Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled

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Abstract

Aims

Hyperkalaemia frequently leads to interruption and discontinuation of neurohormonal antagonists, which may worsen heart failure prognosis. Some studies suggested that sodium-glucose cotransporter 2 inhibitors reduce hyperkalaemia, an effect that may have important clinical implications. This analysis evaluates the effect of empagliflozin on the occurrence of hyper- and hypokalaemia in HF.

Methods and results

EMPEROR-Pooled (i.e. EMPEROR-Reduced and EMPEROR-Preserved combined) included 9583 patients with available serum potassium levels at baseline (98.6% of the total EMPEROR-Pooled population, n = 9718). Hyperkalaemia was identified by investigators’ reports of adverse events, and by a laboratory serum potassium value above 5.5 mmol/L and 6.0 mmol/L. The main outcome was a composite of investigator-reported hyperkalaemia or initiation of potassium binders. Patients with high potassium at baseline were more frequently diagnosed with diabetes and ischaemic HF aetiology and had lower left ventricular ejection fraction and estimated glomerular filtration rate but were more frequently treated with sacubitril/valsartan or mineralocorticoid receptor antagonists. Empagliflozin (compared with placebo) reduced the composite of investigator-reported hyperkalaemia or initiation of potassium binders [6.5% vs. 7.7%, hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.71–0.95, P = 0.01]. Empagliflozin reduced hyperkalaemia rates regardless of the definition used (serum potassium > 5.5 mmol/L: 8.6% vs. 9.9%, HR 0.85, 95% CI 0.74–0.97, P = 0.017; serum potassium > 6.0 mmol/L: 1.9% vs. 2.9%, HR 0.62, 95% CI 0.48–0.81, P < 0.001). The incidence of hypokalaemia (investigator-reported or serum potassium < 3.0 mmol/L) was not significantly increased with empagliflozin.

Conclusions

Empagliflozin reduced the incidence of hyperkalaemia without significant increase in hypokalaemia.

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Introduction

Potassium is the most abundant cation in humans: 98% intracellular (≈140 mmol/L) and 2% extracellular (≈3.8–5.0 mmol/L). Potassium is essential for normal cellular function, and severe potassium abnormalities (i.e., hypokalaemia and hyperkalaemia) can lead to cardiac arrhythmias and death.1–3 Patients with heart failure (HF) experience frequent potassium abnormalities during the disease progression due to HF-related neurohormonal activation, related comorbidities (e.g., chronic kidney disease [CKD], older age, and diabetes mellitus), and treatments (e.g., renin-angiotensin-aldosterone system inhibitors [RAASi], diuretics, and beta-blockers).4,5

Both hypo- and hyperkalaemia have been associated with poor prognosis in HF.6–9 Still, hyperkalaemia has been receiving particular attention because its occurrence may limit the initiation, maintenance, or up-titration of RAASi therapies that improve prognosis in HF.1,3

Empagliflozin reduced the incidence of hyperkalaemia without increasing the risk of hypokalaemia.

Keywords

Potassium • Hyperkalaemia • Heart failure • Empagliflozin
Table 1  Characteristics of the EMPEROR-Pooled population (n = 9583) by categories of serum potassium at baseline

