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RESEARCH ARTICLE

Effects of empagliflozin on cardiovascular and renal outcomes in heart failure with reduced ejection fraction according to age: a secondary analysis of EMPEROR-Reduced

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Aims	Empagliflozin improves cardiovascular and renal outcomes in patients with heart failure (HF) and reduced ejection fraction (HFrEF), but its efficacy and safety across patient's age is not well established.
Methods and results	We assessed the effects of empagliflozin (10 mg daily) versus placebo, on top of standard HF therapy, in symptomatic HFrEF patients with a left ventricular ejection fraction ≤40% and increased natriuretic peptides stratified by age (<65, 65−74, ≥75 years). The primary endpoint was a composite of cardiovascular death or HF hospitalization. Key secondary endpoints included first and recurrent HF hospitalizations and slope of change in estimated glomerular filtration rate (eGFR); the latter was supported by an analysis of a renal composite endpoint (chronic dialysis or renal transplantation or profound and sustained reduction in eGFR). Of 3730 patients, 38% were <65 years, 35% were 65−74 years and 27% were ≥75 years. Compared with placebo, empagliflozin reduced the primary endpoint consistently across the three age groups (hazard ratio 0.71 [95% confidence interval 0.57−0.89] for <65 years, 0.72 [0.57−0.93] for 65−74 years, 0.86 [0.67−1.10] for ≥75 years, interaction p-trend test = 0.24). The effects of empagliflozin were also consistent across age groups for key secondary endpoints of first and recurrent HF hospitalization (p-trend = 0.30), the rate of decline in eGFR (p-trend = 0.78) and the renal composite (p-trend = 0.94). Adverse events (AEs), serious AEs and AEs leading to drug discontinuation increased with age in both treatment arms, but empagliflozin did not increase their incidence over placebo within each age group.
Conclusion	The efficacy and safety of empagliflozin in improving cardiovascular and renal outcomes in HFrEF was consistent across the spectrum of age, including older patients (aged ≥75).

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Graphical Abstract
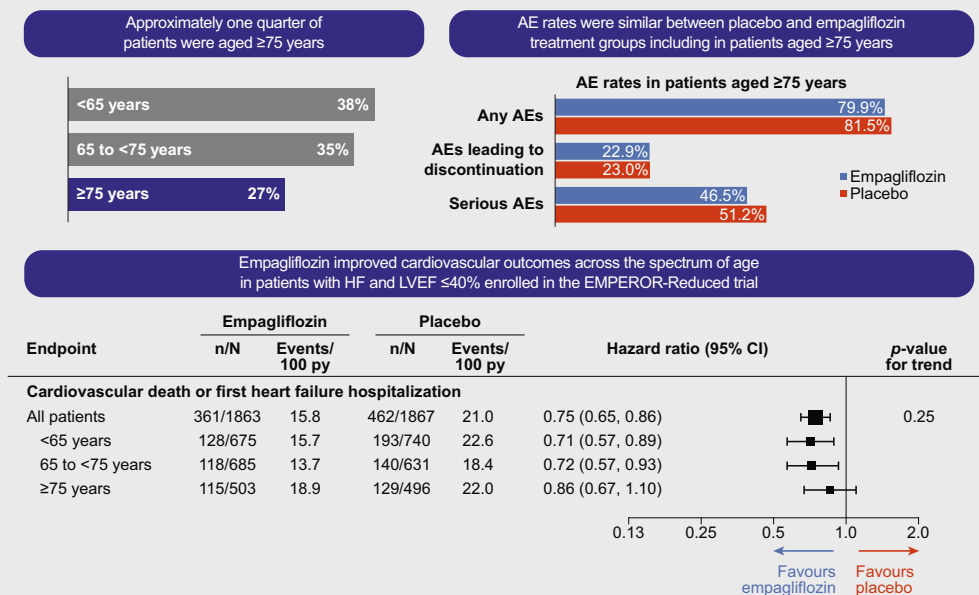
Effects of empagliflozin on cardiovascular and renal outcomes in heart failure with reduced ejection fraction according to age: a secondary analysis of EMPEROR-Reduced (AE, adverse events; HF, heart failure; LVEF, left ventricular ejection fraction).

