natriuresis as a modifiable therapeutic target.

Overall, in the FAST-RESPONSE study, 28% of the patients decided to not collect urine samples after informed consent, which related to the complexity of the monitoring system, required patient actions, and individual patient characteristics. As urinary sodium collection and storage process was entirely dependent on the patients themselves (with a median age of 76 years old), compliance rates remained high - 92% (first-void) and 89% (post-diuretic), and are comparable to those of other more demanding systems. (116–119) This underscores the practicality of implementing such an approach in a real-world setting. Further integration of digital tools, and the use of a point-of-care sensor allowing more patient empowerment , will surely further optimize the feasibility of this method in routine clinical practice. (106)

Interestingly, as already discussed, Martens et al. demonstrated a significant drop in urinary sodium excretion in patients with chronic stable heart failure during the week preceding an ADHF event. (17) In contrast, the FAST-RESPONSE study did not identify such a decline in sodium excretion prior to an ADHF event. While the sample size may be too small to detect this difference, we analyzed patients immediately after ADHF admission, which already exhibited lower natriuresis compared to stable patients. Moreover, urinary sodium excretion levels in the FAST-RESPONSE study were considerably lower, both in stable and congested patients, compared to those in the study by Martens et al. (median 37 [25–56] mmol/L versus mean 82 [±41] mmol/L). (17) This suggests that patients recovering from an ADHF event exhibit a distinct profile with higher sodium avidity or a lower salt intake, making a drop in urinary sodium excretion less apparent. These finding also indicate that sodium excretion patterns may vary considerably among patients, emphasizing the need for individualized monitoring and context-dependent interpretation. Biegus et al. demonstrated already that prognostication through urinary sodium excretion in the setting of acute heart failure is context-dependent and should be interpreted in relationship to the fluid volume status. (68)

While the results of this study are promising, the results should be interpreted as exploratory and hypothesis-generating. In addition, some limitation should be addressed. Although general guidance on sodium and fluid intake was provided, individual variations in intake were not systematically accounted for, which could influence the observed urinary sodium excretion patterns. Future research should aim to address these limitations by focusing on strategies to optimize the feasibility and scalability of implementing urinary sodium monitoring in clinical practice. Additionally, further exploration of patient-specific factors influencing sodium excretion patterns is needed to refine its predictive value. Finally, larger, multicenter trials are warranted to validate these findings and evaluate the integration of urinary sodium monitoring into comprehensive heart failure care protocols, potentially advancing personalized management approaches for this complex disease.

CONCLUSION

The FAST-RESPONSE study provides evidence for the feasibility and clinical relevance of urinary sodium measurements as a non-invasive tool for evaluating clinical stability in patients post-AHF discharge. First-void and post-diuretic urinary sodium concentration were significantly higher in stable heart failure patients post-ADHF. Therefore, it holds potential to guide early interventions, reducing the burden of rehospitalization and mortality. Further research is needed to validate its predictive utility and integrate it into routine clinical practice.

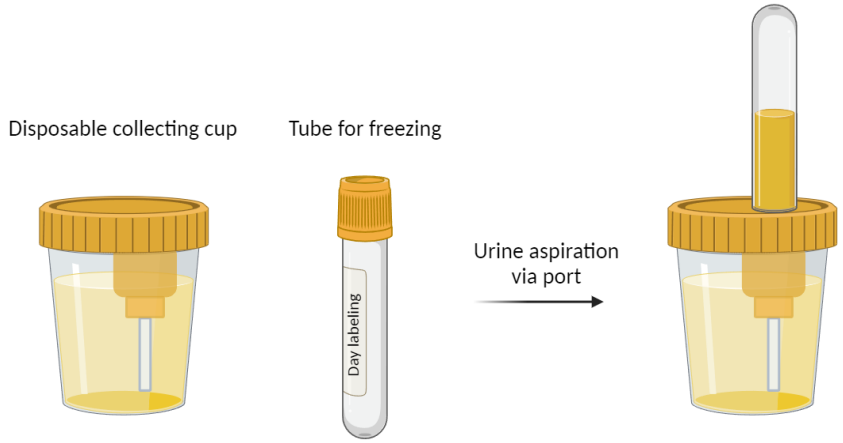
CLINICAL PERSPECTIVES

- Home urinary sodium measurements are feasible in patients with heart failure after an ADHF event.
- Higher levels of first-void urinary sodium concentration predict clinical stability post-discharge.
- A simple one-time first-void urinary sodium post-discharge might aid in guiding which patient are high-risk and deserve closer follow-up.

SUPPLEMENTAL MATERIAL

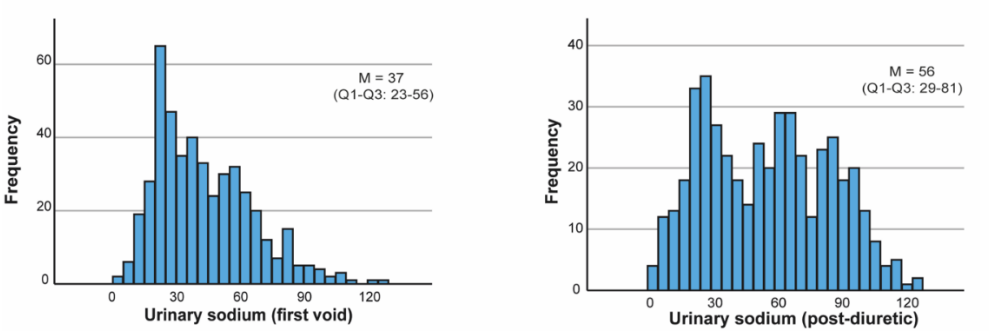
Supplemental figure 1

Spot urine collection through vacuum tube



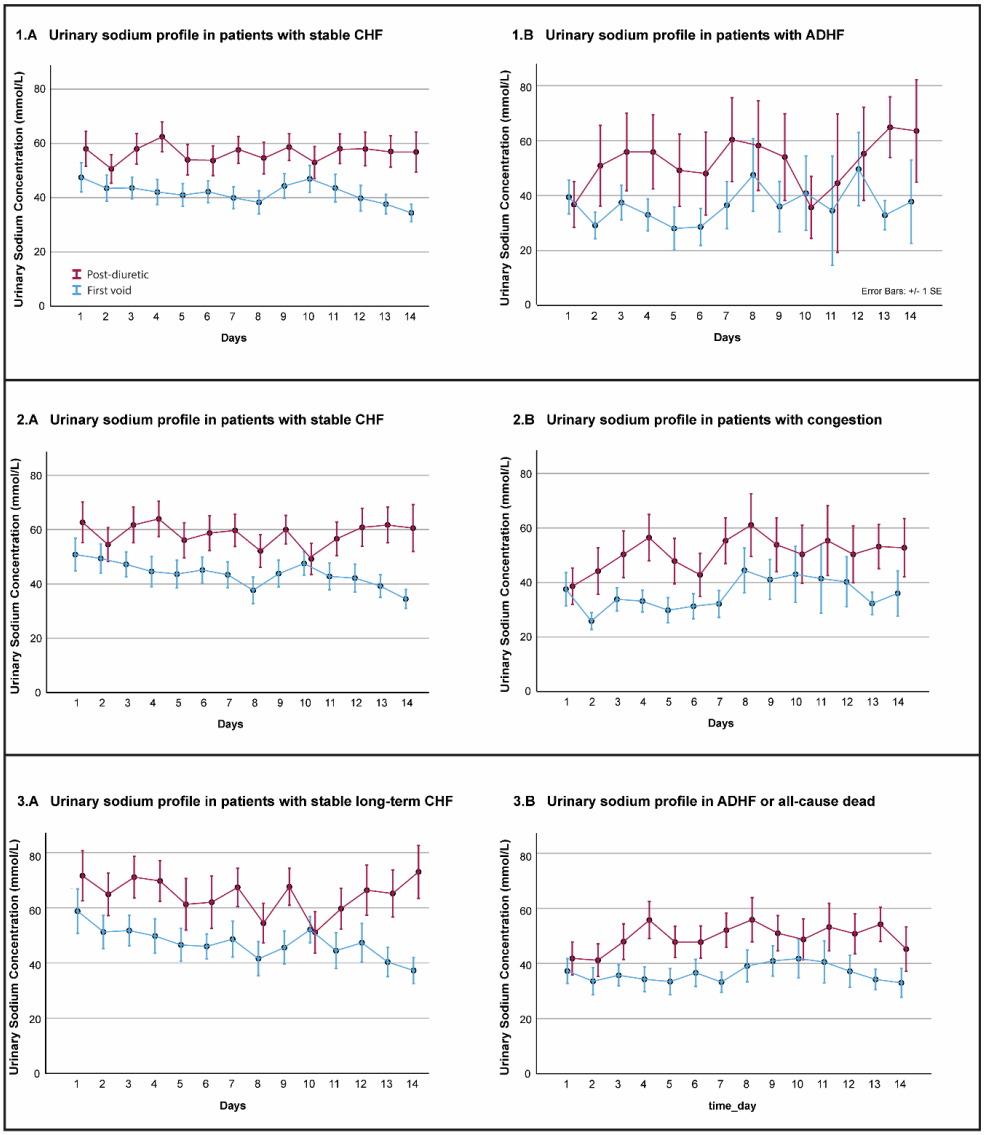
Supplemental figure 2

Histograms of spot urinary sodium concentrations (first void and 2hours after diuretic intake)



Supplemental figure 3

Longitudinal urinary sodium concentration profile of the first void morning spot, spot 2 hours after diuretic intake and the difference between both (1) in patients stable CHF (1. A) or with an ADHF (1.B) during 2-week follow-up; (2) in patients with stable CHF (2.A) or with signs of congestion during 4-week follow-up; and (3) in patients with stable CHF (3.A) or patients with an event of all-cause mortality or heart failure rehospitalization (3.B) within 180 days.



Supplemental table 1

In- and exclusion criteria

INCLUSION CRITERIA
- Older than 18 years - Ability to give written informed consent - Hospitalization with episode of acute decompensated heart failure (NTproBNP >1000 pg/ml) with need for IV diuretics. - Discharged with at least 1mg bumetanide orally (or equivalents*).
EXCLUSION CRITERIA
- Clinical impression of physician that patients or care-giver is unable to correctly gather urine samples or adhere to the protocol. - Patients with an intellectual incapacity to make their own decisions will be excluded from the study. - renal replacement therapy - Absence of a freezer at home (freezer temperature should be -18°C).

** 1mg bumetanide = 40mg furosemide*

Supplemental table 2

Symptom burden at the moment of discharge

	Total (n=50)	Drop-out (n=14)	Analyzed (n=36)	P-value
NYHA Class				0.705
I	11 (22%)	2 (14%)	9 (25%)	
II	26 (52%)	7 (50%)	19 (53%)	
III	11 (22%)	4 (29%)	7 (19%)	
IV	2 (4%)	1 (7%)	1 (3%)	
Edema (Likert grade)				0.278
Grade 1	24 (48%)	8 (57%)	16 (44%)	
Grade 2	17 (34%)	3 (21%)	14 (39%)	
Grade 3	6 (12%)	3 (21%)	3 (8%)	
Grade 4	3 (6%)	0 (0%)	3 (8%)	
Orthopnea	21 (42%)	8 (62%)	13 (36%)	0.190
Bendopnea	17 (34%)	7 (54%)	10 (28%)	0.172
Paroxysmal nocturnal dyspnea	7 (14%)	5 (39%)	2 (6%)	**0.010**
VAS dyspnea	30 (20-50)	35 (22-50)	30 (20-50)	0.483

Supplemental table 3

Guideline-directed medical therapy in HFrEF subgroup

	Total (n=28)	Drop-out (n=9)	Analyzed (n=19)	P-value
Medication				
ACEi/ARB	5 (17.9%)	4 (44.4%)	1 (5.3%)	0.026
ARNI	16 (57.1%)	3 (33.3%)	13 (68.4%)	0.114
Beta-blocker	25 (89.3%)	8 (88.9%)	17 (89.5%)	1.000
MRA	25 (89.3%)	8 (88.9%)	17 (89.5%)	1.000
SGLT2i	12 (42.9%)	1 (11.1%)	11 (57.9%)	**0.039**
Dose LD (mg, furosemide equivalents)	40 (40-80)	40 (30-60)	50 (40-80)	0.175
Devices				
PM	4 (14.3%)	2 (22.2%)	2 (10.5%)	0.574
ICD	14 (50%)	4 (44.4%)	10 (52.6%)	1.000
CRT	4 (14.3%)	2 (22.2%)	2 (10.5%)	0.574
Laboratory				
CKD (<60)	17 (60.7%)	5 (55.6%)	12 (63.2%)	1.000

Supplemental table 4

Baseline demographics between stable CHF and patients experiencing congestion during 4 weeks follow up

	Analyzed (n=36)	Stable CHF (n=23)	Congestion (n=13)	P-value
Age	74.8 ± 9.3	74.2 ± 9.0	75.9 ± 10.1	0.605
Male %	27 (75%)	17 (74%)	10 (77%)	1.000
LVEF (%)	38 (25-55)	30 (25-50)	55 (32-60)	**0.034**
LVEF Class				
HFrEF	19 (53%)	15 (65%)	4 (31%)	0.119
HFmrEF	3 (8%)	1 (4%)	2 (15%)	
HFpEF	14 (39%)	7 (30%)	7 (54%)	
RVSP	35 (26-45)	38 (28-49)	31 (24 -36)	0.096
Ischemic	18 (50%)	12 (52%)	6 (46%)	1.000
Heart rate	68 ± 14	68 ± 14	68 ± 14	0.948
Blood pressure				
Systolic	116 ± 16	117 ± 17	116 ± 15	0.927
Diastolic	65 ± 9	67 ± 10	63 ± 8	0.306
BMI	28.6 (24.5-34.6)	29.0 (23.4-34.0)	28.2 (25.9-37.1)	0.448
Comorbidities				
AF	27 (75%)	18 (78%)	9 (69%)	0.693
Stroke	7 (19%)	2 (9%)	5 (39%)	0.073
COPD	9 (25%)	4 (17%)	5 (39%)	0.235
Dyslipidemia	11 (31%)	8 (35%)	3 (23%)	0.708
Arterial hypertension	24 (67%)	14 (61%)	10 (77%)	0.468
Diabetes Mellitus	18 (50%)	12 (52%)	6 (46%)	1.000
Medication				
ACEi/ARB	9 (25%)	6 (26%)	3 (23%)	1.000
ARNI	14 (39%)	10 (44%)	4 (31%)	0.501
Beta-blocker	30 (83%)	20 (87%)	10 (77%)	0.645
MRA	28 (78%)	20 (87%)	8 (62%)	0.107
SGLT2i	19 (53%)	13 (57%)	6 (46%)	0.730
Dose LD (mg, furosemide equivalents)	40 (40-80)	40 (40-80)	40 (40-80)	0.578
Devices				
PM	4 (11%)	3 (13%)	1 (8%)	1.000
CRT	4 (11%)	3 (13%)	1 (8%)	1.000
ICD	13 (36%)	10 (44%)	3 (23%)	0.292
Laboratory				
Creatinine (mg/dL)	1.56 (1.20-1.82)	1.36 (1.17-1.81)	1.59 (1.50-2.12)	0.253
NTproBNP (ng/L)	2142 (1039-5459)	3037 (1551-5611)	1188 (995-3693)	0.114
Plasma Aldosterone (ng/g)	90 (50-145)	111 (45-143)	70 (51-151)	0.977
PRA (ng/mL/h)	134 (34-409)	137 (28-462)	131 (45-374)	0.885

CHAPTER 5

Long-Term Urinary Sodium Analysis via a Point-Of-Care Urinary Sodium Sensor in Ambulatory Heart Failure

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Submitted, under revision

ABSTRACT

Background: Recent findings indicate that urinary sodium concentration may serve as a non-invasive indicator of diuretic response and decompensation risk in patients admitted with heart failure (HF). However, feasibility and value of long-term urinary sodium monitoring in ambulatory HF using a point-of-care sensor remains uncertain.

Methods: In this prospective, single-center study, patients with stable HF performed home-based urinary sodium measurements twice weekly, once first-void and again two hours after loop diuretic intake, using a point-of-care sensor over a 48-week period. Follow-up visits were scheduled every 12 weeks. Feasibility was assessed based on the number of measurements successfully obtained during the first 3 months. The clinical endpoint was a composite of acute decompensated HF hospitalizations, urgent visits requiring loop diuretic uptitration, all-cause mortality, increased right ventricular systolic pressure of more than 10 mmHg by echocardiography or a rise of more than 25% in NTproBNP levels during follow-up visits.

Results: 76 patients participated in the study, with compliance rates of 84% and 80% during the first 3 months for once- and twice weekly measurements, respectively. At the three-month follow-up visit, 50 patients (66%) chose to continue with the measurements. Patients had a median age of 75(69–79) years, 79% being male, median LVEF was 45 (35–55) %, NT-proBNP levels were 1033 (347-2670) ng/L, and eGFR of 46 (31-65) ml/min/1.73m². First-void urinary sodium concentrations remained stable over time ($p=0.998$), but were significantly lower in patients on loop diuretics (56±23 mmol/L vs. 76±26 mmol/L, $p=0.002$). The clinical endpoint was met by 23 (30%) patients and these patients had consistently lower first-void and post-diuretic sodium concentrations throughout follow-up (respectively, $p<0.001$ and $p=0.006$).

Conclusion: Home urinary sodium monitoring using via a point-of-care sensor is feasible over time, and concentrations remain stable during long-term monitoring. A lower urinary sodium concentration is linked to poorer clinical outcomes, reinforcing its potential role as a prognostic marker in chronic HF.

GRAPHICAL ABSTRACT

Long-term urinary sodium analysis via a point-of-care urinary sodium sensor in ambulatory heart failure

Design

Stable chronic heart failure patients
Inclusion: February, 2023 – November, 2024



Home urinary sodium measurements twice weekly – 48 weeks

Baseline characteristics

N = 76
78.9% male
Age: 75 (69-79) years old
LVEF: 45 (35-55) %

eGFR 46 (31-65) ml/min
NT-proBNP 1033 (347-2670) ng/L

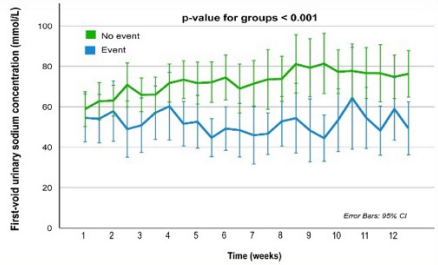
Adherence rate – 3months:
84% - once weekly
79% - twice weekly

Results

First-void Una: 63 (±27) mmol/L
With LD: 56 (±23) mmol/L
Without LD: 76 (±26) mmol/L

Stable pattern over time

ADHF/mortality – lower UNa



Conclusion

A lower urinary sodium concentration is linked to poorer clinical outcomes, reinforcing its potential role as a prognostic marker in chronic HF.

INTRODUCTION

Heart failure (HF) remains a leading cause of hospitalization and healthcare costs, with acute heart failure (AHF) episodes driven primarily by congestion. Despite advancements in guideline-directed medical therapy (GDMT) (8), congestion remains difficult to manage partly due to the lack of reliable markers to guide diuretic titration. Current congestion monitoring strategies, such as weight tracking and symptom recognition, are often cumbersome or unreliable. Pulmonary artery pressure sensors offer guidance and have proven to be effective, however their invasiveness and cost limit widespread use.

Recent evidence suggests that urinary sodium profiling may serve as a marker of non-invasive congestion. Martens et al. measured the first-void urinary sodium concentration in 80 chronic HF patients once weekly during a 30-week follow-up period (through frozen urine samples). They demonstrated that urinary sodium excretion remains stable, but declines prior to an acute decompensated heart failure (ADHF) hospitalization, even before symptom worsening or weight gain. (17) This highlights the potential of real-time sodium monitoring as an early indicator of decompensation. If proven effective, spot urinary sodium measurements via a point-of-care (POC) sensor might facilitate such an approach as a low-cost alternative to enable patient self-empowerment in diuretic management or prompt early medical contact.

The present study explores the feasibility and utility of home-based urinary sodium measurements via a POC in chronic stable HF patients during a one-year follow-up period. In addition, the value of adding a second post-diuretic measurement was evaluated in patients with loop diuretic maintenance therapy.

METHODS

Study design

This was a single-center, prospective, interventional study, conducted at Ziekenhuis Oost-Limburg, Genk, Belgium. The trial protocol was approved by the local ethical committee and executed in compliance with the Declaration of Helsinki. All patients provided written informed consent prior to inclusion.

Study population

Patients were considered eligible when they were older than 18 years old, had stable chronic HF (i.e., no AHF hospitalization or need for intensification of loop diuretic therapy for the last three months) and received a stable dose of GDMT for the last three months. Patients who were deemed unable to follow the study protocol (collect urine samples, handling POC sensor) or patients who were scheduled for renal replacement therapy, were not included into the study.

Baseline and follow-up visit

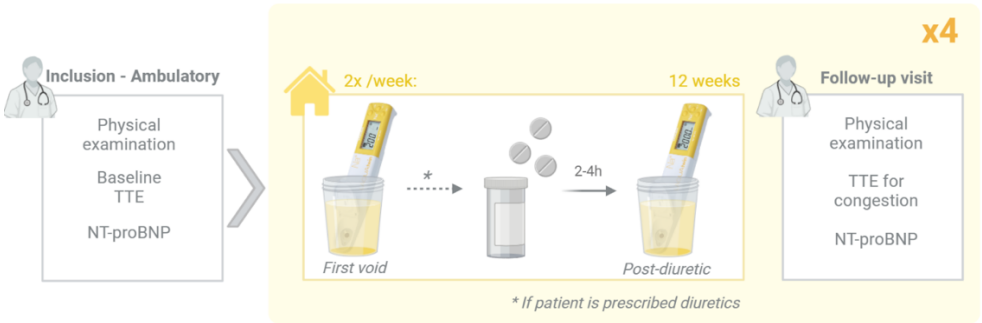
After providing written informed consent, patients were asked to perform (first-void) urinary sodium measurements via a POC sodium sensor (HORIBA) twice weekly for a total period of 48 weeks (Figure 1). Patients who were taking loop diuretic medication were instructed to measure the urinary sodium in the morning twice, once before intake of diuretic (first-void) 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 if any important changes in diet occurred.

At the baseline visit, a comprehensive evaluation was conducted, involving a medical examination, transthoracic echocardiography (TTE), and blood analysis including NT-proBNP measurement. Patients were instructed how to perform the urinary measurements with the POC sensor of HORIBA and instructed about a healthy balanced diet according to European Society of Cardiology (ESC) guidelines avoiding excess sodium intake. One week after inclusion, patients were contacted by phone to evaluate adherence to the protocol.

Follow-up visits were scheduled every 12-weeks, with the main aim of evaluating for signs and symptoms of congestion through clinical examination, echocardiography and blood analysis.

Figure 1

Study procedure and clinical follow-up



Urinary sodium dipstick

The LAQUAtwin Na-11 meter was developed by the HORIBA group and is capable of quantitively measuring sodium concentration in a spot urinary sample, which has been validated previously. (106) The 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 via two standardized sodium concentrations (150ppm and 2000ppm).

Endpoints

The main study clinical endpoint was described as a composite endpoint of HF hospitalizations and urgent HF visits, including up-titration of chronic loop diuretic therapy, all-cause mortality, increase in estimated right ventricular systolic pressure > 10 mmHg on echocardiography at follow-up or relative increase of > 25% in NTproBNP levels with an absolute threshold above 500ng/L. Data for all-cause mortality were censored on March 20, 2025. In addition, the feasibility of home measurements was assessed by the percentage of expected measurements performed once or twice weekly.

Statistical analysis

Normality of continuous data was assessed using a Shapiro-Wilk test. Variables are summarized as means with standard deviations, medians with 25-75th percentile, or numbers with percentages and evaluated using ANOVA, Kruskal-Wallis and chi-square tests as appropriate. 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 or in case of dependent data with the McNemar test. High versus low urinary sodium excreters were defined based on a first void urinary sodium concentration above or below the median. Longitudinal urinary sodium concentrations over time were analyzed using linear mixed modeling for repeated measures including a fixed group (event/no event, stable/high versus low excreter or loop diuretic maintenance versus no loop diuretic maintenance), time effect and its interaction and a random intercept. A first-order autoregressive structure was applied to model the time effect, as measurements of sodium taken closer in time were assumed to exhibit higher correlations. No adjustments for multiplicity were performed, so all reported p-values are exploratory. All the hypotheses testing was 2-sided with a significance level of $\alpha = 0.05$. All statistical analyses were done using SPSS version 29 (IBM® SPSS ® Inc., Chicago, IL, United States).

RESULTS

Baseline demographics

In total, 100 HF patients were prospectively included between February 28th, 2023 and November 13th, 2024. However, 24 patients who underwent baseline evaluation and signed informed consent decided not to participate afterwards because of perceived logistic constraints. Most of the patients were male (78.9%) with a median age of 75 (69-79) years old (table 1). The median estimated glomerular filtration rate (eGFR) was 46 (31-65) ml/min and the median n-terminal pro–B-type natriuretic peptide (NT-proBNP) of 1033 (347-2670) ng/L. The median left ventricular ejection fraction (LVEF) was 45 (35-55) % with 50% having ischemic heart disease, and 33% classified as having HF with reduced ejection fraction (HFrEF). Nevertheless, a high proportion of patients were receiving guideline-directed medical therapy (GDMT), including 88% mineralocorticoid receptor antagonists (MRA), 95% beta-blockers, 91% sodium-glucose cotransporter-2 inhibitors (SGLT2i), and 74% angiotensin receptor-neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARB). Loop diuretics were prescribed in 55 out of the 76 patients (72%) as a maintenance therapy with a dose of 40 (20-40) mg (furosemide equivalents).

Longitudinal urinary sodium measurements

Of the 76 participating patients, 26 (34%) patients decided to stop measuring after the first 3-month visit with time-consuming, difficulty with frustration and physical limitations being the most frequent reasons for discontinuation, while 50 (66%) decided to continue measuring after the first control visit at 3 months follow-up. Baseline characteristics between both groups were comparable (Supplemental table 1). During the first 3 months follow-up, 1447 of the 1824 (76 patients x 12 weeks x 2/w) first-void samples were collected, equaling an adherence rate of 79% during the first 3 months for twice weekly first-void measurements. This was slightly higher for once weekly measurements during the first 3 months (766 of 912, 84%).

Table 1

Baseline characteristics

	All patients (n=76)
Demographics	
Age (years)	75 (69-79)
Males	60 (78.9%)
Heart failure category	
HFrEF	25 (32.9%)
HFmrEF	21 (37.6%)
HFpEF	40 (39.5%)
Ischemic	38 (50.0%)
Physical features	
Heart rate (beats/min)	69 ± 12
Systolic blood pressure (mmHg)	118 ± 16
Diastolic blood pressure (mmHg)	71 ± 12
Weight (kg)	82.8 ± 16.6
BMI (kg/m^2)	27.9 ± 4.3
NYHA functional class	
I	23 (30.3%)
II	29 (38.2%)
III	23 (30.3%)
IV	1 (1.3%)
Comorbidities	
Atrial fibrillation	55 (72.4%)
COPD	11 (14.5%)
Hypertension	51 (67.1%)
Dyslipidemia	50 (65.8%)
Diabetes	21 (27.6%)
Laboratory analysis	
Hemoglobin (g/dL)	13.8 ± 2.0
Sodium (mmol/L)	139 (138-141)
Potassium (mmol/L)	4.47 (4.19-4.84)
Chloride (mmol/L)	103 (101-105)
Bicarbonate (mmol/L)	26.4 (24.2-28.5)
Osmolality (mOsmol/kg H_20)	303 (296-308
Creatinine (mg/dL)	1.45 (1.10-1.95)
Estimated GFR (ml/min)	46 (31-65)
Troponin	22 (14-31)
NT-proBNP (ng/L)	1033 (347-2670)
Plasma renin activation (μU/ml)	201 (81-550)
Plasma aldosterone (ng/L)	169 (79-326)

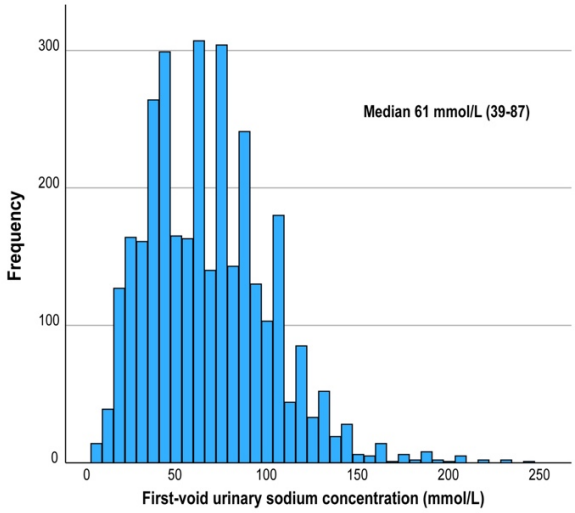
Echocardiography	
LVEF (%)	45 (35-55)
LVEDD (mm)	51 (47-56)
E/e'	10 (9-18)
RVSP (mmHg)	28 (25-33)
TAPSE (mm)	18 (14-21)
Medication	
ARNI/ACEi/ARB	56 (73.7%)
SGLT2i	69 (90.8%)
Beta-blockers	72 (94.7%)
MRA	67 (88.2%)
Loop diuretics	55 (72.4%)
Loop diuretic dose in furosemide equivalents (mg)	40 (20-40)
Devices	
PM	24 (31.6%)
ICD	31 (40.8%)
CRT	22 (28.9%)

Urinary sodium concentration

The median first-void urinary sodium concentration was 63 (±27) mmol/L during the first 3 months and 62 (±25) mmol/L during the whole follow-up. A histogram of the distribution of all first-void urinary sodium concentrations is depicted in Figure 2. Figure 3 depicts the longitudinal first-void urinary sodium profile over time with corresponding 95% confidence interval for the complete follow-up period of 48 weeks. Overall, the urinary sodium concentration remained stable over time (time-effect, p=0.998), although with large individual differences over time (Supplemental figure 1).

Figure 2

Histogram first-void urinary sodium concentration



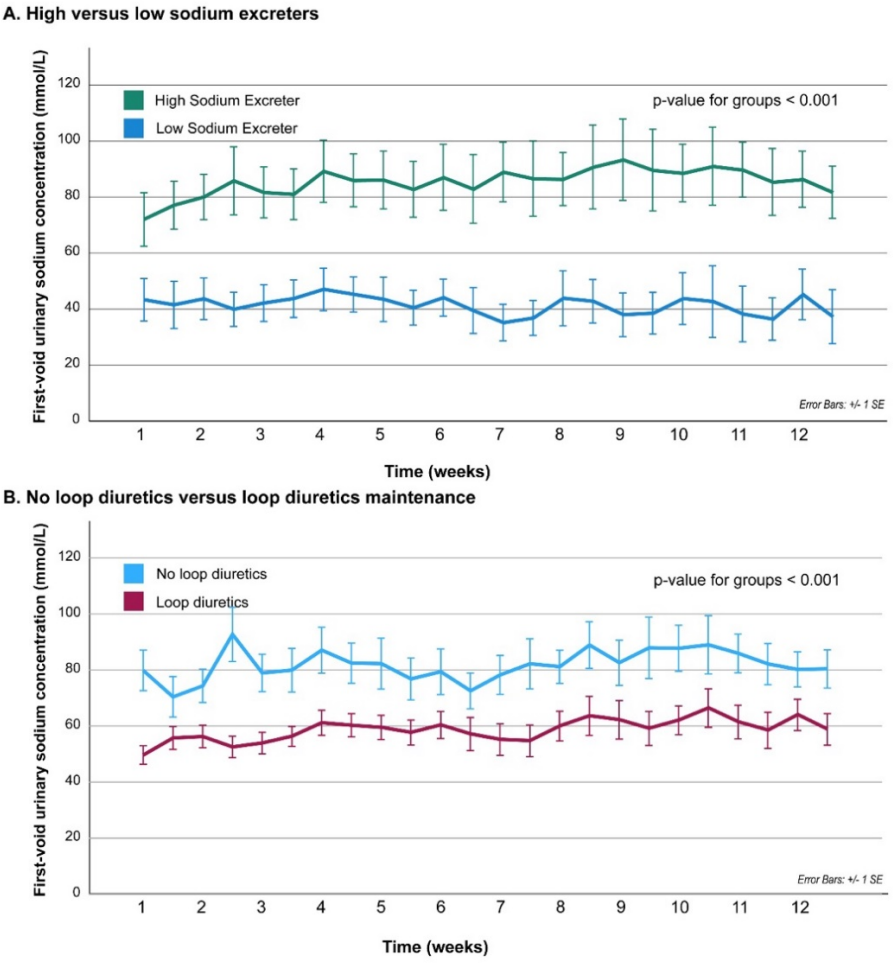
Of the 76 patients, 55 were treated with loop diuretic maintenance therapy and collected a second urinary sample 2-h post-diuretic intake. In those, mean first-void urinary sodium was 56 (±23) mmol/L, which increased to 80 (±34) mmol/L post-diuretic intake (p-value<0.001). In this subgroup, first-void and post-diuretic sodium concentration remained as well relatively stable over time (time-effect respectively, p=0.752 and p=1.000). The first-void urinary sodium concentration was considerably lower in patients on loop diuretics maintenance therapy, compared to patients without (56 (±23) mmol/L versus 76 (± 26) mmol/L, p-value<0.001, Figure 3B).

Supplemental table 2 demonstrated the differences in baseline characteristics between high and low urinary sodium excreters. Evolution over time was relatively stable in both groups and did not differ between both groups (p for interaction time*group = 0.876) (Figure 3A). Low sodium excreters were more often female, had a higher ejection fraction with higher levels of natriuretic peptides, troponins and plasma aldosterone. They were more likely to be treated with loop diuretics as a maintenance therapy and in higher doses compared to high sodium excreters (Supplemental table 2). After multivariate analysis, only being male was

independently associated with being a high sodium excreter (odds ratio 7.95, 95% CI 1.19-53.24; p-value = 0.033, Supplemental table 3). In patients treated with loop diuretic maintenance therapy, first-void and post-diuretic urinary sodium concentration remained stable over time in both low and high sodium excreters (respectively, p=0.820 and p=0.966 versus p=0.135 and p=0.645, Supplemental figure 2).

Figure 3

Urinary sodium evolution during first 12 weeks. A. Median first-void in low versus high excreters and B. Median first-void in patients with and without loop diuretic maintenance



Urinary sodium concentration in relation to outcome

In total, 23 patients experienced a clinical endpoint during the follow-up period. Of these, 10 patients experienced an urgent HF visit with up-titration of loop diuretics maintenance therapy during the measurement period. None required hospitalization. At the follow-up visits, 5 patients experienced a rise in their RVSP and 7 patients an increase in NT-proBNP levels during follow-up. Until the censoring date (mean follow-up period of 334 (172-396) days), 2 patients died, 6 were hospitalized due to HF. Patients with an event had lower blood pressure, higher levels of natriuretic peptide and a higher baseline E/e' ratio. They were more frequently treated with loop diuretics as a maintenance therapy, and at higher dosages. (Table 2).

Table 2

Baseline demographics between patients with or without an event

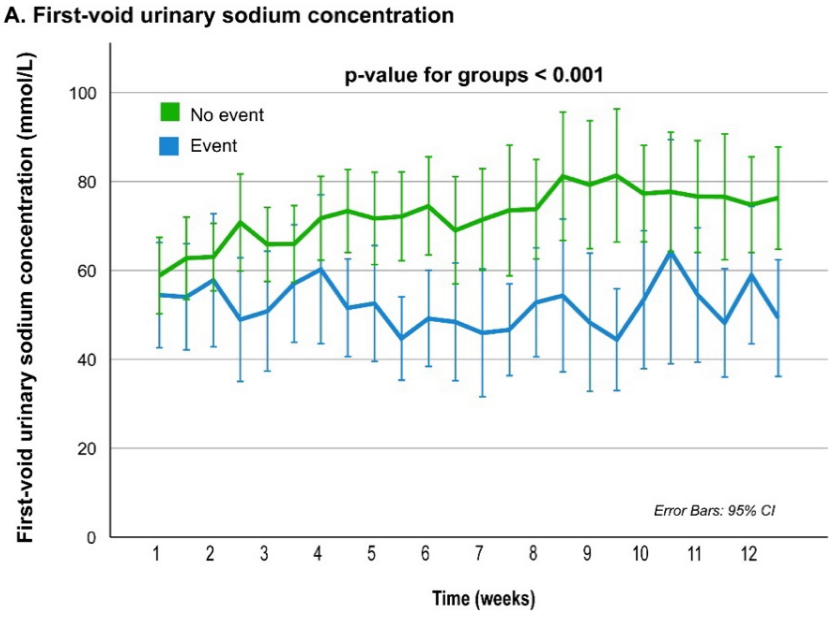
	Analyzed (n=76)	No event (n=53)	Combined event (n=23)	P-value
Demographics				
Age (years)	75 (69-79)	74 (68-79)	76 (72-78)	0.556
Males	60 (78.9%)	42 (79.2%)	18 (78.3%)	1.000
Heart failure category				
HFrEF	25 (32.9%)	16 (30.2)	9 (39.1%)	0.669
HFmrEF	21 (37.6%)	16 (30.2%)	5 (21.7%)	
HFpEF	40 (39.5%)	21 (39.6%)	9 (39.1%)	
Ischemic	38 (50.0%)	25 (48.2%)	13 (56.5%)	0.618
Physical features				
Heart rate (beats/min)	69 ± 12	67 ± 11	73 ± 15	0.093
Systolic blood pressure (mmHg)	118 ± 16	122 ± 16	110 ± 12	**0.007**
Diastolic blood pressure (mmHg)	71 ± 12	74 ± 12	64 ± 10	**0.003**
Weight (kg)	82.8 ± 16.6	83.4 ± 17.4	81.6 ± 15.0	0.681
BMI (kg/m^2)	27.9 ± 4.3	27.9 ± 4.6	27.7 ± 3.8	0.835
NYHA functional class				
I	23 (30.3%)	18 (34.0%)	5 (21.7%)	0.344
II	29 (38.2%)	20 (37.7%)	9 (39.1%)	
III	23 (30.3%)	15 (28.3%)	8 (34.8%)	
IV	1 (1.3%)	0 (0.0%)	1 (4.3%)	

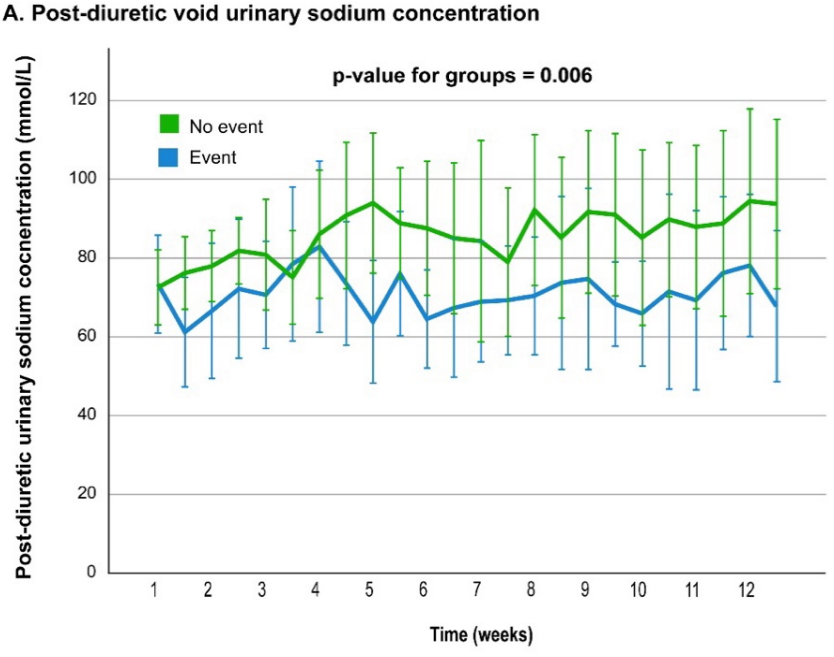
Comorbidities				
Atrial fibrillation	55 (72.4%)	38 (71.7%)	17 (73.9%)	1.000
COPD	11 (14.5%)	7 (13.2%)	4 (17.4%)	0.726
Hypertension	51 (67.1%)	34 (64.2%)	17 (73.9%)	0.441
Dyslipidemia	50 (65.8%)	36 (67.9%)	14 (60.9%)	0.604
Diabetes	21 (27.6%)	11 (20.8%)	10 (43.5%)	0.054
Laboratory analysis				
Hemoglobin (g/dL)	13.8 ± 2.0	14.0 ± 1.9	13.2 ± 2.6	0.109
Sodium (mmol/L)	139 (138-141)	139 (138-141)	139 (138-141)	0.794
Potassium (mmol/L)	4.47 (4.19-4.84)	4.49 (4.21-4.85)	4.39 (4.00-4.79)	0.274
Chloride (mmol/L)	103 (101-105)	103 (102-105)	103 (100-104)	0.089
Bicarbonate (mmol/L)	26.4 (24.2-28.5)	26.0 (24.0-28.2)	27.3 (25.2-30.8)	0.071
Osmolality (mOsmol/kg H_20)	303 (296-308)	303 (296-308)	301 (296-310)	1.000
Creatinine (mg/dL)	1.45 (1.10-1.95)	1.43 (1.09-1.86)	1.47 (1.27-2.38)	0.296
Estimated GFR (ml/min)	46 (31-65)	46 (37-67)	46 (25-57)	0.323
Troponin	22 (14-31)	21 (14-30)	28 (19-43)	0.095
NT-proBNP (ng/L)	1033 (347-2670)	692 (256-2367)	1584 (786-3618)	**0.018**
PRA (μU/ml)	201 (81-550)	175 (79-550)	292 (73-500)	0.975
Aldosterone (ng/L)	169 (79-326)	171 (82-294)	165 (76-382)	0.846
Echocardiography				
LVEF (%)	45 (35-55)	45 (35-55)	45 (30-50)	0.371
LVEDD (mm)	51 (47-56)	51 (47-56)	53 (48-61)	0.197
E/e'	10 (9-18)	9 (8-14)	18 (10-20)	**0.006**
RVSP (mmHg)	28 (25-33)	26 (25-30)	30 (25-40)	0.083
TAPSE (mm)	18 (14-21)	18 (14-21)	17 (13-25)	0.937
Medication				
ARNI/ACEi/ARB	56 (73.7%)	38 (71.7%)	18 (78.3%)	0.777
SGLT2i	69 (90.8%)	48 (90.6%)	21 (91.3%)	1.000
Beta-blockers	72 (94.7%)	49 (92.5%)	23 (100.0%)	0.308
MRA	67 (88.2%)	47 (88.7%)	20 (87.0%)	1.000
Loop diuretics	55 (72.4%)	35 (66.0%)	20 (87.0%)	0.093
Loop diuretic dose in furosemide equivalents (mg)	40 (20-40)	40 (20-40)	40 (20-80)	**0.010**
Devices				
PM	24 (31.6%)	16 (30.2%)	8 (34.8%)	0.790
ICD	31 (40.8%)	23 (43.4%)	8 (34.8%)	0.613
CRT	22 (28.9%)	14 (26.4%)	8 (34.8%)	0.583

Patients with an event had a lower first-void and post-diuretic urinary sodium concentration compared to those without an event and patients without an event were more often labeled as high sodium excreters (60.4% versus 26.1%; p-value=0.012). Figure 4A and B depicts the longitudinal urinary sodium profile (first-void and post-diuretic void) of patients with or without an event. Although the evolution of the first-void urinary sodium excretion over time did not differ between patients with and without an event (p for interaction = 0.199), the first-void urinary sodium excretion over time was significantly lower in those patients with an event (49 ± 20 mmol versus 67 ± 25 mmol/L p<0.001) compared to stable patients (Figure 4A). With regard to the post-diuretic urinary sodium concentration, post-diuretic urinary sodium concentration was significantly lower over time compared to stable patients (69 ± 22 mmol/L versus 85 ± 34 mmol/L, p=0.006, Figure 4B). Evolution over time did not differ between patients with an event and those without (p=0.609).

Figure 4

Median first-void (A) and post-diuretic void (B) urinary sodium evolution in patients with or without an event





DISCUSSION

This was the first study to evaluate the role of longitudinal home-based urinary sodium concentration monitoring using a point-of-care sensor in patients with chronic, stable HF. The study demonstrates that 1) home-measurements are feasible, though compliance tends to drop after 3 months; 2) both first-void and post-diuretic urinary sodium concentration remained relatively stable over time; 3) patients on maintenance loop diuretic therapy maintained diuretic responsiveness, but exhibited a lower first-void urinary sodium excretion compared to those not on loop diuretics; 4) lower first-void and post-diuretic urinary sodium excretion was associated with a higher risk for all-cause mortality or ADHF events compared to higher sodium excretion.

The role of urinary sodium concentration to guide intravenous loop diuretic therapy during an ADHF event is nowadays well-established. (8,23,106,120) Until now, only one other comparable study assessing the role of longitudinal urinary sodium monitoring has been performed via cumbersome weekly urine sample collections. (17) In a comparable sample size and study cohort, a dip in urinary sodium excretion preceded an ADHF event. In the current study, home-measurements via a POC sensor are feasible by patients themselves, even in a patient cohort with a median age of 75 years old. The adherence rate during the first 3 months was 84% for measurements performed at least once weekly, which is comparable to other demanding monitoring systems. (116–118) Therefore, home-measurements of the urinary sodium concentration are feasible for a short period of time, however as time progresses, compliance rates clearly decline. Importantly, although the current study confirmed that first-void and post-diuretic void urinary sodium concentrations were significantly lower in patients with an event compared to stable HF patients, urinary sodium concentrations remained stable in both groups over time. Therefore, a single-spot urinary sodium concentration may be sufficient for prognostic purposes, potentially eliminating the need for daily monitoring. Also, medical therapy was kept constant in this observational study, but it would be of utmost interest to see whether urinary sodium concentration would have been influenced by changes in guideline-directed medical or diuretic therapy, and whether consequent changes in urinary sodium excretion would be associated with better long-term outcome.

In addition to guiding diuretic therapy in ADHF patients, urinary sodium concentrations also have prognostic implications. Higher levels (during an ADHF and in chronic HF) are associated with lower risk for HF rehospitalization and cardiovascular mortality. (17,45,55,75,83) The same observations were made in this study as patients at risk for HF hospitalization and all-cause mortality exhibited a significantly lower urinary sodium excretion. Lower first-void urinary sodium levels may reflect reduced dietary sodium intake; or decreased sodium excretion. (9,17,121) Notably, patients with lower urinary sodium concentrations were more frequently prescribed loop diuretics as part of their maintenance therapy which are known to induce post-diuretic sodium retention (74), that may also account for the observed reduction in first-void urinary sodium concentrations. Additionally, in individuals with more advanced HF, the normal circadian pattern of sodium handling is often disrupted. (122) This can lead to inappropriate sodium reabsorption during periods when increased natriuresis would typically occur—such as in the early morning, following recumbency-induced volume redistribution. This was also reflected in this study by the increased neurohumoral activation (higher levels of plasma aldosterone and renin activation) in the low sodium group.

Next to being a prognostic tool, Martens et al. demonstrated that urinary sodium monitoring might also be used as a non-invasive tool as a dip in urinary sodium excretion was observed the prior to the decompensation event. (17) The current study was not able to confirm these findings due to the lack of acute decompensated events during the measuring period in this study cohort. The study by Martens et al. was performed in a period before sacubitril-valsartan and sodium-glucose cotransporter inhibitors became standard GDMT, which might have led to a reduction in HF events in the current, more stable cohort. In addition, mean urinary sodium concentration was significantly lower in the current cohort and the difference was most probably the result of the higher proportion of patients on loop diuretics which have a lower first-void urinary sodium excretion compared to those without.

There are some limitations in this study that should be addressed. First of all, this is a rather observational small study and results should be interpreted as hypothesis generating. Second, there was a relatively high drop-out (24%). Third,

the study was performed at home, so differences in salt and water intake were not taken into account. Fourth, most of the patients were treated with loop diuretics maintenance therapy, therefore the current study might not be representative for patients without loop diuretics. However, patients on loop diuretic maintenance have in general a more advanced disease stage, making risk prognostication in this subset of patients even more important.

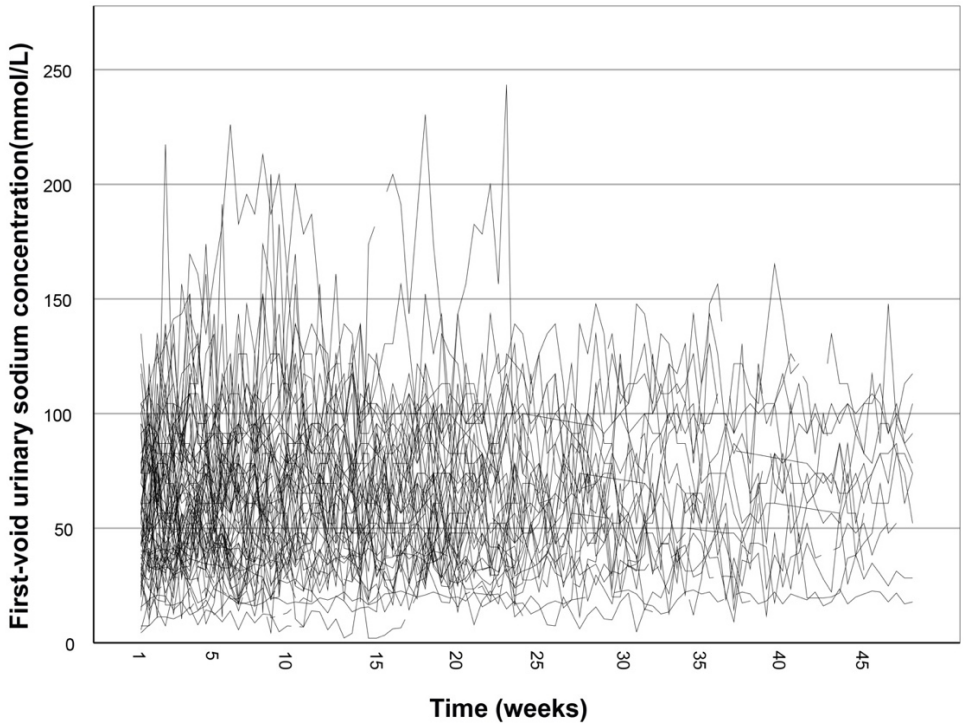
CONCLUSION

The current study demonstrated that home urinary sodium concentration measurements via a point-of-care sensor are feasible in patients with chronic HF. Urinary sodium remained relatively stable over time and patients with a lower first-void urinary sodium excretion were at higher risk for an adverse event.

