European Heart Journal (2022) **43**, 2984–2993
https://doi.org/10.1093/eurheartj/ehac306

CLINICAL RESEARCH
Heart failure and cardiomyopathies

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

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Received 2 December 2021; revised 9 March 2022; accepted 24 May 2022; online publish-ahead-of-print 10 June 2022

See the editorial comment for this article 'Emerging role for SGLT2 inhibitors in mitigating the risk of hyperkalaemia in heart failure', by Subodh Verma *et al*., https://doi.org/10.1093/eurheartj/ehac304.

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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Structured Graphical Abstract

Key Question

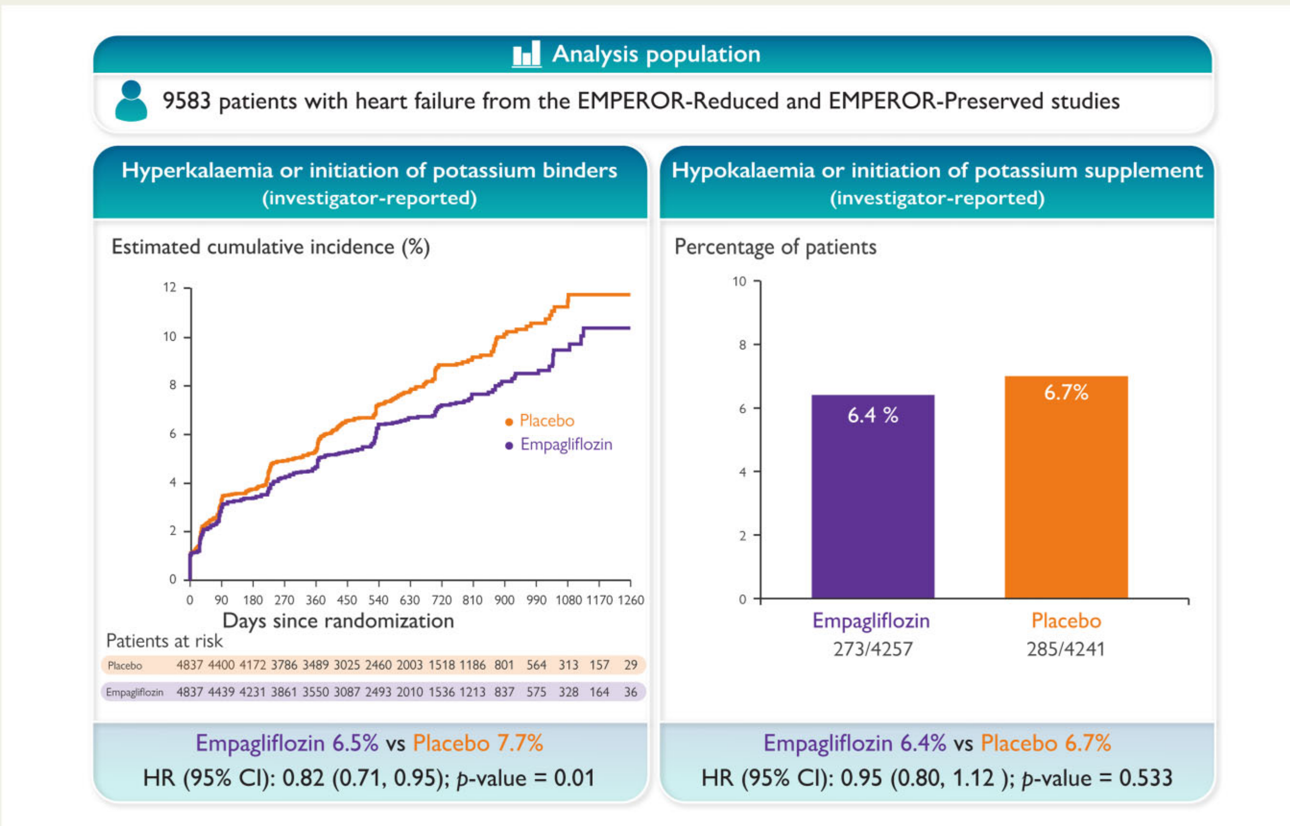
To evaluate the effect of empagliflozin on the occurrence of hyperkalaemia and hypokalaemia in patients with heart failure in EMPEROR-Reduced and EMPEROR-Preserved.