Introduction

The prevalence of heart failure (HF) increases with age, and HF is the most frequent cause for hospital admission in the elderly.[1,2] Previous studies have shown that older HF patients have worse outcomes that may partly be related to the higher burden of comorbidities and the lower use of guideline-recommended therapies.[3–8] Lower prescription rates may in turn result from physicians' concerns about polypharmacy, lower tolerability, and reduced safety or impaired efficacy of these drugs in older patients.[7,9,10]

The sodium−glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin and dapagliflozin have been shown to improve cardiovascular and renal outcomes in HF patients with reduced ejection fraction (HFrEF).[11,12] A secondary analysis of the DAPA-HF trial showed that the benefit of dapagliflozin was consistent across the spectrum of age in HFrEF.[13] The EMPEROR-Reduced trial studied the effect of empagliflozin on cardiovascular and renal outcomes in patients with more advanced disease. In the present study, we evaluated the effect of age on the efficacy, tolerability, and safety of empagliflozin in HFrEF.

Patients and methods

The design of EMPEROR-Reduced has been described in detail elsewhere.[12,14] In brief, the trial randomized 3730 symptomatic HFrEF patients with a left ventricular ejection fraction (LVEF) of 40% or less and increased levels of natriuretic peptides to either empagliflozin 10 mg daily or placebo on top of all appropriate drug and device treatments for HF. The primary endpoint was a composite of cardiovascular death or hospitalization for worsening HF, and the two secondary endpoints were first and recurrent HF hospitalizations and the rate of decline in estimated glomerular filtration rate (eGFR). The latter was supported by an analysis of a renal composite endpoint (chronic dialysis or renal transplantation or profound and sustained reduction in eGFR of ≥40%, or a sustained eGFR <15 ml/min/1.73 m² [if baseline eGFR ≥30] or sustained eGFR <10 ml/min/1.73 m² [if baseline eGFR <30]).

In the present study, we analysed the efficacy and safety outcomes of empagliflozin or placebo according to three commonly used age groups (of similar size), defined as younger than 65, 65−74 and 75 or older. We investigated the effects of empagliflozin versus placebo on the primary and key secondary endpoints along with other pre-specified endpoints including time-to-first HF hospitalization, cardiovascular death, all-cause death, renal endpoints and change in health status at week 52 as evaluated by the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS). We further analysed the effect of age on the primary endpoint and the incidence of adverse events (AEs) in the placebo arm.

Statistical analysis

Analyses were performed according to the intention-to-treat principle for all randomized patients. For time-to-first-event analyses,

differences between the placebo and empagliflozin groups were assessed for statistical significance using a Cox proportional hazards model, with pre-specified covariates of gender, geographical region, diabetes status at baseline, LVEF, and eGFR at baseline. In addition, for the primary endpoint of cardiovascular death or HF hospitalization, considering age as a continuous variable was investigated and differences between age groups in placebo arm are compared separately using a same Cox model. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with cardiovascular death as a competing risk. Between-group difference in the slope of change in eGFR was analysed using a random intercept random slope model including baseline eGFR as linear covariate and sex, region, baseline LVEF, baseline diabetes status, and baseline eGFR-by-time, treatment-by-age group, and treatment-by-time-by-age group as fixed effects; the model allows for randomly varying slope and intercept between patients. For the analysis of changes in eGFR and KCCQ scores, treatment effects were assessed based on changes from baseline using a mixed model for repeated measures (MMRM). eGFR slope and changes in eGFR MMRM analyses were analysed using on-treatment data. The MMRM and the joint frailty model included the same covariates as the Cox model. To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms were added in the models and trend test were performed assuming ordered age categories. Analyses for safety were performed including all patients who had received at least one dose of empagliflozin or placebo. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). All p-values reported are two-sided, and $p < 0.05$ was considered as statistically significant. No adjustments for multiple testing were made.