SUPPLEMENTAL MATERIAL

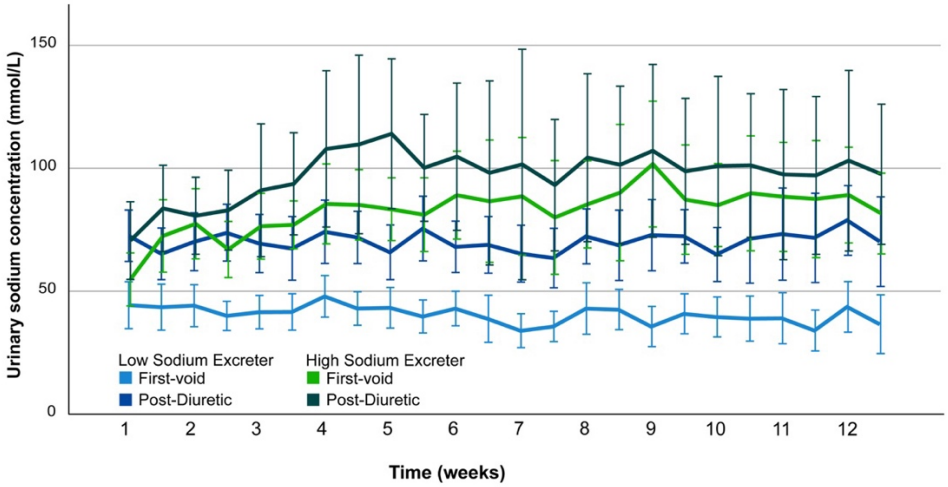
Supplemental figure 1

Individual urinary sodium profiles over time



Supplemental figure 2

Evolution of first-void and post-diuretic void urinary sodium concentration in patients on loop diuretics



Supplemental table 1

Baseline characteristics between patients with long-term and 3-month follow-up

	All patients (n=76)	Long-term follow-up (n=50)	First 3m follow-up (n=26)	P-value
Demographics				
Age (years)	75 (69-79)	74 (68-77)	77 (71-81)	0.211
Males	60 (78.9%)	43 (86.0%)	17 (65.4%)	0.072
Heart failure category				
HFrEF	25 (32.9%)	21 (42.0%)	4 (15.4%)	**0.033**
HFmrEF	21 (37.6%)	10 (20.0%)	11 (42.3%)	
HFpEF	40 (39.5%)	19 (38.0%)	11 (42.3%)	
Ischemic	38 (50.0%)	24 (48.0%)	14 (53.8%)	0.809
Physical features				
Heart rate (beats/min)	69 ± 12	68 ± 12	72 ± 13	0.454
Systolic blood pressure (mmHg)	118 ± 16	117 ± 17	121 ± 12	0.465
Diastolic blood pressure (mmHg)	71 ± 12	70 ± 12	73 ± 14	0.421
Weight (kg)	82.8 ± 16.6	84 ± 16	80 ± 17	0.350
BMI (kg/m^2)	27.9 ± 4.3	27.9 ± 4.6	27.8 ± 3.7	0.976
NYHA functional class				
I	23 (30.3%)	13 (26.0%)	10 (38.5%)	0.319
II	29 (38.2%)	21 (42.0%)	8 (30.8%)	
III	23 (30.3%)	16 (32.0%)	7 (26.9%)	
IV	1 (1.3%)	0 (0.0%)	1 (3.8%)	
Comorbidities				
Atrial fibrillation	55 (72.4%)	36 (72.0%)	19 (73.1%)	1.000
COPD	11 (14.5%)	6 (12.0%)	5 (19.2%)	0.496
Hypertension	51 (67.1%)	33 (66.0%)	18 (69.2%)	1.000
Dyslipidemia	50 (65.8%)	28 (56.0%)	22 (84.6%)	**0.021**
Diabetes	21 (27.6%)	14 (28.0%)	7 (26.9%)	1.000
Laboratory analysis				
Hemoglobin (g/dL)	13.8 ± 2.0	13.9 ± 1.9	13.7 ± 2.1	0.747
Sodium (mmol/L)	139 (138-141)	139 (138-141)	140 (137-141)	0.771
Potassium (mmol/L)	4.47 (4.19-4.84)	4.44 (4.16-4.87)	4.48 (4.32-4.81)	0.810
Chloride (mmol/L)	103 (101-105)	103 (102-105)	102 (101-104)	0.062
Bicarbonate (mmol/L)	26.4 (24.2-28.5)	26.2 (24.0-28.6)	27.4 (24.6-28.5)	0.359
Osmolality (mOsmol/kg H_20)	303 (296-308	301 (295-307)	305 (299-310)	0.121
Creatinine (mg/dL)	1.45 (1.10-1.95)	1.45 (1.09-1.90)	1.55 (1.12-2.03)	0.668
Estimated GFR (ml/min)	46 (31-65)	48 (37-66)	42 (30-62)	0.309

Troponin	22 (14-31)	23 (14-31)	21 (14-30)	0.743
NT-proBNP (ng/L)	1033 (347-2670)	1099 (361-2719)	897 (252-2278)	0.642
Plasma renin activation (μU/ml)	201 (81-550)	175 (76-550)	293 (109-550)	0.231
Plasma aldosterone (ng/L)	169 (79-326)	151 (55-329)	183 (126-264)	0.332
Echocardiography				
LVEF (%)	45 (35-55)	43 (30-55)	45 (40-54)	0.101
LVEDD (mm)	51 (47-56)	53 (48-59)	50 (45-52)	**0.016**
E/e'	10 (9-18)	11 (9-18)	9 (6-25)	0.396
RVSP (mmHg)	28 (25-33)	27 (25-33)	28 (25-36)	0.422
TAPSE (mm)	18 (14-21)	18 (15-24)	16 (13-19)	0.226
Medication				
ARNI/ACEi/ARB	56 (73.7%)	38 (76.0%)	18 (69.2%)	0.588
SGLT2i	69 (90.8%)	45 (90.0%)	24 (92.3%)	1.000
Beta-blockers	72 (94.7%)	48 (96.0%)	24 (92.3%)	0.603
MRA	67 (88.2%)	43 (86.0%)	24 (92.3%)	0.710
Loop diuretics	55 (72.4%)	35 (70.0%)	20 (76.9%)	0.597
Loop diuretic dose in furosemide equivalents (mg)	40 (20-40)	40 (20-60)	30 (20-40)	0.189
Devices				
PM	24 (31.6%)	12 (24.0%)	12 (46.2%)	0.069
ICD	31 (40.8%)	24 (48.0%)	7 (26.9%)	0.090
CRT	22 (28.9%)	16 (32.0%)	6 (23.1%)	0.595

Supplemental table 2

Baseline demographics according to sodium excretion

	Analysed (n=76)	Low sodium (n=38)	High sodium (n=38)	P-value
Demographics				
Age (years)	75 (69-79)	76 (72-79)	74 (67-78)	0.204
Males	60 (78.9%)	24 (63.2%)	36 (94.7%)	**0.001**
Heart failure category				
HFrEF	25 (32.9%)	7 (18.4%)	18 (47.4%)	**0.008**
HFmrEF	21 (37.6%)	10 (26.3%)	11 (28.9%)	
HFpEF	40 (39.5%)	21 (55.3%)	9 (23.7%)	
Ischemic	38 (50.0%)	19 (50.0%)	19 (50.0%)	1.000
Physical features				
Heart rate (beats/min)	69 ± 12	72 ± 15	67 ± 10	0.138
Systolic blood pressure (mmHg)	118 ± 16	117 ± 15	119 ± 17	0.565
Diastolic blood pressure (mmHg)	71 ± 12	69 ± 13	72 ± 12	0.323
Weight (kg)	82.8 ± 16.6	79 ± 16	86 ± 16	0.080
BMI (kg/m^2)	27.9 ± 4.3	27.6 ± 4.3	28.1 ± 4.4	0.577
NYHA functional class				
I	23 (30.3%)	9 (23.7%)	14 (36.8%)	0.486
II	29 (38.2%)	16 (42.1%)	13 (34.2%)	
III	23 (30.3%)	12 (31.6%)	11 (28.0%)	
IV	1 (1.3%)	1 (2.6%)	0 (0.0%)	
Comorbidities				
Atrial fibrillation	55 (72.4%)	27 (71.1%)	28 (73.7%)	1.000
COPD	11 (14.5%)	6 (15.8%)	5 (13.2%)	1.000
Hypertension	51 (67.1%)	26 (68.4%)	25 (65.8%)	1.000
Dyslipidemia	50 (65.8%)	26 (68.4%)	24 (63.2%)	0.809
Diabetes	21 (27.6%)	12 (31.6%)	9 (23.7%)	0.609
Laboratory analysis				
Hemoglobin (g/dL)	13.8 ± 2.0	13.4 ± 2.1	14.2 ± 1.8	0.119
Sodium (mmol/L)	139 (138-141)	140 (138-141)	139 (138-141)	0.570
Potassium (mmol/L)	4.47 (4.19-4.84)	4.43 (4.04-4.83)	4.58 (4.32-4.85)	0.277
Chloride (mmol/L)	103 (101-105)	103 (100-104)	103 (102-105)	0.064
Bicarbonate (mmol/L)	26.4 (24.2-28.5)	27.4 (24.3-29.8)	26.1 (24.0-27.4)	0.077
Osmolality (mOsmol/kg H_20)	303 (296-308)	303 (297-310)	302 (296-308)	0.508
Creatinine (mg/dL)	1.45 (1.10-1.95)	1.45 (1.08-2.06)	1.50 (1.13-1.82)	0.903
Estimated GFR (ml/min)	46 (31-65)	46 (26-60)	47 (39-66)	0.414
Troponin	22 (14-31)	29 (17-39)	21 (14-24)	**0.019**

NT-proBNP (ng/L)	1033 (347-2670)	1381 (664-2922)	589 (269-2447)	**0.031**
Plasma renin activation (μU/ml)	201 (81-550)	246 (102-550)	175 (60-550)	0.812
Plasma aldosterone (ng/L)	169 (79-326)	214 (128-367)	109 (60-226)	**0.025**
Echocardiography				
LVEF (%)	45 (35-55)	50 (40-56)	40 (30-46)	**0.005**
LVEDD (mm)	51 (47-56)	50 (45-53)	53 (49-59)	**0.032**
E/e'	10 (9-18)	16 (9-18)	10 (8-13)	0.160
RVSP (mmHg)	28 (25-33)	28 (25-36)	26 (25-32)	0.109
TAPSE (mm)	18 (14-21)	17 (13-19)	19 (15-25)	0.158
Medication				
ARNI/ACEi/ARB	56 (73.7%)	26 (68.4%)	30 (78.9%)	0.435
SGLT2i	69 (90.8%)	34 (89.5%)	35 (92.1%)	1.000
Beta-blockers	72 (94.7%)	37 (97.4%)	35 (92.1%)	0.615
MRA	67 (88.2%)	35 (92.1%)	32 (84.2%)	0.480
Loop diuretics	55 (72.4%)	34 (89.5%)	21 (55.3%)	**0.002**
Loop diuretic dose in furosemide equivalents (mg)	40 (20-40)	40 (20-65)	20 (20-40)	**0.022**
Devices				
PM	24 (31.6%)	12 (31.6%)	12 (31.6%)	1.000
ICD	31 (40.8%)	13 (34.2%)	18 (47.4%)	0.351
CRT	22 (28.9%)	11 (28.9%)	11 (28.9%)	1.000

Supplemental table 3

Multivariate Binary Regression Analysis for High Sodium excreters

	Odds ratio	95% CI	P-value
Gender - Male	7.948	1.187-53.239	**0.033**
Troponin T	1.036	0.984-1.092	0.175
NT-proBNP	1.000	1.000-1.001	0.821
PRA	1.001	0.998-1.004	0.473
LVEF	1.060	0.997-1.128	0.063
Loop diuretics	0.253	0.057-1.115	0.069

CHAPTER 6

Impact of Dietary Sodium Intake on Urinary Sodium Excretion in Healthy volunteers

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Sodium homeostasis, including renal sodium excretion, plays a crucial role in the occurrence of congestion in patients with heart failure. (9) In recent years, urinary sodium concentration has emerged as a valuable biomarker, particularly in the context of acute heart failure while titrating diuretic therapy to achieve a good diuretic response. (25) Additionally, in chronic heart failure, there is evidence that urinary sodium levels can aid in risk stratification and help to predict episodes of fluid overload. (17) Nevertheless, the exact impact of dietary sodium changes on urinary sodium excretion is not yet fully understood, even in healthy people. Scientific data have challenged the traditional assumption that urinary sodium excretion directly mirrors dietary intake. (123,124) Some evidence suggests that sodium may be buffered in tissues, such as bone and soft tissues (11), potentially affecting urinary excretion patterns beyond a simple intake-output model. The current study aimed to further explore the impact of controlled sodium loading and restriction on urinary sodium excretion patterns in healthy volunteers.

Over a three-week period, participants adhered to a very strict and well-controlled dietary sodium regimen: a low-sodium (< 2 gram – 87 mmol - daily) diet during the first week, a moderate-sodium (4 gram – 174 mmol daily) diet during second week, followed by a return to a low-sodium (< 2 gram- 87 mmol daily) intake in the third week. Throughout the study, participants were advised to maintain a fluid intake of 1.5 to 2 liters daily and to fill out daily food questionnaires. Participants measured their first-void urinary sodium concentration daily using the urinary sodium point-of-care sensor of Horiba (LAQUATwin). (82) In addition, at the end of each week, participants collected a 24-hour urinary collection, and the sodium concentration was measured to assess total urinary sodium excretion. The primary objective was to evaluate changes in urinary sodium excretion patterns following different amounts of sodium intake. The study was approved by the local ethical committee and all participants provided written informed consent.

A total of 15 healthy volunteers were included in the study. Exclusion criteria were a history of heart failure, an eGFR < 50ml/min/1.73m^2 and hypertension. Median age of the participants was 32.0 [23.0-59.0] years old with 6 (40%) men. The systolic and diastolic blood pressure were 120 ± 15 mmHg and 79 ± 11mmHg respectively, with a serum creatinine of 0.80 ± 0.16 mg/dL and a median N-terminal of pro-hormone of B-type natriuretic peptide (NT-proBNP) of 50 [50-115]

ng/L. All participants had a normal left ventricular ejection fraction, no evidence of diastolic dysfunction and none were receiving antihypertensive medication.

Figure 1 illustrates the temporal evolution of urinary sodium concentrations. During the first low-sodium week, a steady state was reached 3 days after the dietary change reflected by a median first-void urinary sodium concentration of 38 [25-52] mmol/L. In the moderate-sodium week, a progressive increase in first-void urinary sodium concentration was observed up to 111 [82-129] mmol/L after 3 days. In the final low-sodium week, first-void urinary sodium concentration decreased again, with a median of 41 [26-68] mmol/L after 3 days. Statistically significant differences in first-void urinary sodium concentrations were noted between the first and second weeks; and between the second and the third weeks (both p=0.001), but not between the first and third week (p=0.256). No participant experienced signs or symptoms of heart failure throughout the study period.

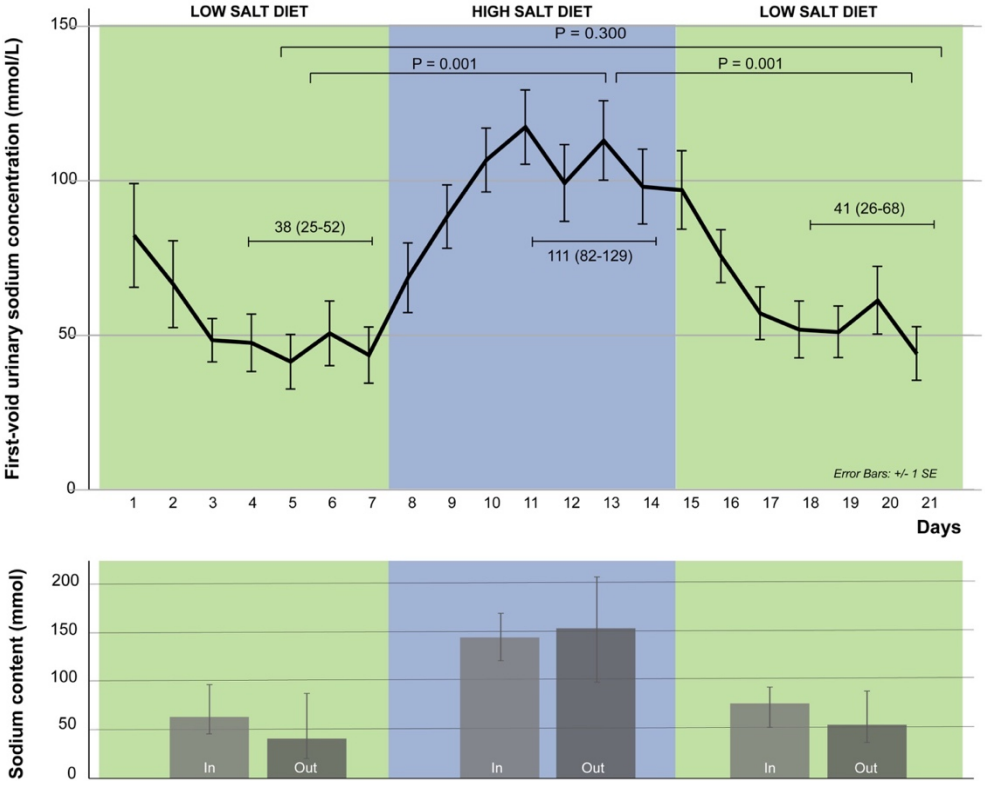
The median 24-hour diuresis during the first week was 1.60 [0.95-2.40] liter, with a median natriuresis of 30 [18-48] mmol/L, yielding a total sodium excretion of 40 [31-80] mmol. In the second week, medium diuresis increased to 1.70 [1.20-2.40] liter with a sodium concentration of 83 [70-104) mmol/L and total sodium excretion of 157 [94-216] mmol. In the third week, values returned to 1.50 [1.00 – 1.80] liters, 33 [25-61] mmol/L and 54 [39-80] mmol respectively. Sodium intake based on the questionnaires on the day of the 24-hour urinary collection was 57 [46-92] mmol for the first week, 144 [122-160] mmol for the second week and 71 [50-87] mmol for the last week. If these results were to be extrapolated to the entire week, they might suggest a positive sodium balance of up to 119 mmol (2.74 g of sodium) during the first and last week, and a negative sodium balance of up to 91 mmol (2.09 g of sodium) during the second week.

This pilot study demonstrates that urinary sodium excretion in healthy individuals closely tracks changes in dietary salt intake, with adaptation occurring within approximately three days of dietary modification. A week of sodium loading significantly increased urinary sodium excretion, which returned to baseline levels within days upon resuming a low-sodium diet. Notably, the absence of a significant difference between the different low-sodium phases suggests that short-term

increases in sodium intake do not have a lasting impact on urinary sodium excretion after returning to a baseline sodium intake. More importantly, it also highlights the kidney's capacity to rapidly adjust its sodium handling in response to dietary changes, reflecting a dynamic renal reserve. In addition, the discrepancy between urinary sodium intake and urinary sodium output across all three weeks could be interpreted as evidence for the hypothesis that sodium may be retained to some extent, particularly during periods of low intake, possibly due to neurohumoral stimulation. Moreover, the positive sodium balance at that time further adds credence to the fact that sodium is stored within the body, likely via interstitial tissue storage, rather than being immediately excreted. Further studies in heart failure populations are warranted to explore whether similar renal sodium handling patterns exist in patients with heart failure.

Figure 1

Evolution of the first-void urinary sodium excretion (mmol/L) in relation to total sodium intake and total sodium output



PART IV

DIURETIC OPTIMIZATION IN ACUTE DECOMPENSATED HEART FAILURE

Research is to see what everybody else has seen,
and to think what nobody else has thought.

- Albert Szent-Gyorgyi -

CHAPTER 7

Optimizing Diuretic Response in Acute Heart Failure: Insights into Cardiorenal Interactions and Therapeutic Strategies

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Heart Fail Journal of India. 2025; 3(1): 11-16

ABSTRACT

Heart failure is characterized by recurrent episodes of congestion, leading to significant morbidity due to frequent hospitalizations. The primary objective of the treatment is to relieve signs and symptoms of congestion. Loop diuretics remain the cornerstone to achieve euvolemia, but their effectiveness varies within and between patients, necessitating an individualized approach. Neurohormonal activation in patients with heart failure increases sodium reabsorption throughout the nephron, with each segment presenting a distinct therapeutic target for enhancing diuresis and natriuresis. This manuscript delves into the underlying cardiorenal mechanisms driving sodium retention in heart failure and explores therapeutic strategies to optimize diuretic efficacy in acute heart failure. Additionally, it highlights the role of urinary sodium concentration in evaluating diuretic response.

INTRODUCTION

The disease course of patients with heart failure (HF) is marked by recurrent episodes of acute HF, significantly contributing to morbidity and mortality. Congestion-related symptoms are the primary reason for urgent medical attention. (8) This manuscript focuses on managing patients with acute decompensated heart failure (ADHF) with volume overload, as most patients presents with congestion rather than symptoms of low output. Neurohumoral activation in HF enhances renal sodium retention, making loop diuretics the cornerstone of treatment to relieve congestion (Class I recommendation). (8) Despite their mode of action, diuretic resistance may arise in patients with more advanced HF, necessitating escalated diuretic therapy for adequate decongestion. (125) This review explores the pathophysiology of neurohormonal and renal interactions in ADHF, therapeutic strategies to enhance diuretic response and tools for monitoring treatment effectiveness.

KEY MECHANISMS OF CONGESTION IN HEART FAILURE

In healthy kidneys, around 25,500 mmol of sodium is filtered daily (sodium 142 mmol/L X glomerular filtration rate (GFR) of 180 L/day), with over 99% reabsorbed. (9) Although minuscule, the sodium excreted fraction is heavily regulated by the kidneys to match dietary intake over time, thereby maintaining a neutral sodium balance. (36) In HF, hemodynamic changes and neurohumoral activation enhance sodium retention, resulting in a positive sodium and water balance. (83)

Renal blood flow (RBF) in HF is often reduced due to increased filling pressures, elevated abdominal pressure, and decreased cardiac output. In order to preserve GFR, afferent arteriole resistance is modulated through autoregulation involving both myogenic and tubuloglomerular feedback mechanisms. (51,126) Therefore, reduced RBF with a preserved GFR leads to an increased filtration fraction (FF). The majority of the filtered sodium is reabsorbed in the proximal tubules (65%). The increased FF in HF elevates peritubular capillary oncotic pressure and facilitates sodium reabsorption in the proximal tubules (glomerulotubular balance). In addition, increased renal lymph flow reduces interstitial colloid

osmotic pressure, leading to an impaired sodium delivery to the distal tubules. (9,83)

The loop of Henle is responsible for the diluting and concentrating ability of the kidney, therefore the fluid reaching the distal tubules will be iso-osmotic and the final urine will be determined by the amount of water reabsorbed in the distal tubules. In HF, neurohormonal activation amplifies sodium reabsorption in the ascending loop, while vasoconstriction of the vase recta reduces medullary washout. This impairs the kidney's ability to dilute urine and excrete free water. Consequently, less sodium and fluid reaches the distal tubules. (9,36)

The macula densa, located at the end of the ascending part of the loop of Henle, regulates sodium balance via tubuloglomerular feedback. In HF, increased sodium reabsorption in the proximal tubule and loop of Henle reduces chloride delivery to the macula densa via the Na+/K+/2Cl- transporter, triggering cyclo-oxygenase-2 and nitric oxide synthetase I. This leads to prostaglandin E and nitric oxide release, reducing afferent arteriole resistance and stimulating renin secretion by the juxtaglomerular cells, consequently activating of the renin-angiotensin-aldosterone system (RAAS) with vasoconstriction of the efferent arterioles. This further increased intraglomerular pressure, GFR and FF. The increase in FF will again lead to an increased sodium reabsorption in the proximal tubule with a further reduction in chloride delivery to the macula densa, hence contributing to disease progression. (36)

In HF, only a small fraction (<10%) of filtered sodium reaches the distal tubules, where fine-tuning of urinary compositions occurs. Low tubular flow, combined with RAAS-induced aldosterone secretion, promotes sodium and water reabsorption in the distal tubules and collecting ducts. Additionally, high interstitial osmotic pressure from the increased loop of Henle reabsorption and low vasa recta flow exacerbated water retention, contributing to fluid overload in HF. (9,36)

DIURETIC THERAPY: MODE OF ACTION

Loop diuretics

Loop diuretics remain the backbone of the diuretic therapy in patients with ADHF. (3) Bound to plasma proteins (>90%), they are actively secreted by organic anion transporters in the proximal tubules. (127) In ADHF, adequate dosing is critical due to frequent kidney dysfunction and hypoproteinemia. Loop diuretics act on the luminal membrane on the ascending loop of Henle (Figure 1), inhibiting the Na+/K+/2Cl- symporter, thereby inducing diuresis. However, they also block the Na+/K+/2Cl- symporter at the macular densa, reducing chloride load and stimulating renin release. Chronic use may lead to distal tubular hypertrophy, enhancing sodium reabsorption and causing diuretic resistance. (3)

In ADHF, intravenous administration is preferred over oral due to potential bowel edema, which might reduce its bioavailability (Class I, LoE B). (8) Loop diuretics exhibit a threshold effect, where doses above the threshold induces natriuresis. Beyond this, higher doses extend the duration of natriuresis without increasing peak effects. (3) The European Society of Cardiology (ESC) guidelines recommend at least 20-40mg intravenous furosemide for diuretic-naïve patients, with higher doses for those with chronic kidney disease. (8) For patients on chronic oral loop diuretics, the intravenous dose should at least match the maintenance oral dose. Early administration of intravenous loop diuretics improves natriuresis, diuresis and lower in-hospital mortality. Loop diuretics, with a half-life up to 6 hours, should be administered 2-3 times daily with at least a 6-hour interval to maximize efficacy and prevent rebound sodium retention.

The Diuretic Optimization Strategies Evaluation (DOSE-AHF) study showed that high-dose diuretics improve diuresis, weight loss, and dyspnea relief compared to low doses, with no difference between bolus and continuous infusion. (128) Importantly, diuretic and natriuretic responses vary among patients, necessitating careful monitoring. (54) Urinary sodium concentration is a promising marker of diuretic effectiveness, directly reflecting their mode of action (see ‘Diuretic response evaluation’). (83) Bolus dosing is generally preferred over continuous

infusion for interpreting urinary sodium levels. However, if continuous infusion is chosen, a bolus dose should precede to reach the natriuretic threshold.

Acetazolamide

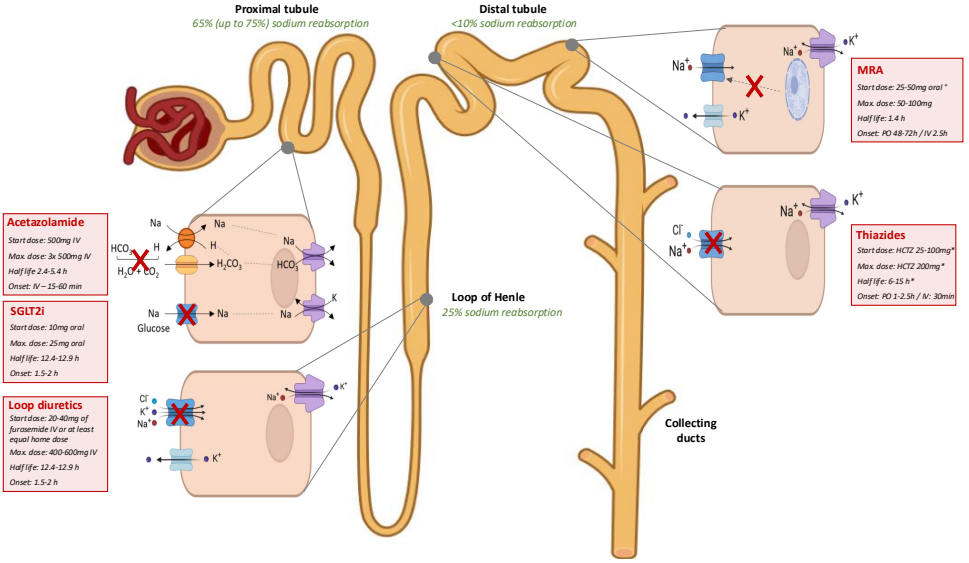
Acetazolamide, a carbonic anhydrase inhibitor, blocks sodium bicarbonate reabsorption in the proximal tubules (Figure 1) (3,81) It offers multiple benefits in HF by which they may prevent loop diuretic resistance; 1) the increased FF results in an even higher amount of sodium reabsorption in the proximal sodium reabsorption, 2) increased sodium delivery to the macula densa (lowering renin release), 3) enhances distal sodium delivery, restoring the effects of endogenous natriuretic peptides. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial showed that adding acetazolamide to intravenous loop diuretics in ADHF led to higher rates of successful decongestion within three days, reflected by greater urine output and natriuresis. (38)

SGLT2i

Sodium-Glucose Cotransporter 2-inhibtors (SGLT2i) act in the proximal tubule, blocking sodium and glucose reabsorption (Figure 1). This leads to glucosuria, osmotic diuresis and a transient increase in natriuresis. (98) The RECEDE-CHF trial demonstrated that adding an SGLT2i to loop diuretics increased 24-h diuresis without raising urinary sodium excretion after 3 days and 6weeks. (99) While SGLT2i may not significantly contribute to achieving a negative sodium balance, they have proven disease-modifying effects (including renoprotection, reduced cardiovascular morbidity and mortality) and are part of the foundational HF therapy, regardless of the ejection fraction. SGLT2i introduction is safe during ADHF and every opportunity should be seized to introduce them as guideline-directed medical therapy (GDMT). (129)

Figure 1

Target site and mode of action of different diuretic agents along the nephron



Cl: Chloride; CO_2: carbon dioxide; H: hydrogen; H_2O: water; HCO_3: bicarbonate; H_2CO_3: carbonic acid; K: Potassium; max.: maximum; MRA: mineralocorticoid receptor antagonist; Na: Sodium; SGLT2i: Sodium-Glucose Cotransporter 2-inhibtors
Conversion factor loop diuretics: 40mg furosemide = 1mg bumetanide = 20 mg torsemide
° Spironolactone: starting dose 25-50mg; maximum dose 50-100mg (up to 400mg in hepatology); half-life 1.4h
Eplerenone: starting dose 25-50mg; half-life 3-6h
** HCTZ: starting dose: 25-100mg; max. dose: 200mg; half-life: 6-15h*
Metolazone: starting dose:2.5-10mg; max. dose: 20mg; half-life: 6-20h
Chlorthalidone: starting dose: 25mg; max. dose: 100mg; half-life: 45-60min
Chlorothiazide: starting dose: 500-1000mg; max. dose: 1000mg; half-life: 45-120min

Thiazides

Thiazides act on the early distal convoluted tubule by blocking the sodium-chloride cotransporter (NCC) (Figure 1), promoting natriuresis and kaliuresis, with 2-3 potassium ions excreted per sodium ion lost. (130) Like look diuretics, they are protein-bound and require active secretion into the tubules, necessitating proper dosing in renal impairment and hypoproteinemia. (131) Unlike other agents, thiazides have slower gastrointestinal absorption and longer half-livers. When combined with loop diuretics, they should ideally be administered hours before loop diuretics to achieve synergy. Chlorothiazide, with a shorter half-life, requires a shorter time-interval.

The Safety and Efficacy of Combination of Loop with Thiazide-type Diuretics in patients with Decompensated Heart Failure (CLOROTIC) trial demonstrated that adding hydrochlorothiazide to loop diuretics enhanced diuresis and weight loss, particularly in patients on chronic loop diuretic therapy. (93) Chronic loop diuretic use can lead to distal tubular hypertrophy and diuretic resistance, which thiazides can overcome. (3)

Mineralocorticoid receptors antagonists

In addition to their direct neurohumoral inhibition, mineralocorticoid receptor antagonists (MRA) induce natriuresis by modulating sodium and potassium channel activity in the late distal nephron (Figure 1). As part of the quadruple GDMT (3), MRAs should be optimized during every HF encounter. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial found no superiority of high-dose spironolactone (100mg) over low-dose (25mg) in 96-h diuresis in patients with ADHF (102), likely due to the slow onset of spironolactone (48-72h). (3) Despite limited diuretic effects, initiating MRAs during ADHF is safe and can prevent hypokalemia from potassium-wasting diuretics. (103) Of course, treatment should always be individualized with temporary cessation in case of hyperkaliemia.

Ultrafiltration

Unlike hemodialysis, ultrafiltration removes water, sodium and small to medium non-protein bound molecules. Evidence for its use in ADHF is limited. (3) The UltrafiltratioN versus IV Diuretics for Patients HospitaLized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial demonstrated that ultrafiltration effectively removes fluid, resulting in greater weight loss. (132) However, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) study found that step-diuretic therapy preserved renal function better, with similar weight loss and fewer adverse events. (133) Therefore, ultrafiltration should be reserved as a last-resort strategy for ADHF patients unresponsive to high-dose combination diuretics.

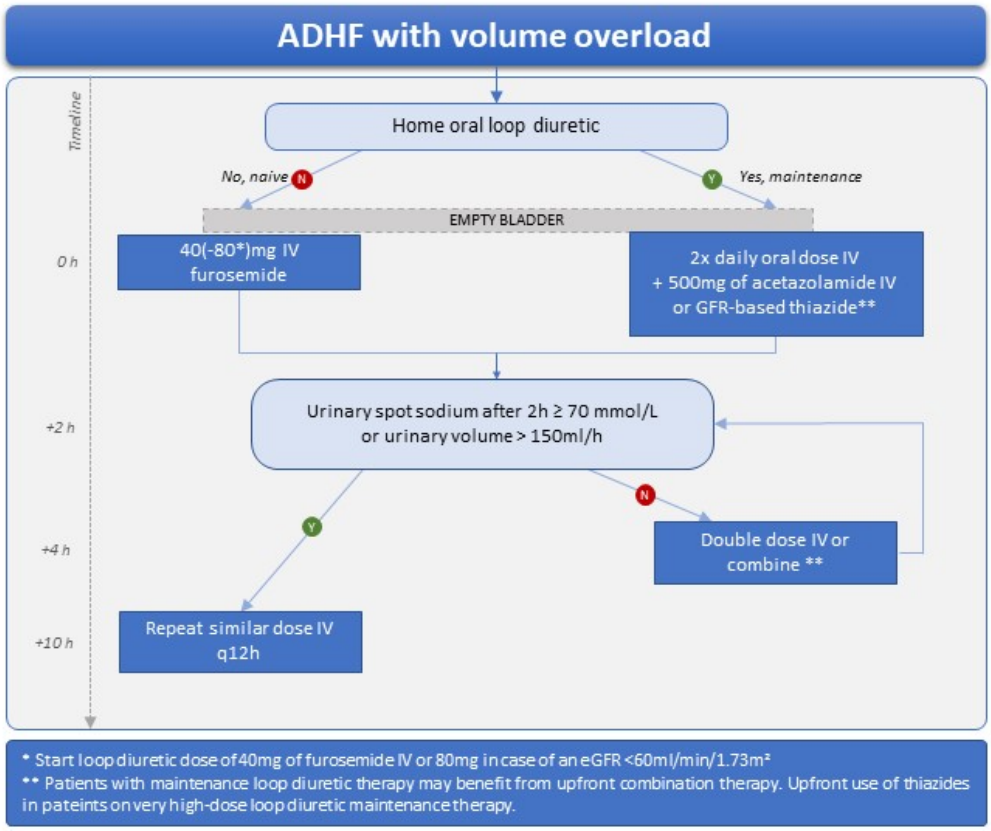
MONITORING DIURETIC RESPONSE

In ADHF, diuretic therapy aims to achieve euvolemia and alleviate congestion, reducing in-hospital mortality and lowering risks of rehospitalization and all-cause mortality. Optimizing diuretic therapy requires an individualized approach and no 'one-size fits all' model exists. (83) Historically, diuretic titration relied on clinical, hemodynamic, biochemical and echocardiographic parameters, which are often inaccurate or too slow to adequately reflect therapy adjustments. (22) The current ESC heart failure guidelines recommend timely diuretic response assessments, using urinary sodium concentration (≥50-70mmol/L) measured 2 hours after diuretic administration or urinary volume (≥100-150ml/h) measured 6 hours after. An inadequate response, diuretic therapy should be escalated through either dose intensification of combination therapies. (8) This approach has been validated prospectively by studies like Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure (PUSH-AHF) and Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF), which demonstrated that natriuresis-guided protocols improve natriuresis, diuresis and length-of-stay, but showed no long-term outcome benefits. (23,120) Both studies asses the protocol only during the first decongestion phase.

Ongoing trials, ESCALATE (NCT04481919) and DECONGEST (NCT05411991), are investigating the applicability of the protocol till decongestion is achieved. On top, DECONGEST evaluates the efficacy of early combination therapy and nephron blockade compared to usual care. However, implementing natriuresis-guided protocols in clinical practice is challenging due to need for frequent, synchronized urine sample collections and laboratory testing. The REadily available UrinAry Sodium analYsis in Patients with Acute Decompensate Heart Failure (EASY-HF) study tested a nurse-led, bedside natriuresis-guided protocol using point-of-care urinary sodium sensors. This approach proved feasible, safe, and effective, increasing natriuresis and diuresis, while being well-received by the nursing teams. (134) Overall, natriuresis-guided protocol –whether nurse-led or physician-guided– enable personalized diuretic titration with early response evaluation. This approach is crucial during hospitalization to promptly relieve congestion and improve patient outcomes (Figure 2).

Figure 2

Flowchart on optimizing diuretic therapy in patients with ADHF



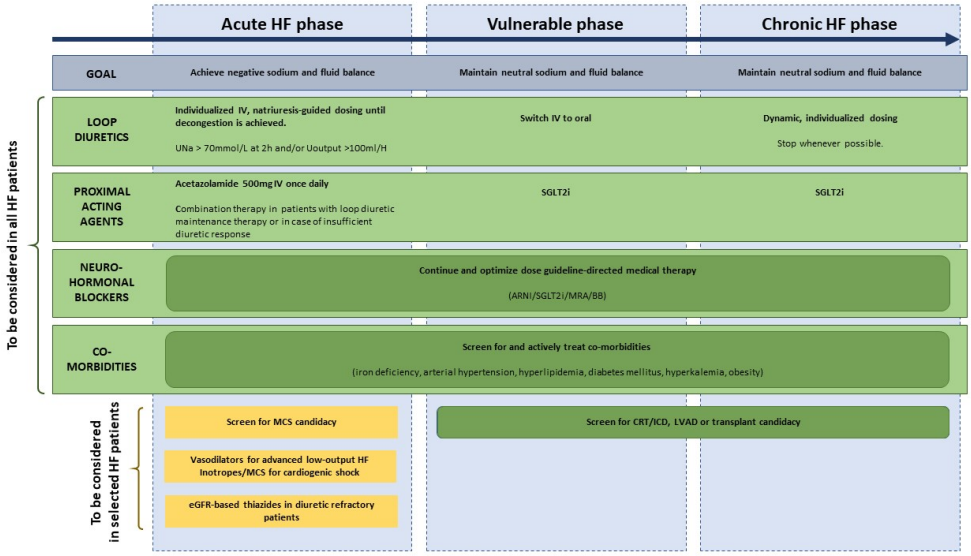
DISCHARGE MANAGEMENT

Although the relieve of congestion remains the primary goal, no prospective diuretic trials have demonstrated that they directly improve long-term outcome. (23,38,93,120) Therefore, every hospitalization should also focus on optimizing HF care, including education, GDMT initiation, treating iron deficiency and implanting/optimizing cardiac resynchronization therapy (Figure 3). (8) Quadruple HF therapy, which mitigates neurohumoral activation and sodium avidity, improves survival and reduces HF hospitalizations. The Safety, Tolerability and Efficacy of Up-titration of Guideline-Directed Medical Therapies for Acute Heart Failure (STRONG-HF) trial demonstrated that rapid uptitration during hospitalization with close follow-up improved quality of life, symptom burden and

outcomes. (135) Chronic loop diuretic maintenance therapy should be reassessed as it correlates with poor long-term outcome. Iron deficiency affects up to 80% of ADHF patients (136) and is defined by serum ferritin level < 100 µg/L or a serum ferritin level 100–300 µg/L with transferrin saturation < 20%. (8) Intravenous iron improves symptoms, quality of life, and reduces hospitalizations.

Figure 3

Optimizing therapy throughout all heart failure phases



CHAPTER 8

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

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ABSTRACT

Background: Whether acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, can improve the efficiency of loop diuretics, potentially leading to more and faster decongestion in patients with acute decompensated heart failure with volume overload, is unclear.

Methods: In this multicenter, parallel-group, double-blind, randomized, placebo-controlled trial, we assigned patients with acute decompensated heart failure, clinical signs of volume overload (i.e., edema, pleural effusion, or ascites), and an N-terminal pro-B-type natriuretic peptide level of more than 1000 pg per milliliter or a B-type natriuretic peptide level of more than 250 pg per milliliter to receive either intravenous acetazolamide (500 mg once daily) or placebo added to standardized intravenous loop diuretics (at a dose equivalent to twice the oral maintenance dose). Randomization was stratified according to the left ventricular ejection fraction (≤40% or >40%). The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy. Secondary end points included a composite of death from any cause or rehospitalization for heart failure during 3 months of follow-up. Safety was also assessed.

Results: A total of 519 patients underwent randomization. Successful decongestion occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; $p<0.001$). Death from any cause or rehospitalization for heart failure occurred in 76 of 256 patients (29.7%) in the acetazolamide group and in 72 of 259 patients (27.8%) in the placebo group (hazard ratio, 1.07; 95% CI, 0.78 to 1.48). Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. The incidence of worsening kidney function, hypokalemia, hypotension, and adverse events was similar in the two groups.

Conclusion: The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion. (Funded by the Belgian Health Care Knowledge Center; ADVOR ClinicalTrials.gov number, NCT03505788.).

INTRODUCTION

Current guidelines recommend the use of intravenous loop diuretics to ameliorate symptoms of fluid overload in patients with acute decompensated heart failure.(25) Despite the use of high-dose loop diuretics (dose equivalent, 2 to 2.5 times the oral maintenance dose), many patients are discharged from the hospital with residual clinical signs of volume overload, a strong predictor of poor outcome.(6,137) For example, in the Diuretic Optimization Strategies Evaluation (DOSE) trial, only 15% of the patients were free from clinical congestion after 72 hours of treatment.(138) Moreover, in the Acute Decompensated Heart Failure National Registry (ADHERE), approximately 20% of the patients were discharged from the hospital with an increase in body weight.(139) Although sequential diuretic therapy has been suggested as a more effective decongestive strategy than loop diuretic therapy alone, decisive evidence regarding effective diuretic agents, administration schedules, and routes of administration is limited.(3,6,25)

Acetazolamide is a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption and may improve diuretic efficiency when added to loop diuretics, thereby potentially facilitating decongestion. Results from an observational study and a small, prospective, randomized trial suggest that the addition of acetazolamide (at a dose of 500 mg administered intravenously once daily) to intravenous loop-diuretic therapy increased urinary sodium excretion, which is an objective metric of diuretic efficiency in patients with acute decompensated heart failure.(57,97) In the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, we examined whether the addition of acetazolamide to standardized intravenous loop-diuretic therapy would improve the incidence of successful decongestion among patients with acute decompensated heart failure.

METHODS

Trial design and oversight

We conducted this multicenter, randomized, parallel-group, double-blind, placebo-controlled, investigator-initiated, academic, clinical trial without industry involvement. Details regarding the trial design and the baseline characteristics of the patients have been published previously,(81,140) and the trial protocol is available with the full text of this article at NEJM.org. Ziekenhuis Oost-Limburg initiated and managed the clinical investigation but was not involved in the data collection or analysis.

The protocol was designed by the first five authors and the last author. A steering committee consisting of 14 academic members, one patient representative, and one independent statistician was responsible for trial oversight and the reporting of results. The trial was conducted and documented in accordance with the protocol and the statistical analysis plan. The trial protocol was approved by a central ethics committee and the Belgian Federal Agency for Medicines and Health Products. All the patients provided written informed consent before any trial-specific procedure commenced.

The clinical trial unit of Ziekenhuis Oost-Limburg oversaw patient recruitment and data collection and storage. An independent clinical end-point committee adjudicated prespecified events (Section S1 in the Supplementary Appendix). The statistical analyses were conducted by an independent academic statistical center (Data Science Institute–CenStat, University Hasselt). The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adult patients who were admitted to the hospital because of acute decompensated heart failure and had at least one clinical sign of volume overload (i.e., edema, pleural effusion, or ascites) and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of more than 1000 pg per milliliter or a B-type natriuretic peptide level of more than 250 pg per milliliter were eligible for participation.(81) In

addition, the receipt of oral maintenance therapy with at least 40 mg of furosemide or an equivalent dose (1 mg of bumetanide or 20 mg of torsemide) for at least 1 month before randomization was required.(81) If pleural effusion or ascites was suspected clinically at any time during the trial, confirmation with radiography or ultrasonography of the chest or with ultrasonography of the abdomen was obtained.

The main exclusion criteria were the receipt of acetazolamide maintenance therapy or treatment with another proximal tubular diuretic including a sodium–glucose cotransporter 2 (SGLT2) inhibitor, a systolic blood pressure of less than 90 mm Hg, and an estimated glomerular filtration rate (GFR) of less than 20 ml per minute per 1.73 m^2 of body-surface area. Treatment with intravenous loop diuretics at a dose of more than 80 mg of furosemide equivalent during the index hospitalization was not allowed before randomization. Details regarding the inclusion and exclusion criteria are provided in Section S2.

Trial procedures

Patients were randomly assigned in a 1:1 ratio to receive an intravenous bolus of acetazolamide (500 mg once daily) or matching placebo, administered immediately after randomization and during the next 2 days or until the occurrence of complete decongestion, which was defined as the absence of any clinical sign of fluid overload other than trace edema. An automated, Web-based system was used for randomization with permuted blocks, with stratification according to the left ventricular ejection fraction (≤40% or >40%) and trial center.

At randomization, oral loop diuretics were stopped, and the patient received an intravenous loop diuretic at double the oral maintenance dose, administered as a single bolus immediately after randomization and split into two doses (separated by ≥6 hours) on each of the next 2 days (Fig. S2). The bolus of acetazolamide or matching placebo was administered simultaneously with the first dose of loop diuretics each day. All the patients received the same maintenance infusion with 500 ml of 5% dextrose and 3 g of magnesium sulfate administered over a period of 24 hours until the end of the treatment phase of the trial. It was recommended

that treating physicians leave the doses of neurohumoral blockers unchanged during the treatment phase. Thereafter, it was strongly recommended that the doses of neurohumoral blockers be adjusted according to the European Society of Cardiology guidelines.(25,141)

According to the diuretic protocol, a timed urine collection was begun after the bladder had been emptied, which coincided with the first bolus of loop diuretics, and was continued until the second morning after randomization (time period ranged from 30 to 48 hours). If the cumulative urinary output over the period of 30 to 48 hours on that morning was less than 3.5 liters and signs of fluid overload were still present, an escalation of decongestive treatment was mandated by the protocol. At the time of enrollment and daily thereafter, the treating physician calculated the congestion score, on a scale from 0 to 10 on the basis of the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3), with higher scores indicating a worse condition on all scales (Fig. S3). This score was calculated before the administration of the morning dose of diuretics during the treatment phase, at discharge, and during 3 months of follow-up.

End points

The primary end point was successful decongestion, which was defined as the absence of signs of volume overload (i.e., no more than trace edema, no residual pleural effusion, and no residual ascites) as assessed by a cardiologist trained in the completion of the congestion score, within 3 days after randomization without an indication for escalation of decongestive therapy (Section S3 in the Supplementary Appendix). Key secondary end points were the composite end point of death from any cause or rehospitalization for heart failure during 3 months of follow-up and the duration of the index hospital admission (i.e., the number of days from randomization until the date of discharge). Exploratory tertiary end points were death from any cause and rehospitalization for heart failure during 3 months of follow-up.

Data regarding adverse events that resulted in the discontinuation of acetazolamide or placebo at the discretion of treating physician and on prespecified adverse events of interest (including severe metabolic acidosis, renal

events, hypokalemia, and hypotension) were collected during the treatment phase. Severe metabolic acidosis was defined as a bicarbonate level of less than 12 mmol per liter. The combined renal safety end point was defined as the doubling of the serum creatinine level from baseline, a decrease of at least 50% in the estimated GFR, or receipt of renal-replacement therapy. Hypokalemia was defined as a potassium level of no more than 3 mmol per liter, and hypotension as a systolic blood pressure of less than 85 mmHg.

Statistical analysis

Details regarding the analytic approach and power calculations have been published previously,(81) and the complete prespecified statistical analysis plan is available with the protocol. On the basis of the results of the DOSE trial,(138) we estimated that 15% of the patients in the placebo group would have successful decongestion. No reliable data were available from large, randomized clinical trials to estimate the occurrence of the primary end point in the acetazolamide group. We estimated that 25% of the patients in the acetazolamide group would have successful decongestion within 3 days after randomization; 25% was chosen to represent a clear, meaningful absolute benefit of 10 percentage points as compared with placebo. Assuming a two-sided alpha of 0.05 and a statistical power of 80%, we calculated the targeted sample size for the trial to be 494, and to account for a potential withdrawal of 5% of the patients, we calculated that the trial would need to enroll 519 patients.

The analyses of the primary and secondary end points were based on the intention-to-treat principle and included data from all the patients who had undergone randomization and received at least one dose of acetazolamide or placebo; four patients were excluded because they did not receive either the trial drug or placebo. The safety population included all the patients who had undergone randomization, according to the treatment or placebo they actually received.

The baseline characteristics of the patients were summarized as means and standard deviations, medians and interquartile ranges, or numbers and percentages. The primary end point was evaluated by means of a generalized

linear mixed model (log-link binomial model) that included a fixed treatment effect, a fixed effect for the stratification factor of the left ventricular ejection fraction, and a random center effect for the calculation of risk ratios and 95% confidence intervals. For the primary end point, prespecified subgroup analyses and a SARS-CoV-2 sensitivity analysis (described in the statistical analysis plan) as well as an exploratory analysis for patients who were discharged alive were also performed.

The composite end point of death from any cause and rehospitalization for heart failure after 3 months of follow-up was assessed in a time-to-event analysis with the use of a Cox proportional-hazards model that included trial group, the stratification factor of the left ventricular ejection fraction, and a random center effect (with the use of a log-normal frailty model) to calculate hazard ratios and 95% confidence intervals; results were summarized with the use of Kaplan–Meier survival curves. The duration of the index hospitalization was compared with the use of a linear mixed model (with fixed effects for treatment and the stratification factor of the left ventricular ejection fraction and a random center effect) after logarithmic transformation to calculate geometric means and the geometric mean ratio and 95% confidence interval.

Differences in diuresis and natriuresis were investigated by means of a linear mixed-effects model. Because the statistical analysis plan did not include a provision for correction for multiplicity when tests for secondary or other outcomes were conducted, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. Safety events were compared with the use of Fisher's exact test.

All the hypothesis testing was two-sided, and a P value of less than 0.05 was considered to indicate significance. All the statistical analyses were performed with the use of SAS software for Windows, version 9.4 (SAS Institute).

RESULTS

Patients

Between November 11, 2018, and January 17, 2022, a total of 2915 patients underwent screening, of whom 519 were randomly assigned to receive either acetazolamide (259 patients) or placebo (260 patients) at 27 sites in Belgium. All patients were followed for 3 months for death from any cause and rehospitalization for heart failure. Details about the randomization and follow-up of the patients are provided in Figure S1. The characteristics of the patients at baseline were well balanced between the two groups (Table 1, S1, and S2). Patients had clinically significant congestion, with a median NT-proBNP level of 6173 pg per milliliter (interquartile range, 3068 to 10,896) and a median congestion score of 4. Edema of the lower limb was the most prevalent sign of volume overload.

Primary endpoint

The primary end point of successful decongestion could not be assessed in 4 patients who underwent randomization because they did not receive the assigned acetazolamide (in 1 owing to the patient's decision, in 1 owing to the physician's decision, and in 1 who was withdrawn because the patient did not meet the inclusion criteria) or placebo (in 1 patient who withdrew informed consent). Successful decongestion occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; p-value < 0.001) (Figure 1A and Table 2). Most of the patients who had been assigned to receive acetazolamide had a more pronounced reduction in congestion score over consecutive days than patients who had been assigned to receive placebo (Figure 1B). A scenario that assumed no successful decongestion in the 3 patients in the acetazolamide group and successful decongestion in the 1 patient in the placebo group who could not be assessed for the primary end point was consistent with the results of the primary analysis (risk ratio, 1.44; 95% CI, 1.15 to 1.79) (Table S3).

Table 1

*Characteristics of the Patients at Baseline**

	Total (n=519)	Placebo (n=260)	Acetazolamide (n=259)
Age – year	78.2±8.9	78.5±8.8	77.9±9.0
Male sex – no. (%)	325 (62.6)	155 (59.6)	170 (65.6)
White race – no. (%)†	514 (99.0)	256 (98.5)	258 (99.6)
Heart rate – beats/min	78±18	77±18	79±19
Blood pressure – mmHg			
Systolic	127±21	127±22	126±20
Diastolic	72±13	73±13	72±13
Weight – kg	84.8±21.4	84.4±19.7	85.3±23.0
Median congestion score at baseline (IQR)‡	4 (3-6)	4 (3-6)	4 (3-5)
Components of congestion score			
Edema§	478 (92.1)	241 (92.7)	237 (92.1)
Pleural effusion	273 (52.6)	143 (55.0)	130 (50.2)
Ascites	46 (8.9)	25 (9.6)	21 (8.1)
Median home maintenance dose of furosemide equivalent (IQR) — mg	60 (40-100)	60 (40-100)	80 (40-120)
Left ventricular ejection fraction			
Mean – %	43±15	43±15	43±15
≤40% – no. (%)	224 (43.2)	111 (42.7)	113 (43.6)
NT-proBNP (IQR) – pg/ml	6,173 (3,068–10,896)	6,483 (3,262–11,839)	5,600 (3,034–10,100)
NYHA functional class – no. (%)			
II	66 (12.7)	35 (13.5)	31 (12.0)
III	296 (57.0)	148 (56.9)	148 (57.1)
IV	157 (30.3)	77 (29.6)	80 (30.9)
Ischemic cause – no. (%)	232 (44.7)	113 (43.5)	119 (45.9)

Serum hemoglobin – g/dL	11.9±2.0	11.9±2.0	11.9±2.0
Sodium – mmol/liter	139±4	140±4	139±4
Median serum creatinine (IQR) – mg/dL	1.5 (1.2-1.9)	1.5 (1.2-1.9)	1.5 (1.2-2.0)
Estimated GFR			
Median (IQR) – ml/min/1.73m²	39 (29-52)	38 (29-51)	40 (30–52)
<60ml/min/1.73m² – no. (%)	424 (81.7)	215 (82.7)	209 (80.7)
Coexisting conditions – no. (%)			
History of atrial fibrillation	376 (72.4)	189 (72.7)	187 (72.2)
Diabetes	245 (47.2)	133 (51.2)	112 (43.2)
Hypertension	389 (75.0)	207 (79.6)	182 (70.3)
Treatment – no. (%)			
ACE inhibitor, ARB, or ARNI	270 (52.0)	140 (53.8)	130 (50.2)
Beta-blocker	419 (80.7)	212 (81.5)	207 (79.9)
Mineralocorticoid receptor antagonist	216 (41.6)	103 (39.6)	113 (43.6)
Loop diuretic	519 (100.0)	260 (100.0)	259 (100.0)
Implantable cardioverter-defibrillator	79 (15.2)	41 (15.8)	38 (14.7)
Cardiac-resynchronization therapy	61 (11.8)	25 (9.6)	36 (13.9)

** Plus–minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, GFR glomerular filtration rate, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.*

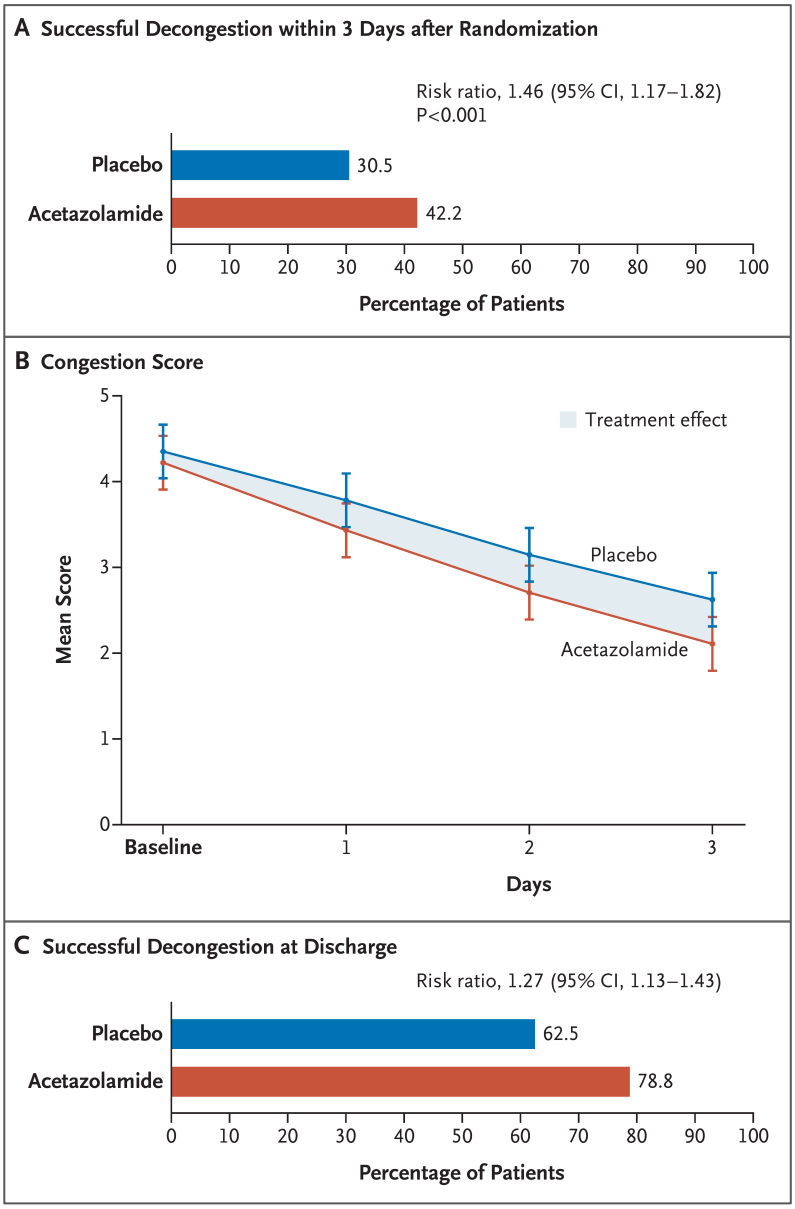
† Race was reported by the patient.