Key Finding

Empagliflozin reduced the composite of investigator-reported hyperkalaemia or initiation of potassium binders, compared with placebo. The incidence of hypokalaemia was not significantly increased with empagliflozin.

Take Home Message

Empagliflozin reduces the incidence of hyperkalaemia, without significant increase in hypokalaemia, in patients with heart failure across the full range of ejection fraction.



Empagliflozin reduced the incidence of hyperkalemia without increasing the risk of hypokalemia.

Keywords Potassium • Hyperkalaemia • Heart failure • Empagliflozin

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.[3] In

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/m^2	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%[b]	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 [e]
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 [e]
UACR, mg/g[c]	30.0 (9.0–116.4)	19.0 (7.1–68.1)	26.0 (9.7–100.0)	0.094 [e]
Heart rate, bpm	72.2 ± 12.4	70.6 ± 11.7	70.4 ± 11.9	0.002
SBP, mmHg	128.8 ± 16.8	128.1 ± 16.3	127.3 ± 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

Table 1 Continued

Serum potassium	<4.0 mmol/L	4.0–5.0 mmol/L	>5.0 mmol/L	*P*-value[c]
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).
AFib, 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.
[a]EMPEROR-Reduced.
[b]EMPEROR-Preserved.
[c]*P*-values from ordinal regression likelihood ratio test.
[d]Median (25th–75th percentile).
[e]Based on log-transformed data.

this regard, trials testing the use of potassium binders to enable RAASi therapy up-titration are underway or have been completed (e.g. DIAMOND, NCT03888066; PRIORITIZE HF, NCT03532009).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduced the incidence of hyperkalaemia in patients with type 2 diabetes (T2D) and CKD[10] and in patients with HF and a reduced ejection fraction using mineralocorticoid receptor antagonists (MRAs).[11,12] In this secondary analysis, we aimed to study the effect of empagliflozin on serum potassium and the use of potassium binders in HF across a wide range of ejection fractions using data from EMPEROR-Pooled (i.e. EMPEROR-Reduced and EMPEROR-Preserved combined).[13]

Methods

Study design and patient population

The design and primary results of the EMPEROR-Pooled analysis have been published previously.[13,14] 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).[15,16] 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 study visit (week 4, 12, 32, 52, and every 24 weeks thereafter) and analysed by the central laboratory. Medication changes and adverse events were recorded throughout the trial.

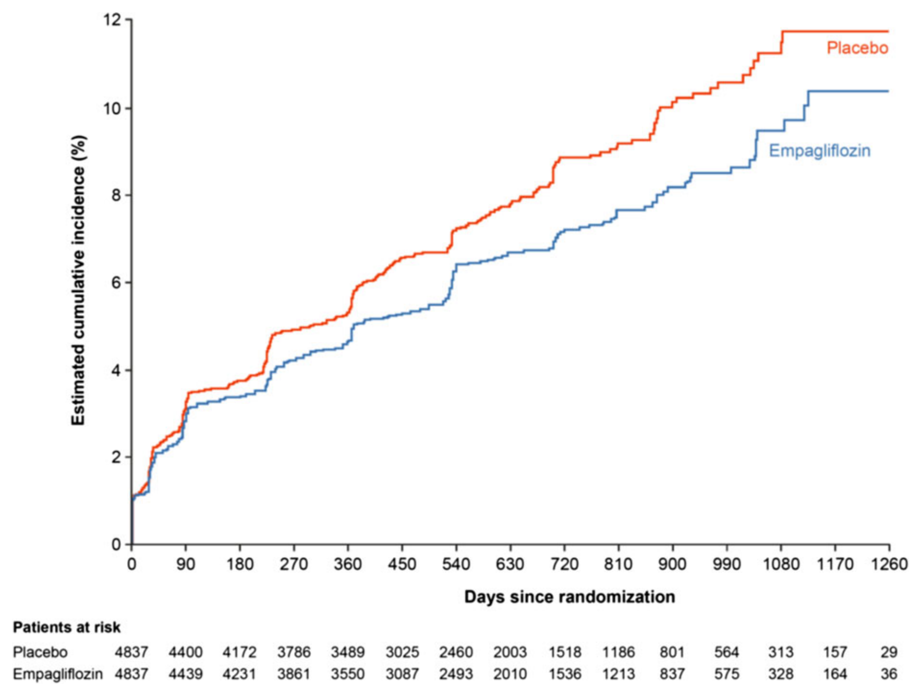


Figure 1 Effect of empagliflozin on the incidence of investigator-reported hyperkalaemia or initiation of potassium binders. Considering all-cause mortality as a competing risk and only including patients not receiving potassium-binding agents at baseline.

