University of Groningen

Electrolyte disturbances in heart failure

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DOI:
[10.33612/diss.196047233](https://doi.org/10.33612/diss.196047233)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Beusekamp, J. (2022). *Electrolyte disturbances in heart failure: focus on sodium and potassium*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.196047233>

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Electrolyte disturbances in heart failure

Focus on sodium and potassium

Joost Coenraad Beusekamp

Financial support from the following institutes and companies is gratefully acknowledged:

- University of Groningen
- The Groningen University Institute for Drug Exploration (GUIDE)
- Graduate School of Medical Sciences
- Vifor Pharma
- Boehringer Ingelheim
- Abbott
- Pfizer
- Teva
- Noord Negentig
- ANW Nederland
- Olink Proteomics
- ChipSoft

Provided by thesis specialist Ridderprint, ridderprint.nl

ISBN: 978-94-6416-393-3

Printing: Ridderprint | www.ridderprint.nl

Layout and design: Marilou Maes | www.persoonlijkproefschrift.nl

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rijksuniversiteit
 groningen

Electrolyte disturbances in heart failure

Focus on sodium and potassium

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 2 februari 2022 om 16.15 uur

door

Joost Coenraad Beusekamp

geboren op 6 juli 1993
te Utrecht

Promotores

Prof. dr. P. van der Meer

Prof. dr. A.A. Voors

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Beoordelingscommissie

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Paranimfen

Dr. J.B. van Praagh

Drs. B.A. de Cort

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENTS

Chapter 1	Introduction and aims	7
Chapter 2	Potassium abnormalities in patients with heart failure from 11 Asian regions: Insights from the ASIAN-HF registry <i>Eur J Heart Fail. 2020 Apr;22(4):751-754</i>	23
Chapter 3a	Potassium and the use of RAAS inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF <i>Eur J Heart Fail. 2018 May;20(5):923-930</i>	35
Chapter 3b	Is hyperkalaemia in heart failure a risk factor or a risk marker? Implications for renin-angiotensin-aldosterone system inhibitor use <i>Eur J Heart Fail. 2018 May;20(5):931-932</i>	63
Chapter 4	Hyperkalaemia and treatment with RAAS inhibitors during acute heart failure hospitalizations and their association with mortality <i>J Am Coll Cardiol HF. 2019 Nov;7(11):970-979</i>	71
Chapter 5	Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF) <i>Eur J Heart Fail. 2020 Apr;22(4):713-722</i>	109
Chapter 6	Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure <i>Eur J Heart Fail. 2021 Jan;23(1):68-78</i>	137
Chapter 7	Effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on potassium handling in patients with acute heart failure <i>Eur J Heart Fail. 2021 Jun;23(6):1049-1052</i>	163
Chapter 8	General discussion and future perspectives	179
Appendices	Dutch summary Nederlandse samenvatting	190
	Acknowledgements Dankwoord	198
	Curriculum vitae	206

1

Introduction and aims

HEART FAILURE

Heart failure (HF) is defined as a condition in which the oxygen requirements of the metabolizing tissues outreach the heart's delivering capacity. This can be caused by specific cardiac abnormalities or an impaired heart function. Up to 30% of the worldwide population develops HF during their lifetime.¹ These patients will present themselves to the treating physician with typical but non-discriminating signs and symptoms. Dyspnoea (either at rest or at exertion) plays a significant role in the clinical syndrome, combined with signs of fluid congestion (i.e. pulmonary rales or ankle swelling). As predicted, the prevalence of HF and the number of HF-related hospitalizations will rise in the upcoming decennia.²

Patients with HF are stratified based on their left ventricular ejection fraction (LVEF). According to the latest guidelines, patients with an LVEF <40% are classified as HF with reduced ejection fraction (HFrEF); an LVEF 40-49% as HF with mid-range ejection fraction (HFmrEF); and an LVEF ≥50% as HF with preserved LVEF (HFpEF).³

Clinically, 'acute' and 'chronic' HF can be distinguished based the onset of the symptoms. Patients with chronic HF develop worsening signs and symptoms over time, in contrast to patients with acute HF, which is characterized by a sudden onset requiring acute treatment.

Regardless of the ejection fraction or the subtype, patients' prognosis remains poor. Half of these patients will die within 5 years after the initial diagnosis.⁴ Despite various clinical trials, no specific treatment has been developed to improve outcomes in patients with acute 'decompensated' HF.³ Treatment mainly relies on (loop) diuretics to relieve signs and symptoms of congestion by increasing the renal salt and water excretion.

For patients with chronic HFrEF, specific drugs developed in the past decades significantly reduced cardiovascular (and renal) morbidity and mortality. These include angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs).⁵⁻²⁰

Recently, four novel HF therapeutics (i.e. sacubitril/valsartan²¹ [angiotensin receptor neprilysin inhibitors (ARNIs) blocks angiotensin receptor and prevents degradation of natriuretic peptides], sodium-glucose cotransporter-2 (SGLT2) inhibitors²²⁻²⁴ [blocks the SGLT2 receptor in the proximal tubule of kidney], omecamtiv mercabil²⁵ [selective cardiac myosin activator], and vericiguat²⁶ [soluble guanylyl cyclase activator which enhances cyclic guanosine monophosphate production] have shown to further improve clinical outcomes of patients with HFrEF.

Unfortunately, none of the conventional HF therapies has proven effective in patients with HFpEF, resulting in still no specific HF treatment for these patients. Of the novel HF therapies, only the effect of sacubitril/valsartan was investigated in patients with HFpEF. Unfortunately, it did not meet the primary endpoint of reducing the total number of hospitalizations for heart failure and death from cardiovascular causes, yet was approved by the United States Food and Drug Administration (FDA) for the treatment of HFpEF.²⁷ Currently, SGLT2-inhibitors are studied in patients with HFpEF as well and the first results are expected in the near future.

Developing and validating novel, life-saving agents only covers one aspect of improving the prognosis of patients with HF. The other important, and possibly concomitant, goal in optimizing the treatment of patients with HF should be to enable these patients to tolerate guideline-directed (dosages of) HF medication. This process of increasing the dosages of the HF drugs as close as possible to the guideline recommendations is referred to as 'up-titration'.

Up-titration

From daily practice we have learned that titrating HF medication to guideline-recommended treatment dosages is hardly achieved. A recent registry from 34 Dutch HF outpatient clinics showed that the majority of Dutch HF patients are treated with ACEi/ARB (86%) and beta-blockers (84%). However, median dosage levels were only 50% and 25% of the recommended target dose, respectively.²⁸ A pan-European observational study investigating up-titration levels of ACEi/ARBs and beta-blockers in 2,100 patients with new-onset or worsening HF showed that only 22% of patients reached recommended ACEi/ARBs dose and 12% of patients

reached recommended dose of beta-blockers after three months of active up-titration.²⁹ Even though this study was designed to document the reason for not achieving guideline-recommended dosages, no specific reason was recorded in the majority of the patients. If known, the reasons were mainly related to specific symptoms or side effects of which hypotension and renal dysfunction were most commonly observed.³⁰ Especially in ACEi/ARBs and MRAs, an increase in serum potassium levels is seen as a major concern.³¹

Electrolytes in heart failure

Multiple electrolytes play a role in the (patho)physiology of the human heart, such as sodium, potassium, calcium, and magnesium. This can be through a direct effect on the metabolizing tissue or via the pharmacological effects of HF treatment. This thesis highlights two electrolytes; sodium and potassium.

Sodium and potassium homeostasis

Both serum sodium and potassium levels are strictly controlled by our intestines' uptake and renal excretion. This process of maintaining the required levels is referred to as 'homeostasis' and is essential in the preservation of a normal function of the neuromuscular cells and the human heart.³²⁻³⁴ At times of a normal renal function, sodium and potassium are mainly reabsorbed in the proximal tubule, the loop of Henle, and the collecting duct.^{35,36} This reabsorption rate is affected by the serum levels of sodium and potassium, the flow rate through the distal tubule, and aldosterone concentration, which binds to an enzyme causing sodium reabsorption and potassium excretion in the distal tubule and the collecting duct.³⁶ Only a small proportion of potassium is excreted via the gastrointestinal tract.

Despite a World Health Organization (WHO) recommendation of a dietary sodium intake of two grams per day (the equivalent of 5 grams of salt per day), a vast proportion of the world's population exceeds this recommendation.³⁷ However, to maintain an adequate function of the human cells, a daily sodium intake of 200-500 milligrams per day would be sufficient. Higher serum sodium levels have been associated with an increased risk of cardiovascular morbidity (including hypertension) and mortality.^{38,39} In HF, a sodium intake above five g/day is associated with an increased risk of cardiovascular events.⁴⁰⁻⁴² In contrast, moderate sodium

intake (2.3–4.6 g/day) has been consistently associated with lower cardiovascular risk in prospective cohort studies, compared to both low and high sodium intake.⁴³ In addition, it has been suggested that an increased dietary potassium intake can attenuate the effects of high sodium intake due to the natriuretic effects of potassium.^{44–47}

A dietary potassium intake of 90 mmol per day (3.5 grams per day) is recommended by the WHO.⁴⁸ In contrast to the abundant sodium intake, many countries fail to meet the recommended potassium intake. Changes in the diet over the past decades might be responsible for failing to meet international recommendations. Earlier diets were predominantly plant-based, consisting of high proportions of potassium, fibres and anti-oxidants. However, the more recent globalization of food production systems led to a more calorie-rich diet, including high sugar, fat, and salt levels.⁴⁹ Altogether, this caused a 400% increase in sodium intake, combined with a 400% decline in potassium intake.⁵⁰

Potassium

Potassium ions are a crucial cation in humans playing a role in the electrophysiology of the neuromuscular cells and the human heart. The distribution of potassium throughout the body results from a complex interplay of excretion (renal and gastrointestinal function, medication, and neurohormonal activation) and intake (diet including supplements and medication). The high potassium concentration within the cell is maintained on a cellular level through the sodium-potassium-adenosine triphosphatase pump (the Na⁺, K⁺-ATPase-pump). Serum (extracellular) potassium levels are generally maintained within narrow limits, typically between 3.5 and 5.0 mmol/L. When serum potassium levels drop below 3.5 mmol/L (hypokalaemia), this increases automaticity, excitability, and depolarization of the cardiac cells.⁵¹ The cardiac repolarization depends on the influx of potassium ions. Therefore, hypokalaemia causes prolonged action potassium and prolonged QT-interval.⁵¹ On the other hand, hyperkalaemia (K⁺>5.0mmol/L) leads to shortening of the QT-time. In general, dyskalaemia (both hypo- and hyperkalaemia) can lead to sudden cardiac due to fatal (ventricular) arrhythmias.³²

Potassium concentrations are affected by multiple comorbidities and therapies. For example, renal dysfunction and diabetes mellitus can cause dyskalaemia.⁵² Additionally, guideline-directed medication including diuretics, ACEi/ARBs, beta-blockers and MRAs impact potassium homeostasis.^{53–55} Since patients with HF frequently suffer from several comorbidities and are treated with a wide range of medication, they are more prone to potassium disturbances.

Despite a vast proportion of studies describing a U-shaped relation between serum potassium levels and mortality in HF patients,^{56–58} reference ranges for serum potassium levels still vary between recommendations from Europe and the United States.^{52,59} In an American review hypokalaemia was defined as a serum potassium < 4.0 mmol/L, whereas hyperkalaemia was defined as K⁺ > 5.5 mmol/L.⁵² Contrastingly, a European expert consensus uses cut-off values of 3.5 mmol/L and 5.0 mmol/L, respectively.⁵⁹

Sodium

Where the concentration of potassium ions is highest inside the cells, is sodium the major cation in the extracellular matrix of the human body.

Multiple HF therapies affect the sodium regulation by the kidney, such as loop diuretics and inhibitors of the renin-angiotensin-aldosterone system. In particular, loop diuretics are used as first line therapy in patients with acute HF who mainly present themselves with signs of fluid congestion. Loop diuretics block the reabsorption of sodium, chloride, and potassium in the thick ascending limb of the loop of Henle. Though, hyponatremia at admission, defined as serum sodium levels below 136 mEq/L, has been associated with increased mortality rates in numerous clinical trials, mostly regarding patients with chronic HF.⁶⁰

Recently, SGLT2-inhibitors have gained a lot of attention in cardiology. They were approved by the American FDA to treat patients with diabetes mellitus type 2. At the time of approval, the working mechanism seemed fairly straightforward. Administering the drug results in blockage of the SGLT2-enzyme in the proximal tubule of the kidneys. Typically, the SGLT2-enzyme reabsorbs both sodium and glucose. Blocking this receptor results in a decreased reabsorption (and assumingly

an increased excretion) of sodium and glucose. Patients with type 2 diabetes benefit from this mechanism by excreting abundant glucose through glycosuria. In landmark diabetes trials, SGLT2-inhibitors surprisingly reduced HF-related rehospitalisations, even though patients with diabetes are more prone to develop HF.^{61–63} This resulted in a unique interest in the field of cardiovascular medicine with consequent HF-related clinical trials showing improvement of cardiac and renal outcomes in patients with HF regardless of being diabetic.^{22–24} Although SGLT2-inhibitors were initially considered to be only a new class of glucose-lowering agents, now we know that their beneficial effects reach much further. Still, their exact cardioprotective mechanism and diuretic effect has not been well established.

1

Aims and outline of the thesis

The optimal use of life-saving and guideline-directed medical therapies in patients with HF is limited by electrolyte disturbances and hyperkalaemia in particular. However, only limited data is available to indicate which patients are prone to developing hyperkalaemia. Additionally, the interaction between serum potassium levels and the up-titration of ACEi/ARB for outcome in patients with HFrEF has not been the focus of previous research. Regarding the novel HF therapies, SGLT2-inhibitors have recently been studied in patients with chronic HF, yet their effect and tolerability in patients with acute HF is unknown. Consequently, we only have limited knowledge on the diuretic effects of these drugs and their effect on sodium and potassium homeostasis.

In general, this thesis aims to investigate the interplay between sodium, potassium, and novel or conventional HF therapies. **Chapter 2** identified which patients with chronic HF are at risk of developing potassium disturbances and tested if this was associated with outcomes in patients included in the ASIAN-HF registry. **Chapter 3** investigated the association between serum potassium levels and the chances of being up-titrated with guideline-directed HF treatment in patients with chronic HF who were treated sub-optimally. Additionally, **Chapter 4** tested the interference of potassium disturbances with HF therapy in patients hospitalized with acute HF. In **Chapter 5**, we prospectively studied the effects of the SGLT2-inhibitor empagliflozin on clinical outcomes in patients with acute decompensated HF. **Chapter 6** assessed the effects of empagliflozin on the renal handling of sodium and glucose in patients

hospitalized with acute decompensated HF. **Chapter 7** studied the effect of SGLT2-inhibition with empagliflozin on serum and urinary potassium levels in patients with acute HF. Finally, we discuss the findings and relevance of this thesis and the future perspectives in **Chapter 8**.

Figure 1. Factors possibly affecting potassium regulation in patients with HF.

RAAS: Renin-Angiotensin-Aldosterone System

SGLT2: Sodium-Glucose cotransporter-2

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Potassium abnormalities in patients with heart failure from 11 Asian regions: Insights from the ASIAN-HF registry

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Eur J Heart Fail. 2020 Apr;22(4):751-754.

Abnormalities in serum potassium concentrations (hypo- and hyperkalaemia) are common in patients with heart failure (HF) and associated with discontinuation or down-titration of guideline-recommended medical therapies and adverse outcomes.¹⁻³ Therefore, current HF guidelines recommend frequent monitoring of serum potassium concentrations.⁴ Although over 60% of the world's population resides in Asia, data on potassium abnormalities in Asian patients with HF are scant and most previous studies on the prevalence and clinical consequences of potassium abnormalities in patients with HF were from Western populations.² The particularly high prevalence of risk factors for potassium abnormalities such as diabetes and chronic kidney disease among Asian patients with HF and the substantial underuse of evidence-based HF pharmacotherapy makes them more vulnerable to potassium abnormalities. Furthermore, the striking regional differences in both patient characteristics and treatment patterns across Asia warrant an examination of potential regional variation in potassium levels and their correlates.^{5,6} Therefore, we investigated the frequency, predictors and clinical outcome associated with potassium abnormalities in Asian patients with HF.

A total of 6480 patients with HF from 46 centres and 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, and Thailand) were prospectively enrolled in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry.⁷ Patients with symptomatic HF (at least one episode of decompensated HF in the previous 6 months resulting in hospital admission or treatment in outpatient clinic) and reduced or preserved ejection fraction, aged >18 years could be enrolled in ASIAN-HF. Patients were excluded if their HF was caused by valvular disease, if they had a life expectancy <1 year, and/or were unable/unwilling to give consent.⁷ Although blood sampling was not required by study protocol, clinically available measurements were routinely recorded in the case report forms and for potassium measurements, serum concentrations were recorded in all participating sites. All patients included provided written informed consent and the study adhered to the medical research principles as recorded in the Declaration of Helsinki.

A total of 5054 (78%) patients had potassium measurements recorded at enrolment. Compared to patients without potassium measurements (n=1426), patients with potassium measurements were older with more comorbidities but similar mean

estimated glomerular filtration rate (eGFR) and were less often treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) and mineralocorticoid receptor antagonists (MRA) but more often treated with beta-blockers and loop diuretics (Supplementary Table 1).

For all sites, hypokalaemia and hyperkalaemia were defined as <3.5 mmol/L and >5.0 mmol/L respectively. Hyperkalaemia was subdivided into mild (>5.0 to <5.5 mmol/L) and moderate/severe (≥ 5.5 mmol/L).^{8,9} The primary outcome was a composite of all-cause mortality and HF rehospitalisation within 1 year and tested using Cox proportional hazards models. Tests for interaction between potassium concentrations and HF subtype were performed. All tests were two-sided and p-values <0.05 were considered statistically significant. Analyses were performed using Stata SE15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Among the 5054 patients (mean age 62 years, 27% women, 81% HFrEF) with available serum potassium concentrations, values ranged from 2.3 to 8.0 mmol/L, with a mean of 4.2 ± 0.56 mmol/L. Hypo- and hyperkalaemia was present in 342 (6.8%) and 356 (7.0%) patients respectively. A total of 98 patients (1.9%) had moderate/severe hyperkalaemia (≥ 5.5 mmol/L). Patients with hyper- or hypokalaemia had a similar NYHA class compared to patients with normokalaemia ($P=0.14$). Patients with hyperkalaemia were less frequently treated with MRAs, patients without potassium abnormalities were treated most frequently with ACEi/ARB, and patients with hypokalaemia were treated most often with loop diuretics ($P<0.05$ for all). A total of 125 patients (2.5%) had moderate/severe hyperkalaemia (≥ 5.5 mmol/L). A slightly lower use of MRAs was seen in patients with moderate/severe hyperkalaemia compared to mild hyperkalaemia (35% versus 46%, $P=0.048$).

Hypokalaemia was most prevalent among patients from Indonesia (19.7%), Hong Kong (17.5%), and Taiwan (10.2%) (Figure 1A), while hyperkalaemia was most prevalent in patients from India (12.7%) and Thailand (10.6%) (Figure 1B) regardless of HF subtype ($P_{\text{interaction}} > 0.5$ for both). These geographic differences remained significant in multivariable analyses after correction for clinical confounders including age, sex, New York Heart Association (NYHA) class, eGFR, history of diabetes, in- or outpatient enrolment, and use of ACEi/ARB, MRA, beta-blockers and loop diuretics.

Figure 1. Percentages of Asian HF patients with potassium abnormalities at baseline per country.

A. Percentage of patients with hypokalaemia (<3.5 mmol/L) per country

B. Percentage of patients with hyperkalaemia (>5.0 mmol/L) per country

Multivariable logistic regression showed that diabetes, impaired renal function, fewer signs and symptoms of HF, lower serum sodium concentrations, and no use of loop diuretics were associated with the presence of hyperkalaemia (Table 1). Patients with hypokalaemia were more often women, with higher heart rates and more signs and symptoms of HF; and were more often treated with loop diuretics (Table 1).

Table 1. Clinical variables associated with hypo- and hyperkalaemia at baseline in multivariable logistic regression models (n=3775 and n=4039 for hypo- and hyperkalaemia respectively).

Factor	Hypokalaemia			Hyperkalaemia		
	OR	Multivariable 95% CI (n=3775)	P-value	OR	Multivariable 95% CI (n=4039)	P-value
Age, per 10 years				1.06	.953 – 1.19	0.271
Female sex	1.39	1.05 – 1.84	0.023			
Heart rate, per 10 bpm	1.15	1.07 – 1.24	<0.001	.945	.870 – 1.03	0.182
SBP, per 20 mmHg	1.08	.965 – 1.22	0.172			
estimated GFR, per doubling	.993	.747 – 1.32	0.964	.522	.396 – .686	<0.001
NYHA Class III/IV, yes vs. no	.964	.725 – 1.28	0.802			
Orthopnoea, yes vs. no	1.12	.825 – 1.53	0.464	.558	.396 – .786	0.001

Table 1. (Continued)

Factor	Hypokalaemia			Hyperkalaemia		
	OR	Multivariable 95% CI (n=3775)	P-value	OR	Multivariable 95% CI (n=4039)	P-value
Peripheral oedema, yes vs. no	1.38	1.05 – 1.81	0.023			
History of:						
Atrial fibrillation/flutter				.774	.559 – 1.07	0.122
Diabetes				1.32	1.01 – 1.71	0.040
Stroke				.455	.244 – .848	0.013
COPD				.713	.433 – 1.17	0.182
Cardiovascular therapy:						
ACEi/ARB	.888	.665 – 1.19	0.420	1.09	.821 – 1.45	0.551
MRA				.835	.638 – 1.09	0.191
Beta-blockers	.751	.564 – 1.00	0.051			
Loop diuretics	1.63	1.10 – 2.41	0.014	.733	.541 – .994	0.045
Laboratory data on baseline:						
Haemoglobin, per 5 g/dL	.972	.703 – 1.34	0.866	1.30	.939 – 1.81	0.114
Sodium, per 10 mmol/L				.556	.423 – .731	<0.001

All listed variables were tested univariate. All variables with a univariate association <0.1 were used in the multivariable models.

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, bpm = beats per minute, COPD = Chronic Obstructive Pulmonary Disease, GFR = Glomerular Filtration Rate, MRA = Mineralocorticoid Receptor Antagonists, NYHA = New York Heart Association, SBP = Systolic Blood Pressure.

A total of 1001 (21.7%) patients died or were hospitalized for HF within 1 year. Hypokalaemia was associated with worse outcomes independent of HF subtype (HR: 1.46 (1.17-1.81), $P=0.001$) with a p-value for interaction >0.5). After correction for clinical confounders (Table 1), hypokalaemia remained significantly associated with worse outcomes (HR 1.28; 95% CI 1.02-1.61; $P=0.035$) but was no longer significant when adjusted for geographical region (HR 1.15; 95% CI 0.91-1.45; $P=0.237$).⁷ However, when analysed as a continuous variable in spline analysis, lower serum potassium concentrations were associated with the primary outcome, even after multivariable adjustment including region. The potassium concentration with the lowest hazard ratio for the primary outcome (4.9 mmol/L, risk nadir) was

set as reference. In contrast, hyperkalaemia at baseline was not associated with worse outcomes (HR: 0.86 (0.66 – 1.12), $P=0.259$).

In this unique study on potassium abnormalities among Asian patients with HF, the overall frequency of hypokalaemia (6.8%) and hyperkalaemia (7.0%) were similar as reported in the Western populations.² Nevertheless, we observed geographical differences, independent of differences in comorbidities, renal function and HF medication. We are unable to explain these findings but might reflect differences in healthcare systems or local practice.⁶ Clinical correlates of potassium abnormalities in Asian patients with HF were similar to those previously reported in Western and European populations and did not differ between geographical regions in Asia.² Based on spline analysis, our results indicate that lower potassium concentrations were associated with more adverse outcomes, which is in line with earlier reports from the US¹⁰, and in contrast to a previous study reporting U-shaped associations.¹ In the study of Aldahl et al., the association between hyperkalaemia and adverse outcomes became significant at relatively high (>5.5 mmol/L) concentrations of serum potassium, which was only present in 1.9% of the patients in our Asian cohort.¹ This study is limited by the fact that serum values were based on the medical records of blood tests of patients performed at the respective medical centres closest to the date of the baseline visit; thus site-to-site differences in measurement technique and/or reporting errors are possible (although the latter was minimized by study monitoring). Unfortunately, no data on potassium supplementation was available.

In conclusion, potassium abnormalities are common among Asian HF patients, with striking regional differences. Hypokalaemia was more frequently observed among patients from Indonesia, Hong Kong, and Taiwan and hyperkalaemia in patients from India and Thailand. Compared to normal potassium concentrations, hypo- and hyperkalaemia did not affect outcomes in adjusted analyses. Yet, on a continuous scale, lower serum potassium concentrations at baseline was related to an increased risk for 1-year mortality or HF rehospitalisation.

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SUPPLEMENTARY MATERIAL

Supplementary figure 1. Restricted cubic spline curve showing hazard ratios for all-cause mortality or HF rehospitalization within 1 year follow-up, as a function of serum potassium concentrations on a continuous scale.

Corrected for: Age, sex, estimated GFR, geographical region, inpatient enrolment, HFrEF/HFpEF, NYHA class, diabetes, on any ACEi/ARB, beta-blockers, MRA, and/or loop diuretics.

Supplementary table 1. Differences in characteristics of patients with and without available serum potassium concentrations at admission.

Variables	No serum potassium at baseline (n=1426)	Serum potassium at baseline (n=5054)	p-value
Age, years	59.0 ± 12.6	62.4 ± 13.4	<0.001
Male sex	394 (27.6%)	1356 (26.8%)	0.55
BMI, kg/m ²	25.2 (22.4, 28.2)	24.3 (21.6, 27.7)	<0.001
Heart rate, b.p.m.	78.3 ± 14.3	79.3 ± 16.5	0.038
Systolic BP, mmHg	120.4 ± 19.7	121.1 ± 21.6	0.29
LV ejection fraction (%)	30 (25, 37)	30 (23, 37)	0.080
eGFR, mL/min/1.73 m ²	67.2 ± 26.6	64.9 ± 28.1	0.24
NYHA class III/IV	347 (26.3%)	1556 (35.0%)	<0.001
Orthopnoea	218 (15.5%)	1150 (22.8%)	<0.001
Peripheral oedema	225 (16.0%)	1402 (27.8%)	<0.001
Coronary artery disease	571 (41.1%)	2404 (47.7%)	<0.001
Atrial fibrillation/flutter	152 (10.9%)	1127 (22.3%)	<0.001
Diabetes	466 (33.5%)	2190 (43.4%)	<0.001
Stroke	47 (3.4%)	387 (7.7%)	<0.001
COPD	70 (5.0%)	472 (9.4%)	<0.001
ACEi/ARB	1022 (78.6%)	3540 (72.4%)	<0.001
MRA	764 (58.7%)	2458 (50.3%)	<0.001
Beta-blockers	952 (73.2%)	3730 (76.3%)	0.019
Loop diuretics	979 (75.2%)	3874 (79.3%)	0.002
Haemoglobin (g/dL)	12.9 ± 2.2	12.9 ± 2.2	0.96
Sodium (mmol/L)	137 (134, 141)	139 (136, 141)	0.36

Values are given as proportions, means (±SD) or medians (IQR)

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, b.p.m. = beats per minute, COPD = Chronic Obstructive Pulmonary Disease, eGFR = estimated Glomerular Filtration Rate, LV = Left Ventricular, MRA = Mineralocorticoid Receptor Antagonists, NYHA = New York Heart Association, Systolic BP = Systolic Blood Pressure.

3a

Potassium and the use of RAAS inhibitors in Heart failure with reduced ejection fraction: data from BIOSTAT-CHF

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Eur J Heart Fail. 2018 May;20(5):923-930.

ABSTRACT

Background

Hyperkalemia is a common comorbidity in patients with heart failure with reduced ejection fraction (HFrEF). Whether it affects the use of RAAS-inhibitors and thereby negatively impacts outcome is unknown. Therefore, we investigated the association between potassium and uptitration of ACE-inhibitor/ARB and its association with outcome.

Methods and results

Out of 2,516 patients from the BIOSTAT-CHF study, potassium levels were available in 1,666 patients with HFrEF. These patients were sub-optimally treated with ACEi/ARB or beta-blockers and were anticipated and encouraged to be uptitrated. Potassium levels were available at inclusion and 9 months. Outcome was a composite of all-cause mortality and HF-hospitalization at 2 years.

Patients were 67 ± 12 years old and 77% was male. At baseline, median serum potassium was $4.2(3.9-4.6)$ mEq/L. After 9 months, 401 (24.1%) patients were successfully uptitrated for ACEi/ARB. During this period, mean serum potassium increased by 0.16 ± 0.66 mEq/L ($p<0.001$). Baseline potassium was an independent predictor for lower obtained dosages of ACEi/ARB (OR 0.70; 95%CI 0.51–0.98). An increase in potassium was not associated with adverse outcomes (HR 1.15; 95%CI 0.86–1.53). No interaction was found between baseline potassium, potassium increase during uptitration or potassium at 9 months and an increase of dose of ACEi/ARB for outcome ($p_{\text{interaction}}$ for all >0.5).

Conclusion

Higher potassium levels are an independent predictor of enduring lower dosages of ACEi/ARB. Higher potassium levels do not attenuate the beneficial effects of uptitration ACEi/ARB.

LIST OF ABBREVIATIONS

ACEi	Angiotensin-Converting Enzyme-Inhibitors
ARBs	Angiotensin Receptor Blockers
BNP	Brain Natriuretic Peptide
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
eGFR	estimated Glomerular Filtration Rate
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonist
NT-proBNP	N-terminal prohormone of Brain Natriuretic Peptide
RAASi	Renin Angiotensin Aldosterone System-Inhibitors

INTRODUCTION

Heart failure (HF) is associated with high mortality and morbidity.¹ Current treatment possibilities for HF patients with a reduced ejection fraction (HFrEF) include ACE-inhibition (ACEi), angiotensin-receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and beta-blockers. These treatments have shown to improve outcomes for patients with HFrEF.²⁻⁵ Unfortunately, administration of recommended doses of guideline directed medication is not often achieved.^{6,7}

In the general population, hyperkalemia is common and may negatively impact administration of adequate dosages of ACEi and ARB.⁸ Unfortunately, knowledge on this association in patients with HF is absent. Additionally, hyperkalemia is associated with worse outcomes and potassium levels are therefore closely monitored during increase of the doses of inhibitors of the RAAS system in clinical trials.⁹⁻¹² Both hyperkalemia as well as the effect of hyperkalemia on tolerating higher doses of RAAS inhibitors can severely impede outcomes and interfere with their survival benefit.^{8,13}

Currently, no data is available on the independent association of potassium levels (or potassium change during treatment) and the achieved dose of ACEi/ARB. Additionally, limited data is available on the interaction between ACEi/ARB and the association between hyperkalemia and clinical outcome in patients with HFrEF.¹⁴ Therefore, we studied the association between serum potassium levels and successful uptitration of ACEi/ARB to HF guideline-directed dosages in the BIOSTAT-CHF cohort, which was specially designed to study effects of uptitration.¹⁵ Furthermore, we studied the interaction between guideline-directed treatment and hyperkalemia on outcomes.

METHODS

Study cohort

For the present study, data from the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF), an international, multicenter, prospective, observational study was investigated. Patients received $\leq 50\%$ of target dosages of ACEi/ARBs and/or beta-blockers at time of inclusion and treating physicians anticipated and encouraged an increase of fraction target dose of ACEi/ARBs and/or beta-blockers to guideline directed levels. Patients were included as in- or outpatients. Potassium was measured at time of inclusion. The first 3 months after inclusion were considered as an active uptitration period, followed by a stabilization period of 6 months. Detailed description of the rationale, design, and implementation of the BIOSTAT-CHF study has been reported elsewhere.¹⁵

For the current study, only HF patients with HFrEF (LVEF<40%) with available potassium levels at baseline were included. Out of 2,516 patients from the original study cohort, 697 patients with a preserved or unknown ejection fraction were excluded. Of the remaining 1,819 patients, serum potassium levels were measured in 1,666 patients. Potassium measurements at 9 months were available in 918 patients (*Supplementary figure 1*).

Definitions and study endpoints

Potassium levels were classified according to clinical reference ranges, i.e. hypokalemia; <3.5 mEq/L, normokalemia; $3.5 - 5.0$ mEq/L, and hyperkalemia; >5.0 mEq/L.¹⁶ We defined successful uptitration as an increase of beta-blockers and ACEi/ARB if patients obtained over 50% of the target dose at 9 months of follow-up and the administered dose at 9 months was greater than the dose administered at baseline according to the ESC-guidelines.¹⁷ Patients who died between baseline and 9 months (N=203) were excluded from this analysis (*supplementary figure 1*). Patients receiving equal guideline recommended target doses (i.e. $\geq 100\%$) at baseline and 9 months were classified as successfully uptitrated patients. Patients receiving $\leq 50\%$ of the guideline-recommended dose were labeled not successfully uptitrated (*Supplementary figure 2*). In sensitivity analysis, we did not include baseline doses and only tested for administered doses of ACEi/ARBs and beta-blocker at

three months.¹⁸ The primary endpoint for outcome analyses of this study was a combined endpoint of all-cause mortality and HF related hospitalizations at 2 years. HF related hospitalizations were determined by the enrolling investigator.

Statistical analysis

For baseline characteristics, study results for continuous variables are presented as the mean ($\pm$ standard deviation), medians ($\pm$ interquartile ranges) or numbers with percentages where appropriate. Baseline characteristics were stratified by serum potassium levels in hypokalemia (<3.5 mEq/L), normokalemia (3.5 - 5.0 mEq/L), and hyperkalemia (>5.0 mEq/L), respectively. An increase or decrease in potassium between baseline and 9 months was determined as more than a 0.1 mEq/L difference between baseline and 9 months. Intergroup differences between more than two groups were tested using the one-way analysis of variance (ANOVA); Kruskal-Wallis test or chi²-test where appropriate. Q-Q plots and histograms were used to visually test all variables for normality. Normality was tested using the Kolmogorov-Smirnov test, when necessary. For further analyses, skewed variables were log-transformed to achieve normal distribution.