‡ Congestion scores range from 0 to 10 and are defined as the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3); on all scales, higher scores indicate a worse condition.

§ Edema was defined as a score of 1 or more (on a scale from 0 [no edema] to 4 [clear pitting edema above the knee]).

Figure 1

Successful Decongestion and Evolution of Congestion Scores



The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy. Congestion scores range from 0 to 10 and are defined as the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3); on all scales, higher scores indicate a worse condition. An exploratory analysis was conducted regarding successful decongestion at discharge among patients who were alive.

In a scenario that excluded the component of need for escalation therapy in the primary end point and only defined successful decongestion as the absence of a congestion score of greater than 1, more patients in the acetazolamide group than in the placebo group had successful decongestion (115 patients [44.9%] vs. 86 [33.2%]; risk ratio, 1.42; 95% CI, 1.15 to 1.76) (Table 2).

The effect of acetazolamide on the primary end point was generally consistent across prespecified subgroups, although the patients who were receiving a higher maintenance dose of loop diuretics appeared to have less benefit than those who were receiving a lower maintenance dose (Figure 2). Among the patients who were alive at discharge, 190 of 241 (78.8%) in the acetazolamide group and 145 of 232 (62.5%) in the placebo group had successful decongestion (risk ratio, 1.27; 95% CI, 1.13 to 1.43) (Figure 1C and Table 2). A sensitivity analysis for the primary end point that considered the timing of cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Belgium (before or after the first case [February 2020]) showed no interaction between SARS-CoV-2 infection and the primary end point (Table S4).

Secondary end points

Death from any cause or rehospitalization for heart failure occurred in 76 of 256 patients (29.7%) in the acetazolamide group and in 72 of 259 patients (27.8%) in the placebo group (hazard ratio, 1.07; 95% CI, 0.78 to 1.48) (Table 2 and Figure S4). The duration of the index hospitalization was a geometric mean of 8.8 days (95% CI, 8.0 to 9.5) in the acetazolamide group and 9.9 days (95% CI, 9.1 to 10.8) in the placebo group (Table 2). Additional data are provided in Tables S5 through S9.

Table 2

*Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse Events**

	Placebo (n=259)	Acetazolamide (n=256)	Treatment effect (95% CI)	P-value
Primary end point				
Successful decongestion within 3 days from randomization – no. (%)	79 (30.5)	108 (42.2)	Risk ratio, 1.46 (1.17–1.82)	<0.001
Secondary end points				
Duration of hospital stay (95% CI) – days‡	9.9 (9.1-10.8)	8.8(8.0-9.5)	0.89 (0.81-0.98)	0.02
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up – no. (%)	72 (28.0)	76 (29.7)	Hazard ratio 1.07 (0.78-1.48)	0.71
Sensitivity analysis of primary end point				
Successful decongestion within 3 days after randomization, regardless of escalation of therapy – no. (%)§	86 (33.2)	115 (44.9)	Risk ratio, 1.42 (1.15-1.76)	0.004
Exploratory analysis				
Successful decongestion at discharge among patients who were alive – no./total no. (%)	145/232 (62.5)	190/241 (78.8)	Risk ratio, 1.27 (1.13 to 1.43)	<0.001
Death from any cause at 3 mo – no. (%)	31 (12.1%)	39 (15.2%)	Hazard ratio, 1.28 (0.78 to 2.05)	
Rehospitalization for heart failure at 3 mo – no. (%)	42 (17.5%)	47 (18.4%)	Hazard ratio, 1.07 (0.71 to 1.59)	
Adverse events				
During treatment phase – no. (%)				
Combined renal safety end point	2 (0.8)	7 (2.7)	—	0.10
Doubling of serum creatinine from baseline	0	2 (0.8)	—	0.24
≥50% sustained decrease in estimated GFR	1 (0.2)	4 (1.6)	—	0.21

Renal replacement therapy during index hospitalization	1 (0.4)	4 (1.6)	—	0.21
Severe metabolic acidosis	0	0	—	—
Hypokalemia	10 (3.9%)	14 (5.5%)	—	0.39
Hypotension	9 (3.5%)	17 (6.6%)	—	0.11
During 3 mo of follow-up – no. (%)				
Serious adverse event	124 (47.9)	123 (48.0)	—	1.00
Adverse event related to placebo or acetazolamide	3 (1.2)	8 (3.1)	—	0.14
Cardiovascular adverse event	122 (47.1)	113 (44.1)	—	0.53

** The primary end point could not be assessed in four patients (one in the placebo group and three in the acetazolamide group) because they did not receive the assigned intervention and the congestion score was not reported by the investigators. The secondary end points were assessed in the same intention-to-treat population that was used for the primary end-point analysis, as stipulated in the statistical analysis plan. Safety end points were assessed in patients according to the treatment they actually received. The determination of relatedness of an adverse event to acetazolamide or placebo was made by the investigator. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. Rehospitalization for heart failure after 3 months, which was an exploratory analysis, was assessed in a competing-risk survival analysis with the use of Fine and Gray's model, with death as the competing risk.*

† The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and with no indication for escalation of decongestive therapy.

‡ Values for duration of hospital stay are geometric means.

§ Escalation of decongestive treatment was mandatory if the patient's urinary output on the morning of the second day after randomization was less than 3.5 liters and the patient still had volume overload.

¶ Severe metabolic acidosis was defined as a bicarbonate level of less than 12 mmol per liter.

‖ Hypokalemia was defined as a potassium level of no more than 3 mmol per liter.

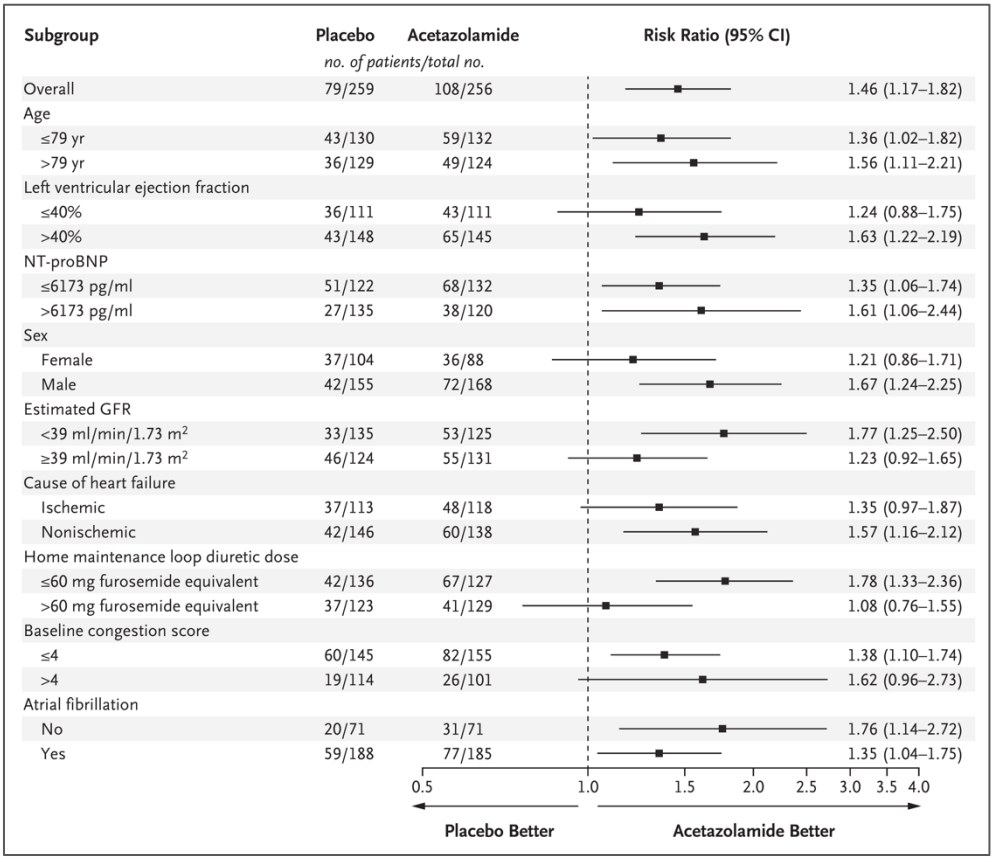
*** Hypotension was defined as a systolic blood pressure of less than 85 mm Hg.*

Diuretic efficacy

The total administered dose of intravenous loop diuretics was similar in the two trial groups (Table S10). On the second morning after randomization, the mean (±SD) urine output was 4.6±1.7 liters in the acetazolamide group and 4.1±1.8 liters in the placebo group, and natriuresis was 468±234 mmol and 369±231 mmol, respectively (Figure 3).

Figure 2

Subgroup Analysis



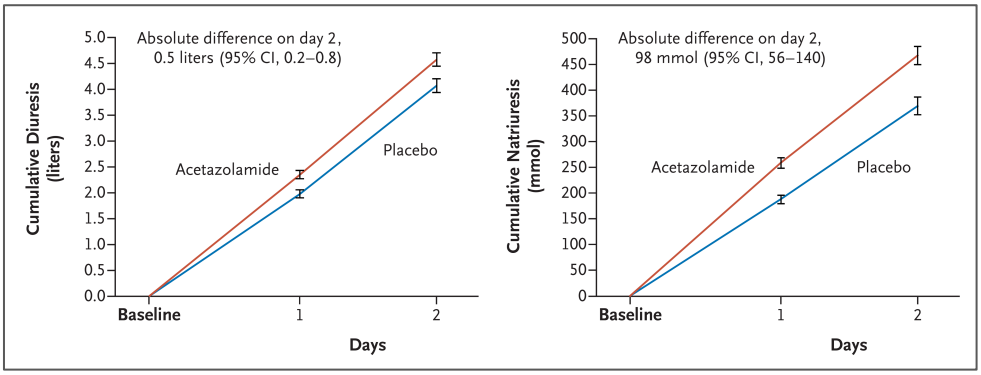
Subgroups that were defined according to age, the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, the estimated glomerular filtration rate (GFR), the home maintenance dose of loop diuretic, and the baseline congestion score were based on observed median values at randomization.

Safety and adverse events

Safety was assessed in the 515 patients (99%) who received acetazolamide or placebo. Severe metabolic acidosis did not occur in any patient during the treatment phase. The incidences of the combined renal safety end point, hypokalemia, and hypotension were similar in the two trial groups. The use of acetazolamide or placebo was stopped at the discretion of the physician because of hypotension (in 4 and 2 patients, respectively) or an increase in the serum creatinine level (in 1 patient in the acetazolamide group). The incidence of adverse events during 3 months of follow-up was similar in the two trial groups (Table 2 and S11).

Figure 3

Diuresis and Natriuresis According to Trial Group



Bars indicate standard errors.

DISCUSSION

In this multicenter, randomized, placebo-controlled trial involving patients with acute decompensated heart failure and volume overload, the addition of acetazolamide to standardized intravenous loop-diuretic therapy was associated with a higher incidence of successful decongestion within 3 days after randomization. Patients who had been treated with acetazolamide had more diuresis and natriuresis, had a shorter hospital stay, and were more likely to be discharged without residual signs of volume overload than those who had received placebo. There did not appear to be a higher incidence of adverse events with acetazolamide treatment.

Our trial involving patients with acute decompensated heart failure showed that acetazolamide, a diuretic agent blocking proximal tubular sodium reabsorption, added to loop-diuretic therapy led to more and faster decongestion and was associated with a shorter duration of hospital stay. The benefit with acetazolamide treatment with regard to decongestion was maintained at discharge, with a higher percentage of patients being discharged from the hospital without residual congestion (difference vs. placebo, 16.3 percentage points). The attainment of successful decongestion (euvolemia) has a class I recommendation from the European and American guidelines for the diagnosis and treatment of heart failure.(8,37) According to clinical trial and registry data, only a minority of patients with acute decompensated heart failure have decongestion at the end of the study period or are discharged without residual congestion.(102,133,138,139,142–146) Given that residual congestion is linked to adverse outcomes, the beneficial effects of acetazolamide therapy are important. The higher incidences of decongestion with acetazolamide treatment than with placebo were most probably related to the early and sustained increase in diuresis and natriuresis that were associated with the addition of acetazolamide. These findings highlight the importance of targeting congestion both early and aggressively and support the use of natriuresis as an indicator of diuretic response.(3,25,33)

The improvement with regard to successful decongestion with acetazolamide was generally consistent across all the prespecified subgroups, except for one comparison suggesting possible heterogeneity, which showed less treatment

benefit among patients receiving a higher oral maintenance dose of loop-diuretic therapy. Other subgroups that were defined to reflect more congestion or more diuretic resistance (e.g., a higher congestion score, lower estimated GFR, or higher NT-proBNP level) did not show any heterogeneity in treatment effect.

The addition of acetazolamide to loop-diuretic therapy was not associated with an increased incidence of adverse events, and the higher incidence of successful decongestion was associated with a shorter duration of hospital stay. However, the risk of death from any cause or rehospitalization for heart failure (secondary composite end point) did not differ significantly between the two trial groups. In our trial, the risk of death or rehospitalization was considerably lower than that in the DOSE trial (50% at 60 days) and in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF; 40% at 60 days).(133,138) The higher incidence of decongestion at discharge and the increase in the dose of neurohumoral blockers during the remainder of the hospital stay in our trial may account for the better outcomes, despite the fact that our trial patients had many coexisting conditions and advanced age. It was reassuring that acetazolamide treatment was not associated with higher incidences of hypokalemia, hypotension, or renal end points. To elucidate the complex relations among degree of decongestion, quality of life, and outcomes in patients with acute decompensated heart failure, more trials of diuretic agents with larger sample sizes are needed.

Our trial has certain limitations. Nearly all the patients who participated in the trial were White, given that the trial recruited exclusively in Belgium, which may limit the generalizability of our results to other racial or ethnic groups. Second, patients also had a history of chronic heart failure and had been receiving long-term outpatient treatment with at least 40 mg of furosemide equivalent. Therefore, results of the strategy we tested may not be applicable to patients with newly diagnosed heart failure. Third, patients in the two trial groups received similar standardized loop diuretics. It is unknown whether similar results may have been obtained with other dose regimens of loop diuretics or other diuretic agents. Fourth, the congestion score that was used for the assessment of the primary end point focused on the presence of edema in the lower limb, pleural effusion, and ascites — findings that are reflective of an assessment of mainly extracellular

volume overload. Finally, during most of the trial period, SGLT2 inhibitors were not indicated and had not been approved as drugs to treat heart failure. To avoid confounding by any imbalance in their use between the trial groups, the trial design excluded their use. Although SGLT2 inhibitors and acetazolamide both exert natriuretic and diuretic effects on the proximal tubules, their mode of action and potency differ substantially.(3) Only 5% of proximal sodium uptake is mediated by SGLT2, whereas 60% is mediated by the apical sodium–hydrogen exchange that is inhibited by acetazolamide.(147–150)

In this placebo-controlled trial, we found that the addition of acetazolamide to standardized intravenous loop-diuretic therapy in patients with acute decompensated heart failure led to a higher incidence of successful decongestion.

SUPPLEMENTARY MATERIAL

Figure S1

Flow diagram of patient inclusion

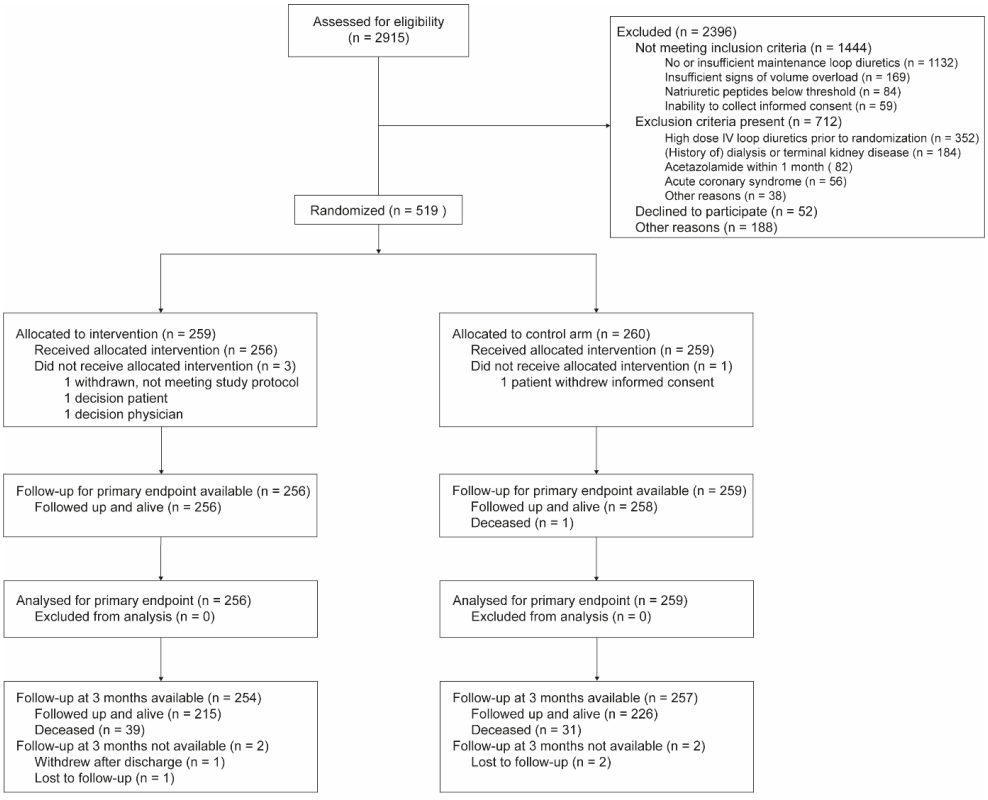
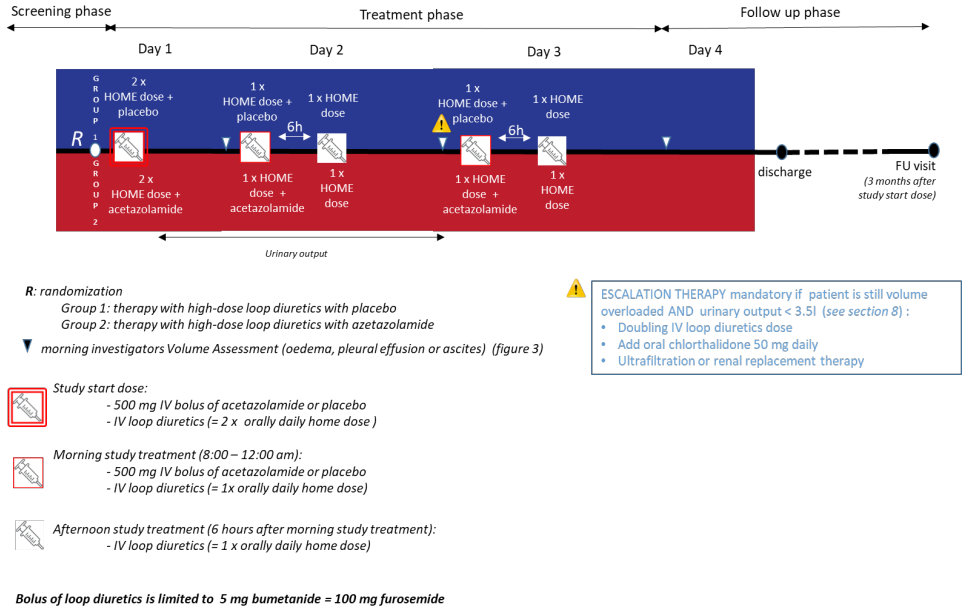


Figure S2

Diuretic protocol



If urinary output on morning of day 3 was <3.5 L and the patient was still volume overloaded, an escalation of decongestive treatment was mandatory. Three options could be chosen at the discretion of the treating physician: (i) doubling of the intravenous dose of loop diuretics (equal to the study starting dose bid); (ii) addition of oral chlorthalidone 50 mg once daily; or (iii) ultrafiltration or renal replacement therapy. The decision to proceed with escalation therapy needed to be collected in the case report form as patients needing escalation were considered not to have reached the primary endpoint of complete decongestion with good loop diuretic efficacy.

Figure S3

Congestion Score

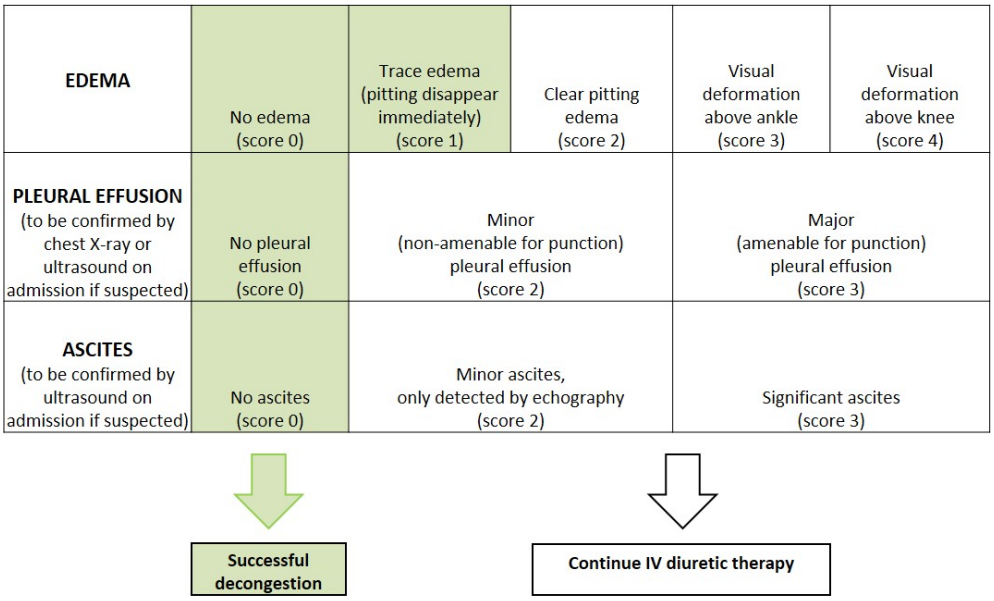
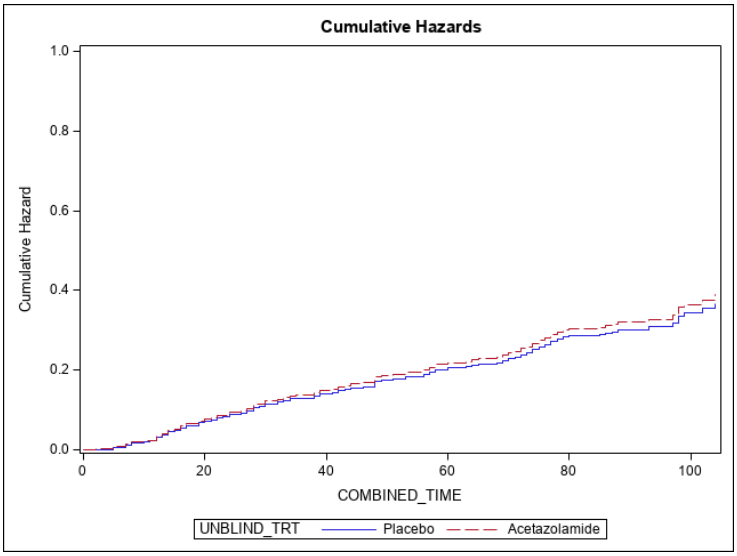


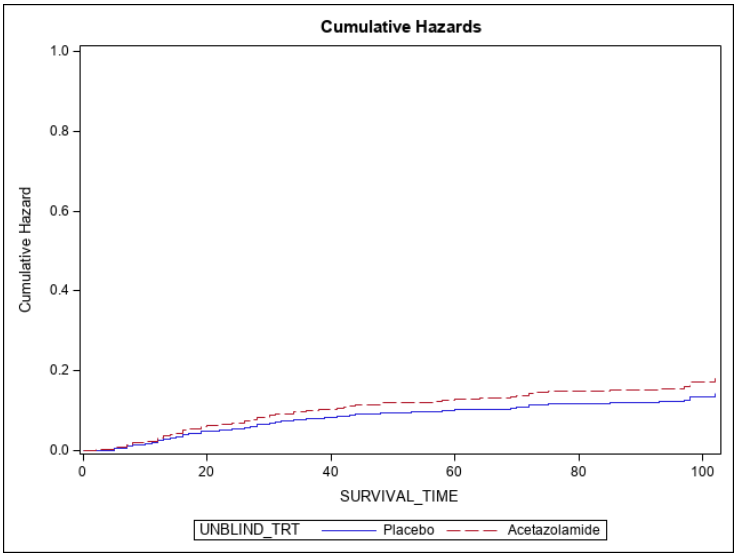
Figure S4

Kaplan Meier Curves for Heart Failure Rehospitalization and All-Cause Mortality. Combined Endpoint

- ***All-cause mortality and heart failure rehospitalization***



- ***All-cause mortality***



- ***Heart failure rehospitalization***

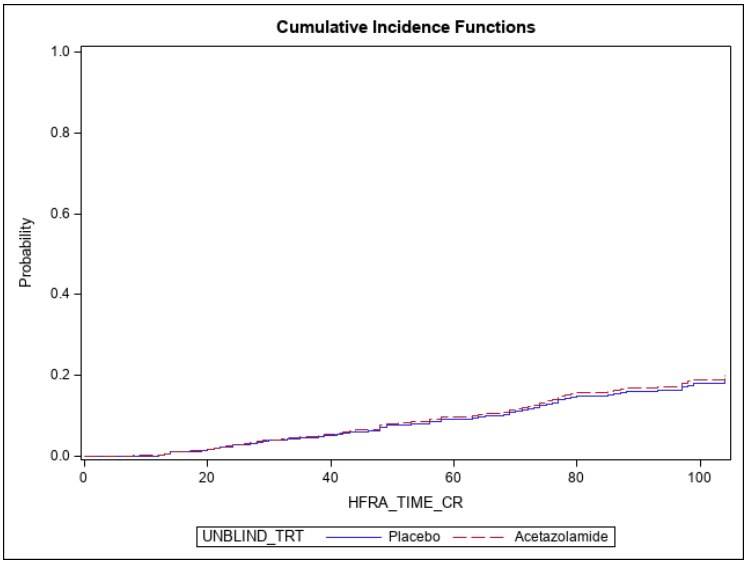


Table S1

Additional Baseline Characteristics

Parameter	Total (n=519)	Acetazolamide (n=259)	Placebo (n=260)
TYPE OF NON-ISCHEMIC	287 (55%)	140 (54%)	147 (57%)
Valvular	104 (20%)	53 (21%)	51 (20%)
Idiopathic	122 (24%)	55 (21%)	67 (26%)
Hypertensive	45 (9%)	24 (9%)	21 (8%)
Toxic	12 (2%)	7 (3%)	5 (2%)
Ischemic CABG	123 (24%)	66 (25%)	57 (22%)
Ischemic PTCA	125 (24%)	62 (24%)	63 (24%)
Ischemic thrombolysis	3 (0.6%)	1 (0.4%)	2 (0.8%)
COMORBIDITIES			
Stroke	62 (12%)	26 (10%)	36 (14%)
Valve surgery	91 (18%)	48 (19%)	43 (17%)
PAD	101 (19%)	46 (18%)	55 (21%)
COPD	101 (19%)	54 (21%)	47 (18%)
CRT/ICD	169 (33%)	84 (32%)	85 (33%)
Pacemaker	72 (14%)	34 (13%)	38 (15%)
ICD	36 (7%)	14 (5%)	22 (8%)
CRT	61 (12%)	36 (14%)	25 (10%)
MALIGNANCY REQUIRING CHEMO/RADIOTHERAPY			
No	461 (89%)	226 (87%)	235 (90%)
Yes, past	45 (9%)	23 (9%)	22 (8%)
Yes, current	8 (2%)	6 (2%)	2 (0.8%)
Yes, past and current	5 (1%)	4 (2%)	1 (0.4%)
Mean arterial pressure (mmHg)	90 ± 13	90 ± 13	91 ± 13
Congestion score at baseline	4 (3-6)	4 (3-5)	4 (3-6)
CONGESTION SCORE AT BASELINE			
2	50 (10%)	24 (9%)	26 (10%)
3	146 (28%)	69 (27%)	77 (30%)
4	107 (21%)	64 (25%)	43 (16%)
5	69 (13%)	38 (15%)	31 (12%)
6	97 (19%)	43 (17%)	54 (21%)
7	26 (5%)	11 (4%)	15 (6%)
8	10 (2%)	4 (1%)	6 (2%)
9	10 (2%)	5 (2%)	5 (2%)
10	4 (0.8%)	1 (0.4%)	3 (1.2%)
BASELINE OEDEMA SCORE			
No oedema (0)	25 (5%)	12 (5%)	13 (5%)
Trace oedema (1)	16 (3%)	10 (4%)	6 (2%)

Pitting oedema-up to ankle (2)	73 (14%)	32 (12%)	41 (16%)
Pitting oedema-up to knee (3)	228 (44%)	114 (44%)	114 (44%)
Pitting oedema-above knee (4)	177 (34%)	91 (35%)	86 (33%)
BASELINE PLEURAL EFFUSION SCORE			
No pleural effusion (0)	246 (47%)	129 (50%)	117 (45%)
Minor pleural effusion (2)	201 (39%)	96 (37%)	105 (40%)
Major pleural effusion (3)	72 (14%)	34 (13%)	38 (15%)
BASELINE ASCITES SCORE			
No ascites (0)	473 (91%)	238 (92%)	235 (91%)
Minor ascites (2)	25 (5%)	14 (5%)	11 (4%)
Significant ascites (3)	21 (4%)	7 (3%)	14 (5%)
Hematocrit (%)	37 ± 6	37 ± 6	37 ± 6
Potassium (mmol/L)	4.2 ± 0.6	4.2 ± 0.6	4.2 ± 0.6
Chloride (mmol/L)	101 ± 5	100 ± 6	101 ± 5
Serum osmolality (mOsm/kg)	298 ± 12	298 ± 13	298 ± 11
Serum urea (mg/dL)	72 (52-100)*	70 (49-100)*	73 (53-99)*
Total protein (g/L)	68 ± 7	68 ± 7	69 ± 7
Albumin (g/L)	39 ± 5	39 ± 5	38 ± 5
Fe (µg/dL)	48 (35-68)*	48 (34-68)*	48 (35-68)*
Ferritin (µg/dL)	115 (63-235)*	111 (60-232)*	116 (65-243)*
Transferrin saturation (%)	14 (9-20)*	14 (9-19)*	14 (9-20)*
LDH (U/L)	272 (228-358)*	276 (232-371)*	268 (222-335)*
Troponin (ng/L)	40 (25-63)*	40 (24-58)*	42 (26-69)*
BNP (pg/mL)	804 (501-1500)*	804 (535-2480)*	951 (402-1500)*
Furosemide	83 (16%)	34 (13%)	46 (18%)
Median dose with P25-P75	40 (40-40)*	40 (40-40)*	40 (40-60)*
Bumetanide	437 (84%)	224 (86%)	212 (82%)
Median dose with P25-P75	2 (1-3)*	2 (1-4)*	2 (1-3)*
Torasemide	3 (0.6%)	1 (0.4%)	2 (0.6%)
Median dose with P25-P75	30 (15- 40)*	30 (30-30)	27.5 (15-40)
Thiazide	34 (7%)	12 (5%)	22 (8%)

OTHER CONCOMITANT MEDICATIONS			
Ivabradine	10 (2%)	4 (2%)	6 (2%)
Hydralazine	9 (2%)	4 (2%)	5 (2%)
Nitrates	28 (5%)	15 (6%)	13 (5%)
Digoxin	34 (7%)	18 (7%)	16 (6%)
Antiplatelet therapy	182 (35%)	92 (36%)	90 (35%)
NOAC/DOAC	275 (53%)	146 (56%)	129 (50%)
VKA	62 (12%)	30 (12%)	32 (12%)
Statin	328 (63%)	168 (65%)	160 (62%)
XO-inhibitor	101 (19%)	54 (21%)	47 (18%)
Amiodarone	119 (23%)	57 (22%)	62 (24%)
Flecainide	7 (1%)	5 (2%)	2 (1%)
EQ5D			
I have no problems in walking about	66 (13%)	33 (13%)	33 (13%)
I have slight problems in walking about	76 (15%)	35 (14%)	41 (16%)
I have moderate problems in walking	138 (27%)	70 (27%)	68 (26%)
I have severe problems in walking	189 (37%)	102 (39%)	87 (34%)
I am unable to walk about	48 (9%)	19 (7%)	29 (11%)
EQ-5D-5L SELF-CARE			
I have no problems washing or dressing myself	180 (35%)	84 (32%)	96 (37%)
I have slight problems washing or dressing myself	90 (17%)	49 (19%)	41 (16%)
I have moderate problems washing or dressing myself	109 (21%)	56 (22%)	53 (21%)
I have severe problems washing or dressing myself	63 (12%)	34 (13%)	29 (11%)
I am unable to wash or dress myself	75 (15%)	36 (14%)	39 (15%)
EQ-5D-5L USUAL ACTIVITIES			
I have no problems doing my usual activities	83 (16%)	37 (14%)	46 (18%)
I have slight problems doing my usual activities	90 (17%)	49 (19%)	41 (16%)
I have moderate problems doing my usual activities	131 (25%)	71 (27%)	60 (23%)
I have severe problems doing my usual activities	111 (22%)	51 (20%)	60 (23%)
	102 (20%)	51 (20%)	51 (20%)

I am unable to do my usual activities			
EQ-5D-5L PAIN DISCOMFORT			
I have no pain or discomfort	197 (38%)	93 (36%)	104 (40%)
I have slight pain or discomfort	102 (20%)	52 (20%)	50 (19%)
I have moderate pain or discomfort	122 (24%)	56 (22%)	66 (26%)
I have severe pain or discomfort	85 (16%)	54 (21%)	31 (12%)
I have extreme pain or discomfort	11 (2%)	4 (1%)	7 (3%)
EQ-5D-5L ANXIETY DEPRESSION			
I am not anxious or depressed	295 (57%)	141 (54%)	154 (60%)
I am slightly anxious or depressed	101 (20%)	51 (20%)	50 (20%)
I am moderately anxious or depressed	72 (14%)	45 (17%)	27 (10%)
I am severely anxious or depressed	36 (7%)	15 (6%)	21 (8%)
I am extremely anxious or depressed	13 (2%)	7 (3%)	6 (2%)
EQ5D health utility index	0.6 (0.4-0.8)*	0.6 (0.3-0.8)*	0.6 (0.4-0.8)*
Health score VAS	52 ± 20	52 ± 19	52 ± 20

CABG: Coronary artery bypass grafting, PTCA: Percutaneous transluminal coronary angioplasty, PAD: Peripheral arterial disease, COPD: Chronic obstructive pulmonary disease, CRT: Cardiac resynchronization therapy, ICD: Implantable cardioverter-defibrillator, VOA: Volume assessment score, Fe: Iron, BNP: B-type natriuretic peptide, VAS: Visual analogue scale.

±: standard deviation

**: Median with P25-P75*

Table S2

Representativeness of Study Participants

Supplementary Table on the Representativeness of Study Participants	
Category	
Condition under investigation	Acute decompensated heart failure with volume overload
Special considerations related to	
- Sex and gender at birth	Heart failure with reduced ejection fraction affects men more often than women with a ratio of 2:1 up to 3:1. Compared to patients with HFrEF, patients with HFpEF are more often women and the characteristics of patients with HFmrEF lay in between.
- Age	The prevalence and incidence of heart failure increases with age, rising to > 10% among patients older than 70 years. The mean age for patients in other acute heart failure trials ranged around 65-70 years, which tends to be higher in registries with a range from 70 to 75 years. Compared to HFrEF, patients with HFpEF are older.
- Race	In the United States, African-Americans and Hispanics are more often diagnosed with heart failure than whites. Differences in incidence were related to differences in comorbidities (arterial hypertension, diabetes mellitus) and socio-economic state. In Belgium, where the study was conducted, > 99% of the population is White.
- Geography	The clinical characteristics vary across the world, with a lower age in Africa and India. The underlying cause of heart failure is diverse within and among world regions. Overall, the mortality and hospitalization rates vary and differences in management depend on several local factors, including financial state and availabilities of medical supply, level of education, health-care organization and tradition.

Other considerations	
Overall representativeness of this trial	The majority of the patients enrolled in ADVOR were men, which is in line with the other acute heart failure trials and registries. At the moment of randomization, the gender at birth was reported, options were male or female. Gender identity was not registered during the study. Patients in the ADVOR trial are older than the patients enrolled in other recent diuretic trials in acute heart failure, but comparable to recent registries from Sweden and UK. Due to advanced therapies and ageing, the age of patients with heart failure increases. However, heart failure patients outside North America and Western Europe are younger, so the age distribution differs from that in some other countries. More than half of the patients had an ejection fraction above 40%, which was considerable higher than in recent diuretic trials. However, around 50% of patients with heart failure have HFpEF. Since patients with HFpEF tends to be older, this may additionally explain the higher age observed in the patients enrolled in ADVOR. The majority of patients enrolled in ADVOR were white, which is expected as the trial was conducted only in Belgium and was comparable to a large registry within the UK. Compared to other acute heart failure trials, the history of atrial fibrillation was higher and patients were less likely to have an ischemic etiology. This difference was most likely caused by the higher rate of patients with a preserved ejection fraction.

Table S3

Worst-Case Sensitivity Analysis for Primary Endpoint

	# Successful decongestion/ # total
Placebo	80/260 (30.77%)
Acetazolamide	108/259 (41.70%)

The primary endpoint could not be assessed in four patients; one in the placebo, and three in the acetazolamide group. A worst case (= successful decongestion achieved in the placebo group and no successful decongestion in the acetazolamide group) sensitivity analysis was performed.

Risk ratio based on the mixed logistic regression model, 1.44; 95% confidence interval, 1.15 to 1.79; p=0.001.

Table S4

SARS-CoV-2 Sensitivity Analysis for Primary Endpoint

Outcome	Placebo	Acetazolamide	Odds-ratio [95%CI]
Primary endpoint			
Pre SARS-CoV-2	35/114 (30.7%)	54/121 (44.6%)	RR 1.52 (1.1 to 2.1)
Since SARS-CoV-2	44/145 (30.3%)	54/135 (40.0%)	RR 1.40 (1.03 to 1.91)
p-value for interaction: 0.7139			

The treatment effect for the primary endpoint is evaluated by means of a generalized linear mixed model, including a fixed treatment effect, a fixed effect for the LVEF stratification factor and random center effect. As a sensitivity analysis, the model will be extended by including a fixed effect (binary) indicating if the endpoint was assessed before or after the first identified SARS-CoV-2 case in Belgium dated 03 February 2020 and the interaction term between this variable and treatment.

Table S5

All Predefined Primary and Secondary Endpoints

Outcome	Placebo	Acetazolamide	Odds-ratio/ GM ratio/HR or absolute difference [95%CI]	P-value
Primary endpoint				
Successful decongestion within 3 days from randomization*	79 (30.5%)	108 (42.2%)	RR 1.46 (1.17 to 1.82)	<0.001
Secondary endpoint				
All-cause mortality and hospitalization for heart failure at 3months	72 (28.0%)	76 (29.7%)	HR 1.06 (0.77 to 1.47)	
All-cause mortality at 3 months	31 (12.1%)	39 (15.2%)	HR 1.26 (0.79 to 2.03)	
Hospitalization for heart failure at 3 months	42 (17.5%)	47 (18.4%)	HR 1.06 (0.70 to 1.59)	
Length of stay (days)	9.9** (9.1-10.8)	8.8** (8.0-9.5)	GM 0.89 (0.81 to 0.98)	
Change EQ5D index at day 4 versus D1	0.117 ± 0.268	0.109 ± 0.264	-0.007 (-0.053 to 0.039)	
Change EQ5D VAS at day 4 versus D1	10.29 ± 17.0	9.4 ± 17.8	-0.87 (-3.92 to 2.18)	
Sensitivity analysis of primary endpoint				
Successful decongestion within 3 days, irrespective of escalation°	86 (33.2%)	115 (44.9%)	RR 1.42 (1.15 to 1.76)	

Exploratory analysis				
Successful decongestion at discharge (for patients alive)•	145 (62.5%)	190 (78.8%)	RR 2.32 (1.13 to 1.43)	

** Successful decongestion, defined as the absence of sings of volume overload within 3 days from randomization without the need for escalation of decongestive therapy.*

° Escalation of decongestive treatment was mandatory if urinary output after 2 days is <3.5 L and the patient was still volume overloaded.

• Patients decongested at discharge

***Geometric Mean (GM)*

HF=heart failure; HR=hazard ratio; RR=relative risk ratio; OR=odds ratio; the widths of confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. Heart failure rehospitalization after 3 months was assessed in a competing risk survival analysis using the Fine and Gray's model taking death as the competing risk.

Table S6

Blood pressure, eGFR, serum creatinine, Na^+, K^+, HCO_3^- at Every Measurement Available During the Treatment Phase

Parameter	D0		D1		D2		D3	
	Placebo	**Acetazolamide**	**Placebo**	**Acetazolamide**	**Placebo**	**Acetazolamide**	**Placebo**	**Acetazolamide**
Systolic blood pressure (mmHg)	127 ± 22	126 ± 20	125 ± 22	115 ± 19	120 ± 22	114 ± 19	120 ± 20	114 ± 19
Diastolic blood pressure (mmHg)	73 ± 13	72 ± 13	69 ± 13	65 ± 15	67 ± 13	64 ± 11	68 ± 12	63 ± 12
eGFR (ml/min/1.73m^2)	38 (29-51)	40 (30-52)	39 (29-53)	38 (28-48)	39 (30-53)	36 (27-47)	39 (29-54)	35 (26-48)
Serum Creatinine (mg/dL)	1.5 (1.2-1.9)	1.5 (1.2-2.0)	1.5 (1.1-1.9)	1.6 (1.3-2.0)	1.5 (1.1-1.9)	1.7 (1.3-2.1)	1.6 (1.2-1.9)	1.7 (1.3-2.2)
Sodium (mmol/L)	140 ± 4	139 ± 4	140 ± 4	140 ± 4	140 ± 4	139 ± 4	140 ± 4	139 ± 4
Potassium (mmol/L)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.6	3.9 ± 0.6	4.0 ± 0.5	3.8 ± 0.5	4.0 ± 0.5	3.9 ± 0.5
Bicarbonate (mmol/L)	26.6 ± 4.2	26.0 ± 4.0	28.2 ± 4.2	26.9 ± 3.7	29.0 ± 4.4	26.0 ± 3.7	29.4 ± 4.6	26.0 ± 3.5

Table S7

Protocol violations

	Number of patients
Eligibility	
(NT-pro) BNP inclusion criterium not met	1
Use of SGLT-2 inhibitor	3
Randomization	
Wrong kit used	3
Treatment Compliance	
SGLT2 inhibitor started during treatment phase	3
Primary Endpoint	
Volume assessment not done after 3 days of diuretic therapy	3

CHAPTER 9

Acetazolamide in Decompensated Heart Failure with Volume Overload trial (ADVOR): Baseline Characteristics

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ABSTRACT

Aims: To describe the baseline characteristics of participants in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial and compare these with other contemporary diuretic trials in acute heart failure (AHF).

Methods and results: ADVOR recruited 519 patients with AHF, clinically evident volume overload, elevated NT-proBNP and maintenance loop diuretics therapy prior to admission. All participants received standardized loop diuretics and were randomized towards once daily intravenous acetazolamide (500 mg) versus placebo, stratified according to study center and left ventricular ejection fraction (LVEF) (≤40% vs. >40%). The primary endpoint was successful decongestion assessed by a dedicated score indicating no more than trace oedema and no other signs of congestion after 3 consecutive days of treatment without need for escalating treatment. Mean age was 78 years, 63% were men, mean LVEF was 43%, and median NT-proBNP 6173 pg/mL. The median clinical congestion score was 4 with an EuroQol-5 dimensions health utility index of 0.6. Patients with LVEF ≤40% were more often male, had more ischemic heart disease, higher levels of NT-proBNP and less atrial fibrillation. Compared with diuretic trials in AHF, patients enrolled in ADVOR were considerably older with higher NT-proBNP levels, reflecting the real-world clinical situation.

Conclusion: ADVOR is the largest randomized diuretic trial in AHF, investigating acetazolamide to improve decongestion on top of standardized loop diuretics. The elderly enrolled population with poor quality of life provides a good representation of the real-world AHF population. The pragmatic design will provide novel insights in the diuretic treatment of patients with AHF.

INTRODUCTION

A high proportion of heart failure (HF) patients experience an episode of acute HF (AHF) during their disease course, often characterized by signs and symptoms of congestion. These episodes are associated with increased morbidity and mortality and are accompanied with a high burden on health-care related costs (137). Current guidelines recommend the use of intravenous loop diuretics to improve symptoms, as a first-line treatment option for all patients with AHF and volume overload, independent of left ventricular ejection fraction (LVEF) (25). Although a recent consensus document on the use of diuretics supports a combinational diuretic therapy as a potential strategy to offset diuretic resistance with accompanying persistent congestion (3,25), many patients are discharged with residual clinical congestion, which is a strong predictor of poor outcome (6). In the Diuretic Optimization Strategies Evaluation (DOSE) study, only 15% of the patients were free from clinical congestion after 72 hours of treatment (138). In the Acute Decompensated Heart Failure National Registry (ADHERE), approximately 20% of the patients were discharged with an increase in body weight (139).

Acetazolamide inhibits sodium reabsorption in the proximal tubules of the nephron and may boost diuretic efficacy when added to loop diuretics thereby facilitating decongestion (81). Both an observational as well as a prospective randomized study demonstrated that the addition of acetazolamide (500mg intravenous) to loop diuretics in patients with AHF enhanced the urinary sodium excretion with approximately 40-100mmol sodium per 40mg furosemide or equivalents use (57,97). In addition, through a ceasing effect on neurohumoral activation, proximal diuretics might effectively reduce plasma volume (36,151,152). The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial investigates whether the addition of acetazolamide on top of standardized (twice home dose) loop diuretics improves decongestion in patients with AHF and clinical signs of volume overload. In this article, we describe the baseline characteristics of patients enrolled in the ADVOR trial and compare them with other contemporary diuretic trials in AHF.

METHODS

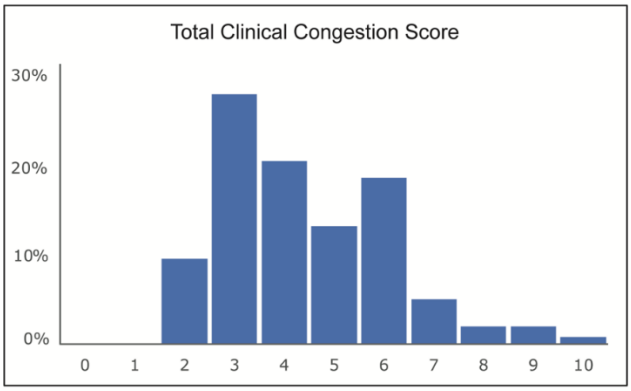
Study design: ADVOR is a pragmatic multicenter, randomized, double-blind, placebo-controlled trial, evaluating the addition of acetazolamide on top of standardized (twice home dose) intravenous loop diuretic therapy in patients with AHF (81). Adults with an elective or emergency hospital admission due to AHF were eligible for enrolment if they had an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 1000 pg/ml or B-type natriuretic peptide (BNP) level > 250 ng/ml, had at least one clinical sign of volume overload (ascites, pleural effusion or oedema) and were on maintenance therapy with at least 40 mg furosemide or equivalents for at least one month (conversion factor 20 mg torsemide = 40 mg furosemide = 1 mg bumetanide) (81). Patients were excluded if they were on acetazolamide maintenance therapy or another proximal nephron acting agent such as a sodium-glucose-linked transporter 2 inhibitor, had a systolic blood pressure < 90 mmHg or an estimated glomerular filtration rate < 20 ml/min/1.73m². Patients were randomized in a 1:1 fashion to loop diuretics in combination with either an intravenous bolus of acetazolamide 500 mg once daily or matching placebo for three consecutive days. Intravenous loop diuretic administration was protocolized as twice the oral home dose, given as a single bolus on the first day and split in two doses on the next two consecutive days. An automated web-based system was used to randomize patients stratified by left ventricular ejection fraction (≤ 40% or > 40%) and study center. The primary endpoint of the ADVOR trial was defined as the rate of successful decongestion on the third morning after randomization (i.e. day 4) without the need for escalating of decongestive therapies for poor loop diuretic efficacy on the morning of day 3. The study was done in accordance with the Declaration of Helsinki and approved by the institutional review board and ethics committees at individual study sites. All patients needed to sign written informed consent prior to inclusion. The details of the study design have been published and the trial is registered at ClinicalTrials.gov (Identifier: NCT03505788) (81).

Clinical congestion score and successful decongestion: The trained investigator had to assess all signs of volume overload and to complete a clinical congestion score every day (Figure 1). This clinical congestion score was based upon the presence or absence and severity of oedema, pleural effusion (to be

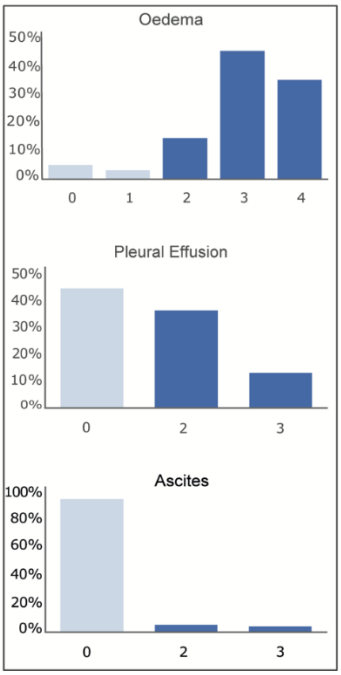
confirmed by chest X-ray or ultrasound) and ascites (to be confirmed by ultrasound). Any patient with a clinical congestion score of ≥ 2, which meant more than trace oedema or the presence of residual pleural effusion or ascites, was considered volume overloaded and diuretic therapy needed to be continued. If the total cumulative urinary output from baseline to the morning of day 3 was less than 3.5 L and persistent clinical congestion was present (congestion score ≥2), escalation of decongestive treatment was mandatory. Successful decongestion was defined as a congestion score ≤1 on the third morning after randomization, without need for escalating treatment because of poor loop diuretic efficacy (81).

Figure 1

Clinical Congestion Score



OEDEMA	No oedema (score 0)	Trace oedema (pitting disappear immediately) (score 1)	Clear pitting oedema (score 2)	Visual deformation above ankle (score 3)	Visual deformation above knee (score 4)
PLEURAL EFFUSION (to be confirmed by chest X-ray or ultrasound if suspected)	No pleural effusion (score 0)	Minor (non-amendable for punction) pleural effusion (score 2)		Major (amendable for punction) pleural effusion (score 3)	
ASCITES (to be confirmed by ultrasound if suspected)	No ascites (score 0)	Minor ascites, only detected by echography (score 2)		Significant ascites (score 3)	



Quality of life: ADVOR also collected EuroQol-5 dimensions (EQ-5D) questionnaires, which is a self-assessed, health-related, quality-of-life questionnaire. The EQ-5D measures quality-of-life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D health utility index ranges from -0.532 (worst health state) to 1 (most optimal health state). (153) EuroQol-Visual Analogue Scale (EQ-VAS) records the patients' self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' (score 100) and 'The worst health you can imagine' (score 0).

Comparison with other acute heart failure trials: The baseline characteristics of the ADVOR trial were compared with the other large randomized diuretic trials enrolling patients with AHF, including DOSE, ATHENA-HF (Aldosterone Targeted Neurohormonal Combined with Natriuresis therapy in Heart Failure), and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) (102,133,138).

Statistical analysis: ADVOR randomized 519 patients. Sample size was calculated based on the results of the DOSE trial, estimating an occurrence of 15% of the primary endpoint in the control group. No reliable data were available for the acetazolamide arm, but a clear meaningful benefit of 10% more congestion was chosen. Considering a type I error rate $\alpha = 0.05$ and a type II error rate $\beta = 0.20$, the target sample size was calculated at 494. A 5% drop-out rate was anticipated, which brings the total sample size to 519. To describe the baseline characteristics, numbers (%) or means ± SD and medians (25th-75th percentile) are given as appropriate. All statistical analyses were done with Statistical Analysis System (SAS) software for Windows, Version 9.4. Copyright ©2016.

RESULTS

Between November 11, 2018 and January 17, 2022, patients were screened for inclusion in 30 sites in Belgium. The first consecutive 519 patients who met in- and exclusion criteria and provided written informed consent were randomized towards acetazolamide or matched placebo.