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, along 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 m^2) with the proportion of patients with an eGFR <30 mL/min/1.73 m^2 being higher (9.8% vs. 4.3%). Patients with baseline

Table 2 Effect of empagliflozin on hyper- and hypokalaemia events

Outcome	Events, *n* (%)		Event rates, 100py		HR (95% CI)	*P*-value
	Empagliflozin	Placebo	Empagliflozin	Placebo		
Hyperkalaemia						
Investigator-reported hyperkalaemia or initiation of potassium binders[a]	313/4837 (6.5)	371/4837 (7.7)	4.1	5.0	0.82 (0.71–0.95)	0.01
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[a]	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[b]	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 [d]	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[c]	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 [d]	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[d]	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. CI, confidence interval; HR, hazard ratio.
[a]Only patients without use of potassium binder at baseline are considered.
[b]Analysis performed in patients with potassium level of ≤ 5.5 mmol/L and without use of potassium binder at baseline only.
[c]Analysis performed in patients with potassium level of ≤ 6.0 mmol/L and without use of potassium binder at baseline only.
[d]Analysis performed in patients with potassium level below resp. above the threshold at baseline.

potassium >5.0 mmol/L were more likely to have diabetes (57.6% vs. 47.7%), ischaemic HF aetiology (45.3% vs. 41.5%), and higher use of RAASi, particularly sacubitril/valsartan (11.6% vs. 8.6%), and MRAs (60.6% vs. 49.9%). On the other hand, compared to patients with normal serum potassium at baseline, those with a potassium <4.0 mmol/L (*n* = 910, 9.5%) were more frequently female, having slightly higher LVEF, more frequently a LVEF >40% (67.6% vs. 62.7%) and fewer ischaemic HF aetiology. They were more frequently treated with thiazide-type diuretic and calcium channel blockers (29.5% vs. 15.0% and 29.6% vs. 21.3%, respectively) but less frequently with RAASi, particularly sacubitril/valsartan (6.3% vs. 8.6%), and MRAs (36.8% vs. 49.9%) (*Table 1*). Median N-terminal pro-B-type natriuretic peptide and troponin levels were higher and haemoglobin lower in both patients with potassium above and below the 4.0 to 5.0 mmol/L range.

Patients with a baseline potassium >6.0 mmol/L, >5.5 mmol/L, and <3.5 mmol/L represented a small minority of the EMPEROR-Pooled population [0.9% (*n* = 82), 3.5% (*n* = 338) and 1.1% (*n* = 106), respectively]. Patients with a baseline potassium >5.5 mmol/L had similar characteristics to those described for patients with a baseline potassium >5.0 mmol/L. Patients with a baseline potassium <3.5 mmol/L had similar characteristics to those described for patients with a baseline potassium <4.0 mmol/L.

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* = 0.01] (*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