Relationship of potassium levels with successful uptitration between baseline and 9 months was studied using logistic regression. In a stepwise manner, this was corrected for clinically relevant confounders of potassium, which age, sex, eGFR, systolic blood pressure, diabetes mellitus, and ACEi/ARB usage at 9 months (in case of beta-blocker uptitration) or beta-blocker usage at 9 months (in case of ACEi/ARB uptitration). Additionally, we corrected for uptitration models that best predicted successful uptitration rates in this cohort for beta-blockers and ACEi/ARB.¹⁸ For beta-blockers, these include age, country of inclusion, diastolic blood pressure, heart rate, and signs of pulmonary congestion. For ACEi/ARB these include sex, BMI, eGFR, alkaline phosphatase, and country of inclusion, as published previously.¹⁸ The association between potassium and outcome is depicted using Kaplan-Meier curves for potassium levels at baseline, potassium levels at 9 months and a change of potassium levels between baseline and 9 months. A difference in survival was tested using the log-rank test. To investigate the association with survival of potassium in multivariable analyses, Cox regression analyses were performed correcting for clinically relevant variables, these include age, sex, eGFR,

hypertension, diabetes mellitus, and ACEi/ARB or beta-blocker use at 9 months. Interaction analyses were performed to investigate the interaction between successful uptitration and its association with outcome of potassium levels (as a continuous variable).

A two-sided p-value <0.05 was considered statistically significant and 95% CI were presented for all odds ratios. For statistical analyses, Stata MP13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.) was used.

RESULTS

Baseline characteristics

Out of a total of 1,666 patients, 114 patients (6.9%) had potassium levels below 3.5 mEq/L, 1,418 patients (85.1%) had normal potassium levels (i.e. 3.5 to 5.0 mEq/L), and 134 patients (8.0%) had hyperkalemia (above 5.0 mEq/L) at baseline (*table 1*). Only 34 (2%) patients had potassium levels above 5.5 mEq/L. In the overall population, mean age ($\pm$ SD) was 67 ± 12 years of which 77% were male. Patients with hyperkalemia were more often men, had lower heart rates and less signs of pulmonary congestion and peripheral edema. Estimated GFR was significantly lower in patients with hyperkalemia and patients with high serum potassium were more often on MRA treatment.

A difference in prevalence of hyper- and hypokalemia across Europe is depicted in *figure 1A and 1B*. Hyperkalemia was particularly prevalent in Slovenia (19%), Poland (13%), Serbia (12%) and Greece (11%) (*figure 1A*). After correction for potential confounders (i.e. renal function, history of diabetes mellitus, history of hypertension, fraction target dose of ACEi/ARB, beta-blocker, and MRA and uptake of diuretics (yes/no) at baseline), rates of hyperkalemia were highest in Slovenia, followed by Poland, Serbia, and Greece (P for all <0.05). Highest rates of hypokalemia were found in the Netherlands (P <0.05) (*supplementary table 1A and 1B*). Differences in listed characteristics between European countries are displayed in *supplementary table 2*.

Table 1. Baseline characteristics

Variables (proportions %)	Total cohort (n=1,666)	Pot < 3.5 (n=114)	3.5 ≤ Pot ≤ 5.0 (n=1,418)	Pot > 5.0 (n=134)	p-value	Trend
Demographics						
Potassium levels (mEq/L)	4.3 (3.9 – 4.6)	3.2 (3.1 – 3.4)	4.3 (4.0 – 4.5)	5.4 (5.2 – 5.5)	NA	NA
Age (years)	69 (60 – 76)	69 (63 – 76)	68 (59 – 77)	70 (62 – 75)	0.808	0.974
Men	1,275 (77)	69 (61)	1,101 (78)	105 (78)	<0.001	0.002
BMI (kg/m ²)	26.9 (24.1 – 30.4)	26.7 (24.2 – 31.4)	26.9 (24.0 – 30.4)	27.0 (24.2 – 30.1)	0.688	0.726
Heart rate (/min)	76 (68 – 90)	80 (70 – 97)	77 (67 – 90)	75 (68 – 90)	0.019	0.020
LVEF (%)	27 ± 7	27 ± 7	27 ± 7	28 ± 7	0.434	0.134
SBP (mmHg)	123 ± 21	126 ± 24	123 ± 21	124 ± 20	0.169	0.903
NYHA class III-IV	557 (38)	30 (32)	484 (39)	43 (38)	0.466	0.476
eGFR (mL/min/1.73 m ²)	65.0 ± 24.1	64.2 ± 24.4	65.8 ± 24.0	56.5 ± 23.7	<0.001	0.015
- eGFR <45 mL/min	347 (21)	23 (20)	280 (20)	44 (33)	0.002	0.009
Signs & symptoms						
Pulmonary congestion	854 (52)	73 (64)	712 (51)	67 (51)	0.035	0.057
Extent of peripheral edema*						
- Not present	595 (44)	21 (23)	511 (44)	63 (52)	<0.001	<0.001
- Above Knee	75 (5)	8 (9)	64 (6)	3 (2)	0.139	0.047
Medical history						
Diabetes mellitus	529 (32)	34 (30)	447 (32)	48 (36)	0.534	0.297
Myocardial infarction	641 (38)	37 (32)	555 (39)	49 (37)	0.330	0.574
Atrial fibrillation	713 (43)	49 (43)	615 (43)	49 (37)	0.314	0.272
Hypertension	976 (59)	71 (62)	826 (58)	79 (59)	0.700	0.632
eGFR <60	747 (45)	52 (46)	614 (43)	81 (61)	0.001	0.012

Table 1. (Continued)

Variables (proportions %)	Total cohort (n=1,666)	Pot < 3.5 (n=114)	3.5 ≤ Pot ≤ 5.0 (n=1,418)	Pot > 5.0 (n=134)	p-value	Trend
COPD	288 (17)	21 (18)	237 (17)	30 (22)	0.238	0.352
Laboratory						
Hemoglobin (g/dL)	13.4 ± 1.9	13.0 ± 1.8	13.4 ± 1.9	13.3 ± 1.8	0.069	0.232
Erythrocytes (10 ^e 12/L)	4.5 (4.1 – 4.9)	4.4 (4.1 – 4.9)	4.5 (4.1 – 4.9)	4.6 (4.1 – 5.0)	0.817	0.632
Platelets (10 ^e 9/L)	214 (173 – 258)	209 (171 – 261)	212 (173 – 257)	228 (187 – 281)	0.019	0.023
NT-proBNP (ng/L) [^]	4447 (2359 – 8824)	4132 (2621 – 7839)	4402 (2250 – 8522)	5947 (3211 – 11124)	0.068	0.155
CRP (mg/L)	12.9 (5.5 – 26.4)	16.5 (8.2 – 30.4)	12.9 (5.4 – 26.4)	10.2 (4.5 – 19.1)	0.002	0.001
Creatinine (μmol/L)	102 (84 – 127)	99 (77 – 124)	101 (83 – 126)	115 (91 – 150)	<0.001	<0.001
Iron (μmol/L)	8 (5 – 13)	8 (5 – 13)	8 (5 – 13)	9 (6 – 13)	0.080	0.028
Medication						
ACE-I/ARB	1,229 (74)	83 (73)	1,046 (74)	100 (75)	0.949	0.746
Beta-blocker	1,390 (83)	91 (80)	1,190 (84)	109 (81)	0.419	0.822
MRA	920 (55)	52 (46)	783 (55)	85 (63)	0.019	0.005
Diuretics	1,665 (100)	114 (100)	1,417 (100)	134 (100)	0.916	0.975
Digoxin	302 (18)	12 (11)	271 (19)	19 (14)	0.034	0.578

Values are given as proportions, means (±SD) or medians (IQR)

ACEI = Angiotensin-Converting Enzyme Inhibitors; ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, BNP = Brain Natriuretic Peptide, COPD = Chronic Obstructive Pulmonary Disease, CRP = C-reactive protein, eGFR = estimated Glomerular Filtration Rate, LVEF = Left Ventricular Ejection Fraction, MRA = Mineralocorticoid Receptor Antagonists, NT-proBNP = N-Terminal prohormone of Brain Natriuretic Peptide, NYHA = New York Heart Association, SBP = Systolic Blood Pressure.

* Extent of peripheral edema was determined in 1,367 patients.

[^] Serum NT-proBNP levels were determined in 736 patients.

Figure 1. Incidence levels of hyperkalemia (A) and hypokalemia (B) per country

During 9 months' follow-up potassium levels increased (0.16 ± 0.66 mEq/L, $p < 0.001$) and 523 (57%) of patients experienced an increase of potassium levels between baseline and 9 months, while 319 (35%) of patients had a decrease in potassium. At 9 months, 21 patients (2.3%) had potassium levels below 3.5 mEq/L, 786 patients (85.4%) had normal potassium levels (i.e. 3.5 to 5.0 mEq/L), and 113 patients (12.3%) were patients with hyperkalemia (above 5.0 mEq/L). Of patients with hypokalemia at baseline, 53.5% also had available data at 9 months. In case of normokalemia and hyperkalemia at baseline, this was 55.6% en 50.7% at 9 months respectively (*supplementary table 3*).

Association of potassium and uptitration of guideline directed medication

After 9 months, uptitration of ACEi/ARB was successful in a total of 401 patients (24.1%). For beta-blockers, successful uptitration was seen in 278 (16.7%) patients (*supplementary figure 2*). Results of logistic regression analyses are shown in *figure 2 and supplementary figure 3*. Higher serum potassium at baseline was associated with lower odds of successful uptitration at 9 months in univariable analyses (OR 0.77; 95%CI 0.62–0.95; $p=0.016$; per increment of 1.0 mEq/L potassium). Also after correcting for clinically relevant confounders (i.e. age, sex, eGFR, systolic blood pressure, diabetes mellitus, and beta-blocker usage at 9 months), higher potassium levels at baseline showed a significant association with less successful uptitration (OR 0.80; 95%CI 0.64–0.99; $p=0.043$). When correcting for the previously published uptitration model, higher potassium levels at baseline were still associated with lower odds of successful uptitration (OR 0.70; 95%CI 0.51–0.98; $p=0.035$). After excluding patients already on ACEi/ARB target dose, potassium remained predictive for successful uptitration when correcting for both the uptitration model (OR 0.52; 95%CI 0.35–0.78; $p=0.002$) and model 3 (OR 0.66; 95%CI 0.50–0.87; $p=0.003$). Further adjustment by MRA uptake at target dose (yes/no) did not change the association between baseline potassium levels and ACEi/ARB uptitration when correcting for the uptitration model (OR 0.54 95%CI 0.35–0.81; $p=0.003$) as well as for model 3 (OR 0.68; 95%CI 0.51–0.89; $p=0.006$). No interaction was observed between potassium and renal function for successful uptitration ($P_{\text{interaction}}=0.988$) suggesting that the association between hyperkalemia and uptitration is similar across the renal function spectrum. In sensitivity analysis, baseline serum potassium was univariable associated with uptitration success of ACEi/ARB (OR 0.81; 95%CI 0.67–0.98; $p=0.031$). However, this was attenuated after multivariable adjustment ($p=0.086$). As expected, no association was found between baseline potassium levels and uptitration of beta-blockers. Higher serum potassium levels at 9 months were not associated with successful uptitration of ACEi/ARB or beta-blockers (*supplementary figure 3*). A potassium increase over 9 months was associated with successful uptitration of ACEi/ARB (OR 1.37; 95%CI 1.09–1.72; $p=0.008$), but not for beta-blockers.

Figure 2. Odds Ratios (95% CI) for successful uptitration of ACEi/ARB depicted for baseline potassium (as continuous variable).

Model 1: Corrected for age, sex, and eGFR.

Model 2: Corrected model 1, systolic blood pressure, and diabetes mellitus.

Model 3: Corrected for model 2 and beta-blocker usage at 9 months.

Uptitration Model: Corrected for BIOSTAT-CHF uptitration model, including: sex, BMI, eGFR, alkaline phosphatase, and country of inclusion.

Potassium and outcome

Results of survival analyses are presented in *figure 3a/b, supplementary figure 4*, and *Table 2*. Overall, 627 (37.6%) patients reached the combined endpoint at 2 years. Hypo- and hyperkalemia at baseline or potassium analyzed on a continuous scale were not associated with worse outcomes (*Table 2*). Similarly, a change between potassium levels at baseline and 9 months or potassium levels at 9 months were not significantly related to outcome. When used as a continuous variable, potassium change during 9 months was not associated with outcome (HR 0.98; 95%CI 0.81-1.19; $p=0.844$). Potassium levels at baseline, a change of potassium during uptitration or potassium levels after uptitration, did not attenuate the beneficial effects of successful uptitration of ACEi/ARBs or beta-blockers ($P_{\text{interaction}}$ for all >0.5).

Figure 3. Combined endpoint of all-cause mortality and HF-hospitalization rates stratified by serum potassium levels in mEq/L at baseline (A) and 9 months (B). **Table 2.** Cox proportional hazard regression model for the analysis of event rates for the combined endpoint (all-cause mortality + HF-hospitalizations) in HF patients stratified by potassium levels on baseline, 9 months, and potassium change.

	<3.5 mEq/L	3.5-5.0 mEq/L	>5.0 mEq/L
	HR (CI), p-value		HR (CI), p-value
Baseline			
(n of patients ; n of event)	(114 ; 46)	(1,418 ; 530)	(134 ; 51)
Univariable	1.10 (0.83-1.47), 0.493	ref	1.01 (0.77-1.31) 0.968
Model 1	1.11 (0.83-1.48), 0.493	ref	0.90 (0.69-1.18) 0.448
Model 2	1.12 (0.84-1.50), 0.430	ref	0.88 (0.67-1.15) 0.353
Model 3	1.13 (0.84-1.51), 0.419	ref	0.89 (0.68-1.17) 0.406
9 months			
(n of patients ; n of event)	(21 ; 12)	(786 ; 212)	(113 ; 43)
Univariable	1.65 (0.61-4.48), 0.328	ref	1.34 (0.80-2.24) 0.270
Model 1	1.85 (0.68-5.04), 0.231	ref	1.22 (0.72-2.05) 0.466
Model 2	1.75 (0.63-4.81), 0.280	ref	1.19 (0.70-2.01) 0.518
Model 3	1.97 (0.71-5.49), 0.193	ref	1.19 (0.70-2.01) 0.513
Change	Decrease	No change	Increase
(n of patients ; n of event)	(319 ; 103)	(78 ; 17)	(523 ; 146)
Univariable	1.26 (0.96-1.65), 0.101	ref	1.23 (0.93-1.64) 0.148
Model 1	1.25 (0.95-1.65), 0.105	ref	1.17 (0.88-1.56) 0.275
Model 2	1.27 (0.96-1.66), 0.091	ref	1.15 (0.87-1.54) 0.328
Model 3	1.23 (0.94-1.62), 0.135	ref	1.15 (0.86-1.53) 0.341

Model 1: Corrected for age, sex, and eGFR

Model 2: Corrected for age, sex, eGFR, systolic blood pressure, and diabetes mellitus

Model 3: Corrected for the age, sex, eGFR, systolic blood pressure, and diabetes mellitus, ACEi/ARB usage at 9 months, or beta-blocker usage at 9 months

DISCUSSION

This study shows that low and high serum potassium levels are common among patients with HFrEF. Potassium levels above 5.0 mEq/L were observed in 8% of HFrEF patients across Europe and being particularly prevalent in Eastern Europe and Greece. Furthermore, higher baseline potassium levels were an independent predictor of unsuccessful uptitration of ACEi/ARBs in HFrEF patients. Potassium levels or changes in potassium levels during uptitration were not associated with worse outcomes. Furthermore, a potassium increase during uptitration did not attenuate the beneficial effects of uptitration of ACEi/ARBs. The findings of this study might have implications for clinical practice, suggesting that lowering potassium levels in patients with hyperkalemia might lead to improved guideline directed treatment with ACEi and ARB. These data are important considering the availability of new potassium lowering drugs.^{19,20}

Our study shows an overall rate of baseline potassium abnormalities of 6.9% and 8.0% for hypo- and hyperkalemia respectively. Our results show a difference in prevalence of potassium abnormalities between European countries, even after rigorous multivariable correction, which might reflect differences in health systems or local practice.¹⁸ Our findings are in line with earlier reports from the Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial (6% and 9% respectively) and 6.7% and 3.3% in the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure (COACH) trial.¹⁴ Overall, potassium levels increased during uptitration of ACEi/ARB, with 2.3% of patients having hypokalemia and 12.3% of patients having hyperkalemia at 9 months. During 9 months of follow-up, a significant increase of potassium was seen in the majority of patients (57.4%) and can be explained by the actively increased doses of ACEi and ARB. Unfortunately, the study design did not allow for analysis on early changes (e.g. <1 month) after dose adjustments.

In this study, higher potassium levels at baseline were associated with less uptitration of ACEi/ARB. This suggests that HF patients with hyperkalemia at the start of therapy are at greater risk for lower doses or discontinuation of ACEi/

ARB, which impede outcomes.^{6,18} This is in line with earlier reports from a general patient population where high potassium levels were found to be responsible for a significant proportion of discontinuation or lowering of dosage of ACEi and ARB. Here, discontinuation or lowering of dosages of ACEi/ARB were associated with more adverse outcomes.⁸ Also in previous results from the BIOSTAT-CHF study, sub-optimal dosages of ACEi/ARB were associated with worse outcomes in HF patients.¹⁸ This suggests that lower dosages and/or discontinuation of ACEi/ARB due to high potassium levels severely impede outcomes.

Hypokalemia at baseline or at 9 months was not associated with worse outcomes. This is in line with earlier reports from the COACH, PROTECT and EVEREST trials, where potassium also did not show an independent association with outcome.^{14,21} Nevertheless, reports on the association of potassium with outcome are mixed. Previous results of post-hoc analyses performed in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial showed that hypokalemia (<4.0 mEq/L) is associated with adverse outcomes and amplified the beneficial effect of eplerenone.^{22,23} Additionally, a propensity matched study from Ahmed et al. showed that hypokalemia is associated with more adverse outcomes.²² In another sub-analysis of the Digitalis Investigation Group trial, Bowling et al. shows that this was also true for HF patients with CKD and that potassium also predicts a combined endpoint of all-cause mortality and HF rehospitalizations.²⁴ However, it has been suggested that the association of hypokalemia with adverse outcomes reflect lower usage of MRA or higher diuretic usage and dosage, on which data was often not available in previous reports.^{22,24-26}

Regardless of its association with outcome, potassium levels did not attenuate the beneficial effects of ACEi/ARB and beta-blockers. Previously, results from the Randomized Aldactone Evaluation Study (RALES) showed that hyperkalemia was associated with higher mortality rates, but did not interfere with the beneficial effects of spironolactone.⁹ The EMPHASIS-HF trial showed that the favorable effects of eplerenone on outcome did not differ for hyperkalemic compared to normokalaemic patients.²⁵ Additionally, a sub-analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial showed that potassium levels also did not interfere with the beneficial effects of

Candesartan.²⁷ The findings of the current study confirm results of the post-hoc analysis of the CHARM trial, but also show that potassium levels do not interfere with the beneficial effects of ACEi/ARB uptitration. Previously, Lund et al. discussed the association between ACEi/ARB usage and renal function, indicating that even in HF patients with severe renal insufficiency, administering ACEi/ARB improves outcome^{28,29} Nevertheless, it should be noted that potassium levels as well as increases of potassium levels during uptitration took place within the relative “normal” range of potassium levels of 3.0 mEq/L and 5.5 mEq/L. Additionally, our study shows for the first time that potassium increases during uptitration of ACEi and ARBs do not interfere with the beneficial effects of these lifesaving therapies.

Study limitations

This is a post-hoc analysis, which comes with the usual limitations of selection bias. Potassium levels were only measured twice, at baseline and at 9 months of follow-up. A non-repetitive measurement could falsely positive diagnose a HF patient with hyperkalemia. Repeated measurements could correct for this deviation, but were not available. Unfortunately, potassium levels were not monitored after the first 3 months of active uptitration. This would provide additional data on potassium fluctuations over time. Additionally, patients with no potassium measurement at 9 months could have died, suggesting caution in interpreting data on potassium and outcome at 9 months. Furthermore, we did not have any information about potassium supplementation as well as on diuretic dosages, which might interfere with potassium levels.

Conclusion

Potassium abnormalities are prevalent among HF patients. Higher potassium levels are associated with lower rates of successful uptitration of ACEi/ARBs. Potassium abnormalities are not related to adverse outcomes and do not attenuate the beneficial effects of successful uptitration of ACEi/ARBs.

Funding

BIOSTAT-CHF was funded by the European Commission [FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29].

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SUPPLEMENTARY MATERIAL

Table S1. Differences in characteristics of patients with and without potassium levels at 9 months.

Factor	No potassium	Potassium at 9 months	P-value
N	748	918	
Age (years), mean (SD)	67.2 (12.5)	67.7 (11.6)	0.390
Women (%)	171 (22.9%)	220 (24.0%)	0.600
BMI (kg/m ²), mean (SD)	27.4 (5.2)	27.9 (5.5)	0.081
Ischemic etiology (%)	356 (49.1%)	404 (44.3%)	0.055
LVEF (%), median (IQR)	27.0 (20.0, 33.0)	28.0 (23.0, 33.0)	0.240
NYHA class			0.006
I	51 (6.8%)	80 (8.7%)	
II	366 (48.9%)	404 (44.0%)	
III	233 (31.1%)	267 (29.1%)	
IV	27 (3.6%)	30 (3.3%)	
Not assessed	71 (9.5%)	137 (14.9%)	
SBP, mean (SD)	121.0 (20.9)	124.6 (21.0)	<0.001
DBP, mean (SD)	73.6 (11.9)	76.2 (13.1)	<0.001
LVEF (%), median (IQR)	26.9 (7.0)	27.4 (6.7)	0.12
HR, mean (SD)	80.5 (18.5)	80.2 (19.6)	0.72
Signs and symptoms			
Extent of peripheral edema			0.062
Not Present	246 (39.9%)	349 (46.5%)	
Ankle	188 (30.5%)	219 (29.2%)	
Below Knee	147 (23.9%)	143 (19.0%)	
Above Knee	35 (5.7%)	40 (5.3%)	
Elevated JVP			0.014
No	316 (61.0%)	441 (67.6%)	
Yes	177 (34.2%)	172 (26.4%)	
Uncertain	25 (4.8%)	39 (6.0%)	
Hepatomegaly	148 (19.8%)	106 (11.6%)	<0.001
Orthopnea	293 (39.2%)	256 (27.9%)	<0.001
Medical history (%)			
Anemia	265 (36.5%)	262 (29.7%)	0.004
Atrial fibrillation	341 (45.6%)	372 (40.5%)	0.038
Diabetes mellitus	267 (35.7%)	262 (28.5%)	0.002
COPD	133 (17.8%)	155 (16.9%)	0.63
Hypertension	438 (58.6%)	538 (58.6%)	0.98

Table S1. (Continued)

Factor	No potassium	Potassium at 9 months	P-value
Peripheral arterial disease	90 (12.0%)	70 (7.6%)	0.002
Medication			
Loop diuretics	746 (99.7%)	913 (99.5%)	0.38
ACE-Digoxin	154 (20.6%)	148 (16.1%)	0.019
Aldosterone antagonist	421 (56.3%)	499 (54.4%)	0.43
Laboratory; median (IQR)			
Potassium (mEq/L)	4.2 (3.9, 4.6)	4.3 (3.9, 4.6)	0.9
NT-proBNP (ng/L)	5819.5 (2995.0, 11491.0)	3709.0 (1957.0, 6962.5)	<0.001

Table S2. Differences in rates of hyperkalaemia and hypokalaemia in Europe after correction for renal function, history of diabetes mellitus, history of hypertension, fraction target dose of ACEi/ARB, beta-blockers, and MRA, and uptake of diuretics (yes/no) at baseline.

Country	Odds Ratio	95% CI	P-value
HYPERKALAEMIA			
Sweden	Ref	Ref	N.A.
Slovenia	25.4	(2.60–248.7)	0.005
Poland	14.6	(1.89–113.4)	0.010
Serbia	14.16	(1.84–108.7)	0.011
Greece	11.86	(1.52–92.5)	0.018
Italy	7.80	(0.99–61.6)	0.051
Germany	6.37	(0.68–60.1)	0.106
The Netherlands	3.75	(0.47–29.9)	0.212
United Kingdom	3.90	(0.33–45.6)	0.277
Norway	3.39	(0.34–34.0)	0.299
France	2.17	(0.23–20.1)	0.496
HYPOKALAEMIA			
Sweden	Ref	Ref	N.A.
The Netherlands	8.27	(1.10–62.1)	0.040
France	6.85	(0.89–52.9)	0.065
Italy	5.56	(0.72–42.8)	0.099
Norway	5.79	(0.69–48.7)	0.106
Germany	4.56	(0.49–42.6)	0.183
Poland	2.94	(0.37–23.6)	0.309
United Kingdom	2.55	(0.22–29.2)	0.453
Greece	2.04	(0.25–16.5)	0.506
Serbia	1.04	(0.12–8.97)	0.969
Slovenia	1	N.A.	N.A.

Table S3. Differences in clinical variables across Europe

Variables (proportions)	The Netherlands	France	Germany	Serbia	Slovenia	Greece	Italy	Norway	Sweden	Poland	United Kingdom	P-value
eGFR (mL/ min/1.73m ²)	63.3 ± 22.0	64.1 ± 24.9	59.3 ± 23.1	65.8 ± 24.1	60.0 ± 15.4	63.8 ± 21.8	64.9 ± 27.7	71.9 ± 25.8	60.0 ± 22.4	69.3 ± 23.9	63.8 ± 25.9	0.019
Diabetes mellitus	62 (25)	54 (33)	32(57)	86 (30)	3 (14)	101(41)	80 (33)	17 (21)	14 (19)	69 (35)	11 (24)	<0.001
Hypertension	122 (48)	88 (54)	47 (84)	219 (77)	19 (90)	142 (57)	143 (59)	24 (30)	30 (42)	125 (63)	17 (38)	<0.001
ACEi/ARB	179 (71)	105 (64)	50 (89)	241 (84)	10 (48)	166 (67)	173 (72)	62 (78)	59 (82)	147 (74)	37 (82)	<0.001
Fraction target dose (median + IQR)	0.25 (0.00 – 0.50)	0.25 (0.00 – 0.50)	0.50 (0.25 – 0.50)	0.25 (0.13 – 0.50)	0.00 (0.00 – 0.50)	0.14 (0.00 – 0.31)	0.25 (0.00 – 0.50)	0.25 (0.13 – 0.50)	0.44 (0.13 – 0.75)	0.25 (0.00 – 0.50)	0.33 (0.13 – 0.50)	<0.001
MRA	98 (39)	58 (35)	42 (75)	212 (74)	16 (76)	151 (61)	149 (62)	20 (25)	24 (33)	119 (60)	31 (69)	<0.001
Diuretics	251 (100)	164(100)	56 (100)	286 (100)	21 (100)	249 (100)	241 (100)	80 (100)	72 (100)	200 (100)	45 (100)	0.847

Table S4. Frequencies of patients with follow-up data on potassium levels at 9 months stratified by hypokalaemia, normokalaemia, and hyperkalaemia at baseline.

N	<3.5	3.5–5.0	>5.0	Total
Baseline	114	1,418	134	1666
9 months	61	789	68	918
% of baseline	53.5	55.6	50.7	55.2

Figure S1. Flowchart displaying the inclusion of patients for this study.

Figure S2. Flowchart displaying the different pathways by which uptitration of ACEi/ARB and beta-blockers was considered successful.

Figure S3. Odds ratios [95% confidence intervals (CI)] for successful uptitration of ACEi/ARB depicted for potassium on 9 months and potassium change (as continuous variables).

Model 1: Corrected for age, sex, and eGFR

Model 2: Corrected for age, sex, eGFR, hypertension, and diabetes mellitus

Model 3: Corrected for age, sex, eGFR, hypertension, diabetes mellitus, and beta-blocker usage at 9 months

Uptitration Model: Corrected for BIostat-CHF uptitration model:

- Sex, BMI, eGFR, alkaline phosphatase, and country of inclusion

Figure S4. Combined endpoint of all-cause mortality and heart failure hospitalization rates stratified by potassium change (in mEq/L) over 9 months.

3b

Is hyperkalaemia in heart failure a risk factor or a risk marker? Implications for renin–angiotensin–aldosterone system inhibitor use

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Eur J Heart Fail. 2018 May;20(5):931-932.

For clinicians caring for patients with heart failure (HF), acute or chronic kidney disease (CKD), and/or diabetes mellitus, dyskalaemia and optimization of diuretics and renin–angiotensin–aldosterone system inhibitors (RAASi) are everyday concerns. Although we understand cellular and renal potassium regulation, surprisingly little is known about the causal relationships between these syndromes, drug effects, and outcomes.

In this issue of the Journal, Beusekamp *et al.*¹ studied potassium, use of RAASi drugs, and outcomes in patients with HF and reduced ejection fraction (HFrEF) from the well characterized longitudinal BIOSTAT-CHF cohort. At baseline, hypokalaemia ($K < 3.5$ mEq/L) was present in 6.9% and hyperkalaemia ($K > 5.0$ mEq/L) in 8.0%. In unadjusted and adjusted Cox models, neither hypo- or hyperkalaemia, nor increases or decreases in potassium at 9 months, were significantly associated with the composite outcome of all-cause death or HF hospitalization up to 2 years. However, in univariable and several multivariable logistic regression models, higher baseline potassium was associated with lower odds of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) uptitration. So is hyperkalaemia a risk marker or a risk factor for poor outcomes in HF?

Does dyskalemia cause poor outcomes? Several studies indicate that the relationship between potassium and outcomes exhibits a U-shaped relationship in HF and/or CKD.^{2,3} However, the extent of multivariable adjustment in these studies has been variable. In the present analysis, hypo- or hyperkalaemia were not significantly associated with outcomes. However, the sample size of 1666 was modest and a closer examination reveals nominal hazard ratios substantially above 1.0 for baseline hypo- but not hyperkalaemia. Similarly, in a study of 13 015 patients in the Swedish HF Registry, in univariable analysis, the relationship between potassium and long-term outcomes was U-shaped, but in multivariable analyses, hypo- but not hyperkalaemia was associated with worse outcomes.⁴ Taken together, these data suggest that hyperkalaemia is not a risk factor but a risk marker, but a risk marker for what?

Does hyperkalaemia attenuate the benefit of RAASi drugs? In RALES⁵ and EMPHASIS-HF⁶ the benefit of mineralocorticoid receptor antagonists was

independent of potassium levels and persisted even with severe hyperkalaemia. In BIOSTAT-CHF, there was no interaction between baseline potassium, potassium increases, or 9-month potassium levels and the benefit of uptitrating RAASi. In an analysis of patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² in the Swedish HF Registry, ACEi/ARB use was associated with the same benefit as in patients with eGFR ≥ 30 mL/min/1.73 m², and as demonstrated in randomized trials of ACEi/ARB in HFrEF.⁷

So what is the problem with hyperkalaemia? We believe BIOSTAT-CHF and other studies show that it is primarily not a risk factor but a risk marker that leads to suboptimal use of RAASi, especially mineralocorticoid receptor antagonists, which in turn is causative in poor outcomes (*Figure 1*). Numerous studies have demonstrated suboptimal use and/or dosing of RAASi in the real world, that this underuse is associated with worse outcomes,⁸⁻¹¹ and that quality improvement efforts improve use of evidence-based HF drugs and ultimately outcomes.¹² In the present analysis, the salient finding was that hyperkalaemia at baseline was associated with failure to uptitrate RAASi, consistently in univariable analysis and in several multivariable models.

Figure 1. Hyperkalaemia is a risk marker for poor outcomes by leading to dose reduction or discontinuation of renin-angiotensin-aldosterone system inhibitors (RAASi).

What can be done? Taken together, these findings suggest that the main goal for patients with HFrEF and concomitant CKD and/or hyperkalaemia should be to optimize RAASi use. This can potentially be achieved by diligent monitoring of renal function and electrolytes and persistence in attempting to introduce and uptitrate these agents. Indeed, while eGFR <30 mL/min/1.73 m² or potassium >5.0 –

5.2 mEq/L were exclusion criteria for most RAASi drug trials, the European Society of Cardiology HF guidelines recommend that these drugs not be dose-reduced or discontinued until potassium goes above 5.5 mEq/L.¹³ Another possibility is using novel potassium binders to enable RAASi use. Both patiromer and sodium zirconium cyclosilicate were shown to be effective in lowering potassium and maintaining normokalaemia in patients with HF and hyperkalaemia.^{14,15} Whether such a strategy can enable use of RAASi agents and translate into improved outcomes in patients with HFrEF and CKD and/or hyperkalaemia remains to be shown.

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4

Hyperkalemia and treatment with RAAS-inhibitors during acute heart failure hospitalizations and their association with mortality

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J Am Coll Cardiol HF. 2019 Nov;7(11):970-979.

ABSTRACT

Objectives

This study investigated associations between incident hyperkalemia during acute heart failure (HF) hospitalizations and changes in renin–angiotensin–aldosterone-system inhibitors (RAASi).

Background

Hyperkalemia is a potential complication of RAASi. For patients with HF, fear of hyperkalemia may lead to failure to deliver guideline-recommended doses of RAASi.

Methods

Serum potassium concentrations were measured daily from baseline (<24h of admission) until discharge or day 7 in 1,589 patients enrolled in the PROTECT trial. Incident hyperkalemia was defined as at least one episode of potassium >5.0 mEq/L. The primary outcome was all-cause mortality at 180 days.