Baseline characteristics

The ADVOR trial included an elderly population with a mean age of 78 ± 9 years. Most patients were male (63%) with mean LVEF of 43 ± 15% (Table 1). The etiology was ischemic in 45%. Most patients had NYHA functional class III or IV symptoms (87%). Cardiovascular comorbidities were very prevalent. Importantly, the median baseline estimated glomerular filtration rate (eGFR) was 39 ml/min/1.73m² (29-52 ml/min/1.73m²) and 82 % had stage 3 chronic kidney disease or worse (eGFR < 60 ml/min/1.73m²). A CRT and/or ICD device was previously implanted in 19% of all patients and in 36% of the patients with HFrEF. The mean heart rate was 78 ± 18 beats per minute, the mean systolic blood pressure 127 ± 21 mmHg and mean diastolic blood pressure 72 ± 13 mmHg. Patients had significant congestion with median NT-proBNP of 6173 (3068-10896) pg/mL and a clinical congestion score of 4 (3 - 6), which was independent of LVEF (Table 1 and Supplemental figure 1). Oedema was the most important sign of volume overload, with 78% of the patients exhibiting oedema up to the knee or above (score ≥ 3), and 53% had pleural effusion with only 9% having ascites (Supplemental figure 1). The degree of oedema, pleural effusion and ascites at presentation with AHF did not differ between patients with an LVEF ≤ 40% or > 40% (Supplemental figure 1). At baseline, a urinary catheter was used in 51% of the patients.

Table 1 describes the baseline characteristics after stratification for the LVEF ≤ or > 40% (strata used in randomization). Patients with an ejection fraction ≤ 40% were younger, more frequently male, were less likely to have atrial fibrillation or flutter and had more frequently an ischemic etiology. The NT-proBNP was clearly higher in patients with a reduced ejection fraction (9137 [5108-18714] vs. 4393 [2414 – 8124] pg/mL), yet clinical congestion scores were similar (Table 1).

Table 1

Baseline characteristics

	Overall (n=519)	EF ≤ 40% (n=225)	EF > 40% (n=294)
Age (years)	78.2 ± 8.9	76.2 ± 9.5	79.8 ± 8.1
Men	325 (63%)	176 (78%)	149 (51%)
LVEF (%)	43 ± 15	29 ± 8	54 ± 8
Ischemic etiology	232 (45%)	136 (60%)	96 (33%)
Comorbidities			
Previous CABG	123 (24%)	66 (29%)	57 (19%)
Previous valve surgery	91 (18%)	36 (16%)	55 (19%)
Previous PTCA	125 (24%)	82 (36%)	43 (15%)
History of atrial fibrillation or flutter	376 (72%)	145 (64%)	231 (79%)
Stroke	62 (12%)	29 (13%)	33 (11%)
Diabetes	245 (47%)	110 (49%)	135 (46%)
Hypertension	389 (75%)	157 (70%)	232 (79%)
Peripheral arterial disease	101 (19%)	48 (21%)	53 (18%)
Current smoker	48 (9%)	29 (13%)	19 (6%)
COPD	101 (19%)	42 (19%)	59 (20%)
Malignancy	58 (11%)	24 (11%)	34 (12%)
NYHA			
II	66 (13%)	34 (15%)	32 (11%)
III	296 (57%)	127 (57%)	169 (57%)
IV	157 (30%)	64 (28%)	93 (32%)
ICD	79 (15 %)	70 (31%)	9 (3%)
CRT	61 (12%)	46 (20%)	15 (5%)
Weight (kg)	84.8 ± 21.4	85.0 ± 20.2	84.7 ± 22.4
Heart rate (beats/min)	78 ± 18	77 ± 17	79 ± 19
Systolic blood pressure (mmHg)	127 ± 21	123 ± 19	130 ± 22
Clinical congestion score	4 (3 – 6)*	4 (3 – 6)*	4 (3 – 6)*
Serum hemoglobin (g/dL)	11.9 ± 2.0	12.4 ± 1.9	11.5 ± 1.9
Hematocrit (%)	36.6 ± 5.9	38.2 ± 5.7	35.4 ± 5.7
Sodium (mmol/L)	139 ± 4	140 ± 4	139 ± 5
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.6
Chloride (mmol/L)	100.6 ± 5.3	101.3 ± 4.8	100.0 ± 5.7
Bicarbonate (mmol/L)	26.3 ± 4.1	25.6 ± 3.9	26.8 ± 4.1
Serum urea (mg/dL)	72 (52 - 100)*	80 (59 - 109)*	65 (49 - 90)*
Serum creatinine (mg/dL)	1.5 (1.2 - 1.9)*	1.7 (1.3 - 2.1)*	1.4 (1.1 - 1.7)*
eGFR (ml/min/1.73m²)	39 (29 - 52)*	36 (27 - 50)*	42 (31 - 53)*
eGFR <60ml/min/1.73m²	424 (82%)	184 (82%)	240 (82%)

Ferritin (µg/dL)	115 (63 - 235)*	126 (69 - 275)*	101 (60 - 200)*
Troponin (ng/L)	40 (25 - 63)*	46 (31 - 72)*	37 (22 - 59)*
NT-proBNP (pg/mL)	6173 (3068 - 10896)*	9137.0 (5108 - 18714)*	4393 (2414 - 8124)*

COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass graft, CRT: cardiac resynchronization therapy, eGFR: estimated glomerular filtration rate, ICD: implantable cardioverter-defibrillator, LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, NYHA: New York Heart Association, PTCA: percutaneous transluminal coronary angioplasty
Plus-minus values are means ± standard deviation * *Median with P25-P75*

The maintenance therapy of the enrolled patients is described in Table 2. As required for inclusion, all patients were treated with loop diuretics at home, with the majority receiving bumetanide (84%). The median dose of maintenance therapy was 60 mg furosemide or equivalents. Most patients (81%) were treated with beta-blockers. Despite the high frailty and degree of chronic kidney disease, 52% were taking an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or sacubitril/valsartan and 42% were prescribed a mineralocorticoid receptor antagonist (MRA).

In line with the current guidelines for HF, the prescription of neurohormonal inhibitors (ACEi/ARB/ARNI), MRA and beta-blockers was higher in patients with a lower ejection fraction (Supplemental figure 2).

Overall, the median EQ-5D health utility index was 0.6. Activities of daily living and mobility were mostly impaired and fewer self-reported impairments were noted with regards to anxiety/depression (Figure 2). Patients in the ADVOR-trial reported a mean health score of 52 (40-65) out of 100 on the VAS.

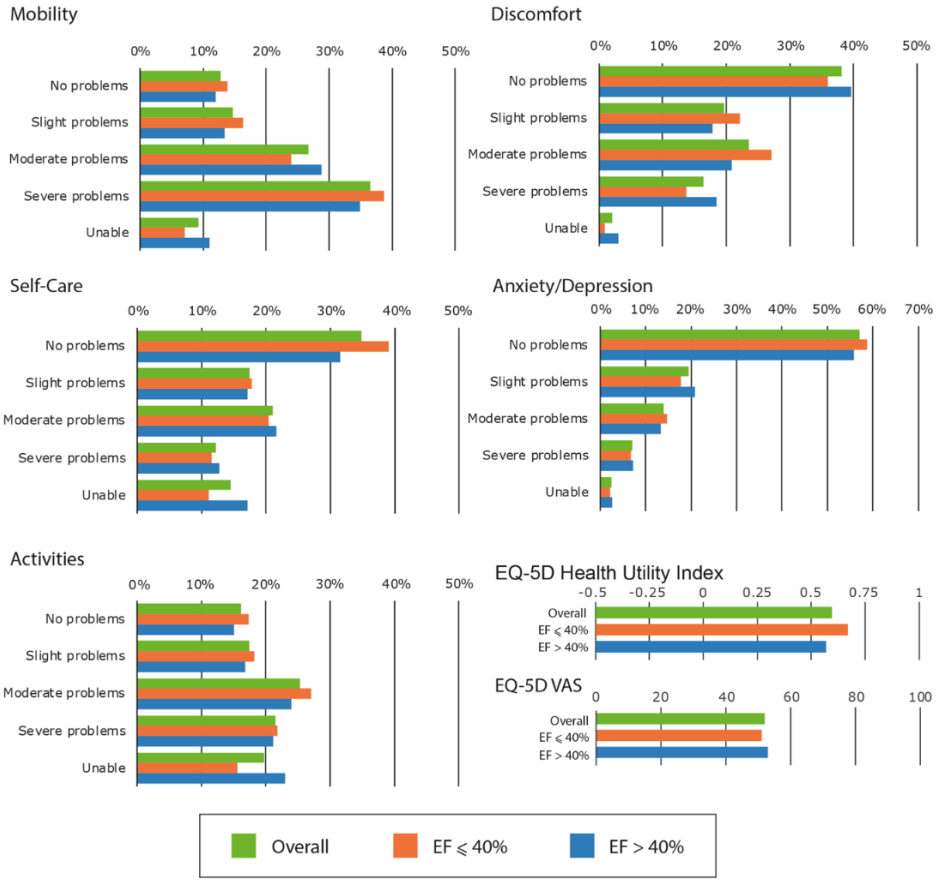
Table 2

Maintenance therapy

	Overall (n=519)	EF ≤ 40% (n=225)	EF > 40% (n=294)
Maintenance dose - furosemide equivalents (mg)	60 (40-100) *	70 (40-100) *	60 (40-120) *
Thiazides	34 (7%)	14 (6%)	20 (7%)
ACEi/ARB/ARNI	270 (52%)	137 (61%)	133 (45%)
ACEi	141 (27%)	57 (25%)	84 (29%)
ARB	53 (10%)	12 (5%)	41 (14%)
ARNI	76 (15%)	68 (30%)	8 (3%)
Beta-blocker	419 (81%)	194 (86%)	225 (77%)
MRA	216 (42%)	112 (50%)	104 (35%)
Ivabradine	10 (2%)	9 (4%)	1 (0.3%)
Hydralazine	9 (2%)	6 (3%)	3 (1%)
Nitrates	28 (5%)	11 (5%)	17 (6%)
Digoxin	34 (7%)	12 (5%)	22 (7%)
Antiplatelets	182 (35%)	91 (40%)	91 (31%)
Anticoagulation	337 (65%)	135 (60%)	202 (69%)
Statin	328 (63%)	155 (69%)	173 (59%)
Amiodarone	119 (23%)	60 (27%)	59 (20%)

ACEi: Angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ARNI: Angiotensin Receptor-Neprilysin Inhibitor, BB: beta-blockers, MRA: Mineralocorticoid receptor antagonist Median with P25-P75*

Figure 2
EQ-5D quality of life according to different domains



Comparison with other acute heart failure trials

ADVOR is the largest randomized diuretic trial performed in patients with AHF. Similar to ADVOR, all the other large diuretic trials included patients across the full range of LVEF. The primary endpoint of ADVOR is focused on effective decongestion, assessed by trained HF physicians who were blinded for treatment allocation and confirmed with technical exam (in case of pleural effusion / ascites). In contrast, the primary endpoints of DOSE, ATHENA-HF and CARRESS-HF were more secondary derivatives of the elimination of residual congestion (change in NT-proBNP, change in weight or visual analogue scale of wellbeing). (Supplemental table 1)

Patients enrolled in ADVOR were older than those in the DOSE, ATHENA-HF and CARRESS-HF (Table 3). Most participants were male in all four trials. The ejection fraction was slightly higher in ADVOR with a lower rate of ischemic HF compared to the others. Comorbidities were equally common with a higher history of atrial fibrillation/flutter in ADVOR. Only ADVOR and DOSE required maintenance therapy with loop diuretics for at least one month prior to enrolment. However, the rate of maintenance therapy with loop diuretics in patients enrolled in ATHENA-HF and CARRESS-HF was also very high (96% and 94%). In ADVOR 52% and 81% of the patients received respectively an ACEi/ARB/ARNI and a beta-blocker, which is similar to the ACEi/ARB and beta-blocker use in the other trials. The prescription of MRA was higher in ADVOR (42%) than in DOSE and CARRESS-HF (respectively 28% and 20%) and obviously higher than ATHENA-HF (11%) as a result of the study design (Figure 3).

Median NT-proBNP levels in ADVOR were considerably higher than in DOSE, ATHENA-HF and CARRESS-HF (Table 3). Overall, the renal function assessed by serum creatinine did not differ between patients enrolled in ADVOR, DOSE and ATHENA-HF, but renal function in CARRESS-HF was worse.

Figure 3

Baseline prescription of guideline-directed medical therapy in ADVOR and other diuretic trials

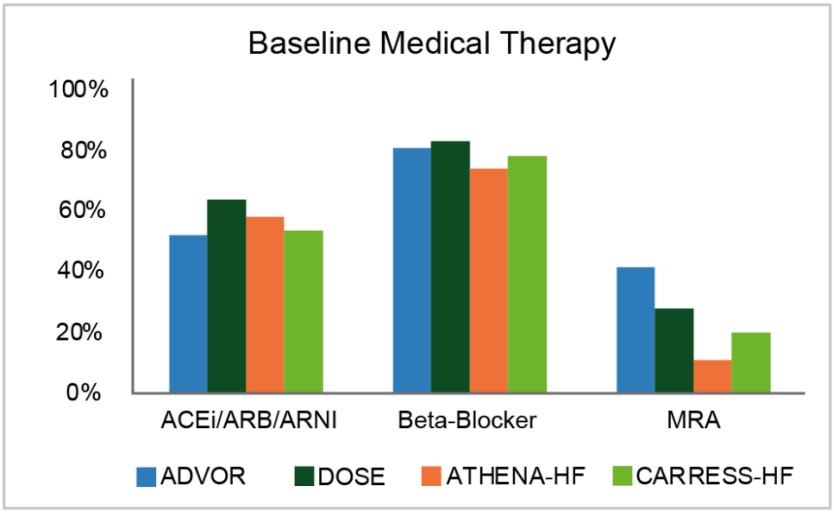


Table 3

Comparison baseline characteristics in diuretic trials in acute heart failure

	ADVOR (n=519)	DOSE (n=308)	ATHENA-HF (n=360)	CARRESS-HF (n=188)
Intervention	Acetazolamide or matched placebo on top of high dose loop diuretics	IV furosemide: - high versus low-dose - continuous versus intermittent bolus	High dose spironolactone (100mg) versus placebo or 25mg spironolactone	Stepped pharmacological therapy versus ultrafiltration
Primary endpoint	Successful decongestion (score < 2)	AUC VAS (wellbeing) and change in serum creatinine	Change in log NT-proBNP levels	Change in serum creatinine level and change in weight
Age (years)	78 ± 9	66	65*	68*
Men (%)	63%	73%	64%	75%
Ejection fraction (%)	43% ± 15	35% ± 18%	34%	37 ± 18%
Proportion EF	LVEF > 40% 57%	LVEF ≥ 50% 27%	LVEF > 45% 27%	
Ischemic etiology (%)	45%	57%	63 %	61%
History of AF or AFl (%)	72%	53%	48%	54%
Diabetes mellitus (%)	47%	51%	41%	66%
ICD (%)	15%	39%	16%	
CRT (%)	12%		16%	
Loop diuretics (%)	100%	100%	96%	94%
Dose of oral furosemide or equivalents (mg/day)	60 (40 - 100)*	131 ± 51.4	80 (40 - 160)*	120 (80 - 160)* versus 120 (80 - 240)*
ACEi/ARB/ARNI (%)	52%	64%	60%	54%
Beta-blocker (%)	81%	83%	74%	78%

MRA (%)	42%	28%	11%	20%
Systolic blood pressure (mmHg)	127 ± 21	119.5 ± 20.0	122 *	
Heart rate (bpm)	78 ± 18	78.5 ± 16.0	79*	
Sodium (mmol/L)	139 ± 4	138 ± 4	140 (138 - 142) *	137 ± 4
Creatinine (mg/dL)	1.5 (1.2 - 1.9) *	1.5 ± 0.5	1.2 *	2.09 (1.71 - 2.65)* versus 1.90 (1.57 - 2.37)*
eGFR (ml/min/1.73m²)	39 (29 - 52)*		55 (46 – 71)* versus 58 (45 – 75) *	
NT-proBNP (pg/ml)	6173 (3068-10896) *	3790 (1890 – 8781) *	4176 (1936 - 7456) * versus 4028 (2472 – 10048) *	4007 (1128 - 8534)* versus 5013 (2310 - 10381)*

DISCUSSION

ADVOR is to date the largest randomized diuretic trial performed in patients with AHF. The pragmatic set-up of the ADVOR-trial enabled an enrolment of patients representing daily clinical practice, which is evident by the high degree of congestion, the advanced age and frequent comorbidities, as well as the expected distribution of patients according to the LVEF. Compared to other randomized diuretic trials, ADVOR enrolled a more elderly population with significant congestion as evidenced by high NT-proBNP levels (6173 pg/mL) and congestion score, which corresponds to the patient profile observed in clinical practice. Signs and symptoms of congestion could not distinguish patients with reduced and preserved ejection fraction (Supplemental figure). ADVOR is designed to determine if the addition of acetazolamide, a proximal working diuretic agent, on top of standardized (twice home dose) loop diuretics will lead to more effective and efficient decongestion in those patients. Importantly, achieving decongestion has a class I recommendation of the ESC Guidelines for the diagnosis and treatment of acute and chronic HF (4). As such, the results of ADVOR are extremely important because registry and clinical trial data report that only a minority of AHF patients are discharged without residual congestion (138,139).

Compared to other diuretic trials, patients in ADVOR had higher levels of NT-proBNP (102,133). Moreover, all patients had unequivocal clinical signs of severe volume overload, reflected in the clinical congestion score (78% of patients had > grade 2 oedema and 53% had pleural effusion) and the overall very high levels of NT-proBNP. The average age of 78 years is clearly older than the patients enrolled in DOSE, ATHENA-HF and CARRESS-HF, where the mean age was around 65 years and even older than in large AHF registries (139,142–146,154). The most recent large registries, i.e. the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT-R) (145) and the GREAT registry (143), had both a median age of 71 years. However, clinical trials and registries, mainly done in cardiology wards, do not always represent the real-world population encountered in daily clinical practice (155). Patients in a recent cohort study in the Belgian primary care setting (2) and a large population-based study in the United Kingdom (156), representing a less selected population, had a comparable age as the ADVOR trial. This was confirmed in a Swedish Heart Failure Registry (SwedeHF)

(157) and in a retrospective observational study in the United States in which the mean age was approximately 77 years for patients with stable chronic HF and 78 years for patients with a worsening heart failure event (158). A prospective observational trial, conducted in 4041 patients admitting with AHF in Japan without any exclusion criteria, demonstrated an even higher median age of 80 years (159). Therefore, patients in ADVOR are very similar as those seen in real-world clinical practice. This makes ADVOR the largest and first diuretic trial in AHF for which the results will be more representative for the global HF population including all age categories.

While the presence of comorbidities was similar between all diuretic trials, the study design of CARRESS-HF required worsening renal function as inclusion criteria, which subsequently explains the worse kidney function observed in CARRESS-HF. However, 82% of patients included in ADVOR had chronic kidney disease defined as an eGFR < 60 ml/min/1.73m^2. The prognostic impact of any reduction in eGFR is well-established in HF and therefore the population included in ADVOR is at very high risk for adverse events (160–162).

Additionally, on top of length of hospital stay, HF hospitalization and all-cause mortality, ADVOR will also report on a self-reported quality-of-life score as secondary endpoint. A consensus paper of the ESC emphasizes the importance of gaining insight into the patients' experience and perspective (163). This is even more important in an elderly patient population with many co-morbidities in which quality-of-life might be as important as longevity. Moreover, an inverse association between the self-assessed quality-of-life score and all-cause mortality and HF hospitalizations has been reported (164). The EQ-5D of the patients in the ADVOR-trial was considerably lower than the average EQ-5D for the Belgian population (153). As expected in patients with a high congestion score and in an elderly population, patients enrolled in ADVOR reported mostly problems with mobility and daily activities. However, the majority denied any moderate or major problems with self-care or anxiety / depression. In the ADVOR-trial, the self-reported visual analogue scale scored a mean of only 52 out of 100, which was comparable between patients with an ejection fraction ≤ and > 40% but clearly lower than the average for the Belgian population of 77.1 (153).

Randomization towards acetazolamide or matched placebo was stratified based on ejection fraction below or above 40%, which enables an equally representation of both groups in the intervention and placebo group. Overall, baseline clinical characteristics were similar between the two prespecified groups of ejection fraction in ADVOR with the exception of a higher level of NT-proBNP and less history of atrial fibrillation or flutter in the LVEF ≤ 40% group, which is reflected in the slightly lower prescription of DOACs. This difference in natriuretic peptides between patients with HFrEF and HFpEF has been described in both AHF and chronic HF (165–167). In patients with HFrEF, the eccentric remodeling is associated with a higher increase in wall stress compared to the concentric remodeling in patients with HFpEF. As the release of natriuretic peptides depends on the degree of wall stress, this will be higher in patients with HFrEF than with HFpEF (168). As the clinical congestion score was similar between both groups, the difference in NT-proBNP in our cohort probably reflects different pathophysiological processes rather than a difference in clinical volume overload.

A particularly important consideration in any HF trial is the adequacy of background treatment. Overall, there was a high prescription of medical HF therapy in ADVOR, in line with current HF guidelines with a higher degree in the group with the lower ejection fraction. The prescription of ACEi/ARB is lower in ADVOR than in other diuretic trials, but comparable when adjusted for ARNI use. The use of beta-blocker was comparable to DOSE, ATHENA-HF and CARRESS-HF, however the use of MRA was obviously higher. ADVOR represents a vulnerable patient population that despite baseline medical therapy is still at a very high risk for decompensation. ADVOR allowed a broad inclusion for all AHF patients with signs of volume overload and maintenance therapy with at least 40mg furosemide or equivalents for at least one month.

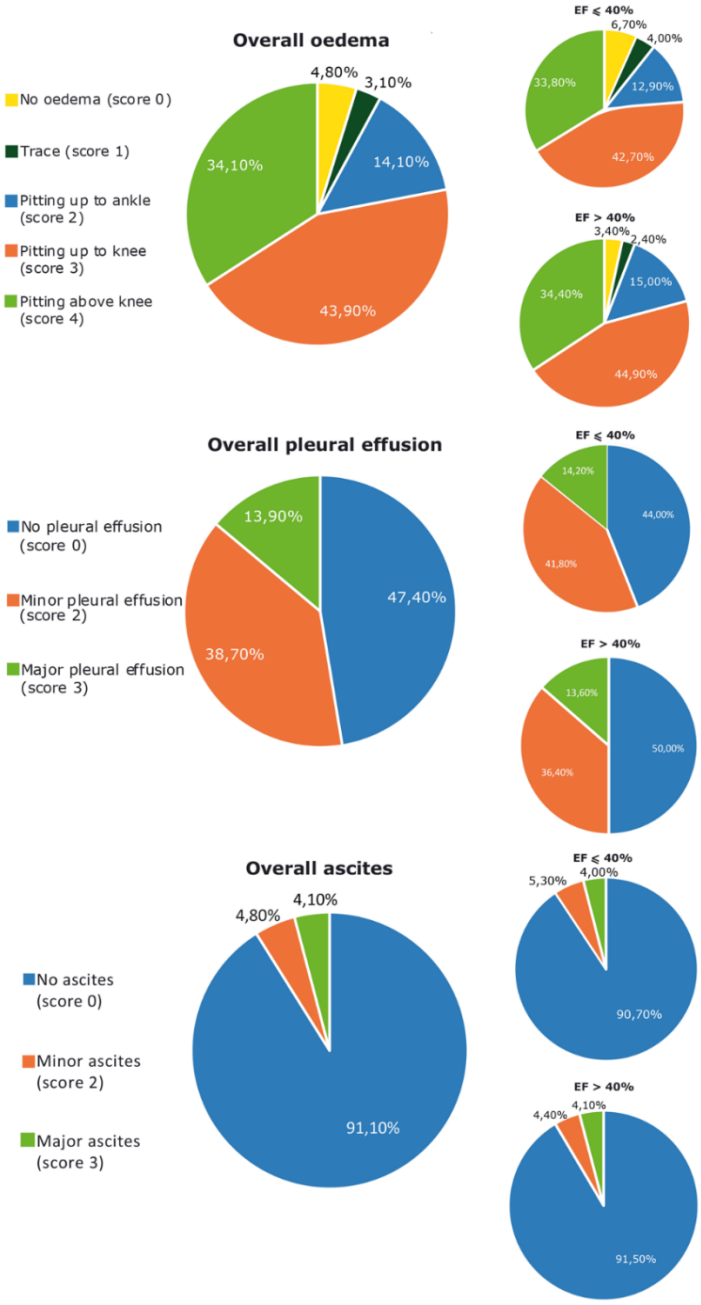
CONCLUSION

ADVOR is a multicenter, double-blinded, placebo-controlled randomized trial and is the largest diuretic trial in AHF performed to date. The higher age of the study population is more reflective of a real-world HF population than previous diuretic trials in AHF. Furthermore, despite adequate maintenance therapy, patients were severely congested, with pronounced clinical signs of volume overload and elevated levels of natriuretic peptides. As such, the results of ADVOR will provide contemporary and novel insights in the diuretic treatment of patients with AHF and fluid overload.

SUPPLEMENTAL MATERIAL

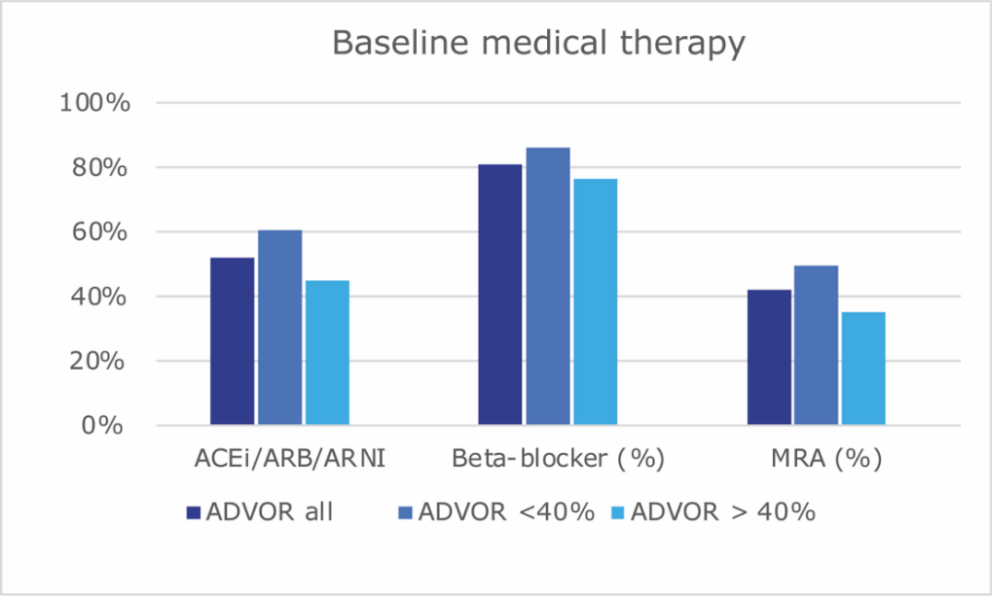
Supplemental figure 1

Baseline clinical congestion score



Supplemental figure 2

Baseline heart failure medication according to LVEF



Supplemental table 1

Study design of diuretic trials in AHF

	ADVOR	DOSE	ATHENA-HF	CARRESS-HF
Number	519	308	360	188
LVEF	All	All	All	All
Inclusion	AHF with signs of volume overload and NTproBNP >1000pg/ml or BNP > 250 ng/ml	AHF with signs and symptoms of volume overload	AHF with signs and symptoms and NT-proBNP >1000pg/ml	AHF with signs and symptoms, worsening renal function and persistent congestion
Maintenance diuretics	minimum 40mg furosemide or equivalents >1month	80-240mg furosemide or equivalents >1month	no or low-dose (12.5-25mg) spironolactone	no required
Intervention	Acetazolamide or matched placebo on top of high dose loop diuretics	IV furosemide: - high versus low-dose - continuous versus intermittent bolus	High dose spironolactone (100mg) versus placebo or 25mg spironolactone	Stepped pharmacological therapy versus ultrafiltration
Primary endpoint	Successful decongestion (score <2)	AUC VAS (wellbeing) and change in serum creatinine	Change in log NT-proBNP levels	Change in serum creatinine level and change in weight
Timing primary endpoint	Third morning after hospitalisation	72 hours	96 hours	96 hours
Cr/eGFR exclusion	eGFR <20ml/min/1.73m²	Serum creatinine >3.0mg/dL	eGFR <30ml/min/1.73m²	Serum creatinine >3.5mg/dL

AHF: acute heart failure, AUC: area under the curve, IV: intravenous, Cr: serum creatinine, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, VAS: visual analogue scale.

CHAPTER 10

Renal function and decongestion with acetazolamide in acute decompensated heart failure: the ADVOR trial

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ABSTRACT

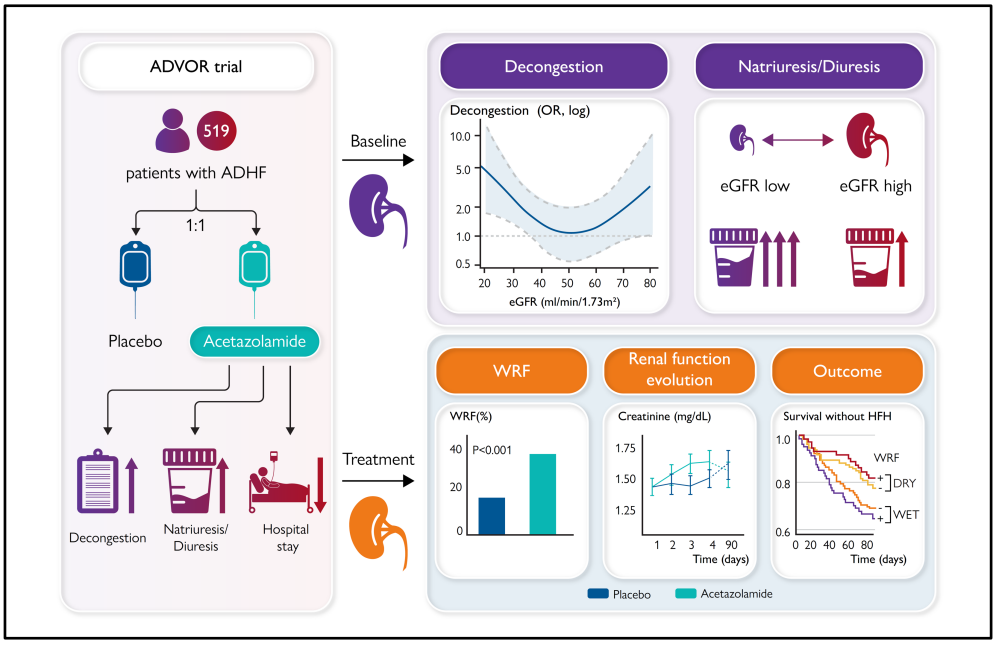
Background and aims: In the ADVOR trial, acetazolamide improved decongestion in acute decompensated heart failure (ADHF). Whether the beneficial effects of acetazolamide are consistent across the entire range of renal function remains unclear.

Methods: This is a prespecified analysis of the ADVOR trial that randomized 519 patients with ADHF to intravenous acetazolamide or matching placebo on top of intravenous loop diuretics. The main endpoints of decongestion, diuresis, natriuresis and clinical outcomes are assessed according to baseline renal function. Changes in renal function are evaluated between treatment arms.

Results: On admission, median estimated glomerular filtration (eGFR) was 40 (30-52) mL/min/1.73m². Acetazolamide consistently increased the likelihood of decongestion across the entire spectrum of eGFR (p-interaction=0.977). Overall, natriuresis and diuresis was higher with acetazolamide, with a higher treatment effect for patients with low eGFR (both p-interaction<0.007). Acetazolamide was associated with a higher incidence of worsening renal function (WRF) (rise in creatinine ≥0.3mg/dL) during the treatment period (40.5% vs. 18.9%; p<0.001), but there was no difference in creatinine after 3 months (p=0.565). This was not associated with a higher incidence of heart failure hospitalizations and mortality (p-interaction=0.467). However, decongestion at discharge was associated with a lower incidence of adverse clinical outcomes irrespective of the onset of WRF (p-interaction=0.805).

Conclusion: Acetazolamide is associated with a higher rate of successful decongestion across the entire range of renal function with more pronounced effects regarding natriuresis and diuresis in patients with a lower eGFR. While WRF occurred more frequently with acetazolamide, this was not associated with adverse clinical outcomes.

GRAPHICAL ABSTRACT



INTRODUCTION

Almost 50% of patients with heart failure have chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, which is associated with an impaired diuretic response. Consequently, achieving decongestion in such patients becomes a more arduous task. (160,169) In addition, worsening renal function (WRF), assessed by an increase in serum creatinine, is reported in up to 20-40% of the patients with acute decompensated heart failure (ADHF) (9,169). Although highly prevalent, few trials have investigated diuretic strategies in patients with impaired renal function (170).

In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, a stepped diuretic protocol was as effective as ultrafiltration in achieving decongestion in patients with WRF and persistent congestion. (133) The stepped diuretic protocol used high doses of loop diuretics with association of thiazides in case of insufficient diuretic response. Recent trials such as the Combining Loop with Thiazide Diuretics for Decompensated Heart Failure (CLOROTIC) and the Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) have focused on an upfront strategy of combinational diuretics assessing the impact on decongestive response in comparison to a loop diuretic only strategy (38,93).

In the ADVOR trial, in which 82% of the patients had CKD (140), the addition of intravenous acetazolamide to standardized intravenous loop diuretics improved diuretic efficacy in patients with ADHF and volume overload, resulting in a higher incidence of successful decongestion and shorter hospital stay (38). Whether the effects of acetazolamide observed in the ADVOR trial are consistent across the entire range of baseline renal function remains unclear. In addition, limited information is available about the impact of acetazolamide on renal function and the potential prognostic meaning of these treatment-induced alterations. Therefore, a prespecified subanalysis addressing these questions was conducted.

METHODS

Study design

The methods and results of the ADVOR trial (NCT03505788) have been published previously (81,140). Patients admitted for ADHF were eligible for inclusion if they had at least one clinical sign of volume overload (i.e., ascites, pleural effusion, or oedema), elevated natriuretic peptides (NT-proBNP > 1000 pg/mL or BNP > 250 pg/mL), and oral maintenance therapy with at least 40 mg of furosemide (or equivalent dose) for at least one month. Main exclusion criteria were acetazolamide maintenance therapy before randomization, treatment with sodium-glucose-linked transporter 2 (SGLT2) inhibitors, a systolic blood pressure <90 mmHg, or an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73m². Participants were randomly assigned in a 1:1 fashion to treatment with an intravenous bolus of acetazolamide (500 mg once daily) or matching placebo in addition to standardized intravenous loop diuretic therapy (twice oral home dose daily) upon randomization and during the next 2 days. The study complied with principles outlined in the Declaration of Helsinki and was approved by all local ethic committees from participating centers. All participants provided written informed consent.

Endpoints

The primary endpoint of the ADVOR trial was defined as successful decongestion on the third morning after randomization without the need for escalation of decongestive therapies due to poor loop diuretic efficacy (defined as total urinary output below 3.5 L on the second morning after randomization). Successful decongestion was defined as the absence of signs of volume overload (no pleural effusion, no ascites and not more than trace oedema). Key secondary endpoints were the length of index hospital stay, cumulative diuresis (ml) and natriuresis (mmol) during the first 2 days after randomization and the composite endpoint of first occurrence of death from any cause or rehospitalization for heart failure during a 3-month follow-up period.

Renal function assessment

Serum creatinine was measured by the local hospital's laboratories and reported through the clinical report forms. Blood samples including creatinine levels were collected per protocol at randomization (baseline=day 1), day 2, day 3, day 4 and after 3 months. The eGFR (according to the CKD-EPI formula, expressed as mL/min/1.73m^2) reported by local labs at the sites was used in this analysis. (171)

Statistical analysis

Baseline characteristics are summarized as means and standard deviations, medians and 25-75th percentile, or numbers and percentages and evaluated using ANOVA, Kruskal-Wallis and chi-square tests as appropriate. The primary and secondary (binary) endpoints were evaluated using a generalized linear mixed model (logit binomial model) which included a fixed treatment effect and random intercept to calculate odds ratios and 95% confidence intervals. For interaction analysis with baseline eGFR, eGFR was entered into the model as a fixed effect interaction term with treatment allocation. This was done with eGFR both as a categorical variable (eGFR above and below the median) and according to KDIGO classification (172) and on a continuous scale, using restricted cubic splines. Continuous endpoints (urine output, natriuresis and length of stay) were assessed using a similar generalized linear mixed regression model. The models were performed unadjusted and adjusted for baseline differences with p-value < 0.05 between patients with an eGFR $\leq$ and > 40ml/min/1.73m^2, i.e. age, heart rate, diastolic blood pressure, oedema score, home maintenance dose of furosemide (ln transformed), NT-proBNP (ln transformed), serum hemoglobin, potassium, troponin T (ln transformed). Longitudinal changes in serum creatinine level according to treatment allocation were assessed using a linear mixed-effects models with repeated measurements over time including fixed treatment effect, time and its interaction and including also a random intercept. No imputation for missing data was performed as this was generally low (below 5%) for the in-hospital treatment period. WRF was defined as an increase in serum creatinine of at least 0.3mg/dL at any point during the treatment phase (i.e. first 4 days). A sensitivity analysis with a relative increase in serum creatinine of 25% was performed as comparison. (173) Predictors of WRF were assessed using binomial logistic regression models. Variables with a p-value below 0.05 were included in

a multivariable model. The combined endpoint of all-cause mortality and heart failure rehospitalization after 3 months was assessed in a time-to-event analysis using a Cox proportional hazard model including the occurrence of WRF and the occurrence of WRF in relation to clinical congestion state. Interaction between WRF and congestion state was evaluated with a generalized linear mixed model. No adjustments for multiplicity were performed, so all reported p-values are exploratory. All the hypotheses testing was 2-sided with a significance level of α=0.05. All statistical analyses were done using SPSS version 28.

RESULTS

Baseline characteristics

In total, 519 patients were included in the ADVOR trial and renal function was available in all patients at baseline. The median serum creatinine was 1.49 (1.17-1.94) mg/dL with a median estimated glomerular filtration rate (eGFR) of 40 (30-52; range 13-118) ml/min/1.73m^2. The distribution of renal function, including the proportion of patients with eGFR ≤ and > 40 mL/min/1.73m^2 or KDIGO class, was well balanced between the two treatment groups (Figure 1 panel A respectively panel B). Table 1 illustrates the baseline features of patients with eGFR ≤ and > 40 mL/min/1.73m². Of note, patients with an eGFR ≤ 40 mL/min/1.73m^2 were more likely to be older, had a higher home maintenance dose of loop diuretics and a higher baseline level of natriuretic peptides. Overall, the ejection fraction, NYHA class, total congestion score and prescription rate of guideline-directed medical therapy did not differ between patients with an eGFR ≤ and > 40 mL/min/1.73m^2.

Treatment effect of acetazolamide according to baseline renal function

The treatment effect of acetazolamide for the different endpoints according to the baseline eGFR are shown in Table 2. The primary endpoint of successful decongestion after three days was higher in patients treated with acetazolamide (odds ratio [OR] = 1.97; 95% confidence interval [CI] [1.29-3.02]; p-value=0.002) when adjusted for baseline differences between patients with low vs. high baseline eGFR. Baseline eGFR did not modify the treatment effect of acetazolamide on the primary endpoint for high vs. low eGFR (p-interaction =

0.672) or over the entire range of eGFR as a continuous variable (p-interaction=0.977) (Figure 2). There was also no difference in the treatment effect when baseline eGFR was evaluated according to the KDIGO categories (p-interaction=0.852) (Supplemental table 1). The secondary combined endpoint of all-cause mortality and heart failure hospitalizations after 90-days did not differ between the placebo and the acetazolamide group. In an analysis adjusted for baseline differences, there was no significant treatment interaction between patients with a high vs. low baseline eGFR (p-interaction=0.636, Table 2). There was also no treatment interaction for the individual endpoints of all-cause mortality (p-interaction=0.553) or heart failure hospitalizations (p-interaction=0.439, Table 2). Treatment with acetazolamide reduced length of hospital stay compared with the placebo group (geometric mean: 8.7 ± 1.7 days vs 9.8 ± 1.8 days; geometric mean ratio = 1.14; 95% CI [1.03-1.26]; p-value=0.009), and this effect was not modified by low vs. high baseline eGFR (p-interaction=0.684). When assessed according to baseline KDIGO categories, there was no significant treatment interaction with regards to the combined (p-interaction=0.613, Supplemental table 1) or individual end points of all-cause mortality and heart failure hospitalizations (respectively, p-interaction=0.474 and p-interaction=0.296; Supplemental table 1). All aforementioned results were similar in unadjusted analyses (Supplemental table 2).

Table 1

Baseline characteristics of patients with an estimated glomerular filtration rate (eGFR) ≤ and > 40 ml/min/1.73m²

	Total (n=519)	eGFR ≤40ml/min/ 1.73m² (n=265)	eGFR >40ml/min /1.73m² (n=254)	P-value
Acetazolamide	259 (49.9%)	129 (48.7%)	130 (51.2%)	0.599
Age (years)	78 ± 9	80 ± 8	77 ± 10	**<0.001**
Female	194 (37.4%)	109 (41.1%)	85 (33.5%)	0.085
Heart rate (bpm)	78 ± 18	76 ± 19	80 ± 18	**0.036**
Systolic BP (mmHg)	127 ± 21	126 ± 21	127 ± 20	0.617
Diastolic BP (mmHg)	72 ± 13	70 ± 13	74 ± 13	**0.001**
Weight (kg)	84.8 ± 21.4	83.3 ± 20.6	86.4 ± 22.1	0.099
Congestion score	4 (3-6)	4 (3-6)	4 (3-6)	0.630
Components of congestion				
Edema				**0.019**
0	25 (4.8%)	16 (6.0%)	9 (3.5%)	
1	16 (3.1%)	2 (0.8%)	14 (5.5%)	
2	73 (14.1%)	35 (13.2%)	38 (15.0%)	
3	228 (43.9%)	119 (44.9%)	109 (42.9%)	
4	117 (34.1%)	93 (35.1%)	84 (33.1%)	
Pleural effusion				0.442
0	246 (47.5%)	124 (47.0%)	122 (48.0%)	
2	201 (38.8%)	108 (40.9%)	93 (36.6%)	
3	71 (13.7%)	32 (12.1%)	39 (15.4%)	
Ascites				0.841
0	473 (91.1%)	241 (90.9%)	232 (91.3%)	
2	25 (4.8%)	14 (5.3%)	11 (4.3%)	
3	21 (4.0%)	10 (3.8%)	11 (4.3%)	
Home maintenance dose of furosemide (mg)	60 (40-100)	80 (40-132.2)	40 (40-100)	**<0.001**
LVEF (%)	43 ± 18	42 ± 17	44 ±15	0.129
NT-proBNP (pg/mL)	6134 (3034-10765)	7386 (3883-14417)	4435 (2517-8907)	**<0.001**
NYHA class				0.233
II	66 (12.7%)	40 (15.1%)	26 (10.2%)	
III	296 (57.0%)	145 (54.7%)	151 (59.5%)	
IV	157 (30.3%)	80 (30.2%)	77 (30.3%)	
Ischemic cause	232 (44.7%)	123 (46.4%)	109 (42.9%)	0.428
Hemoglobin (g/dL)	11.9 ± 2.0	11.7 ± 1.9	12.1 ± 2.1	**0.015**
Sodium (mmol/L)	139.5 ± 4.3	139.7 ± 4.0	139.2 ± 4.6	0.265
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	4.1 ± 0.6	**<0.001**

Serum creatinine (mg/dL)	1.49 (1.17-1.94)	1.92 (1.64-2.215)	1.17 (1.00-1.40)	**<0.001**
eGFR (mL/min/1.73m²)	40 (30-52)	30 (25-34)	54 (45-67)	**<0.001**
Troponin T	40.0 (24.6-63.3)	45.0 (28.5-71.9)	35.3 (22.0-54.5)	**<0.001**
Coexisting conditions				
Atrial fibrillation	376 (72.4%)	193 (72.8%)	183 (72.0%)	0.845
Diabetes	245 (47.2%)	134 (50.6%)	111 (43.7%)	0.135
Hypertension	389 (75.0%)	199 (75.1%)	190 (74.8%)	1.000
Peripheral artery disease	101 (19.5%)	55 (20.8%)	46 (18.1%)	0.506
Treatment				
ACEi, ARB, or ARNI	269 (51.8%)	136 (51.3%)	133 (52.4%)	0.861
Beta blocker	419 (80.7%)	221 (83.4%)	198 (78.0%)	0.121
MRA	216 (41.6%)	115 (43.4%)	101 (39.8%)	0.423

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Figure 1

Distribution eGFR per treatment category; continuous (A) and KDIGO classification (B)

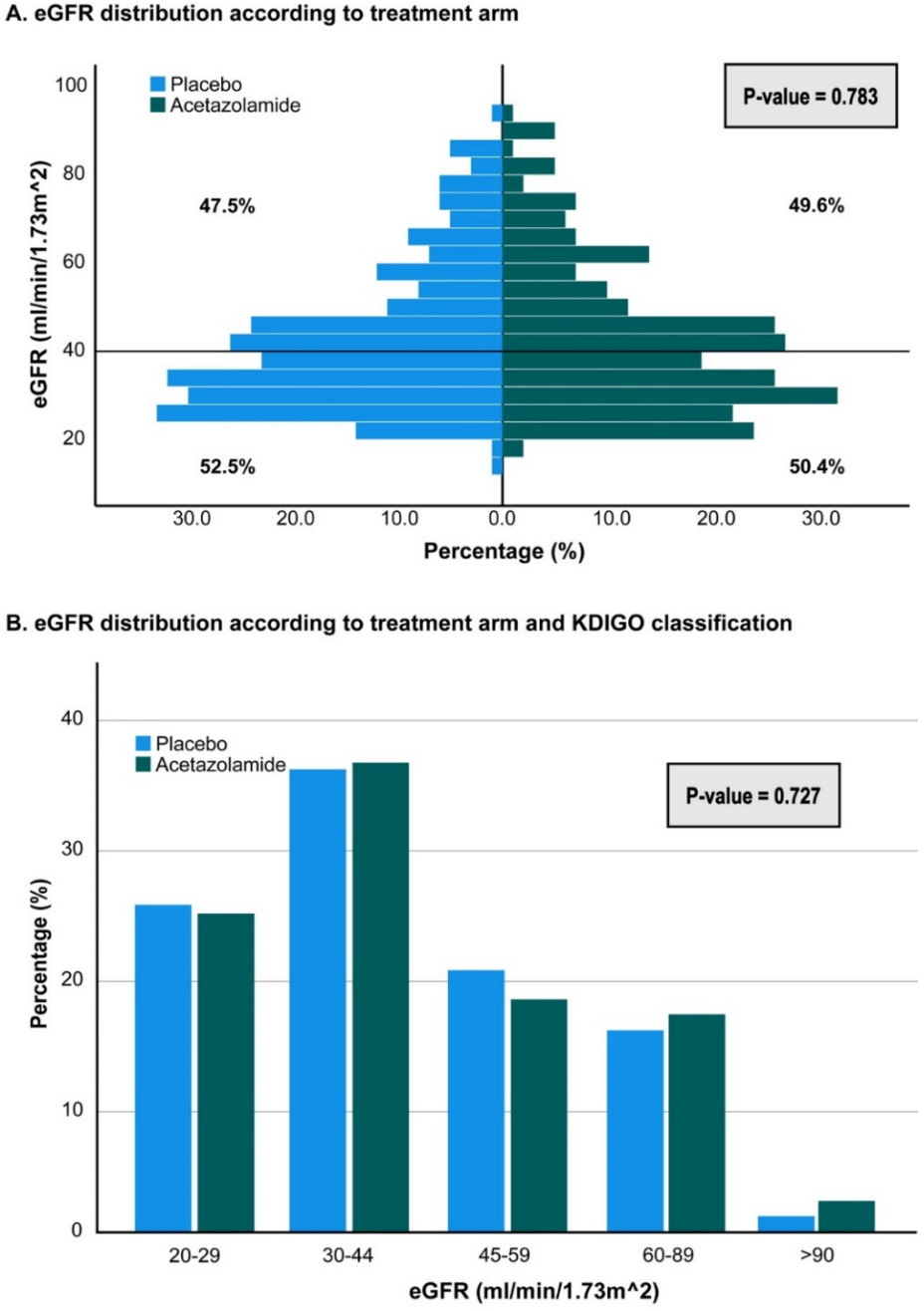


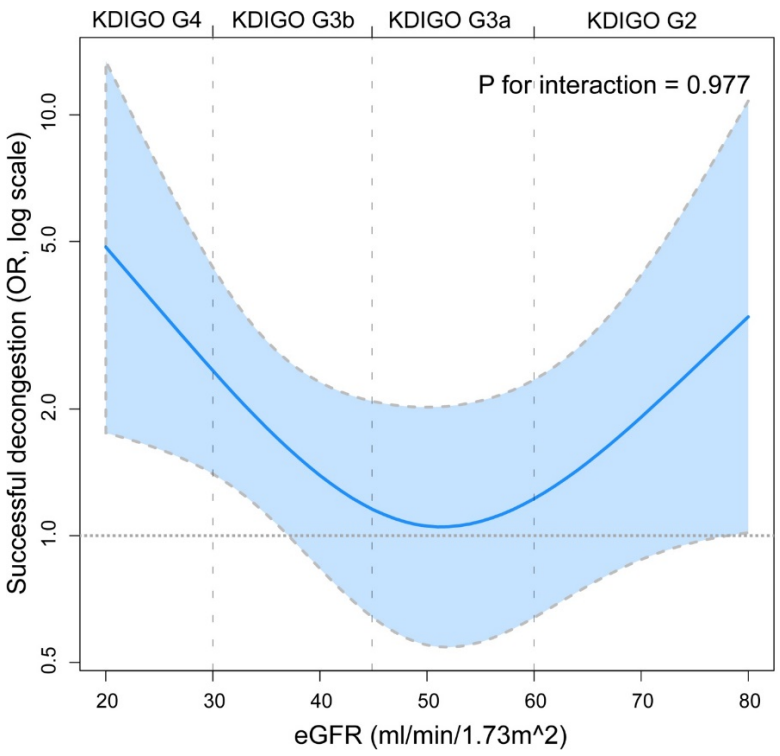
Table 2

Treatment effect of acetazolamide according to median eGFR

Parameter	Placebo n (%)	Acetazolamide n (%)	Adjusted OR/HR (95% CI)	P-value	*P-interaction
Primary endpoint (OR)					
Overall	79/259 (30.5%)	108/256 (42.2%)	1.97 (1.29-3.02)	0.002	
eGFR ≤ 40 ml/min/1.73m^2	34/136 (25.0%)	54/129 (41.9%)	2.32 (1.27-4.24)		0.672
eGFR > 40 ml/min/1.73m^2	45/123 (36.6%)	54/127 (42.5%)	1.79 (0.97-3.30)		
Primary endpoint with or without need for escalation (OR)					
Overall	86/259 (33.2%)	115/256 (44.9%)	2.01 (1.31-3.08)	0.001	
eGFR ≤ 40 ml/min/1.73m^2	41/136 (30.1%)	57/129 (44.2%)	2.04 (1.12-3.73)		0.994
eGFR > 40 ml/min/1.73m^2	45/123 (36.6%)	58/127 (45.7%)	2.08 (1.11-3.89)		
Complete decongestion at discharge (OR)					
Overall	145/250 (58.0%)	190/252 (75.4%)	2.37 (1.54-3.65)	<0.001	
eGFR ≤ 40 ml/min/1.73m^2	77/132 (58.3%)	91/127 (71.7%)	1.88 (1.02-3.45)		0.467
eGFR > 40 ml/min/1.73m^2	68/118 (57.6%)	99/125 (79.2%)	3.00 (1.56-5.77)		
All-cause mortality and heart failure hospitalization (HR)					
Overall	72/259 (27.8%)	76/256 (29.7%)	1.09 (0.78-1.54)	0.618	
eGFR ≤ 40 ml/min/1.73m^2	43/136 (31.6%)	47/129 (36.4%)	1.17 (0.75-1.83)		0.636
eGFR > 40 ml/min/1.73m^2	29/123 (23.6%)	29/127 (22.8%)	0.99 (0.96-1.02)		
All-cause mortality (HR)					
Overall	31/259 (12.0%)	39/256 (15.2%)	1.36 (0.82-2.24)	0.230	
eGFR ≤ 40 ml/min/1.73m^2	18/136 (13.2%)	24/129 (18.6%)	1.45 (0.74-2.83)		0.553
eGFR > 40 ml/min/1.73m^2	13/123 (10.6%)	15/127 (11.8%)	1.51 (0.67-3.40)		
Heart failure hospitalization (HR)					
Overall	45/259 (17.4%)	47/256 (18.4%)	1.09 (0.71-1.69)	0.684	
eGFR ≤ 40 ml/min/1.73m^2	25/136 (18.4%)	29/129 (22.5%)	0.98 (0.95-1.02)		0.439
eGFR > 40 ml/min/1.73m^2	20/123 (16.3%)	18/127 (14.2%)	1.00 (0.50-2.00)		

Figure 2

Treatment effect of acetazolamide on decongestion (primary endpoint) across eGFR

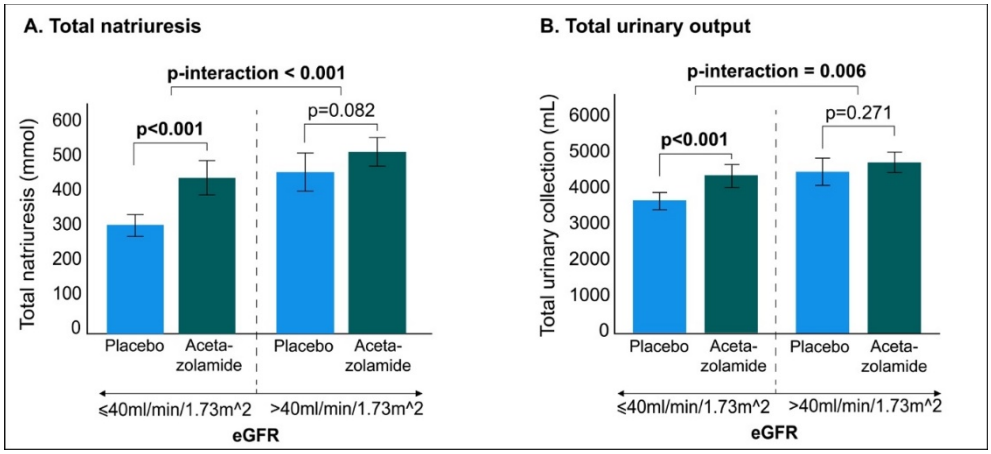


Effect of the renal function on treatment effect for natriuresis and diuresis

Overall, acetazolamide resulted in more diuresis (4572 ± 1725 mL versus 4069 ± 1806 mL; p-value=0.001) and natriuresis (468 ± 234 mmol vs. 369 ± 231 mmol; p-value<0.001) after 2 days compared with placebo. Although acetazolamide was associated with a higher natriuresis and diuresis in both low and high baseline eGFR, the treatment effect of acetazolamide was more pronounced in patients with low baseline eGFR for both diuresis (p-interaction=0.006) and natriuresis (p-interaction <0.001) (Figure 3 and Supplemental table 3).