Subgroup Category	N with event / N analysed Empa 10mg	vs Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	313/4837	371/4837	0.82 (0.71, 0.95)	
Study				0.8241
EMPEROR-Preserved	195/2986	235/2980	0.81 (0.67, 0.98)	
EMPEROR-Reduced	118/1851	136/1857	0.84 (0.65, 1.07)	
Age (years)				0.2498
<65	81/1264	100/1344	0.83 (0.62, 1.11)	
65 to <75	121/1799	114/1715	1.00 (0.77, 1.29)	
≥75	111/1774	157/1778	0.69 (0.54, 0.88)	
Race				0.4862
White	222/3604	246/3552	0.87 (0.73, 1.04)	
Black/African-American	18/ 256	30/ 259	0.55 (0.30, 0.98)	
Asian	56/ 735	69/ 733	0.76 (0.54, 1.08)	
Other including mixed race	14/ 214	21/ 261	0.84 (0.43, 1.65)	
Baseline BMI (kg/m²)				0.4631
<25	82/1259	110/1248	0.68 (0.51, 0.91)	
≥25 to <30	104/1640	116/1640	0.98 (0.75, 1.27)	
≥30	127/1938	145/1909	0.81 (0.63, 1.02)	
Baseline eGFR (CKD-EPI) (mL/min/1.73 m²)				0.0120
≥60	111/2457	102/2463	1.10 (0.84, 1.43)	
45 to <60	81/1221	110/1238	0.74 (0.56, 0.99)	
30 to <45	92/ 899	116/ 888	0.78 (0.59, 1.02)	
<30	29/ 259	43/ 245	0.54 (0.34, 0.87)	
Baseline UACR (mg/g)				0.9975
Normal (<30)	141/2758	180/2777	0.78 (0.63, 0.97)	
Microalbuminuria (30 to ≤300)	114/1535	125/1544	0.92 (0.71, 1.18)	
Macroalbuminuria (>300)	57/ 521	65/ 495	0.72 (0.51, 1.03)	
Baseline NYHA				0.3953
I/II	228/3817	268/3838	0.85 (0.71, 1.01)	
III/IV	85/1020	103/ 999	0.73 (0.55, 0.98)	
History of hypertension				0.9411
No	36/ 789	44/ 804	0.83 (0.54, 1.29)	
Yes	277/4048	327/4033	0.82 (0.70, 0.96)	
History of HHF (in the last 12 months)				0.0317
No	234/3568	256/3600	0.91 (0.76, 1.08)	
Yes	79/1269	115/1237	0.63 (0.47, 0.84)	
Baseline diabetes status				0.3785
Diabetic	186/2377	230/2390	0.78 (0.64, 0.94)	
Non-diabetic	127/2460	141/2447	0.89 (0.70, 1.13)	
Baseline use of MRA				0.2610
No	138/2423	142/2363	0.91 (0.72, 1.16)	
Yes	175/2414	229/2474	0.77 (0.63, 0.93)	

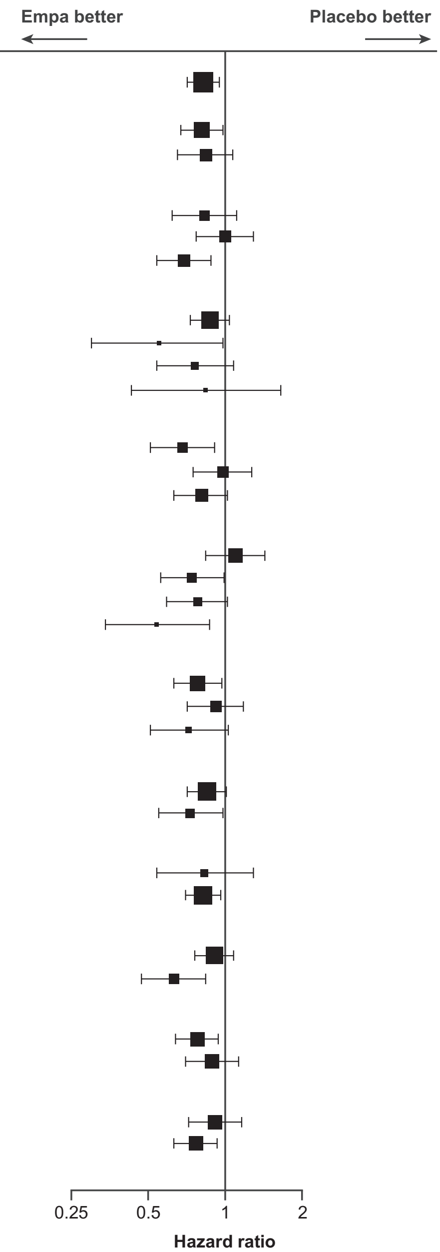


Figure 2 Effect of empagliflozin on investigator-reported hyperkalaemia or the initiation of potassium binders in subgroups of interest. Based on Cox proportional hazard model adjusted for age (continuous), baseline estimated glomerular filtration rate (continuous), baseline left ventricular ejection fraction (continuous), study, region, baseline diabetes status, sex, treatment, subgroup, and subgroup and treatment interaction. In subgroups with more than two categories (except for race), an interaction trend test was performed. BMI, body mass index; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urine albumin-to-creatinine ratio.