Results

Overall, serum potassium concentrations increased from 4.3 ± 0.6 mEq/L at baseline to 4.5 ± 0.6 mEq/L at discharge/day 7 ($p < 0.001$). Patients developing incident hyperkalemia ($n=564$; 35%) were more often on mineralocorticoid antagonists (MRAs) prior to hospitalization and were more likely to have them down-titrated during hospitalization, independent of confounders. Incident hyperkalemia was not associated with adverse outcomes. Yet, down-titration of MRAs during hospitalization was independently associated with 180-day mortality (HR 1.73; 95%CI 1.15–2.60), regardless of incident hyperkalemia ($P_{\text{interaction}} > 0.1$). Patients with incident hyperkalemia, who were discharged on the same or an increased dose of MRAs (HR 0.52; 95%CI 0.32–0.85) or ACEi/ARB (HR 0.47; 95%CI 0.29–0.77) had a lower 180-day mortality.

Conclusions

Incident hyperkalemia is common in patients hospitalized for acute HF and is not associated with adverse outcomes. Incident hyperkalemia is associated with down-titration of MRAs, but patients who maintained or increased their dose of MRAs and/or ACEi/ARB during acute HF hospitalization had better 180-day survival.

LIST OF ABBREVIATIONS

ACEi	Angiotensin-Converting Enzyme-Inhibitors
ARB	Angiotensin Receptor Blockers
BNP	Brain Natriuretic Peptide
eGFR	estimated Glomerular Filtration Rate
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
MRAs	Mineralocorticoid Receptor Antagonist
RAASi	Renin Angiotensin Aldosterone System-Inhibitors

INTRODUCTION

The treatment of heart failure requires the use of a variety of agents that may cause both hypo and hyperkalemia and both may be associated with a higher mortality in some clinical settings.¹⁻⁵

Hospitalizations for worsening heart failure is often associated with intensification of diuretic therapy that may cause hypokalemia, and initiation or adjustment of the dose of life-saving therapies including renin-angiotensin-aldosterone system inhibitors (RAASi), which may cause hyperkalemia.⁶ Accordingly, guidelines recommend close monitoring of serum potassium during hospitalizations for HF and that RAASi, both angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARB) and mineralocorticoid receptor antagonists (MRAs), should be avoided or down-titrated if serum potassium exceeds 5.0 mEq/L.⁷⁻⁹

Higher serum potassium concentrations are associated with less successful up-titration of ACEi/ARB in patients with chronic HF.¹⁰ Similarly, among patients with chronic HF, hyperkalemia is associated with underuse of mineralocorticoid receptor antagonists (MRAs).^{11,12} However, data on the association between incident hyperkalemia and up- or down-titration of RAASi during hospitalization for acute HF are scant.

Therefore, we investigated the relationship between hyperkalemia and adjustment of the dose of RAASi in patients hospitalized with acute HF and subsequent clinical outcome.

METHODS

Study design and population

Patients enrolled in the PROTECT trial (Placebo-Controlled Randomized Study of the Selective A₁ Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function), who had measurements of serum potassium on at least 5 days during their index hospital admission were

included in this analysis. Differences in clinical characteristics between patients included and excluded using these criteria are shown in supplementary table 1. Detailed descriptions of the design, implementation, and results have been reported elsewhere.^{13,14} In short, patients with pre-existing HF, mild or moderate renal impairment (estimated creatinine clearance, 20–80 mL/min), increased plasma concentrations of brain natriuretic peptides, and breathlessness at rest or minimal exertion associated with symptoms and signs of volume overload requiring intravenous diuretic therapy who had a serum potassium ≥ 3.5 mEq/L (or 3.0–3.5 mEq/L if potassium was given intravenously), were enrolled within 24 hours of admission and randomized to Rolofylline (a selective A_1 adenosine receptor antagonist) or placebo.

Definitions and study endpoints

Serum concentrations of potassium were classified according to clinical reference ranges, i.e. hypokalemia (<3.5 mEq/L) and hyperkalemia (>5.0 mEq/L).¹⁵ Serum potassium concentrations were measured daily from baseline (<24 hours) until discharge or until day 7. Patients were classified as 'Incident hypokalemia' if they developed hypokalemia at some point (≥ 1 time) during hospitalization, but no hyperkalemia. The 'Normal potassium' group was defined as having a serum potassium of 3.5–5.0 mEq/L for all measurements until discharge or day 7. Patients who developed hyperkalemia during hospitalization (once or more), but never had hypokalemia, were classified as 'Incident hyperkalemia'. Patients developing both hypo- and hyperkalemia during hospitalization ($n=34$) were excluded for this analysis.

A change in serum potassium was defined as difference of ≥ 0.2 mEq/L between day 1 and discharge or day 7. Worsening renal function (WRF) was defined as a creatinine change until day 7 (from baseline) ≥ 0.3 mg/dL in accordance with an earlier study originating from the PROTECT cohort.¹⁶ Changes in cardiovascular treatment were stratified into four categories, i.e. treated neither at admission or discharge, dose decreased or discontinued (down-titration), no dose change, or dose increased or initiated (up-titration). All-cause mortality at 180 days was the primary outcome for this analysis and the composite of rehospitalization

for cardiovascular or renal causes or all-cause mortality through 60 days was a secondary outcome of interest.

Statistical analysis

For baseline characteristics, means $\pm$ standard deviations, medians (interquartile ranges), or numbers with percentages were used as appropriate. Characteristics were stratified by the various clinical ranges (incident hypokalemia, normal potassium throughout hospitalization, incident hyperkalemia) until discharge or day 7. Differences between groups were tested using the one-way analysis of variance (ANOVA), chi-square test, or Kruskal-Wallis test as appropriate. To test all variables for normality, histograms or Q-Q plots were used. If in doubt, normality was tested via the Kolmogorov-Smirnov test. To achieve normal distribution for further analysis, skewed variables were log-transformed.

Intergroup differences related to changes in doses of ACEi/ARB and MRAs during hospitalization were depicted using stacked bar charts and tested using chi-square tests. To correct for treatment indication-bias, analyses related to the effect of ACEi/ARB and MRA up- or down-titration were corrected for the probability of obtaining this specific therapy. For this correction we used inverse probability weighting (IPW) with the probability to be up-titrated for either ACEi/ARB or MRAs.¹⁷ We performed IPW by doing logistic LASSO penalization analysis using all 69 variables averaged over 5 imputation sets for both ACEi/ARB and MRA separately. We defined successful treatment as those who were able to be up-titrated or remained constant doses of either ACEi/ARB or MRA. The derived weights were used in the subsequent survival analysis.

The association of clinical variables with incident hypo- and hyperkalemia was tested using logistic regression analyses. All variables with a univariate association <0.1 were used in multivariable models. Similar logistic regression models were used to test the predictive value of incident hyperkalemia on dose changes in cardiovascular treatment. The effect of baseline serum potassium concentrations (on a continuous scale) or the number of days hyperkalemia occurred on down-titration of ACEi/ARB or MRA was tested using logistic regression models as well.

In addition, we created a robust multivariable model including clinically relevant confounders.

Cox proportional hazard models were used to test the effects of up- or down-titration of ACEi/ARB and MRAs on outcome, adjusting for age, sex, logarithm of estimated glomerular filtration rate (eGFR), and logarithm of total diuretic dosage of loop diuretics (oral dose/2 + IV dose until day 7 or discharge) (Model 1) and for the PROTECT Risk Engine.¹⁸ This model includes 8 variables measured at baseline; age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum albumin, creatinine, sodium, and urea concentrations. Interaction analyses were performed to investigate the interaction for outcome between changes in cardiovascular treatment during hospitalization and potassium abnormalities. The effect of incident dyskalemia on outcome was depicted using Kaplan Meier curves and tested in multivariate analysis using Cox proportional hazard models correcting for Model 1 or the PROTECT Risk Engine.¹⁸

A two-sided p-value <0.05 was considered statistically significant. Stata SE15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC) was used for statistical analyses.

RESULTS

Baseline characteristics

Overall, serum potassium concentrations increased from 4.3 ± 0.6 mEq/L at baseline to 4.5 ± 0.6 mEq/L at discharge or day 7, $p < 0.001$. The average potassium change during hospitalization was 0.22 ± 0.68 mEq/L. Incident hypokalemia occurred in 265 patients (17%) and incident hyperkalemia in 564 patients (35%). Out of these, 28 patients (5%) had hyperkalemia at only one day of hospitalization. In total, 34 patients (2%) had episodes of both hypo- and hyperkalemia. Only for frequency analyses, we narrowed the definition of incident hyperkalemia to >5.5 mEq/L (moderate hyperkalemia) or >6.0 mEq/L (severe hyperkalemia). Then 226 (14%) and 87 (5%) patients were classified as incident hyperkalemia, respectively.

Patients with incident hyperkalemia were younger, with fewer signs of congestion, a higher heart rate, and a lower prevalence of atrial fibrillation/flutter ($P < 0.05$ for all) but had similar renal function (eGFR) to other patient groups. However, WRF until day 7 was observed more frequently in the groups with incident dyskalemia (25% for incident hypokalemia, 17% for normokalemia, and 26% for incident hyperkalemia, $p < 0.001$). Patients who developed incident hyperkalemia were more often on MRAs (53%) and ACEi/ARB (78%) prior to hospitalization compared to patients with incident hypokalemia or who had a 'normal potassium' (35% and 44% for MRAs, and 68% and 77% for ACEi/ARB, respectively) (table 1). In a multivariable analysis, patients with incident hyperkalemia were younger, more often treated with MRAs, and received lower doses of loop diuretics during hospitalization. In addition, hyperkalemic episodes were associated with lower serum sodium concentrations, a higher platelet count, and higher serum concentrations of chloride and BUN (supplementary table 2).

Independent predictors of incident hypokalemia were lower serum concentrations of chloride, higher serum concentrations of bicarbonate and BNP, higher doses of loop diuretics, and not receiving MRAs at baseline (supplementary table 3).

Table 1. Baseline characteristics, stratified by incident hypokalemia, always normal potassium, and incident hyperkalemia during hospitalization until discharge or day 7.

Variables	Level	Total cohort (n=1589)	Hypokalemia ≥ 1 (n=265)	No abnormalities (n=760)	Hyperkalemia ≥ 1 (n=564)	p-value
Demographics:						
Potassium (mEq/L)		4.3 $\pm$ 0.6	3.7 $\pm$ 0.5	4.2 $\pm$ 0.4	4.7 $\pm$ 0.6	N.A.
Age, years		70.0 $\pm$ 11.4	70.5 $\pm$ 12.5	70.7 $\pm$ 11.1	68.8 $\pm$ 11.2	0.007
Male sex		1060 (66.7%)	165 (62.3%)	527 (69.3%)	368 (65.2%)	0.072
BMI, kg/m ²		28.7 $\pm$ 6.1	28.6 $\pm$ 6.4	29.1 $\pm$ 6.3	28.3 $\pm$ 5.6	0.074
eGFR, mL/min/1.73 m ²		48.6 $\pm$ 19.3	48.4 $\pm$ 18.8	49.1 $\pm$ 18.6	47.9 $\pm$ 20.4	0.53
NYHA class						0.17
	I/II	249 (16.5%)	47 (18.8%)	122 (16.9%)	80 (15.0%)	
	III	751 (49.8%)	122 (48.8%)	375 (51.9%)	254 (47.6%)	
	IV	507 (33.7%)	81 (34.4%)	226 (31.3%)	200 (37.5%)	
Systolic BP, mmHg		124.8 $\pm$ 17.5	125.2 $\pm$ 19.6	124.7 $\pm$ 17.3	124.7 $\pm$ 16.8	0.93
Heart rate, b.p.m.		80.6 $\pm$ 15.5	80.1 $\pm$ 16.2	79.7 $\pm$ 15.2	81.9 $\pm$ 15.6	0.034

Table 1. (Continued)

Variables	Level	Total cohort (n=1589)	Hypokalemia ≥ 1 (n=265)	No abnormalities (n=760)	Hyperkalemia ≥ 1 (n=564)	p-value
Signs & symptoms:						
Orthopnea		1349 (85.7%)	219 (83.9%)	659 (87.6%)	471 (83.8%)	0.10
Angina pectoris		383 (24.1%)	61 (23.0%)	159 (20.9%)	163 (28.9%)	0.003
Edema & raised JVP		433 (30.3%)	92 (37.6%)	202 (29.8%)	139 (27.5%)	0.018
Rales		165 (10.4%)	30 (11.3%)	69 (9.1%)	66 (11.7%)	0.27
History of:						
Hospitalization for HF previous year		802 (50.5%)	138 (52.1%)	382 (50.3%)	282 (50.0%)	0.85
Myocardial infarction		794 (50.1%)	121 (45.7%)	384 (50.7%)	289 (51.3%)	0.28
Hypertension		1268 (79.8%)	201 (75.8%)	619 (81.4%)	448 (79.4%)	0.14
Hyperlipidemia		777 (48.9%)	134 (50.6%)	397 (52.2%)	246 (43.6%)	0.007
Current smoker		317 (20.0%)	50 (18.9%)	169 (22.3%)	98 (17.4%)	0.080
COPD or asthma		309 (19.5%)	51 (19.2%)	148 (19.5%)	110 (19.5%)	0.99
Diabetes mellitus		723 (45.5%)	116 (43.8%)	342 (45.0%)	265 (47.0%)	0.64
Atrial fibrillation/flutter		857 (54.2%)	143 (54.2%)	423 (55.8%)	291 (52.1%)	0.040
Cardiovascular treatment:						
Beta-blockers		1219 (76.7%)	204 (77.0%)	590 (77.6%)	425 (75.4%)	0.62
ACEi/ARB		1202 (75.6%)	181 (68.3%)	583 (76.7%)	438 (77.7%)	0.009
MRA		726 (45.7%)	93 (35.1%)	337 (44.3%)	296 (52.5%)	<0.001
Digoxin		476 (30.0%)	70 (26.4%)	236 (31.1%)	170 (30.1%)	0.36
IV loop diuretic dose administered on day 1		80 (40, 140)	100 (60, 180)	80 (40, 150)	80 (40, 120)	<0.001
Oral dosage loop diuretic administered on day 1		40 (25, 60)	40 (20, 80)	40 (25, 60)	40 (25, 60)	0.32
Treated with Rolofylline (study drug)		1,052 (66.2%)	187 (70.6%)	480 (63.2%)	385 (68.3%)	0.039
Laboratory:						
BNP (pg/mL)		452 (258, 830)	581 (324, 981)	393 (243, 751)	461 (263, 826)	<0.001
Albumin (g/dL)		3.8 $\pm$ 0.4	3.8 $\pm$ 0.5	3.9 $\pm$ 0.4	3.9 $\pm$ 0.4	0.039
Bicarbonate (mEq/L)		24.0 $\pm$ 3.8	25.3 $\pm$ 3.9	24.1 $\pm$ 3.6	23.2 $\pm$ 3.8	<0.001

Table 1. (Continued)

Variables	Level	Total cohort (n=1589)	Hypokalemia ≥ 1 (n=265)	No abnormalities (n=760)	Hyperkalemia ≥ 1 (n=564)	p-value
Chloride (mEq/L)		101.1 $\pm$ 4.9	99.8 $\pm$ 5.5	101.2 $\pm$ 4.6	101.6 $\pm$ 5.0	<0.001
Sodium (mEq/L)		139.5 $\pm$ 4.1	139.8 $\pm$ 4.5	139.6 $\pm$ 3.9	139.3 $\pm$ 4.2	0.17
Urea (BUN) (mg/dL)		29 (22, 40)	29 (21, 40)	28 (22, 39)	31 (23, 42)	0.028
Uric acid (mg/dL)		9.0 $\pm$ 2.6	9.4 $\pm$ 2.8	8.9 $\pm$ 2.5	9.0 $\pm$ 2.5	0.032
Serum glucose (mg/dL)		126 (103, 163)	132 (106, 159)	126 (103, 164)	123 (99, 166)	0.46
Hemoglobin (g/dL)		12.7 $\pm$ 2.0	12.6 $\pm$ 2.0	12.7 $\pm$ 1.9	12.9 $\pm$ 2.0	0.14
Platelets ($\times 10^9/L$)		217 (175, 271)	205 (163, 251)	215 (173, 269)	226 (180, 284)	0.002
White blood cells ($\times 10^9/L$)		7.5 (6.1, 9.3)	7.3 (5.8, 9.3)	7.4 (6.0, 9.3)	7.7 (6.3, 9.2)	0.16
Total cholesterol (mg/dL)		148 $\pm$ 45	139 $\pm$ 45	146 $\pm$ 44	154 $\pm$ 46	<0.001

Values are given as proportions, means ($\pm$ SD) or medians (IQR)

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, BNP = Brain Natriuretic Peptide, b.p.m. = beats per minute, BUN = Blood Urea Nitrogen, COPD = Chronic Obstructive Pulmonary Disease, eGFR = estimated Glomerular Filtration Rate, HFpEF = Heart Failure with preserved Ejection Fraction, IV= intravenous, JVP = Jugular Venous Pressure, MRA = Mineralocorticoid Receptor Antagonists, NYHA = New York Heart Association, Systolic BP = Systolic Blood Pressure.

Changes in cardiovascular treatment

For patients with incident hyperkalemia, MRAs were more often down-titrated (15%) compared to patients whose potassium remained in the normal range (9%) or with incident hypokalemia (8%) (figure 1 and supplementary table 4). After correcting for confounders (i.e. age, sex, eGFR, and total doses of loop diuretics until day 7 or discharge) or correction for all variables with a univariate association with MRA down-titration (univariable $P < 0.1$), this association remained significant (OR 1.81; 95%CI 1.27–2.58, $p = 0.001$ and OR 1.89; 95%CI 1.32–2.72, $p = 0.001$, respectively). In sensitivity analyses using IPW, this association was not attenuated (OR 1.88; 95%CI 1.30–2.73, $p = 0.001$). Doses of ACEi/ARB were not decreased more frequently in patients with incident hyperkalemia compared to patients with normal potassium concentrations throughout or those with incident hypokalemia ($P = 0.296$). Patients with incident hypokalemia were less often treated with MRA or ACEi/ARB during hospitalization (figure 1). However, after multivariable adjustment this was no longer

significant for either therapies class ($P=0.061$ and $P=0.380$ respectively). Difference at baseline between subgroups of treatment change for ACEi/ARB and MRA are listed in supplementary tables 5 and 6 respectively.

Figure 1. Changes in cardiovascular therapy between admission and discharge for ACEi/ARB and MRA. Stratified by developing incident hypokalemia, normal potassium concentrations throughout hospitalization, and incident hyperkalemia during hospitalization, p-value for overall intergroup differences.

In univariable analysis, the number of days with hyperkalemia was not associated with ACEi/ARB down-titration (OR: 1.06 (0.89–1.27), $p=0.517$) (table 2). However, the number of instances that hyperkalemia occurred was associated with down-titration of MRAs (OR: 1.26 (1.09–1.47), $p=0.003$). This association remained significant after correction for variables with a univariable association with MRA down-titration (OR: 1.23 (1.04–1.44), $p=0.014$) or after robust correction for various clinical confounders (OR: 1.41 (1.02–1.97), $p=0.040$).

When tested on a continuous scale, baseline serum potassium was not associated with ACEi/ARB down-titration (table 2). Yet, it was positively associated with MRA down-titration (OR: 1.45 (1.10–1.91), $p=0.008$) in univariable analysis. However, this effect was no longer significant after correction for clinical confounders (OR: 1.51 (0.87–2.62), $p=0.139$).

Table 2. The association between the magnitude of hyperkalemia (defined as the number of days hyperkalemia occurred (1 to 7 days)) or patients' serum potassium concentrations at baseline (on a continuous scale) and treatment down-titration.

Down-titration	Univariable	Model 1*	Model 2*
ACEi/ARB	OR (CI), p	OR (CI), p	OR (CI), p
Number of days with hyperkalemia	1.06 (0.89 – 1.27), 0.517	N.A.	N.A.
Baseline serum potassium, per 1 mEq/L	1.02 (0.78 – 1.33), 0.879	N.A.	N.A.
MRA	OR (CI), p	OR (CI), p	OR (CI), p
Number of days with hyperkalemia	1.26 (1.09 – 1.47), 0.003	1.23 (1.04 – 1.44), 0.014	1.41 (1.02 – 1.97), 0.040
Baseline serum potassium, per 1 mEq/L	1.45 (1.10 – 1.91), 0.008	1.35 (1.01 – 1.80), 0.043	1.51 (0.87 – 2.62), 0.139

* Model 1: Corrected for heart rate, logarithm of eGFR, history of hyperlipidemia, history of smoking, NYHA-class, treatment with beta-blockers, and treatment with MRAs (in ACEi/ARB) or treatment with ACEi/ARB (in MRA)

* Model 2: Corrected for age, sex, BMI, logarithm of eGFR, NYHA-class, left ventricular ejection fraction, systolic blood pressure, history of COPD, history of diabetes mellitus, history of atrial fibrillation, treatment with beta-blockers, treatment with ACEi/ARB, treatment with Rolofylline, edema & raised jugular venous pressure, intravenous dose of loop diuretics, serum sodium concentrations, serum BNP concentrations, and serum hemoglobin concentration.

Incident potassium disturbances, RAAS-I therapy, and outcome

Overall, 269 (17%) patients died within 180 days and 434 patients (27%) experienced the composite secondary outcome. No association was observed between incident hypo- or hyperkalemia and either outcome or the composite outcome (supplementary figure 1), even when hyperkalemia was defined as >5.5 mEq/L. However, the number of days a patient suffered from hyperkalemia was associated with 180-day mortality, even after correction for the PROTECT Risk Engine (HR 1.14 (1.00–1.30), $p=0.049$).

Compared to constant doses, down-titration or absence of ACEi/ARB at baseline and discharge/day 7 was associated with a higher 180-day mortality on both unadjusted and adjusted analyses (table 3). Furthermore, when using IPW, the

associations persisted (HR 2.56; 95%CI 1.83–3.60, $p < 0.001$, respectively). A similar pattern was observed for MRA down-titration during hospitalization. Also for MRAs, IPW did not attenuate this association (HR 1.67; 95%CI 1.11–2.49, $p = 0.013$). Additional correction for treatment with the study drug (Rolofylline) or placebo had no impact on outcomes.

Table 3. Cox proportional hazard regression for mortality risk at 180 days after change in cardiovascular treatment during hospitalization.

Change in cardiovascular treatment	Univariable	Model 1 [§]	PROTECT Risk Engine*
ACEi/ARB			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	1.03 (0.69 – 1.52), 0.895	1.01 (0.70 – 1.48), 0.940	1.02 (0.68 – 1.52), 0.939
Dose decreased or discontinued	2.12 (1.49 – 3.02), <0.001	1.97 (1.40 – 2.75), <0.001	1.68 (1.17 – 2.42), 0.005
Subject taking neither currently nor at randomization	2.58 (1.84 – 3.62), <0.001	1.89 (1.35 – 2.62), <0.001	1.85 (1.28 – 2.65), 0.001
MRA			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	1.21 (0.83 – 1.74), 0.322	1.14 (0.80 – 1.63), 0.472	1.11 (0.76 – 1.61), 0.595
Dose decreased or discontinued	1.66 (1.11 – 2.49), 0.013	1.57 (1.06 – 2.33), 0.026	1.73 (1.15 – 2.60), 0.008
Subject taking neither currently nor at randomization	1.31 (0.95 – 1.80), 0.095	1.12 (0.82 – 1.51), 0.479	1.15 (0.82 – 1.61), 0.408

HR, Hazard Ratio; CI, Confidence Interval

[§] Model 1: Corrected for age, sex, logarithm of eGFR, and logarithm of total dose of loop diuretics until day 7 or discharge (IV + oral/2)

* Corrected for PROTECT Risk Engine: age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum urea, creatinine, sodium, and albumin concentrations

Incident hyperkalemia had no impact on the association between RAASi and a favorable outcome. Patients with incident hyperkalemia and constant doses or increasing doses of MRA had a lower mortality (HR 0.58; 95%CI 0.37–0.91) compared to patients who did not receive an MRA or who had doses reduced. Additional IPW analysis did not attenuate this beneficial effect (HR 0.52; 95%CI 0.32–0.85). Similarly, patients with incident hyperkalemia and constant or increasing doses of ACEi/ARB had a lower mortality (HR 0.46; 95%CI 0.28–0.75). This association was not attenuated in an IPW analysis (HR 0.47; 95%CI 0.29–0.77). No interaction was observed between incident hyperkalemia and up-titration of ACEi/ARB or MRAs during hospitalization for either all-cause mortality at 180 days or the secondary composite outcome ($P_{\text{interaction}} > 0.1$ for all). Additionally, when tested in potassium sub-groups, patients with incident hyperkalemia and ACEi/ARB down-titration had a worse 180-day prognosis compared to patients with stable ACEi-/ARB doses. This was not seen for MRA (supplementary table 9).

DISCUSSION

This analysis shows that patients hospitalized for acute HF often develop hyperkalemia and if they do, they are more likely to have doses of MRAs reduced or stopped. Although incident hyperkalemia was not directly associated with longer-term outcomes, incident hyperkalemia was associated with lower use of RAASi. Patients who developed hyperkalemia fared better if the doses of MRA or ACEi/ARB were held constant or increased.

We are unaware of any other trial of hospital admission for HF with such a high density of measurements of serum potassium. More than half of patients in this analysis developed either hypo- or hyperkalemia during hospital admission. Hyperkalemia was most prevalent occurring in 35% of patients at least once, while 17% of patients experienced hypokalemia at least once during hospitalization. Incident serum potassium >5.5 mEq/L or >6.0 mEq/L was seen in 14% and 5% of patients, respectively. Many clinical trials of heart failure, especially involving RAASi, excluded patients with a baseline serum potassium >5.0 mEq/L which was designed to reduce the risk of developing severe hyperkalemia.^{19,20} Earlier reports from the PROTECT trial reported that 6% of acute HF patients had hyperkalemia

at baseline.²¹ In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, 14.6% of patients hospitalized with worsening heart failure had hyperkalemia at discharge.²² In a recent study, exploring the effect of long-term monitoring of serum potassium after hospitalizations for acute HF, 5.6% of patients developed hyperkalemia post-discharge.⁴

Patients at risk for developing hyperkalemia during hospitalization were more often treated with MRAs prior to hospitalization, in keeping with the results of the RALES Randomized Aldactone Evaluation Study) and EMPHASIS-HF trials (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), which showed that patients treated with MRAs developed hyperkalemia more often during follow up.^{20,23} Many trials of HF have shown that older patients with diabetes and renal dysfunction treated with RAASi are more likely to develop hyperkalemia.²¹⁻²⁴ The fact that we did not find similar associations with *incident* hyperkalemia suggests that changes in RAASi may be of overriding importance during hospitalization for acute HF. However, within the 'incident hyperkalemia' group, patients who were down-titrated with ACEi/ARB or MRAs, more frequently had a history of diabetes mellitus and showed a worse renal function compared to patients with incident hyperkalemia and stable doses or up-titration of ACEi/ARB or MRAs (supplementary tables 5 and 6). The greater incidence of hyperkalemia in younger people in our study may reflect greater efforts and success in treating them with MRA. Hypokalemia was strongly associated with not being treated with an MRA. In addition, by using a multi-day method of in-hospital monitoring, our study indicated that patients with a higher severity of hyperkalemia (defined as more days with serum potassium concentrations above 5.0 mEq/L), were more likely to be down-titrated with MRAs.

In this study, a mortality rate of 17% was seen after a follow-up period of 180 days. For the combined outcome of all-cause mortality and cardiovascular or renal rehospitalization at 60 days an incidence rate of 27% was seen (supplementary table 8). Similar to previous reports, incident hypo- or hyperkalemia during hospitalization was not associated either with mortality or our secondary composite outcome.^{21-23,25} However, incident hyperkalemia was strongly associated with down-titration of MRA therapy which was, in turn, associated with a worse prognosis. A

previous report from the Swedish HF Registry indicated that hyperkalemia was not related to underuse of MRAs.²⁶ In contrast, analyses of the BIOSTAT-CHF cohort, including patients with chronic HF, indicated hyperkalemia to be associated with less successful up-titration of ACEi/ARB and underuse of MRA.^{10,12} Unfortunately, no specific data on up- or down-titration of MRA therapy was available in this chronic HF cohort. Additionally, real-world data of the SCREAM study (Stockholm CREAtinine Measurements) indicated hyperkalemia to be common after MRA initiation, yet with frequent therapy interruption as a consequence, especially among participants with chronic kidney disease.¹¹

Our results indicated higher survival rates, after up-titration or constant doses of either MRAs or ACEi/ARB, are also seen in patients with incident hyperkalemia. This indicates that hyperkalemia at times of intense cardiovascular treatment might not attenuate the beneficial effects of these therapeutic agents, which is in accordance to earlier findings from a post-hoc analysis of the EMPHASIS-HF trial regarding chronic HFrEF patients.²⁷ This might be of additional interest, taking the novel therapeutics to lower serum potassium concentrations into account.^{28,29}

Study limitations

The PROTECT trial did not include patients with serum potassium concentrations below 3.0 mEq/L. Patients with serum potassium concentrations between 3.0–3.5 could only be included in case potassium was supplemented parentally. However, no data is available regarding the dose supplements. In patients with chronic HF, oral potassium supplements did not affect mortality³⁰ The associations highlighted in this paper need to be considered in the light of a clinical trial setting. For instance, the proportion of patients treated with the study drug (Rolofylline) was not equally distributed between potassium subgroups ($p=0.039$). Since an earlier study by Liu et al. indicated that the effect of Rolofylline on mortality is similar throughout the spectrum of baseline serum potassium concentrations, we do not expect this finding to be of major impact on our results.³¹ Besides, treatment with Rolofylline had no impact on our multivariable outcome models. Changes in RAASi were recorded between baseline and day 7, whereas serum potassium concentrations were measured daily. We did not record why investigators changed doses of RAASi, which will have been influenced by patients' symptoms and signs,

blood pressure and renal function. Additionally, since changes in RAASi were only recorded within this specific time window, the effects of dose adjustments after day 7 might have affected outcomes. The incidence of hyperkalemia and its effect on RAASi use might be distorted, compared to clinical practice, by the close monitoring of patients and their serum potassium. In clinical practice, serum potassium will usually be measured less often, which may mean that hyperkalemia is often missed but is more severe when it eventually is. We only included patients with five or more measurements of serum potassium which effectively excluded early deaths. Of 47 (3%) patients who died within 7 days of enrollment, 14 (30%) patients showed a serum potassium concentration $>5.0\text{mEq/L}$ at some point during hospitalization. Serum potassium concentrations may fluctuate markedly in the acute setting and may not reflect post-discharge measurements. This could account for the dissociation between in-patient measurements of potassium and long-term outcome that we observed. Other reports suggest that hypo- and hyperkalemia are strongly related to in-patient prognosis (UK National HF Audit on ~30,000 patients).

Conclusion

Incident hyperkalemia is common during hospitalization for acute HF but is not associated with a worse post-discharge prognosis. However, incident hyperkalemia is associated with underuse of MRAs, which is associated with an increased risk of mortality at 180 days. Survival analyses indicate that patients still benefit from constant doses or up-titration of MRAs and/or ACEi/ARB despite incident hyperkalemia in a clinical setting.

Clinical Perspectives: Even though incident hyperkalemia is common during hospitalization for acute HF, it does not result in impaired prognosis. However, it is associated with down-titration of MRAs, which is associated with worse outcomes. The authors reported patients with incident hyperkalemia, who were discharged on the same or an increased dose of MRAs and/or ACEi/ARB had a lower 180-day mortality.

Translational Outlook: This study provides data for associations between incident hyperkalemia and RAASi to tailor this therapy in patients hospitalized for acute HF. These data may also support the design of trials to, for example, explore the serum

potassium concentration at which RAASi doses should be reduced, should be reconsidered. The effect of treatments designed to manage hyperkalemia should be assessed not only to determine if they can increase the proportion of patients achieving target doses of RAASi but if this strategy leads to reductions in morbidity and mortality.

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SUPPLEMENTARY MATERIAL

Online Table 1. Differences at admission between patients with and without ≥ 5 potassium measurements throughout hospitalization.