Results

The mean age of patients enrolled in EMPEROR-Reduced was 67 years (empagliflozin arm, 67.2 ± 10.8 years; placebo arm, 66.5 ± 11.2 years). The distribution of age in the study population is outlined in online supplementary *Figure S1*. Out of a total of 3730 patients, 1415 (38%) were younger than 65 years, 1316 (35%) were aged 65−74, and 999 (27%) were 75 or older.

The baseline features of patients according to age are reported in *Table 1*. Patients in the oldest age group were more likely to be female and to suffer from comorbidities such as arterial hypertension and atrial fibrillation. Systolic blood pressure, LVEF and N-terminal pro-brain natriuretic peptide (NT-proBNP) increased with age, while body mass index (BMI) and eGFR declined. Functional capacity according to New York Heart Association class and health status by KCCQ-CSS did not differ significantly among groups. The frequency of HF hospitalization within the preceding 12 months declined with age. Regarding HF therapies, the use of renin−angiotensin−aldosterone system inhibitors, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor−neprilysin inhibitor (ARNi) and mineralocorticoid receptor antagonists (MRA), declined with age, while the use of beta-blockers did not differ significantly among age groups. Inversely, use of device therapies, particularly cardiac resynchronization therapy (CRT), increased with age.

In the placebo arm, the incidence rate of the primary endpoint of cardiovascular death or HF hospitalization was lower in the middle-age group compared to the youngest group (hazard ratio

[HR] 0.79, 95% confidence interval [CI] 0.63, 0.99, $p = 0.04$), but did not differ between the oldest and the youngest groups (HR 0.89 [95% CI 0.69,1.14], $p = 0.36$; *Figure 1*). This difference was driven by a lower incidence rate of HF hospitalization in the middle-age group (HR 0.71 [95% CI 0.54, 0.93], $p = 0.01$) versus the youngest group.

The effects of empagliflozin versus placebo on the primary endpoint of cardiovascular death or HF hospitalization was consistent across the three age groups (p for trend test = 0.25). Empagliflozin also reduced the primary endpoint compared with placebo across the spectrum of patient age taken as a continuous variable (p for interaction = 0.24; online supplementary *FigureS2*). The effects of empagliflozin compared to placebo were consistent in the three age groups also for the key secondary endpoints of first and recurrent HF hospitalization (p for trend test = 0.30) and slope of change in eGFR per year (p for trend test = 0.78). The same was true for other pre-specified endpoints including cardiovascular death (p for trend test = 0.88), all-cause death (p for trend test = 0.85), time-to-first HF hospitalization (p for trend test = 0.40) and the renal composite outcome (p for trend test = 0.95; *Figure 1*).

Concerning renal function, eGFR exhibited an initial drop after empagliflozin initiation that was similar across age groups and this initial drop was attenuated by week 12, followed thereafter by a slower rate of decline compared with placebo in all three age groups (mean slope of change: <65 years, −0.62; 65−75 years, −0.75; ≥75 years, −0.074 ml/min/1.73 m^2). The effect of empagliflozin versus placebo on the change in the KCCQ-CSS through week 52 was also consistent in the three age groups (+1.98 [95% CI 0, 3.95] in <65 years, +1.43 [95% CI −0.61, 3.48] in 65−74 years +1.12 [95% CI −1.30, 3.54] in ≥75 years, p for trend test = 0.57).

The incidence of AEs, serious AEs and AEs leading to drug discontinuation increased with age in both treatment arms (*Table 2*). Within each age group, empagliflozin did not increase the incidence of AEs compared with placebo. Regarding AEs of specific interest in patients aged 75 or older, such as hypotension, hypoglycaemia, volume depletion, urinary tract infections, hypo- and hyperkalaemia, empagliflozin was not associated with an increase in these AEs compared with placebo.