Figure 3

Relationship between baseline eGFR – natriuresis/urinary output and treatment arm after 2 days



Change in renal function over time according to treatment arm

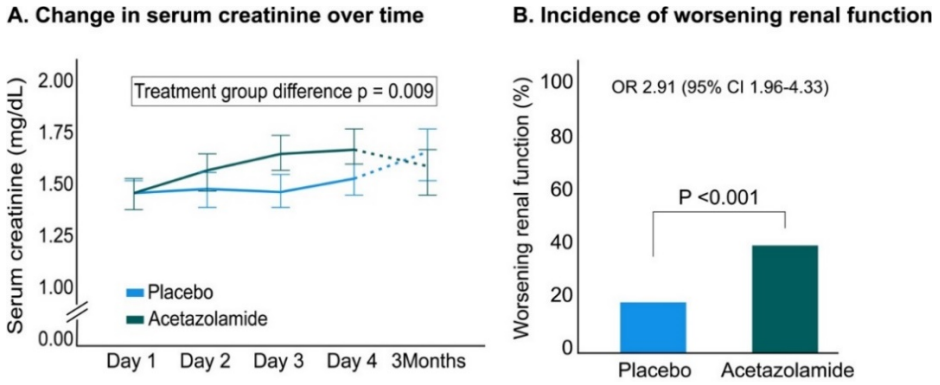
In total, 153 patients (out of 516 patients, 29.7%) experienced WRF during the treatment phase. Figure 4 panel A shows the evolution of serum creatinine during the treatment phase (day 1 to day 4). Patients in the acetazolamide arm showed a modestly higher increase in creatinine in comparison with patients in the placebo arm (mean difference = 0.11 mg/dL, 95% CI [0.02-0.20], p-value=0.009). Acetazolamide was associated with a higher incidence of WRF (104 out of 257 patients [40.5%] vs. 49 out of 259 patients [18.9%]; OR = 2.91; 95% CI, [1.96-4.33]; p-value<0.001) (Figure 4, panel B). A sensitivity analysis accounting for a 25% increase in serum creatinine demonstrated similar findings (75 out of 257 patients treated with acetazolamide [29.2%] and 40 out of 259 patients in the control arm [15.4%]; OR = 2.26; 95% CI, [1.47-3.47]; p-value<0.001). After three months, there was no longer a difference in serum creatinine between the acetazolamide arm (1.62 [1.19-2.04] mg/dL) and placebo arm (1.69 [1.24-2.11] mg/dL) (p-value=0.565). One patient in the placebo group and 4 patients in the acetazolamide group received renal replacement therapy during hospitalization (p-value=0.21).

Relationship between WRF and outcomes

Patients with WRF had a higher baseline weight, higher incidence of ischemic cardiomyopathy and diabetes, higher levels of serum potassium and creatinine and lower baseline levels of natriuretic peptides (Supplemental table 4).

Figure 4

Change in serum creatinine over time and incidence of worsening renal function



Worsening renal function was defined as as a rise of at least 0.3mg/dL in serum creatinine

Patients with WRF were more likely to be treated with acetazolamide and had a higher incidence of successful decongestion within three days (47.1% versus 31.6%; OR 1.93; 95% CI [1.31-2.74]; p-value<0.001). Table 3 shows the independent predictors from a multivariable model associated with the development of WRF. Both decongestion (OR 1.78; 95% CI [1.17-2.70], p=0.007) and randomization towards acetazolamide (OR 2.88; 95% CI [1.88-4.40]; p <0.001) were associated with higher odds of WRF. There was no difference with regards to heart failure hospitalizations and all-cause mortality between patients with or without WRF during hospitalization (HR 0.99; 95% CI [0.70-1.41]; p-value=0.964). The occurrence of WRF did not modify the treatment effect of acetazolamide on the combined endpoint of heart failure hospitalizations and all-cause mortality (p for interaction=0.467) (Supplemental figure 1). Figure 5 shows the relation between WRF, decongestion and clinical outcome. Supplemental figure 2 demonstrates the separate curves for decongestion and WRF on the clinical outcome. Decongestion at discharge was associated with a lower rate of the composite endpoint of heart failure hospitalization or all-cause mortality in

both patients with WRF (HR 0.51; 95% CI [0.27-0.94]; p=0.032) or without WRF (HR 0.63, 95% CI [0.40-0.99], p=0.046) (p-interaction=0.805).

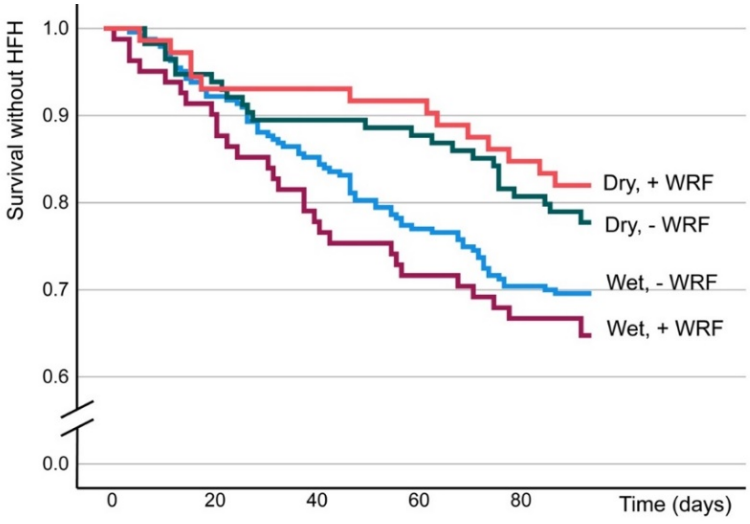
Table 3

Multivariable analysis for covariates associated with worsening renal function

	Univariable (OR, 95% CI)	P-value	Multivariable (OR, 95% CI)	P-value
Acetazolamide	2.91 (1.96-4.34)	<0.001	2.88 (1.88-4.40)	<0.001
Male sex	0.59 (0.39-0.88)	0.010		
Weight (kg)	1.02 (1.01-1.02)	0.001	1.02 (1.01-1.03)	0.002
Ischemic cause (%)	1.66 (1.13-2.43)	0.009	1.56 (1.03-2.37)	0.035
Potassium (mmol/L)	1.38 (1.00-1.89)	0.050		
Serum creatinine*	2.04 (1.15-3.64)	0.015		
NT-proBNP*	0.83 (0.67-1.02)	0.072		
Diabetes	1.87 (1.27-2.74)	0.001	1.63 (1.06-2.50)	0.025
ACEi, ARB, or ARNI	1.49 (1.01-2.18)	0.043		
Successful Decongestion	1.93 (1.31-2.84)	0.001	1.78 (1.17-2.70)	0.007

Figure 5

Relationship between the composite outcome of heart failure hospitalizations and all-cause mortality, congestion state and worsening renal function (WRF)



DISCUSSION

The main findings of this prespecified analysis of the ADVOR trial are that acetazolamide on top of loop diuretics increased the rate of successful decongestion, irrespectively of baseline renal function. Importantly, the positive effects of acetazolamide on natriuresis and diuresis are larger in patients with a lower baseline eGFR. While acetazolamide increases the risk of WRF during decongestive therapy, there is no difference in renal function or clinical outcome after three months follow-up. Importantly, decongestion remains to be associated with improved outcomes irrespectively of WRF.

In the ADVOR trial, the use of acetazolamide on top of standardized intravenous loop diuretics was associated with more successful decongestion within 3 days and at discharge. Due to hemodynamic and neurohormonal alterations, proximal tubular sodium and water reabsorption is increased in patients with chronic heart failure (9). Acetazolamide is a diuretic agent that specifically targets the proximal tubules to address these alterations.

In patients with an impaired renal function, higher doses of intravenous loop diuretics are often needed to reach a sufficient diuretic response as delivery of loop diuretics depends on renal perfusion. Indeed, loop diuretics are protein bound and need to be actively secreted in the proximal tubules to reach their acting site in the tubular lumen in the more distal part of the ascending loop of Henle (3,174). In patients with lower eGFR and ADHF, it is particularly difficult to attain successful decongestion. Therefore, there is an urgent need for agents that can enhance the response to loop diuretics. This is illustrated by the fact that in the ADVOR trial, patients with an eGFR <40 mL/min/1.73m² required higher maintenance doses of loop diuretics as an indicator of more diuretic resistance at home. It is reassuring and important that this predefined analysis confirmed that the combination therapy with acetazolamide did enhance decongestive response independent of baseline renal function. Moreover, a proportionally higher natriuresis and diuresis was observed in patients with a lower renal function, suggesting a higher benefit in inhibiting proximal sodium reabsorption in these patients, which probably relates to treatment and further prevention of loop diuretic resistance (175). Importantly, this is in contrast with hydrochlorothiazide (which works distal in the

nephron) as the recently reported subanalysis of CLOROTIC indicated a better decongestive response with hydrochlorothiazide on top of loop diuretics mostly in patients with higher eGFR (176). Since sodium-glucose cotransporter 2 inhibitors (SGLT2i) were excluded, the interaction with acetazolamide, baseline renal function and SGLT2i could not be evaluated. Of note, SGLT2i were excluded in ADVOR given the lack of evidence for its use in this patient population at the time. They exhibit their mode of action at the level of the proximal tubules by enhancing glucosuria by blocking sodium-glucose reabsorption resulting in an osmotic diuresis, mainly in diabetic patients with significant glucosuria (177–179). However, their natriuretic effect is limited in extent and time and their glucosuric effect is dose-dependent and diminishes with a lower renal function (180). Both the Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been stabilized (EMPULSE) trial and the Dapagliflozin versus Metolazone in Heart Failure Resistant to Loop Diuretics (DAPA-RESIST) trial have evaluated the use of SGLT2i in patients with ADHF. However, diuresis and weight change were used as a metric for diuretic efficiency instead of urinary collections and SGLT2i were mostly only added days after admission. (101,181) In contrast to patients with a lower renal function, most of the patients with a higher eGFR already exhibit a good diuretic response on loop diuretics. Thus, the presented data once again provide further evidence that the combination of acetazolamide with loop diuretics is a crucial strategy to enhance decongestion by inhibiting proximal sodium reabsorption. Moreover, the additional natriuretic and diuretic effect of acetazolamide is more pronounced in patients with a lower eGFR.

With regard to the combined endpoint of all-cause mortality and heart failure rehospitalizations, there was numerically a slightly higher event rate in patients treated with acetazolamide. However, this was non-significant and there was even a trend towards lower in-hospital mortality in patients treated with acetazolamide (38). In addition, it is also important to emphasize that the overall event rate for the ADVOR-trial was only 28.7% at 3 months with 17.7% being admitted for heart failure hospitalizations. This was considerably lower compared with previous ADHF trials, such as the DOSE trial (42% already at 2 months) and the CLOROTIC trial (18.3% for all-cause mortality and 36.1% for readmissions at 3 months). This probably relates to the fact that better decongestion was achieved at discharge

(71% overall) and the good implementation of HFA-ESC guidelines with frequent out-patient visits and implementation of GDMT in participating centers in Belgium. The lower event rate is important as in those settings a few extra events in one arm due to the play of chance affect the hazard ratio more. Importantly, the occurrence of WRF did not modify the treatment effect of acetazolamide on this clinical outcome.

During the acute treatment phase, the incidence of WRF was higher in the acetazolamide arm. Main predictors for the onset of WRF were treatment with acetazolamide, successful decongestion, diabetes and a higher baseline weight. Diabetes and obesity are known risk factors for reduced glomerular reserve and chronic kidney disease (160,182). WRF often accompanies decongestion, as a result of multifactorial hemodynamic alterations including intravascular volume contraction and neurohormonal activation, and is not necessarily associated with worse outcomes (31). In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, patients with a greater reduction in filling pressures were at higher risk of WRF, but this was not associated with an increased hazard of all-cause mortality among patients successfully decongested at discharge (183,184). In contrast, WRF with persisting signs of congestion is associated with worse outcomes (6). Therefore, WRF is usually not a sign of renal injury in case of successful decongestion (185–188). As acetazolamide was associated with a higher diuresis and natriuresis, the higher incidence of WRF is probably merely a reflection of more effective decongestion as significantly more patients were decongested in the WRF group. Therefore, these data corroborate previous findings that WRF during the decongestive phase should not immediately be a reason to cease diuretic therapy (pseudo-WRF) (31). The lack of true renal injury in these patients is supported by the fact that there was no longer a difference in renal function between both treatment groups after 3 months, no increase in the need for renal replacement therapy, an increase in diuresis instead of oliguria and the absolute difference in creatinine between two groups was at most modest (mean difference = 0.11 mg/dL, 95% CI [0.02-0.20]). More importantly, this analysis confirmed that WRF during ADHF always needs to be interpreted in the context of decongestion. Especially as there was no difference in the incidence of the combined endpoint of all-cause mortality and

heart failure hospitalizations or in the separate endpoints of all-cause mortality or heart failure hospitalizations between patients with or without WRF. A better clinical outcome was mostly driven by successful decongestion irrespective of the occurrence of WRF. Therefore, pursuing complete decongestion at discharge should remain the most important treatment goal irrespective of changes in renal function during the treatment phase. Modest increases in creatinine can be expected in parallel with the improved decongestive response of acetazolamide.

LIMITATIONS

Several limitations should be mentioned. First, although this is a prespecified analysis of the ADVOR trial, the results are exploratory to provide a better understanding of the results of the main trial, but should be considered hypothesis-generating. Second, as a baseline renal function with an eGFR below 20 mL/min/1.73m^2 was an exclusion criterium, no information is available regarding the effects of acetazolamide in this subpopulation.

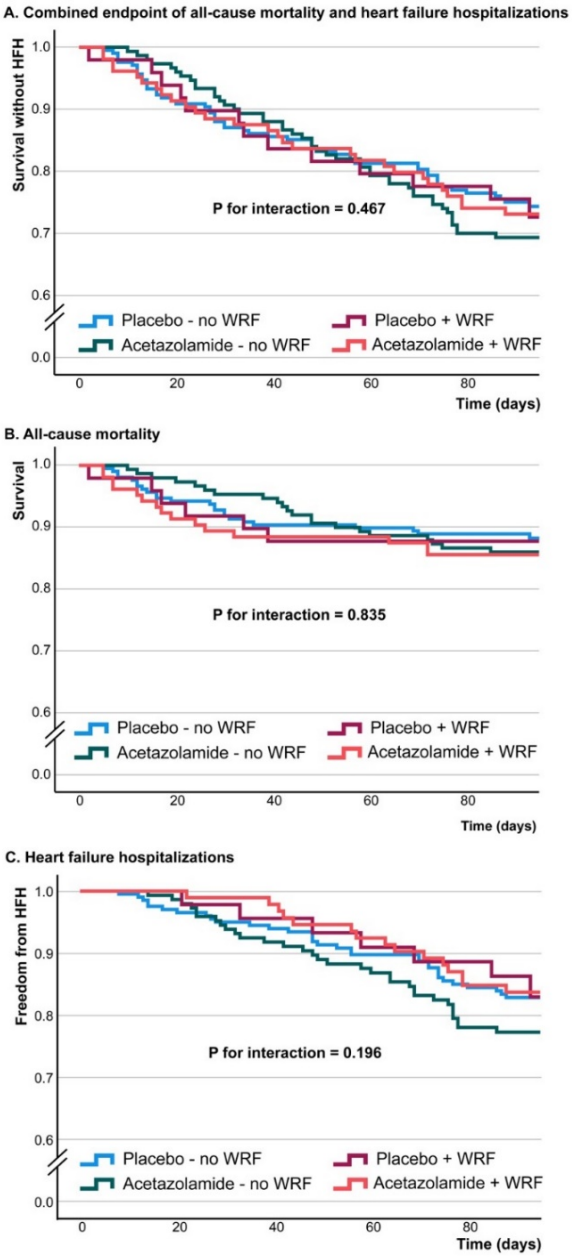
CONCLUSION

Acetazolamide increases the likelihood of successful decongestion in patients with acute decompensated heart failure with volume overload and this effect is independent of baseline renal function. The effects of acetazolamide on natriuresis and diuresis were larger in patients with low eGFR. Treatment with acetazolamide was associated with a higher incidence of WRF during treatment, but without a difference in renal function after 3 months. WRF did not modify the beneficial effect of successful decongestion on heart failure hospitalization and mortality.

SUPPLEMENTAL MATERIAL

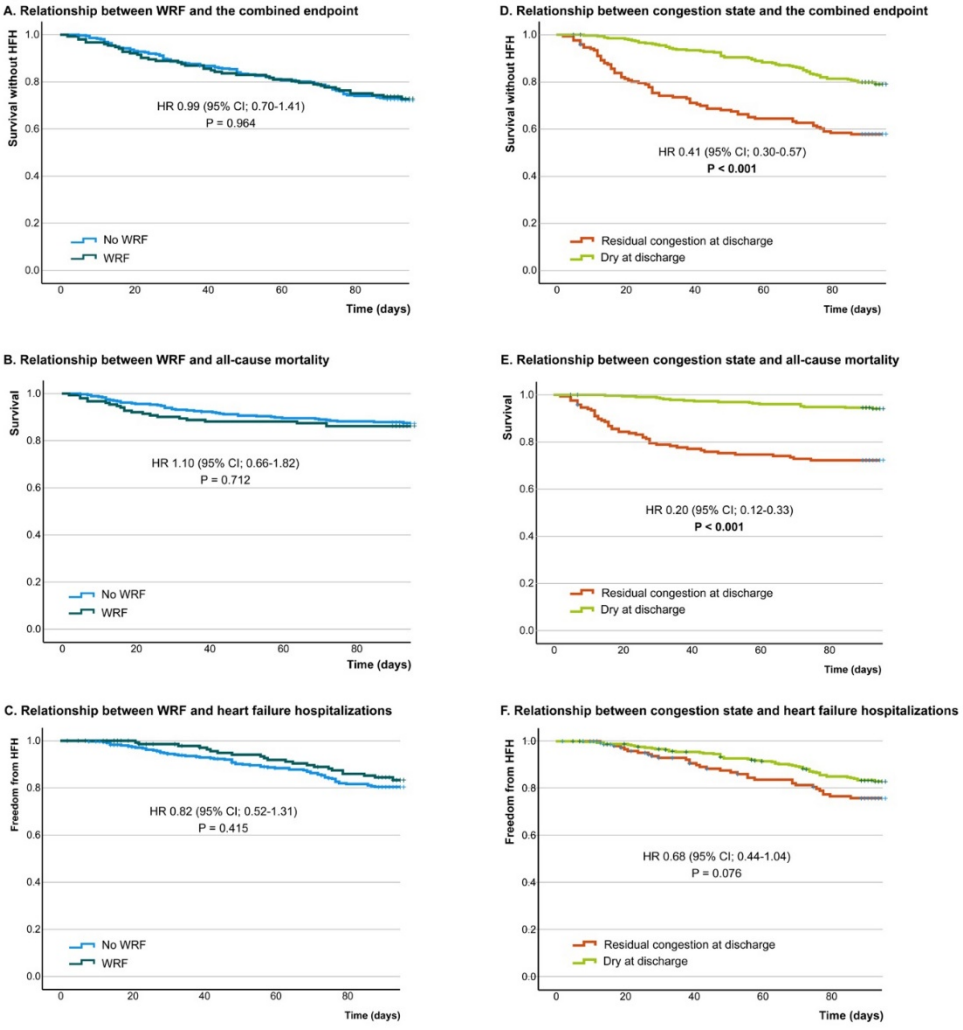
Supplemental figure 1

Relationship between clinical outcomes, treatment arm and worsening renal function (WRF).



Supplemental figure 2

Relationship between worsening renal function (A, B, C) or congestion state (D, E, F) and clinical outcomes



Supplemental table 1

Treatment effect of acetazolamide across KDIGO stage (unadjusted and adjusted)

Parameter	Placebo n (%)	Acetazolamide n (%)	OR/HR (95% CI)	P-value	*P-interaction	Adjusted OR/HR (95% CI)	Adjusted p-value	Adjusted *p-interaction
Primary endpoint (OR)								
Overall	79/259 (30.5%)	108/256 (42.2%)	1.77 (1.18-2.63)	0.005		1.97 (1.29-3.02)	0.002	
eGFR 20-29 mL/min/1.73m^2	12/67 (17.9%)	27/65 (41.5%)	3.26 (1.46-5.27)			2.89 (1.14-7.31)		
eGFR 30-44 mL/min/1.73m^2	31/94 (33.0%)	39/95 (41.1%)	1.48 (0.76-2.87)		0.126	1.88 (0.92-3.85)		0.852
eGFR 45-59 mL/min/1.73m^2	22/54 (40.7%)	17/47 (36.2%)	0.80 (0.32-2.00)			1.25 (0.45-3.44)		
eGFR > 60 mL/min/1.73m^2	14/44 (31.8%)	25/49 (51.0%)	2.55 (0.98-6.60)			2.42 (0.82-7.10)		
Primary endpoint with or without need for escalation (OR)								
Overall	86/259 (33.2%)	115/256 (44.9%)	1.77 (1.19-2.64)	0.005		2.01 (1.31-3.08)	0.001	
eGFR 20-29 mL/min/1.73m^2	16/67 (23.9%)	44/132 (33.3%)	2.40 (1.13-5.10)		0.300	2.18 (0.86-5.51)		0.967
eGFR 30-44 mL/min/1.73m^2	34/94 (36.2%)	41/95 (43.2%)	1.41 (0.72-2.73)			1.94 (0.94-4.02)		
eGFR 45-59 mL/min/1.73m^2	22/54 (40.7%)	19/47 (40.4%)	0.99 (0.40-2.46)			1.54 (0.56-4.22)		
eGFR > 60 mL/min/1.73m^2	14/44 (31.8%)	27/49 (55.1%)	3.10 (1.20-8.05)			3.88 (1.13-13.3)		

Complete decongestion at discharge (OR)								
Overall	145/250 (58.0%)	190/252 (75.4%)	2.21 (1.51-3.24)	<0.001		2.37 (1.54-3.65)	<0.001	
eGFR 20-29 mL/min/1.73m^2	36/64 (56.3%)	48/63 (76.2%)	2.49 (1.15-5.37)			2.36 (0.92-6.07)		
eGFR 30-44 mL/min/1.73m^2	55/91 (60.4%)	68/95 (71.6%)	1.64 (0.89-3.04)		0.717	1.97 (0.95-4.09)		0.573
eGFR 45-59 mL/min/1.73m^2	30/53 (56.6%)	32/45 (71.1%)	2.03 (0.80-5.13)			2.44 (0.88-6.74)		
eGFR > 60 mL/min/1.73m^2	24/42 (57.1%)	42/49 (85.7%)	4.01 (1.53-10.5)			3.23 (1.09-9.59)		
Risk for all-cause mortality and heart failure admission (HR)								
Overall	72/259 (27.8%)	76/256 (29.7%)	1.07 (0.78-1.48)	0.667		1.09 (0.78-1.54)	0.618	
eGFR 20-29 mL/min/1.73m^2	23/67 (34.3%)	25/65 (38.5%)	1.12 (0.64-1.98)			1.06 (0.54-2.07)		
eGFR 30-44 mL/min/1.73m^2	29/94 (30.9%)	31/95 (32.6%)	1.07 (0.64-1.77)		0.011	0.99 (0.58-1.71)		0.613
eGFR 45-59 mL/min/1.73m^2	12/54 (22.2%)	13/47 (27.7%)	1.31 (0.60-2.88)			1.47 (0.63-3.41)		
eGFR > 60 mL/min/1.73m^2	8/44 (18.2%)	7/49 (14.3%)	0.77 (0.28-2.14)			0.92 (0.29-2.91)		
All-cause mortality (HR)								
Overall	31/259 (12.0%)	39/256 (15.2%)	1.28 (0.80-2.04)	0.313		1.36 (0.82-2.24)	0.230	
eGFR 20-29 mL/min/1.73m^2	11/67 (16.4%)	13/65 (20.0%)	1.20 (0.54-2.67)		0.222	0.95 (0.37-2.57)		0.474

eGFR 30-44 mL/min/1.73m^2	12/94 (12.8%)	13/95 (13.7%)	1.06 (0.48-2.31)			1.13 (0.48-2.70)		
eGFR 45-59 mL/min/1.73m^2	5/54 (9.3%)	9/47 (19.1%)	2.18 (0.73-6.50)			2.55 (0.77-8.39)		
eGFR > 60 mL/min/1.73m^2	3/44 (6.8%)	4/49 (8.2%)	1.22 (0.27-5.44)			1.98 (0.24-16.72)		
Heart Failure hospitalization (HR)								
Overall	45/259 (17.4%)	47/256 (18.4%)	1.07 (0.71-1.61)	0.751		1.09 (0.71-1.69)	0.684	
eGFR 20-29 mL/min/1.73m^2	12/67 (17.9%)	15/65 (23.1%)	1.29 (0.60-2.76)			1.39 (0.58-3.33)		
eGFR 30-44 mL/min/1.73m^2	19/94 (20.2%)	22/95 (23.2%)	1.17 (0.63-2.17)		0.018	1.10 (0.56-2.14)		0.296
eGFR 45-59 mL/min/1.73m^2	8/54 (14.8%)	6/47 (12.8%)	0.93 (0.32-2.67)			1.04 (0.34-3.23)		
eGFR > 60 mL/min/1.73m^2	6/44 (13.6%)	4/49 (8.2%)	0.58 (0.16-2.06)			0.59 (0.15-2.36)		

Adjusted for: Age, heart rate, diastolic blood pressure, odema, home maintenance dose of furosemide (LN), NT-proBNP (LN), serum hemoglobin, potassium, troponin T (LN)

Supplemental table 2

Treatment effect of acetazolamide across eGFR categories and KDIGO stage (unadjusted)

Parameter	Placebo n (%)	Acetazolamide n (%)	OR/HR (95% CI)	P-value	*P-interaction
Primary endpoint (OR)					
Overall	79/259 (30.5%)	108/256 (42.2%)	1.77 (1.18-2.63)	0.005	
eGFR ≤ 40 mL/min/1.73m^2	34/136 (25.0%)	54/129 (41.9%)	2.16 (1.28-3.65)		0.146
eGFR > 40 mL/min/1.73m^2	45/123 (36.6%)	54/127 (42.5%)	1.34 (0.75-2.37)		
eGFR 20-29 mL/min/1.73m^2	12/67 (17.9%)	27/65 (41.5%)	3.26 (1.46-5.27)		0.126
eGFR 30-44 mL/min/1.73m^2	31/94 (33.0%)	39/95 (41.1%)	1.48 (0.76-2.87)		
eGFR 45-59 mL/min/1.73m^2	22/54 (40.7%)	17/47 (36.2%)	0.80 (0.32-2.00)		
eGFR > 60 mL/min/1.73m^2	14/44 (31.8%)	25/49 (51.0%)	2.55 (0.98-6.60)		
Primary endpoint with or without need for escalation (OR)					
Overall	86/259 (33.2%)	115/256 (44.9%)	1.77 (1.19-2.64)	0.005	
eGFR ≤ 40 mL/min/1.73m^2	41/136 (30.1%)	57/129 (44.2%)	1.98 (1.13-3.46)		0.536
eGFR > 40 mL/min/1.73m^2	45/123 (36.6%)	58/127 (45.7%)	1.56 (0.88-2.77)		
eGFR 20-29 mL/min/1.73m^2	16/67 (23.9%)	44/132 (33.3%)	2.40 (1.13-5.10)		0.300
eGFR 30-44 mL/min/1.73m^2	34/94 (36.2%)	41/95 (43.2%)	1.41 (0.72-2.73)		
eGFR 45-59 mL/min/1.73m^2	22/54 (40.7%)	19/47 (40.4%)	0.99 (0.40-2.46)		
eGFR > 60 mL/min/1.73m^2	14/44 (31.8%)	27/49 (55.1%)	3.10 (1.20-8.05)		
Complete decongestion at discharge (OR)					
Overall	145/250 (58.0%)	190/252 (75.4%)	2.21 (1.51-3.24)	<0.001	
eGFR ≤ 40 mL/min/1.73m^2	77/132 (58.3%)	91/127 (71.7%)	1.91 (1.09-3.36)		0.449
eGFR > 40 mL/min/1.73m^2	68/118 (57.6%)	99/125 (79.2%)	2.80 (1.58-4.93)		
eGFR 20-29 mL/min/1.73m^2	36/64 (56.3%)	48/63 (76.2%)	2.49 (1.15-5.37)		

eGFR 30-44 mL/min/1.73m^2	55/91 (60.4%)	68/95 (71.6%)	1.64 (0.89-3.04)		0.717
eGFR 45-59 mL/min/1.73m^2	30/53 (56.6%)	32/45 (71.1%)	2.03 (0.80-5.13)		
eGFR > 60 mL/min/1.73m^2	24/42 (57.1%)	42/49 (85.7%)	4.01 (1.53-10.5)		
Combined endpoint of all-cause mortality and heart failure admission (HR)					
Overall	72/259 (27.8%)	76/256 (29.7%)	1.07 (0.78-1.48)	0.667	
eGFR ≤ 40 mL/min/1.73m^2	43/136 (31.6%)	47/129 (36.4%)	1.20 (0.79-1.80)		0.023
eGFR > 40 mL/min/1.73m^2	29/123 (23.6%)	29/127 (22.8%)	0.96 (0.57-1.61)		
eGFR 20-29 mL/min/1.73m^2	23/67 (34.3%)	25/65 (38.5%)	1.12 (0.64-1.98)		0.011
eGFR 30-44 mL/min/1.73m^2	29/94 (30.9%)	31/95 (32.6%)	1.07 (0.64-1.77)		
eGFR 45-59 mL/min/1.73m^2	12/54 (22.2%)	13/47 (27.7%)	1.31 (0.60-2.88)		
eGFR > 60 mL/min/1.73m^2	8/44 (18.2%)	7/49 (14.3%)	0.77 (0.28-2.14)		
All-cause mortality (HR)					
Overall	31/259 (12.0%)	39/256 (15.2%)	1.28 (0.80-2.04)	0.313	
eGFR ≤ 40 mL/min/1.73m^2	18/136 (13.2%)	24/129 (18.6%)	1.41 (0.77-2.61)		0.145
eGFR > 40 mL/min/1.73m^2	13/123 (10.6%)	15/127 (11.8%)	1.12 (0.53-2.35)		
eGFR 20-29 mL/min/1.73m^2	11/67 (16.4%)	13/65 (20.0%)	1.20 (0.54-2.67)		0.222
eGFR 30-44 mL/min/1.73m^2	12/94 (12.8%)	13/95 (13.7%)	1.06 (0.48-2.31)		
eGFR 45-59 mL/min/1.73m^2	5/54 (9.3%)	9/47 (19.1%)	2.18 (0.73-6.50)		
eGFR > 60 mL/min/1.73m^2	3/44 (6.8%)	4/49 (8.2%)	1.22 (0.27-5.44)		
Heart Failure hospitalization (HR)					
Overall	45/259 (17.4%)	47/256 (18.4%)	1.07 (0.71-1.61)	0.751	
eGFR ≤ 40 mL/min/1.73m^2	25/136 (18.4%)	29/129 (22.5%)	1.29 (0.75-2.20)		0.068
eGFR > 40 mL/min/1.73m^2	20/123 (16.3%)	18/127 (14.2%)	0.87 (0.46-1.64)		
eGFR 20-29 mL/min/1.73m^2	12/67 (17.9%)	15/65 (23.1%)	1.29 (0.60-2.76)		0.018
eGFR 30-44 mL/min/1.73m^2	19/94 (20.2%)	22/95 (23.2%)	1.17 (0.63-2.17)		
eGFR 45-59 mL/min/1.73m^2	8/54 (14.8%)	6/47 (12.8%)	0.93 (0.32-2.67)		
eGFR > 60 mL/min/1.73m^2	6/44 (13.6%)	4/49 (8.2%)	0.58 (0.16-2.06)		

Supplemental table 3

Effect on natriuresis and diuresis of acetazolamide across GFR categories (unadjusted and adjusted)

Parameter	Placebo Mean ± SD	Acetazolamide Mean ± SD	Absolute difference (95% CI) unadjusted	Absolute difference (95% CI) adjusted	P-value	*P-interaction
Effect on urinary output (mL)						
Overall	4069 ± 1806	4572 ± 1725	-503 (-812 to 194)	-324 (-638 to -9)	0.001 (u) 0.044 (a)	
eGFR ≤ 40 mL/min/1.73m^2	3684 ± 1413	4381 ± 1822	-697 (-1094 to -30)	-541 (-940 to 143)		<0.001 (u) 0.006 (a)
eGFR >40 mL/min/1.73m^2	4502 ± 2087	4764 ± 1605	-262 (-730 to 206)	-148 (-641 to 344)		
Effect on natriuresis (mmol)						
Overall	369 ± 231	468 ± 234	-97 (-139 to 55)	-83 (-126 to -40)	<0.001 (u) <0.001 (a)	
eGFR ≤ 40 mL/min/1.73m^2	304 ± 163	435 ± 252	-131 (-185 to -78)	-123 (-179 to - 67)		<0.001 (u) <0.001 (a)
eGFR >40 mL/min/1.73m^2	444 ± 270	499 ± 210	-56 (-118 to 7)	-50 (-116 to 16)		

Adjusted for: Age, heart rate, diastolic blood pressure, odema, home maintenance dose of furosemide (LN), NT-proBNP (LN), serum hemoglobin, potassium, troponin T (LN).

(a): adjusted; CI: confidence interval; SD: standard deviation;

(u): unadjusted

Supplemental table 4

Baseline differences between patients with or without worsening renal function

	No WRF (n=363)	WRF (n=152)	P-value
Acetazolamide	153 (42.1%)	104 (68.0%)	<0.001
Age (years)	78.5 (9.1)	77.5 (8.4)	0.231
Male sex	215 (59.2%)	109 (71.2%)	0.013
Heart rate (bpm)	77.6 (17.6)	78.9 (19.9)	0.445
Systolic BP (mmHg)	125.6 (20.3)	128.6 (21.5)	0.133
Diastolic BP (mmHg)	72.0 (13.0)	72.3 (12.8)	0.816
Weight (kg)	82.7 (20.7)	89.6 (22.5)	<0.001
Home maintenance dose of furosemide (mg)	60 (40-100)	75 (40-130)	0.651
LVEF (%)	43.4 (15.0)	42.5 (15.3)	0.510
NYHA class			0.247
II	52 (14.3%)	14 (9.2%)	
III	206 (56.7%)	89 (58.2%)	
IV	105 (28.9%)	50 (32.7%)	
Ischemic cause (%)	149 (41.0%)	82 (53.6%)	0.012
Serum hemoglobin (g/dL)	11.8 (2.0)	12.0 (2.0)	0.503
Sodium (mmol/L)	139.3 (4.4)	139.8 (4.2)	0.216
Potassium (mmol/L)	4.2 (0.6)	4.3 (0.6)	0.049
Serum creatinine (mg/dL)	1.48 (1.12-1.95)	1.55 (1.30-1.49)	0.034
eGFR	40 (29-54)	39 (30-49)	0.380
Troponin T	41.0 (24.0-65.0)	40.0 (25.3-59.5)	0.403
NT-proBNP (pg/mL)	6744 (3262-11642)	5072 (2649-9645)	0.030
Atrial fibrillation	267 (73.6%)	107 (69.9%)	0.450
Diabetes	155 (42.7%)	89 (58.2%)	0.001

CHAPTER 11

Acetazolamide, residual congestion and clinical outcomes in acute heart failure – a prespecified analysis of the ADVOR trial

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Submitted, under revision

ABSTRACT

Aims: Acetazolamide, an inhibitor of proximal tubular sodium reabsorption, improves decongestion in acute heart failure (AHF). The aim of the current subanalysis is to evaluate which factors contribute to successful decongestion and the impact of acetazolamide on 3-month clinical outcomes.

Methods: This analysis of the ADVOR trial, that randomized 519 patients with AHF to intravenous acetazolamide or matching placebo, assessed the relationship between acetazolamide treatment, residual congestion, and all-cause mortality and/or heart failure hospitalization (HFH).

Results: After 90 days, 148 patients (28.7%) experienced the combined endpoint of all-cause mortality and heart failure hospitalization. Predictors of the occurrence of this endpoint were higher baseline doses of loop diuretics (HR=1.60; 95% CI= [1.26-2.03]; p<0.001) and higher natriuretic peptide levels (HR=1.34; 95% CI = [1.09-1.65]; p=0.006). Acetazolamide lowered the risk of residual congestion (OR=0.54, 95% CI = [0.36-0.82]), and residual congestion at day 3 (HR=1.70, 95% CI = [1.18-2.43], p=0.004) and at discharge (HR=2.43, 95% CI = [1.76-3.36], p<0.001) were associated with a worse clinical outcome. The presence of residual congestion despite use of acetazolamide was associated with the highest event rate for all-cause mortality or HFH (p=0.019).

Conclusion: Residual congestion after decongestive treatment for AHF is associated with an increased risk of all-cause mortality and HFH. The upfront addition of acetazolamide reduced the incidence of residual congestion. However, patients with residual congestion despite acetazolamide use are at excessive risk for mortality and HFH, identifying a subset of patients requiring specialized heart failure care.

INTRODUCTION

Heart failure is a global problem with increasing incidence and prevalence worldwide. Signs and symptoms of congestion are the main reason for patients with heart failure to seek medical attention. Despite implementation of disease-modifying agents, hospitalization rates have been reported to exceed 20% within 1 year in ambulatory patients with heart failure. (28,29,189) After an acute heart failure (AHF) event, the risk for rehospitalization or all-cause mortality is even higher, mounting to 25% within 3 months and 50% within one year. (7,30,135,190) Residual congestion at discharge has been associated with adverse outcomes in observational studies. (191,192) Therefore, current guidelines recommend to pursue complete decongestion at discharge. (8,192) The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial has demonstrated that adding intravenous acetazolamide to standardized intravenous loop diuretic therapy in patients with AHF and volume overload improves the chance of successful decongestion within 3 days and at discharge, increases diuretic response and reduces length of stay. (38) The current prespecified analysis of the ADVOR trial aims to determine (a) which factors were associated with reaching effective decongestion and (b) the relationship between acetazolamide and 3-month outcome.

METHODS

Study design

The methods and results of the ADVOR trial (NCT03505788) have been published previously (38,81). Briefly, patients enrolled were adults who were admitted for AHF. Patients were required to have a N-terminal pro-B-type natriuretic peptide (NT-proBNP) level >1000 pg/mL or B-type natriuretic peptide level >250 pg/mL, with at least one clinical sign of volume overload (i.e., ascites, pleural effusion, or oedema), despite oral maintenance therapy with at least 40 mg of furosemide (or an equivalent dose) for at least one month. Main exclusion criteria comprised acetazolamide maintenance therapy before randomization, treatment with sodium-glucose-linked transporter 2 inhibitors, systolic blood pressure <90 mmHg, or an estimated glomerular filtration rate <20 mL/min/1.73m². Participants were randomly assigned in a 1:1 fashion to treatment with an intravenous bolus of acetazolamide (500 mg once daily) or matching placebo in addition to standardized intravenous loop diuretic therapy (twice oral home dose daily) upon randomization and during the next 2 days. The study complies with principles outlined in the Declaration of Helsinki, was approved by all local ethic committees from participating centers and all participants provided written informed consent.

End points

The primary end point of the ADVOR trial was defined as successful decongestion on the second morning after randomization (i.e., day three) without the need for escalation of decongestive therapies due to poor loop diuretic efficacy (defined as total urinary output below 3.5 L on the morning of day two). Successful decongestion was defined as the absence of pleural effusion and ascites and not more than trace oedema. Secondary end points were the length of index hospital stay and the first occurrence of the composite end point of death from any cause or rehospitalization for heart failure during a 3-month follow-up period. Heart failure hospitalizations were adjudicated and defined as either a hospital admission or an unscheduled contact at the emergency department for worsening heart failure with the administration of intravenous loop diuretics.

Statistical analysis

Baseline characteristics are summarized as means and standard deviations, medians and 25-75th percentile, or numbers and percentages and evaluated using chi-square, ANOVA and Kruskal-Wallis tests as appropriate. Predictors of residual congestion were assessed using binomial logistic regression models, with variables with a p-value below 0.05 being used in multivariable models. The combined and individual end points of heart failure hospitalizations and all-cause mortality were assessed in a time-to-event analysis using a Cox proportional hazard model including the decongestion state and treatment arm to calculate hazard ratio and 95% confidence interval. The model was adjusted for known heart failure prognosticators, i.e., sex, diabetes, mean arterial blood pressure, heart rate, home maintenance dose loop diuretics, serum sodium, serum creatinine, serum troponin T levels and natriuretic peptide levels. Logarithmic transformation was performed for skewed variables. All the hypotheses testing was 2-sided with a significance level of α = 0.05. All statistical analyses were done using SPSS version 28.

RESULTS

Baseline features of patients with or without heart failure hospitalization and all-cause mortality

In the ADVOR-trial, 519 patients were randomized towards either acetazolamide (259/519) or matching placebo (260/519). Four patients lacked the assessment of the combined end point of heart failure hospitalizations and all-cause mortality and were excluded from this sub-analysis. Therefore, the final patient population for this analysis consisted of 515 patients. Table 1 illustrates baseline features of patients with or without heart failure hospitalizations and/or all-cause mortality during follow-up. Of the 515 patients, 92 (18%) patients experienced a heart failure hospitalization and 70 (14%) patients died during 90-day follow-up. Patients who died or were hospitalized due to heart failure were more likely to receive a higher maintenance loop diuretic dose, have a lower systolic blood pressure and higher congestion score (mainly driven by edema) at the moment of admission. Their blood analyses showed lower levels of sodium, chloride and albumin, higher natriuretic peptide levels, a higher level of troponin and a more pronounced kidney impairment. Multivariable regression analysis indicated that a higher dose of maintenance loop diuretic therapy (Hazard Ratio [HR], 1.60; 95% confidence interval [CI], 1.26-2.03; $p<0.001$) and higher levels of natriuretic peptides (HR, 1.34; 95% CI, 1.09-1.65; $p=0.006$) were independently associated with a higher risk for the combined endpoint of heart failure hospitalizations and all-cause mortality.

Table 1

Baseline characteristics based on clinical outcome at 3 months

	Total (n=515)	Alive, non-rehospitalized (n=367)	Dead or rehospitalized (n=148)	P-value
Acetazolamide	256 (49.7%)	180 (49.0%)	76 (51.4%)	0.697
Age	78.2 (±8.9)	78.4 (±8.9)	77.9 (±8.7)	0.525
Male sex	323 (62.7%)	225 (61.3%)	98 (66.2%)	0.315
Heart rate	78.0 (±18.3)	77.7 (±18.8)	78.9 (±16.9)	0.478
Blood pressure				
Systolic	126.5 (±20.7)	127.9 (±20.3)	123 (±21.4)	**0.017**
Diastolic	72.1 (±13.0)	72.8 (±13.2)	70.4 (±12.3)	0.059
Weight	84.5 (±20.6)	84.1 (±19.8)	84.4 (±22.6)	0.520
Components of congestion				
Edema				**0.005**
0	25 (4.9%)	21 (5.7%)	4 (2.7%)	
1	16 (3.0%)	14 (3.8%)	2 (1.4%)	
2	72 (14.0%)	59 (16.1%)	13 (8.8%)	
3	227 (44.1%)	164 (44.7%)	63 (42.6%)	
4	175 (34.0%)	109 (29.7%)	66 (44.6%)	
Pleural effusion				0.859
0	243 (47.2%)	174 (47.4%)	69 (46.6%)	
2	200 (38.8%)	140 (38.1%)	60 (40.5%)	
3	71 (13.8%)	52 (14.2%)	19 (12.8%)	
Ascites				0.344
0	469 (91.1%)	337 (91.8%)	132 (89.2%)	
2	25 (4.9%)	18 (4.9%)	7 (4.7%)	
3	21 (4.0%)	12 (3.3%)	9 (6.1%)	

Home maintenance dose of furosemide equivalents	60.0 (40.0-100.0)	60.0 (40.0-100.0)	80.0 (40.0-200.0)	**<0.001**
LVEF (%)	43.2 (±15.1)	43.5 (±15.2)	42.4 (±14.9)	0.470
NT-proBNP (ng/L)	6137 (3038-10896)	5459 (2962-9828)	7532 (3502-13998)	**0.003**
NYHA				0.473
II	65 (12.6%)	46 (12.5%)	19 (12.8%)	
III	295 (57.3%)	216 (59.9%)	79 (53.4%)	
IV	155 (30.1%)	105 (28.6%)	50 (33.8%)	
Ischemic (%)	231 (44.9%)	170 (46.3%)	61 (41.2%)	0.328
Hemoglobin (g/dL)	11.9 (±2.0)	11.9 (±2.0)	11.8 (±1.9)	0.403
Sodium (mmol/L)	139.5 (±4.3)	139.7 (±4.4)	138.8 (±4.1)	**0.024**
Potassium (mmol/L)	4.2 (±0.6)	4.2 (±0.6)	4.3 (±0.6)	0.111
Chloride (mmol/L)	100.6 (±5.3)	101.0 (±5.5)	99.6 (±4.9)	**0.006**
Bicarbonate (mmol/L)	26.3 (±4.1)	26.1 (±4.0)	26.6 (±4.3)	0.230
Osmolality (mOsmol/kg H20)	299 (290-305)	298 (290-304)	300 (290-308)	0.146
Serum urea (mg/dL)	72.0 (52.0-100.0)	67.7 (49.0-92.0)	85.5 (59.0-112.5)	**<0.001**
Serum creatinine (mg/dL)	1.49 (1.18-1.94)	1.43 (1.13-1.88)	1.59 (1.33-2.05)	**<0.001**
eGFR (mL/min/1.73m^2)	39.9 (29.3-52.0)	42.0 (30.0-56.0)	34.5 (29.3-45.5)	**<0.001**
<60 mL/min/1.73m²	421 (81.7%)	288 (78.5%)	133 (89.9%)	**0.002**
Albumin (g/L)	38.6 (±4.8)	38.9 (±4.8)	37.7 (±4.8)	**0.017**
LDH (U/L)	272 (228-358)	268 (220-350)	287 (238-365)	0.081
Troponin T (ng/L)	40.0 (24.7-63.8)	39.0 (23.9-59.0)	45.7 (31.3-76.1)	**0.005**
Coexisting conditions				
Atrial fibrillation	373 (72.4%)	261 (71.1%)	112 (75.7%)	0.328
Stroke	62 (12.0%)	48 (13.1%)	14 (9.5%)	0.296
Diabetes	243 (47.2%)	167 (45.5%)	76 (51.4%)	0.243
Hypertension	385 (74.8%)	282 (76.8%)	103 (69.6%)	0.093
Valve surgery	90 (17.5%)	63 (17.2%)	27 (18.2%)	0.798

PAD	101 (19.6%)	82 (22.3%)	19 (12.8%)	**0.014**
COPD	101 19.6%)	71 (19.3%)	30 (20.3%)	0.807
Treatment – no. % at baseline				
ACEi, ARB, or ARNI	267 (51.8%)	197 (53.7%)	70 (47.3%)	0.206
Beta-blocker	415 (80.6%)	302 (82.3%)	113 (76.4%)	0.140
MRA	214 (41.6%)	138 (37.6%)	76 (51.4%)	**0.006**

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker, GFR: glomerular filtration rate, HR: heart rate, LDH: lactate dehydrogenase, LVEF: Left ventricular ejection fraction, MRA: mineralocorticoid receptor antagonist, NT-proBNP: N-terminal pro-B-type natriuretic peptide, PAD: peripheral arterial disease

Residual congestion

Residual congestion was apparent in 57.8% versus 69.5% (odds ratio [OR], 0.60; 95% CI, 0.42-0.86; p=0.006) at 3 days and 21.2% versus 37.5% (OR; 0.45; 95% CI, 0.30-0.67; p<0.001) at discharge in the acetazolamide and placebo group, respectively. A multivariate analysis of the factors associated with the residual congestion at day 3 and at the moment of discharge are represented in Table 2. Randomization towards acetazolamide treatment, lower baseline bicarbonate and natriuretic peptides levels and a lower loop diuretic maintenance dose were independent predictors of successful decongestion. In a multivariable regression model, randomization to acetazolamide was independently associated with a lower risk for residual congestion at day 3 (OR 0.54; 95% CI, 0.36-0.82; p=0.004) and at the moment of discharge (OR 0.45; 95% CI, 0.30-0.69; p<0.001). (Table 2)

The combined end point occurred in 40 out of 187 patients (21.4%) who were appropriately decongested at day three and in 108 out of 328 patients (32.9%) with residual congestion upon the same moment (HR 1.70, 95% confidence interval [CI], 1.18-2.45, p=0.004). (Supplemental figure S1). Residual congestion at discharge was also associated with a higher risk for the combined end point of all-cause mortality and heart failure hospitalizations (HR 2.43, 95% CI, 1.76-3.37, p<0.001).

Relationship between acetazolamide, residual congestion and outcome

The incidence of the combined end point did not differ between the treatment groups (placebo n=72, acetazolamide n=76, HR 1.07, 95% CI, 0.78-1.48; p=0.667). With regard to the individual end points, 31 (12.0%) patients in the placebo group and 39 (15.2%) patients in the acetazolamide group died during 3-month follow-up (HR 1.28; 95% CI, 0.80-2.04; p=0.313). With regard to heart failure hospitalizations, 45 (17.4%) patients in the placebo group and 47 (18.4%) patients in the acetazolamide group were rehospitalized during 3-month follow-up (HR 1.07; 95% CI, 0.71-1.59; p=0.751). There was a trend towards a higher in-hospital mortality in the placebo group (18/259 patients, 6.9%) compared to the acetazolamide arm (11/256 patients, 4.3%) (OR, 0.60; 95% CI, 0.28-1.30).

Table 2

Factors associated with the residual congestion at day 3 and at discharge (unadjusted and adjusted)

	Univariate (OR, 95% CI)	P-value	Multivariate (OR, 95% CI)	P-value
Residual congestion at day 3				
Age	1.016 (0.996-1.037)	0.121		
Gender	0.889 (0.614-1.287)	0.534		
Ischemic cause	0.963 (0.671-1.381)	0.836		
Diabetes	0.881 (0.615-1.262)	0.490		
Acetazolamide	0.601 (0.419-0.864)	**0.006**	0.543 (0.360-0.819)	**0.004**
Mean arterial pressure	0.987 (0.973-1.000)	0.058		
Home maintenance dose of furosemide eq.*	1.425 (1.078-1.884)	**0.013**	1.411 (1.028-1.937)	**0.033**
Serum sodium	0.974 (0.933-1.017)	0.233		
Serum chloride	0.956 (0.922-0.990)	0.013		
Serum bicarbonate	1.056 (1.009-1.105)	0.019	1.063 (1.009-1.118)	**0.022**
Serum creatinine	1.420 (0.993-2.029)	0.055		
Troponin T*	1.283 (1.022-1.610)	**0.032**		
NT-proBNP*	1.722 (1.394-2.127)	**<0.001**	1.534 (1.209-1.945)	**<0.001**
Median congestion score at baseline*	7.248 (4.245-12.374)	**<0.001**	5.223 (2.961-9.214)	**<0.001**
Residual congestion at discharge				
Age	1.008 (0.987-1.029)	0.477		
Gender	0.955 (0.650-1.403)	0.813		
Ischemic cause	1.295 (0.892-1.879)	0.174		
Diabetes	1.204 (0.830-1.746)	0.328		
Acetazolamide	0.451 (0.308-0.660)	**<0.001**	0.450 (0.295-0.687)	**<0.001**
Mean arterial pressure	0.993 (0.979-1.008)	0.347		
Home maintenance dose of furosemide eq.*	1.202 (0.914-1.582)	0.188		

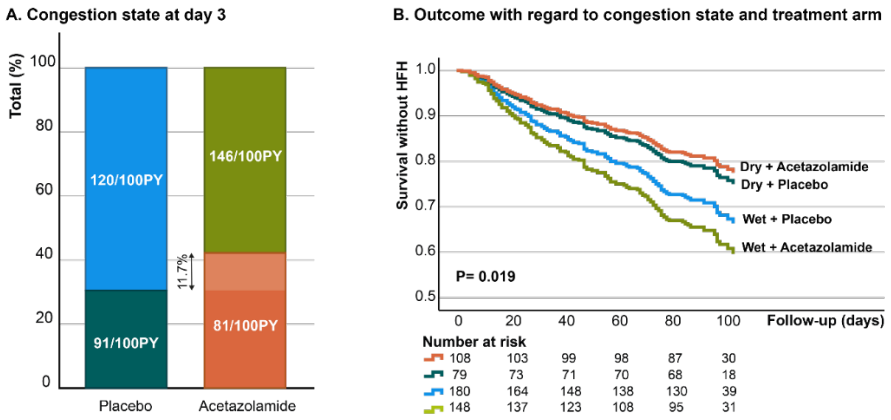
Serum sodium	0.965 (0.926-1.007)	0.101		
Serum chloride	0.979 (0.946-1.013)	0.215		
Serum bicarbonate	1.001 (0.956-1.048)	0.980		
Serum creatinine	1.130 (0.789-1.618)	0.506		
Troponin T*	1.560 (1.216-2.001)	**<0.001**	1.460 (1.124-1.897)	**0.005**
NT-proBNP*	1.460 (1.186-1.796)	**<0.001**		
Median congestion score at baseline*	5.201 (3.041-8.898)	**<0.001**	5.264 (2.962-9.355)	**<0.001**

* *log transformation*

Figure 1 illustrates the relation between randomization towards acetazolamide, residual congestion and outcome for the combined endpoint of heart failure hospitalization and all-cause mortality. Event rate per 100 patient years (PY) was the lowest in the patients who received acetazolamide and were assessed as decongested at day 3 (81 events per 100 PY) and highest for patients with residual congestion despite treatment with acetazolamide (146 events per 100 PY). Kaplan-Meier curves are presented in Figure 1. Randomization towards acetazolamide was associated with an increase of 11.7% more patients being decongested and having a better outcome (Figure 1). The interaction term between acetazolamide and decongestion on mortality/heart failure rehospitalization was not significant (p for interaction = 0.704).