Variables	Level	Included in analysis (n=1589)	Excluded from analysis (n=447)	p-value
Demographics:				
Potassium (mEq/L)		4.3 $\pm$ 0.6	4.2 $\pm$ 0.6	0.042
Age, years		70.0 $\pm$ 11.4	70.8 $\pm$ 12.0	0.16
Male sex		1060 (66.7%)	305 (68.5%)	0.47
BMI, kg/m ²		28.7 $\pm$ 6.1	29.1 $\pm$ 6.4	0.29
eGFR, mL/min/1.73 m ²		48.6 $\pm$ 19.3	47.3 $\pm$ 18.8	0.24
NYHA class	I/II	249 (16.5%)	96 (22.9%)	<0.001
	III	751 (49.8%)	231 (55.1%)	
	IV	507 (33.7%)	92 (22.0%)	
HFpEF (EF >45%)		115 (15.2%)	38 (17.4%)	0.44
Systolic BP, mmHg		124.8 $\pm$ 17.5	122.5 $\pm$ 17.8	0.014
Heart rate, b.p.m.		80.6 $\pm$ 15.5	78.4 $\pm$ 15.1	0.008
Signs & symptoms:				
Orthopnea		1349 (85.7%)	327 (76.8%)	<0.001
Angina pectoris		383 (24.1%)	64 (14.5%)	<0.001
Edema & raised JVP		433 (30.3%)	111 (27.7%)	0.30
Rales		165 (10.4%)	34 (7.8%)	0.10
History of:				
Hospitalization for HF previous year		802 (50.5%)	201 (45.2%)	0.048
Myocardial infarction		794 (50.1%)	207 (46.7%)	0.21
Hypertension		1268 (79.8%)	348 (78.2%)	0.46
Hyperlipidemia		777 (48.9%)	278 (62.6%)	<0.001
Current smoker		317 (20.0%)	103 (23.1%)	0.15
COPD or asthma		309 (19.5%)	93 (21.0%)	0.48
Diabetes mellitus		723 (45.5%)	199 (44.8%)	0.80
Atrial fibrillation/flutter		857 (54.2%)	247 (56.3%)	0.44
Cardiovascular treatment:				
Beta-blockers		1219 (76.7%)	328 (74.5%)	0.34
ACEi/ARB		1202 (75.6%)	333 (75.7%)	0.99

Online Table 1. (Continued)

Variables	Level	Included in analysis (n=1589)	Excluded from analysis (n=447)	p-value
MRA		726 (45.7%)	162 (36.9%)	0.001
Digoxin		476 (30.0%)	93 (21.2%)	<0.001
IV loop diuretic dose administered on day 1		80 (40, 140)	80 (60, 160)	<0.001
Oral dosage loop diuretic administered on day 1		40 (25, 60)	40 (40, 60)	0.083
Laboratory:				
BNP (pg/mL)		4512 (258, 830)	434 (232, 700)	0.12
Albumin (g/dL)		3.8 ± 0.4	3.8 ± 0.4	0.89
Bicarbonate (mEq/L)		24.0 ± 3.8	24.1 ± 3.9	0.61
Chloride (mEq/L)		101.1 ± 4.9	99.7 ± 5.0	<0.001
Sodium (mEq/L)		139.5 ± 4.1	138.3 ± 4.0	<0.001
Urea (BUN) (mg/dL)		29 (22, 40)	31 (22, 45)	0.067
Uric acid (mg/dL)		9.0 ± 2.6	8.9 ± 2.7	0.34
Serum glucose (mg/dL)		126 (103, 163)	124 (103, 162)	0.88
Hemoglobin (g/dL)		12.7 ± 2.0	12.5 ± 2.0	0.093
Platelets (x10 ⁹ /L)		217 (175, 271)	217 (166, 273)	0.61
White blood cells (x10 ⁹ /L)		7.5 (6.1, 9.3)	7.3 (6.0, 9.2)	0.51
Total cholesterol (mg/dL)		148 ± 45	146 ± 42	0.47

Values are given as proportions, means (±SD) or medians (IQR)

ACEi = Angiotensin-Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blockers, BMI = Body Mass Index, BNP = Brain Natriuretic Peptide, b.p.m. = beats per minute, BUN = Blood Urea Nitrogen, COPD = Chronic Obstructive Pulmonary Disease, eGFR = estimated Glomerular Filtration Rate, HFpEF = Heart Failure with preserved Ejection Fraction, IV= intravenous, JVP = Jugular Venous Pressure, MRA = Mineralocorticoid Receptor Antagonists, NYHA = New York Heart Association, Systolic BP = Systolic Blood Pressure.

Online Table 2. Baseline characteristics stratified by the number of days hyperkalemia occurred.

Factor	Level	No incident hyperkalemia (n=1025)	1 episode of hyperkalemia (n=264)	2 episodes of hyperkalemia (n=141)	>2 episodes of hyperkalemia (n=159)	p-value
Age, years		70.6 (11.5)	69.0 (11.7)	69.1 (11.5)	68.0 (10.0)	0.012
Sex		692 (67.5%)	176 (66.7%)	85 (60.3%)	107 (67.3%)	0.40
BMI, kg/m ²		29.0 (6.3)	29.0 (6.0)	27.7 (5.2)	27.7 (5.1)	0.011
eGFR, mL/min/1.73 m ²		48.9 (18.7)	49.7 (20.5)	46.8 (18.8)	46.0 (21.4)	0.16
NYHA class	I/II	169 (17.4%)	38 (15.1%)	23 (17.3%)	19 (12.8%)	0.35
	III	497 (51.1%)	119 (47.2%)	61 (45.9%)	74 (49.7%)	
	IV	307 (31.6%)	95 (37.7%)	49 (36.8%)	56 (37.6%)	
LVEF, %		30 (20, 40)	30 (25, 44)	28 (25, 35)	34 (25, 40)	0.21
HFpEF (EF >45%)		72 (14.6%)	22 (17.7%)	10 (14.3%)	11 (15.7%)	0.85
Systolic BP, mmHg		124.8 (17.9)	124.2 (17.3)	125.1 (16.7)	125.3 (16.0)	0.93
Diastolic BP, mmHg		74.0 (11.9)	74.9 (11.3)	74.6 (11.4)	75.7 (10.8)	0.31
Heart rate, b.p.m.		79.8 (15.4)	82.0 (15.5)	80.4 (15.3)	83.1 (16.0)	0.031
Respiratory rate		21.1 (4.4)	21.4 (4.3)	21.8 (6.2)	21.7 (4.9)	0.24
Atrial fibrillation at presentation		187 (42.7%)	43 (46.7%)	16 (34.8%)	30 (48.4%)	0.47
Valve disease		418 (40.9%)	98 (37.5%)	53 (37.6%)	45 (28.3%)	0.022
Mitral regurgitation		374 (36.5%)	90 (34.4%)	49 (34.8%)	42 (26.4%)	0.10
Aortic stenosis		43 (4.2%)	8 (3.0%)	4 (2.8%)	3 (1.9%)	0.42
Aortic regurgitation		71 (6.9%)	13 (4.9%)	10 (7.1%)	9 (5.7%)	0.65
Heart failure (HF)		974 (95.0%)	252 (95.5%)	133 (94.3%)	149 (93.7%)	0.86
Hospitalization for HF previous year		520 (50.7%)	142 (53.8%)	69 (48.9%)	71 (44.7%)	0.32
No. of HF hospitalizations		1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.19
Ischemic heart disease		715 (69.9%)	189 (71.6%)	101 (71.6%)	114 (72.2%)	0.89
Myocardial infarction		505 (49.4%)	140 (53.0%)	73 (51.8%)	76 (48.1%)	0.67
Hypertension		820 (80.0%)	210 (79.5%)	111 (78.7%)	127 (79.9%)	0.99
Stroke or PVD		188 (18.4%)	54 (20.5%)	27 (19.1%)	29 (18.2%)	0.88
Anemia		386 (42.7%)	90 (39.0%)	49 (38.3%)	53 (39.6%)	0.58
Thyroid disease		109 (10.6%)	38 (14.4%)	6 (4.3%)	14 (8.8%)	0.014
Depression		74 (7.2%)	8 (3.0%)	7 (5.0%)	8 (5.0%)	0.065
Hyperlipidemia		531 (51.8%)	123 (46.6%)	63 (44.7%)	60 (37.7%)	0.005
Current smoker		219 (21.4%)	46 (17.4%)	31 (22.0%)	21 (13.3%)	0.066
COPD or asthma		199 (19.4%)	53 (20.2%)	25 (17.7%)	32 (20.1%)	0.94

Online Table 2. (Continued)

Factor	Level	No incident hyperkalemia (n=1025)	1 episode of hyperkalemia (n=264)	2 episodes of hyperkalemia (n=141)	>2 episodes of hyperkalemia (n=159)	p-value
Diabetes mellitus		458 (44.7%)	122 (46.2%)	69 (48.9%)	74 (46.5%)	0.78
History of Atrial Fibrillation/Flutter		566 (55.4%)	145 (55.6%)	66 (46.8%)	80 (51.0%)	0.21
AICD		171 (16.7%)	39 (14.8%)	22 (15.6%)	8 (5.0%)	0.002
Biventricular pacemaker		103 (10.0%)	20 (7.6%)	10 (7.1%)	6 (3.8%)	0.047
Pacemaker		136 (13.3%)	31 (11.8%)	11 (7.8%)	15 (9.4%)	0.18
Beta-blockers		794 (77.5%)	203 (76.9%)	105 (74.5%)	117 (73.6%)	0.66
ACE-I/ARB		764 (74.5%)	205 (77.7%)	107 (75.9%)	126 (79.2%)	0.50
MRA		430 (42.0%)	123 (46.6%)	77 (54.6%)	96 (60.4%)	<0.001
Digoxin		306 (29.9%)	67 (25.4%)	44 (31.2%)	59 (37.1%)	0.085
Nitrates		265 (25.9%)	72 (27.3%)	38 (27.0%)	42 (26.4%)	0.97
Hydralazine		34 (3.3%)	4 (1.5%)	3 (2.1%)	0 (0.0%)	0.053
CCBs		140 (13.7%)	30 (11.4%)	14 (9.9%)	22 (13.8%)	0.51
On study drug (Rofloxylline)		667 (65.1%)	182 (68.9%)	108 (76.6%)	95 (59.7%)	0.011
Orthopnea		878 (86.7%)	228 (86.7%)	113 (80.1%)	130 (82.3%)	0.11
Dyspnea at rest (NYHA IV)		584 (58.8%)	163 (62.7%)	92 (66.7%)	103 (66.5%)	0.10
Angina pectoris		220 (21.5%)	81 (30.7%)	28 (19.9%)	54 (34.0%)	<0.001
CCS Class III & IV		64 (29.4%)	29 (36.7%)	9 (33.3%)	20 (37.7%)	0.51
Edema		286 (27.9%)	86 (32.6%)	35 (24.8%)	40 (25.2%)	0.25
Jugular venous distension		391 (42.4%)	92 (38.8%)	49 (37.4%)	58 (42.3%)	0.58
Edema & raised JVP		294 (31.9%)	64 (27.0%)	35 (26.7%)	40 (29.2%)	0.36
Rales		99 (9.7%)	30 (11.4%)	18 (12.8%)	18 (11.3%)	0.61
IV loop diuretic dose administered on Day 1		80 (40, 160)	80 (40, 120)	80 (40, 120)	60 (40, 100)	<0.001
Oral dose loop diuretics on Day 1		40 (20, 60)	40 (25, 60)	40 (25, 60)	40 (40, 60)	0.37
BNP		447.8 (257.1, 834.4)	454.9 (269.5, 829.9)	451.6 (251.7, 789.7)	493.9 (264.7, 829.6)	0.87
Albumin (g/dL)		3.8 (0.4)	3.8 (0.4)	3.9 (0.4)	3.9 (0.5)	0.44
Bicarbonate (mEq/L)		24.4 (3.7)	23.6 (3.8)	23.1 (3.7)	22.6 (3.8)	<0.001
Chloride (mEq/L)		100.8 (4.9)	101.3 (5.2)	101.5 (4.8)	102.2 (4.7)	0.004
Sodium (mEq/L)		139.7 (4.1)	139.4 (4.3)	139.2 (4.0)	139.2 (4.3)	0.33
Potassium (mEq/L)		4.1 (0.5)	4.5 (0.6)	4.7 (0.6)	4.9 (0.6)	<0.001

Online Table 2. (Continued)

Factor	Level No incident hyperkalemia (n=1025)	1 episode of hyperkalemia (n=264)	2 episodes of hyperkalemia (n=141)	>2 episodes of hyperkalemia (n=159)	p-value
Urea(Bun) (mg/dL)	29 (22, 39)	29 (22, 42)	32 (23, 42)	34 (23, 44)	0.016
Uric Acid (mg/dL)	9.1 (2.6)	9.0 (2.4)	8.8 (2.6)	9.0 (2.7)	0.79
Glucose, Random, Serum (mg/dL)	128 (105, 162)	121 (99, 159)	126 (103, 171)	121 (97, 175)	0.21
Hgb (g/dL)	12.6 (1.9)	12.9 (2.0)	12.7 (1.9)	13.0 (2.2)	0.12
Platelets (x10 ⁹ /L)	213 (170, 262)	223 (178, 274)	231 (178, 279)	235 (187, 299)	0.009
Wbc (x10 ⁹ /L)	7.4 (5.9, 9.3)	7.6 (6.3, 9.2)	7.7 (6.3, 9.4)	7.8 (6.4, 9.1)	0.36
Cholesterol, Total (mg/dL)	144 (44)	148 (43)	157 (48)	160 (46)	<0.001
Potassium change between baseline and discharge/day7	0.2 (-0.2, 0.6)	0.3 (-0.4, 0.8)	0.4 (-0.1, 1.0)	0.4 (-0.1, 0.9)	<0.001

Online Table 3. Clinical variables associated with incident hyperkalemia during acute HF hospitalization in a multivariable model.

Factor	OR	95% CI	P-value	OR	Multivariable 95%CI (n=1145)	P-value
Age, per 10 years	.867	.793 – .948	0.002	.864	.763 – .978	0.021
Female sex	1.11	.891 – 1.38	0.360			
BMI, per 10 kg/m ²	.834	.700 – .992	0.041	.963	.764 – 1.21	0.751
Heart rate, per 10 bpm	1.09	1.02 – 1.16	0.010	1.06	.974 – 1.16	0.169
SBP, per 20 mmHg	0.993	.883 – 1.12	0.903			
eGFR, per doubling	.804	.624 – 1.04	0.092	.927	.528 – 1.63	0.791
Edema/JVP, yes vs. no	.811	.639 – 1.03	0.087	.840	.628 – 1.12	0.242
<i>History of: (yes vs. no)</i>						
Hyperlipidemia	.720	.585 – .885	0.002	.747	.573 – .973	0.030
Stroke	.931	.649 – 1.34	0.700			
COPD or asthma	1.01	.777 – 1.31	0.960			
Myocardial infarction	1.08	.881 – 1.33	0.453			
Atrial fibrillation	.875	.711 – 1.08	0.205			
Diabetes Mellitus	1.10	.893 – 1.35	0.378			
Congestive HF	1.19	1.02 – 1.39	0.025	1.08	.886 – 1.31	0.458

Online Table 3. (Continued)

Factor	OR	95% CI	P-value	OR	Multivariable 95%CI (n=1145)	P-value
Therapy prior to hospitalization, yes vs. no						
ACEi/ARB	1.19	.931 – 1.51	0.165			
MRA	1.53	1.24 – 1.88	<0.001	1.54	1.18 – 2.01	0.001
Beta-blockers	.890	.699 – 1.13	0.341			
Loop diuretics doses (IV + oral) until discharge or day 7:						
	.796	.705 – .898	<0.001	.746	.628 – .886	0.001
<i>Laboratory data on baseline:</i>						
BNP, per doubling	1.01	.885 – 1.15	0.885			
Hemoglobin, per 5 g/dL	1.32	1.00 – 1.75	0.048	1.40	.961 – 2.04	0.080
Platelet count, per doubling	1.58	1.15 – 2.17	0.004	1.76	1.16 – 2.66	0.007
White blood cells, per doubling	1.46	1.05 – 2.03	0.023	1.13	.733 – 1.73	0.586
Albumin, per g/dL	1.13	.890 – 1.44	0.313			
Bicarbonate, per 5 mEq/L	.648	.559 – .752	<0.001	1.03	.804 – 1.31	0.840
Chloride, per 5 mEq/L	1.18	1.06 – 1.32	0.002	1.80	1.40 – 2.33	<0.001
Total cholesterol, per 100 mg/dL	1.60	1.27 – 2.02	<0.001	1.48	1.07 – 2.04	0.019
Glucose, per doubling	.953	.711 – 1.28	0.748			
Sodium, per 5 mEq/L	.892	.787 – 1.01	0.072	.537	.399 – .725	<0.001
Blood urea nitrogen, per doubling	1.32	1.06 – 1.66	0.015	2.30	1.38 – 3.83	0.001
Uric acid, per 5 mg/dL	.919	.748 – 1.13	0.420			

Online Table 4. Clinical variables associated with incident hypokalemia during acute HF hospitalization in a multivariable model.

Factor	OR	95% CI	P-value	OR	Multivariable 95%CI (n=986)	P-value
Age, per 10 years	1.05	.935 – 1.18	0.399			
Male sex	1.26	.962 – 1.66	0.093	1.34	.928 – 1.93	0.118
BMI, per 10 kg/m ²	.971	.779 – 1.21	0.795			
Heart rate, per 10 bpm	.979	.899 – 1.07	0.623			
SBP, per 20 mmHg	1.03	.887 – 1.20	0.694			

Online Table 4. Clinical variables associated with incident hypokalemia during acute HF hospitalization in a multivariable model.

Factor	OR	95% CI	P-value	OR	Multivariable 95%CI (n=986)	P-value
eGFR, per doubling	.995	.718 – 1.38	0.978			
Edema/raised JVP, yes vs. no	1.48	1.11 – 1.98	0.007	1.25	.867 – 1.81	0.230
History of: (yes vs. no)						
Hyperlipidemia	1.08	.832 – 1.41	0.552			
Stroke	.945	.593 – 1.51	0.812			
COPD or asthma	.983	.704 – 1.37	0.919			
Myocardial infarction	.809	.621 – 1.05	0.117			
Atrial fibrillation	.998	.766 – 1.30	0.989			
Diabetes Mellitus	.920	.705 – 1.20	0.536			
Congestive HF	.915	.751 – 1.11	0.375			
Therapy prior to hospitalization, yes vs. no						
ACEi/ARB	.639	.479 – .854	0.002	.820	.559 – 1.20	0.310
MRA	.590	.449 – .777	<0.001	.512	.359 – .730	<0.001
Beta-blockers	1.02	.744 – 1.39	0.911			
Loop diuretics doses (IV + oral) until discharge or day 7:	1.48	1.26 – 1.75	<0.001	1.23	1.00 – 1.50	0.045
<i>Laboratory data on baseline:</i>						
BNP, per doubling	1.43	1.20 – 1.71	<0.001	1.30	1.04 – 1.62	0.020
Hemoglobin, per 5 g/dL	.850	.598 – 1.21	0.365			
Platelet count, per doubling	.585	.396 – .863	0.007	.642	.386 – 1.07	0.087
White blood cells, per doubling	.729	.482 – 1.10	0.135			
Albumin, per g/dL	.678	.502 – .916	0.011	.819	.528 – 1.27	0.373
Bicarbonate, per 5 mEq/L	1.71	1.43 – 2.04	<0.001	1.90	1.49 – 2.42	<0.001
Chloride, per 5 mEq/L	.733	.643 – .836	<0.001	.820	.684 – .983	0.032
Total cholesterol, per 100 mg/dL	.580	.420 – .800	0.001	.930	.592 – 1.46	0.752
Glucose, per doubling	.957	.658 – 1.39	0.819			
Sodium, per 5 mEq/L	1.10	.934 – 1.30	0.252			
Blood urea nitrogen, per doubling	.974	.729 – 1.30	0.856			
Uric acid, per 5 mg/dL	1.41	1.09 – 1.82	0.009	1.11	.790 – 1.56	0.550

Online Table 5. Changes in cardiovascular therapy between admission and discharge for ACEi/ARB and MRA. Stratified by developing incident hypokalemia, normal potassium concentrations throughout hospitalization, and incident hyperkalemia during hospitalization.

Change in cardiovascular treatment	Incident hypokalemia	Normal potassium	Incident hyperkalemia	P-value
ACEi/ARB				
Dose increased or initiated	55 (21.4%)	114 (15.6%)	109 (20.3%)	0.038
No dose changes	119 (46.3%)	432 (58.9%)	319 (59.3%)	0.002
Dose decreased or discontinued	40 (15.6%)	91 (12.4%)	63 (11.7%)	0.26
No use	43 (16.7%)	96 (13.1%)	47 (8.7%)	0.002
MRAs				
Dose increased or initiated	62 (24.1%)	125 (17.1%)	97 (18.1%)	0.034
No dose changes	82 (31.9%)	321 (43.8%)	237 (44.2%)	0.003
Dose decreased or discontinued	20 (7.8%)	63 (8.6%)	82 (15.3%)	<0.001
No use	93 (36.2%)	223 (30.5%)	120 (22.4%)	<0.001

Online Table 6. Baseline characteristics of patients who developed hyperkalemia, according to dose changes of ACEi/ARB.

Factor	Level	Hyperkalemia and no therapy / down-titration (n=110)	Hyperkalemia and constant dosages / up-titration (n=428)	p-value
Age, years		69.1 (10.7)	68.4 (11.4)	0.54
Sex		74 (67.3%)	275 (64.3%)	0.55
BMI, kg/m ²		28.5 (5.6)	28.2 (5.6)	0.61
eGFR, mL/min/1.73 m ²		41.9 (20.0)	50.0 (20.6)	<0.001
NYHA class	I/II	15 (14.4%)	61 (15.0%)	0.20
	III	57 (54.8%)	185 (45.5%)	
	IV	32 (30.8%)	161 (39.6%)	
LVEF, %		31 (25, 45)	30 (25, 40)	0.76
HFpEF (EF >45%)		8 (17.8%)	33 (16.1%)	0.78
Systolic BP, mmHg		123.8 (17.6)	125.0 (16.6)	0.52
Diastolic BP, mmHg		74.1 (11.2)	75.3 (11.1)	0.29
Heart rate, b.p.m.		82.1 (15.9)	81.6 (15.4)	0.76
Respiratory rate		22.5 (6.4)	21.4 (4.4)	0.042
Atrial fibrillation at presentation		17 (42.5%)	68 (45.3%)	0.75

Online Table 6. (Continued)

Factor	Level	Hyperkalemia and no therapy / down-titration (n=110)	Hyperkalemia and constant dosages / up-titration (n=428)	p-value
Valve disease		39 (35.5%)	145 (34.1%)	0.79
Mitral regurgitation		34 (30.9%)	135 (31.7%)	0.88
Aortic stenosis		3 (2.7%)	10 (2.3%)	0.81
Aortic regurgitation		6 (5.5%)	23 (5.4%)	0.98
Heart failure (HF)		104 (94.5%)	407 (95.1%)	0.81
Hospitalization for HF previous year		55 (50.0%)	212 (49.5%)	0.93
No. of HF hospitalizations		1 (1, 2)	1 (1, 2)	0.84
Ischemic heart disease		78 (70.9%)	304 (71.0%)	0.98
Myocardial infarction		61 (55.5%)	215 (50.2%)	0.33
Hypertension		85 (77.3%)	340 (79.4%)	0.62
Stroke or PVD		15 (13.6%)	91 (21.3%)	0.071
Anemia		44 (47.8%)	139 (36.7%)	0.049
Thyroid disease		17 (15.5%)	35 (8.2%)	0.021
Depression		3 (2.7%)	19 (4.4%)	0.42
Hyperlipidemia		55 (50.0%)	180 (42.1%)	0.13
Current smoker		24 (21.8%)	74 (17.3%)	0.27
COPD or asthma		23 (20.9%)	83 (19.4%)	0.73
Diabetes mellitus		62 (56.4%)	193 (45.1%)	0.035
History of Atrial Fibrillation/Flutter		63 (57.8%)	214 (50.5%)	0.17
AICD		21 (19.1%)	46 (10.7%)	0.018
Biventricular pacemaker		10 (9.1%)	25 (5.9%)	0.22
Pacemaker		11 (10.0%)	42 (9.8%)	0.96
Beta-blockers		87 (79.1%)	320 (74.8%)	0.35
ACE-I/ARB		76 (69.1%)	340 (79.4%)	0.021
MRA		57 (51.8%)	223 (52.1%)	0.96
Digoxin		43 (39.1%)	123 (28.7%)	0.036
Nitrates		32 (29.1%)	116 (27.1%)	0.68
Hydralazine		1 (0.9%)	6 (1.4%)	0.68
CCBs		17 (15.5%)	44 (10.3%)	0.13
On study drug (Roflofylline)		68 (61.8%)	302 (70.6%)	0.078
Orthopnea		93 (85.3%)	360 (84.3%)	0.79
Dyspnea at rest (NYHA IV)		64 (60.4%)	274 (64.8%)	0.40
Angina pectoris		32 (29.1%)	127 (29.7%)	0.91

Online Table 6. (Continued)

Factor	Level	Hyperkalemia and no therapy / down-titration (n=110)	Hyperkalemia and constant dosages / up-titration (n=428)	p-value
CCS Class III & IV		13 (41.9%)	43 (34.7%)	0.45
Edema		34 (30.9%)	118 (27.6%)	0.49
Jugular venous distension		44 (44.4%)	143 (37.6%)	0.22
Edema & raised JVP		33 (33.3%)	96 (25.3%)	0.11
Rales		14 (12.7%)	45 (10.5%)	0.51
IV loop diuretic dose administered on Day 1		80 (40, 120)	75.6 (40, 120)	0.28
Oral dose loop diuretics on Day 1		40 (40, 80)	40 (25, 60)	0.018
BNP		443 (250, 874)	455 (267, 802)	0.91
Albumin (g/dL)		3.9 (0.4)	3.9 (0.4)	0.87
Bicarbonate (mEq/L)		22.5 (4.1)	23.5 (3.6)	0.010
Chloride (mEq/L)		101.8 (5.1)	101.7 (4.9)	0.84
Sodium (mEq/L)		139.4 (3.7)	139.4 (4.1)	1.00
Potassium (mEq/L)		4.8 (0.63)	4.7 (0.57)	0.027
Urea(Bun) (mg/dL)		37.5 (26.0, 53.5)	29.0 (22.0, 40.0)	<0.001
Uric Acid (mg/dL)		9.0 (2.6)	8.9 (2.5)	0.72
Glucose, Random, Serum (mg/dL)		135 (103, 175)	121 (99, 162)	0.082
Hgb (g/dL)		12.4 (1.9)	13.0 (2.1)	0.028
Platelets (x10 ⁹ /L)		234 (189, 289)	223 (179, 280)	0.34
Wbc (x10 ⁹ /L)		7.9 (5.9, 9.1)	7.6 (6.4, 9.2)	0.85
Cholesterol, Total (mg/dL)		1467 (48)	156 (43.)	0.063
Potassium change between baseline and discharge/day7		0.2 (-0.4, 0.8)	0.4 (-0.2, 0.9)	0.052
1 episode of hyperkalemia		56 (50.9%)	199 (46.5%)	0.41
2 episodes of hyperkalemia		27 (24.5%)	106 (24.8%)	0.96
3 episodes of hyperkalemia		14 (12.7%)	60 (14.0%)	0.73
4 episodes of hyperkalemia		5 (4.5%)	31 (7.2%)	0.31
5 episodes of hyperkalemia		1 (0.9%)	18 (4.2%)	0.095
6 episodes of hyperkalemia		5 (4.5%)	11 (2.6%)	0.28
7 episodes of hyperkalemia		2 (1.8%)	3 (0.7%)	0.28

Online Table 7. Baseline characteristics of patients who developed hyperkalemia, according to dose changes of MRAs.

Factor	Level	Hyperkalemia and no therapy / down-titration (n=110)	Hyperkalemia and constant dosages / up-titration (n=428)	p-value
Age, years		70.7 (10.4)	67.3 (11.6)	<0.001
Sex		124 (61.4%)	224 (67.1%)	0.18
BMI, kg/m ²		28.3 (5.8)	28.3 (5.5)	0.99
eGFR, mL/min/1.73 m ²		41.9 (22.2)	52.2 (18.8)	<0.001
NYHA class	I/II	33 (17.2%)	42 (13.2%)	0.15
	III	96 (50.0%)	145 (45.7%)	
	IV	63 (32.8%)	130 (41.0%)	
LVEF, %		35 (28, 45)	30 (25, 37)	0.004
HFpEF (EF >45%)		21 (22.1%)	20 (12.9%)	0.056
Systolic BP, mmHg		126.2 (17.0)	123.8 (16.8)	0.11
Diastolic BP, mmHg		74.0 (11.3)	75.6 (10.9)	0.12
Heart rate, b.p.m.		80.8 (14.9)	82.3 (15.6)	0.29
Respiratory rate		21.4 (4.2)	21.8 (5.2)	0.45
Atrial fibrillation at presentation		38 (44.7%)	46 (44.2%)	0.95
Valve disease		56 (27.9%)	127 (38.3%)	0.014
Mitral regurgitation		52 (25.7%)	116 (34.9%)	0.026
Aortic stenosis		6 (3.0%)	7 (2.1%)	0.52
Aortic regurgitation		9 (4.5%)	19 (5.7%)	0.53
Heart failure (HF)		192 (95.0%)	317 (94.9%)	0.94
Hospitalization for HF previous year		104 (51.5%)	161 (48.2%)	0.46
No. of HF hospitalizations		1 (1, 2)	1 (1, 2)	0.63
Ischemic heart disease		136 (67.3%)	245 (73.4%)	0.14
Myocardial infarction		96 (47.5%)	179 (53.6%)	0.17
Hypertension		171 (84.7%)	252 (75.4%)	0.011
Stroke or PVD		43 (21.4%)	63 (18.9%)	0.48
Anemia		87 (50.6%)	96 (32.2%)	<0.001
Thyroid disease		20 (9.9%)	31 (9.3%)	0.81
Depression		9 (4.5%)	13 (3.9%)	0.75
Hyperlipidemia		100 (49.5%)	135 (40.4%)	0.040
Current smoker		46 (22.8%)	52 (15.6%)	0.037
COPD or asthma		38 (18.9%)	67 (20.1%)	0.74
Diabetes mellitus		111 (55.0%)	143 (42.8%)	0.006

Online Table 7. (Continued)

Factor	Level	Hyperkalemia and no therapy / down- titration (n=110)	Hyperkalemia and constant dosages / up- titration (n=428)	p-value
History of Atrial Fibrillation/ Flutter		104 (51.7%)	172 (52.1%)	0.93
AICD		22 (10.9%)	43 (12.9%)	0.50
Biventricular pacemaker		14 (7.0%)	20 (6.0%)	0.65
Pacemaker		23 (11.4%)	30 (9.0%)	0.36
Beta-blockers		156 (77.2%)	250 (74.9%)	0.53
ACE-I/ARB		157 (77.7%)	257 (76.9%)	0.84
MRA		73 (36.1%)	207 (62.0%)	<0.001
Digoxin		54 (26.7%)	112 (33.5%)	0.099
Nitrates		60 (29.7%)	88 (26.3%)	0.40
Hydralazine		2 (1.0%)	5 (1.5%)	0.62
CCBs		32 (15.8%)	29 (8.7%)	0.011
On study drug (Rolofylline)		140 (69.3%)	228 (68.3%)	0.80
Orthopnea		170 (84.6%)	281 (84.4%)	0.95
Dyspnea at rest (NYHA IV)		129 (65.8%)	208 (62.8%)	0.49
Angina pectoris		56 (27.7%)	103 (30.8%)	0.44
CCS Class III & IV		20 (37.0%)	36 (35.6%)	0.86
Edema		50 (24.8%)	101 (30.2%)	0.17
Jugular venous distension		74 (39.4%)	113 (39.1%)	0.95
Edema & raised JVP		52 (27.7%)	77 (26.6%)	0.81
Rales		25 (12.4%)	34 (10.2%)	0.43
IV loop diuretic dose administered on Day 1		80 (40, 120)	60 (40, 115)	0.12
Oral dose loop diuretics on Day 1		40 (40, 60)	40 (25, 60)	0.090
BNP		435 (255, 786)	479 (267, 826)	0.55
Albumin (g/dL)		3.9 (0.4)	3.9 (0.4)	0.36
Bicarbonate (mEq/L)		22.7 (3.7)	23.7 (3.7)	0.002
Chloride (mEq/L)		102.0 (4.9)	101.5 (5.0)	0.34
Sodium (mEq/L)		139.1 (4.1)	139.6 (4.0)	0.17
Potassium (mEq/L)		4.7 (0.57)	4.6 (0.59)	0.027
Urea(Bun) (mg/dL)		37 (26, 48)	27 (21, 39)	<0.001
Uric Acid (mg/dL)		9.1 (2.6)	8.8 (2.5)	0.19
Glucose, Random, Serum (mg/dL)		124 (103, 175)	122.5 (97, 160)	0.080
Hgb (g/dL)		12.2 (1.9)	13.3 (2.0)	<0.001

Online Table 7. (Continued)

Factor	Level	Hyperkalemia and no therapy / down-titration (n=110)	Hyperkalemia and constant dosages / up-titration (n=428)	p-value
Platelets (x10 ⁹ /L)		233 (186, 297)	219 (178, 275)	0.064
Wbc (x10 ⁹ /L)		7.9 (6.5, 9.6)	7.5 (6.2, 9.0)	0.10
Cholesterol, Total (mg/dL)		152 (47)	155 (43)	0.34
Potassium change between baseline and discharge/day7		0.3 (-0.3, 0.9)	0.4 (-0.2, 0.9)	0.62
1 episode of hyperkalemia		87 (43.1%)	167 (50.0%)	0.12
2 episodes of hyperkalemia		53 (26.2%)	80 (24.0%)	0.55
3 episodes of hyperkalemia		30 (14.9%)	43 (12.9%)	0.52
4 episodes of hyperkalemia		14 (6.9%)	22 (6.6%)	0.88
5 episodes of hyperkalemia		6 (3.0%)	13 (3.9%)	0.58
6 episodes of hyperkalemia		8 (4.0%)	8 (2.4%)	0.30
7 episodes of hyperkalemia		4 (2.0%)	1 (0.3%)	0.050

Online Table 8. Cox proportional hazard regression for mortality risk at 180 days after change in cardiovascular treatment during hospitalization, stratified by potassium subgroup. All analyses were corrected for the PROTECT Risk Engine*.

Change in cardiovascular treatment	Incident hypokalemia (n=252)	Normal potassium (n=721)	Incident hyperkalemia (n=531)
ACEi/ARB			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	1.55 (0.65 – 3.75), 0.324	1.19 (0.65 – 2.17), 0.571	0.61 (0.29 – 1.26), 0.184
Dose decreased or discontinued	2.20 (0.89 – 5.44), 0.089	1.52 (0.87 – 2.66), 0.142	1.91 (1.05 – 3.47), 0.033
No use	2.21 (1.43 – 7.17), 0.005	1.90 (1.13 – 3.17), 0.015	1.21 (0.55 – 2.67), 0.636
MRA			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	1.50 (0.65 – 3.44), 0.339	0.82 (0.46 – 1.45), 0.490	1.37 (0.70 – 2.78), 0.376
Dose decreased or discontinued	2.99 (1.11 – 8.03), 0.029	1.59 (0.83 – 3.01), 0.159	1.68 (0.86 – 3.29), 0.127
No use	1.22 (0.53 – 2.80), 0.639	1.00 (0.61 – 1.63), 0.985	1.44 (0.79 – 2.62), 0.232

HR, Hazard Ratio; CI, Confidence Interval

* Corrected for PROTECT Risk Engine: age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum urea, creatinine, sodium, and albumin concentrations

Online Table 9. Cox proportional hazard regression for the composite of rehospitalization for cardiovascular or renal causes or all-cause mortality through 60 days after change in cardiovascular treatment during hospitalization.