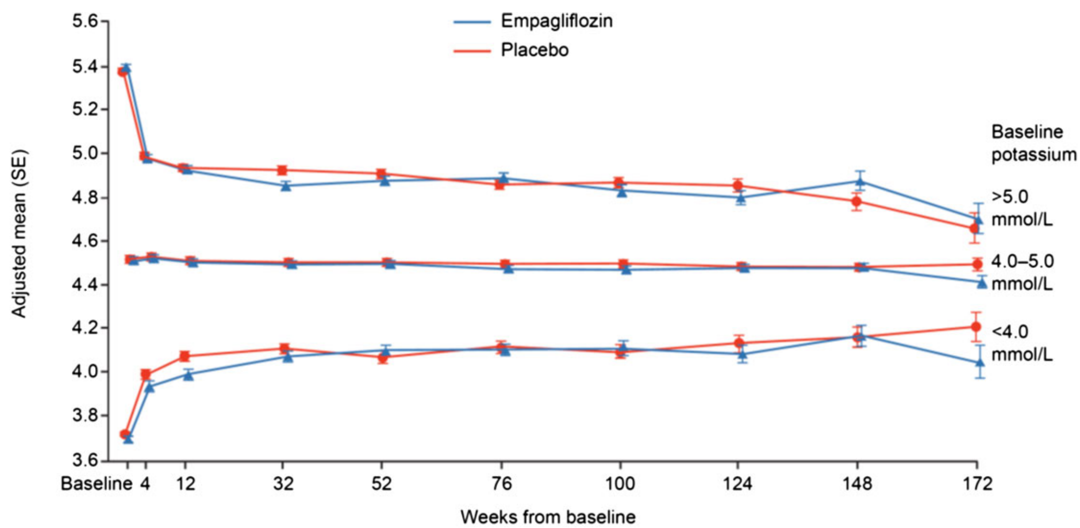
albumin to creatinine ratio, NYHA class, hypertension, diabetes, and MRA use) but was more pronounced in patients with lower eGFR and among those with a hospitalization for HF (HHF) in the past 12 months (trend or interaction $P < 0.05$ for both) (*Figure 2*).

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



	Baseline	4	12	32	52	76	100	124	148	172
Baseline potassium >5.0 mmol/L										
Placebo	768	754	738	658	571	440	286	176	90	29
Empagliflozin	762	752	733	666	549	424	263	157	82	28
Baseline potassium 4.0–5.0 mmol/L										
Placebo	3495	3444	3342	3058	2712	2166	1420	878	525	172
Empagliflozin	3512	3461	3373	3123	2755	2191	1464	918	520	187
Baseline potassium <4.0 mmol/L										
Placebo	445	441	416	383	344	285	185	116	81	30
Empagliflozin	447	442	430	393	342	265	188	118	75	26

Figure 3 Effect of empagliflozin on potassium over time by baseline potassium. All *P*-values for the treatment differences are >0.05; except for baseline potassium < 4.0 mmol/L: week 12 ($P < 0.05$), baseline potassium 4.0–5.0 mmol/L: week 172 ($P < 0.05$), baseline potassium > 5.0 mmol/L: week 32 ($P < 0.001$). Based on mixed model repeated measures analysis. All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

Supplementary material online, *Table S1*). 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 0.72, 95% CI 0.65–0.81; for potassium >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.[10] 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.

Acknowledgements

Graphical assistance was provided by 7.4 Limited and supported financially by Boehringer Ingelheim. Editorial assistance was provided by Elevate Scientific Solutions and supported financially by Boehringer Ingelheim.

Data sharing

To ensure independent interpretation of clinical study results and enable authors to fulfil 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.

Funding

The EMPEROR-Reduced and Preserved trials were funded by Boehringer Ingelheim and Eli Lilly and Company (EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977 and EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

Conflict of interest: J.P.F. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, outside the submitted work. F.Z. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer and, Cellprothera, other from CVCT, and Cardiorenal, outside the submitted work. J.B. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave and Vifor, outside the submitted work. G.F. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Medtronic, Vifor, Servier, Novartis, Bayer, Amgen and Boehringer Ingelheim, outside the submitted work. I.R. and B.J.K. are employees of Boehringer Ingelheim. ES is employee of mainanalytics GmbH, contracted by Boehringer Ingelheim. SJP reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, outside the submitted work. S.A. reports personal fees from Boehringer Ingelheim, during the conduct of the study; grants and personal fees from Abbott Vascular, Vifor, personal fees from Bayer, Boehringer Ingelheim, Brahms GmbH, Cardiac Dimensions, Cordio, Novartis and Servier, outside the submitted work. M.P. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Abbvie, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Cytokinetics, Johnson & Johnson, Eli Lily & Company, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, Theravance, and Casana, outside the submitted work.

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