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Beusekamp, Joost C.; Tromp, Jasper; Boorsma, Eva M.; Heerspink, Hiddo J. L.; Damman, Kevin; Voors, Adriaan A.; van der Meer, Peter

*Published in:*  
European Journal of Heart Failure

*DOI:*  
[10.1002/ejhf.2197](https://doi.org/10.1002/ejhf.2197)

**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:*  
2021

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

*Citation for published version (APA):*

Beusekamp, J. C., Tromp, J., Boorsma, E. M., Heerspink, H. J. L., Damman, K., Voors, A. A., & van der Meer, P. (2021). Effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on potassium handling in patients with acute heart failure. *European Journal of Heart Failure*, 23(6), 1049–1052. <https://doi.org/10.1002/ejhf.2197>

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## RESEARCH LETTER

doi:10.1002/ejhf.2197

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

Disturbances of potassium homeostasis are common in patients hospitalised for heart failure (HF).<sup>1,2</sup> This increased risk of hypo- and hyperkalaemia is caused by haemodynamic 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.<sup>2,3</sup> Therefore, current HF guidelines recommend close monitoring of serum potassium concentrations in patients hospitalised with HF.<sup>4</sup>

Treatment with sodium–glucose co-transporter 2 (SGLT2) inhibitors reduces the risk of worsening HF and cardiovascular death in ambulant patients with HF.<sup>5,6</sup> In acute HF, SGLT2 inhibitors increase diuresis despite a temporary decline in estimated glomerular filtration rate (eGFR).<sup>7,8</sup> Due to the effects of SGLT2 inhibitors on renal function, an impact on potassium homeostasis might be expected. Although 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.<sup>9</sup> Therefore, blocking the SGLT2 receptor might affect potassium homeostasis.

Data on the risk of potassium disturbances after initiating treatment with SGLT2 inhibitors remain inconsistent. In patients with diabetes, dapagliflozin did not affect serum potassium concentrations.<sup>10</sup> However, patients on mineralocorticoid receptor antagonist (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.<sup>11</sup> 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.<sup>6,12</sup> 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.<sup>13</sup> Contrastingly, no differences in the frequency of hyperkalaemia were seen in the large canagliflozin trials (CREDENCE and CANVAS).<sup>14,15</sup> 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.<sup>7</sup> 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:  $\text{FEK (\%)} = \frac{\text{urinary potassium (mmol/L)} \times \text{serum creatinine (mmol/L)}}{\text{serum potassium (mmol/L)} \times \text{urinary creatinine (mmol/L)}} \times 100\%$ . 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  $\times$  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; StataCorp LLC, College Station, TX, USA). 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.<sup>7</sup> In short, patients were 76 (38–89) years old, 33% were women and mean baseline eGFR was  $55 \pm 17$  mL/min/1.73 m<sup>2</sup>. Background treatment with angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, 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 ( $P = 0.788$ ) (online supplementary Table S3). 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,  $P = 0.399$ ].

In the total population, median (interquartile range) serum potassium concentrations increased from baseline until 96 h after admission [0.4 (–0.1–0.6) mEq/L,  $P < 0.001$ ]. In total, 33 patients (42%) received potassium supplementation in the first 96 h 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, vs. 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 and 1B). Fractional excretion of potassium remained constant through the course of treatment, irrespective of the study drug (Figure 1C and 1D) and no interaction with use of an MRA was seen (online supplementary Figure S1 and Table S1).

The proportion of patients on MRA therapy between groups was similar at baseline (19 for empagliflozin and 18 for placebo;  $P = 0.807$ ) (Table 1). Of the patients without

**Table 1** Differences in characteristics at baseline of patients with and without potassium supplementation and with/without mineralocorticoid receptor antagonist initiation