Discussion

In the present secondary analysis of the EMPEROR-Reduced trial, the efficacy and safety of empagliflozin compared with placebo, on top of appropriate medical and device HF therapies, was consistent across all age groups in HFrEF patients (*Graphical Abstract*). This analysis extends the findings of a similar study on dapagliflozin to a HF population with more advanced disease, and therefore, the totality of evidence on SGLT2i in HFrEF shows that these drugs are effective and safe regardless of patient age.[13]

Knowing the impact of HF therapies across the spectrum of patient age is important for several reasons. First, older patients have previously been underrepresented in clinical trials,[15,16] including trials studying neurohormonal inhibitors in HFrEF.[17,18] The mean age of patients enrolled in EMPEROR-Reduced was 67 years, with two thirds of patients being 65 years or older and one fourth of them being 75 or older. This age distribution is consistent

Table 1 Baseline patient features by age groups

	Age group, years			*p*-value
	<65	**65–74**	**≥75**	
Patients, *n* (%)	1415 (37.9)	1316 (35.3)	999 (26.8)	–
Age, years	55.5 ± 7.6	69.4 ± 2.8	79.5 ± 3.5	<0.0001
Female sex, *n* (%)	340 (24.0)	289 (22.0)	264 (26.4)	0.04
Race[a], *n* (%)				<0.0001
White	879 (62.1)	971 (73.8)	779 (78.0)	
Black	151 (10.7)	64 (4.9)	42 (4.2)	
Asian	303 (21.4)	220 (16.7)	149 (14.9)	
Other or missing	82 (5.8)	61 (4.6)	29 (2.9)	
Region, *n* (%)				<0.0001
North America	143 (10.1)	131 (10.0)	151 (15.1)	
Latin America	609 (43.0)	425 (32.3)	252 (25.2)	
Europe	365 (25.8)	542 (41.2)	446 (44.6)	
Asia	192 (13.6)	169 (12.8)	132 (13.2)	
Other	106 (7.5)	49 (3.7)	18 (1.8)	
NYHA class III/IV, *n* (%)	354 (25.0)	315 (23.9)	261 (26.1)	0.48
Body mass index, kg/m^2	28.5 ± 5.7	28.1 ± 5.2	26.8 ± 5.0	<0.0001
Systolic blood pressure, mmHg	119.9 ± 15.3	122.8 ± 15.9	123.9 ± 15.4	<0.0001
LVEF, %	26.5 ± 6.2	27.6 ± 5.9	28.5 ± 5.8	<0.0001
NT-proBNP, pg/ml, median (IQR)	1671 (978, 2995)	1903 (1117, 3501)	2255 (1412, 4098)	<0.0001*
HF cause, *n* (%)				<0.0001
Ischaemic	607 (42.9)	753 (57.2)	569 (57.0)	
Non-ischaemic	808 (57.1)	563 (42.8)	430 (43.0)	
CV history, *n* (%)				
HF hospitalization within 12 months	476 (33.6)	385 (29.3)	290 (29.0)	0.02
Arterial hypertension	921 (65.1)	980 (74.5)	797 (79.8)	<0.0001
Atrial fibrillation	333 (23.5)	530 (40.3)	506 (50.7)	<0.0001
Diabetes mellitus	722 (51.0)	680 (51.7)	454 (45.4)	0.01
eGFR, ml/min/1.73 m^2 (CKD-EPI)	73.4 ± 22.1	59.0 ± 18.2	49.9 ± 16.5	<0.0001
KCCQ-CSS	70.0 ± 22.8	71.4 ± 21.2	70.8 ± 21.7	0.25
HF therapies, *n* (%)				
ACEi or ARB	1001 (70.7)	938 (71.3)	661 (66.2)	0.02
ARNi	292 (20.6)	235 (17.9)	200 (20.0)	0.17
ACEi, ARB or ARNi	1278 (90.3)	1162 (88.3)	853 (85.4)	0.0010
Beta-blockers	1338 (94.6)	1256 (95.4)	939 (94.0)	0.29
MRA	1117 (78.9)	925 (70.3)	619 (62.0)	<0.0001
ICD (ICD or CRT-D)	388 (27.4)	451 (34.3)	331 (33.1)	0.0002
CRT (CRT-D or CRT-P)	94 (6.6)	180 (13.7)	164 (16.4)	<0.0001