| Serum potassium | <4.0 mmol/L | 4.0–5.0 mmol/L | >5.0 mmol/L | P-value\(^c\) |
|-----------------|-------------|----------------|-------------|--------------|
| No. of patients | 910 (9.5)   | 7116 (74.3)    | 1557 (16.2) |              |
| Age, years      | 69.9 ± 11.3 | 69.8 ± 10.4    | 70.4 ± 9.8  | 0.12         |
| Male sex, n. (%)| 521 (57.3)  | 4508 (63.4)    | 1036 (66.5) | <0.001       |
| BMI, kg/m²      | 29.4 ± 6.0  | 29.1 ± 5.8     | 28.7 ± 5.7  | 0.003        |
| BMI categories, n. (%) |          |                |             | 0.004        |
| BMI <25         | 237 (26.0)  | 1832 (25.7)    | 423 (27.2)  |              |
| BMI 25–30       | 276 (30.3)  | 2456 (34.5)    | 559 (35.9)  |              |
| BMI >30         | 397 (43.6)  | 2828 (39.7)    | 575 (36.9)  |              |
| Race, n (%)     |             |                |             | 0.010        |
| White           | 635 (69.8)  | 5246 (73.7)    | 1178 (75.7) |              |
| Asian           | 155 (17.0)  | 1116 (15.7)    | 217 (13.9)  |              |
| Black           | 57 (6.3)    | 381 (5.4)      | 69 (4.4)    |              |
| Other or missing| 63 (6.9)    | 373 (5.2)      | 93 (6.0)    |              |
| Region, n (%)   |             |                |             | <0.001       |
| North America   | 154 (16.9)  | 841 (11.8)     | 133 (8.5)   |              |
| Latin America   | 206 (22.6)  | 1989 (28.0)    | 556 (35.7)  |              |
| Europe          | 360 (39.6)  | 3002 (42.2)    | 619 (39.8)  |              |
| Asia            | 121 (13.3)  | 904 (12.7)     | 149 (9.6)   |              |
| Other           | 69 (7.6)    | 380 (5.3)      | 100 (6.4)   |              |
| LVEF, %         | 46.2 ± 15.5 | 44.2 ± 15.1    | 41.8 ± 15.2 | <0.001       |
| LVEF categories, n (%) |        |                |             | <0.001       |
| LVEF ≤40%\(^a\) | 295 (32.4)  | 2656 (37.3)    | 724 (46.5)  |              |
| LVEF >40%\(^d\) | 615 (67.6)  | 4460 (62.7)    | 833 (53.5)  |              |
| NT-proBNP, pg/mL\(^d\) | 1369 (659–2676) | 1240 (651–2217) | 1484 (759–2622) | 0.002 * |
| Troponin T, ng/mL\(^d\) | 20.8 (12.7–32.8) | 18.5 (12.3–28.1) | 22.0 (14.8–33.8) | <0.001 * |
| UACR, mg/g\(^c\) | 30.0 (9.0–116.4) | 19.0 (7.1–68.1) | 26.0 (9.7–100.0) | 0.094 * |
| Heart rate, bpm  | 72.2 ± 12.4 | 70.6 ± 11.7    | 70.4 ± 11.9 | 0.002        |
| SBP, mmHg        | 1288 ± 16.8 | 1281 ± 16.3    | 1273 ± 16.3 | 0.019        |
| DBP, mmHg        | 76.1 ± 10.5 | 75.1 ± 10.7    | 73.9 ± 10.7 | <0.001       |
| eGFR, mL/min/1.73 m\(^2\) | 63.0 ± 20.9 | 62.6 ± 20.3 | 54.1 ± 19.7 | <0.001       |
| eGFR categories, n (%) |        |                |             | <0.001       |
| eGFR ≥60         | 498 (54.7)  | 3808 (53.5)    | 564 (36.2)  |              |
| eGFR 45 to <60   | 223 (24.5)  | 1792 (25.2)    | 422 (27.1)  |              |
| eGFR 30 to <45   | 142 (15.6)  | 1212 (17.0)    | 419 (26.9)  |              |
| eGFR <30         | 47 (5.2)    | 303 (4.3)      | 152 (9.8)   |              |
| Potassium, mmol/L| 3.7 ± 0.2   | 4.5 ± 0.3      | 5.4 ± 0.3   | NA           |
| Haemoglobin, g/dL| 13.3 ± 1.6  | 13.5 ± 1.6     | 13.3 ± 1.7  | 0.007        |
| NYHA class III/IV, n (%) | 219 (24.1) | 1401 (19.7) | 376 (24.1) | 0.20 |
| HF diagnosis, years | 4.9 ± 5.4  | 5.0 ± 5.6      | 5.3 ± 5.8   | 0.069        |

Continued
Methods

Study design and patient population

The design and primary results of the EMPEROR-Pooled analysis have been published previously. In brief, the EMPEROR-Pooled combined individual patient data from EMPEROR-Reduced and EMPEROR-Preserved, the two phase III international, multicentre, randomized, double-blind, parallel-group, placebo-controlled trials that enrolled adult patients with chronic HF with New York Heart Association (NYHA) class II-IV symptoms for at least 3 months and elevated natriuretic peptide levels across a wide range of left ventricular ejection fractions (LVEFs) <40% in EMPEROR-Reduced and >40% with no prior measurement ≤40% in EMPEROR-Preserved.

The protocol of each trial complied with the Declaration of Helsinki was approved by the ethical committee of the participating sites, and all patients gave written informed consent to participate in the study.