Change in cardiovascular treatment	Univariable	Model 1 [§]	PROTECT Risk Engine*
ACEi/ARB			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	0.74 (0.54 – 1.01), 0.058	0.74 (0.54 – 1.01), 0.062	0.77 (0.56 – 1.06), 0.113
Dose decreased or discontinued	1.64 (1.24 – 2.17), <0.001	1.55 (1.17 – 2.06), 0.002	1.48 (1.11 – 1.97), 0.007
No use	2.31 (1.79 – 2.99), <0.001	1.98 (1.51 – 2.61), <0.001	2.01 (1.53 – 2.64), <0.001
MRA			
No dose change (Reference)	HR (CI), p	HR (CI), p	HR (CI), p
Dose increased or initiated	0.86 (0.63 – 1.16), 0.319	0.82 (0.60 – 1.11), 0.205	0.88 (0.65 – 1.20), 0.434
Dose decreased or discontinued	1.30 (0.94 – 1.80), 0.114	1.20 (0.86 – 1.67), 0.276	1.28 (0.92 – 1.79), 0.140
No use	1.49 (1.18 – 1.88), 0.001	1.34 (1.05 – 1.70), 0.018	1.43 (1.12 – 1.83), 0.004

HR, Hazard Ratio; CI, Confidence Interval

[§] Model 1: Corrected for age, sex, logarithm of eGFR, and logarithm of total dose of loop diuretics until day 7 or discharge (IV + oral/2)

* Corrected for PROTECT Risk Engine: age, previous HF hospitalizations, peripheral edema, systolic blood pressure, serum urea, creatinine, sodium, and albumin concentrations.

Supplementary figure 1. All-cause mortality at 180 days (A) and all-cause mortality and cardiovascular/renal rehospitalization at 60 days (B) stratified by incident potassium abnormalities during acute HF hospitalization.

5

Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)

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Eur J Heart Fail. 2020 Apr;22(4):713-722.

ABSTRACT

Aims

Inhibition of sodium–glucose co-transporter 2 (SGLT2) reduces the risk of death and heart failure (HF) admissions in patients with chronic HF. However, safety and clinical efficacy of SGLT2 inhibitors in patients with acute decompensated HF are unknown.

Methods and results

In this randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study, we randomized 80 acute HF patients with and without diabetes to either empagliflozin 10 mg/day or placebo for 30 days. The primary outcomes were change in visual analogue scale (VAS) dyspnoea score, diuretic response (weight change per 40mg furosemide), change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of stay. Secondary outcomes included safety and clinical endpoints. Mean age was 76 years, 33% were female, 47% had *de novo* HF and median NT-proBNP was 5236 pg/mL. No difference was observed in VAS dyspnoea score, diuretic response, length of stay, or change in NT-proBNP between empagliflozin and placebo. Empagliflozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo [4 (10%) vs. 13 (33%); $P = 0.014$]. Urinary output up until day 4 was significantly greater with empagliflozin vs. placebo [difference 3449 (95% confidence interval 578–6321) mL; $P < 0.01$]. Empagliflozin was safe, well tolerated, and had no adverse effects on blood pressure or renal function.

Conclusions

In patients with acute HF, treatment with empagliflozin had no effect on change in VAS dyspnoea, diuretic response, NT-proBNP, and length of hospital stay, but was safe, increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days.

INTRODUCTION

Multiple randomized clinical trials indicated that sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce the risk for heart failure (HF) hospitalization in patients with type 2 diabetes.^{1–4} Although only a minority of patients included in these trials had pre-existing HF, the results showed the potential to also improve outcomes in patients with established HF.^{3,5–8} Beneficial effects in patients with established chronic HF were shown in a recent trial where the SGLT2 inhibitor dapagliflozin reduced the risk of death and HF admissions in patients with established chronic HF with a reduced ejection fraction (HFrEF), either with or without diabetes.⁹ These beneficial effects are at least partly explained by the diuretic/natriuretic effects of SGLT2 inhibitors, although other mechanisms such as direct cardiometabolic and renal enhancing effects have been proposed as well.^{10–12}

Acute (decompensated) HF is one of the leading causes of hospital admissions worldwide with a post-discharge mortality and rehospitalization risk as high as 20–30% within the first 3 to 6 months. Unlike chronic HF, there is no established therapy available that improves clinical outcome in acute HF.¹³ Despite treatment with loop diuretics, many are discharged with residual congestion, which is related to an even higher risk of early rehospitalization and death.¹⁴ Renal failure and worsening renal function in patients with acute HF are common and related to an impaired outcome when diuretic response is poor.^{15,16} Based on both the promising pharmacological profile of the SGLT2 inhibitor empagliflozin and the demonstrated benefits on HF and renal outcomes, we hypothesized that empagliflozin exerts positive effects in patients admitted with acute HF, with or without diabetes mellitus.

METHODS

Study design

EMPA-RESPONSE-AHF was an investigator initiated randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study in subjects admitted for acute (decompensated) HF. Patients with and without type 2 diabetes mellitus could participate. A total of 80 eligible subjects were randomized in a 1:1 ratio to receive

either empagliflozin 10 mg/day or matched placebo. A blocked randomization was used (size 4), with stratification by study site. Investigators used a web-based randomization system to determine treatment assignment. The trial was executed in five cardiology centres in the Netherlands (online supplementary *Appendix S1*). The trial was approved by the ethics committee at each study centre and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All participating patients provided written informed consent. This trial was registered with ClinicalTrials.gov, number NCT03200860.

Patient population

Eligible patients were male or female aged >18 years who were hospitalized for acute HF, defined as all of the following: (i) dyspnoea at rest or with minimal exertion, (ii) signs of congestion, such as oedema, rales, and/or congestion on chest radiograph, (iii) brain natriuretic peptide (BNP) ≥ 350 pg/mL or N-terminal pro BNP (NT-proBNP) ≥ 1400 pg/mL (for patients with atrial fibrillation: BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL), and (iv) treated with loop diuretics at screening. Patients needed to have an estimated glomerular filtration rate (based on the Chronic Kidney Disease Epidemiology Collaboration formula¹⁷) ≥ 30 mL/min/1.73m² between presentation and randomization. Exclusion criteria were: (i) type 1 diabetes mellitus, (ii) dyspnoea primarily due to non-cardiac causes, (iii) cardiogenic shock, (iv) acute coronary syndrome within 30 days prior to randomization, (v) planned or recent percutaneous or surgical coronary intervention within 30 days prior to randomization, (vi) signs of ketoacidosis and/or hyperosmolar hyperglycaemic syndrome (pH > 7.30 and glucose > 15 mmol/L and HCO₃ > 18 mmol/L), (vii) pregnant or nursing (lactating) women, (viii) current participation in any interventional study, (ix) inability to follow instructions or comply with follow-up procedures, (x) any other medical conditions that would put the patient at risk or influence study results in the investigator's opinion, or that the investigator deemed unsuitable for the study.

Patients were randomized within 24 h of presentation to the hospital. After informed consent, patients were randomly assigned to one of the treatment groups and received the assigned (blinded) therapy after baseline assessment, which included assessment of HF signs and symptoms, visual analogue scale (VAS) dyspnoea score,

vital signs, demographics, and urine and plasma sampling. During 4 days following randomization, patients were evaluated daily per protocol and included evaluation of HF signs and symptoms, vital signs, weight, laboratory assessments (including NT-proBNP at day 4), plasma and urine sampling and assessment of adverse events (AE). Three of four primary outcome measures (VAS dyspnoea score, NT-proBNP, diuretic response) were assessed at day 4. If a patient was discharged before day 4, assessment took place outside the hospital at day 4. Randomized treatment was continued through day 30, when a study visit was carried out and assessments were repeated. Patients were followed until day 60 for AE, and the study was concluded by a telephone call at day 60 to assess AE and vital status.

Study endpoints

The primary endpoints of this study were (i) change in dyspnoea, VAS from baseline to day 4, (ii) diuretic response (defined as Δ weight kg/[$(\text{total intravenous dose})/40\text{mg}] + [(\text{total oral dose})/80\text{mg}]$ furosemide or equivalent loop diuretic dose) through day 4, (iii) length of initial hospital stay, and (iv) percentage change in NT-proBNP from baseline to day 4.¹⁸

Secondary endpoints of the study included worsening HF (defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy for HF or mechanical ventilatory, renal or circulatory support), all-cause death and/or HF readmission through day 30 and through day 60 as part of AE assessment.

Safety endpoints included (i) AE (general), (ii) AE that lead to treatment discontinuation, (iii) serious AE (which could include a secondary endpoint), (iv) AE of special interest (AESI), including hepatic injury, worsening renal function, metabolic acidosis, ketoacidosis and diabetic ketoacidosis (online supplementary *Methods S1*).

Randomized treatment was required to be discontinued per protocol if systolic blood pressure dropped below 90mmHg or decreased below 100mmHg with signs/symptoms of hypotension, or signs of ketoacidosis and/or hyperosmolar hyperglycaemic syndrome, or any increase in serum creatinine >50%. Treating physicians were encouraged to reinstitute randomized treatment after resolution of the above mentioned criteria.

Statistical analysis

Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD), on-normally distributed variables as median and 25th–75th percentile. Categorical variables are presented as numbers (percentage). Power calculation was based on capturing the primary outcome measures in the placebo group with a degree of certainty. With 40 patients in the control group, a given mean continuous response can be estimated within ± 0.2 SD with 80% confidence intervals (CI). We estimated the following mean responses for the primary outcome measures (in the placebo group):

1. Change in VAS dyspnoea score: $1756 \pm 2353 \text{ mm} \times \text{h}$ at day 4.
2. Diuretic response [of $0.56 \pm 0.78 \text{ kg/40mg furosemide}$ (or equivalent)] at day 4.
3. Length of stay 9.6 to 10.5 days (± 9.1).
4. Percentage change in NT-proBNP 24 (-1.0 – 88.7)% (SD 67%) at day 4.

Consequently, 40 patients per group would provide approximately 80% power to detect standardized mean treatment differences of approximately 0.48 SDs at the two-sided 20% significance level for this pilot study. The difference in change in dyspnoea VAS from baseline to day 4 was assessed by comparing the area under the curve (AUC) of change in VAS dyspnoea score by Student's *t*-test. To do so, individual changes in VAS score were visualized (virtually) as a curve where the x-axis shows study day baseline to day 4, and y-axis shows VAS score. Using this approach, AUC for each study day (trapezoids) can be calculated, and added together, resulting in an overall VAS AUC score ($\text{mm} \times \text{h}$) that can be compared across treatment groups.¹⁹ Difference in diuretic response and percentage change in NT-proBNP at day 4 was assessed by Student's *t*-test. Difference in length of stay was assessed by Wilcoxon rank-sum test. All analyses were carried out in the full analysis set based on the intention-to-treat principle where all randomized patients were analysed. As this was an exploratory study with limited power, all four individual primary endpoints were tested separately, with no formal correction for multiplicity. Only as a sensitivity analysis, if at least two out of four primary endpoints showed significant difference in the same direction (favouring either investigational drug or placebo), a Bonferroni correction would be applied ($P < 0.05$).

Figure 1: Consort Diagram

ACS, acute coronary syndrome; AHF, acute heart failure; eGFR, estimated glomerular filtration rate; HHS, hyperosmolar hyperglycaemic syndrome; NP, natriuretic peptide; NT-proBNP, N-terminal pro brain natriuretic peptide; VAS, visual analogue scale.

As an exploratory analysis, and for graphical presentation, individual responses to the above-mentioned endpoints were standardized. This was done by dividing the difference from the overall mean (or log transformed mean if non-normally distributed) of each endpoint by the overall SD of that variable, which generates a z-score. The treatment effect can then be measured by the mean difference of standardized z-scores, which was visually presented on a forest plot by mean $\pm$ 80% CI (given $P < 0.2$).

Then, all four standardized scores for each individual endpoints were averaged, and mean treatment difference and associated 95% CI for this overall treatment effect visually presented. Statistical analysis for the treatment difference was carried out by Student's *t*-test. Two tailed *P*-values <0.2 were considered statistically significant for the (exploratory) primary endpoints with 80% CI. Statistical analyses were performed using STATA SE 12.0 (Stata Corp., College Station, TX, USA).

RESULTS

Patients

From December 2017 through July 2019 patients were enrolled at five centres in the Netherlands. The CONSORT diagram of this study is presented in *Figure 1*. A total of 80 patients were randomized (41 to empagliflozin and 39 to placebo). One patient randomized to empagliflozin withdrew informed consent, leaving 40 empagliflozin and 39 placebo patients for our analyses. *Table 1* shows the baseline characteristics in the two groups. Mean age of the patients was 76 years, 33% were female, 47% had *de novo* acute HF, mean left ventricular ejection fraction was 36%, and median NT-proBNP was 5236 pg/mL. One third of patients had type 2 diabetes mellitus. Groups were reasonably well-balanced, although patients in the empagliflozin group were older, more often female and had lower NT-proBNP levels.

Table 1. Baseline characteristics

Variable	Randomized Treatment		P-value
	Empagliflozin	Placebo	
N	40	39	
Age	79 (73 – 83)	73 (61-83)	0.14
Females (N (%))	16 (40)	10 (26)	0.17
Caucasian race (%)	100	95	0.15
Body weight at baseline (kg)	87 ± 23	83 ± 20	0.42
SBP (mmHg)	127 ± 22	121 ± 25	0.25
DBP (mmHg)	76 ± 15	72 ± 15	0.27
HR (mmHg)	83 ± 19	80 ± 23	0.50
Respiratory rate (breaths/min)	19 ± 4	20 ± 5	0.60
NYHA class (% III/IV)	92	97	0.57

Table 1. (Continued)

Variable	Randomized Treatment		P-value
	Empagliflozin	Placebo	
LVEF if known (%) (n =46)	36 ± 17	37 ± 14	0.87
De Novo acute HF (%)	48	46	0.90
Ischemic aetiology (%)	28	29	0.89
Medical History (%)			
Myocardial infarction	30	38	0.43
Hypertension	68	56	0.31
Atrial fibrillation/flutter	78	64	0.19
Diabetes mellitus type II	38	28	0.38
Cerebrovascular accident	5	5	0.98
COPD	28	26	0.85
Cancer	38	13	0.012
Medical Therapy (%)			
ACEi	40	47	0.51
ARB	5	3	0.45
Beta-blocker	70	66	0.69
MRA	48	45	0.81
Loop diuretic	100	100	NA
ICD	8	23	0.054
CRT	15	13	0.78
Laboratory at Baseline			
NT-proBNP (pg/mL)	4406 (2873-6979)	6168 (3180-10489)	0.14
Serum creatinine (µmol/L)	114 ± 34	116 ± 33	0.72
eGFR (mL/min/1.73m ²)	55 ± 18	55 ± 18	0.97
Sodium (mmol/L)	135 ± 17	135 ± 5	0.99

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

Primary outcome

Results of the primary endpoints are presented in *Figure 2*. The AUC of the change in dyspnoea VAS over the first 4days was $1264 \pm 1211\text{mm} \times \text{h}$ in the

empagliflozin group vs. $1650 \pm 1240 \text{ mm} \times \text{h}$ in the placebo group ($P = 0.18$). Diuretic response through day 4 was -0.35 ± 0.44 kg/40mg furosemide equivalents in the empagliflozin group vs. -0.12 ± 1.52 kg/40 mg furosemide equivalents in the placebo group ($P = 0.37$). Percentage change in NT-proBNP through day 4 was $-46 \pm 32\%$ in the empagliflozin group vs. $-42 \pm 31\%$ in the placebo group ($P = 0.63$). Length of hospital stay was 8 (6–10) days in the empagliflozin group vs. 8 (6–9) days in the placebo group ($P = 0.58$). There were no differences in the primary outcome measures in subgroups of *de novo* vs. decompensated HF.

A summary of the four endpoints, standardized by z-scores, are presented in *Figure 3*. The overall combined z-score was not significantly different between empagliflozin and placebo (mean difference -0.019 , 95% CI -0.306 to 0.269 ; $P = 0.90$).

Figure 2: Primary endpoints

A) Change in VAS Dyspnea, B) Diuretic Response, C) Percentage change in NT-proBNP, D) Length of stay. Error bars represent 80% confidence intervals for B and C.

AUC: Area Under the Curve, VAS: Visual Analogue Scale, NTproBNP: N Terminal Pro Brain Natriuretic Peptide, SD: Standard Deviation

Figure 3. Z-score presentation of primary endpoints and combined z-score

CI: Confidence Interval, VAS: Visual Analogue Scale, NTproBNP: N Terminal Pro Brain Natriuretic Peptide, SD: Standard Deviation

Secondary and exploratory analyses

Figure 4 shows the incidence of in-hospital worsening HF, death, and/or HF hospital readmission. A combined endpoint of in-hospital worsening HF, rehospitalization for HF or all-cause death at 60 days occurred in 4 patients (10%) in the empagliflozin group vs. 13 patients (33%) in the placebo group ($P = 0.014$). Online supplementary Table S1 provides the data for the individual components. There was a greater, but not statistically different, drop in diastolic blood pressure in the empagliflozin treated patients, similar reductions in systolic blood pressure and heart rate, and no differences in renal function were demonstrated up until day 4 (online supplementary Figure S1). Patients randomized to empagliflozin more often had a diuretic response better than 0.4 kg decrease/40 mg furosemide equivalent compared with placebo (42% vs. 24%, $P = 0.14$).

Figure 4. Clinical events

HF: Heart failure, WHF: Worsening heart failure

In a subset of patients, urinary output and net fluid loss were available. The effects of empagliflozin on urinary output and net fluid balance are presented in *Figure 5*. At day 1, there was a significantly greater urine output with empagliflozin (3442 ± 1922 mL) compared with placebo (2400 ± 993 mL) ($P = 0.013$; $n = 58$). Net fluid loss at day 1 was also greater with empagliflozin (-2163 ± 1896 mL) compared with placebo (-1007 ± 1049 mL) ($P = 0.009$; $n = 53$). After 4 days, the difference in cumulative urine output (3449 , 95% CI 578 – 6321 mL; $n = 28$) was significantly greater ($P = 0.02$), whereas net fluid loss with empagliflozin was greater (2701 , 95% CI -586 to 8988 mL, $n = 25$; $P = 0.10$). Weight change after 4 days was -2.83 ± 3.15 kg in the empagliflozin group vs. -2.30 ± 3.26 kg in the placebo group ($P = 0.48$). Median loop diuretic dose (re-calculated to furosemide) through day 4 was 320 (194 – 466) mg furosemide in the empagliflozin group and 300 (200 – 500) mg furosemide in the placebo group ($P = 0.94$).

Figure 5. Urinary output and net fluid balance through day 4

A) Cumulative Urine Output, B) Cumulative Net Fluid balance

CI: Confidence Interval

Safety

Safety data are presented in *Table 2*. The incidence rates of AE were similar in subjects treated with placebo or empagliflozin. Patients randomized to empagliflozin had significantly lower number of cardiovascular AE compared with placebo (9 vs. 17 events, $P = 0.046$). This was mostly due to more frequent worsening HF events in the placebo group. We did not find an excess in urinary tract infections or other adverse effects with the use of empagliflozin. There were 8 serious adverse events in the empagliflozin group vs. 11 in the placebo group ($P = 0.54$). The causes of these events are listed in online supplementary *Table S2*. Overall, seven patients in the empagliflozin group and five patients in the placebo group discontinued study medication due to AE ($P = 0.36$) (online supplementary *Table S3*). There was no difference in the occurrence of AESI. Four patients (10%) in the empagliflozin and three patients (8%) in the placebo group developed a worsening renal function AESI ($P = 0.74$), while one patient with type 2 diabetes in the placebo group experienced diabetic ketoacidosis (online supplementary *Table S4*). There was no sign that empagliflozin was associated with more renal events as the renal/urinary AE rate was similar, and the occurrence of worsening renal function or acute kidney injury was also not different between treatment groups. Online supplementary *Table S5* lists all individual AE.

Table 2. Adverse Events

Adverse event	Empagliflozin (n = 40)	Placebo (n = 39)	P-value
Overall	55	63	
Cardiovascular	9 (23)	17 (44)	0.046
Respiratory	3 (8)	2 (5)	0.67
Gastro Intestinal	6 (15)	9 (23)	0.36
Psychiatric	0 (0)	1 (3)	0.31
Renal/Urinary	15 (38)	13 (33)	0.70
Reproductive	0 (0)	0 (0)	NA
Metabolic	9 (23)	9 (23)	0.95
Musculoskeletal	5 (13)	5 (13)	0.97
Thromboembolic	1 (0)	0 (0)	NA
Infectious	1 (3)	0 (0)	0.32
Other	6 (15)	7 (18)	0.72

NA, not applicable.

First events in a category in an individual patient are shown as n (%).

DISCUSSION

In this randomized, double-blind, placebo-controlled, multicentre pilot study on the safety and efficacy of empagliflozin in patients with acute (decompensated) HF, change in VAS dyspnoea, reduction in NT-proBNP, diuretic response (weight loss per 40 mg furosemide) and length of hospital stay were similar with empagliflozin and placebo. Empagliflozin increased cumulative urinary volume and net fluid balance in a subset of patients. Importantly, empagliflozin appeared to be safe and well tolerated, without major effects on heart rate and blood pressure. Finally, we observed significantly fewer deaths, in-hospital worsening of HF and/or HF readmissions through day 60. As far as we know, this is the first randomized, double-blind, placebo-controlled trial on the effects of a SGLT2 inhibitor in patients with acute HF. SGLT2 inhibitors were originally designed as glucose-lowering agents for glycaemic control. In four large randomized controlled trials in patients with diabetes, SGLT2 inhibitors consistently reduced cardiovascular events, and HF hospitalizations in particular. These data prompted the design of large phase III clinical trials on the effects of SGLT2 inhibitors in patients with established chronic HF, irrespective of whether they had diabetes or not.^{20,21} Recently, main results of

the first trial, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), were presented and published.⁹ In 4474 patients with HFrEF with and without diabetes, dapagliflozin reduced the risk of a composite endpoint of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death. These effects were accompanied by an improvement of quality of life. These beneficial effects of dapagliflozin in patients with HFrEF on quality of life were recently confirmed in a smaller study.²² Until now, no data on the effects of SGLT2 inhibitors in patients admitted with acute HF, irrespective of left ventricular ejection fraction and diabetes status, have been available. In the present study, we could not show any significant differences for the primary endpoints between empagliflozin and placebo. First, despite both a significantly greater urinary output and a more negative net fluid balance, there was no reduction in dyspnoea, as recorded by a VAS. Second, we did not observe an improvement in diuretic response, defined as weight change per 40mg of furosemide (or equivalent dose of another loop diuretic).¹⁸ This endpoint was chosen to correct for a decreased use of loop diuretic when symptoms had recovered more quickly in the empagliflozin treated patients. However, symptoms in hospital did not recover more quickly and diuretic use during the first 4 days were similar in both groups. Thirdly, although we observed an expected large drop in NT-proBNP in the first days of hospital admission in all patients, we did not demonstrate a greater drop in patients treated with empagliflozin. These findings are similar to a recent study with dapagliflozin in patients with chronic HFrEF.²²

Finally, length of hospital stay was not shortened by empagliflozin, probably since it may be determined by multiple factors other than those specifically related to improvement in HF, particularly in an elderly, fragile, high-risk patient cohort such as included in this study. We observed a significant reduction of a combined endpoint of in-hospital worsening HF, death and/or hospital readmission through day 60. However, these data should be interpreted with caution for two major reasons. Firstly, this study was not powered and not designed to show an effect on clinical endpoints, and the number of events is very low. Secondly, there was no significant reduction in the pre-defined secondary endpoint of death and/or hospital readmission within 30 days. Nevertheless, the reduction in clinical endpoints is consistent with previous morbidity and mortality benefits for SGLT2

inhibitors in diabetes and in line with results of the DAPA-HF trial in patients with chronic HFrEF.⁹ If anything, our results suggest this novel HF treatment can safely be initiated in a high-risk population of acute HF patients and should pave the way for larger studies. Although loop diuretics and nitrates (in selected patients) remain the mainstay of the treatment of acute HF, several drugs have been investigated but failed to improve clinical outcomes in patients with acute HF. Most of these investigational drugs had significant effects on blood pressure and/or renal function.^{23–25} However, in our small pilot study, we did not find any clinically relevant effect on blood pressure, heart rate, or renal function. In addition, empagliflozin drug was safe and well tolerated with less AE than in placebo treated patients. Specifically, empagliflozin therapy was not associated with more frequent worsening of renal function or renal AE. Finally, we found a remarkable effect on urinary output and net fluid balance. These findings strongly support an incremental diuretic effect with empagliflozin treatment, which has not been previously shown in patients with HF. The disconnect between this increase in diuresis, without an effect on symptoms or markers of volume overload is probably related to the limited correlation between these variables in clinical practice. Whether the beneficial effects of SGLT2 inhibitors on clinical outcomes in patients with HFrEF are related to their diuretic effect or whether they are mediated via other pathways where SGLT2 inhibitors exert their actions remains to be established.

Limitations

This study has several limitations. First and foremost, this study is limited by the number of patients and should be considered as a pilot study. The results of this study should therefore be interpreted with caution. Secondly, we screened many more patients than were included in the study due to different reasons. Although for this reason the generalizability of the finding to the average acute HF patient can be questioned, the characteristics of our patients included suggest it represents the phenotype of acute HF patients currently admitted. Thirdly, the number of missing urinary collections and fluid intake limits the interpretability of the data on urinary output and net fluid loss, although an effect was already observed after 24 h. Finally, there was no standardized protocol for in-hospital treatment of acute HF and no protocol for diuretic therapy, which means individual differences in the treatment of these patients may have impacted the results.

Conclusion

In this randomized, double-blind, placebo-controlled pilot study in patients with acute (decompensated) HF, empagliflozin was safe and well tolerated, but did not improve dyspnoea, NT-proBNP, diuretic response and length of hospital stay. However, empagliflozin was associated with greater urinary output and a reduction in a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days. Larger randomized clinical trials with SGLT2 inhibitors are greatly needed to further study the possible beneficial role of SGLT2 inhibitors in patients with acute HF.

Acknowledgements

The authors wish to thank Prof. W.H. van Gilst, PhD, Prof. R.T. Gansevoort, MD, PhD, and Prof. J.G.P. Tijssen, PhD, for being part of the Data Safety Monitoring Board of the EMPA-RESPONSE-AHF study.

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SUPPLEMENTARY MATERIAL

Appendix S1. EMPA-RESPONSE-AHF site list and investigators

Overall study Principle Investigators:

- Prof dr. A.A. Voors
- Prof dr. H.J. Lambers Heerspink

Sites

- 1) University Medical Center Groningen
Investigator: Dr. K. Damman
Inclusion: 55
- 2) Antonius Ziekenhuis Sneek
Investigator: Dr. H.P. Swart
Inclusion: 10
- 3) TREANT ziekenhuisgroep
Investigator: Dr. T.D.J. Smilde
Inclusion: 7
- 4) ISALA klinieken Zwolle
Investigator: Dr. A. Elvan
Inclusion: 3
- 5) Jeroen Bosch Ziekenhuis Den Bosch
Investigator: Dr. J.W.M. van Eck
Inclusion: 5

Methods S1. AESI Definitions

• Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- An elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample
- An isolated elevation of ALT and/or AST ≥ 5 fold ULN

These laboratory findings constitute a hepatic injury alert and the patients showing these abnormalities need to be followed up according to medical abnormalities need to be followed up according to medical judgement.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test.

- **Worsening Renal Function**

either defined by:

- drop in eGFR below ($<$) 20 mL/min/1.73m² in the first 5 days of randomized treatment

or

- A serum creatinine value showing > 2 fold increase from baseline and is above the ULN.

For the AESI “Worsening renal function” the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as judged clinically necessary and initiate follow-up laboratory test of creatinine according to medical judgement. Additionally, the Investigator shall provide information on the medical handling of the AESI, including changes in concomitant treatment.

- **Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)**

In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA).

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgement should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in the table below.

Table: Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

* Nitroprusside reaction method

** Calculation: $2[\text{measured Na (mEq/L)} + \text{glucose (mg/dL)}]/18$

*** Calculation: $(\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-)$ (mEq/L)

Figure S1. Changes in vitals and serum creatinine

Table S1. Cardiovascular outcome

Cardiovascular Outcome	Empagliflozin	Placebo	P-value
Overall	40	39	
Worsening Heart Failure, n (%)	1 (2.5)	5 (12.8)	0.11
30 day mortality, n (%)	1 (2.5)	1 (2.6)	0.75
60 day mortality, n (%)	1 (2.5)	3 (7.7)	0.36
60 day HF rehospitalization, n (%)	2 (5.0)	5 (12.8)	0.26
60 day mortality or HF rehospitalization, n (%)	3 (7.5)	8 (20.5)	0.12
60 day HF rehospitalization or WHF, n (%)	3 (7.5)	10 (25.6)	0.037
60 day mortality or HF rehospitalization or WHF, n (%)	4 (10.0)	13 (33.3)	0.014

Mortality is all cause mortality. WHF: Worsening heart failure to Day 5 post randomization (or discharge if earlier), defined as worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilatory, renal or circulatory support.)

Table S2. Serious adverse events

Adverse Event	Empagliflozin	Placebo	P-value
Overall	8	11	0.54
WHF	3 (8)	4 (10)	
WRF	1 (3)	0 (0)	
AKI	1 (3)	0 (0)	
Angioedema	1 (3)	0 (0)	
Hypovolemic Shock	0 (0)	1 (3)	
Delirium	0 (0)	1 (3)	
Heart Failure	0 (0)	1 (3)	
Atrial Fibrillation	0 (0)	1 (3)	
S. Aureus bacteriemia	1 (3)	0 (0)	
Syncope	1 (3)	1 (3)	
Respiratory Failure	0 (0)	1 (3)	

All serious adverse events counted, multiple similar events in one patient possible

AKI: Acute Kidney Injury, WHF: Worsening Heart Failure, WRF: Worsening Renal Function

Table S3. Adverse events leading to treatment discontinuation

Adverse Event	Empagliflozin	Placebo	P-value
Overall	7	5	0.36
WRF	1 (3)	1 (3)	
AKI	1 (3)	0 (0)	
Angioedema	1 (3)	0 (0)	
HHS	1 (3)	0 (0)	
Itching	1 (3)	0 (0)	
Ketoacidosis	0 (0)	1 (3)	
Nausea	0 (0)	2 (5)	
Noro virus	1 (3)	0 (0)	
Syncope	1 (3)	0 (0)	
Urinary Tract Infection	0 (0)	1 (3)	

AKI: Acute Kidney Injury, HHS: hyperosmolar hyperglycemic syndrome, WRF: Worsening Renal Function

Table S4. Adverse events of special interest

AESI	Empagliflozin	Placebo	P-value
Overall	4	4	0.29
Hepatic	0 (0)	0 (0)	NA
Renal	4 (10)	3 (8)	0.74
DKA	0 (0)	1 (3)	0.30

AESI: Adverse Event of Special Interest, DKA: Diabetic Keto Acidosis

Table S5. List of all adverse events according to treatment

Adverse Event (n (%))	Empagliflozin	Placebo
Acute Kidney Insufficiency	1 (3)	0 (0)
Anemia	1 (3)	2 (5)
Angioedema	1 (3)	0 (0)
Aortic Valve Stenosis	0 (0)	1 (3)
Atrial Fibrillation	0 (0)	2 (5)
Barrett Esophagus	0 (0)	1 (3)
Bursitis	1 (3)	1 (3)
Chest Pain	2 (5)	0 (0)

Table S5.(Continued)

Adverse Event (n (%))	Empagliflozin	Placebo
Cough	1 (3)	0 (0)
Coughing	1 (3)	0 (0)
Cramp In Hands	0 (0)	1 (3)
Cramp In Legs	2 (5)	1 (3)
Creatinine Increase	3 (8)	3 (8)
Cystitis	1 (3)	0 (0)
Dehydration	1 (3)	0 (0)
Delirium	0 (0)	1 (3)
Disorientated	1 (3)	0 (0)
Diarrhoea	0 (0)	3 (8)
Dizziness / Light-headedness	2 (5)	0 (0)
Dry Mouth	1 (3)	0 (0)
Fallen Out Of Bed	1 (3)	0 (0)
Fatigue	0 (0)	1 (3)
Phlebitis	1 (3)	0 (0)
Gout	1 (3)	1 (3)
Haematuria	2 (5)	1 (3)
High Hco3	0 (0)	2 (5)
High Urea	0 (0)	1 (3)
Hyperglycaemia	1 (3)	0 (0)
Hyperkalaemia	0 (0)	1(3)
Hyperosmolar Hyperglycaemic Syndrome	3 (8)	0 (0)
Hypokalaemia	4 (10)	5 (13)
Hyponatremia	1 (3)	0 (0)
Hypotension	2 (5)	3 (8)
Hypovolemic Shock	0 (0)	1 (3)
Incident Tremor	0 (0)	1 (3)
Increased (Right) Cardiac Pressures	0 (0)	1 (3)
Increased CRP	0 (0)	1 (3)
Inflammation Spleen	1 (3)	0 (0)
Irregular Heartbeat	0 (0)	1 (3)
Ischemic Heart Failure	1 (3)	0 (0)
Itching	1 (3)	0 (0)
Ketoacidosis	0 (0)	1 (3)
Low Blood Pressure	0 (0)	2 (5)
Lower Back Pain	1 (3)	2 (5)

Table S5.(Continued)

Adverse Event (n (%))	Empagliflozin	Placebo
Mandibular Sensory Loss	0 (0)	1 (3)
Nausea	3 (8)	4 (10)
Nausea/Vomiting	2 (5)	2 (5)
Noro Virus	1 (3)	0 (0)
NT-proBNP Increase	1 (3)	0 (0)
Obstipation	1 (3)	1 (3)
Occasional Hypersensitivity/Swelling Cheek	1 (3)	0 (0)
Pain Due To Catheter	1 (3)	0 (0)
Pain Right Wrist	0 (0)	1 (3)
Painful Hip	1 (3)	0 (0)
THI Procedure	0 (0)	1 (3)
Respiratory Failure	0 (0)	1 (3)
Respiratory Tract Infection	1 (3)	1 (3)
S. aureus Bacteraemia	1 (3)	0 (0)
Serious Collapse	1 (3)	1 (3)
Sideropenia	0 (0)	1 (3)
Significant Lactate Change	0 (0)	1 (3)
Symptomatic Hypotension	1 (3)	0 (0)
Systemic Amyloidosis	0 (0)	1 (3)
Thrombus After Transurethral Resection Bladder Tumour	1 (3)	0 (0)
Traumatic Supraspinatus Rupture	0 (0)	1 (3)
Two-Vessel Disease	0 (0)	1 (3)
Urea Increase	5 (13)	7 (18)
Urinary Tract Infection	1 (3)	1 (3)
Ventricular Tachycardia	0 (0)	1 (3)
Worsening Heart Failure	3 (8)	10 (26)
Worsening Renal Function	4 (10)	5 (13)

Patients with multiple similar events are counted once, while different events in a single patient are represented in each category.