Plus-minus values are means ± standard deviation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor−neprilysin inhibitor; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-clinical summary score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
[a]Race was self-reported; patients who identified with ≥1 race or with no race were classified as other.
*Based on log-transformed value.

with that reported by recent HF registries in Europe and US.[19,20] Two recent randomized clinical trials examining the efficacy and safety of dapagliflozin (DAPA-HF) and vericiguat (VICTORIA) in HFrEF also enrolled patients with a mean age of 66 and 67 years, respectively.[11,21] The previously reported age-related differences in HF patient characteristics were also confirmed by the present study.[6,7] Systolic blood pressure, NT-proBNP, and LVEF increased with age along with the prevalence of arterial hypertension and

atrial fibrillation. Older patients also had lower BMI and worse renal function than younger patients.

Second, older HFrEF patients are less frequently treated with guideline-recommended therapies compared to younger patients according to large registries.[7,22] This was also seen in the present analysis, in which standard HF drug therapy declined with increasing age, with the exception of ARNi, the use of which was generally higher in EMPEROR-Reduced compared to other contemporary
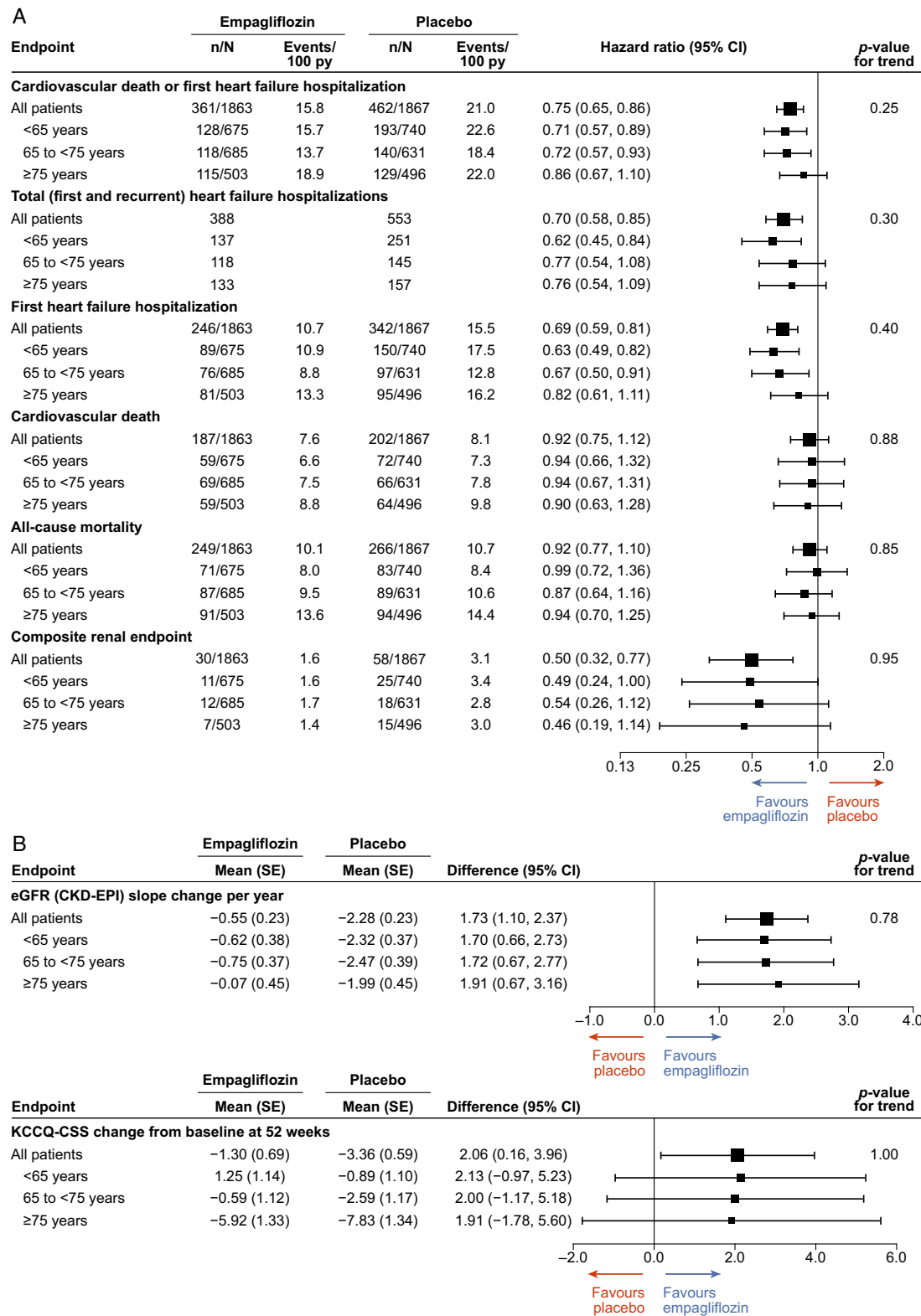
A