Randomization, study visits, and event definition

Patients were randomized in a double-blind manner to receive placebo or empagliflozin 10 mg daily (1:1 ratio), in addition to their usual therapy. Following entry into the trial, treatments for HF or other medical conditions (including potassium binders) could be initiated, discontinued, or altered at the clinical discretion of the investigator.

Serum potassium was collected at randomization and each subsequent visit, defined as ≤75th percentile.

Table 1

| Table 1 Continued |
|-------------------|
| Serum potassium   | <4.0 mmol/L | 4.0–5.0 mmol/L | >5.0 mmol/L | P-value |
| HHF <12 months, n (%) | 263 (28.9) | 1836 (25.8) | 394 (25.3) | 0.091 |
| Ischaemic HF, n (%) | 320 (35.2) | 2956 (41.5) | 706 (45.3) | <0.001 |
| AFib/flutter, n (%) | 481 (52.9) | 3369 (47.3) | 668 (42.9) | <0.001 |
| Hypertension, n (%) | 806 (88.6) | 5885 (82.7) | 1321 (84.8) | 0.21 |
| Diabetes, n (%) | 431 (47.4) | 3391 (47.7) | 897 (57.6) | <0.001 |
| ACEi/ARBs, n (%) | 666 (73.2) | 5349 (75.2) | 1197 (76.9) | 0.038 |
| ARNI, n (%) | 57 (6.3) | 611 (8.6) | 181 (11.6) | <0.001 |
| Beta-blockers, n (%) | 801 (88.0) | 6385 (89.7) | 1395 (89.6) | 0.35 |
| Thiazides, n (%) | 268 (29.5) | 1065 (15.0) | 172 (11.0) | <0.001 |
| Loop diuretics, n (%) | 710 (78.0) | 5233 (73.5) | 1164 (74.8) | 0.27 |
| MRAs, n (%) | 335 (36.8) | 3552 (49.9) | 944 (60.6) | <0.001 |
| CCBs, n (%) | 269 (29.6) | 1515 (21.3) | 299 (19.2) | <0.001 |
| Potassium binders, n (%) | 3 (0.3) | 23 (0.3) | 11 (0.7) | 0.065 |
| Potassium supplement, n (%) | 162 (17.8) | 882 (12.4) | 155 (10.0) | <0.001 |
| ICD, n (%) | 115 (12.6) | 1032 (14.5) | 236 (15.2) | 0.12 |
| CRT (CRT-D or CRT-P), n (%) | 35 (3.8) | 348 (4.9) | 77 (4.9) | 0.32 |
| Empagliflozin rand., n (%) | 451 (49.6) | 3561 (50.0) | 775 (49.8) | 0.98 |

Values are n (%), mean (standard deviation), or median (interquartile range).

AFL, atrial fibrillation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; ICD, implantable cardioverter defibrillator with or without cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NA, not available; NYHA, New York Heart Association; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

aEMPEROR-Reduced.
bEMPEROR-Preserved.
cP-values from ordinal regression likelihood ratio test.
dMedian (25th–75th percentile).
Based on log-transformed data.
We identified investigator-reported hyperkalaemia and hypokalaemia events by searching for Medical Dictionary for Regulatory Activities preferred terms of ‘hyperkalaemia’, ‘potassium increased’, ‘hypokalaemia’, and ‘potassium decreased’. In addition, hyperkalaemia leading to discontinuation and serious hyperkalaemia leading to hospitalization were assessed as adverse event of special interest.

The new initiation of potassium-binding agents during the trial (sodium polystyrene sulphonate, calcium polystyrene sulphonate, patiromer, patiromer calcium, zirconium silicate, and sodium zirconium cyclosilicate) was identified from concomitant medications.

Hyperkalaemia and hypokalaemia were also defined using laboratory-based definitions: new serum potassium >5.5 mmol/L ‘hyperkalaemia’, new serum potassium >6.0 mmol/L ‘severe hyperkalaemia’, new serum potassium <3.0 mmol/L ‘severe hypokalaemia’.

Endpoints
In the present study, the main outcome was a composite of investigator-reported hyperkalaemia or the new initiation of potassium binders. Other outcomes of interest included the individual components of the main outcome, the occurrence of investigator-reported hypokalaemia or the new initiation of potassium supplement (and its components), the occurrence of hypo- and hyperkalaemia, and potassium changes over time.