6

Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure

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Eur J Heart Fail. 2021 Jan;23(1):68-78.

ABSTRACT

Aims

Sodium-glucose cotransporter-2 (SGLT2) inhibitors improve clinical outcome in patients with heart failure (HF), but the mechanisms behind their beneficial effects are not yet fully understood. We examined the effects of empagliflozin on renal sodium and glucose handling in patients with acute HF.

Methods and results

This study was a predefined sub-study of a double-blind, randomized, placebo-controlled, multicenter study (EMPA-RESPONSE-AHF). Patients were allocated within 24 hours of an acute HF admission to either empagliflozin 10 mg/day (n=40) or placebo (n=39) for 30 days. Markers of glucose and sodium handling were measured daily during the first 96 hours and at day 30.

Patients were 76 (range 38-89) years old and 33% had diabetes. The use of loop diuretics during the first 96 hours was similar in both groups. Empagliflozin increased fractional glucose excretion with a peak after 24 hours (21.8 vs 0.1%; $P<0.001$), without affecting plasma glucose concentration, while fractional sodium and chloride excretion and urinary osmolality remained unchanged (P for all >0.3). However, empagliflozin increased plasma osmolality (delta osmolality at 72 hours: 5 ± 8 versus 2 ± 5 mOsm/kg; $P=0.049$). Finally, there was an early decline in eGFR with empagliflozin versus placebo (-10 ± 12 vs. -2 ± 12 mL/min/1.73m² $P=0.009$), which recovered within 30 days.

Conclusion

In patients with acute HF, empagliflozin increased fractional glucose excretion and plasma osmolality, without affecting fractional sodium excretion or urine osmolality and caused a temporary decline in eGFR. This suggests that empagliflozin stimulates osmotic diuresis through increased glycosuria rather than natriuresis in patients with acute HF.

Graphical abstract

Graphical representation of changes in urinary and plasma volume and osmolality. As more glucose is excreted as a result of sodium-glucose co-transporter 2 (SGLT2) inhibition, more water is drawn to the urine keeping osmolality constant. As a result of increased electrolyte free water excretion, plasma osmolality is moderately increased and total volume of plasma and interstitial fluid is decreased.

INTRODUCTION

In patients with diabetes and/or chronic kidney disease, sodium glucose cotransporters-2 (SGLT2) inhibitors consistently showed beneficial effects on cardiovascular outcomes and particularly on HF hospitalizations.¹⁻⁴ Recently one larger randomized clinical trial demonstrated that dapagliflozin reduced cardiovascular death and HF hospitalizations in patients with established chronic HF with reduced ejection fraction (HFrEF) with and without diabetes.⁵ A post-hoc analysis showed that treatment with dapagliflozin was safe and effective regardless of diuretic use or dose.⁶ The beneficial effects of SGLT2-inhibitors on HF outcomes have been attributed to cardiometabolic and renal protective qualities, as well as to its diuretic properties. These were even described in chronic 'stable' euvolemic HF.⁶⁻⁸ In acute HF, we recently showed that early addition of empagliflozin to standard diuretic treatment increased cumulative diuresis after 4 days with a possible reduction in HF related events.⁹ However the mechanisms behind increased diuresis of SGLT2 inhibitors in acute HF are unknown.^{10,11} In the present mechanistic study, we investigated the effect of SGLT2 inhibition on renal function, and urinary sodium, chloride and glucose excretion in acute HF patients randomized to either empagliflozin or placebo.

METHODS

Patients

The present study is a predefined analysis of the EMPA-RESPONSE-AHF trial of which the rationale and main results have been published recently.⁹ In short, EMPA-RESPONSE-AHF was a double-blind, placebo-controlled multicenter pilot study enrolling 79 patients in 5 centers in the Netherlands, on the safety and efficacy of empagliflozin in patients with acute HF. Within 24 hours of hospital admission, patients were randomized 1:1 to either empagliflozin 10 mg (for 30 days) (n=40) or matching placebo (n=39). The trial was approved by the ethics committee at each study center and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients participating in the trial provided written informed consent.

Biomarkers

Spot urine and plasma samples were collected at baseline, daily during the first 96 hours of hospitalization and after 30 days. Serum sodium, glucose, and creatinine and spot urinary creatinine and sodium were measured as part of safety monitoring and were analyzed according to procedures of the local laboratories of each participating hospital. Urinary glucose, chloride and osmolality were measured at a central laboratory in the University Medical Center Groningen (UMCG) in frozen samples. All samples were stored at -80°C within 2 hours of collection and thawed before analysis. Urinary glucose was measured only after database lock to ensure maintenance of the double-blind nature of the trial. Urinary chloride and potassium were measured using ISE indirect reagents for COBAS C, the measuring range for potassium is 3-100 mmol/L with an analytical variation of <5%, the measuring range for chloride is 20-250 mmol/L, with an analytical variation of <5%. Urinary glucose was measured using the GLUC3 pack for COBAS C, the measuring range for urinary glucose is 0.11-249.6 mmol/L (normal range: 0.06-0.83 mmol/L), with a variation of ~1%. Urinary osmolality, the total number of solute particles (or osmoles) per kilogram of fluid, was both measured and calculated in order to gain insight in the constituents of urine osmolality. Urine osmolality was measured using an automatic freezing point depression osmometer (Osmo Station OM-6050, ARKRAY), with a measuring range of 0-2000 mOsm/kg and an analytical variation of <1%. Between measurements tubes were capped to prevent evaporation.

Aldosterone concentrations were measured using the Aldosterone RIA kit by MT diagnostics. Renin concentrations were measured using the Renin Kit III by Cis Bio International. Aldosterone and renin measurements were performed in the Pharmacology laboratory of the Erasmus Medical Centre Rotterdam.

Calculation of urinary osmolality was done according to the following formula: $\text{osmolality} = 2 * [\text{Na}^+] + 2 * [\text{K}^+] + [\text{Glucose}] + [\text{Urea}]$, with all concentrations being concentrations of molecules in urine. The same formula was used to calculate plasma osmolality. All fractional excretion percentages were calculated by a standard formula: $100\% * \text{FE}_x = (\text{U}_x * \text{P}_{\text{creat}}) / (\text{P}_x * \text{U}_{\text{creat}})$, in which U_x is the urinary concentration of the analyte and P_x represents the plasma concentration of the analyte. U_{creat} and P_{creat} represent urinary and plasma concentrations of creatinine, respectively.

In sensitivity analysis, estimated 24-hour urinary sodium excretion was calculated using the earlier defined formula by the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) investigators.¹²

Statistical analysis

Baseline characteristics were explored using a t-test for normally distributed variables and a Mann Whitney U-test for non-normally distributed variables. For further analysis variables were normalized by logarithmic transformation where necessary. The effect of empagliflozin use on changes in clinical outcomes (i.e., eGFR, systolic blood pressure, plasma and urinary osmolality, FeNa, FeCl and FeGlu, renin, aldosterone) during 96h and 30 days were analyzed with repeated measures linear mixed-effect (LME) models, which account for individual variations in changes and intercepts by estimating the random effects for per individual. To correct for their highly skewed nature renin and aldosterone were log-transformed before being analyzed in the linear mixed models. For each clinical variable change from baseline was calculated and used as an outcome in the LME model. We performed a nested model adjusted for baseline values and time. Whereas, for each outcome a second model was performed including baseline values, time, treatment arm and the treatment x time interaction term. Further, we compared the two models: without and with the treatment interaction term using analysis of variance (ANOVA), where a P-value <0.05 was considered significant for a treatment effect during the full treatment period (either 96 h or 30 days depending on the variable). The effect of empagliflozin on changes in outcome at specific time point were considered significant for interaction terms $P < 0.05$. LME models were conducted using the `lme` function in the “nlme” package. All analyses were performed in R studio, version 1.3.959.¹³

RESULTS

Baseline characteristics of the study population have been published elsewhere.⁹ In brief, patients were 76 (range 38-89) years old, 33% were female and median NT-proBNP was 5236 (IQR 3482 – 8276) pg/mL. Background medical treatment at baseline was similar between the groups and there were no differences in loop diuretic doses, vasodilator or inotrope use or guideline recommended HF medication. Baseline estimated glomerular filtration rate (eGFR) was 55 ± 18 mL/min/1.73m², median plasma glucose was 7.8 (IQR 6.2 – 8.9) mmol/L and 33% had a history of type 2 diabetes mellitus. In urine, glucose concentrations at baseline were 0.1 (IQR 0.1 – 0.2) mmol/L, with low fractional glucose excretion (0.1% (IQR 0.1 – 0.1)). In urine, baseline osmolality was 335 (IQR 322 – 380) mOsm/kg, whereas median plasma osmolality was 305 (IQR 302 – 311) mOsm/kg. Before start of randomized treatment but within 24 hours of admission and after initiation of loop diuretic therapy, spot urinary sodium was 99 (IQR 67 – 111) mmol/L, with a fractional sodium excretion of 2.2 (IQR 0.9 – 4.3) %. No between group differences were observed between patients treated with empagliflozin or placebo for any of these baseline variable (Table 1).

Table 1: Baseline characteristics

	Empagliflozin (n=40)	Placebo (n=39)	p-value
Age (years)	79 (73 - 83)	73 (61 - 83)	0.141
Female sex (%)	16 (40)	10 (26)	0.263
Systolic blood pressure (mmHg)	128 $\pm$ 22	121 $\pm$ 25	0.253
eGFR (mL/min/1.73m ²)	53 $\pm$ 18	54 $\pm$ 16	0.824
Plasma osmolality (mOsm/kg)	305 (302 - 309)	305 (302 - 312)	0.691
Urine osmolality (mOsm/kg)	330 (322 - 379)	341 (324 - 384)	0.530
<i>Serum levels of:</i>			
Creatinine (mg/dL)	1.3 $\pm$ 0.4	1.3 $\pm$ 0.4	0.723
Urea (mmol/L)	11.0 (7.5 - 12.8)	9.0 (7.3 - 13.1)	0.916
Sodium (mmol/L)	140 (137 - 142)	140 (138 - 142)	0.806
Potassium (mmol/L)	3.9 (3.5 - 4.2)	3.9 (3.5 - 4.4)	0.406
Glucose (mmol/L)	7.9 (6.2 - 9.6)	7.7 (6.3 - 8.8)	0.323
Renin (pg/mL)	12.4 (4.8 – 63.4)	80.1 (14.0 – 179.3)	0.011
Aldosterone (pg/mL)	182.3 (130.5 – 292.0)	192.7 (114.6 – 344.3)	0.653

Table 1: (Continued)

	Empagliflozin (n=40)	Placebo (n=39)	p-value
<i>Urinary levels of:</i>			
Creatinine (mmol/L)	3.5 (1.9 - 5.5)	3.4 (2.0 - 5.1)	0.944
Urea (mmol/L)	111 (60 - 142)	98 (78 - 140)	0.976
Sodium (mmol/L)	100 (68 - 110)	92 (69 - 112)	0.734
Potassium (mmol/L)	27 (21 - 33)	29 (20 - 41)	0.399
Glucose (mmol/L)	0.2 (0.1 - 0.3)	0.1 (0.1 - 0.2)	0.264
<i>Fractional excretion of (in %):</i>			
Sodium	2.1 (0.9 - 4.1)	2.2 (0.9 - 4.4)	0.964
Glucose	0.1 (0.1 - 0.1)	0.1 (0.0 - 0.1)	0.890

Categorical variables are depicted as N (%), normally distributed variables are depicted as mean $\pm$ SD, non-parametric variables are depicted as median (IQR), abbreviations: eGFR: estimated Glomerular Filtration Rate.

Table 2 shows plasma and spot urinary electrolytes over time, stratified by treatment arm. Empagliflozin significantly decreased spot urinary sodium concentration as compared with placebo. The most pronounced effect was seen after 48 hours (56.2 vs 79.0 mmol/L, $P=0.011$). In contrast, treatment with empagliflozin did not change fractional excretion of sodium (FeNa) at any time point as compared with placebo (Table 2, Figure 1a, $P=0.956$ for ANOVA difference between models with and without treatment interaction), indicating that while net urinary sodium concentration decreases, a similar amount of glomerularly filtered sodium is reabsorbed in the renal tubuli compared with placebo. In sensitivity analysis, median calculated 24-hour sodium excretion after 24 hours also did not show differences between patients treated with empagliflozin compared with placebo ($P=0.235$). Moreover, no differences in the occurrence of hyponatremia was seen between both treatment arms ($p>0.2$), delta serum sodium from baseline to 96 hours also did not change between the treatment arms (-0.17 vs -0.18 mmol/L, $P=0.99$), nor did empagliflozin change serum sodium at any time point ($P=0.302$ for ANOVA difference between models with and without treatment interaction). Likewise, urinary chloride excretion was lower in patients treated with empagliflozin, but fractional excretion of chloride was unaltered by empagliflozin use (Figure 1b, $P=0.922$ for ANOVA difference between models with and without treatment interaction).

Table 2: Urinary parameters over course of treatment

	Empagliflozin (n=40)	Placebo (n=39)	p-value
Spot urinary sodium, in mmol/L			
Baseline	90 ± 31	87 ± 35	0.706
24 hours	69 ± 28	85 ± 37	0.040
48 hours	56 ± 29	79 ± 44	0.011
72 hours	63 ± 41	70 ± 27	0.400
96 hours	56 ± 29	69 ± 32	0.089
30 days	60 ± 30	56 ± 28	0.683
Fractional excretion of sodium, in %			
Baseline	2.1 (0.9 - 4.1)	2.2 (0.9 - 4.4)	0.964
24 hours	1.4 (0.9 - 2.4)	1.5 (0.6 - 3.2)	0.874
48 hours	1.0 (0.3 - 1.7)	1.4 (0.7 - 2.1)	0.256
72 hours	1.4 (0.8 - 1.7)	1.0 (0.6 - 2.3)	0.840
96 hours	0.8 (0.4 - 1.9)	1.0 (0.7 - 1.7)	0.476
30 days	0.7 (0.3 - 1.7)	0.7 (0.4 - 2.0)	0.388
Spot urinary glucose, in mmol/L			
Baseline	0.2 (0.1 - 0.3)	0.1 (0.1 - 0.2)	0.264
24 hours	50.4 (17.1 - 94.8)	0.2 (0.1 - 0.3)	<0.001
48 hours	41.3 (17.2 - 79.1)	0.2 (0.1 - 0.3)	<0.001
72 hours	35.2 (16.2 - 96.2)	0.2 (0.1 - 0.3)	<0.001
96 hours	30.3 (9.9 - 75.2)	0.2 (0.1 - 0.4)	<0.001
30 days	13.1 (1.6 - 58.9)	0.2 (0.1 - 0.3)	<0.001
Fractional excretion of glucose, in %			
Baseline	0.1 (0.1 - 0.1)	0.1 (0.0 - 0.1)	0.890
24 hours	21.8 (10.1 - 29.8)	0.1 (0.1 - 0.1)	<0.001
48 hours	13.6 (5.4 - 24.0)	0.1 (0.0 - 0.1)	<0.001
72 hours	16.0 (4.2 - 24.4)	0.1 (0.0 - 0.1)	<0.001
96 hours	6.0 (2.5 - 21.8)	0.1 (0.0 - 0.1)	<0.001
Spot urinary urea, in mmol/L			
Baseline	108.0 (60.8 - 142.1)	97.5 (77.6 - 139.5)	0.881
24 hours	136.0 (93.3 - 172.7)	124.0 (91.3 - 191.6)	0.935
48 hours	160.2 (116.0 - 194.0)	159.3 (111.3 - 105.7)	0.840
72 hours	154.5 (122.9 - 185.0)	157.5 (128.5 - 207.5)	0.426
96 hours	179.6 (121.0 - 256.7)	172.2 (144.9 - 233.0)	0.427
30 days	214.0 (141.0 - 272.6)	166.6 (85.2 - 294.5)	0.333
Fractional excretion of urea, in %			
Baseline	37.9 (30.3 - 45.0)	37.6 (28.0 - 48.5)	0.984
24 hours	33.1 (28.6 - 41.9)	35.3 (21.4 - 43.0)	0.664
48 hours	29.6 (22.2 - 39.3)	30.5 (25.7 - 39.7)	0.572
72 hours	31.1 (26.3 - 37.1)	32.0 (24.9 - 39.2)	0.952
96 hours	32.4 (24.2 - 38.0)	33.5 (29.5 - 39.0)	0.346

Figure 1: FeNa, FeGlu, and FeCl progression over the course of treatment

For each clinical variable changes from baseline were calculated and used as outcomes in LME models. Two models were performed, one adjusted for baseline values, the second model adjusted for baseline values and the interaction term between treatment and time. In each panel the results for the ANOVA tests between the two models is depicted, (likelihood ratio and p-value). For placebo (blue) and empagliflozin (red) mean values are shown with dots, the bars represent standard error. A p-value for interaction between each time point and treatment is shown.

Empagliflozin significantly increased both urinary glucose concentration and fractional excretion of glucose (FeGlu), with a peak in FeGlu after 24 hours (median 21.4% vs 0.1%, $P < 0.001$, Table 2). Even though FeGlu decreased over the course

of treatment, it was still significantly higher in patients treated with empagliflozin compared with placebo after 96 hours (median 6.0% vs 0.1%, $P<0.001$). A similar pattern was seen for urinary glucose concentration up to 30 days of treatment (Table 2). Plasma glucose levels however were not changed by empagliflozin use ($P=0.763$ for ANOVA difference between models with and without treatment interaction). FeGlu was similar in patients with and without diabetes in the empagliflozin arm ($P=0.182$ for interaction, Supplementary Figure 2). Plasma urea was additionally increased in patients treated with empagliflozin, while fractional excretion of urea and urinary urea remained unaffected ($P=0.036$, 0.99 and 0.782 for ANOVA difference between models with and without treatment respectively).

During the first 72 hours, empagliflozin caused a significant decrease in eGFR (-10 ± 12 vs -2 ± 12 mL/min/1.73m²) compared with placebo ($P=0.009$), as shown in Table 3. This significant decline in eGFR was attenuated at 96 hours and 30 days ($P=0.133$ and 0.681 respectively). In addition, empagliflozin significantly increased urinary output (cumulative urinary output after 48 hours: 6084 ± 2480 mL vs. 4222 ± 1911 mL $P=0.010$, $N = 41$), which resulted in a greater negative fluid balance (cumulative fluid balance after 48 hours: -3050 (IQR $-1280 - -4753$) mL vs. -1200 mL (IQR $-710 - -2425$), $P=0.010$, $N = 38$).

Table 3: eGFR over course of treatment

	Empagliflozin (n=40)	Placebo (n=39)	p-value
eGFR, in mL/min/1.73m ²			
Baseline	53 $\pm$ 18	54 $\pm$ 16	0.824
24 hours	44 $\pm$ 14	52 $\pm$ 19	0.022
48 hours	43 $\pm$ 16	53 $\pm$ 19	0.013
72 hours	42 $\pm$ 16	54 $\pm$ 18	0.006
96 hours	45 $\pm$ 18	53 $\pm$ 20	0.101
30 days	50 $\pm$ 21	54 $\pm$ 19	0.511
Change in eGFR from baseline, in mL/min/1.73m ²			
24 hours	-9 $\pm$ 9	-2 $\pm$ 8	0.002
48 hours	-10 $\pm$ 12	-2 $\pm$ 10	0.004
72 hours	-10 $\pm$ 12	-2 $\pm$ 12	0.009
96 hours	-7 $\pm$ 11	-3 $\pm$ 15	0.133
Day 30	-6 $\pm$ 15	-4 $\pm$ 16	0.681

eGFR= estimated Glomerular filtration rate

Even though urinary volumes significantly increased after initiation of empagliflozin, no impact on urinary osmolality was seen (Figure 2c). In other words, the number of *particles per kilogram of urine* did not change despite a larger urinary volume. However, a significant shift was seen in the constituents making up urine osmolality, with glucose making up a larger proportion of the total urinary particles compared with placebo (Figure 3). Measured and calculated urine osmolality showed a strong correlation (r of log-transformed variables 0.91 – 0.99) (Supplementary Table 1).

Figure 2: Delta eGFR, delta systolic blood pressure progression, delta urine osmolality and delta plasma osmolality over the course of treatment

For each clinical variable changes from baseline were calculated and used as outcomes in LME models. Two models were performed, one adjusted for baseline values, the second model adjusted for baseline values and the interaction term between treatment and time. In each panel the results for the ANOVA tests between the two models is depicted, (likelihood ratio and p-value). For placebo (blue) and empagliflozin (red) mean values are shown with dots, the bars represent standard error. A p-value for interaction between each time point and treatment is shown.

Figure 3: Composites of urinary molecules making up osmolality

Osmolality per time point for both empagliflozin and placebo. Volumes depicted on the bars represent total urinary volume per 24 hours, y axis represents spot urinary osmolality.

* N = 58; † N = 47; ‡ N = 44; § N = 35

At baseline, plasma osmolality was similar in both groups. During the first 72 hours, empagliflozin modestly increased plasma osmolality (delta plasma osmolality 5 ± 8 mOsm/kg vs 2 ± 5 mOsm/kg; $P=0.049$). Moreover, we found a significant interaction for plasma osmolality between time at 72 hours and treatment effect ($P=0.031$, Figure 2d).

Median baseline renin was 28.8 pg/ml (range 1.0 – 1820 pg/ml), median baseline aldosterone was 185.9 pg/ml (31.0 – 1810 pg/ml). Median plasma renin concentration at baseline was higher in the placebo group than in the empagliflozin group (12.4 pg/ml vs. 80.1 pg/ml, $P=0.011$). Empagliflozin significantly increased renin with a peak after 72 hours, after which a plateau was reached and significance was lost ($P=0.016$ for ANOVA between models with and without treatment effect) (Figure 4a). Aldosterone was not altered by empagliflozin use ($P=0.217$ for ANOVA between models with and without treatment effect) (Figure 4b).

Figure 4: Delta renin and aldosterone over the course of treatment

For renin and aldosterone (both log-transformed) changes from baseline were calculated and used as outcomes in LME models. Two models were performed, one adjusted for baseline values, the second model adjusted for baseline values and the interaction term between treatment and time. In each panel the results for the ANOVA tests between the two models is depicted, (likelihood ratio and p-value). For placebo (blue) and empagliflozin (red) mean values are shown with dots, the

bars represent standard error. A p-value for interaction between each time point and treatment is shown.

No significant correlations, as analyzed with linear regression, could be seen for log FeGlu and log FeNa, for log FeGlu and fluid balance or for log FeNa and fluid balance (Supplementary Figure 1).

DISCUSSION

In this predefined post-hoc analysis of the EMPA-RESPONSE-AHF trial, we found that patients with acute HF receiving empagliflozin had a higher urinary output and a more negative fluid balance. Interestingly, fractional sodium excretion did not increase and urinary osmolality remained similar between both groups. Nonetheless, fractional glucose excretion significantly increased after initiation of empagliflozin. Moreover, empagliflozin temporarily reduced renal function in the first days after an acute heart failure hospital admission.

The increase in fractional glucose excretion with SGLT2-inhibition by empagliflozin was expected, as blocking the receptor responsible for tubular reabsorption of glucose would intuitively lead to increased excretion of filtered glucose. Importantly, fractional glucose excretion was similar in patients with and without diabetes and plasma glucose levels remained unchanged, suggesting that pre-existing diabetes and/or plasma glucose supply to the glomerulus do not play an important role. Our finding that fractional sodium excretion was not increased with empagliflozin was somewhat unexpected, since blockage of the SGLT2 receptor in the proximal tubule prevents reabsorption of both glucose and sodium. However, it is well known that in contrast to glucose, sodium can be reabsorbed throughout the entire tubule. Therefore, our findings suggest that sodium reabsorption might have been blocked by empagliflozin in the proximal tubule, and that this was compensated by an increased reabsorption of sodium in the rest of the tubule and collecting duct.¹⁴

Similar to a post-hoc analysis of the EMPA-REG OUTCOME Trial, a transient decline in eGFR was seen after initiating treatment with empagliflozin.¹⁵ This course in eGFR over time was seen in the CANVAS program as well.¹⁶ This has been postulated

to be related to the juxtaglomerular feedback mechanism and a correction in glomerular hyperfiltration.^{17,18} Loss of chloride is sensed by the macula densa in the distal convoluted tubule and leads to release of adenosine, causing afferent vasoconstriction and a decreased renal blood flow, in order to spare salt. If we assume that the established drop in GFR is indeed the result of activation of the macula densa, there should still be high levels of sodium and chloride present in the distal convoluted tubule in order for juxtaglomerular feedback mechanism to be activated.¹⁹ This would mean that although we do not find increased concentrations of sodium in the urine, proximal tubular sodium resorption is indeed diminished. This notion is further supported by the fact that renin levels were increased compared with placebo for the first 72 hours, following a similar pattern compared to drop in eGFR. The increased osmotic diuresis resulting from glycosuria probably leads to an increase in renin levels. Of course, these results need to be interpreted in light of background therapy and one should be wary to draw conclusions based on these data alone. Consequently, sodium is likely reabsorbed distally from the macula densa, e.g. in the collecting duct. In the collecting ducts multiple mediators regulate urine dilution and sodium reabsorption, one of which is vasopressin.²⁰ Yet, since urinary osmolality remained unchanged and vasopressin only plays a minor role in sodium reabsorption, it is unlikely that an increase in vasopressin is truly responsible for this increase in sodium reabsorption in the collecting duct. We did not find an increase in aldosterone after initiation of empagliflozin, making aldosterone an unlikely cause for distal tubular or collecting duct sodium reabsorption. Other drivers of sodium reabsorption include insulin and insulin like growth factor-1, while endothelin-1 and nitric oxide decrease sodium reabsorption.²¹⁻²³ The precise contribution of each of these factors on sodium reabsorption in the collecting duct after blocking the SGLT2 receptor and treatment with loop diuretics have to be assessed in future studies.

Interestingly, our data show a modest increase in plasma osmolality. These effects were even more pronounced in patients with lower serum sodium and lower plasma osmolality. In our data no effect on serum sodium could be found, which might be explained by the fact that only a small proportion of patients presented with hyponatremia and the lowest measured sodium upon admission was 129 mmol/L. Moreover, this might position SGLT2 inhibitors as a treatment for tissue

congestion or residual congestion as increased plasma osmolality attracts fluid from the interstitial space into the blood stream.²⁴ This notion is supported by earlier findings that the SGLT2 inhibitor dapagliflozin has been calculated to reduce interstitial fluid volume 3 times more than it reduces blood volume, compared to an interstitial fluid reduction of only 66% of the reduction in blood volume by bumetanide.²⁵ The fact that empagliflozin did not lower blood pressure in these severely diseased patients despite larger negative fluid balance also supports the theory of a more stable refill rate from interstitial fluid to plasma as a result of increased plasma osmolality. However, we have to account for the small study group here and the fact that other larger trials did find a reduction of 5-10 mmHg in systolic blood pressure after initiation of a SGLT2 inhibitors.^{26,27} Still, this increase in plasma osmolality might also be expected since distal diluting segments receive higher tubular flow as a result of empagliflozin. The kidneys perceive this as a state of hypervolemia which, through stimulation of the countercurrent system of the vasa recta, leads to more distal sodium reabsorption and less free water clearance.²⁸

As described earlier, the majority of HF patients are discharged with residual congestion with consequent impaired prognosis.²⁹ Our analyses might provide insights into new possibilities to overcome residual congestion due to significantly improved net fluid loss (negative fluid balance) and increased plasma osmolality. Naturally, our data need to be validated in another (larger) clinical cohorts.

Taken together, our findings that empagliflozin increased fractional excretion of glucose, while both fractional excretion of sodium and urinary osmolality remained unchanged, suggest that empagliflozin most prominently stimulates osmotic diuresis as a result of increased fractional excretion of glucose instead of natriuresis. Our results are in line with earlier studies that reported that SGLT2-inhibitors increased urinary volume without an increase in fractional sodium excretion.^{8,30} In another study comprising of patients with type 2 diabetes and stable chronic HF (median NT-proBNP: 399 pg/mL) an early increase in urinary sodium excretion was seen. However, in this study fluid administration was high in these patients, sodium intake was not standardized per protocol, and intermittent urinary measurements were only obtained throughout the first six hours. Therefore, the circadian rhythm

in sodium excretion could still have affected these findings. Since we included acute HF patients with more signs and symptoms of fluid congestion (median NT-proBNP: 5236 pg/mL), differences might further be explained by our sicker cohort with likely even higher neurohumoral activation potentially leading to increased sodium reabsorption and eventually maintaining fractional excretion of sodium constant. This is in contrast to a study in patients with euvolemic, stable HF, where empagliflozin increased both fractional excretion of glucose and sodium, and even exhibited a small synergistic effect of concomitant treatment with intravenous bumetanide.⁷

Limitations

Several potential limitations of the present study can be identified. The first limitation of this study is the relatively small sample size. Second, we collected spot urine samples and not 24-hour measurements. Consequently, we do not know the total sodium output over the course of hospitalization. Conceivably, increased volumes of urine, even with a lower concentration of sodium, will eventually lead to an increased absolute total of urinary sodium. As per protocol, treating physicians were blinded to the treatment arm and urinary excretion of glucose. However, urinary levels of sodium excretion were measured in the local labs and could therefore be perceived in the electronic medical records. Third, plasma levels of glucose were not measured at the 30-day follow-up visit, as this was not incorporated in the study protocol. Therefore, no fractional excretion of glucose could be calculated at day 30. Fourth, the timing of loop diuretic administration was not standardized. This was left to the discretion of the treating physician. Therefore, some patients were on continuous loop diuretic infusion, while others were on intravenous bolus loop diuretic treatment. So, the natriuretic effect of a recent loop diuretic bolus, rather than that of empagliflozin cannot be ruled out. Still, considering the randomized nature of this trial, these treatment differences should be equal in both arms. Moreover, patients in both treatment arms were on equal total doses of intravenous and oral loop diuretics, and the number of patients on either oral or intravenous loop (bolus vs. continuous) diuretics were similar as well (Supplementary Table 2). Additionally, calculating fractional excretion levels relies on measured plasma creatinine levels. These values changed throughout follow-up which might have affected calculated values of fractional excretion.

Conclusion

In patients hospitalized with acute HF, empagliflozin caused an increase in urinary output, fractional glucose excretion and plasma osmolality, without affecting fractional sodium excretion or urine osmolality. Additionally, a significant, temporary decline in eGFR was seen. These results suggest that empagliflozin primarily stimulates osmotic diuresis in patients with acute HF through increased glycosuria rather than through natriuresis.

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SUPPLEMENTARY MATERIAL

Supplementary table 1: Correlation between measured and calculated urine osmolality per time point

EMPAGLIFLOZIN	2 [Na+] + 2[K+] + [Glucose] + [Urea]				
	Calculated urinary osmol	Measured urinary osmol	Spearman rho	Pearson r of log(variables)	
	Baseline	342 (320 – 378)	330 (322 – 379)	0.88	0.94
	24 hours	396 (354 – 426)	399 (352 – 443)	0.92	0.93
	48 hours	398 (367 – 448)	407 (371 – 489)	0.88	0.95
	72 hours	401 (371 - 476)	395 (374 – 494)	0.94	0.95
96 hours	415 (358 – 535)	430 (366 - 569)	0.97	0.99	
PLACEBO	Calculated urinary osmol	Measured urinary osmol	Spearman rho	Pearson r of log(variables)	
	Baseline	359 (326 – 375)	341 (324 – 384)	0.90	0.93
	24 hours	376 (348 – 434)	388 (345 – 410)	0.90	0.91
	48 hours	386 (348 – 476)	397 (357 – 450)	0.92	0.96
	72 hours	388 (361 – 452)	389 (357 – 435)	0.95	0.97
	96 hours	390 (367 – 511)	395 (361 – 496)	0.91	0.97

Supplementary table 2: Median cumulative dose of loop diuretics per patient during the first 96 hours of hospitalization

Time point	Empagliflozin (n = 40)		Placebo (n = 39)		p-value
Oral dose of loop diuretics received (furosemide dose or equivalent)					
Prior to Baseline	0 [0, 0]	n = 6	0 [0, 10]	n = 10	0.404
Baseline - 24 hours	0 [0, 0]	n = 7	0 [0, 0]	n = 9	0.458
24 hours - 48 hours	0 [0, 80]	n = 18	0 [0, 80]	n = 17	0.974
48 hours - 72 hours	40 [0, 80]	n = 23	0 [0, 80]	n = 19	0.850
72 hours - 96 hours	0 [0, 5]	n = 10	0 [0, 40]	n = 11	0.691
Intravenous dose of loop diuretics received (furosemide dose or equivalent)					
Prior to Baseline	160 [80, 242]	n = 38	148 [80, 200]	n = 37	0.189
Baseline - 24 hours	156 [80, 200]	n = 34	125 [80, 200]	n = 31	0.328
24 hours - 48 hours	20 [0, 160]	n = 20	0 [0, 160]	n = 19	0.899
48 hours - 72 hours	0 [0, 80]	n = 26	0 [0, 113]	n = 24	0.625
72 hours - 96 hours	0 [0, 45]	n = 11	0.00 [0, 0]	n = 9	0.626
Total cumulative diuretic dose of loop diuretics received (oral and intravenous combined)					
Baseline	160 [86, 243]		152 [88, 220]		0.505
24 hours	322 [200, 429]		310 [184, 385]		0.438
48 hours	408 [240, 582]		372 [240, 506]		0.563
72 hours	442 [307, 666]		410 [300, 582]		0.776
96 hours	490 [319, 698]		435 [360, 679]		0.546
Number of patients on continuous vs. bolus loop diuretics					
Continuous	19		15		0.417
Bolus	7		14		0.064
Continuous + bolus	8		5		0.390

7

Effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on potassium handling in patients with acute heart failure

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Eur J Heart Fail. 2021 Jun;23(6):1049-1052.