Figure 1

Congestion state at day 3 based on treatment arm and event rate per 100 patient years per category (A) and Kaplan-Meier curves (B)



Guideline-directed medical therapy

Except for a clear increase in the prescription of mineralocorticoid receptor antagonists, guideline-directed medical therapy (GDMT) prescription rate declined in both treatment arms after the AHF hospitalization (Table 3 and supplemental table 1). Although all patients were treated with loop diuretics at the moment inclusion, this was reduced by approximately 25% at 3-month follow-up. With regard to 3-month outcome of all-cause death and heart failure rehospitalization,

there was no difference in the prescription of GDMT, neither in the change over time between both groups (Supplemental table S2).

Table 3

Guideline-directed medical therapy prescription over time

	Placebo	Acetazolamide	P-value
Beta-blockers			*0.480
Screening	208 (80.9)	203 (79.6)	0.740
Day 4	180 (70.6)	193 (74.5)	0.325
Discharge	192 (74.4)	200 (77.2)	0.474
3months follow-up	167 (64.5)	170 (66.1)	0.712
ACE/ARB			*0.486
Screening	96 (37.2)	92 (35.8)	0.784
Day 4	77 (29.8)	88 (34.1)	0.345
Discharge	89 (34.6)	89 (34.6)	1.000
3months follow-up	68 (26.5)	74 (28.7)	0.622
ARNI			*0.676
Screening	39 (15.0)	38 (14.7)	1.000
Day 4	40 (15.4)	39 (15.1)	1.000
Discharge	55 (21.2)	48 (18.5)	0.509
3months follow-up	49 (18.8)	40 (15.4)	0.352
MRA			*0.330
Screening	110 (43.0)	100 (38.8)	0.370
Day 4	113 (44.3)	110 (43.3)	0.858
Discharge	152 (60.1)	155 (61.5)	0.785
3months follow-up	122 (48.2)	138 (54.1)	0.214
Loop diuretics			*0.311
Screening	260 (100)	259 (100)	
Dose	77.5 (40-120)	60 (40-100)	0.357
Discharge	233 (89.6)	244 (94.2)	0.076
Dose	80 (40-100)	80 (40-100)	0.479
3 months follow-up	196 (75.4)	203 (78.4)	0.466
Dose	40 (5-100)	50 (30-100)	0.289

DISCUSSION

The ADVOR trial demonstrated that the addition of acetazolamide to loop diuretic therapy led to a higher incidence of decongestion in patients with acute decompensated heart failure with volume overload and this additional analysis evaluated the relationship between acetazolamide, residual decongestion and clinical outcome. The main messages of this analysis are: (1) Randomization towards acetazolamide is independently associated with a lower risk for residual congestion on day 3 and at discharge, which are independently associated with better clinical outcomes, (2) residual congestion after 3 days despite therapy with acetazolamide identifies a sicker phenotype of patients allowing for potential intensification of care, (3) there was no signal towards harm with treatment with acetazolamide, and a trend towards lower in-hospital mortality in these patients was noted, (4) heart failure hospitalization is associated with a more advanced disease stage with overall a lower prescription rate of GDMT after hospitalization.

Signs and symptoms of volume overload are the main reason to seek medical attention in patients with acute heart failure. Judicious titration of diuretic therapy has a class I recommendation to relieve congestion and prevent worsening heart failure (3,25,37), considering that residual congestion is associated with an increased risk for rehospitalization and mortality which was clearly also the case in the ADVOR trial. (6,191) Patients with an adverse outcome were more likely to have a higher dose of maintenance loop diuretic therapy and higher levels of natriuretic peptides, suggesting more advanced stage of heart failure and an increased vulnerability to subsequent events. Despite the benefit of acetazolamide on reaching euvolemia, it failed to demonstrate a benefit in the long-term outcome on heart failure hospitalization. Interestingly, the same observation has been made in other diuretic trials. Despite the beneficial effect on dyspnea relieve and higher fluid loss in the high-dose compared to the low-dose arm, there was no difference on the 60-day composite endpoint of mortality and heart failure rehospitalizations (63 events and 67 events, respectively; hazard ratio with high dose, 0.83; 95% CI, 0.60 to 1.16; p=0.28). (138) The Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial demonstrated the beneficial effect on weight loss and diuresis of a thiazide on top of loop diuretics without a benefit on 90-days

mortality and rehospitalization risk (hazard ratio 1.25; 95% CI: 0.81 to 1.92; p=0.32). (93) Lastly, the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial demonstrated that the addition of MRA in AHF was well tolerated, however did not influence 30-day mortality or readmission rate (adjusted HR, 1.22; 95% CI, 0.68-2.19; p =0.50). (102) While treating patients with AHF, it is important to realize that the main goal of the therapy is to improve signs and symptoms of congestion, which are the drivers for patients to seek medical attention, despite being treated with GDMT. While acetazolamide on top of loop diuretics very effectively improved decongestion rates in safe, effective manner at low cost, it might be not be not realistic to expect that a therapy given in hospital for a couple of days will influence long-term outcome. The current subanalysis also confirms the association between congestion state and long-term outcome. This corroborates previous findings of observational and other post-hoc analysis of randomized controlled trials, which demonstrated that an increased risk for adverse outcome was primarily seen in patients with residual congestion at discharge. (138,192–195). Acetazolamide has a strong effect on decongestion both at day 3 and at discharge, reducing the chance of residual congestion. Importantly patients who remained congested despite treatment with acetazolamide had the highest risk for adverse outcome. As such, this subanalysis suggest that upfront use of acetazolamide is not only a predictor of more decongestion, but also that it can help to refine the risk early in the course of the acute heart failure admission, which could have important clinical translations.

During AHF, achieving fully decongestion while optimizing GDMT should be the main focus of the treatment and patients being discharged with residual congestion should receive closer follow-up as they have an increased risk for adverse events.. (8) Despite the proven benefits on hard outcomes of GDMT, the current study demonstrated a non-significant, however gradual decrease in the prescription of these agents during hospitalization and follow-up. Importantly, this downtitration occurred despite that uptitration of GDMT was warranted by the ADVOR protocol and the fact that these patients were followed in dedicated HF centers. Episodes of AHF mandate the addition of intravenous diuretic agents, which often lead to temporarily downtitration of guideline-directed medical

therapy (GDMT) because of hypotension or worsening glomerular filtration. (23,24). More important, the hospitalization for AHF represents an additional physiological insult, signifying progression to a more advanced stage of disease, with reduced tolerability to GDMT.

Compared with other aforementioned diuretic trials in AHF, patients enrolled in ADVOR were considerably older with higher NT-proBNP levels, reflecting the real-world clinical situation. (38) Nevertheless, the overall event size for adverse outcome in the ADVOR trial was lower (14% for all-cause mortality and 18% for readmissions at 90-days follow-up) in comparison to other trials such as the DOSE trial (11% for all-cause mortality and 29% for readmissions at 60-days follow-up) and the CLOROTIC trial (18% for all-cause mortality and 36% for readmissions at 3 months). This may be related to the fact that better decongestion and follow-up probably improved overall outcome in the trial. Despite a reduction in heart failure hospitalization, mortality rate has remained relatively stable. This can be attributed to the older multimorbid trial population, in which all-cause mortality is largely driven by non-cardiovascular events, which are less impacted by heart failure management. Moreover, the overall rate of non-cardiovascular hospitalizations remains high, likely due to the presence of multiple comorbidities in this patient population (28). These comorbidities often lead to some level of congestion, necessitating IV diuretics. As a result, hospitalizations are typically due to a combination of factors, making it challenging to determine whether congestion is the primary cause or a secondary effect, especially when the degree of congestion is not carefully considered. Despite this, every hospitalization for heart failure should be viewed as an opportunity not only for complete decongestion prior to discharge but also for the optimization of GDMT, which is critical for improving long-term prognosis (25).

LIMITATIONS

While this study is a predefined post-hoc analysis of the ADVOR-trial, the results should be interpreted as hypothesis-generating., the lower event rate is important as in those settings a few extra events in one arm due to the play of chance affect the hazard ratio more. Therefore, the current study was not powered for an

evaluation of all-cause mortality and heart failure hospitalization. In addition, the follow-up period might have been too short to detect meaningful differences between treatment groups.

CONCLUSION

The upfront addition of acetazolamide on top of standardized intravenous loop diuretics has demonstrated to improve the rate of successful decongestion in the ADVOR trial. In addition, the current analysis confirms that residual congestion is associated with adverse outcomes. Especially, residual decongestion after use of thorough decongestive strategies with high dose loop diuretics in combination with acetazolamide identifies a very high-risk group allowing for rapid intensification of heart failure treatments and follow up in an attempt to alter the course. The current analysis further reassures that use of acetazolamide is safe and not associated with a higher risk of all-cause mortality.

SUPPLEMENTAL MATERIAL

Supplemental table S1

Prescription rate from screening to follow-up

	Screening	Follow-up	P-value
Overall			
Beta-blockers	411/512 (80.3%)	338/516 (65.5%)	**<0.001**
ACEi/ARB	189/515 (36.7%)	143/515 (27.8%)	**<0.001**
ARNI	76/519 (14.6%)	89/519 (17.1%)	0.080
MRA	211/514 (41.1%)	259/508 (51.0%)	**<0.001**
Alive at 90 days			
Beta-blockers	351/431 (81.4%)	288/435 (66.2%)	**<0.001**
ACEi/ARB	164/434 (37.8%)	127/435 (29.2%)	**<0.001**
ARNI	63/438 (14.4%)	72/438 (16.4%)	0.188
MRA	179/433 (41.3%)	214/430 (49.8%)	**0.002**

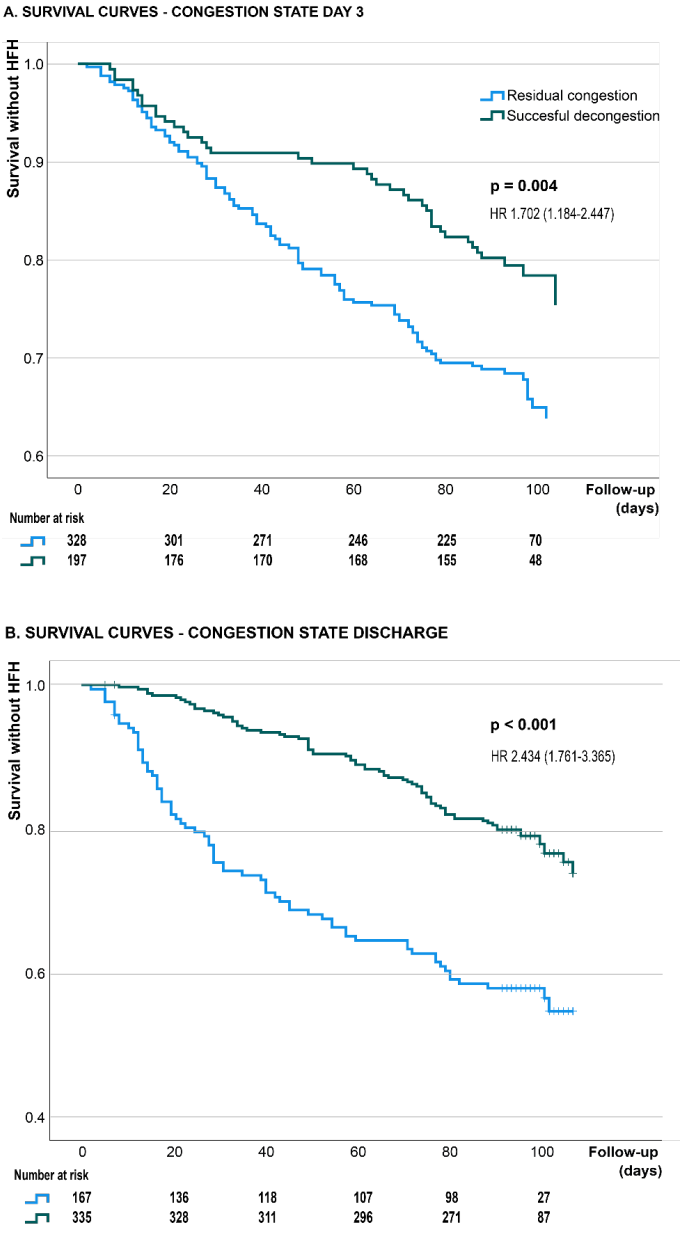
Supplemental table S2

Evolution of guideline-directed medical therapy and loop diuretics over time between patients experiencing an event and those with stable heart failure

	No event	Death or rehospitalized	P-value
Beta-blockers			*0.625
Screening	293 (80.9)	117 (80.1)	0.901
D4	262 (72.2)	109 (74.1)	0.742
DS	280 (76.5)	110 (74.8)	0.732
3m FU	238 (65.4)	98 (66.2)	0.918
ACE/ARB			*0.075
Screening	133 (36.6)	55 (37.2)	0.920
D4	113 (31.0)	52 (35.1)	0.404
DS	132 (36.4)	46 (31.3)	0.306
3m FU	106 (29.1)	36 (24.5)	0.327
ARNI			*0.063
Screening	51 (13.9)	26 (17.6)	0.339
D4	52 (14.2)	27 (18.2)	0.280
DS	66 (18.0)	37 (25.0)	0.088
3m FU	54 (14.7)	35 (23.6)	**0.020**
MRA			*0.176
Screening	144 (39.7)	64 (43.5)	0.428
D4	158 (44.1)	62 (42.2)	0.694
DS	211 (58.9)	94 (65.3)	0.225
3m FU	178 (49.3)	80 (55.6)	0.237
Loop diuretics			*0.941
Screening	367 (100)	148 (100)	
Dose	60 (40-100)	80 (40-150)	0.224
Discharge	337 (91.8)	136 (91.9)	1.000
Dose	80 (40-100)	80 (40-100)	0.128
Follow-up	281 (76.6)	115 (77.7)	0.818
Dose	40 (20-100)	60 (40-100)	0.241

Supplemental figure 1

Survival curves according to decongestion state at different time points; i.e. decongestion at day 3 (A) as primary end point of the ADVOR trial, decongestion at day 3 (B) and decongestion at the moment of discharge



HFH: heart failure hospitalizations

PART V

GUIDELINE-DIRECTED MEDICAL THERAPY OPTIMIZATION IN CHRONIC HEART FAILURE

Research is formalized curiosity.

It is poking and prying with a purpose.

- Zara Neale Hurston -

CHAPTER 12

Optimization of Heart Failure Management: Insights into GDMT and Loop Diuretic Utilization in a Specialized Heart Failure Clinic

Evelyne Meekers, Zara Arcidiacono, Romy Baptist, François Croset, Marie Miseur, Ruben Knevels, Jeroen Dauw, Sebastiaan Dhont, Jonas Erzeel, Marnicq Van Es, Petra Nijst, Pieter Martens, Matthias Dupont, Wilfried Mullens

Submitted, under revision

ABSTRACT

Background and aims: Loop diuretic maintenance therapy has been associated with worse clinical outcomes in heart failure patients. Despite this, recent heart failure trials report high prescription rates. Optimal guideline-directed medical therapy (GDMT) may reduce need for loop diuretics and improve long-term outcomes. This study evaluated loop diuretic and GDMT prescription patterns in a heart failure clinic of a Belgian tertiary hospital cohort and compared findings to recent heart failure trials and the Swede-HF registry.

Methods: This prospective registry included consecutive heart failure patients with a left ventricular ejection fraction (LVEF) ≤50% from the heart failure outpatient clinic starting from November 23, 2023 to May 22, 2024 up to the inclusion of 1000 patients. Data on baseline characteristics, medications, echocardiography and laboratory were extracted from electronical health records.

Results: Among the included patients, 543 (54.3%) had heart failure with reduced ejection fraction (HFrEF) (LVEF <40%) at the moment of the consultation. Median age was 72 (63-80) years, with a median LVEF of 45% (35-45). Most were male (72.6%), with median serum creatinine of 1.15 (0.93-1.45) mg/dL and eGFR of 60 (43-77) mL/min/1.73m². Hypertension (56%), atrial fibrillation (47%), and coronary revascularization (53%) were common comorbidities. GDMT prescription rates were high, with 68.7% on triple or quadruple therapy, while only 27% received loop diuretics (81.5% and 34%, respectively, for HFrEF). Baseline characteristics and GDMT prescription rates were comparable to recent registries and trials, but loop diuretic prescriptions were significantly lower in the current cohort.

Conclusion: This study highlights progress in heart failure management but emphasizes the need for a patient-centered approach in a heart failure clinic which enables optimization of care, and allows addressing comorbidities, and reduction in loop diuretic dependence.

GRAPHICAL ABSTRACT

Optimizing Heart Failure Care: Insights from GDMT and Loop Diuretic Utilization in a Belgian Tertiary Hospital

Meekers E., Arcidiacono Z., Baptist R., Croset F., Miseur M., Knevels R., Dauw J., Dhont S., Erzeel J., Van Es M., Nijst P., Martens P., Dupont M., Mullens W.*

Prospective registry of 1,000 heart failure patients (LVEF <50%)

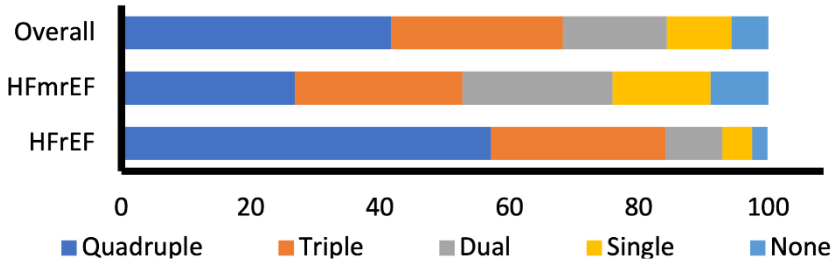
Goal:
GDMT & loop diuretic prescription in tertiary hospital

Baseline demographics:

- 72 (63-80) years
- 73% male
- 54% LVEF < 40%
- 52% ischemic
- eGFR 60 (43-77) ml/min

Results:

- 69% triple or quadruple GDMT (HFrEF 82%)
- 27% loop diuretics (HFrEF 34%)
  - Female gender
  - Older
  - Lower LVEF
  - Higher creatinine
  - Higher NT-proBNP



INTRODUCTION

Heart failure (HF) remains a prevalent and challenging condition, characterized by high morbidity and mortality rates worldwide. Signs of congestion are the main reason for hospitalization and loop diuretics are widely used in heart failure management to alleviate and prevent congestion and fluid overload. (8) However, evidence from prior studies highlights significant concerns regarding their association between their long-term use with worse outcome. Higher doses of chronic loop diuretics have been consistently associated with increased morbidity, mortality, and worsening kidney function. (196,197) Several studies demonstrated a dose-dependent relationship between loop diuretic use and poor clinical outcomes, including higher rates of hospitalization and death, although bias by indication remains despite adjustment for covariates. (20,138,198,199) Recent guidelines advocate for minimizing reliance on loop diuretics through the optimization of guideline-directed medical therapy (GDMT), such as renin-angiotensin-aldosterone inhibitors (RAASi) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), which decrease renal sodium avidity and have demonstrated renal protection. These advances in GDMT have significantly improved outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Some data even have shown that GDMT can alter natriuresis. (200) Despite their beneficial effects, the adoption and optimization of these therapies in real-world settings remain suboptimal.

This study aimed to assess the implementation of GDMT in a contemporary real-world heart failure patient cohort of a tertiary center, evaluating GDMT and loop diuretic prescription rates. Additionally, the findings will be compared to recent landmark trials and registry data to provide broader context and insights into real-world clinical practice.

METHODS

Study design and patient inclusion

This study was a single-center, prospective registry, conducted at Ziekenhuis Oost-Limburg (Genk, Belgium). Consecutive patients attending a dedicated outpatient heart failure visit were included if they had a left ventricular ejection fraction (LVEF) ≤ 50% (assessed by transthoracic echocardiogram (TTE) or cardiac magnetic resonance imaging (CMR)) at the time of enrollment and signs and symptoms of heart failure according to the ESC guidelines. (25) Patient enrollment continued until the database contained 1,000 eligible individuals. Patients were excluded if they met any of the following criteria: a current LVEF > 50%, no recent LVEF assessment within the past three months, or absence of a clinical heart failure diagnosis according to the European Society of Cardiology Guidelines. (25) Only patients scheduled for a dedicated heart failure outpatient visit were eligible for inclusion. Sample size was set at 1000 consecutive heart failure patients in order to obtain a representative view on current heart failure care.

At the moment of the visit, baseline demographics, medical history, current medication, presence of a cardiac implantable electronic device, echocardiographic data and laboratory findings were recorded. Medication data included dosages for all components of guideline-directed medical therapy (GDMT) and loop diuretics, documented as a percentage of the maximum recommended dose (Supplemental table 1). For laboratory data, the most recent results were noted, with a cutoff date of January 1, 2022 (enrollment started November 23, 2023). Echocardiographic data were stored and analyzed offline by an independent cardiologist (F.C.) using AGFA HealthCare. According to the World Health Organization, anemia is defined as a hemoglobin concentration < 12 g/dL in women and < 13 g/dL in men. Iron deficiency is defined according to the ESC guidelines; i.e., either a serum ferritin concentration <100 ng/mL or 100-299 ng/mL with a transferrin saturation < 20%. (8)
The findings of this registry were subsequently compared to data from recent heart failure trials, TITRATE-HF and the SwedeHF registry, to contextualize the results and evaluate differences in patient characteristics, medication use, and

adherence to GDMT guidelines. For an adequate comparison, only the subcohort of chronic heart failure patients from TITRATE-HF was included.

Statistical analysis

Normality of continuous data was assessed using a Shapiro-Wilk test. Variables are summarized as means with standard deviations, medians with 25-75th percentile, or numbers with percentages and evaluated using ANOVA, Kruskal-Wallis and chi-square tests, as appropriate. 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. The dosage of the included heart failure medications was expressed relative to the daily target dose of each medication specified in the European Society of Cardiology guidelines. Dosage of loop diuretics was displayed as the furosemide equivalent dose, meaning that one mg of bumetanide equals 40 mg of furosemide for further analysis. Predictors of GDMT and loop diuretic prescription were assessed using binomial logistic regression models. Variables with a p-value below 0.10 were included in a multivariable model. On February 6th 2025, all patients were reassessed, and censoring was applied to evaluate all-cause mortality. A time-to-event analysis was conducted using a Cox proportional hazards model, incorporating variables such as loop diuretic prescription and GDMT prescription rates. No adjustments for multiplicity were performed, so all reported p-values are exploratory. All the hypotheses' tests were 2-sided with a significance level of α = 0.05. All statistical analyses were done using SPSS version 29 (IBM® SPSS ® Inc., Chicago, IL, United States).

RESULTS

Baseline demographics

All patients were included between 23 November 2023 and 22 May 2024. Overall, most of the patients (73%) were male with a median age of 72 (63-80) years old (table 1). The median left ventricular ejection fraction (LVEF) was 45 (35-45) % with a median estimated right ventricular systolic pressure of 25 mmHg (22-31). Hypertension (56%), hyperlipidemia (56%), atrial fibrillation (47%) and a history of coronary revascularization (53%) were frequent comorbidities. Approximately 50% of the patients were known with chronic kidney disease (i.e., estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2).

Of the 1000 patients included, 54% were known with heart failure with a reduced ejection fraction (HFrEF) and the remaining patients had heart failure with mildly reduced ejection fraction (HFmrEF). Based on comorbidities or age, there were no significant differences between patients with HFrEF and patients with HFmrEF. There were slightly, but statistically significantly more women in the HFmrEF category. Patients with HFrEF had, overall, a more impaired kidney function, and were more likely to have an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) device. Prescription rate of GDMT and loop diuretics was higher in patients with HFrEF.

Table 1

Baseline characteristics between patients with heart failure with reduced and mildly reduced ejection fraction

	Total (n=1000)	HFrEF (n=543)	HFmrEF (n=457)	P-value
Age (years)	72 (63-80)	73 (63-80)	72 (63-80)	0.684
Male (%)	726 (72.6%)	414 (76.2%)	312 (68.3%)	**0.005**
Vital signs				
Heart Rate (bpm)	68 ± 14	67 ± 15	70 ± 13	**0.013**
Systolic blood pressure (mmHg)	123 ± 20	120 ± 18	127 ± 21	**<0.001**
Diastolic blood pressure (mmHg)	72 ± 11	71 ± 10	74 ± 11	**<0.001**
Comorbidities				
Hypertension	562 (56.2%)	305 (56.2%)	257 (56.2%)	1.000
Diabetes Mellitus	260 (26.0%)	147 (27.1%)	113 (24.7%)	0.426
Hypercholesterolemia	557 (55.7%)	305 (56.2%)	252 (55.1%)	0.750
Atrial fibrillation/flutter	474 (47.4%)	269 (49.5%)	205 (44.9%)	0.144
Peripheral artery disease	212 (21.2%)	123 (22.7%)	89 (19.5%)	0.244
PCI/PTCA/CABG	532 (53.2%)	311 (57.3%)	221 (48.4%)	**0.005**
Valve surgery	107 (10.7%)	61 (11.2%)	46 (10.1%)	0.608
Echocardiographic data				
LVEF (%)	45 (35-45)	35 (30-40)	45 (45-50)	**<0.001**
LVEDD (mm)	50 (± 8)	53 ± 9	47 ± 7	**<0.001**
Diastolic dysfunction				**0.032**
Grade 1	277 (27.7%)	148 (27.3%)	129 (28.2%)	
Grade 2	59 (5.9%)	33 (6.1%)	26 (5.7%)	
Grade 3	72 (7.2%)	51 (9.4%)	21 (4.6%)	
Indeterminate	592 (59.2%)	311 (57.3%)	281 (61.5%)	
RVSP (mmHg)	25 (22-31)	25 (22-33)	25 (22-30)	0.482
TAPSE (mm)	20 (16-25)	19 (15-25)	21 (18-26)	**0.046**
Mitral valve insufficiency (grade)	1 (0-1)	1 (1-1)	1 (0-1)	**<0.001**

Laboratory				
Hemoglobin (g/dL)	13.5 (± 2.0)	13.6 ± 1.9	13.3 ± 2.0	**0.033**
Sodium (mmol/L)	139 (137-141)	139 (137-141)	139 (137-141)	0.323
Potassium (mmol/L)	4.32 (4.02-2.64)	4.36 (4.07-4.67)	4.25 (3.96-4.61)	**<0.001**
Creatinine (mg/dL)	1.15 (0.93-1.45)	1.22 (1.02-1.62)	1.05 (0.86-1.31)	**<0.001**
eGFR (mL/min/1.73m^2)	60 (43-77)	57 (39-71)	65 (48-82)	**<0.001**
NT-proBNP (ng/L)	1651 (570-4793)	1850 (762-5065)	1389 (375-3929)	**0.016**
Medication				
ARNI or ACEi/ARB	778 (77.8%)	456 (84.0%)	322 (70.5%)	**<0.001**
ARNI	444 (44.4%)	318 (58.6%)	126 (27.6%)	**<0.001**
ACEi/ARB	336 (33.6%)	140 (25.8%)	196 (42.9%)	**<0.001**
MRA	654 (65.4%)	410 (75.5%)	244 (53.4%)	**<0.001**
BB	848 (84.8%)	493 (90.8%)	355 (77.7%)	**<0.001**
SGLT2i	612 (61.2%)	409 (75.3%)	203 (44.4%)	**<0.001**
Statins	697 (69.7%)	394 (72.6%)	303 (66.3%)	**0.027**
Amiodarone	141 (14.1%)	104 (19.2%)	37 (8.1%)	**<0.001**
Antiplatelets	484 (48.4%)	274 (50.5%)	210 (46.0%)	0.162
Anticoagulants	418 (41.8%)	234 (43.1%)	184 (40.3%)	0.367
Loop diuretics (%)	273 (27.3%)	185 (34.0%)	88 (19.3%)	**<0.001**
Loop diuretics dose in furosemide eq.	40 (20-40)	40 (20-40)	30 (20-40)	0.242
Cardiac Implantable Electronic Device				
Pacemaker	64 (6.4%)	28 (5.2%)	36 (7.9%)	0.244
CRT	343 (34.3%)	198 (36.5%)	145 (31.7%)	**0.004**
ICD	360 (36.0%)	272 (50.1%)	88 (19.3%)	**<0.001**
PAP sensor	14 (1.4%)	10 (1.8%)	4 (0.9%)	0.178

GDMT prescription

Overall, prescription rates reached 78% for angiotensin receptor-neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARB), 65% for mineralocorticoid receptor antagonists (MRA), 85% for beta-blockers, and 61% for sodium-glucose cotransporter-2 inhibitors (SGLT2i) (Table 2). In general, prescription patterns were higher in patients with HFrEF (all p-value<0.001), with the exception of the prescription of ACEi/ARB which was higher in the HFmrEF group (p<0.001) (Figure 1A). Despite the higher prescription rate in the HFrEF group, the overage dose of prescribed therapies did not differ between patients with HFrEF and those with HFmrEF.

In total, 69% received triple or quadruple heart failure therapy. This proportion was even higher in the HFrEF group, with 82% of the patients receiving either 3 or 4 GDMT medications (Figure 1B). Patients with HFrEF were more likely to receive higher proportions of combination therapy than patients with HFmrEF (p<0.001). Overall, patients receiving triple or quadruple therapy were generally younger, were more frequently diagnosed with diabetes mellitus, and had a slightly lower blood pressure and heart rate (Supplemental table 1). On echocardiography, they had lower pulmonary artery pressures with a higher grade of mitral valve insufficiency. These patients were more likely to have higher levels of serum potassium and serum creatinine. With regard to other treatments, patients on triple or quadruple therapy were more often treated with loop diuretics and were more likely to have a cardiac implantable electronic device (CIED). However, if only patients with HFrEF were included in the analysis, only left ventricular ejection fraction and lower NT-proBNP levels were associated with higher GDMT prescription. The prescription rate of loop diuretics did not differ between both groups; however, the prescribed dose was higher in patients with lower GDMT prescription (Supplemental table 2).

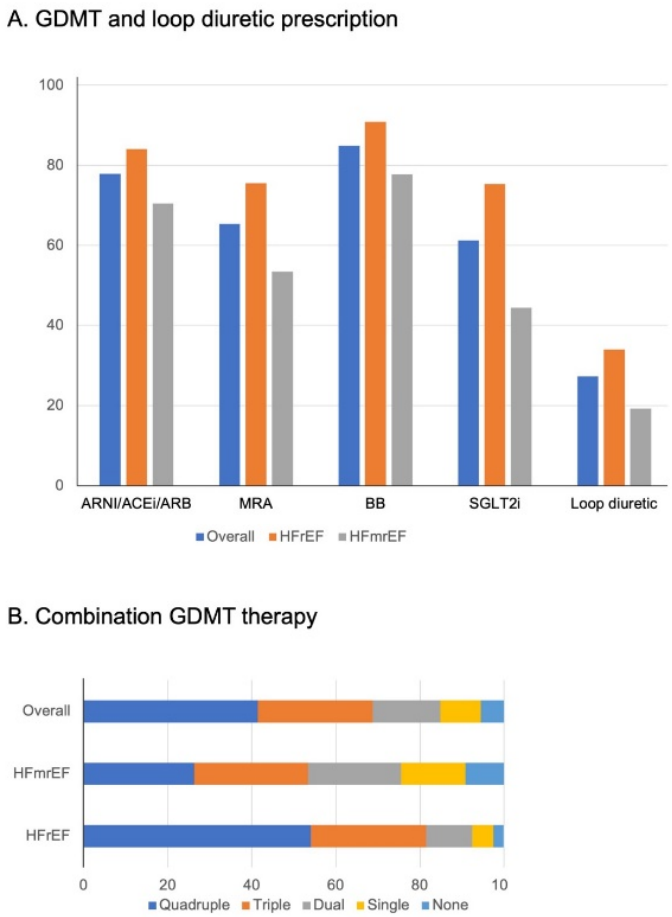
Table 2

Guideline-directed medical therapy prescription rate and dosing

Median % of target dose (IQR)	Total (n=1000)	HFrEF (n=543)	HFmrEF (n=457)	P-value
ARNI/ACEi/ARB	778 (77.8%)	456 (84.0%)	322 (70.5%)	**<0.001**
Median dose in % target dose (95% CI)	50 (25-50)	50 (25-50)	50 (25-50)	0.664
ARNI (%)	444 (44.4%)	318 (58.6%)	126 (27.6%)	**<0.001**
Median dose in % target dose (95% CI)	25 (25-50)	25 (25-50)	25 (25-50)	0.633
ACE/ARB	336 (33.6%)	140 (25.8%)	196 (42.9%)	**<0.001**
Median dose in % target dose (95% CI)	50 (25-50)	44 (25-50)	50 (25-64)	0.067
ACE	250 (25.0%)	146 (31.9%)	104 (19.2%)	**<0.001**
Median dose in % target dose (95% CI)	50 (25-52)	50 (25-50)	50 (25-100)	0.212
ARB	87 (8.7%)	50 (10.9%)	37 (6.8%)	**0.024**
Median dose in % target dose (95% CI)	25 (17-50)	25 (13-50)	25 (25-50)	0.187
MRA	654 (65.4%)	410 (75.5%)	244 (53.4%)	**<0.001**
Median dose in % target dose (95% CI)	50 (25-50)	50 (25-50)	50 (25-50)	0.664
BB	848 (84.8%)	493 (90.8%)	355 (77.7%)	**<0.001**
Median dose in % target dose (95% CI)	50 (25-50)	50 (25-75)	50 (25-50)	**0.042**
SGLT2i	612 (61.2%)	409 (75.3%)	203 (44.4%)	**<0.001**
Median dose in % target dose (95% CI)	100 (100-100)	100 (100-100)	100 (100-100)	**0.015**
Combination therapy	**Total (n=1000)**	**HFrEF (n=543)**	**HFmrEF (n=457)**	**P-value**
Total quadruple therapy	414 (41.4%)	294 (54.1%)	120 (26.3%)	**<0.001**
Quadruple ARNI	317 (31.7%)	236 (43.5%)	81 (17.7%)	
Quadruple ACE/ARB	97 (9.7%)	58 (10.7%)	39 (8.5%)	
Triple therapy	273 (27.3%)	149 (27.4%)	124 (27.1%)	
Dual therapy	161 (16.1%)	60 (11.0%)	101 (22.1%)	
Monotherapy	97 (9.7%)	27 (5.0%)	70 (15.3%)	
None of GDMT medications	55 (5.5%)	13 (2.4%)	42 (9.2%)	

Figure 1

Classes of guidelines-directed medical therapy and combinational therapy



Loop diuretic prescription

In total, 27.3% received loop diuretics as a maintenance therapy at home. Baseline characteristics between patients with and without loop diuretics differed significantly (Supplemental table 3). Overall, patients with loop diuretics were older, had a lower blood pressure and were known with more comorbidities. Loop diuretics were more often prescribed in patients with HFrEF, more severe diastolic dysfunction, higher pulmonary artery pressures or more pronounced mitral insufficiency. Patients on loop diuretics had lower hemoglobin, more impaired kidney function and higher natriuretic peptides.

Long-term outcome

In total, 60 patients died during a median follow-up period of 346 days (25th-75th percentile: 309-395; minimum 11 days; maximum 687 days). Patients who died were older, had a lower BMI, lower blood pressure, and were more frequently diagnosed with atrial fibrillation or peripheral artery disease. On echocardiography they had a lower left ventricular ejection fraction and higher right ventricular systolic pressures. Generally, they had worse kidney function, higher natriuretic peptides and lower hemoglobin levels. Patients who died received RAASi less frequently and loop diuretics more frequently as a maintenance therapy.

Comparison with recent trials and SwedeHF

The subgroup of HFrEF patients from the current database includes 543 patients and reflects an older population compared to recent HFrEF trials such as DAPA-HF and EMPEROR-Reduced, however the cohort was comparable to those in registries such as SwedeHF and TITRATE-HF (Table 3). Across all trials and registries, between 66-77% of the HFrEF patients were male, and the rate of comorbidities were similar. Regarding treatment, 84% of patients received ARNI or ACEi/ARB in the studied population, with ARNI use notably higher (58.6%) than reported in DAPA-HF and EMPEROR-Reduced. Beta-blockers and MRAs were widely used (90.8% and 75.5%, respectively), consistent with trial populations. SGLT2 inhibitors were only reported in the TITRATE-HF with a comparable prescription rate in the current cohort (61% versus 65%). More importantly, use of loop diuretics was significantly lower than in SwedeHF and TITRATE-HF (34% versus 76% and 56%). Importantly, the current database showed a substantial higher implantation rate of CRT and ICD (respectively, 36.5% and 50.1%) compared to the trials and registries.

Table 3

Comparison of the current database (HFrEF population) with recent trials and SwedeHF

	Database HFrEF (n=543)	SwedeHF registry (n=17,809)	DAPA-HF (n=4744)	EMPEROR-reduced (n=3730)	HEART-FID (n=3065)	TITRATE-HF Chronic HF population (n=2240)
History and demographics						
Age (years)	73 (63-80)	74 (65-80)	66.3 (±10.9)	67 (±11)	69 (±11)	71 (63-78)
Male (%)	414 (76.2%)	13305 (74.7%)	3635 (76.6%)	2837 (76.1%)	2028 (66.2%)	1611 (71.9%)
Heart Rate (bpm)	67 ± 15	70 (61-78)	72 ± 12	71 ± 12 72 ± 12	73 ± 10 73 ± 11	70 (62-80)
Systolic blood pressure (mmHg)	120 ± 18		112 ± 16	123 ± 16 121 ± 15	124 ± 16 123 ± 16	124 ± 20
Hypertension	305 (56%)	8659 (50.0%)		2698 (72.3%)		1082 (48.3%)
Diabetes Mellitus	147 (27%)	4780 (27.0%)	2605 (54.9%)	1856 (49.8%)	1385 (45.2%)	567 (25.3%)
Atrial fibrillation/flutter	269 (49.5%)	8848 (55.5%)	1687 (35.6%)	1369 (36.7%)	1340 (43.7%)	442 (21.7%)
LVEF; median (IQR)	35 (30-40)		31 ± 7	28 ± 6 27 ± 6	31 ± 7 31 ± 7	35 (30-42)
Laboratory						
Hemoglobin (g/dL)	13.6 ± 1.9	13.5 (12.3-14.6)			12.5 (±1.4)	
eGFR (mL/min/1.73m^2)	57 (39-71)	59 (44-78)	66 ± 20 66 ± 19	62 ± 22	59 ± 22 61 ± 22	60 (46-75)
NT-proBNP (ng/L)	1850 (762-5065)	2070 (844-4640)	1428 (857-2655) 1446 (857-2641)	1887 (1077-3429) 1926 (1153-3525)	1486 (727-3045) 1424 (710-2884)	904 (325-2275)

Medication						
ARNI or ACEi/ARB	456 (84.0%)	16574 (93%)				89%
ARNI	318 (58.6%)	1273 (7.1%)	508 (10.7%)	727 (14.5%)	909 (29.7%)	57.9%
ACEi/ARB	140 (25.8%)	ACEi: 9639 (54.1%) ARB: 5662 (31.8%)	ACEi: 2661 (56.1%) ARB: 1307 (27.6%)	2600 (69.7%)	1824 (59.6%)	
MRA	410 (75.5%)	8573 (48.3%)	3370 (71.0%)	2661 (71.3%)	1705 (55.6%)	75%
BB	493 (90.8%)	16593 (93.2%)	4558 (96.1%)	3533 (94.7%)	2833 (92.5%)	88%
SGLT2i	409 (75.3%)					64%
Statins	394 (72.6%)	10000 (56.2%)				58%
Amiodarone	104 (19.2%)					10%
Antiplatelet agents	274 (50.5%)	7110 (40.0%)				
Anticoagulants	234 (43.1%)	9158 (51.5%)				63%
Loop diuretics (%)	185 (34.0%)	10036 (76.3%)	4433 (93.4%)			56%
Cardiac Implantable Electronic Device						
CRT	198 (36.5%)	2235 (12.5%)	1242 (26.2%)	442 (11.8%)	462 (15.1%)	
ICD	272 (50.1%)	2779 (15.6%)	354 (7.5%)	1171(31.4%)	979 (32.0%)	

DISCUSSION

This study was a prospective registry, including 1000 consecutive HF patients with LVEF < 50% visiting the outpatient heart failure clinic of a tertiary hospital center in Belgium. Key findings of the study include that 1) the baseline characteristics of the patient cohort were comparable to those reported in recent heart failure trials and the SwedeHF registry, reflecting a real-world, old and comorbid population; 2) GDMT was more frequently prescribed in HFrEF patients compared to HFmrEF, with 82% receiving triple or quadruple therapy, highlighting strong adherence to evidence-based care; 3) loop diuretics were prescribed in only 27.3% of patients, predominantly those with severe heart failure or comorbidities. This study provides valuable insights into the characteristics, treatment patterns, and management of heart failure in a contemporary outpatient cohort. The findings underscore the progress in adherence to GDMT, likely causing decreased need for maintenance loop diuretic therapy.

Quadruple heart failure therapy receives a class I recommendation to treat patients with HFrEF and IIb for patients with HFmrEF. Loop diuretics are recommended to relieve signs and symptoms of congestion (Class I). (8) All individual pillars of the quadruple heart failure therapy have demonstrated to improve morbidity and mortality, with an additional benefit of combinational therapy. (27,201–207) Patient receiving all four pillars are estimated to have a relative risk reduction of approximately 60% for individual endpoints of all-cause death, cardiovascular death and heart failure hospitalizations. (207) Despite this, implementation in daily practice remains limited with clinical inertia as one of the most reversible factors. (208–211) The current database collected data from a specialized heart failure care unit and highlights the importance of physicians critically evaluating and optimizing GDMT to achieve high implementation rates in real-world patients with HFrEF. This demonstrates that with careful attention to therapy optimization, it is possible to translate evidence-based guidelines into routine practice, ultimately improving patient outcomes. Comparable results were noted by the TITRATE-HF study, which showed that prescription rates were considerably higher in dedicated heart failure units, highlighting the importance of strategies committed to GDMT optimization. (212) As clinical inertia is the main reason for insufficient GDMT uptitration (misperception of stable heart failure,

risk-treatment paradox, …) (209,212–214), it is important to optimize heart failure clinics with a transmural heart failure disease management strategy. Every encounter with the patient should be used as a moment to reevaluate GDMT, loop diuretic dosing, and comorbidities (215–219). A structured transmural approach enhances therapy optimization by integrating multidisciplinary collaboration, ensuring continuous follow-up, and engaging in remote monitoring strategies to detect early signs of decompensation. By bridging inpatient and outpatient care, this model reduces hospitalizations, facilitates early intervention, and improves adherence to GDMT.

Overall, the study population reflected the heart failure population seen in daily practice, with most of the patients with reduced ejection fraction being male with a median age around 72 years old with a high burden of comorbidities (atrial fibrillation, hypertension, hyperlipidemia, ..). (220) Patients with HFrEF had more frequently a history of ischemic heart disease, worse kidney function and higher natriuretic peptides. As expected, prescription rates of all four pillars were higher in patients with HFrEF (class I recommendation) compared to HFmrEF, with 82% and 53% receiving triple or quadruple therapy, respectively. In contrast to the HFrEF population, there are no dedicated prospective trials evaluating individual therapies specifically in patients with HFmrEF. As a result, treatments in this subpopulation are primarily supported by meta-analyses and retrospective studies, leading to a class IIb recommendation in current guidelines. (8) Importantly, in this cohort, once therapy was prescribed, the median doses were comparable to those in the HFrEF group. This underscores the need to optimize treatment by striving for the highest tolerated dose in every patient, regardless of their underlying ejection fraction.

Loop diuretics remain a cornerstone of symptom management in heart failure, particularly for relieving congestion. However, their association with worse outcomes at higher doses is well-documented. (20,138,198,199) In our study, 27% of patients (34% in HFrEF population) were prescribed loop diuretics, which was significantly lower compared to recent trials and the SwedeHF registry (76%). The difference in prescription rates may partly be explained by their methodological differences. SwedeHF is a nationwide registry that includes both inpatients and outpatients, with data entry from hospitals and primary care

centers, whereas the current cohort focuses on a dedicated outpatient heart failure clinic. Additionally, the inclusion of inpatients in SwedeHF may reflect a higher degree of congestion in some patients, potentially leading to an increased need for loop diuretics. In our cohort, loop diuretics were primarily prescribed in older patients with more severe heart failure, more comorbidities, and worse hemodynamic profiles. Clinicians should consider vigorous GDMT optimization to minimize reliance on loop diuretics. The prescription of loop diuretics should be a dynamic and carefully managed process, with frequent reassessments to evaluate the feasibility of dose downtitration. Possible tools for guiding diuretic titration are pulmonary artery pressure (PAP) monitoring devices, which have shown in several trials that PAP-guided therapy leads to improved heart failure management by reducing hospitalizations and optimizing diuretic dosing. (14,221,222) By providing real-time hemodynamic data, these devices facilitate a more personalized approach to volume management with dynamic changes in loop diuretic therapy.

CONCLUSION

In conclusion, this study highlights the strengths and challenges in contemporary heart failure management. While adherence to GDMT in HFrEF has improved significantly, there remains room for enhancing care and addressing key comorbidities such as iron deficiency. A comprehensive, patient-centered approach to heart failure management is crucial to further improve outcomes, minimize dependence on loop diuretics, and maximize the benefits of recent therapeutic advancements.

SUPPLEMENTAL MATERIAL

Supplemental table 1

Univariate analyses between patients with three or more GDMT prescriptions and those with less

	Total (n=1000)	Triple or quadruple GDMT (n=687)	Others (n=313)	P-value
Age (years)	72 (63-80)	72 (62-79)	74 (63-82)	0.058
Male (%)	726 (72.6%)	498 (72.5%)	228 (72.8%)	0.939
Vital signs				
Heart Rate (bpm)	68 ± 14	68 ± 14	69 ± 15	0.083
Systolic blood pressure (mmHg)	123 ± 20	121 ± 19	129 ± 21	**<0.001**
Diastolic blood pressure (mmHg)	72 ± 11	71 ± 10	75 ± 12	**<0.001**
Comorbidities				
Hypertension	562 (56.2%)	386 (56.2%)	176 (56.2%)	1.000
Diabetes Mellitus	260 (26.0%)	194 (28.2%)	66 (21.1%)	**0.020**
Hypercholesterolemia	557 (55.7%)	382 (55.6%)	175 (55.9%)	0.945
Atrial fibrillation/flutter	474 (47.4%)	337 (49.1%)	137 (43.8%)	0.133
Peripheral artery disease	212 (21.2%)	149 (21.7%)	63 (20.1%)	0.617
PCI/PTCA/CABG	532 (53.2%)	373 (54.3%)	159 (50.8%)	0.306
Valve surgery	107 (10.7%)	80 (11.6%)	27 (8.6%)	0.185
Echocardiographic data				
LVEF (%)	45 (35-45)	40 (35-45)	45 (41-50)	**<0.001**
LVEDD (mm)	50 (± 8)	51 ± 8	48 ± 8	**<0.001**
Diastolic dysfunction Grade 1 Grade 2 Grade 3 Indeterminate	 277 (27.7%) 59 (5.9%) 72 (7.2%) 592 (59.2%)	 199 (29.0%) 37 (5.4%) 54 (7.9%) 397 (57.8%)	 78 (24.9%) 22 (7.0%) 18 (5.8%) 195 (62.3%)	0.320
RVSP (mmHg)	25 (22-31)	25 (22-31)	26 (24-35)	**0.022**
TAPSE (mm)	20 (16-25)	20 (16-26)	21 (17-25)	0.576
Mitral valve insufficiency (grade)	1 (0-1)	1 (1-1)	1 (0-1)	**<0.001**

Laboratory				
Hemoglobin (g/dL)	13.5 (± 2.0)	13.7 ± 2.0	13.0 ± 1.9	**<0.001**
Sodium (mmol/L)	139 (137-141)	139 (137-141)	139 (137-141)	0.205
Potassium (mmol/L)	4.32 (4.02-2.64)	4.36 (4.05-4.67)	4.23 (3.96-4.54)	**<0.001**
Creatinine (mg/dL)	1.15 (0.93-1.45)	1.17 (0.97-1.50)	1.09 (0.89-1.38)	**0.011**
eGFR ($mL/min/1.73m^2$)	60 (43-77)	58 (43-76)	64 (45-80)	**0.025**
NT-proBNP (ng/L)	1651 (570-4793)	1579 (548-4254)	2267 (668-6353)	0.167
Medication				
ARNI or ACEi/ARB	778 (77.8%)	635 (93.1%)	143 (46.0%)	**<0.001**
MRA	654 (65.4%)	610 (88.8%)	44 (14.1%)	**<0.001**
BB	848 (84.8%)	658 (95.8%)	190 (60.7%)	**<0.001**
SGLT2i	612 (61.2%)	570 (83.0%)	42 (13.5%)	**<0.001**
Statins	697 (69.7%)	492 (71.7%)	205 (65.7%)	0.063
Amiodarone	141 (14.1%)	114 (16.6%)	27 (8.7%)	**<0.001**
Antiplatelets	484 (48.4%)	320 (46.6%)	164 (52.6%)	0.088
Anticoagulants	418 (41.8%)	312 (45.5%)	106 (34.0%)	**<0.001**
Loop diuretics (%)	273 (27.3%)	207 (30.1%)	66 (21.2%)	**0.004**
Loop diuretics dose in furosemide equivalents	40 (20-40)	40 (20-40)	40 (20-40)	0.209
Cardiac Implantable Electronic Device				
Pacemaker	64 (6.4%)	32 (5.0%)	32 (10.8%)	**0.002**
CRT	343 (34.3%)	266 (41.4%)	77 (25.9%)	**<0.001**
ICD	360 (36.0%)	316 (49.2%)	44 (14.8%)	**<0.001**
PAP sensor	14 (1.4%)	12 (1.9%)	2 (0.7%)	0.247

Supplemental table 2

Univariate analyses between patients with three or more GDMT prescriptions and those with less in patients with HFrEF

	Total (n=477)	Triple or quadruple GDMT (n=401)	Others (n=76)	P-value
Age (years)	72 (62-79)	71 (62-78)	74 (63-84)	0.053
Male (%)	365 (76.5%)	304 (75.8%)	61 (80.3%)	0.462
Vital signs				
Heart Rate (bpm)	68 ± 14	68 ± 14	70 ± 16	0.245
Systolic blood pressure (mmHg)	119 ± 18	119 ± 18	122 ± 20	0.238
Diastolic blood pressure (mmHg)	71 ± 11	71 ± 10	72 ± 12	0.434
Comorbidities				
Hypertension	269 (56.4%)	220 (54.9%)	49 (64.5%)	0.131
Diabetes Mellitus	129 (27.0%)	111 (27.7%)	18 (23.7%)	0.573
Hypercholesterolemia	273 (57.2%)	231 (57.6%)	42 (55.3%)	0.706
Atrial fibrillation/flutter	235 (49.3%)	193 (48.1%)	42 (55.3%)	0.263
Peripheral artery disease	111 (23.3%)	95 (23.7%)	16 (21.1%)	0.660
PCI/PTCA/CABG	276 (57.9%)	240 (59.9%)	36 (47.4%)	0.057
Valve surgery	47 (9.9%)	41 (10.2%)	6 (7.9%)	0.676
Echocardiographic data				
LVEF (%)	35 (30-40)	35 (30-40)	40 (35-40)	**0.002**
LVEDD (mm)	53 ± 9	53 ± 9	53 ± 9	0.661
Diastolic dysfunction Grade 1 Grade 2 Grade 3 Indeterminate	 150 (31.4%) 33 (6.9%) 47 (9.9%) 247 (51.8%)	 131 (32.7%) 24 (6.0%) 37 (9.2%) 209 (52.1%)	 19 (25.0%) 9 (11.8%) 10 (13.2%) 38 (50.0%)	0.143
RVSP (mmHg)	25 (23-33)	25 (22-31)	28 (25-38)	**0.031**
TAPSE (mm)	19 (16-25)	19 (15-25)	18 (15-24)	0.621
Mitral valve insufficiency (grade)	1 (1-1)	1 (1-1)	1 (1-1)	0.800
Laboratory				
Hemoglobin (g/dL)	13.7 ± 1.9	13.8 ± 1.9	13.2 ± 1.7	**0.036**

Sodium (mmol/L)	139 (137-141)	139 (137-141)	139 (137-141)	0.861
Potassium (mmol/L)	4.35 (4.05-4.67)	4.35 (4.05-4.67)	4.38 (4.09-4.63)	0.862
Creatinine (mg/dL)	1.22 (1.01-1.59)	1.22 (1.02-1.56)	1.23 (0.99-1.88)	0.306
eGFR (mL/min/1.73m^2)	57 (39-71)	57 (40-73)	57 (32-67)	0.331
NT-proBNP (ng/L)	2112 (822-5074)	1782 (769-4545)	5083 (1479-8991)	**0.018**
Medication				
ARNI or ACEi/ARB	404 (85.4%)	372 (93.5%)	32 (42.7%)	**<0.001**
MRA	371 (77.8%)	356 (88.8%)	15 (19.7%)	**<0.001**
BB	429 (89.9%)	385 (96.0%)	44 (57.9%)	**<0.001**
SGLT2i	377 (79.0%)	360 (89.8%)	17 (22.4%)	**<0.001**
Statins	352 (73.8%)	305 (76.1%)	47 (61.8%)	**0.015**
Amiodarone	96 (20.1%)	84 (20.9%)	12 (15.8%)	0.351
Antiplatelets	246 (51.6%)	204 (50.9%)	42 (55.3%	0.532
Anticoagulants	209 (43.8%)	182 (45.4%)	27 (35.5%)	0.130
Loop diuretics (%)	163 (34.2%)	136 (33.9%)	27 (35.5%)	0.793
Loop diuretics dose in furosemide equivalents	40 (20-40)	40 (20-40)	40 (20-80)	**0.026**
Cardiac Implantable Electronic Device				
Pacemaker	27 (5.9%)	19 (4.9%)	8 (11.1%)	0.053
CRT	184 (40.0%)	156 (40.2%)	28 (38.9%)	0.896
ICD	268 (58.3%)	240 (61.9%)	28 (38.9%)	**<0.001**
PAP sensor	12 (2.6%)	10 (2.6%)	2 (2.8%)	1.000