Statistical analysis
Baseline characteristics were compared across categories of baseline potassium using ordinal regression likelihood ratio test. Associations between baseline potassium categories and subsequent outcomes were studied by comparing the placebo event rates across categories. For potassium-related outcomes, differences between the placebo and empagliflozin groups were assessed using a Cox proportional hazards model including the prespecified baseline covariates of age, sex, geographical region, diabetes, study, LVEF, and estimated glomerular filtration rate (eGFR) according to the intention-to-treat principle, and only including patients not receiving potassium-binding agents at baseline in the endpoints that included this component. The total number of hospitalizations (first and recurrent) was analysed using a joint frailty model with cardiovascular death as competing risk including the same factors as in the Cox model. We assessed the consistency of empagliflozin effect on the main outcome across a range of clinically relevant participant characteristics including age, sex, eGFR, LVEF, body mass index (BMI), diabetes mellitus, diuretic use, and baseline serum potassium, alone with the respective interaction or trend tests. The effect of empagliflozin on potassium changes over time was studied using a linear mixed model for repeated measures with adjustment for the covariates referenced above and treatment-by-visit interaction. P-values and 95% confidence intervals (CIs) presented in this report have not been adjusted for multiplicity. All analyses were performed using SAS, version 9.4 (SAS Institute).

Results
Patient characteristics by baseline potassium categories
A total of 9583 patients with available baseline potassium were included in the present analysis (98.6% of the EMPEROR-Pooled population, n = 9718). Compared to patients with a serum potassium between 4.0 and 5.0 mmol/L at baseline (n = 7116, 74.3%), those with a potassium >5.0 mmol/L (n = 1557, 16.2%) had a lower mean LVEF (41.8 vs. 44.2%), more frequently a LVEF ≤40% (46.5% vs. 37.3%), and a lower mean eGFR (54.1 vs. 62.6 mL/min/1.73 m²) with the proportion of patients with an eGFR <30 mL/min/1.73 m² being higher (9.8% vs. 4.3%). Patients with baseline
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Table 2  Effect of empagliflozin on hyper- and hypokalaemia events

| Outcome                                                                 | Events, n (%) | Event rates, 100py | HR (95% CI) | P-value |
|--------------------------------------------------------------------------|---------------|--------------------|-------------|---------|
| Hyperkalaemia                                                            |               |                    |             |         |
| Investigator-reported hyperkalaemia or initiation of potassium binders* | 313/4837 (6.5)| 371/4837 (7.7)     | 4.1         | 5.0     | 0.82 (0.71–0.95) | 0.001 |
| Investigator-reported hyperkalaemia                                      | 295/4859 (6.1)| 347/4852 (7.2)     | 3.9         | 4.6     | 0.83 (0.71–0.97) | 0.018 |
| Initiation of potassium binders*                                         | 73/4837 (1.5) | 85/4837 (1.8)      | 0.9         | 1.1     | 0.80 (0.59–1.10) | 0.174 |
| Potassium >5.5 mmol/L or new initiation of potassium binders*            | 426/4600 (9.3)| 499/4609 (10.8)    | 6.5         | 7.8     | 0.83 (0.72–0.94) | 0.004 |
| Potassium >5.5 mmol/L                                                   | 399/4621 (8.6)| 456/4622 (9.9)     | 6.1         | 7.1     | 0.85 (0.74–0.97) | 0.017 |
| Potassium >6.0 mmol/L or new initiation of potassium binders*            | 145/4718 (3.1)| 204/4746 (4.3)     | 2.1         | 3.0     | 0.68 (0.55–0.85) | <0.001 |
| Potassium >6.0 mmol/L                                                   | 89/4740 (1.9) | 139/4761 (2.9)     | 1.3         | 2.0     | 0.62 (0.48–0.81) | <0.001 |
| Hypokalaemia                                                             |               |                    |             |         |
| Investigator-reported hypokalaemia or initiation of potassium supplement | 273/4257 (6.4)| 285/4241 (6.7)     | 4.1         | 4.3     | 0.95 (0.80,1.12) | 0.533 |
| Investigator-reported hypokalaemia                                       | 115/4859 (2.4)| 96/4852 (2.0)      | 1.5         | 1.2     | 1.20 (0.91–1.57) | 0.197 |
| Initiation of potassium supplement                                       | 245/4257 (5.8)| 266/4241 (6.3)     | 3.7         | 4.0     | 0.91 (0.77,1.08) | 0.293 |
| Serum potassium <3.0 mmol/L                                             | 26/4781 (0.5)| 19/4790 (0.4)      | 0.4         | 0.3     | 1.35 (0.75,2.45) | 0.316 |

Based on Cox proportional hazard model adjusted for age (cont.), baseline estimated glomerular filtration rate (cont.), baseline left ventricular ejection fraction (cont.), study region, baseline diabetes status, sex and treatment. Shown are adverse events up to 7 days and serum potassium levels up to 3 days following discontinuation of the study medication.