Disturbances of potassium homeostasis are common in patients hospitalised for heart failure (HF).^{1,2} This increased risk of hypo- and hyperkalaemia is caused by hemodynamic changes, treatment with diuretics and renin–angiotensin–aldosterone system (RAAS) inhibitors, and the high prevalence of comorbidities (e.g. diabetes and renal dysfunction) in these patients.^{2,3} Therefore, current HF-guidelines recommend close monitoring of serum potassium concentrations in patient hospitalised with HF.⁴

Treatment with sodium glucose co-transporter 2 inhibitors (SGLT2-inhibitors) reduces the risk of worsening heart failure and cardiovascular death in ambulant patients with HF.^{5,6} In acute HF, SGLT-2 inhibitors increase diuresis despite a temporary decline in estimated glomerular filtration rate (eGFR).^{7,8} Due to the effects of SGLT2-inhibitors on renal function, an impact on potassium homeostasis might be expected. Even though the largest proportion of potassium is reabsorbed in the loop of Henle, reabsorption of sodium, chloride, and water in the proximal tubule causes an electrical and chemical potassium gradient which leads to (passive) potassium reabsorption.⁹ Therefore, blocking the SGLT-2 receptor might affect potassium homeostasis.

Data on the risk of potassium disturbances after initiating treatment with SGLT-2 inhibitors remain inconsistent. In patients with diabetes, dapagliflozin did not affect serum potassium concentrations.¹⁰ However, patients on MRA therapy included in the DAPA-HF trial had a 50% lower chance of developing moderate/severe hyperkalaemia when treated with dapagliflozin compared with placebo.¹¹ The frequency of hyperkalaemia in the EMPA-REG OUTCOME trial was lower for patients treated with empagliflozin compared with placebo, whereas the EMPEROR-Reduced trial showed no difference.^{6,12} Canagliflozin increased serum potassium concentrations in patients with type 2 diabetes, with a more pronounced effect at higher dosages, concomitant treatment with RAAS-inhibitors, or impaired renal function.¹³ Contrastingly, no differences in the frequency of hyperkalaemia were seen in the large canagliflozin trials (CREDENCE and CANVAS).^{14,15} None of these studies reported on renal potassium handling as reflected by urinary potassium concentrations. Therefore, we studied the effects of the addition of empagliflozin,

on top of loop diuretic therapy, on renal potassium handling in patients hospitalised with acute HF.

We performed a post-hoc analysis of the multicentre, double-blind EMPA-RESPONSE-AHF trial.⁷ Briefly, 79 patients admitted for acute HF were randomised 1:1 to empagliflozin 10 mg (for 30 days) (n=40) or placebo (n=39). All participating patients provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki. The effect of empagliflozin on (fractional excretion of) potassium was analysed with repeated measures linear mixed-effect models. Fractional excretion of potassium (FEK) was calculated using the following formula: $\text{FEK (\%)} = (\text{urinary potassium [mmol/L]} \times \text{serum creatinine [mmol/L]}) / (\text{serum potassium [mmol/L]} \times \text{urinary creatinine [mmol/L]}) \times 100\%$. Random effects were established on the individual level. Change from baseline potassium was calculated and used as an outcome in the linear mixed-effect model. We analysed a nested model adjusted for baseline values and time. Next, a second model was performed including baseline values, time, treatment arm and the treatment x time interaction term. Both models were compared using analysis of variance (ANOVA). All tests were two-sided and p-values <0.05 were considered statistically significant. Analyses were performed using Stata SE15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Linear mixed-effect models were conducted using the lme function in the “nlme” package, performed in R studio, version 1.3.959.

Patients' characteristics at baseline are described elsewhere.⁷ In short, patients were 76 (38–89) years old, 33% were women and mean baseline eGFR was 55±17 mL/min/1.73m². Background treatment with ACEi/ARB, MRA, and beta-blocker was similar between both treatment arms at baseline. Median loop diuretic dose (re-calculated to furosemide) through day 4 was 308 (200–480) mg furosemide for the entire cohort, without a difference between both treatment arms (p=0.788). Serum potassium concentrations at baseline were similar (3.9 [3.5–4.2] mEq/L for empagliflozin and 3.9 [3.5–4.5] mEq/L for placebo; P=0.406). Baseline urinary potassium concentrations were similar between patients treated with empagliflozin (27 [21–33] mmol/L) and placebo (29 [20–41] mmol/L, P=0.399).

Table 1. Differences in characteristics at baseline of patients with and without potassium supplementation (left panel) and with/without MRA initiation (right panel)

Factor	Without potassium supplementation (N=46)	With potassium supplementation (N=33)	p-value	Empagliflozin + MRA Placebo + MRA initiation (N=4)	initiation (N=15)	p-value
Age	76 (68, 83)	78 (71, 82)	0.93	79 (74, 85)	72 (61, 83)	0.29
Female sex	17 (37%)	9 (27%)	0.37	1 (25%)	4 (27%)	0.95
Body weight (kg)	86 (21)	84 (22)	0.62	75 (9)	88 (21)	0.24
Systolic blood pressure (mmHg)	127 (25)	121 (22)	0.31	143 (39)	121 (23)	0.16
Heart rate (bpm)	78 (18)	87 (25)	0.088	76 (17)	85 (28)	0.58
NYHA classification III	34 (77%)	25 (76%)	0.27	2 (50%)	10 (67%)	0.14
LVEF (%)*	36 (22, 50)	35 (25, 50)	0.78	29 (29, 29)	32 (22, 40)	0.79
HFrEF*	14 (56%)	11 (52%)	0.81	1 (100%)	6 (60%)	0.43
eGFR (CKD-EPI) (mL/min/1.73m2)	54 (17)	57 (19)	0.52	62 (24)	67 (20)	0.63
NT-proBNP (pg/mL)	5104 (3026, 9871)	4918 (3453, 8019)	0.58	3781 (3511, 4759)	3904 (3180, 6168)	0.76
Admission duration (total days)	7 (6, 10)	9 (6, 10)	0.23	8 (5, 12)	9 (7, 10)	0.69
Atrial fibrillation or flutter	32 (70%)	24 (73%)	0.76	2 (50%)	10 (67%)	0.54
History of hypertension	27 (59%)	22 (67%)	0.47	4 (100%)	11 (73%)	0.25
History of hypercholesterolemia	21 (46%)	16 (48%)	0.80	2 (50%)	9 (60%)	0.72
History of diabetes	16 (35%)	10 (30%)	0.68	2 (50%)	4 (27%)	0.37
Loop diuretics	45 (100%)	33 (100%)	N.A.	4 (100%)	15 (100%)	N.A.
ACE-inhibitor	16 (36%)	18 (55%)	0.095	1 (25%)	4 (27%)	0.95
Angiotensin II receptor blocker	8 (18%)	7 (21%)	0.70	1 (25%)	4 (27%)	0.95
Angiotensin II receptor - Neprilysin	2 (4%)	1 (3%)	0.75	0 (0%)	0 (0%)	N.A.

Table 1. (Continued)

Factor	Without potassium supplementation (N=46)	With potassium supplementation (N=33)	p-value	Empagliflozin + MRA Placebo + MRA initiation (N=4)	p-value
Beta-blocker	28 (62%)	25 (76%)	0.21	2 (50%)	8 (53%)
Mineralocorticoid receptor antagonist	21 (47%)	15 (45%)	0.92	0 (0%)	0 (0%)
Cholesterol lowering drugs	20 (44%)	13 (39%)	0.66	1 (25%)	8 (53%)
Diuretic dose (re-calculated to furosemide) through day 4 (mg)	300 (165, 560)	320 (200, 440)	0.79	160 (120, 180)	280 (200, 600)
Serum potassium at baseline (mmol/L)	4.1 (3.8, 4.3)	3.7 (3.5, 4.1)	0.002	3.6 (3.4, 4.1)	3.8 (3.4, 4.3)
Episodes of hypokalaemia until day 4 (in number of patients)	10 (8)	24 (13)	0.14	3 (1)	14 (7)
Episodes of hyperkalaemia until day 4 (in number of patients)	5 (5)	6 (5)	0.482	0 (0)	2 (2)

* only available in a subset of 46 patient

In the total population, median (IQR) serum potassium concentrations increased from baseline until 96 hours of admission (0.4 [-0.1–0.6] mEq/L, $p < 0.001$). In total, 33 patients [42%] received potassium supplementation in the first 96 hours of hospital admission, with no difference between treatment arms (17 patients [43%] for empagliflozin and 16 patients [41%] for placebo, $P = 0.894$) (Table 1). Dosages of potassium supplementation were similar between both arms (3600 [3000–5400] mg of potassium chloride in patients treated with empagliflozin, versus 3600 [1800–6075] mg in patients on placebo [$p = 0.974$]) and were independent of loop diuretic dose. No differences in serum potassium concentrations or change in serum potassium concentrations were observed between both treatment arms (Figure 1a/b). Fractional excretion of potassium remained constant through the course of treatment, irrespective of the study drug (Figure 1c/d) and no interaction with use of an MRA was seen (Supplementary Figure 1 and Supplementary Table 1).

For each clinical variable changes from baseline were calculated and used as outcomes in linear mixed-effect models. Two models were performed, one adjusted for baseline values, the second model adjusted for baseline values and the interaction term between treatment and time. In each panel, the results for the ANOVA tests between the two models are depicted (likelihood ratio and P -value). For placebo and empagliflozin, mean values are shown with dots, the bars represent standard error. A P -value for interaction between each time point and treatment is shown.

The proportion of patients on MRA therapy between the groups was similar at baseline (19 for empagliflozin and 18 for placebo [$P = 0.807$]) (Table 1). Of the patients without MRA therapy (21 per arm), 15 patients (71%) were initiated on an MRA throughout follow-up in the placebo group, compared with 4 patients (19%) in the empagliflozin group ($P = 0.035$).

Overall, this suggests that empagliflozin did not change fractional potassium excretion despite an initial decline in eGFR in patients with acute HF. Similarly, empagliflozin did not change serum potassium concentrations. However, initiation of an MRA during hospital admission was done less frequently in patients treated with empagliflozin compared with those on placebo. This is in line with a recent

post-hoc analysis from the EMPEROR-Reduced trial.¹⁶ We cannot provide a clear explanation for this finding, since baseline eGFR, proportion of patients with HFrEF, number of hyperkalaemic events, duration of hospitalisation, and concomitant medication (except for loop diuretics) were all similar between both treatment arms (Table 1 and Supplementary Table 2a/b). Still, physicians may have been discouraged to initiate an MRA since empagliflozin caused an initial decline in eGFR in these patients.⁸

Figure 1. Fractional potassium excretion (A), change in fractional potassium excretion (B), serum potassium (C), and change in serum potassium (D) over the course of treatment in a linear mixed-effect model.

Our study was limited by the post-hoc design and the small sample size. Results should, therefore, be interpreted with caution and might be replicated in ongoing larger trials.¹⁷ Secondly, we collected untimed spot urine samples and not 24-hour measurements. Thirdly, optimisation of medical (HF) therapy was left to the treating physician without a requirement to document the reason for initiation or modification. Fourthly, no data on serum magnesium was available to correct for the effect of magnesium on potassium excretion.¹⁸ Lastly, a large proportion of patients received potassium supplementation (42%), while only 21 out of 79 patients (27%) had a measured serum potassium concentration below 3.5 mEq/L during hospitalisation (Table 1). Since potassium supplementation was left to the treating physician, we cannot fully explain this finding. Data on potassium supplementation in HF is scarce. The Danish national registry reported that 80.7% of patients with chronic HF were treated with potassium supplements.¹⁹ Contrastingly, Núñez et al. described a proportion of 7.6% in patients recently hospitalised with acute HF.¹ Due to aggressive treatment with loop diuretics, proportions might even be higher in acute HF, as was indicated by this study, while study treatment had no impact on rates of potassium supplementation. Real-world data and documentation on potassium supplementation in (future) HF trials will help us to understand the clinical practice better. To conclude, empagliflozin did not change (renal) potassium handling in patients hospitalised with acute HF when compared with placebo.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. P for interaction between the use of an MRA and treatment group (empagliflozin or placebo) for the fractional excretion levels of potassium over time estimated in a linear mixed effect model

Timepoint	P-value
T = 24 hours	0.2280
T = 48 hours	0.4859
T = 72 hours	0.2422
T = 96 hours	0.6649
T = 30 days	0.2766

Supplementary table 2a. Differences in baseline characteristics of patients in the empagliflozin arm with and without MRA-initiation while hospitalised (all without MRA at baseline)

Factor	Empa without MRA-initiation (N=17)	Empa with MRA-initiation (N=4)	p-value
Age	81 (74, 85)	79 (74, 85)	0.79
Systolic blood pressure	127.6 (17.5)	142.5 (39.0)	0.25
LVEF*	55 (50, 57)	29 (29, 29)	0.22
eGFR (CKD-EPI) (mL/min/1.73m ²)	53.8 (18.9)	61.8 (23.5)	0.47
Serum potassium	4.1 (3.9, 4.2)	3.6 (3.4, 4.1)	0.26
Admission duration (days)	7.5 (6.0, 10.0)	8.0 (5.0, 12.0)	0.81
ACE-inhibitor	6 (35%)	1 (25%)	0.69
Angiotensin II Receptor Blocker	4 (24%)	1 (25%)	0.95
ARNI	0 (0%)	0 (0%)	N.A.
Beta-Blocker	12 (71%)	2 (50%)	0.43
MRA	0 (0%)	0 (0%)	N.A.
Diuretic dose through day 4 (40mg furosemide equivalents)	8.0 (6.0, 11.0)	4.0 (3.0, 4.5)	0.022
Diuretic response through day 4 (weight change per 40 mg furosemide equivalents)	-0.3 (-0.4, -0.1)	-0.3 (-0.7, 0.2)	0.84

* only available in 9 and 1 patients per arm respectively

Supplementary table 2b. Differences in baseline characteristics of patients in the placebo arm with and without MRA-initiation while hospitalised (all without MRA at baseline)

Factor	Placebo without MRA- initiation (N=6)	Placebo with MRA- initiation (N=15)	p-value
Age	84 (80, 86)	72 (61, 83)	0.10
Systolic blood pressure	122 (25)	121 (23)	0.93
LVEF*	50 (43, 54)	32 (22, 40)	0.022
eGFR (CKD-EPI) (mL/min/1.73m ²)	50 (18)	67 (20)	0.079
Serum potassium	4.1 (3.8, 4.5)	3.8 (3.4, 4.3)	0.16
Admission duration (days)	7.5 (7.0, 9.0)	9.0 (7.0, 10.0)	0.61
ACE-inhibitor	4 (67%)	4 (27%)	0.088
Angiotensin II Receptor Blocker	0 (0%)	4 (27%)	0.16
ARNI	0 (0%)	0 (0%)	N.A.
Beta-Blocker	5 (83%)	8 (53%)	0.20
MRA	0 (0%)	0 (0%)	N.A.
Diuretic dose through day 4 (40mg furosemide equivalents)	7.3 (7.0, 7.7)	7.0 (5.0, 15.0)	0.75
Diuretic response through day 4 (weight change per 40 mg furosemide equivalents)	-0.2 (-0.3, 0.3)	-0.3 (-0.6, -0.0)	0.25

* only available in 6 and 10 patients per arm respectively

Supplementary table 3a. Cumulative diuretics dose during the first days of hospitalisation for patients who were initiated with an MRA, stratified by treatment arm.

Cumulative diuretic dose after ... (40mg furosemide equivalents)	Empagliflozin + MRA initiation (N=4)	Placebo + MRA initiation (N=15)	p-value
24 hours	1.0 (0.8, 1.5)	3.8 (2.5, 5.0)	0.010
48 hours	2.0 (1.5, 2.5)	5.5 (3.6, 8.0)	0.014
72 hours	3.0 (2.0, 3.5)	6.5 (4.1, 12.0)	0.014
96 hours	4.0 (3.0, 4.5)	7.0 (5.0, 15.0)	0.021

Supplementary table 3b. Diuretics dose per day during the first days of hospitalisation for patients who were initiated with an MRA, stratified by treatment arm.

Diuretic dose (40mg furosemide equivalents)	Empagliflozin + MRA initiation (N=4)	Placebo + MRA initiation (N=15)	p-value
0 – 24 hours	1.0 (0.8, 1.5)	3.8 (2.5, 5.0)	0.010
24 – 48 hours	1.0 (0.8, 1.0)	1.5 (0.5, 4.0)	0.36
48 – 72 hours	1.0 (0.5, 1.0)	1.0 (0.5, 3.1)	0.30
72 – 96 hours	1.0 (1.0, 1.0)	1.0 (0.5, 3.0)	0.67

Supplementary figures

Supplementary figure 1. Fractional potassium excretion over the course of treatment and stratified by the use of an MRA in a linear mixed effect model

8

General discussion and future perspectives

Current medical guideline recommendations for treating patients with HF include ACEi/ARB/sacubitril/valsartan, MRAs, and beta-blockers.¹ Overall, these therapies have proven effective in patients with HFrEF and have significantly improved outcomes for these patients. However, a vast proportion of the patients with HFrEF are not treated with guideline-recommended dosages of these drugs due to various causes, of which one is hyperkalaemia. This thesis investigated the interplay between sodium, potassium, and HF therapies.

Patients with HF clinically at risk for potassium disturbances

In **Chapter 2**, we identified which patients with chronic HF are at risk of developing potassium disturbances and checked associations with outcomes in patients included in the ASIAN-HF registry. In this cohort, 6.8% and 7.0% of patients with chronic HF had hypo- and hyperkalaemia, respectively. Only 1.9% of patients had moderate to severe hyperkalaemia ($K^+ \geq 5.5$ mmol/L). In multivariable analysis, women with higher heart rates and more signs of congestion (i.e. oedema and treatment with loop diuretics) were more likely to have hypokalaemia. Hyperkalaemia was associated with diabetes mellitus, chronic kidney disease, and lower serum sodium concentrations. We observed large regional differences. Hypokalaemia was most prevalent in Indonesia, Hong Kong, and Taiwan, whereas hyperkalaemia was most prevalent in India and Thailand, regardless of the ejection fraction (HFrEF vs. HFpEF) and independent of clinical confounders. In our outcome analyses, hypo- and hyperkalaemia were not related to worse prognosis compared to normokalaemia. However, lower serum potassium levels were associated with an increased risk of HF-rehospitalization or death after 1 year on a continuous scale.

Interference of serum potassium levels with guideline-directed therapy

In **Chapter 3**, we investigated the association between serum potassium levels and the chances of being up-titrated with guideline-directed HF treatment in sub-optimally treated patients with chronic HF. In this European cohort, 6.9% and 8.0% of patients presented with hypo- and hyperkalaemia, respectively. Hyperkalaemia was mainly observed in Eastern Europe and Greece. In itself, (change in) serum potassium levels during follow-up were not associated with prognosis. Most importantly, higher serum potassium levels at baseline showed to be an independent predictor of unsuccessful up-titration with ACEi/ARB. However,

an increase in serum potassium during follow-up (i.e. titrating dosages of ACEi/ARB) did not attenuate the beneficial effects of up-titration. The accompanying editorial by prof. Lund and prof. Pitt provided further insights into the interaction between hyperkalaemia.

In contrast to the chronic HF cohort used in the previous chapter, **Chapter 4** tested the interference of potassium disturbances with HF therapy in patients hospitalized with acute HF. Patients were monitored daily during the first seven days of hospitalization or until discharge, whichever came earlier. In this international cohort, 35% of patients developed hyperkalaemia at least once while hospitalized compared to 17% of patients developing hypokalaemia at least once. Patients developing hyperkalaemia were more likely to have their MRA treatment being down-titrated or discontinued. Incident hyperkalaemia was no independent predictor of impaired prognosis, yet down-titration or discontinuation of the RAASi was. Even in patients with hyperkalaemia, the prognosis was better if dosages of MRA or ACEi/ARB remained constant or were increased.

SGLT2-inhibitors in HF

In **Chapter 5**, we prospectively studied the effects of empagliflozin on clinical outcomes in patients with acute decompensated HF. This randomized, double-blind, placebo-controlled, multicentre pilot study on the safety and efficacy of empagliflozin in patients with acute (decompensated) HF showed no difference between empagliflozin and placebo on the combined primary endpoint (change in dyspnoea, reduction in NT-proBNP, diuretic response, and length of in-hospital stay). Administering empagliflozin was well tolerated and seemed safe based on the low number of adverse events. Empagliflozin increased cumulative urinary volume and net negative fluid balance in a subset of patients. Additionally, a significantly lower rate of deaths, in-hospital worsening of HF and/or HF readmissions through day 60 were observed in the empagliflozin arm compared with placebo.

Chapter 6 assessed the effects of empagliflozin on the renal handling of sodium and glucose in patients hospitalized with acute decompensated HF. This post hoc analysis added to the findings in chapter 5 on the higher urinary output and the more negative fluid balance in patients with acute HF receiving empagliflozin.

This was despite an initial (temporarily) decline in the estimated glomerular filtration rate in the first days after initiating empagliflozin. Based on the working mechanism of SGLT2-inhibitors (blocking the reabsorption of sodium and glucose in the proximal tubule), we hypothesized that the higher urinary output would be the result of an increased natriuresis. Interestingly, the fractional excretion of sodium did not increase after initiating empagliflozin. Moreover, urinary osmolality remained similar between both groups despite an increased fractional excretion of glucose after initiation of empagliflozin. In an accompanying editorial by prof. Mullens and dr. Martens, they further elaborated on the 'smart osmotic' properties of SGLT2-inhibitors via two simultaneous mechanisms. The osmotic effect results in an improved mobilization of the interstitial fluid on one hand, whereas on the other hand, the site of action of empagliflozin improves intrarenal hemodynamics.

In **Chapter 7**, we studied the effect of SGLT2-inhibition with empagliflozin on serum and urinary potassium levels in patients with acute HF. The results suggested no effect of empagliflozin on the fractional potassium excretion despite an initial decline in eGFR in patients with acute HF. Similarly, serum potassium levels were not altered by empagliflozin compared with placebo. Surprisingly, initiation of treatment with an MRA was performed less often in patients treated with empagliflozin while hospitalized than those treated with placebo irrespective of the clinical characteristics of these patients making them more/less prone to be initiated with an MRA.

FUTURE PERSPECTIVES

Hypokalaemia

This thesis highlights that potassium abnormalities are common in patients with HF and earlier data suggested that both hypokalaemia and hyperkalaemia are associated with worse outcomes.^{2,3} There is a specific paucity of data on the role of hypokalaemia in patients with HF. No data is available on the best strategy to prevent and/or treat hypokalaemia in these patients. Potassium supplementation is easily administered, yet providing a more MRA-centred algorithm to increase potassium levels, might provide more significant benefits in the long term. This might be something to focus on in future trial designs.

Potassium binding agents

As mentioned in the introduction, current therapeutic options to actively lower serum potassium levels have not been changed since the 1950s and are feared because of their side effects or are not suitable for chronic use. Two novel drugs were developed to lower serum potassium levels, i.e. sodium zirconium cyclosilicate and patiomer. The potassium-lowering effects of these drugs were tested in the HF population as and showed promising results on their tolerability and efficacy.⁴⁻⁶ Looking towards the future, two clinical trials should be mentioned here. First, the 'Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure' (PRIORITIZE HF) trial will test if patients prone to developing hyperkalaemia and receiving sodium zirconium cyclosilicate (compared with placebo) tolerate higher dosages of ACEi and MRAs after 3 months. Secondly, the 'Patiomer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure' (DIAMOND) will test if actively lowering the potassium levels with patiomer enables higher tolerated dosages of RAASi and, more importantly, relates to improved prognosis. If these potassium binding agents prove beneficial, even higher dosages of MRAs might be explored. Moreover, the stricter potassium monitoring in these trials might in itself affect outcomes in patients with HF. Additionally, patients with HF and an (estimated) glomerular filtration rate below 30 are currently withheld from treatment with an MRA due to the risk of developing hyperkalaemia. Possibly, these patients might also benefit from the beneficial effects of MRA therapy if the novel binding agents attenuate the risk of developing hyperkalaemia.

Dietary counselling

Besides the potassium binding agents, a stricter dietary regimen could also affect potassium levels. Even though it was based on low quality evidence, a recent meta-analysis in patients with chronic kidney disease indicated that dietary potassium restriction seemed to be effective in maintaining a low serum potassium levels in patients with normal serum potassium levels at baseline.⁷ Even though the effect of dietary potassium in patients with HF has not been the focus of clinical trials before, this might contribute to more optimal potassium homeostasis in patients prone to developing potassium disturbances. If future data provides evidence indicating that

more patients are enabled to remain their potassium levels within the reference range, I foresee a more significant role for dietary counselling in patients with HF.

Point of care

As mentioned in the introduction and based on the 2016 ESC Heart Failure guidelines, it is recommended to frequently (daily) measure serum potassium levels during in-patient optimization of HF therapy.¹ This enables the physician to correct severe potassium abnormalities, to adjust the HF therapy as required, to tolerate a mild or moderate hyperkalaemia, and to re-evaluate during the following days. However, most HF patients are seen at the outpatient clinic. Any abnormality in the potassium homeostasis during the out-patient visit might directly lead to a change in their life-saving RAASI. Consequently, the measurement will be repeated after approximately a week to check if the levels are again within the reference ranges after down-titrating the agent. Maybe in the (nearby) future, novel point-of-care devices might enable physicians in the outpatient clinic to tolerate mild/moderate hyperkalaemia when these patients repeatedly self-measure their potassium concentrations combined with remote monitoring/consulting.

Sequencing HF therapy

Since the latest European HF guidelines (originating from 2016), the therapeutic options for treating patients with HF have increased significantly which might affect the role of potassium as well. SGLT2-inhibitors, omecamtiv mercabil, and vericiguat have proven effective in improving the prognosis of patients with HF. However, until today it is unknown which combination will provide the strongest benefit in terms of outcomes and quality of life for patients with HF. Recently, a new algorithm was proposed by HF-specialists John J.V. McMurray and Milton Packer.⁸ They offer a simultaneous therapeutic start with a beta-blocker and an SGLT2-inhibitor based on the striking reducing effect of sudden (cardiac) death and HF (re)hospitalizations. As a second step, they advise adding an ARNI (sacubitril/valsartan) 1 or 2 weeks after the first step in patients who would tolerate this based on their systolic blood pressure. If a physician questions the hemodynamic stability, this could first be evaluated by starting an ARB, before switching to an ARNI. The last step would be adding an MRA with an interval of 1 or 2 weeks. This step should only be performed in patients with normal serum potassium levels and adequate renal function.

Based on the proposed sequence, several advantages are expected for clinicians. ARNIs can reduce the risk of renal insufficiency compared with ACEi/ARBs. Both ARNIs and SGLT2-inhibitors can reduce the risk of developing hyperkalaemia in patients with HF treated with an MRA.⁹ Therefore, this might enable more patients to tolerate an MRA. Most importantly, the time it takes from starting a single therapy to complete/optimal medical treatment will be way shorter than in the current situation with up-titration of the conventional HF drugs.

Conclusion

The general aim of this thesis was to study the interplay between sodium, potassium, and both novel and conventional HF therapies. Regarding the interaction of serum potassium levels and conventional HF treatment, the following main conclusions can be drawn. Hyperkalaemia occurs in approximately 7-8% of patients with chronic HF from European and Asian countries. In patients with acute decompensated HF, this prevalence was even higher. Patients were more prone to develop hyperkalaemia if they had concomitant diseases as renal dysfunction, diabetes mellitus, and hyponatraemia. Both in acute and chronic HF, hyperkalaemia/higher serum potassium levels limited the possibility to titrate HF therapy to guideline-recommended dosages. Still, if patients remained on therapy and/or the prescribed dosages, hyperkalaemia did not affect the beneficial effects of these agents.

Regarding our research on the SGLT2-inhibitor empagliflozin in patients with acute HF, we can conclude that administering empagliflozin was well tolerated and seemed safe. Moreover, a lower rate of the combined endpoint of deaths, in-hospital worsening of HF and/or HF readmissions through day 60 was observed in patients treated empagliflozin compared with placebo. From a more mechanistical point of view we showed that treatment with empagliflozin led to a higher urinary output despite a temporarily decline in eGFR after treatment initiation. We found no effect on the fractional excretion of sodium or potassium. Moreover, urinary osmolality remained similar between both groups despite an increased fractional excretion of glucose after initiation of empagliflozin.

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Appendices

Dutch Summary | Nederlandse samenvatting

Acknowledgements | Dankwoord

Curriculum Vitae

NEDERLANDSE SAMENVATTING

Hartfalen

Hartfalen is een ernstige aandoening van het hart waarbij het hart niet meer in staat is om voldoende bloed rond te pompen in het lichaam. Patiënten met hartfalen presenteren zich met typische, maar niet-specifieke, klachten van kortademigheid, vermoeidheid, verminderde inspanningstolerantie en oedemen (het vasthouden van vocht). Geschat wordt dat ongeveer 30% van de wereldbevolking hartfalen ontwikkelt tijdens hun leven en dat dit percentage zal toenemen als gevolg van de vergrijzing.

Patiënten met hartfalen worden ingedeeld op basis van de pompfunctie van hun hart, de ejectiefractie (LVEF). Patiënten met een LVEF <40% worden geclassificeerd als hartfalen met een verminderde (reduced) ejectiefractie (HFrEF); met een LVEF 40-49% als hartfalen met een 'mid-range' ejectiefractie (HFmrEF); en een LVEF ≥50% als hartfalen met een behouden (preserved) ejectiefractie (HFpEF). Daarnaast kan onderscheid worden gemaakt tussen patiënten met acuut en chronisch hartfalen. Patiënten met chronisch hartfalen ontwikkelen langzaam verergerende symptomen over langere tijd, terwijl patiënten met acuut hartfalen een zeer spontane/acute verslechtering doormaken die snelle behandeling vereist. Onafhankelijk van de verschillende subtypen is de prognose van patiënten met hartfalen slecht. Ongeveer de helft van de patiënten met hartfalen overlijdt binnen 5 jaar na het stellen van de diagnose.

Tot nu toe richt de behandeling van acuut hartfalen zich met name op het verminderen van de tekenen van overvulling (bijv. kortademigheid en oedemen) door de zout- en waterexcretie in de nier te vergroten. Voor acuut hartfalen bestaan geen medicijnen die de prognose/overleving verbeteren.

Voor patiënten met HFrEF bestaan wel medicijnen die de cardiovasculaire morbiditeit en mortaliteit verbeteren. Hierbij gaat het om angiotensine converterend enzym (ACE)-remmers, angiotensinereceptorblokkers (ARBs'), bètablokkers en aldosteronreceptorantagonisten ofwel mineraal corticoïd receptorantagonisten (MRA's). Kortgeleden zijn daar meerdere nieuwe therapieën aan toegevoegd die

effectief bleken in het behandelen van patiënten met hartfalen. Van die nieuwe medicijnen zullen de sodium glucose cotransporter-2 (SGLT2)-remmers ook behandeld worden in dit proefschrift. SGLT2-remmers blokkeren de SGLT2-receptor in de proximale tubulus van de nier en daarmee blokkeren ze de terugresorptie van natrium en glucose.

Helaas is geen van de conventionele therapieën voor hartfalen effectief gebleken voor patiënten met HFpEF. Van de nieuwere therapieën zijn de resultaten neutraal of nog niet bekend, wat betekent dat er op het moment nog geen specifieke behandeling bestaat voor HFpEF.

Kortgezegd kan worden gesteld dat de prognose van patiënten met hartfalen op twee manieren kan worden verbeterd. Ofwel nieuwe, betere medicijnen moeten worden ontwikkeld ofwel een groter gedeelte van de patiënten moet in staat gesteld worden om hogere doseringen van het reeds bestaande medicament te verdragen. Het proces om de doseringen te verhogen tot wat geadviseerd wordt in de internationale richtlijnen wordt 'optitratie' genoemd.

Optitratie

Helaas wordt een groot gedeelte van de patiënten met hartfalen niet behandeld met de doseringen die geadviseerd worden. Verschillende factoren hebben invloed op de dosis van ACEi/ARB's, bètablokkers en MRA's waarvan hypotensie (lage bloeddruk) en een verslechterde nierfunctie de bekendste zijn. Daarnaast wordt een stijging van het kalium in het bloed gevreesd bij behandeling met ACEi/ARB's en MRA's.

Elektrolyten in hartfalen

Verschillende elektrolyten spelen een rol in de (patho)fysiologie van het hart. In dit proefschrift wordt gefocust op de rol van natrium en kalium.

Zowel de natrium- als de kaliumconcentraties worden strak gereguleerd door de opname in onze darmen en de uitscheiding door (met name) de nieren. Het proces om deze concentraties zo stabiel mogelijk te houden wordt 'homeostase' genoemd en is essentieel voor het behoud van een normale functie van de verschillende

typen cellen in het menselijk lichaam. Bij een normale nierfunctie worden natrium en kalium met name geresorbeerd in de proximale tubulus, de lis van Henle en de verzamelbuis. Onder andere de concentraties van natrium en kalium, de perfusie van de nieren en de concentratie van het hormoon aldosteron (wisselt kalium uit voor natrium in de verzamelbuis van de nier) zijn hierop van invloed. Slechts een klein gedeelte van het kalium wordt uitgescheiden met de feces.