Supplemental table 3

Univariate analysis between patients with or without loop diuretics

	Total (n=1000)	No loop diuretics (n=727)	Loop diuretics (n=273)	P-value
Age (years)	72 (63-80)	70 (61-78)	77 (70-84)	**<0.001**
Male (%)	726 (72.6%)	539 (74.1%)	187 (68.5%)	0.080
Vital signs				
Heart Rate (bpm)	68 ± 14	68 ± 14	68 ± 14	0.556
Systolic blood pressure (mmHg)	123 ± 20	125 ± 20	120 ± 20	**0.001**
Diastolic blood pressure (mmHg)	72 ± 11	74 ± 11	70 ± 11	**<0.001**
Comorbidities				
Hypertension	562 (56.2%)	394 (54.2%)	168 (61.5%)	**0.038**
Diabetes Mellitus	260 (26.0%)	174 (23.9%)	86 (31.5%)	**0.019**
Hypercholesterolemia	557 (55.7%)	406 (55.8%)	151 (55.3%)	0.887
Atrial fibrillation/flutter	474 (47.4%)	289 (39.8%)	185 (67.8%)	**<0.001**
Peripheral artery disease	212 (21.2%)	124 (17.1%)	88 (32.2%)	**<0.001**
PCI/PTCA/CABG	532 (53.2%)	385 (53.0%)	147 (53.8%)	0.831
Valve surgery	107 (10.7%)	59 (8.1%)	48 (17.6%)	**<0.001**
Echocardiographic data				
HFrEF	543 (54.3%)	358 (49.2%)	185 (67.8%)	**<0.001**
LVEF (%)	45 (35-45)	45 (35-50)	40 (30-45)	**<0.001**
LVEDD (mm)	50 ± 8	49 ± 8	52 ± 9	**<0.001**
Diastolic dysfunction Grade 1 Grade 2 Grade 3 Indeterminate	 277 (27.7%) 59 (5.9%) 72 (7.2%) 592 (59.2%)	 226 (31.1%) 42 (5.8%) 31 (4.3%) 428 (58.9%)	 51 (18.7%) 17 (6.2%) 41 (15.0%) 164 (60.1%)	**<0.001**
RVSP (mmHg)	25 (22-31)	25 (22-30)	28 (25-35)	**<0.001**
TAPSE (mm)	20 (16-25)	20 (16-25)	20 (16-26)	0.867
Mitral valve insufficiency (grade)	1 (0-1)	1 (0-1)	1 (1-1)	**<0.001**
Laboratory				
Hemoglobin (g/dL)	13.5 ± 2.0	13.7 ± 1.9	12.9 ± 2.1	**<0.001**
Sodium (mmol/L)	139	139	139	0.247

	(137-141)	(137-141)	(137-141)	
Potassium (mmol/L)	4.32 (4.02-2.64)	4.31 (4.02-4.64)	4.33 (4.01-4.68)	0.879
Creatinine (mg/dL)	1.15 (0.93-1.45)	1.07 (0.91-1.29)	1.40 (1.12-1.83)	**<0.001**
eGFR (mL/min/1.73m^2)	60 (43-77)	66 (51-81)	44 (32-60)	**<0.001**
NT-proBNP (ng/L)	1651 (570-4793)	1036 (323-3237)	2484 (1235-5617)	**<0.001**
Medication				
ARNI or ACEi/ARB	778 (77.8%)	581 (80.0%)	197 (73.8%)	**0.037**
MRA	654 (65.4%)	438 (60.3%)	216 (79.1%)	**<0.001**
BB	848 (84.8%)	606 (83.4%)	242 (88.6%)	**0.038**
SGLT2i	612 (61.2%)	414 (57.0%)	198 (72.8%)	**<0.001**
Combination therapy None Single Dual Triple Quadruple	 55 (5.5%) 97 (9.7%) 161 (16.1%) 273 (27.3%) 414 (41.4%)	 49 (6.7%) 78 (10.7%) 120 (16.5%) 199 (27.4%) 281 (38.7%)	 6 (2.2%) 19 (7.0%) 41 (15.0%) 74 (27.1%) 133 (48.7%)	**0.004**
Statins	697 (69.7%)	511 (70.5%)	186 (68.1%)	0.487
Amiodarone	141 (14.1%)	70 (9.6%)	71 (26.0%)	**<0.001**
Antiplatelets	484 (48.4%)	376 (51.8%)	108 (39.6%)	**<0.001**
Anticoagulants	418 (41.8%)	253 (34.9%)	165 (60.4%)	**<0.001**
Cardiac Implantable Electronic Device				
Pacemaker	64 (6.4%)	33 (4.8%)	31 (12.6%)	**<0.001**
CRT	343 (34.3%)	231 (33.3%)	112 (45.5%)	**<0.001**
ICD	360 (36.0%)	255 (36.8%)	105 (42.7%)	0.109
PAP sensor	14 (1.4%)	1 (0.1%)	13 (5.3%)	**<0.001**

Supplemental table 4

Univariate analysis between patients who died or survived during the follow-up period

	Survived (n=940)	Dead (n=60)	P-value
Age (years)	72 (62-79)	81 (74-87)	**<0.001**
Male (%)	680 (72.3%)	46 (76.7%)	0.551
Vital signs			
BMI (kg/m^2)	27 (24-30)	24 (21-28)	**<0.001**
Heart Rate (bpm)	68 ± 13	68 ± 24	0.968
Systolic blood pressure (mmHg)	124 ± 20	116 ± 22	**0.005**
Diastolic blood pressure (mmHg)	73 ± 11	68 ± 13	**0.001**
Comorbidities			
Hypertension	520 (55.5%)	40 (66.7%)	0.107
Diabetes Mellitus	241 (25.6%)	19 (31.7%)	0.292
Hypercholesterolemia	526 (56.0%)	31 (51.7%)	0.592
Atrial fibrillation/flutter	431 (45.9%)	43 (71.7%)	**<0.001**
Peripheral artery disease	193 (20.5%)	19 (31.7%)	**0.050**
PCI/PTCA/CABG	506 (53.8%)	26 (43.3%)	0.142
Valve surgery	99 (10.5%)	8 (13.3%)	0.516
Echocardiographic data			
HFrEF	440 (47.9%)	37 (62.7%)	0.088
LVEF (%)	45 (35-50)	40 (25-45)	**<0.001**
LVEDD (mm)	50 ± 8	50 ± 9	0.596
Diastolic dysfunction			**<0.001**
Grade 1	275 (29.3%)	2 (3.3%)	
Grade 2	52 (5.5%)	7 (11.7%)	
Grade 3	59 (6.3%)	13 (21.7%)	
Indeterminate	554 (58.9%)	38 (63.3%)	
RVSP (mmHg)	25 (22-30)	35 (30-40)	**<0.001**
TAPSE (mm)	20 (16-25)	19 (14-25)	0.571
Mitral valve insufficiency (grade)	1 (0-1)	1 (1-2)	**<0.001**
Laboratory			
Hemoglobin (g/dL)	13.6 ± 1.9	11.8 ± 2.3	**<0.001**
Sodium (mmol/L)	139 (137-141)	139 (135-142)	0.370
Potassium (mmol/L)	4.32 (4.02-4.64)	4.25 (3.92-4.63)	0.220

Creatinine (mg/dL)	1.13 (0.93-1.42)	1.51 (1.12-2.13)	**<0.001**
eGFR (mL/min/1.73m^2)	61 (44-78)	42 (28-56)	**<0.001**
NT-proBNP (ng/L)	1,587 (549-4,181)	5,147 (1,338 -15,327)	**<0.001**
Medication			
ARNI or ACEi/ARB	741 (79.3%)	37 62.7%)	**0.005**
MRA	621 (66.1%)	33 (55.0%)	0.092
BB	795 (84.6%)	53 (88.3%)	0.577
SGLT2i	578 (61.6%)	34 (57.6%)	0.582
Combination therapy			0.473
None	50 (5.3%)	5 (8.3%)	
Single	89 (9.5%)	8 (13.3%)	
Dual	149 (15.9%)	12 (20.0%)	
Triple	258 (27.4%)	15 (25.0%)	
Quadruple	394 (41.9%)	20 (33.3%)	
Loop diuretics	238 (25.3%)	35 (58.3%)	**<0.001**
Statins	661 (70.5%)	36 (60.0%)	0.109
Amiodarone	120 (12.8%)	21 (35.0%)	**<0.001**
Antiplatelets	460 (49.0%)	24 (40.0%)	0.185
Anticoagulants	383 (40.8%)	25 (58.3%)	**0.010**

CHAPTER 13

Home-based urinary sodium monitoring via point-of-care testing for personalized diuretic titration in heart failure management: The EASY-STOP Study

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ABSTRACT

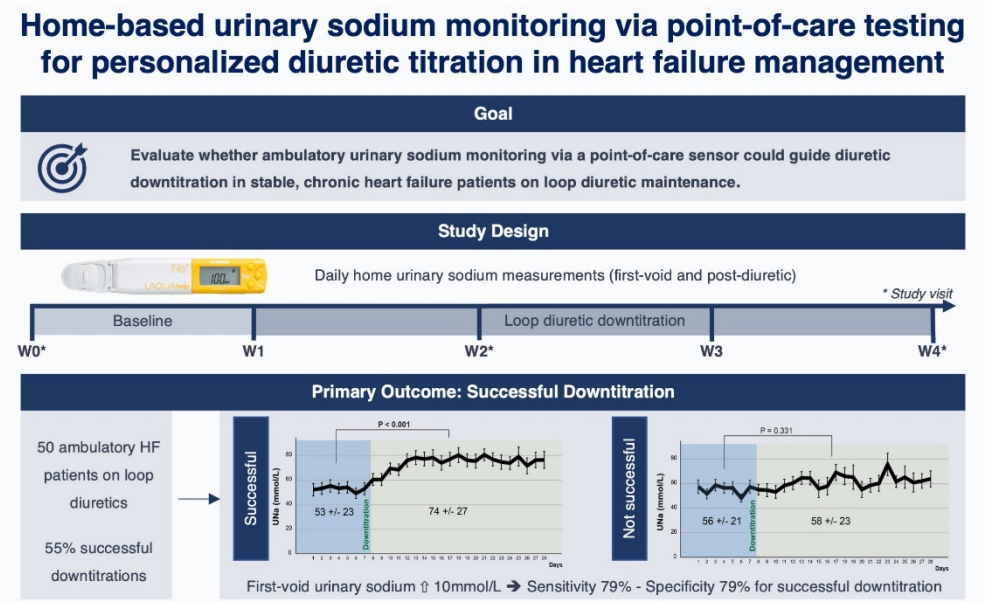
Background: Loop diuretics alleviate symptoms in heart failure (HF), but despite recommendations for dynamic dosing, implementation in practice remains challenging. The EASY-STOP trial investigated whether ambulatory urinary sodium monitoring using a point-of-care sensor could guide diuretic downtitration.

Methods: This prospective, single-center study enrolled 50 euvolemic HF patients on stable guideline-directed medical therapy for ≥3months and receiving maintenance loop diuretic (≥20mg furosemide equivalent daily). After a one-week baseline phase of daily self-measured first-void and post-diuretic urinary sodium assessment, loop diuretics were gradually reduced by 50% and discontinued when ≤20mg furosemide equivalents. Urinary monitoring continued for another three weeks. Successful downtitration was defined as remaining congestion-free (no rise in NYHA class ≥I, edema, pleural effusion, ascites, rise in RVSP ≥10mmHg, or worsening diastolic dysfunction ≥1 grade). Investigators and patients were blinded for urinary sodium analysis during the study.

Results: Patients were 75 (68-79) years old, had LVEF 46 (± 11) %, estimated glomerular filtration rate 47(35-65) mL/min and NT-proBNP 899(326-2558) ng/L. Among the 50 patients, 62 diuretic downtitrations were performed, of which 34(55%) were successful. Baseline urinary sodium before loop diuretic downtitration was similar both groups. However, patients who successfully achieved downtitration exhibited a significant increase in first-void urinary sodium following downtitration (53 to 74 mmol/L, $p<0.001$), whereas those requiring reinitiation showed no significant change (56 to 58 mmol/L, $p=0.331$). A 10 mmol/L increase predicted successful downtitration with 79.4% sensitivity and 78.6% specificity (AUC=0.851).

Conclusions: Point-of-care urinary sodium monitoring may represent a non-invasive and personalized approach to diuretic titration in HF management. Further trials are warranted to validate its clinical utility and long-term benefits.

GRAPHICAL ABSTRACT



INTRODUCTION

Heart failure (HF) remains a leading cause of hospitalization worldwide, with congestion being the primary driver of admissions. (223) Loop diuretics are widely used to alleviate congestion and hold a Class I recommendation in HF guidelines to provide relief of signs and symptoms of fluid overload. (25) Despite their widespread use in 76 to 94% of patients in registries and recent HF trials (27–29,202,224–226), loop diuretics are not part of the guideline-directed medical therapy (GDMT) aimed at improving long-term outcomes. Paradoxically, higher loop diuretic maintenance dosing has been consistently associated with poorer prognosis in HF, including an increased risk of rehospitalization and mortality, with patients on higher diuretic doses experiencing worse long-term outcomes. (20,88,198,199). Although this relationship may be confounded by disease severity, as patients with advanced HF often require higher doses of loop diuretics. Nevertheless, loop diuretics are known to induce electrolyte disturbances, neurohumoral activation, hypotension (potentially limiting the use of disease modifying guideline-directed medical therapy) and progressive kidney dysfunction. Consequently, current recommendations advocate for individualized loop diuretic dosing, with dynamic adjustments over time and using the lowest effective dose. (3) Despite their frequent use, no standardized or widely applicable metrics exist for optimal diuretic titration in clinical practice. Weight-based adjustments are often unreliable due to daily fluctuations because of hydration status and measurement errors, and patients often struggle to recognize early signs of congestion, leading to delayed adjustments and preventable hospitalizations. Pulmonary artery pressure sensors have emerged as the most effective remote congestion monitoring tool in selected symptomatic HF patients, demonstrating reduction in HF-related hospitalizations. (14,221,222) However, their invasive nature, high cost, and limited accessibility prevent widespread implementation. Given these challenges, there is a critical need for a practical, non-invasive, and cost-effective approach to guide diuretic titration. The 'REadily available UrinAry Sodium analYsis to STOP Loop Diuretics in patients with Heart Failure' (EASY-STOP) study aims to evaluate whether urinary sodium measurements could serve as a novel biomarker for dynamic, home-based diuretic adjustment enabling patient-driven optimization of diuretic therapy.

METHODS

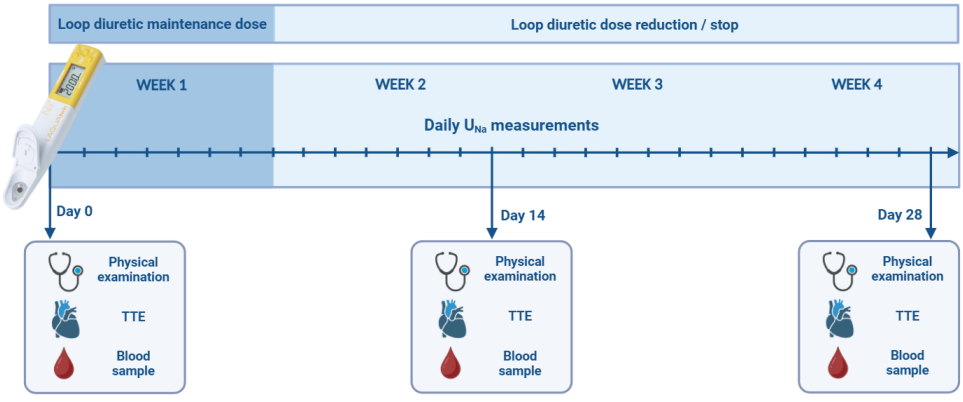
Study population and trial design

Consecutive patients with chronic heart failure were prospectively enrolled from a single tertiary heart failure clinic (Ziekenhuis Oost-Limburg, Genk, Belgium). Eligible patients were adults (>18 years) who provided written informed consent. Inclusion criteria compromised (1) stable chronic heart failure without hospitalization for HF the preceding 6 months, (2) ongoing maintenance therapy with loop diuretics (minimum of 20mg of furosemide equivalents daily (= 0.5 mg of bumetanide)) for at least the last 6 months (3) absence of clinical signs of congestion (limited to trace ankle edema, with no pleural effusion or ascites) and stable normal right ventricular systolic pressures and (4) stable doses of guideline-directed medical therapy for at least three months. Key exclusion criteria included (1) inability to collect timed urine samples; (2) inability to use the point-of-care sodium sensor (LAQUAtwin Na-11 meter, HORIBA) and (3) current or planned for renal replacement therapy.

The study was carried out in accordance with the Declaration of Helsinki. The trial protocol was approved by the local ethical committee. All patients provided written informed consent prior to inclusion.

Figure 1

Study design



Baseline data collection

Following informed consent, patients underwent a standardized baseline evaluation, which included a comprehensive medical history, medication assessment, physical examination, transthoracic echocardiography, and blood sampling (Figure 1). The estimated glomerular filtration rate (eGFR) was calculated by the creatinine-based CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Additionally, patients received dietary counseling in accordance with the European Society of Cardiology (ESC) heart failure guidelines, emphasizing a balanced healthy diet and the avoidance of excessive sodium intake. (25)

Daily urinary sodium measurements and vital signs

During the baseline visit, patients received detailed instructions on the collection of ambulatory spot urine samples and the use of the HORIBA point-of-care sensor for urinary sodium quantification. Participants were instructed to collect a first-void urine sample daily on awaking. While on oral diuretic therapy, they were also required to collect a second urine sample two hours after diuretic intake. Urinary sodium concentration measurements were self-performed using the LAQUAtwin Na-11 meter (HORIBA). (82) This advanced liquid sensor provides a quantitative assessment of sodium concentration in spot urine samples (Supplemental figure 1). Before their first measurement, patients calibrated the sensor using standard reference solutions (150ppm and 2000ppm). The accuracy of the sensor had been validated prior to study initiation. (106) The ion-selective membrane interacts selectively with the pre-specified ions and generates a voltage that scales with concentration. The result is immediately readable and results are given in parts per million (PPM). Patients were instructed to collect these data, which were converted to mmol/L only after the monitoring period and collection of end-points. In addition to urinary sodium measurements, patients recorded their daily weight and blood pressure.

Diuretic downtitration and clinical follow-up visits

Following enrollment, patients continued their baseline loop diuretic regimen and collected urinary sodium samples twice daily (first morning void and two hours after diuretic intake) for one week (Figure 1). After this week, loop diuretic dose was reduced by 50% or discontinued if they were taking furosemide 20 mg equivalents daily. If patients could remain on a reduced loop diuretic dose after successful downtitration (with 50%) without occurrence of congestion, they were eligible for a second consecutive downtitration (again with 50%). After diuretic downtitration, patients continued daily urinary sodium measurements for three weeks - once daily (first morning void) if diuretics were discontinued, or twice daily (including a two hours post-diuretic intake sample) if the dose was reduced. Prescheduled study visits were conducted at weeks 2 and 4 (i.e., 1 and 3 weeks post-downtitration). Physicians were blinded to urinary sodium measurement and diuretic dosing at the study visit. Patients were provided with an emergency contact and instructed to seek medical attention from the study team in the event of congested-related symptoms. During follow-up visits, participants underwent a physical examination, transthoracic echocardiography and laboratory assessments. During the downtitration process, no changes in GDMT or other medications were allowed as this could have interfered with urinary sodium values.

Endpoints

Emerging congestion was defined as the need for reinitiation or escalation of loop diuretic therapy due to (1) the development of congestion characterized by either increase in New York Heart Association (NYHA) class ≥ I, edema, pleural effusion or ascites and/or (2) a rise in right ventricular systolic pulmonary artery pressures (RVSP) (≥ 10 mmHg) (measured on echocardiography, without the addition of right atrial pressure) or worsening diastolic dysfunction with > 1 grade on transthoracic echocardiography. Urinary sodium monitoring was discontinued if a predefined study endpoint was reached before to the scheduled 4-week study completion visit.

Statistics

Normality of continuous data was assessed using a Shapiro-Wilk test. Variables are summarized as means with standard deviations, medians with 25-75th percentile, or numbers with percentages and evaluated using ANOVA, Kruskal-Wallis and Chi-square tests as appropriate. 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 or in case of dependent data with the McNemar test. The mean urinary sodium concentration prior and post-diuretic downtitration were compared using a paired-sample t-test. Linear mixed model was used to analyze the time effect of the urinary sodium concentration prior and post-diuretic downtitration. Due to the anticipated occurrence of missing values in the repeated-measures design, mixed modeling was selected over repeated-measures analysis of variance. A first-order autoregressive structure was applied to model the time effect, as measurements of sodium taken closer in time were assumed to exhibit higher correlations. The model included the fixed effect of time and a random intercept. To assess the group effect (successful downtitration or reinitiation of diuretics), this was added as a fixed effect in the model. Linear mixed model was also used to evaluate the evolution of different laboratory parameters over time, with a fixed effect of time and group (and their interaction) and random intercept. A linear mixed-effects model was used for a two-slope analysis to evaluate changes in first-void urinary sodium concentration before and after loop diuretic downtitration, with time, phase (pre vs. post-downtitration) and group (successful vs. reinitiated) as fixed effects, and a random intercept to account for within-subject variability. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative ability of urinary sodium concentration in predicting successful diuretic downtitration. The area under the curve (AUC) was calculated to quantify the predictive performance, with an AUC of 0.5 indicating no discriminative ability and an AUC of 1.0 representing perfect discrimination. To determine the optimal urinary sodium concentration threshold for predicting successful downtitration, Youden’s index was applied, where the highest J value identifies the cutoff point that maximizes the sum of sensitivity and specificity.

No adjustments for multiplicity were performed. All the hypotheses testing was 2-sided with a significance level of α = 0.05. All statistical analyses were done using SPSS version 29 (IBM® SPSS ® Inc., Chicago, IL, United States).

RESULTS

Baseline characteristics

A total of 50 patients were enrolled between August 26th, 2024 and January 10th, 2025. The median age of the study population was 75 (68-79) years with a predominance of male participants (72%) (Table 1). The median eGFR was 47 (35-65) mL/min and the median n-terminal pro–B-type natriuretic peptide (NT-proBNP) 899 (326-2558) ng/L. The mean ejection fraction was 46 (± 11) % with 46% having ischemic heart disease, and 26% classified as having heart failure with reduced ejection fraction (HFrEF). Mitral regurgitation (MR) was mild (median grade 1 (0-1)) with none of the patient having moderate or severe MR. Nevertheless, a high proportion of patients were receiving guideline-directed medical therapy (GDMT), including 84% mineralocorticoid receptor antagonists (MRA), 94% beta-blockers, 84% sodium-glucose cotransporter-2 inhibitors (SGLT2i), and 68% angiotensin receptor-neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARB). The median maintenance loop diuretic dose was 20 (20-40) mg of furosemide.

Table 1

Baseline characteristics

	Total (n=50)	LVEF <40% (n=13)	LVEF ≥40% (n=37)	P-value
Demographics				
Age (years)	75 (68-79)	73 (67-77)	77 (67-81)	0.412
Males	36 (72.0%)	13 (100.0%)	23 (62.2%)	**0.010**
Heart failure category				
HFrEF	13 (26.0%)	13 (100.0%)	0 (0.0%)	**<0.001**
HFmrEF	16 (32.0%)	0 (0.0%)	16 (43.2%)	
HFpEF	21 (42.0%)	0 (0.0%)	21 (56.8%)	
Ischemic	23 (46.0%)	8 (61.5%)	15 (40.4%)	0.215
Physical features				
Heart rate (beats/min)	70 ± 12	66 ± 10	72 ± 12	0.171
Systolic blood pressure (mmHg)	120 ± 19	113 ± 21	122 ± 17	0.182
Diastolic blood pressure (mmHg)	69 ± 11	69 ± 12	69 ± 12	0.885

Weight (kg)	83.9 ± 16.4	80.0 ± 13.2	85.2 ± 17.3	0.327
BMI (kg/m^2)	29.0 ± 4.9	26.6 ± 3.6	29.9 ± 5.0	**0.033**
NYHA functional class				
I	16 (32.0%)	5 (38.5%)	11 (29.7%)	0.836
II	22 (44.0%)	5 (38.5%)	17 (45.9%)	
III	12 (24.0%)	3 (23.1%)	9 (24.3%)	
IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Comorbidities				
Atrial fibrillation	34 (68.0%)	9 (69.2%)	25 (67.6%)	1.000
COPD	7 (14.0%)	1 (7.7%)	6 (16.2%)	0.660
Hypertension	31 (62.0%)	5 (38.5%)	26 (70.3%)	0.054
Dyslipidemia	24 (48.0%)	3 (23.1%)	21 (56.8%)	0.062
Diabetes	17 (34.0%)	3 (23.1%)	14 (37.8%)	0.499
Coronary revascularization	23 (46.0%)	8 (61.5%)	15 (40.5%)	0.215
PAD	10 (20.0%)	3 (23.1%)	7 (18.9%)	0.707
Laboratory analysis				
Hemoglobin (g/dL)	14.2 ± 1.7	14.1 ± 2.1	14.2 ± 1.6	0.944
Sodium (mmol/L)	139.9 ± 3.2	139.9 ± 3.8	139.9 ± 3.0	0.950
Potassium (mmol/L)	4.55 ± 0.54	4.61 ± 0.38	4.53 ± 0.59	0.652
Chloride (mmol/L)	102.3 ± 3.0	102.7 ± 3.4	102.1 ± 2.8	0.590
Bicarbonate (mmol/L)	26.6 ± 3.0	27.1 ± 2.8	26.4 ± 3.1	0.522
Osmolality (mOsmol/kg H_20)	301 (295-306)	300 (295-305)	301 (295-307)	0.644
Creatinine (mg/dL)	1.39 (1.05-1.70)	1.55 (1.23-2.21)	1.26 (0.96-1.68)	0.144
Estimated GFR (mL/min)	47 (35-65)	47 (30-58)	47 (37-74)	0.445
NT-proBNP	899 (326-2558)	2585 (1215-3132)	770 (246-1666)	**0.011**
Echocardiography				
LVEF (%)	46 ± 11	32 ± 6	51 ± 6	**<0.001**
LVEDD (mm)	52 ± 7	59 ± 8	50 ± 6	**<0.001**
Mitral regurgitation (grade)	1 (0-1)	1 (0-2)	2 (0.25-1)	0.567
E/e’	13.4 ± 6.4	14. 6 ± 6.8	13.0 ± 6.4	0.528
TAPSE (mm)	19 ± 6	20 ± 5	19 ± 6	0.590
RVSP (mmHg)	27 (24-32)	25 (22-30)	29 (24-33)	0.378
Medication				
ARNI/ACEi/ARB	34 (68.0%)	10 (76.9%)	24 (64.0%)	0.508
SGLT2i	42 (84.0%)	13 (100.0%)	29 (78.4%)	0.093
Beta-blockers	47 (94.0%)	12 (92.3%)	35 (94.6%)	1.000
MRA	42 (84.0%)	12 (92.3%)	30 (81.1%)	0.662

Urinary sodium profile prior to diuretic reduction

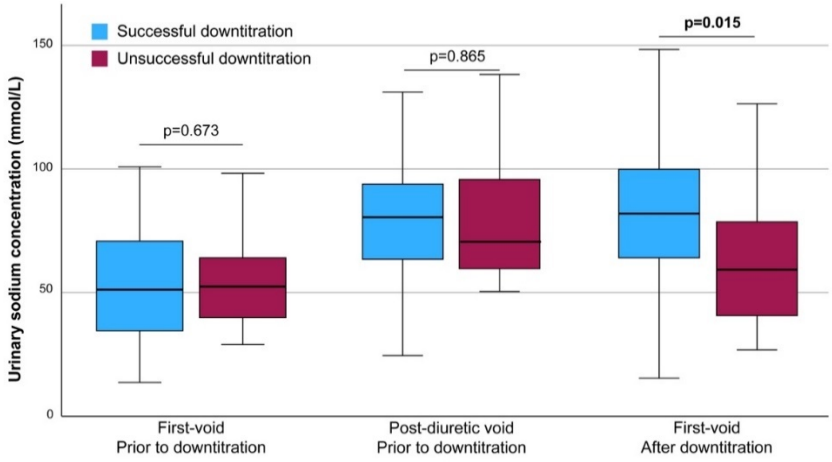
Among 50 patients, 38 patients were on the lowest dose and directly downtitrated to no diuretics, while the remaining 12 underwent two consecutive downtitrations, leading to 62 total diuretic downtitrations. Among the 868 samples (62 x 2x/day x 7 days), 26 (3.0%) first void samples and 36 (4.1%) post-diuretic samples were missing. During the first week before diuretic downtitration, the mean first-void urinary sodium concentration was 55 (± 22) mmoL/L, increasing to 74 (± 22) mmol/L two hours after diuretic intake ($p < 0.001$). There was no significant variation in urinary sodium concentration over time in either the first-void (p-value=0.079) or post-diuretic void samples (p-value = 0.231) (Supplemental figure 2).

Diuretic downtitration and impact on urinary sodium excretion

Of the 62 downtitrations, 34 (55%) were successful, while 28 (45%) required reinitiation of their previous diuretic dose. The reasons for failed diuretic downtitration included most frequently increase in RVSP more than 10mmHg (15/28, 54%), increase in NYHA class ≥ 1 (14/28, 50%), presence of oedema (13/28, 46%), more than 2kg increase in weight (13/28, 46%) and increase in diastolic dysfunction (8/28, 29%). Patients with unsuccessful downtitration had a lower systolic blood pressure (p-value=0.038) and lower rate of cardiac resynchronization therapy (p-value=0.047). However, other baseline characteristics including diuretic dosing did not differ significantly between both groups (Supplemental table 1). Notably, there was a non-significant trend towards lower median NT-proBNP levels in patients who were able to successfully downtitrate their loop diuretics and (p=0.185). The median time to diuretic reinitiation was 9 (7-21) days.

Figure 2

Urinary sodium concentration first-void and post-diuretic void (prior and after downtitration) in patients with and without successful downtitration



In the week preceding downtitration, urinary sodium concentrations were comparable between groups, the first void (53 ± 23 mmol/L versus 56 ± 21 mmol/L, p-value=0.673) and post-diuretic void samples (74 ± 23 mmol/L and 73 ± 21 mmol/L, p-value=0.865) (Figure 2). Following diuretic downtitration, first void urinary sodium excretion significantly increased to 74 (± 27) mmol/L in those with successful downtitration (p<0.001), whereas only a modest non-significant increase to 58 (± 23) mmol/L was observed in those requiring diuretic reinitation/escalation (p=0.331) (Figure 3). The trajectory of first-void urinary sodium concentration before and after diuretic intake also differed significantly between the successful and unsuccessful downtitration groups (p<0.001, Estimate=193.6, 95% CI: 122.7-264.6).

Figure 3

Evolution of the first void urinary sodium profile in patients with successful loop diuretic downtitration (A) and in patients with need for diuretic reinitiation (B)

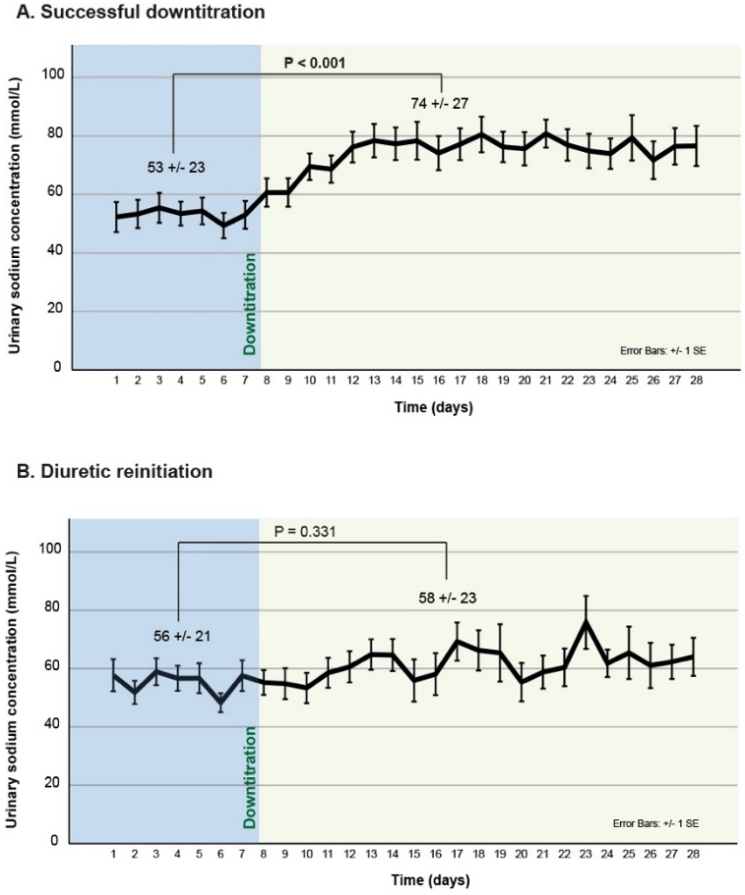
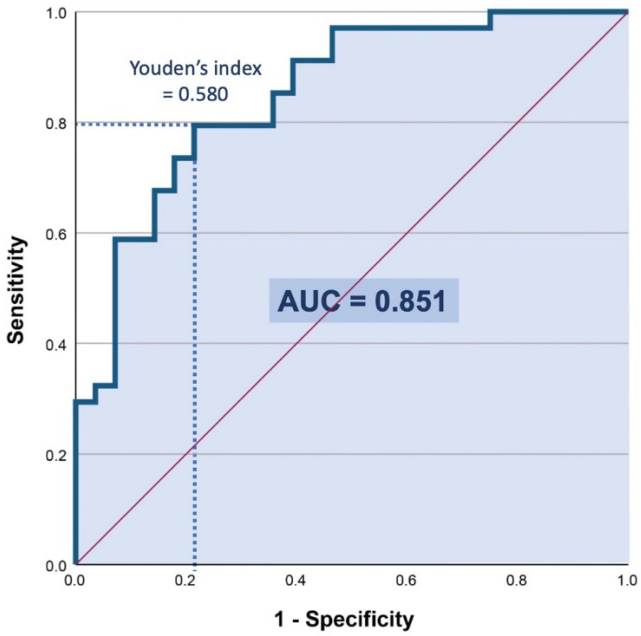


Figure 4 depicts the ROC curve analysis for the change in first void urinary sodium excretion following diuretic downtitration (area under the curve = 0.851). An increase in urinary sodium excretion of >10 mmol/L demonstrated a sensitivity of 79.4% and specificity of 78.6% (Youden's index of 0.580), with a positive predictive value of 81.8% and negative predictive value of 75.9%.

Figure 4

ROC curve for prediction of successful diuretic downtitration



Urinary sodium excretion in patients on higher dose diuretics

Of the 62 downtitrations, 23 had an initial loop diuretic dose exceeding 20mg of furosemide equivalents, meaning they remained on a reduced diuretics dose post-downtitration. The median pre-downtitration dose in this subgroup was 40 (40-80) mg of furosemide. Among these patients, diuretic downtitration was successful in 13 (57%), comparable to the overall cohort. There were no significant differences in urinary sodium concentration between first-void and post-diuretic void urinary sodium concentration, or in the difference diuretic response (i.e., difference between pre- and post-diuretic void sodium concentration) between those with or without successful downtitration, both before and after dose reduction (Supplemental table 2). Comparable to the overall cohort, there was a significant increase in first-void urinary sodium excretion post-diuretic downtitration in patients who were successfully downtitrated (39 ± 21

mmol/L to 54 ± 21 mmol/L, p<0.001), while this was not significant in patients who required diuretic reinitiation (43 ± 12 mmol/L to 45 ± 15 mmol/L, p=0.426).

Longitudinal laboratory analyses

Over time, both hemoglobin and sodium levels remained stable, with no significant differences observed in trajectories between patients with or without successful downtitration (p=0.359 and p=0.112, respectively) (Supplemental table 3). Compared to patients without successful downtitration, glomerular filtration rate showed a non-significant trend to improvement over time in patients with successful downtitration (Supplemental figure 3). NT-proBNP levels numerically increased after downtitration in both groups, but in those with successful downtitration, levels returned to baseline after 3 weeks (relative change 14.7 [± 45.3]% versus 25.2 [± 59.2]%). The difference in NT-proBNP changes over time between groups narrowly missed statistical significance (p for interaction = 0.058) (Supplemental table 3).

Change in body weight and right ventricular systolic pressure

Following loop diuretic downtitration, both body weight and RVSP remained relatively stable over time in the entire study population with mean changes of +0.14 [± 1.14] kg and +2.5 [± 6.1] mmHg, respectively. An evolution of the weight over time is depicted in Supplemental figure 4. Importantly, only patients who were unable to maintain a lower diuretic dose exhibited a clear trend towards greater increase in body weight (+0.45 [± 1.20] kg versus -0.11kg [± 1.04] kg, p=0.071) and RVSP (+ 3.9 [± 6.2] mmHg versus +1.1 [± 5.8] mmHg, p=0.094). However, these differences did not reach statistical significance.

DISCUSSION

The EASY-STOP study was the first study evaluating home-based urinary sodium concentration monitoring as a potential tool to guide loop diuretic downtitration in patients with stable chronic heart failure on GDMT and maintenance loop diuretics. The study yielded several key findings; 1) home-based sodium measurements using a point-of-care sensor were feasible, with a high compliance rate of 93%. 2) Loop diuretic downtitration was successfully achieved in over half of the patients, without recurrence of congestion-related symptoms. 3) Patients who successfully reduced their diuretic dose showed a significant increase in first-void urinary sodium excretion following downtitration, whereas patients who developed congestion did not exhibit an increase after diuretic downtitration. 4) The absence of an increase in urinary sodium following diuretic downtitration was also associated with a rise in RVSP, similar to the changes observed in the CardioMEMS trials, indicating the need for diuretic escalation. 5) An increase of 10 mmol/L had a positive predictive value of 81.8% and negative predictive value 75.9% for successful downtitration. These findings suggest that home-based urinary sodium monitoring may serve as a practical, non-invasive biomarker for individualized diuretic management in chronic heart failure allowing self-empowerment of diuretic therapy.

A key observation of the study was that loop diuretics were successfully downtitrated in more than half of the patients (55%) without recurrence of congestion, highlighting that a significant subset of chronic heart failure patients may be overexposed to chronic diuretic therapy. Similar findings were observed in other trials (75,76), which demonstrated that gradual de-escalation of diuretics can safely be achieved in a substantial proportion of chronic heart failure patients. Although cessation of low-dose maintenance loop diuretic therapy may be feasible in a large proportion of stable HF, close monitoring is necessary as diuretic cessation is associated with a reduction in total natriuresis and diuresis, leading to clear signs and symptoms of congestion in almost half of the patients which could not be picked up with commonly recommended tools like weight monitoring (74). Notably, also in the current study traditional clinical predictors such as baseline characteristics, echocardiography, and laboratory parameters did not distinguish patients who could successfully reduce diuretics from those requiring

reinitiation. Although higher baseline natriuretic peptides are associated with a higher risk for recurrence of congestion, there is no clear cut-off and an individualized approach with monitoring remains key. (74) The EASY-STOP study demonstrated that short-term urinary sodium monitoring in patients eligible for diuretic downtitration may provide a cost-effective alternative. While signs of congestion requiring diuretic reinitiation emerged only after a median of 9 (7-21) days, changes in first-void urinary sodium concentration were detectable already within a few days post-downtitration and highly predictive for the occurrence of congestion. In patients who were able to discontinue diuretics, the morning urinary sodium increased in comparison to the levels before diuretic downtitration. This indicates a more physiologically balanced pattern of overall natriuresis following the discontinuation of diuretics. Notably, the majority of natriuresis in patients on maintenance diuretics occurs after the intake of diuretic therapy. Patients who tolerate downtitration demonstrate an increase in morning urinary sodium excretion, suggesting they possess sufficient natriuretic reserve and reduced intrinsic renal sodium avidity. In contrast, patients who fail downtitration do not exhibit this compensatory increase in sodium excretion, indicating a dependence on loop diuretics to maintain appropriate volume status through enhanced natriuresis. Specifically, an increase of $\geq$ 10 mmol/L in first-void urinary sodium excretion was associated with high sensitivity (79.4%) and specificity (78.5%) for predicting successful downtitration. (35,227,228) Importantly, post-diuretic sodium concentration and the difference in diuretic response (i.e., change in post-diuretic versus first-void urinary sodium concentration) were not able to predict downtitration success. Therefore, this simplifies the practical implementation of urinary sodium monitoring by necessitating only a single first-void sodium measurement as a monitoring tool as the measurement post-diuretic added no additional value.

Since baseline clinical parameters fail to predict successful downtitration in stable chronic heart failure patients, a stepwise reduction strategy under close monitoring necessitating frequent patient contacts (in-office or telephone). Until now, this approach remained the only practical approach to achieve the lowest effective diuretic dose to prevent congestion before symptom onset. This principle also underlies the use of pulmonary artery pressure sensors in high-risk patients,

which allows for early intervention and optimized diuretic management. (14,221,222) However, due to their invasive nature, high cost, and requirement for long-term monitoring, these devices are reserved for patients at high-risk of decompensation despite optimal guideline-directed medical and device therapy. Notably, the use of CardioMEMS was associated with a modest (between 2 to 8 mmHg) reduction in mean pulmonary artery pressure (mPAP) at 12 months compared to standard care in the hemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial (222,229), and Remote hemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF) trial (221). Typically, it is recommended to intervene only when there is a 3–5 mm Hg change in PAP over two to three days to prevent overt congestion. Remarkably, the rise in RVSP, similar to the changes observed in the CardioMEMS trials, indicating the need for diuretic escalation, was seen only in patients who did not exhibit an increase in first-void urinary sodium after diuretic downtitration. Therefore, the use of point-of-care urinary sodium sensors may potentially serve as a surrogate for chronic pulmonary artery pressure (PAP) monitoring, awaiting validation in a large randomized controlled trial (RCT).

In conclusion, the EASY-STOP trial suggests that short-term urinary sodium monitoring could be incorporated into routine heart failure management to facilitate personalized diuretic therapy. Given the non-invasive, rapid, and accessible nature of point-of-care sodium measurement, this approach holds promise for ambulatory heart failure care. Future research should focus on validating these findings in larger cohorts and exploring the long-term clinical impact of sodium-guided diuretic titration. An increase of 10 mmol/L in first-void urinary sodium concentration may serve as a practical biomarker for successful diuretic reduction. By providing real-time insight into diuretic response and sodium excretion, this approach may enable individualized, titrated, and dynamic diuretic management, ultimately improving congestion control and clinical outcomes in patients with heart failure. These findings support the need for larger, multicenter trials in a broader heart failure cohort to confirm its clinical applicability and long-term benefits in heart failure management.

LIMITATIONS

This study had some limitations that should be addressed. First, it was a single-center study with a small sample size (n=50) of only chronic stable HF patients on low doses of loop diuretics, potentially limiting the generalizability of findings. Second, while the short follow-up period (3 weeks) confirmed early safety and feasibility, long-term effects on fluid status, renal function, and cardiovascular outcomes require further investigation. Lastly, compliance with home sodium monitoring was high in this controlled study setting, but may differ in real-world practice and in other HF phenotypes.

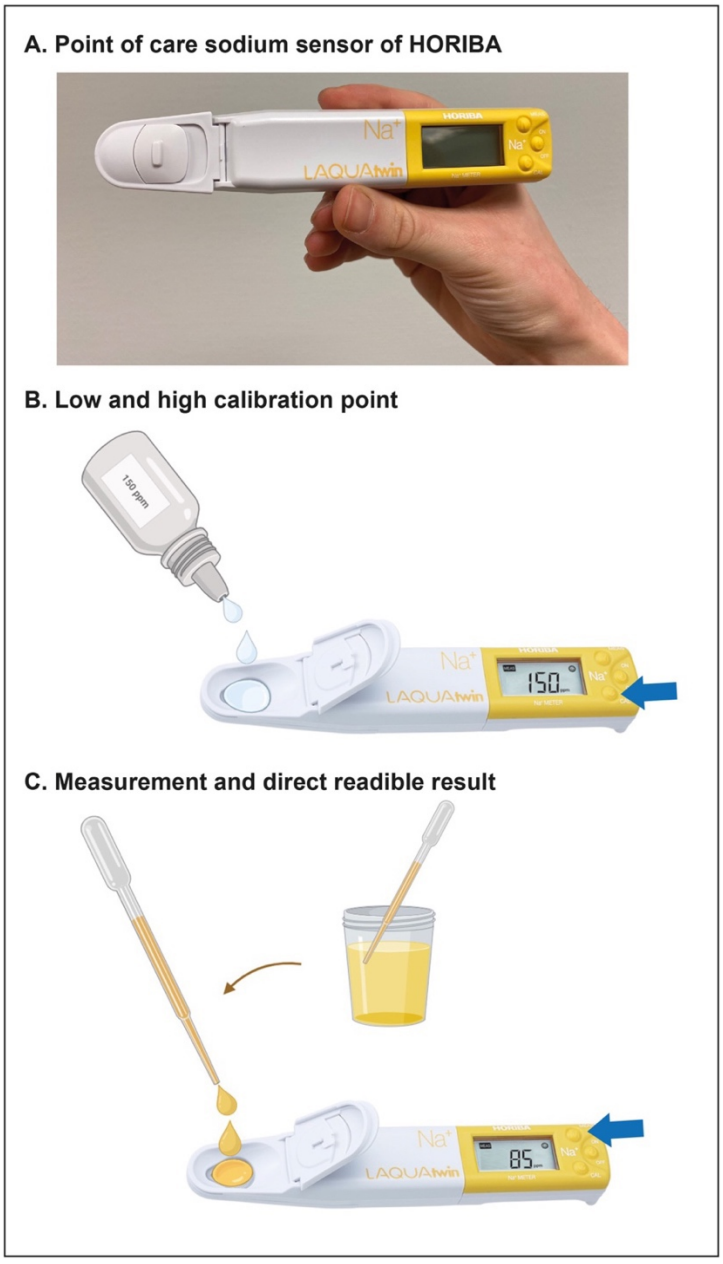
CONCLUSION

The EASY-STOP study provides the first evidence that urinary sodium monitoring via a point-of-care sensor is feasible by patients them-self at home and might be usable as a non-invasive, and predictive tool for guiding loop diuretic downtitration in chronic heart failure patients.

SUPPLEMENTAL MATERIAL

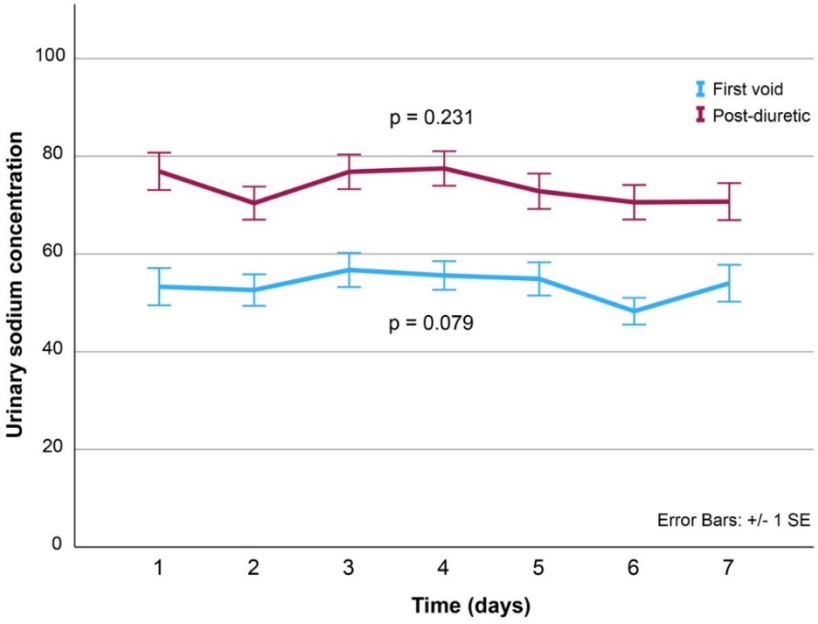
Supplemental figure 1

Point-of-Care sensor for sodium concentration by Horiba



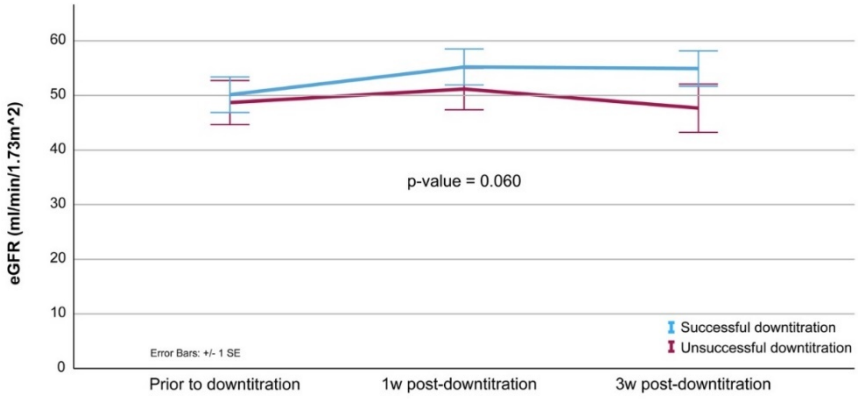
Supplemental figure 2

Stability of the urinary sodium profile during the first week on maintenance loop diuretic therapy



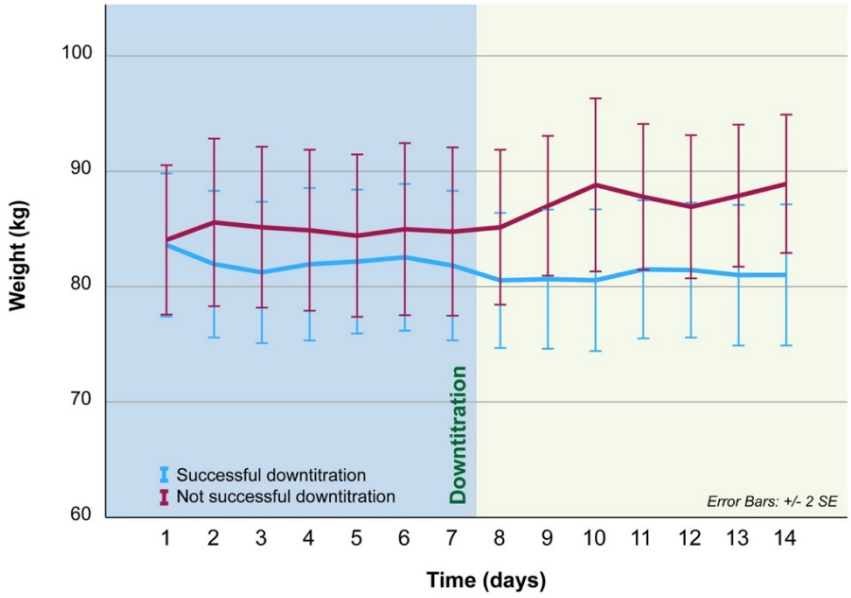
Supplemental figure 3

Evolution of glomerular filtration rate over time compared between patients with or without successful downtitration



Supplemental figure 4

Evolution weight over time



Supplemental table 1

Baseline characteristics between patients with successful and unsuccessful diuretic downtitration

	Downtitration successful (n=34)	Downtitration unsuccessful (n=28)	P-value
Age (years)	75 (71-80)	76 (70-79)	0.702
Male gender (%)	25 (73.5%)	19 (67.9%)	0.780
Ischemic	13 (38.2%)	16 (57.1%)	0.201
Heart rate (beats/min)	73 ± 11	68 ± 11	0.085
Systolic blood pressure (mmHg)	113 ± 20	125 ± 16	**0.038**
Diastolic blood pressure (mmHg)	67 ± 11	70 ± 12	0.281
Weight (kg)	82.3 ± 15.7	84.7 ± 16.4	0.566
BMI (kg/m^2)	29.0 ± 4.8	29.1 ± 4.6	0.892
NYHA			0.996
I	10 (29.4%)	8 (28.6%)	
II	17 (50.0%)	14 (50.0%)	
III	7 (20.6%)	6 (21.4%)	
IV	0 (0.0%)	0 (0.0%)	
Atrial fibrillation	21 (61.8%)	20 (71.4%)	0.590
COPD	3 (8.8%)	4 (14.3%)	0.691
Hypertension	25 (73.5%)	17 (60.7%)	0.413
Dyslipidemia	16 (47.1%)	13 (46.4%)	0.990
Diabetes	10 (29.4%)	11 (39.3%)	0.434
Coronary revascularization	16 (47.1%)	15 (53.6%)	0.799
Peripheral artery disease	7 (20.6%)	6 (21.4%)	1.000
Hemoglobin (g/dL)	13.9 ± 1.6	13.9 ± 1.8	0.970
Sodium (mmol/L)	139.4 ± 3.0	140.7 ± 3.0	0.128
Potassium (mmol/L)	4.51 ± 0.54	4.68 ± 0.52	0.214
Chloride (mmol/L)	102.2 ± 2.8	102.9 ± 2.8	0.405
Bicarbonate (mmol/L)	26.0 ± 2.9	27.2 ± 2.8	0.156
Osmolality (mOsmol/kg H_20)	302 (295-308)	299 (295-305)	0.494
Creatinine (mg/dL)	1.42 (1.10-1.67)	1.40 (1.04-1.92)	0.865
Estimated GFR (mL/min)	46 (38-65)	49 (30-62)	0.854
NT-proBNP (ng/L)	682 (249-2411)	1215 (593-2668)	0.185
LVEF (%)	47 ± 9	44 ± 13	0.276
LVEDD (mm)	51.6 ± 7.5	52.3 ± 6.9	0.698
Mitral regurgitation (grade)	1 (0-1)	1 (1-1)	0.478
E/e'	13.3 ± 6.3	14.9 ± 8.9	0.459
TAPSE (mm)	20 ± 6	17 ± 5	0.166

RVSP (mmHg)	29 (24-32)	27 (23-33)	0.855
ARNI/ACEi/ARB	23 (67.6%)	19 (67.0%)	1.000
SGLT2i	28 (82.4%)	23 (82.1%)	1.000
Beta-blockers	32 (94.1%)	26 (92.9%)	1.000
MRA	31 (91.2%)	21 (75.0%)	0.163
Thiazides	1 (2.9%)	1 (3.6%	1.000
Loop diuretic dose in furosemide equivalents (mg)	20 (20-40)	20 (20-40)	0.921
PM	9 (26.5%)	5 (17.9%)	0.546
ICD	10 (29.4%)	8 (28.6%)	1.000
CRT	13 (38.2%)	4 (14.3%)	**0.047**

Supplemental table 2

Urinary sodium profile prior and after loop diuretic downtitration for first-void, post-diuretic void and delta between both (subgroup, patients with downtitration and no cessation of loop diuretics)

	No Event (n=13)	Event (n=10)	P-value
Prior to downtitration			
First void	39 ± 21	43 ± 12	0.626
Post-diuretic void	62 ± 23	74 ± 28	0.267
Delta	23 ± 17	31 ± 32	0.431
After downtitration			
First void	54 ± 21	45 ±15	0.282
Post-diuretic void	74 ± 20	63 ± 20	0.155
Delta	20 ± 20	18 ± 25	0.842
	Delta prior	**Delta After**	**P-value**
No Event	23 ± 17	20 ± 20	0.524
Event	31 ± 32	18 ± 25	0.187
	First-void prior to stop	**First-void after stop**	
No Event	39 ± 21	54 ± 21	**<0.001**
Event	43 ± 12	45 ±15	0.426

Supplemental table 3

Blood analysis – evolution over time grouped per outcome

	Prior	1w post	3w post	
Hemoglobin (g/dL)				0.359
No event	13.9 ± 1.6	13.6 ± 1.5	13.9 ± 1.4	
Event	13.9 ± 1.8	13.6 ± 2.0	13.4 ± 1.8	
Sodium (mmoL/L)				0.112
No event	139.4 ± 3.0	139.7 ± 3.0	140.0 ± 2.8	
Event	140.7 ± 3.0	140.0 ± 2.5	139.4 ± 2.8	
eGFR (mL/min/1.73m^2)				0.060
No event	46 (38-65)	51 (41-68)	49 (42-69)	
Event	49 (30-62)	52 (39-61)	52 (34-59)	
NT-proBNP (ng/L)				0.058
No event	682 (249-2411)	898 (277-2951)	753 (282-2487)	
Event	1215 (593-2668)	1309 (638-3964)	1441 (649-3024)	

* *p-value for time-event interaction*

CHAPTER 14

Rationale and Design of the Renal-Based Optimization of Quadruple Heart Failure Therapy Study: ReQUAD-HF

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On behalf of the ReQUAD-HF investigators.