HR, hazard ratio.

*aOnly patients without use of potassium binder at baseline are considered.

*bAnalysis performed in patients with potassium level of ≤3.5 mmol/L and without use of potassium binder at baseline only.

*cAnalysis performed in patients with potassium level of ≤6.0 mmol/L and without use of potassium binder at baseline only.

*dAnalysis performed in patients with potassium level below resp. above the threshold at baseline.

Effect of empagliflozin on potassium-related outcomes and safety

Compared with placebo, empagliflozin reduced the occurrence of investigator-reported hyperkalaemia or new initiation of potassium binders [6.5% vs. 7.7%, hazard ratio (HR) 0.82, 95% CI 0.71–0.95, P = 0.011 (Figure 1); investigator-reported hyperkalaemia (6.1% vs. 7.2%, HR 0.83, 95% CI 0.71–0.97, P = 0.018); potassium >5.5 mmol/L or new initiation of potassium binders (9.3% vs. 10.8%, HR 0.83, 95% CI 0.72–0.94, P = 0.004); potassium >5.5 mmol/L (8.6% vs. 9.9%, HR 0.85, 95% CI 0.74–0.97, P = 0.017); potassium >6.0 mmol/L or new initiation of potassium binders (3.1% vs. 4.3%, HR 0.68, 95% CI 0.55–0.85, P < 0.001); potassium >6.0 mmol/L (1.9% vs. 2.9%, HR 0.62, 95% CI 0.48–0.81, P < 0.001). The use of potassium binders was not significantly reduced with empagliflozin (1.5% vs. 1.8%, HR 0.80, 95% CI 0.59–1.10, P = 0.17) (Table 2). The adverse event of serious hyperkalaemia leading to hospitalization was 11 (0.2%) in the empagliflozin group and 24 (0.5%) in the placebo group.

Hyperkalaemia leading to trial drug discontinuation occurred in 2 patients on placebo and no patient on empagliflozin.

The effect of empagliflozin to reduce investigator-reported hyperkalaemia or new initiation of potassium binders was consistent across both trials and most studied subgroups (age, BMI, race, LVEF, urine...
The occurrence of investigator-reported hypokalaemia or new initiation of potassium supplement, each component, and the occurrence of a serum potassium <3.0 mmol/L were not significantly increased with empagliflozin treatment (Table 2).

Serum potassium over time was not significantly different between empagliflozin and placebo groups, neither by baseline potassium (Figure 3) nor overall (see Supplementary material online, Figure S1).

**Effect of empagliflozin on efficacy outcomes across baseline potassium levels**

For the treatment effect of empagliflozin on major outcomes, we observed heterogeneity in some outcomes of interest (see
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Whereas the effect of empagliflozin on the primary composite of HHF or cardiovascular death, first and total HHF was attenuated in patients with a serum potassium >5.0 mmol/L, empagliflozin consistently reduced the extended composite outcome (cardiovascular death, HHF or equivalent events [urgent care or emergency room visits requiring intravenous therapy for worsening HF] or visit reporting intensification of diuretics) across baseline potassium levels. For the composite of HHF or cardiovascular death the treatment effect in patients with a serum potassium >4.0 mmol/L was HR 0.74, 95% CI 0.56–0.97; for potassium 4.0–5.0 mmol/L HR 1.02, 95% CI 0.82–1.27 (interaction trend \( P = 0.024 \)). A similar pattern was observed for first and total HHF (interaction trend \( P = 0.011 \) and 0.067, respectively). For the extended composite, HRs were as follows: serum potassium <4 mmol/L HR 0.80, 95% CI 0.65–1.00; potassium 4.0–5.0 mmol/L HR 0.71, 95% CI 0.65–0.78; potassium >5.0 mmol/L HR 0.82, 95% CI 0.69–0.98 (interaction trend \( P = 0.64 \)). Similarly, the effect of empagliflozin to slow the decline in eGFR was not modified by baseline potassium levels (interaction trend \( P = 0.31 \)). Also, the effect of empagliflozin on fatal outcomes, including sudden death, was not modified by baseline potassium levels (see Supplementary material online, Table S1).