Factor	Without potassium supplementation (n = 46)	With potassium supplementation (n = 33)	P-value	Empagliflozin + MRA initiation (n = 4)	Placebo + MRA initiation (n = 15)	P-value
Age (years)	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 class III	34 (77%)	25 (76%)	0.27	2 (50%)	10 (67%)	0.14
LVEF (%) <sup>a</sup>	36 (22, 50)	35 (25, 50)	0.78	29 (29, 29)	32 (22, 40)	0.79
HFrEF <sup>a</sup>	14 (56%)	11 (52%)	0.81	1 (100%)	6 (60%)	0.43
eGFR (CKD-EPI) (mL/min/1.73 m <sup>2</sup> )	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 (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 hypercholesterolaemia	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 receptor—neprilysin inhibitor	2 (4%)	1 (3%)	0.75	0 (0%)	0 (0%)	N.A.
Beta-blocker	28 (62%)	25 (76%)	0.21	2 (50%)	8 (53%)	0.91
Mineralocorticoid receptor antagonist	21 (47%)	15 (45%)	0.92	0 (0%)	0 (0%)	N.A.
Cholesterol-lowering drugs	20 (44%)	13 (39%)	0.66	1 (25%)	8 (53%)	0.31
Diuretic dose (re-calculated to furosemide) through day 4 (mg)	300 (165, 560)	320 (200, 440)	0.79	160 (120, 180)	280 (200, 600)	0.021
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)	0.84
Episodes of hypokalaemia until day 4 (in number of patients)	10 (8)	24 (13)	0.14	3 (1)	14 (7)	0.58
Episodes of hyperkalaemia until day 4 (in number of patients)	5 (5)	6 (5)	0.482	0 (0)	2 (2)	0.440

ACE, angiotensin-converting enzyme; CKD-EPI, chronic kidney disease-Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

<sup>a</sup>Only available in a subset of 46 patients.

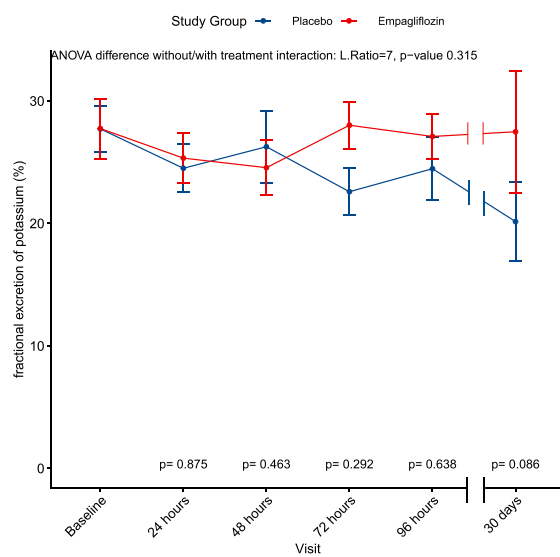
MRA therapy (21 per arm), 15 patients (71%) were initiated on an MRA throughout follow-up in the placebo group, compared with 4 patients (19%) in the empagliflozin group ( $P = 0.035$ ).

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.<sup>16</sup> We cannot provide a clear explanation for this finding, since baseline eGFR, proportion of patients with HF with reduced ejection fraction, number of hyperkalaemic events, duration of hospitalisation, and concomitant medication (except for loop diuretics) were all similar between both treatment arms (Table 1 and online supplementary Table S2). Still, physicians may have been discouraged to initiate an MRA since empagliflozin caused an initial decline in eGFR in these patients.<sup>8</sup>

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.<sup>17</sup> Secondly, we collected untimed spot urine samples and not 24 h 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 were available to correct for the effect of magnesium on potassium excretion.<sup>18</sup> 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



**Figure 1** Depicting 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. 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.

was left to the treating physician, we cannot fully explain this finding. Data on potassium supplementation in HF are scarce. The Danish national registry reported that 80.7% of patients with chronic HF were treated with potassium supplements.<sup>19</sup> Contrastingly, Núñez *et al.*<sup>1</sup> described a proportion of 7.6% in patients recently hospitalised with acute HF. 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.

### Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Conflict of interest:** none declared.

**Joost C. Beusekamp<sup>1</sup>,  
Jasper Tromp<sup>1,2,3</sup>, Eva M. Boorsma<sup>1</sup>,  
Hiddo J.L. Heerspink<sup>1,4</sup>,  
Kevin Damman<sup>1</sup>, Adriaan A. Voors<sup>1</sup>,  
and Peter van der Meer<sup>1\*</sup>**

<sup>1</sup>University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;

<sup>2</sup>National Heart Centre Singapore & Duke-National University of Singapore, Singapore;

<sup>3</sup>Saw Swee Hock School of Public Health, National University of Singapore, Singapore; and <sup>4</sup>George Institute for Global Health, Sydney, Australia

\*Email: p.van.der.meer@umcg.nl

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