Endpoint	Empagliflozin		Placebo		Hazard ratio (95% CI)	p-value for trend
	n/N	Events/ 100 py	n/N	Events/ 100 py		
Cardiovascular death or first heart failure hospitalization						
All patients	361/1863	15.8	462/1867	21.0	0.75 (0.65, 0.86)	0.25
<65 years	128/675	15.7	193/740	22.6	0.71 (0.57, 0.89)	
65 to <75 years	118/685	13.7	140/631	18.4	0.72 (0.57, 0.93)	
≥75 years	115/503	18.9	129/496	22.0	0.86 (0.67, 1.10)	
Total (first and recurrent) heart failure hospitalizations						
All patients	388		553		0.70 (0.58, 0.85)	0.30
<65 years	137		251		0.62 (0.45, 0.84)	
65 to <75 years	118		145		0.77 (0.54, 1.08)	
≥75 years	133		157		0.76 (0.54, 1.09)	
First heart failure hospitalization						
All patients	246/1863	10.7	342/1867	15.5	0.69 (0.59, 0.81)	0.40
<65 years	89/675	10.9	150/740	17.5	0.63 (0.49, 0.82)	
65 to <75 years	76/685	8.8	97/631	12.8	0.67 (0.50, 0.91)	
≥75 years	81/503	13.3	95/496	16.2	0.82 (0.61, 1.11)	
Cardiovascular death						
All patients	187/1863	7.6	202/1867	8.1	0.92 (0.75, 1.12)	0.88
<65 years	59/675	6.6	72/740	7.3	0.94 (0.66, 1.32)	
65 to <75 years	69/685	7.5	66/631	7.8	0.94 (0.67, 1.31)	
≥75 years	59/503	8.8	64/496	9.8	0.90 (0.63, 1.28)	
All-cause mortality						
All patients	249/1863	10.1	266/1867	10.7	0.92 (0.77, 1.10)	0.85
<65 years	71/675	8.0	83/740	8.4	0.99 (0.72, 1.36)	
65 to <75 years	87/685	9.5	89/631	10.6	0.87 (0.64, 1.16)	
≥75 years	91/503	13.6	94/496	14.4	0.94 (0.70, 1.25)	
Composite renal endpoint						
All patients	30/1863	1.6	58/1867	3.1	0.50 (0.32, 0.77)	0.95
<65 years	11/675	1.6	25/740	3.4	0.49 (0.24, 1.00)	
65 to <75 years	12/685	1.7	18/631	2.8	0.54 (0.26, 1.12)	
≥75 years	7/503	1.4	15/496	3.0	0.46 (0.19, 1.14)	

Scale: 0.13 0.25 0.5 1.0 2.0 — ← Favours empagliflozin / Favours placebo →

B

Endpoint	Empagliflozin Mean (SE)	Placebo Mean (SE)	Difference (95% CI)	p-value for trend
eGFR (CKD-EPI) slope change per year				
All patients	−0.55 (0.23)	−2.28 (0.23)	1.73 (1.10, 2.37)	0.78
<65 years	−0.62 (0.38)	−2.32 (0.37)	1.70 (0.66, 2.73)	
65 to <75 years	−0.75 (0.37)	−2.47 (0.39)	1.72 (0.67, 2.77)	
≥75 years	−0.07 (0.45)	−1.99 (0.45)	1.91 (0.67, 3.16)	