Discussion

In more than 9500 HF patients across a wide range of ejection fractions, our study shows that empagliflozin (vs. placebo) reduced the rate of new-onset hyperkalaemia or new initiation of potassium binders without increasing the incidence of hypokalaemia in a significant manner (Structured Graphical Abstract). These findings are clinically important and expand the potential benefits of empagliflozin in HF.

Patients with high potassium at baseline were more frequently diagnosed with diabetes and ischaemic HF aetiology, had reduced LVEF and impaired renal function, but were more frequently treated with RAASi, particularly sacubitril/valsartan or MRAs. Patients with these characteristics are at high risk of developing hyperkalaemia, and in the presence of even mild hyperkalaemia (serum potassium >5.0–5.5 mmol/L) many clinicians reduce the dose, withhold, or stop RAASi which may lead to HF worsening and a poor prognosis.\(^3,17,18\) Therefore, by reducing the incidence of hyperkalaemia, empagliflozin treatment may enable the concomitant use or up-titration of RAASi to target doses. In this regard, we have previously documented that patients randomized to empagliflozin were less likely to stop MRA therapy throughout the follow-up.\(^12\)

The effect to reduce hyperkalaemia incidence likely represents a SGLT2i class effect reported across different populations.
An analysis from CREDENCE trial showed that canagliflozin (vs. placebo) reduced the rate of investigator-reported hyperkalaemia or initiation of potassium binders (HR 0.78, 95% CI 0.64–0.95) and laboratory-determined hyperkalaemia (serum potassium ≥ 6.0 mmol/L, HR 0.77, 95% CI 0.61–0.98), without increasing the risk of hypokalaemia in patients with T2D and CKD. In the DAPA-HF and EMPEROR-Reduced trials, where 70% of participants were using MRAs at baseline, dapagliflozin and empagliflozin reduced the incidence of moderate-to-severe hyperkalaemia, defined as serum potassium > 6.0 mmol/L, particularly among patients receiving MRAs.11,12 Patients with CKD and those who had a recent HHF also have a high risk of hyperkalaemia; such risk can be reduced with SGLT2i in a pronounced fashion.

The mechanisms by which empagliflozin reduced hyperkalaemia are uncertain and likely multifactorial. It is possible that, by increasing the sodium and water delivery to the distal nephron, kaliuresis could also be enhanced with empagliflozin treatment.19 In addition, by slowing the decline in eGFR over time, empagliflozin may contribute to the maintenance of potassium homeostasis compared with placebo.20 By decreasing the rate of HHF, empagliflozin may also decrease hyperkalaemia resulting from multiple interventions and therapeutic shifts that often occur during hospital stay.21

The effect of empagliflozin to reduce the composite of HHF or cardiovascular death, first and total HHF appeared attenuated in patients with baseline potassium levels > 5.0 mmol/L. However, such pattern was not observed when urgent visits for worsening HF, intravenous diuretic use or outpatient diuretic intensification were considered or for the reduction in eGFR slope decline. Also, when investigating the kidney effects of canagliflozin in patients with T2D and CKD in the CREDENCE trial, patients with high baseline potassium seemed to have experienced a greater benefit with canagliflozin treatment than those with low baseline potassium.10 Therefore, interactions between baseline potassium and treatment efficacy may not represent a replicable finding of SGLT2i.

**Limitations**

Several limitations should be acknowledged in our study. Hypo- and hyperkalaemia were investigator-reported and therefore could vary across study sites, but not between the empagliflozin and placebo groups. In addition, the results were confirmed by laboratory-determined potassium levels. Management of hypo- and hyperkalaemia, including the initiation of potassium binders or potassium supplements, was left at the discretion of the treating physician and we did not assess duration of treatment. Furthermore, we did not measure urinary potassium, and therefore we cannot determine if empagliflozin reduced potassium through a kaliuretic effect; dedicated studies should address this question. Patients included in the EMPEROR trials had to meet certain inclusion/exclusion criteria; as a consequence, these findings cannot be generalized to all HF patients.

**Conclusion**

Empagliflozin reduced the incidence of hyperkalaemia without excessive hypokalaemia in HF patients across a wide range of ejection fractions.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Data sharing**

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant material. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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