To be submitted

ABSTRACT

Aims: Despite the well-documented benefits and guideline recommendations for quadruple therapy in patients with heart failure with reduced ejection fraction (HFrEF), prescription rate in daily practice remains suboptimal. The Renal-based Optimization of QUADruple Therapy in Patients With Heart Failure With Reduced Ejection Fraction (ReQUAD-HF) study aims to evaluate whether the use of renal-based guideline-directed medical therapy (GDMT) enhances the adoption and implementation of these therapies.

Methods: The ReQUAD-HF is an investigator-initiated, international, multicenter, randomized, open-label, endpoint-blinded study, which aims to include 354 patients with HFrEF. Patients are randomized towards either usual care or the intervention arm with the use of guideline-directed medical therapy (GDMT) optimization flowcharts, tailored to the patient's renal function. Randomization will be stratified based on study center, inpatient versus outpatient setting, and baseline estimated glomerular filtration rate (eGFR) (cut-off of 45 mL/min/1.73m²). The primary endpoint is a composite score of GDMT intake after 3 months. Safety endpoints consist of worsening renal function, hyperkalemia or hypotension and/or bradycardia with hemodynamic consequences. Secondary endpoints include the combined endpoint of all-cause mortality and heart failure hospitalization, change in NT-proBNP levels and eGFR 3 months after inclusion.

Conclusion: The ReQUAD-HF will investigate whether a renal-based protocol will optimize GDMT prescription in patients with HFrEF.

INTRODUCTION

Heart failure (HF) remains a prevalent disease with an increasing incidence due to the aging population, leading to a prevalence of more than 10% in patients above 70 years. Despite significant advancements in pharmacological treatment options in recent years, the prognosis for patients with HF remains poor, characterized by high morbidity, mortality and a reduced quality of life. (230–232) Current HF medications have proven to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF) and the most recent guidelines of the European Society of Cardiology (ESC) emphasis the need for early initiation and uptitration of quadruple heart failure therapy (beta-blockers (BB), angiotensin receptor/neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors (ACEi), mineralocorticoid receptor antagonist (MRA) and sodium/glucose cotransporter 2 inhibitor (SGLT2i). (8) Despite the beneficial effects, drug implementation is often hampered by concerns about worsening renal function, hyperkalemia, symptomatic hypotension, and physician inertia. (233–235) Up to 65% of patients with heart failure have a renal function below 60 mL/min/1.73m² and the proportion of patients using guideline-directed medical therapy (GDMT) decreases as the renal dysfunction increases despite being at higher risk for adverse outcomes, especially if medically treated suboptimal. (236)

A consensus document of the Heart Failure Association (HFA) of the ESC, endorsed a patient-tailored renal-function based approach for initiation and uptitration of guideline-directed medical therapy. (234) The Renal-based Optimization of QUADruple Therapy in Patients With Heart Failure With Reduced Ejection Fraction (ReQUAD-HF) study has the goal to evaluate the safety and efficacy of a renal-based protocol-driven up-titration of GDMT in patients with HFrEF.

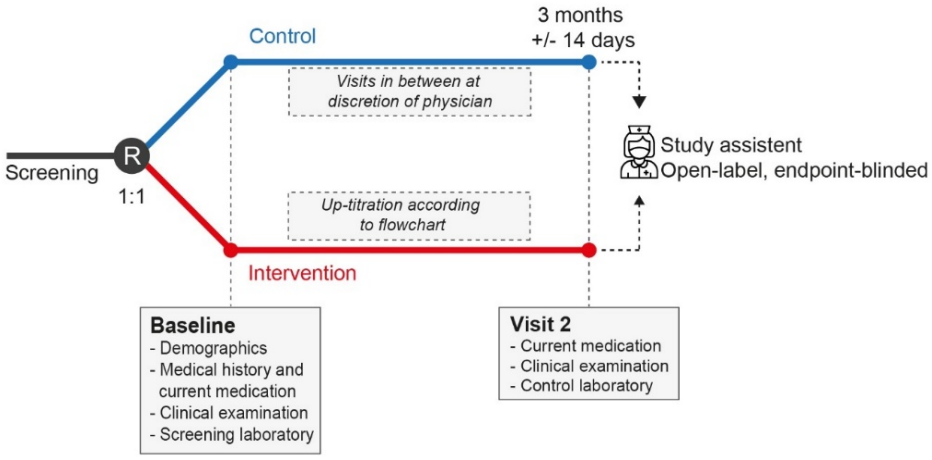
REQUAD-HF STUDY

Study Design

The ReQUAD-HF study is an investigator-initiated, prospective, international, multicenter, randomized trial. Participants will be randomized to either usual care or protocolized GDMT optimization. Due to the design, the study is open-label, but the endpoint assessment is blinded. Patients in the usual care group are managed according to the guidelines by their regular treating physician, whereas those in the intervention group are treated by a different physician trained in the study protocol, eliminating the need for cluster randomization. The aim is to enroll in at least 10 different countries to ensure feasibility of the protocol worldwide. The study is open-label endpoint-blinded, meaning that the endpoint will be collected by an independent study nurse or physician blinded to the treatment arm. The primary endpoint is after three months, with the possibility of an extension of the study with an additional study visit at 12 months. All patients will need to provide written informed consent prior to inclusion. The study has been approved by the local ethics committees of the participating centers and the study complies with the declaration of Helsinki. The study has been registered at Clinical.Trials.gov (NCT06273280).

Figure 1

Study design



Patient eligibility

Patients are eligible for inclusion if they have HFrEF (left ventricular ejection fraction (LVEF) ≤ 40%, assessed within the last three months prior to inclusion by any technical exam) and a functional New York Health Association Class of at least 2. Patients can be enrolled from the outpatient clinic or during hospitalization for an acute heart failure episode. Exclusion criteria are patients with an eGFR below 20 mL/min/1.73m² (during screening), those already receiving quadruple heart failure therapy or those on triple therapy with an eGFR < 30 mL/min/1.73m² or a serum potassium level above 6 mmol/L. In addition, patients with hemodynamic instability (use of intravenous inotropes, vasopressors or a systolic blood pressure below 90 mmHg) are excluded from the study. A full list of in- and exclusion criteria are listed in Table 1.

Table 1

In- and exclusion criteria

INCLUSION CRITERIA
- Patients older than 18 years - Patients should be able to give written informed consent - Left ventricular ejection fraction ≤ 40%, assessed LVEF imaging within last three months of inclusion (TTE/MIBI/CMR) - Patients not yet on quadruple heart failure therapy. - NYHA ≥ II
EXCLUSION CRITERIA
- Hemodynamic instability at the moment of screening; use of IV inotropes, use of IV vasopressors or a systolic blood pressure below 90mmHg. - Recent acute coronary syndrome (< 1 month) - Already on triple GDMT in case of eGFR < 30 mL/min/1.73m^2 or a potassium above 6 mmol/L - Chronic kidney disease with an eGFR < 20 mL/min/1.73m² (within 30 days from randomization), planned for dialysis or already treated with chronic dialysis. - Implantation of a cardiac resynchronization therapy (CRT) within 3 months - Adult congenital heart disease - Previous heart transplantation or currently/planned for ventricular assist device - Women who are pregnant or breastfeeding - Unable to participate in 3 months follow-up due to logistic issues

Study Intervention

Patients are screened from the outpatient clinic and hospital cardiology unit. After fulfilment of in- and exclusion criteria and registration of current GDMT (class and dose) and dose of loop diuretics, patients are randomized towards usual care or intervention group and scheduled the same day or within a week for the first study visit (Figure 1). Stratified randomization will be used to ensure a balanced treatment allocation within stratum defined by study center, in- versus out-patient enrolment and renal function with a cut-off of 45 mL/min/1.73m². If no recent laboratory analysis with renal function (within 30 days) is available, a blood analysis should be performed prior to randomization to rule out any exclusion criteria. Patients randomized towards the usual care group continue to receive care by their treating physician. Optimization of medical therapy is advised according to the current guidelines, but left at the discretion of the treating physician. Visits in between are at the discretion of the treating physicians. Patients randomized towards the intervention group will receive optimization of medical therapy according to the provided flowcharts. The flowcharts are derived from a recommendation based upon an HFA position statement explaining how to up-titrate GDMT based upon renal function. (237) Three different protocols are provided, based on the renal function (eGFR > 60 mL/min/1.72m², > 30-60 mL/min/1.72m², 20-30 mL/min/1.72m²). At the baseline study visit and after 3 months, demographic and clinical information, NYHA class and a blood sample are collected. After 3 months (+14 days), patients are contacted by the independent study assistant, who is blinded for the treatment allocation, to register current GDMT intake (class and dose) and dose of loop diuretics.

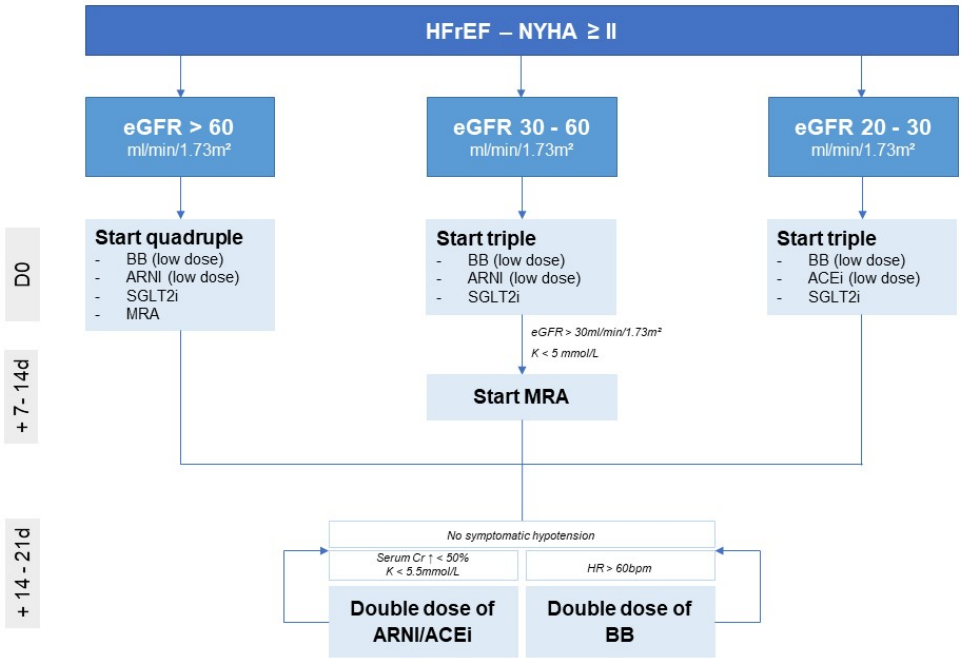
Renal-based GDMT protocols

Physicians treating patients in the intervention arm will be trained for the use of GDMT flowcharts. The flowcharts differ based on the underlying eGFR (Figure 2). In case that the eGFR is above 60 mL/min/1.73m², a low dose of all four pillars of GDMT can be safely initiated at the same time. Depending on the local reimbursement regulation, it is advised to start immediately with ARNI instead of ACEi. Therapy can be doubled every 14 to 21 days until target dose (or maximum tolerated dose) is reached if there is no acute kidney injury, hyperkalemia or bradycardia. In case of a baseline eGFR between 30 and 60 mL/min/1.73m^2, MRA

prescription is scheduled 7-14days after initiation of BB, ARNI and SGLT2i, under the condition that serum potassium levels and eGFR remains acceptable. Afterwards, the same protocol with doubling every 14-21 days until target dose (or maximum tolerated dose) is applicable. In case that the eGFR was between 20 and 30 mL/min/1.73m², physicians are advised to prescribe low dose triple therapy. It is recommended to start with ACEi/ARB instead of ARNI and not to initiate MRA. Same intervals and conditions for up-titration are applicable. Irrespective of renal function, some general safety recommendations are given with regard to timing blood analysis and approach in case of hyperkalemia or renal dysfunction (supplementary material 1).

Figure 2

GDMT up-titration flowcharts based on renal function



Objectives and endpoints

The primary objective of the ReQUAD-HF study is to evaluate whether GDMT prescription with the guidance of renal-based flowcharts can be performed safely and improve adoption and implementation of these therapies in patients with HFrEF. The primary endpoint measures a composite score of GDMT. Scoring is determined by a weighted system: 3 points are assigned if the dose is less than 50% of the target, and 4 points if the dose is 50% or more of the target. Additionally, prescribing quadruple therapy adds 1 point (Figure 3). Patients receiving ACEi/ARB instead of ARNI receive a slightly lower score: 2.5 points for doses less than 50% of the target and 3.5 points for doses 50% or more of the target. The target dose refers to the dosing levels recommended by the ESC guidelines. (8) Medication not endorsed by the guidelines as heart failure therapy, being classified as beta-blocker or RAAS-I (i.e., sotalol, olmesartan) are scored 2, regardless of the dose. The maximal achievable score is 15. This scoring system has been developed in order to give a weight to the dosing as well as to the combination of GDMT. Secondary endpoints are the combined endpoint of all-cause mortality and heart failure hospitalizations, change in prescription rate per GDMT class, change in NT-proBNP levels and eGFR after three months. In addition, some safety endpoints (renal function, potassium and bradycardia) will be collected (supplementary material 2).

Figure 3

Composite scoring system

	+2.5	**+3**	**Add +1 if**
Beta-blocker		Any dose	≥ 50% of target dose
MRA		Any dose	
ACEi/ARB	Any dose		≥ 50% of target dose
ARNI		Any dose	≥ 50% of target dose
SGLT2i		Any dose	
	Add +1 if all 4 GDMT's are given		

Sample size and power

The study is powered for its primary endpoint, i.e., a weighed composite score of maximal GDMT. Considering a type I error rate α = 0.05 and a type II error rate β = 0.10 (statistical power of 90%), we calculated a total sample size of 300 in order to detect an absolute difference of 1.5 between the usual care and intervention group with a standard deviation of 4. A dropout rate of 15% is anticipated, which brings the total sample size to 354 patients.

Statistical plan

Baseline characteristics will be described for both groups. Data are reported as mean and standard deviation when normally distributed, as median and 25th – 75th percentile when non-normally distributed. The Student T test, Mann-Whitney U, Fisher's exact or Pearson chi-square tests will be used to determine significant differences between baseline variables for patients. The primary endpoint will be analyzed according to the intention-to-treat principle and will include data from all the patients who have undergone randomization with notation of baseline medication. The primary endpoint will be evaluated using a generalized linear mixed model with a random patient and center effect and a fixed effect for randomized arm in addition to the covariates used as the stratification factor of in- or out-patient enrolment and baseline renal function. Depending on the distribution of the residuals, transformation might be needed for the composite GDMT score. The composite end point of first occurrence of rehospitalization for heart failure or death from any cause after 3 months of follow-up will be assessed in a time-to-event analysis with the use of a Cox proportional-hazards mode and results will be summarized with the use of Kaplan–Meier survival curves. Differences in NT-pro-BNP levels and renal function will be evaluated using a linear-mixed effect model. Statistically significance will be set at a two-tailored probability level of < 0.05.

DISCUSSION

Pharmacological therapy remains the cornerstone in the treatment of patients with HFrEF to reduce heart failure hospitalizations, reduce mortality and improve quality of life. (8) The 'four pillars' of this treatment - consisting of ARNI/ACEi, MRA, BB and SGLT2i - form the foundation of pharmacotherapy in these patients, all of which have proven to reduce mortality and morbidity (Class I, Level A recommendation). (8) Current ESC guidelines recommend up-titrating to the doses used in clinical trials (or to the maximally tolerated dose), but don't provide specific guidance on how this should be done in patients with renal dysfunction. In addition, the guidelines lack specific directions on how to initiate and optimize GDMT, potentially contributing to the poor implementation in daily clinical practice due to various barriers. (238,239)

Only recently, based upon the results of Safety, Tolerability and Efficacy of Up-titration of Guideline-Directed Medical Therapies for Acute Heart Failure (STRONG-HF) study, high-intensity care for initiation and up-titration of oral HF therapies with close follow-up in the first 6 weeks after discharge for an acute HF hospitalization is recommended to reduce HF readmission or all-cause death. (135,240). Importantly, the STRONG-HF study was performed in a high-risk study population with a recent HF hospitalization and elevated NT-proBNP levels (>2,500 ng/L) under strict and regular follow up of the treatment team. Although there was no difference in severe adverse events, there was a higher incidence in hypotension, hyperkalemia and renal impairment in the high-intensity group. Notably, the usual care group underwent minimal to no up-titration. These effects might be even more pronounced in the typical daily HFrEF patient, as patients in STRONG-HF only received triple therapy, almost no ARNI, and one third of the patients had heart failure with mildly reduced or preserved ejection fraction. Therefore, this might implicate that a slightly more careful approach might be necessary in daily practice as HFrEF patients in daily life are typically older with multiple comorbidities including chronic kidney disease. The ReQUAD-HF study aims to overcome poor implementation in all HFrEF patients by providing strategies for optimizing GDMT based upon renal function and detailed flow charts, applicable in daily life, in all symptomatic HFrEF population.

Chronic kidney disease and the perceived risk of renal impairment remains a significant challenge in GDMT optimization, which often results in the underuse of GDMT. Importantly, misinterpretation of renal function changes is a leading cause of insufficient dosing of guideline-directed medical therapy. Indeed, some degree of laboratory renal changes is expected following the introduction of GDMT due to alterations in renal physiology and should not be immediately interpreted as definitive signs of renal injury. (237) Therefore, these changes should not lead to the premature withdrawal of therapy. Understanding the physiological changes induced by these medications are crucial when dealing with GDMT optimization. By reducing vasoconstriction of the efferent glomerular arterioles, RAASi have well established nephroprotective effects in patients with chronic kidney disease, while concomitant temporarily reducing glomerular filtration. (241) SGLT2i are most recently added to the foundational therapy of heart failure. By blocking the sodium-glucose reabsorption in the proximal tubule, more chloride reaches the macula densa. Adenosine release, through the tubuloglomerular feedback mechanism, results in afferent vasoconstriction and reduces the detrimental hyperfiltration. Although a drop in eGFR is physiologically expected after renin-angiotensin-aldosterone system inhibitors (RAASi) and SGLT2i introduction, they all have proven to be nephroprotective in the long-run. Finally, while beta-blockers most typically not induce a drop in eGFR, they tend to increase renal blood flow by reducing alfa-adrenergic effects, resulting in less vasoconstriction of both afferent and efferent vasodilatation. Moreover, by blocking the beta-adrenergic effect, renin release and angiotensin II production is reduced. (237,242)

All GDMT trials have proven effectiveness with an impact on life expectancy and quality of life, regardless of the renal function. (234,243) Nevertheless, only 15% of the patients with an eGFR between 30-45 mL/min/1.73m² receive triple therapy after an acute heart failure event, which even further declines to 5% in patients with an eGFR below 30 mL/min/1.73m². (237) Surprisingly, in patients with a preserved renal function (eGFR > 90 mL/min/1.73m²) the prescription of triple therapy was only marginally better (around 40%). (236) The initial drop in renal function after drug initiation is most often transient and ARNI and SGLT2i have even proven to be renoprotective with an attenuation in the annual eGFR decline in the long-term. (31,234) In patients with chronic kidney disease, the event rate for heart failure hospitalizations and mortality increases as renal function declines.

(236,244) Importantly, this leads to the risk-treatment paradox. The perceived risk for complications of GDMT is higher, although the absolute benefit with regard to morbidity and mortality is even more important in patient with chronic kidney disease. Therefore, the HFA has suggested flowcharts based on renal function to up-titrate GDMT in patients with HFrEF with a more precautious schedule in patients with more advanced chronic kidney disease. (237) As the individual drugs already have a beneficial effect in low dose, simultaneous titration of GDMT is strongly recommended. In addition, they enhance each other's tolerability. The advice is to start with a low dose of beta-blockers and ARNI/ACEi and to double the dose every 14-21 days if the therapy is well tolerated. Different precautions are set based on the underlying renal function. As data on safety and efficacy for MRA in patients with an eGFR < 30 mL/min/1.73m^2 are missing, no recommend-dations were made in these patients for MRA use. These flowcharts have been translated into the current study protocol of the ReQUAD-HF study. By providing step-by-step guidance on optimizing GDMT, the goal is to present protocols that can be immediately applied in daily practice.

The benefit of GDMT on mortality and heart failure hospitalizations has already consistently been proven and will therefore not be the primary goal of the study. As implementation of GDMT is the major barrier in clinical practice, the chosen primary endpoint of the study is a composite score of the prescription of GDMT, while also evaluating safety. A meta-analysis of Tromp et al. demonstrated that the combination of all four pills has an additional benefit on all-cause mortality and heart failure hospitalizations. (207) Therefore, the composite scoring system used in the study assesses not only the dose of the GDMT prescribed, but also the combination of all four pills.

The open-label design of the ReQUAD-HF study might be perceived as a limitation. However, different physicians per treatment arm are involved in the study and in order to minimize bias and improve data integrity, the endpoint is blinded. While the recommendations of the HFA consensus document are available for every stage of renal dysfunction, also for patients with end-stage renal disease, an eGFR below 20 mL/min/1.73m^2 is an exclusion criterion for the ReQUAD-HF study. This decision has been made with the goal to provide a pragmatic study protocol which is immediately applicable in daily practice by a broad audience of physicians. The

study committee of the ReQUAD-HF judged that heart failure patients with an eGFR below 20 mL/min/1.73m^2 required more specialized care by a dedicated heart failure specialist and nephrologist. Therefore, it is opted to not include these patients in the protocol.

CONCLUSION

The ReQUAD-HF study will evaluate whether a renal-based GDMT up-titration protocol, according the HFA proposition, will improve GDMT prescription rate in patients with heart failure with reduced ejection fraction.

SUPPLEMENTAL MATERIAL

Supplementary material 1

General safety recommendations

Timing blood analysis
After initiation or up-titration of ARNI/ACEi/ARB, MRA or SGLT2i, consider performing a blood analysis after 10-14 days to control renal function and electrolytes.
Hyperkalemia
If potassium levels are increased to 5.5-6 mmol/L, consider adding a potassium-binder and to reduce ACEi/ARB or ARNI and MRA with 50%. If potassium level drops below 5.5 mmol/L, it may be considered to repeat the previous step together with a potassium-binder.
If potassium levels are higher than 6 mmol/L, consider to temporary stop ACEi/ARB/ARNI and MRA and to add a potassium-binder. If potassium level drops below 5.5 mmol/L, it may be considered to repeat a reduced dose (50%) of the previous step together with a potassium-binder.
Renal dysfunction
If creatinine level increases with more than 50%, it should be considered to temporary interrupt treatment with ACEi/ARB, ARNI or MRA. In function of the evolution of the renal function, consider rechallenging with a reduced dose (50%).
Mycotic infections
In case of SGLT2i-caused genital mycotic infections, it is advised to prescribe oral antifungal therapy (preferred a single dose of oral fluconazole).

Supplementary material 2

Objectives and endpoints

Primary objective	Primary endpoint
Maximize GDMT prescription and dose optimization in patients with heart failure.	The composite score of maximal guideline-directed medical therapy 3 months after inclusion.

Secondary objectives	Secondary endpoints
To investigate whether a protocol-driven up-titration of GDMT leads to an improvement in clinical outcome.	- All-cause mortality and heart failure hospitalization after three months of follow-up.
To investigate whether a protocol-driven up-titration of GDMT improves remodeling in patients with heart failure with a reduced ejection fraction.	- Change in NT-proBNP. - Change in eGFR, calculated with the CKD-EPI formula.

Exploratory objectives	Exploratory endpoints
Clinical improvement.	- All-cause mortality after 3 months - Heart failure hospitalizations after 3 months.
Up-titration per class of GDMT.	- % taking a certain class of GMDT. - % taking ≥ 50% of target dose of ACEi/ARB/ARNI or BB.

Safety objective	Safety endpoint
To investigate whether a protocol-driven up-titration of GDMT is safe in patients with heart failure, regardless of the renal function.	Hospital admission secondary to GDMT up-titration, assessed by blinded adjudication committee: - Acute kidney failure: increase in serum creatinine of more than 50% or an absolute serum creatinine > 3mg/dL. - Hyperkalemia: serum potassium above 6 mmol/L with cessation of GDMT, association of K-binders or (temporary) dialysis. - Hypotension or bradycardia with hemodynamic consequences.

PART VI

DEVICES IN CHRONIC HEART FAILURE

The beginning is scary, and the end is sad,

but everything in between...

- Bob Marley -

CHAPTER 15

Analyzing the Accuracy of Pressure Measurements During Exercise with Pulmonary Artery Pressure Sensors – Insights from the ACTION-MEMS Study

Evelyne Meekers, Thibault Petit, Jeroen Dauw, Henri Gruwez, Sebastiaan Dhont, Evert Luwel, Petra Nijst, Matthias Dupont, Philippe Bertrand, Pieter Martens, Wilfried Mullens

Eur J Heart Fail. 2024; 26 (523-524)

The CardioMEMS-HF System is a wireless pulmonary artery pressure (PAP) device developed for the follow-up of PAP at rest in patients with chronic heart failure in order to reduce episodes of congestion. The evaluation of exercise hemodynamics, particularly through echocardiography, has gained considerable attention in heart failure and there is a paucity of data regarding the feasibility and accuracy of the CardioMEMS-HF system during exercise. Therefore, the primary objective of the ACTION-MEMS (The **AC**curacy of pressure measuremen**T**s during exerc**I**se with pulm**ON**ary artery pressure sensors (Cardio**MEMS**)) study was to establish the feasibility and accuracy of measuring PAP during exercise with this device compared to echocardiography. The secondary objective was to evaluate whether a similar increase in PAP was measurable with the sensor via a simple exercise, which could be performed at home and potentially used for diagnostic and/or therapeutic strategies.

In this prospective, mono-centric observational study, 10 patients with a CardioMEMS-HF device performed a semi-supine bicycle stress-echocardiography with simultaneous recording of PAP via echocardiography (right-sided) as well as via the sensor (left-sided, with the racket positioned behind the left thorax) (Figure 1A). Agitated saline contrast was used to enhance the Doppler signal for the estimation of the peak tricuspid regurgitant velocity. (245) All images were obtained by an experienced imaging cardiologist and analyzed offline by two independent cardiologists. Afterwards, a 3 minutes walking test was performed with measurements via the sensor prior and immediately after the exercise. Patients older than 18 years with a CardioMEMS device implanted for at least 3 months, were included from the outpatient clinic in Ziekenhuis Oost-Limburg (Genk, Belgium). Exclusion criteria were the inability to perform exercise testing and a poor tricuspid regurgitant signal despite contrast injection. The study was approved by the local ethical committee and all participants provided written informed consent. A Pearson's correlation was run to assess the relationship between the two measuring methods and between the exercise and walking test. For the latter, the slope for each method was calculated based on the measurement prior to the exercise and at the peak during or immediately after the exercise.

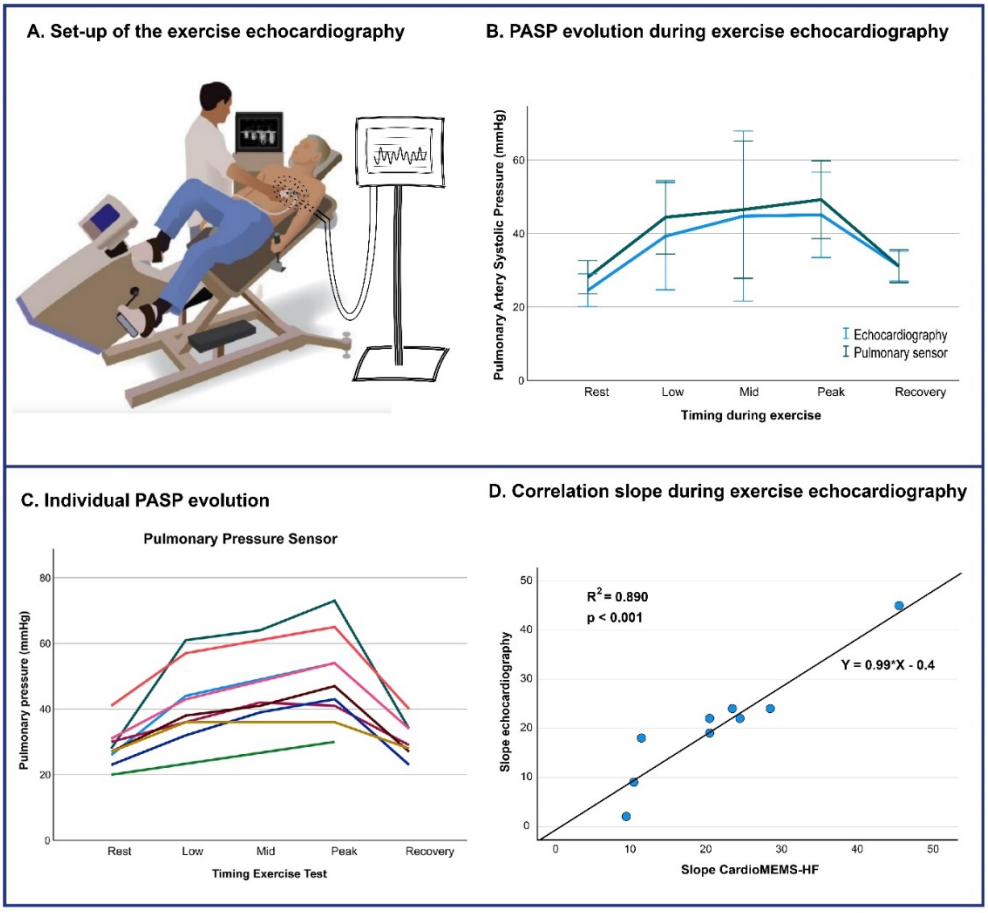
Of the 19 patients screened, 10 patients fulfilled the in- and exclusion criteria. The mean age of the patients was 78 ± 9 years, 30% were female and the mean ejection fraction was 39 ± 12%. The median time from implantation of the PAP sensor to the study protocol was 2.6 (1.6-3.5) year. In 9 out of 10 patients (90%), measurements with the device were feasible during the exercise protocol. In the remaining patient, no signal could be captured in semi-supine position. The peak workload achieved during the bicycle test was 34 (± 15) Watt. In total, 37 simultaneous measurements of PAP with both echocardiography as with the pulmonary sensor were obtained during exercise testing. PAP increased during exercise (Figure 1B and 1C) in all patients. There was a statistically significant strong positive correlation between both slopes, measured from rest to peak exercise, of the systolic PAP increase, $r(7) = 0.94$, $r^2 = 0.89$, $p<0.001$ (Figure 1D).

The mean systolic PAP assessed by CardioMEMS-HF system prior to the walking test was 25 (± 6) mmHg and increased significantly to 36 (± 11) mmHg afterwards (p-value=0.003). Patients with a higher resting systolic PAP tended to have a higher increase in PAP post-exercise testing (correlation 0.84, p-value=0.009). The slope of the PAP increase during the walking test correlated with the slope of the PAP measurements during the exercise echocardiography ($r(6) = 0.76$, $r^2 = 0.58$, p-value=0.028).

In the current healthcare model, there is a shift from a hospital-centered to a patient-centered approach at home with a central role for remote monitoring. PAP devices are able to detect hemodynamic changes during an early stage of congestion, providing a tool to tackle congestion prior to the onset of symptoms. (14,221,222) This study now also demonstrates the feasibility and accuracy of measuring PAP during exercise with a PAP sensor. A short walking test, easily reproducible in ambulatory testing, was able to demonstrate an increase in PAP immediately after the exercise. Khedraki et al demonstrated similar findings in a cohort of 66 patients and highlighted the importance of the posture during sequential PAP measurements. (246) This study supports the feasibility to assess exercise hemodynamics non-invasively in chronic heart failure patients via the CardioMEMS-HF System. Whether these additional measurements might help to further guide medical therapy in these patients and improve home monitoring, remains to be elucidated.

Figure 1

Set-up of the stress-echocardiography by bicycle protocol (A) and the mean (B) and individual systolic pulmonary artery pressure (sPAP) evolution during exercise, measured with the pulmonary pressure sensor (C). The correlation during exercise between the slope (rest to peak exercise) measured with the CardioMEMS-HF device and with continuous wave during transthoracic echocardiography is displayed in panel D.



Medicine is the only profession that labors incessantly to destroy the reason for its own existence.

- James Bryce -

GENERAL DISCUSSION

The aim of this doctoral thesis was to enhance our comprehension of congestion in heart failure, the role of urinary sodium in chronic and acute heart failure patients and to explore innovative ways to improve our current heart failure care. The thesis was divided in three parts investigating different topics within the main subject.

PART I | PATHOPHYSIOLOGY OF CONGESTION IN HEART FAILURE AND THE IMPACT ON URINARY SODIUM EXCRETION

The primary focus of this doctoral thesis has been on the pathophysiology of congestion, with particular emphasis on the urinary sodium avidity. In heart failure, an interplay between heart and kidney result in neurohumoral upregulation, which results in an increased renal sodium avidity along all segment of the tubuli. The enhanced sodium reabsorption and consequent water retention will result in a net positive sodium and water balance (i.e., more water and sodium in than out). Together with the redistribution of the splanchnic venous system, this results in increased cardiac filling pressures with consequently signs and symptoms of congestion. As a reduced urinary sodium excretion is key in the pathophysiological process of ADHF, it seems rationale that this might aid in guiding therapy, while also holding prognostic information.

During an ADHF hospitalization, the main goal is to achieve a net negative fluid balance and to restore euvolemia, mainly through the use of diuretic therapy. However, diuretic response differs between and within patients. Historically, frequent assessments of the diuresis were necessary to evaluate whether the dosing of the diuretic therapy was sufficient. Since 2019 after the HFA consensus document, there has been more attention towards a role of urinary sodium to target therapies with adaptations of these recommendations in the ESC-HFA guidelines of 2021. Afterwards, 2 large trials demonstrated the benefit of such a strategy. Despite the convincing evidence, adaptation in daily practice remains limited due to the cumbersome protocol with multiple steps. In the EASY-HF study, we have demonstrated in a small, randomized-controlled trial of 60 patients

admitted with ADHF that a fully nurse-led natriuresis guided protocol with the use of a point-of-care urinary sodium sensor resulted in a better natriuretic and diuretic response with a trend towards a shorter length of stay compared to the current standard-of-care (i.e., physician-guided therapy). The point-of-care sensor enabled a bedside result which made it possible to close the loop for the nursing staff, i.e. administration of loop diuretic, collecting urine sample with immediate measurement and adaptation of the diuretics based on the result through the aid of a predefined flowchart. The sensor and the protocol were assessed as easily usable by the nursing team. Despite the small sample size, this study has a large impact as this might be broadly implementable and facilitate heart failure care across multiple departments in the hospital. It allows optimization of diuretic strategies without the immediate interference of a physician, leading to more rapid symptom relieve, possible shorter length-of-stay with a consequent reduction in health care expenses. The sidenote of this story is the fact that currently only one type of point-of-care sensor for urinary sodium measurements (HORIBA, LAQUATwin) is available. Although the firm is working on a CE label for medical use and it might be expected in 2026, standard in-hospital use (without a study context) is until then not possible.

After discharge for an ADHF event, there is a large risk for rehospitalization during this vulnerable phase and close follow-up is recommended, however not always possible. Therefore, we aimed to make a better risk stratification through the use of urinary sodium measurements at home. The FAST-RESPONSE study evaluated the urinary profile in patients at home after discharge for an ADHF. Despite the novel GDMT with improvements in outcome, the study confirmed the ongoing high-risk for rehospitalization and all-cause mortality in this subset of heart failure patients with an event rate exceeding 50% after 180 days. Daily collection for two consecutive weeks demonstrated that the urinary sodium in this high-risk population was relatively stable over time and patients remained diuretic responsive after hospitalization with a greater sodium excretion post-diuretic therapy compared to the first-void sample. However, patient who experienced an event had a significantly lower first and post-diuretic void compared to stable heart failure patients. As the urinary sodium concentration remained relatively stable over time, this means that a one-time urinary sodium measurement holds

great predictive value to distinguish patients at higher risk with need for closer follow-up. Unfortunately, the current study was not able to demonstrate a predictive value for the onset of the event. However, we should acknowledge that the study duration of 14 days immediately post-discharge might be have been too short to see any differences. In addition, patients had a relatively low urinary sodium excretion post-discharge, probably related to the fact that they were fully decongested. Further research might be indicated to elucidate whether urinary sodium monitoring is a meaningful tool during this high-risk phase.

Of course, the ultimate scenario is to keep patients with chronic heart failure congestion-free without need for hospitalization. Martens et al. demonstrated that a drop in urinary sodium excretion preceded an ADHF event. In order to optimize monitoring strategies, we evaluated the role of home urinary sodium measurements by the patients themselves. In total, 76 patients measured via a point-of-care sensor the urinary sodium concentration at home twice a week for 48 consecutive weeks. Once patients decided to start measuring, compliance rate was high during the first 3 months (almost 80%). However, 1 out of 3 patients decided to stop measuring after the first follow-up visit at 3 months. Also, in this patient cohort, urinary sodium measurements remained relatively stable over time with a higher median urinary sodium excretion in chronic stable heart failure patients compared those experiencing an ADHF event. It should be noted that chronic heart failure patients on maintenance loop diuretic therapy remained diuretic responsive, but these patients exhibited a lower first-void urinary sodium excretion compared to those not on loop diuretics, reflecting a higher intrinsic renal sodium avidity in patients on loop diuretic maintenance therapy. Also, in this stable group of patients, patients with a lower urinary sodium excretion were at higher risk for all-cause mortality and heart failure hospitalization. It should be noted that the patient profile of this subset of chronic heart failure patients completely differs from patients after an ADHF event, with a significantly lower event rate. During the measuring period, none of the patients required IV diuretics with the need for hospitalization.

Although two distinct profiles, it seems that the urinary sodium concentration was predictive in both cohort with patients with a higher intrinsic sodium avidity at

higher risk for rehospitalization. Therefore, for future research, it would be extremely interesting whether urinary sodium concentration could be used as a target to individualize heart failure therapy in order to prevent heart failure hospitalizations and mortality.

One of the pathways could be to reduce loop diuretic maintenance therapy to the lowest necessary dose in stable chronic heart failure patients. Loop diuretic therapy is associated with an increased risk for mortality and hospitalization and reduction in GDMT uptitration, with patients on higher doses at higher risk. Of course, this might be biased as patients with more advanced heart failure might require higher doses to maintain euvolemia. In the EASY-STOP study, 50 patients with chronic stable heart failure on loop diuretics were asked to measure the urinary sodium concentration on a daily base during a run-in phase of 1 week, after which the loop diuretics were downtitrated and measurements continued for another 3 weeks. Importantly, in patients who remained euvolemic on a lower loop diuretic dose or even without loop diuretics, a significant increase in first-void urinary sodium excretion was noted compared to patients who had an unsuccessful uptitration. In the current cohort, no other patient characteristics or laboratory parameters were able to predict which patients would be able to successfully downtitrate their diuretics. In addition, the increase in first-void natriuresis was already apparent after a few days, while the median time to diuretic reinitiation was 9 (7-21) days. So, the urinary sodium profile was already able to predict success prior to the onset of symptoms. So, patients who were successfully downtitrated had a reduction in their intrinsic renal sodium avidity.

For future research, it would be interesting to investigate whether GDMT initiation and uptitration also has an influence on the urinary sodium profile. As mentioned above, if this is the case, it would be interesting to examine whether a specific sodium target should be reached in order to have a beneficial effect on the long-term outcome.

One important limitation of the urinary sodium approach should be mentioned. As our dietary sodium intake fluctuates, this might of course have a direct impact on the urinary sodium excretion. However, there are two important side notes that

should be acknowledged. Patients with heart failure are advised to limited sodium intake and normally have a more stable dietary sodium pattern than healthy volunteers. In addition, Nijst et al. have demonstrated that the sodium is not immediately excreted once ingested, but is stored to some extent in the interstitial tissue. During this doctoral thesis, a small pilot trial in healthy volunteers demonstrated that after a salt load the urinary sodium excretion gradually increases towards a novel steady-state. However, with a lower total sodium excretion than intake, which indeed suggests some kind of sodium storage in the body. In addition, urinary sodium gradually decreased towards baseline after resumption of dietary salt-restriction, which means that short-term fluctuations in dietary salt intake probably have a low impact on long-term urinary sodium monitoring. However, the current examined population consisted healthy volunteers and whether these findings can be extrapolated towards heart failure patients needs to be investigated.

PART II | TREATMENT OF ACUTE HEART FAILURE

As mentioned previously, hospitalizations for acute decompensated heart failure with signs and symptoms of congestion are the most common and burdensome complication in patients with chronic heart failure. Loop diuretics, which inhibit sodium reabsorption in the loop of Henle, have a class I recommendation to relieve signs and symptoms of congestion. However, in patients with advanced cardiorenal syndrome, the response to loop diuretics may be diminished due to increased sodium reabsorption along other tubular sites, reducing natriuretic efficacy. In those cases, combination diuretic therapy targeting multiple sites along the nephron may enhance natriuresis.

Acetazolamide is a long-existing diuretic agent, acting in the proximal tubule. As the vast majority of sodium is reabsorbed in the proximal tubule, the addition of acetazolamide to loop diuretics could improve decongestion. This strategy has been examined in the multicenter, randomized, double-blind, placebo-controlled ADVOR trial. The addition of acetazolamide to standardized loop diuretics was associated with a 46% higher incidence of successful decongestion after 3 days

and a 27% increase at discharge. This was confirmed by a higher natriuresis and diuresis, with a shorter length-of-stay in the hospital. Therefore, the ADVOR trial provided important and strong evidence in favor of routine combinational diuretic therapy with acetazolamide and loop diuretics in patients with acute heart failure. Moreover, the beneficial effect of acetazolamide was consistent across the full eGFR range, with even more pronounced effects regarding natriuresis and diuresis in patients with a lower eGFR. During decongestion, a drop in kidney function is common and may represent pseudo-worsening renal function (WRF) when it occurs alongside effective diuresis. Although WRF was more frequent in patients treated with acetazolamide, this was not associated with adverse clinical outcomes and did not affect long-term kidney function. In contrast, WRF in persistently congested patients is associated with the poorest long-term outcome. Despite the beneficial effect on decongestion, the ADVOR trial was not able to demonstrate any beneficial impact on all-cause mortality and heart failure hospitalization on the long-term. Irrespective of treatment, having residual congestion after decongestive treatment is associated with an increased risk of adverse long-term outcome. As mentioned previously, the upfront addition of acetazolamide reduced the incidence of residual congestion. However, if patients have residual congestion despite treatment with acetazolamide, these patients are at prohibitive risk, identifying a subset of patients requiring specialized heart failure care.

PART III | OPTIMIZATION OF CHRONIC HEART FAILURE

Guideline-directed medical therapy optimization is crucial in patients with chronic heart failure as these therapies improve long-term outcome with a better quality of life, and a reduction in heart failure hospitalization and mortality. In patients with heart failure with a reduced ejection fraction, this consists of 4 pillars of medication. Preferably, patients are treated with all four in the highest tolerable dose. Despite the clear recommendations, registries have demonstrated that prescription rates remain suboptimal, mostly due to physician-inertia and the perceived risk of hypotension, hyperkalemia and worsening renal function. During this doctoral thesis, a multicenter prospective randomized trial has been set-up in order to evaluate the benefit of a renal-based uptitration protocol compared to

standard-of-care. If confirmed or if proven beneficial, the applicability to use such a flowchart for general heart failure patients may be extended, which would improve overall implementation of GDMT and therefore also patients' outcome.

CONCLUSION

In summary, this doctoral thesis aimed to deepen our understanding of congestion in heart failure, with a specific focus on urinary sodium as both a therapeutic guide and prognostic marker. Urinary sodium concentration is a direct reflection of the intrinsic renal sodium avidity and a predictor of clinical outcomes in both acute and chronic heart failure. Nurse-led natriuresis-guided protocols and home-monitoring systems using point-of-care sensors showed promise in optimizing diuretic therapy and identifying high-risk patients. Moreover, the addition of acetazolamide to loop diuretics improved decongestion outcomes, and should be used in acute heart failure diuretic-protocols. Finally, we are exploring the potential of renal-based strategies to enhance guideline-directed medical therapy in chronic heart failure patients, highlighting the importance of personalized, proactive care to improve patient outcomes.

LAY SUMMARY

Understanding and Managing Fluid Accumulation in Heart Failure: A New Look at Salt in Urine

Background

Heart failure is a chronic condition which occurs when the heart muscle doesn't pump blood as well as it should. In this case, blood often backs up and fluid can build up in the body (called 'congestion'), causing symptoms of shortness of breath, swollen legs and fatigue. This often leads to hospital visits, which are stressful for the patient and costly for the society. The main reason for this fluid accumulation is increased salt and water retention by the kidneys.

Aim of this research

This doctoral thesis focused on how we can better understand and treat fluid build-up in heart failure. If someone with heart failure is holding on to too much salt and water, this leads to congestion. Therefore, one simple way to do this might be by looking at how much salt is excreted in the urine.

Key findings

1. **Salt in the urine can help guide treatment**
   Normally, patients hospitalized for fluid accumulation receive water pills (diuretics) to get rid of the extra fluid and salt. As everyone responds differently to this medication, it might be challenging to find the right dose for the right patient. Research demonstrated that by measuring salt in urine, nurses and doctors get a better idea of which patients require higher doses of water pills to get rid of the fluid. In addition, when nurses use a simple device at the bedside to check the salt in the urine, they could adjust treatment faster, leading to quicker improvement in patients and possible shorter hospital stays.

2. **Measuring salt levels at home could predict patients at higher risk**
   After leaving the hospital, there is a high chance they might need to come back because of fluid build-up within a short time interval. This research investigated whether people could check their own urine salt levels at home using a small device, which might probably help to detect problems early. The study found

that people with lower salt in their urine were more likely to retain fluid again. Just one urine test could help doctors predict which patients might need more attention after discharge.

3. **Reducing water pills in stable patients based on the urinary sodium content**

   Some people with stable heart failure take water pills as a continuous therapy at home to prevent recurrence of fluid accumulation. These pills can have side effects and may not always be needed. However, it is very difficult to predict which patients need water pills on a chronic base. In a study during this doctoral research, patients were asked to slowly lower their dose or stop their pills while checking their urine salt with the device at home. If their salt levels increased after stopping their medication or reducing their dose, they had less chances of recurrence of fluid accumulation.

4. **Combining different water pills in patients with fluid accumulation in the hospital**

   During hospital stay, some people do not always pee enough on certain water pills. In one study, the combination of two different waters pills was examined and it seemed that the combination helped to get rid of more fluid faster.

5. **Improving medication prescription in patients with heart failure**

   People with heart failure should normally be treated with several pills in order to live longer and have lower chances on fluid accumulation. Sometimes, doctors hesitate to prescribe these pills. During this doctoral research, a study has been started to investigate whether a flowchart might help to safely prescribe these medications, improving patients' health.

Conclusion

This research shows that something as simple as checking salt in the urine can help doctors and nurses better manage heart failure patients, both in the hospital and at home. It can help tailor treatments and predict patients at risk. After more research, this approach could become part of everyday care for people living with heart failure.

POPULARISERENDE SAMENVATTING

Achtergrond

Hartfalen is een chronische aandoening, waarbij de hartspier het bloed niet voldoende rondgepompt krijgt om normaal te kunnen functioneren. Hartfalen gaat gecompliceerd met episoden van vochtopstapeling in het lichaam (‘congestie’), wat leidt tot klachten zoals kortademigheid en gezwollen benen met helaas vaak noodzaak tot ziekenhuisopnames. Een belangrijke oorzaak van deze vochtophoping is dat de nieren te veel zout en water vasthouden.

Doel van het onderzoek

Dit onderzoek richtte zich op betere manieren om vochtophoping bij hartfalen te begrijpen en te behandelen. Omdat het vasthouden van te veel zout en water leidt tot congestie, zou het meten van de hoeveelheid zout in de urine een eenvoudige manier kunnen zijn om dit te monitoren.

Belangrijkste bevindingen

1. **Zoutmetingen als leidraad voor de behandeling van hartfalen**
   Patiënten opgenomen met vochtophoping krijgen plasmedicatie (diuretica) om overtollig vocht en zout kwijt te raken. Omdat iedereen anders reageert, is het soms lastig om de juiste dosering te vinden waarbij het vocht efficiënt uitgeplast wordt. Het meten van zout in de urine kan artsen en verpleegkundigen helpen om te bepalen of iemand meer medicatie nodig heeft. Daarbij hebben we aangetoond dat als verpleegkundigen een klein apparaatje aan het bed gebruiken om het urinair zoutgehalte te meten, hierop de therapieën onmiddellijk aangepast konden worden, wat leidde tot snellere ontwatering en mogelijk een korter ziekenhuisverblijf.

2. **Zoutmetingen thuis kunnen het risico op heropname voorspellen**
   Na ontslag uit het ziekenhuis lopen veel patiënten het risico dat het vocht weer terugkomt. Tijdens dit onderzoek werd aan patiënten gevraagd om thuis hun eigen urinezout te meten met een klein apparaatje. Patiënten met lage zoutwaarden in hun urine hadden meer kans om opnieuw problemen te krijgen. Zelfs één enkele meting kan artsen helpen om te zien welke patiënten extra opvolging nodig hebben omdat ze een hoger risico hebben.

3. **Het afbouwen van plasmedicatie begeleiden bij stabiele patiënten**
   Sommige mensen met stabiel hartfalen gebruiken langdurig plastabletten om te voorkomen dat het vocht terugkomt, maar dat is misschien niet altijd nodig. Het is moeilijk in te schatten wie de medicatie echt nodig heeft, dus vaak wordt de medicatie niet aangepast aangezien het enige alternatief is de medicatie te verminderen/stoppen en afwachten of de klachten terugkomen. In dit onderzoek werden patiënten gevraagd om hun dosis langzaam te verlagen of te stoppen, terwijl ze het zoutgehalte in hun urine thuis controleerden. Als hun zoutwaarde steeg, hadden ze minder kans op terugkerende vochtophoping.

4. **Plasmedicatie combineren ter behandelen van vochtopstapeling in het ziekenhuis**
   Sommige patiënten plassen niet genoeg met één soort plastablet tijdens een ziekenhuisopname. De ADVOR-studie onderzocht de combinatie van een lang bestaande plasmedicatie aan een tweede, standaard gebruikte plaspil en dit toonde aan dat de combinatie leidde tot een snellere en efficiëntere verwijdering de wateroverbelasting bij patiënten opgenomen met hartfalen.

5. **Verbeteren van het voorschrijven van hartfalen-medicatie**
   Mensen met hartfalen zouden verschillende belangrijke medicijnen moeten krijgen met als doel hun langer klachtenvrij te houden, overleving te verbeteren en opnames in het ziekenhuis te vermijden. Desondanks wordt deze essentiële medicatie te weinig voorgeschreven. Dit onderzoek zette een studie op om te kijken of een eenvoudige leidraad artsen helpt om het voorschrijfgedrag te verbeteren, en hierdoor de gezondheid van patiënten.

Conclusie

Deze thesis heeft aangetoond dat iets eenvoudigs als het meten van het zoutgehalte in de urine artsen en verpleegkundigen kan helpen om patiënten met hartfalen beter te behandelen, zowel in het ziekenhuis als thuis. Het kan helpen de therapie af te stellen op maat van de patiënt en patiënten met een verhoogd risico te identificeren. Verder onderzoek is nodig, maar een dergelijke aanpak zou een vast onderdeel kunnen worden van de zorg voor patiënten met hartfalen.

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