Kalium speelt ook een belangrijke rol in de elektrofysiologie van verschillende cellen, waaronder de hartspiercellen. Serumconcentraties (extracellulair) van kalium worden strikt gecontroleerd met een concentratie van 3,5 tot 5,0 mmol/L als referentiewaarde. Wanneer de concentraties dalen tot onder de 3,5 mmol/L spreekt men van hypokaliëmie en wanneer deze stijgen tot boven de 5,0 mmol/L spreekt men van hyperkaliëmie. Beiden zijn geassocieerd met (mogelijk) fatale hartritmestoornissen en verslechterde uitkomsten.

De kaliumconcentraties worden ook beïnvloed door verschillende comorbiditeiten (bijv. diabetes en nierfunctiestoornissen) en behandelingen. Ook de bewezen effectieve behandeling van hartfalen met ACEi/ARB's, bètablokkers en MRA's beïnvloeden de kaliumhuishouding. Gezien het feit dat patiënten met hartfalen vaak (meerdere) comorbiditeiten hebben en daarnaast, indien mogelijk, behandeld worden met de genoemde therapieën, maakt het dat zij extra vatbaar zijn voor het ontwikkelen van een hypo-/hyperkaliëmie.

Waar de concentraties van kalium het hoogst zijn in de cellen, bevindt natrium zich met name in de extracellulaire matrix. Ook voor natrium geldt dat de regulatie in de nier beïnvloed wordt door verschillende therapieën voor hartfalen. Patiënten met acuut hartfalen presenteren zich bijvoorbeeld met de eerdergenoemde tekenen van overvulling. Dit wordt behandeld door gebruik te maken van lisdiuretica (plasmedicatie). Lisdiuretica blokkeren de resorptie van natrium, waardoor meer natrium (zout) en daarmee water wordt uitgeplast.

Recent hebben de SGLT2-remmers grote interesse verkregen binnen het veld van de cardiologie. Deze medicijnen zijn al enige tijd goedgekeurd voor de behandeling van diabetes mellitus type 2 door de American Food and Drug Administration

(FDA). Het werkingsmechanisme leek relatief simpel. SGLT2-remmers blokkeren de SGLT2-receptor in de proximale tubulus van de nier. Normaalgesproken zorgt dit enzym voor de resorptie van natrium en glucose. Het blokkeren van deze receptor zorgt dus voor een verminderde terugresorptie (en een veronderstelde verhoogde uitscheiding) van natrium en glucose. Dit zorgt ervoor dat patiënten met diabetes type 2 gemakkelijker hun overvloedige glucose verliezen door het uit te plassen. In de grote internationale studies bleek dat diabetespatiënten die behandeld werden met SGLT2-remmers een significant kleinere kans hadden op hartfalen-gerelateerde ziekenhuisopnames. Dit terwijl deze patiënten juist een verhoogd risico hebben op het ontwikkelen van hartfalen. Daarom werden deze medicijnen vervolgens onderzocht bij patiënten met hartfalen en ook daaruit bleek een overweldigende verbetering van cardiale en renale uitkomsten onafhankelijk van het feit of patiënten diabetes hadden. Hoewel SGLT2-remmer dus initieel werden gezien als een nieuwe klasse van orale antidiabetica, weten we nu dat hun gunstige effecten veel verder reiken. Toch is hun exacte beschermende en diuretische effect nog niet goed bekend.

Doel van dit proefschrift

In dit proefschrift is de wisselwerking onderzocht tussen de elektrolyten natrium en kalium enerzijds en de conventionele en meer moderne therapieën voor hartfalen anderzijds. Daarbij wordt de focus gelegd op de interactie tussen kalium en de conventionele behandeling van hartfalen. Daarnaast wordt onderzocht in welke mate de behandeling met SGLT2-remmers interfereert met de huishouding van natrium en kalium.

Patiënten met een verhoogd risico op het ontwikkelen van afwijkende kaliumconcentraties

In **hoofdstuk 2** hebben we patiënten geïdentificeerd met chronisch HFrEF die een verhoogd risico hadden op het hebben van een verhoogd/verlaagd kalium in hun bloed. Hiervoor is gebruik gemaakt van een cohort van ruim 6.000 patiënten uit Azië (ASIAN-HF registry). In dit cohort had 6,8% van de patiënten een hypokaliëmie en 7,0% hyperkaliëmie. Boven de 5,5 mmol/L wordt gesproken van matige hyperkaliëmie en boven de 6,0 mmol/L van ernstige hyperkaliëmie. Slechts 1,9% van de patiënten had een kalium boven de 5,5 mmol/L. Analyse toonde aan dat

het hebben van een hypokaliëmie geassocieerd was met het vrouwelijk geslacht, een hogere hartslag en meer tekenen van overvulling (oedeem en behandeling met diuretica). Hyperkaliëmie was dan weer geassocieerd met diabetes mellitus, nierfunctiestoornissen en lagere natriumspiegels in het bloed. Grote internationale verschillen werden geobserveerd. Zo kwam hypokaliëmie het meest voor in Indonesië, Hong Kong en Taiwan, terwijl hyperkaliëmie het meest voorkwam in India en Thailand. Deze bevindingen waren onafhankelijk van het type hartfalen (HFrEF versus HFpEF) en klinische factoren. Zowel hypo- als hyperkaliëmie had geen effect op overleving in vergelijking tot patiënten met een normaal kalium. Toch viel, afgebeeld op een continue schaal, op dat lagere kaliumspiegels geassocieerd waren met een verhoogd risico op overlijden of heropnames in het ziekenhuis gerelateerd aan hartfalen binnen 1 jaar.

De interactie tussen kalium in het bloed en behandeling van hartfalen volgens de internationale richtlijnen

In **hoofdstuk 3a** hebben we gekeken naar de associatie tussen het serum kalium en optitratie van medicatie voor hartfalen, zoals geadviseerd in de internationale richtlijnen. Hiervoor hebben wij specifiek gekeken naar een Europees cohort van patiënten dat bij de start suboptimaal behandeld werd en gedurende negen maanden werd opgetitreerd. In dit Europese cohort had 6,9% van de patiënten een hypokaliëmie aan het begin en 8,0% van de patiënten een hyperkaliëmie. Ook hier werden grote internationale verschillen gevonden. Zo bleek hyperkaliëmie het meest frequent voor te komen in Oost-Europa en Griekenland. Zowel de kaliumwaarde aan het begin, de waarde na negen maanden, als het verschil gedurende die negen maanden had geen effect op de prognose van deze patiënten. Wel bleek dat patiënten met een hogere kaliumwaarde aan het begin van het onderzoek een kleinere kans hadden om na negen maanden behandeld te worden volgens de richtlijnen. Dit terwijl een stijging in het kalium gedurende deze negen maanden geen afbreuk deed aan de gunstige effecten van optitratie met ACEi/ARB.

Onze resultaten over de interactie tussen hyperkaliëmie, therapie met ACEi/ARBs en uitkomsten zijn becommentarieerd door prof. Lund en prof. Pitt, beschreven in **hoofdstuk 3b**. Zij concluderen dat onze bevindingen suggereren dat het belangrijkste doel binnen de behandeling van patiënten met HFrEF ligt in het

optimaliseren van het gebruik van ACEi/ARB en MRAs. Ook benoemen zij dat de nieuwe kaliumbinders (patiomer en sodium zirconium cyclosilicate) er mogelijk voor kunnen zorgen dat hogere doseringen van deze medicatie getolereerd worden.

Waar in hoofdstuk 3 gekeken wordt naar patiënten met chronisch hartfalen, hebben we ons in **hoofdstuk 4** gefocust op patiënten die zijn opgenomen met acuut (gedecompenseerd) hartfalen. Patiënten werden dagelijks gemonitord (inclusief labafname voor kalium) gedurende de eerste zeven dagen van de opname of tot ontslag wanneer dat voor de zevende dag viel. Gedurende de beschreven periode ontwikkelde meer dan de helft van de patiënten in dit internationale cohort een afwijkend kalium. In totaal ontwikkelde 35% van de patiënten minimaal eenmaal een hyperkaliëmie en 17% minimaal eenmaal een hypokaliëmie. Patiënten die een hyperkaliëmie ontwikkelden, hadden een grotere kans om hun behandeling met een MRA gestopt te zien worden of te zien worden verlaagd in dosering. Net als in het chronische cohort was de kaliumafwijking op zichzelf niet geassocieerd met een verslechterde prognose. Echter leidde het verlagen/stoppen van de medicatie wel tot verminderde uitkomsten. Zelfs bij de patiënten die een hyperkaliëmie ontwikkelden, was hun prognose beter wanneer de doseringen van hun medicatie gelijk bleven of verder verhoogd werden.

SGLT2-remmers en hartfalen

In **hoofdstuk 5** hebben we het effect van de SGLT2-remmer empagliflozine prospectief onderzocht in een studie van tachtig patiënten opgenomen met acuut gedecompenseerd hartfalen. Deze gerandomiseerde, dubbelblinde, placebogecontroleerde, multicenter pilotstudie naar de veiligheid en effectiviteit van empagliflozine in patiënten met acuut hartfalen liet geen verschil zien tussen empagliflozine en placebo voor het gecombineerde eindpunt (verandering in klachten van kortademigheid, daling in NT-proBNP, diuretische respons en duur van de ziekenhuisopname). Toediening van empagliflozine werd goed getolereerd en leek veilig op basis van de lage frequentie van ongewenste effecten/bijwerkingen. Empagliflozine zorgde voor een verhoogde urineproductie en een sterker negatieve vochtbalans in een gedeelte van de patiënten. Daarnaast kwam de combinatie van sterfte, verslechtering van hartfalen tijdens de opname, en hartfalengerelateerde

heropnames binnen 60 dagen significant minder vaak voor in de groep behandeld met empagliflozine dan in de groep die een placebo kreeg toegediend.

Hoofdstuk 6 beschrijft de effecten van empagliflozine op de huishouding van natrium en glucose in de nieren bij het in hoofdstuk 5 beschreven cohort van patiënten met acuut hartfalen. Deze post-hoc analyse sloot aan op de bevindingen van hoofdstuk 5 over de grotere urineproductie en de meer negatieve vochtbalans in de patiënten die behandeld werden met empagliflozine. Dit werd gezien ondanks een initiële (tijdelijke) afname van de geschatte glomerulaire filtratiesnelheid (een geschatte maat voor nierfunctie) in de eerste dagen na het starten met empagliflozine. Gebaseerd op het werkingsmechanisme van SGLT2-remmers (het blokkeren van de terugresorptie van natrium en glucose in de proximale tubulus van de nier) hadden wij verwacht dat de verhoogde urineproductie het gevolg zou zijn van een verhoogde natriurese (zout uitplassen). Verrassend genoeg bleek echter dat de fractionele uitscheiding van zout niet toenam na het starten van empagliflozine. Bovendien bleef de osmolariteit van de urine gelijk tussen beide groepen ondanks de verhoogde (fractionele) uitscheiding van glucose na het starten van empagliflozine.

In **hoofdstuk 7** hebben we het effect van empagliflozine op de concentratie van kalium in het bloed en de urine onderzocht. Ook hier werd gebruik gemaakt van het cohort van patiënten opgenomen met acuut hartfalen. Onze resultaten suggereerden dat er geen effect is van empagliflozine op de fractionele uitscheiding van kalium door de nier ondanks de (initieel) verslechterde nierfunctie. Ook de kaliumconcentratie in het bloed werd niet beïnvloed door empagliflozine in vergelijking tot placebo. Wel bleek dat een behandeling met een aldosteronantagonist (MRA) minder vaak werd gestart bij patiënten die behandeld werden met empagliflozine vergeleken met patiënten uit de placeboarm. Dit werd gezien ondanks het feit dat de klinische profielen van de patiënten gelijk waren tussen beide studiemarmen.

DANKWOORD

Geachte prof. dr. Van der Meer, beste Peter, na een introductiegesprek bij prof. dr. Van Veldhuisen werd mij geadviseerd met jou contact op te nemen als beoogd begeleider voor mijn stage wetenschap. Dat bleek een schot in de roos. We bespraken de verschillende opties en kwamen er al snel uit dat de rol van kalium binnen hartfalen meer aandacht verdiende dan het op dat moment kreeg. Ik werd direct opgenomen in een ervaren onderzoeksgroep met mensen die elkaar, ook los van de wetenschappelijke inhoud, graag zien en spreken. In een van de tussentijdse evaluaties heb ik weleens benoemd dat jouw onderzoeksgroep streeft naar het hoogste en dat iedereen daarbij juist ook voor elkaar een stapje harder wil lopen. Ik heb me enorm op mijn gemak gevoeld bij jou en binnen de onderzoeksgroep en daarvoor ben ik je zeer dankbaar.

Geachte prof. dr. Voors, beste Adriaan, ik wil u heel hartelijk danken voor het delen van uw (wetenschappelijke) enthousiasme de afgelopen jaren. Met groot plezier heb ik de vrijdagen bijgewoond om stil te staan bij de bevindingen van de andere onderzoekers of van mijzelf. U hebt een unieke gave om de onderzoekers te laten voelen waar de meerwaarde van het onderzoek zit. Daarnaast werkt u aan de hand van het overzicht altijd met iedereen toe naar het einddoel, waardoor ik nooit het gevoel heb gehad te verdwalen in alle mogelijkheden. Als laatste wil ik kwijt dat ik de snelheid waarmee u inhoudelijk en opbouwend commentaar kunt geven op een artikel echt ongekend vind. Zeer veel dank!

Beste Jasper, ik heb de eer om de eerste te zijn die met jou als co-promotor mag promoveren. Ik kan jou bij de (hopelijk vele) promovendi die nog mogen volgen van harte aanbevelen. Ondanks dat je er een sport van maakte dat niemand precies wist waar je je op de planeet bevond, was je voor mij altijd bereikbaar en een heel belangrijke hulplijn. Je hebt een unieke wetenschappelijke gave, kunt ongekend snel werken en bent een heel prettig mens om mee samen te werken. Daarom is de prachtige stap je zo gegund om als associate professor te werken aan de University of Public Health in Singapore. Toch hoop ik je ook nog geregeld hier in Groningen te treffen!

Geachte leden van de beoordelingscommissie, beste prof. dr. M.P. van den Berg, prof. dr. S.J.I. Bakker en prof. dr. H.P. Brunner-La Rocca, hartelijk dank voor het positief beoordelen van mijn proefschrift.

Beste dr. Damman en prof. dr. Lambers Heerspink, beste Kevin en Hiddo, op advies van Adriaan zijn jullie de twee geweest die mij in een vroege fase binnen mijn onderzoekstraject verantwoordelijk durfden te maken voor een klinische studie. Ik vond het prachtig om bij alle facetten betrokken te zijn die bij de Empa-Response-AHF studie kwamen kijken. Het is een avontuur geworden waar ik met enorm veel plezier en voldoening op terugkijk. Enorm veel dank voor deze kans en het uitgesproken vertrouwen.

Geachte prof. dr. Van Veldhuisen, in 2015 klopte ik bij u aan. We bespraken dat ik graag de masterfase van mijn studie wilde beginnen met mijn wetenschappelijke stage. U gaf een uitgebreide toelichting van de afdeling en gaf daarbij ook eerlijk aan dat de lat erg hoog ligt, maar dat men elkaar helpt om dat niveau te bereiken en te behouden. Op die manier heb ik het ook zeker ervaren. De enorme ervaring gecombineerd met een goede sfeer zorgt ervoor dat de onderzoeksgroep keer op keer successen behaalt. Ik wil u bedanken voor de samenwerking en verwijzing naar Peter en Adriaan die mij zo fantastisch begeleid hebben.

Dear prof. dr. Lam, dear Carolyn, Tiew-Hwa, Wan Ting, Xuanyi, and Wouter, dear team Singapore, thank you for the great collaboration between Groningen and Singapore. In March 2019, I had the opportunity to visit the National Heart Centre in Singapore for a week. This under the expectation to come back and extend our collaboration in a later stage. I still feel that missing out on that longer stay was one of the biggest personal setbacks due to COVID-19. A special thanks to Carolyn, for attending our research meetings every Friday and creating such a positive atmosphere.

Beste Alma, Minke en Daniëlle, heel veel dank voor jullie zeer adequate ondersteuning en de gezellige praatjes als ik even in persoon langskwam om iets te regelen of te bespreken.

Beste collega's van de Cardio Research,

Het is niet voor niets dat het ook in coronatijd dringen geblazen was om op de Cardio Research te kunnen werken. De spaarzame plekken die beschikbaar waren gesteld, bleken continu volgeboekt. Dit omdat jullie met elkaar een enorm goede sfeer creëren en daarmee laten jullie de passanten, die wij als arts-onderzoekers eigenlijk zijn, enorm thuis voelen. Heel veel dank daarvoor!

Beste collega's "op de vierde" en in het triadegebouw Koen, Bernadet, Eva, Bob, Bart, Olivier, Iris, Lisa, Iziah, Yildau, Tom, Marie-Sophie, Abdullah, Jordy, Jan Walter, Hellen, Sina, Suzanne, Sylwia, Paulien, Ruben, Mariëlle, Bao-Oanh, Bastiaan, Joylene, Vicente, Sebastiaan, Gijs, Anne, Victor, Remco, Haye, Alice, Niels, Janny, Herman, Silke, Marloes, Mathilde, Martijn, Annet, Nienke, Salva, Kirsten, Navin, Martin, David, Carolin, Aad, Karla, Katja en Arnold dank voor een prachtige tijd. A special thanks to Mario, Tim and Nils. I had a great time in 'De groote griet' with you guys, cheering and drinking on another (European) success of Ajax.

Nadat ik eerst een jaar onderdeel mocht zijn van de organisatie van het International Student Congress Of bio(Medical) Sciences (ISCOMS) in 2014, mocht ik een jaar later mijn eigen organisatie van 28 man samenstellen om de editie van 2015 tot een ongekend succes te maken. Enorm veel tijd heb ik mogen doorbrengen met Arlette, Piter, Willemijn, Valérie, Henk, Marije, Arianne en Annelou als Dagelijks Bestuur. Samen werd elke vergadering een feest en elke borrel naar een hoger niveau getild. Ik vind het prachtig dat ons etentje op de maandagavond nog zo vaak als mogelijk doorgaat en hoop daar nog een lange periode van te mogen genieten. Bauke, Dorien, Fien, Lotte, Teske, Anne Linde, David, Thomas, Annelot, Ireen, Mirre, Uzaifa, Maarten, Mila, Lize, Annelie, Anouk, Tijmen en Emmalie, jullie waren toppers. De efficiëntste organisatie zullen we zeker niet geweest zijn, maar met elkaar was het een feest om in ons mooie huisje te werken. Daarnaast heeft het organiseren van ISCOMS ervoor gezorgd dat ik daarna zelf onderzoek wilde doen. Na zo veel internationale studenten uit ongeveer 60 verschillende landen zo enthousiast gezien te hebben, werd het tijd om zelf te ondervinden hoe het is om onderzoek te doen en daarvan is dit proefschrift het eindresultaat.

Binnen dit dankwoord gaat natuurlijk een speciale dank uit naar Ruud en Paul. Jullie waren meer dan advisors. Jullie betrokkenheid bij ons op zowel organisatorisch als persoonlijk vlak was ongekend. ISOMS kon niet een soortgelijk succes zijn zonder jullie en we hadden er als organisatie dan ook lang niet zo veel plezier uit gehaald.

Lieve Derek, Mathijs, Oscar, Lilian, Jasper en Boris, in grote tegenstelling tot wat ik hierboven over ISOMS schrijf, zijn wij met elkaar een heel nieuw concept begonnen. Meer dan het idee om een vereniging op te richten voor studenten met een interesse in de chirurgie was er niet. Geen letter stond op papier, geen euro op de rekening. Vanaf dag 1 van de Vereniging Chirurgie voor Medisch Studenten (VCMS) hebben we er samen de schouders ondergezet om iets te creëren dat ik inmiddels toch wel als gevestigde naam durf te beschouwen. Af en toe voelde het of ik daar op een zeer gewilde plek zat, maar met een verkeerde/andere ambitie. Ik hoefde geen chirurg te worden, maar had wel een ongekende fascinatie voor het vak. Daarnaast deelde ik een groot gedeelte van de tijd jullie visie, waardoor we samen heel veel hebben klaargespeeld op organisatorisch niveau. Inmiddels hebben we het concept meerdere keren mogen overdragen aan nieuwe, enorm bevlogen groepen die het verder geprofessionaliseerd hebben. Dus wie weet wat het in de toekomst nog mag worden en waar we op onze oude dag op mogen terugkijken.

800 coassistenten uit het gehele land een prachtig weekend bezorgen waarin ze ook nog eens veel leren over zichzelf en wat er mogelijk is voor hun toekomst. Het was onze taak om dat in ruim 1.5 jaar voor elkaar te krijgen voor het Nationaal Coassistenten Congres van 2019. Ik denk dat we hier ruimschoots in zijn geslaagd en terug mogen kijken op een prachtig congres. Een speciale dank voor het Dagelijks Bestuur bestaande uit Liselore, Charlotte, Jara, Leonoor, Thomas, Lynn en Gijs. Wie had gedacht dat acht willekeurige individuen van de acht verschillende medische faculteiten zo goed met elkaar overweg zouden kunnen. De weg tot en met het congres is in belangrijke mate door jullie een groot feest geworden. Helaas laten de verschillende agenda's het niet meer toe om elkaar te zien met de frequentie die we zouden willen, maar ik weet zeker dat we het tot in de eeuwigheid zullen blijven proberen. En natuurlijk wil ik mijn fantastische commissie met Cathelijne, Irene, Henk en Piter bedanken. Ik denk dat we Groningen op de enige

juiste manier hebben vertegenwoordigd en vanuit onze functie een prachtig en veelzijdig programma in elkaar hebben gedraaid. Ik kijk met veel plezier terug op onze inhoudelijke bijdrage, maar waarschijnlijk toch het meest op de momenten dat het minder om de inhoud ging.

Zowel de Masterraad tijdens het eerste jaar coschappen in Groningen als de Coraad tijdens het tweede jaar in Zwolle was, ondanks de hoge frequentie waarin de samenstelling wisselde, continu een enorm gezellige groep. Samen hebben we mooie plannen doorgevoerd, nieuwe ideeën geïnitieerd, fantastische weekenden gehad en enorm relativerende avonden gehad. Ik wil jullie daar allen enorm voor danken!

JC Scafati, 18 jongens die gasten werden en nu mannen zijn. Scafati, Derulo, Prijsduif of Nathan, we hebben zeer uiteenlopende stempels op ons hoofd gedrukt, maar al met al veranderde het weinig aan wie we waren. Wellicht waren we wel het laatste jaar waarin je nog ongegeneerd 'langstudeerder' mocht zijn dus daar is bij ons ook veel gebruik van gemaakt. In eerste instantie deed ik hier niet echt aan mee, maar gelukkig kwam snel de ommekeer door de bestuurs- en onderzoeksjaren. Inmiddels is iedereen aan het werk op plekken die zij leuk vinden en functies aan het bekleden waar zij trots op mogen zijn. Ik ben er trots op dat wij de tijd hebben genomen om verder naar elkaar toe te groeien en altijd voor elkaar klaar te staan. Wel hoop ik dat de aantrekkende kracht van het westen spoedig zal afnemen, zodat ik in ieder geval een deel van jullie weer iets dichterbij me heb.

Huize EKT. Lieve oud-huisgenoten, huisgenoten en nieuwste generatie aan de Nieuwe Blekerstraat, voor jullie een speciale en centrale plek binnen dit dankwoord. Wat heb ik zes prachtige jaren met jullie mogen beleven. Of het nu domweg spelletjes spelen was of tot diep in de nacht aan tafel zitten om aan het einde van de zit minstens de halve wereld verbeterd te hebben, het heeft mij enorm veel plezier en mooie herinneringen gebracht. Ik vind het heerlijk dat velen van jullie trouw zijn gebleven aan het noorden en dat we elkaar nog veelvuldig opzoeken. Natuurlijk ook een speciale dank voor Max en Dodo, de trouwe viervoeters die ons huis tot een nog mooiere plek maakten/maken.

Casa di Laurea. Het eerste huis waar ik ging wonen na het 'echte studentenhuis'. Met een deel van club zijn we dit huis begonnen om elkaar te ondersteunen in het afstuderen... We hebben elkaar zeker met veel dingen ondersteund, maar of afstuderen daar nu altijd bovenaan de prioriteitenlijst stond, is maar zeer de vraag. Toch is het goed om te zien dat iedereen meer dan goed terecht is gekomen. Ik ben trots dat we daar samen in die tijd de basis voor hebben gelegd. Ik vond het een prachtige tijd met jullie!

Casa Carry (Martijn, Tim K., Tim van V. en Tjerk). Met jullie als huisgenoten heb ik een prachtig M2-jaar mogen beleven in Zwolle. Zo dicht bij het ziekenhuis dat we zelfs in de regen droog aankwamen, maar zodra we thuiskwamen was het ziekenhuis heel ver weg. Een baken van gezelligheid, slappe grappen, elkaar op je plek zetten en vooral veel gevloek en getier. Een ideale combinatie om alle nieuwe indrukken van dat jaar een beetje te relativieren. Al met al een heerlijk jaar waar ik jullie zeer dankbaar voor ben.

Lieve Jara, Flora en Annemarie, na mijn jaar in Zwolle was het tijd om terug te keren naar Groningen voor de laatste fase van mijn master. Dat werd ook het moment dat ik bij jullie mocht intrekken en voor het eerst van mijn leven met dames ging samenwonen. Als je het aan mijn vrienden vraagt, ging dat me net iets te gemakkelijk af en was ik binnen no-time gewend aan een avondje op de bank met thee en koekjes. Er is veel gebeurd in die periode en ik kijk er met een goed gevoel op terug hoe we er voor elkaar zijn geweest bij zowel de hoogte- als de dieptepunten. Naar het einde toe moesten de thee en koekjes weer worden ingeruild, want jullie besloten om je toekomst iets zuidelijker te vervolgen. Marco, Jewan en Rick kwamen voor jullie in de plaats wat resulteerde in weer een nieuwe dynamiek. Projecten binnen huis werden ineens aangepakt, kastdeurtjes werden weer vast gedraaid en een nieuwe ijskast voor wat relativiserende drankjes werd geïnstalleerd. Een heerlijke setting om in thuis te komen, dank daarvoor!

Lieve Kim, Stephanie, Jan en Eelco, de welbekende maatjes van thuisthuis. Helaas is het gezien de wisselende agenda's altijd nodig om direct een volgende afspraak vast te leggen als we elkaar zien, maar het getuigt er ook van dat we dit altijd graag opnieuw willen vastleggen. Ik geniet van de gezellige avonden die we altijd met

elkaar hebben en het ongekende aantal oude koeien dat dan uit de sloot gehaald wordt. Hopelijk kunnen we dat nog lang blijven doen.

Tsja en dan mijn paranimfen, Jasper en Boris. Jullie zijn natuurlijk eerder al kort genoemd in dit dankwoord, maar gezien jullie dubbelrol mag ik hier nog minstens een volle alinea aan jullie wijden. De mensen die heel geïnteresseerd zijn in hoe wij elkaar hebben leren kennen, kunnen dit teruglezen in het proefschrift van Jasper, maar concluderend kunnen we stellen dat het op veel toeval berust. Toch zijn we inmiddels al ruim 7 jaar een onafscheidelijke drie-eenheid. Ik vind het heerlijk dat Jasper en ik met onze nieuwe academische graad in de meerderheid zijn ten opzichte van Boris, al denk ik nog steeds niet dat we hem kunnen overstemmen. Ik kijk enorm uit naar alle uitjes op de boot, fiets of ski's die ons nog te wachten staan en waar we met gepast hoofddeksel een kaartje zullen leggen. Bedankt voor jullie steun en vertrouwen. Natuurlijk gaat er ook veel dank uit naar Elmire en Laura. En en en... de nieuwe grote/kleine trots; Elea!

Lieve familie Lieverse (Louis en Jasmijn, Charlotte, Relinde en Sylvia, Tom en Jorrit, en Daniëlle), natuurlijk wil ik ook jullie enorm bedanken voor de steun in de afgelopen jaren. Een weekendje tussendoor bij jullie deed me in vele opzichten altijd goed. Bij jullie thuis voelt het voor mij als een mini-vakantie en daarbij nemen jullie altijd uitgebreid de tijd om stil te staan bij de ervaringen van iedereen. Daarnaast houden jullie elkaar op een unieke manier scherp, zodat je zeker weet dat je Son weer verlaat met beide benen op de grond en mocht je met iets te veel ego zijn gekomen, dan kun je weer keurig van vooraf aan beginnen om dat op te bouwen. Ik geniet bij jullie en met jullie!

Dag Femke, lief zussie, eigenlijk heb ik aan jou te danken dat ik geneeskunde doe. Zonder jouw tip had ik biologie al in een vroeg stadium laten vallen. Toen ik eenmaal begon, was jij al ver in je studie fysiotherapie gevorderd. Dat maakte dat wij samen konden sparren over het menselijk lichaam. Jij behaalde je diploma en legde de eed af als fysiotherapeut. Ongeveer tegelijkertijd begon ik aan mijn onderzoekstraject. Men vertelt je van tevoren dat een promotietraject een lastige fase kan zijn in je leven. Toch valt dat in het niet bij de uitdagingen die jij hebt doorstaan de afgelopen periode. Gelukkig heeft dit ons ook mooie dingen gebracht. Ondanks dat ik (erfelijk

belast) nooit zo'n beller ben geweest, hebben we nu uitgebreid de tijd genomen om daar verandering in te brengen. Ik vind het knap hoe je altijd zo opgewekt blijft en ben enorm trots op je!

Lieve Jochem, ik vind het ongekend hoe goed je binnen onze familie past. Je kunt volledig jezelf zijn en elke opmerking plaatsen nog voor je hem hebt gedacht. Daarnaast heb je ook een meer timide kant, waarmee je hebt laten zien een ongekenste steun te zijn voor Femke. Daar ben ik je enorm dankbaar voor en ik hoop dat je samen met Miepje nog lang onze koude kant blijft.

Lieve papa en mama, gelukkig zijn jullie heel vaak van dichtbij komen bekijken hoe het met de studie en het onderzoek ging. De vreugde waarmee jullie hier elke keer door het stadje lopen, doet mij altijd enorm goed. Het is prachtig om te zien hoe jullie met elkaar en met ons kunnen genieten. Dank voor jullie vertrouwen en steun om er af en toe net wat langer over te mogen doen en daarbij mijn eigen route te mogen kiezen. Dit heeft er allemaal toe geleid dat dit proefschrift het eindresultaat heeft kunnen worden. Een eindresultaat waar ik trots op ben.

Lieve Michelle, lieve Miepje, eigenlijk was je nog voor mijn promotietraject begon al benieuwd hoe ik een (liefdevolle) alinea over jou zou schrijven. Meestal blinken we niet uit in het over en weer geven van complimentjes, maar genieten we er meer van om de ander belachelijk te maken, zowel met als zonder publiek. Maar voor deze keer zal ik een uitzondering maken en je de credits geven die je meer dan verdient. Lieve Miepje, ik ben er trots op dat je al jaren mijn vriendinnetje bent. Ik vind het dan ook knap dat je het al die tijd met mij uithoudt, maar heb gelukkig elke dag het gevoel dat je dat nog heel lang gaat volhouden. Juist daarom hoop ik dat het ons in de nabije toekomst gegund is om samen ergens onze intrek te nemen.

CURRICULUM VITAE

Joost Coenraad Beusekamp was born on July 6th 1993 in Utrecht, the Netherlands. He attended both primary (De Palster) and secondary (Koningin Wilhelmina College) school in Culemborg and finished secondary school in 2011. That same year he started Medical School at the University of Groningen. During the third year of the Bachelor, Joost was part of the organising committee of the International Student Congress of (bio)Medical Sciences (ISCOMS). This congress enables approximately 600 students from over 50 countries to present their (bio)medical research on an international stage. The year after, he became the president of ISCOMS and was ultimately responsible for the 22nd edition of this congress.

Seeing all these enthusiastic students from all over the world, convinced him to explore a scientific career for himself as well. Therefore, he contacted prof. dr. Peter van der Meer and prof. dr. Adriaan Voors and proposed to do his research clerkships prior to his clinical rotations. This collaboration under the daily supervision of dr. Jasper Tromp resulted in his first publication in the European Journal of Heart Failure and led to a successful application for the MD/PhD programme of the Junior Scientific Masterclass in Groningen. This programme provides students with a personal grant of approximately €70,000 to fulfil your own research projects and to combine this with your clinical rotations. These research projects resulted in several scientific papers including one on the outcomes of the randomized-clinical trial Joost executed under the direct supervision of prof. dr. Adriaan Voors, prof. dr. Hiddo Lambers Heerspink and dr. Kevin Damman.

The first and second year of his clinical rotations were spent in Groningen and Zwolle respectively, and Joost finalised his clinical rotations at the Cardiology Department of the University Medical Center Groningen (UMCG). During these clerkships, he was part of the executive board of the 'Nationaal Coassisten Congres 2019', which was a three-day congress for medical interns to explore all the possibilities for their future either inside or outside of the hospital.

After obtaining his medical degree, he participated as a sub-investigator in several international clinical trials at the Cardio Research Department of the UMCG. Apart

from his scientific position and his work as a clinician, Joost also works as an on-call emergency physician for several geriatric care facilities in and around Groningen.

Joost presented his research at several international conferences including conferences of the European Society of Cardiology and online lectures for the Physicians' Academy for Cardiovascular Education. His PhD programme has resulted in this thesis, which he plans to defend on Wednesday 02 February 2022.