Scale: −1.0 0.0 1.0 2.0 3.0 4.0 — ← Favours placebo / Favours empagliflozin →

Endpoint	Empagliflozin Mean (SE)	Placebo Mean (SE)	Difference (95% CI)	p-value for trend
KCCQ-CSS change from baseline at 52 weeks				
All patients	−1.30 (0.69)	−3.36 (0.59)	2.06 (0.16, 3.96)	1.00
<65 years	1.25 (1.14)	−0.89 (1.10)	2.13 (−0.97, 5.23)	
65 to <75 years	−0.59 (1.12)	−2.59 (1.17)	2.00 (−1.17, 5.18)	
≥75 years	−5.92 (1.33)	−7.83 (1.34)	1.91 (−1.78, 5.60)	

Scale: −2.0 0.0 2.0 4.0 6.0 — ← Favours placebo / Favours empagliflozin →

Figure 1 Forest plots for main cardiovascular and renal outcomes *(A)* and across estimated glomerular filtration rate (eGFR) and Kansas City Cardiomyopathy Questionnaire- clinical summary score (KCCQ-CSS) *(B)* by age groups. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SE, standard error; py, patient-years.

Table 2 Summary of adverse events and adverse events of interest by treatment status and age groups

Category of AEs, n (%)	Age group, years					
	<65		65–75		≥75	
	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin
	n = 739 / Incidence rate per 100 py	n = 675 / Incidence rate per 100 py	n = 628 / Incidence rate per 100 py	n = 685 / Incidence rate per 100 py	n = 496 / Incidence rate per 100 py	n = 503 / Incidence rate per 100 py
Patients with any AEs	558 (75.5) / 158.3	493 (73.0) / 136.4	501 (79.8) / 156.1	525 (76.6) / 148.5	404 (81.5) / 195.1	402 (79.9) / 169.2
AEs leading to study drug discontinuation	113 (15.3) / 12.6	92 (13.6) / 11.2	101 (16.1) / 13.1	115 (16.8) / 13.6	114 (23.0) / 19.8	115 (22.9) / 19.4
Serious AEs	340 (46.0) / 53.5	249 (36.9) / 38.3	302 (48.1) / 53.5	289 (42.2) / 44.1	254 (51.2) / 59.9	234 (46.5) / 51.4
Hypotension	63 (8.5) / 7.5	64 (9.5) / 8.3	45 (7.2) / 6.0	60 (8.8) / 7.5	55 (11.1) / 10.3	52 (10.3) / 9.2
Acute renal failure	78 (10.6) / 9.2	57 (8.4) / 7.2	60 (9.6) / 8.2	68 (9.9) / 8.4	54 (10.9) / 9.8	50 (9.9) / 8.9
Confirmed hypoglycaemic events[a]	18 (2.4) / 2.0	10 (1.5) / 1.2	5 (0.8) / 0.7	12 (1.8) / 1.4	5 (1.0) / 0.9	5 (1.0) / 0.8
Volume depletion	70 (9.5) / 8.4	66 (9.8) / 8.6	52 (8.3) / 7.0	68 (9.9) / 8.5	62 (12.5) / 11.8	63 (12.5) / 11.3
UTI	24 (3.9) / 2.7	13 (1.9) / 1.6	21 (3.3) / 2.8	29 (4.2) / 3.5	27 (5.4) / 4.7	27 (5.4) / 4.7
Genital infections	7 (0.9) / 0.78	10 (1.5) / 1.23	2 (0.3) / 0.26	10 (1.5) / 1.19	3 (0.6) / 0.57	11 (2.2) / 1.87
Hyperkalaemia	35 (4.7) / 4.0	30 (4.4) / 3.8	41 (6.5) / 5.5	42 (6.1) / 5.2	39 (7.9) / 7.1	29 (5.8) / 5.0
Hypokalaemia	12 (1.6) / 1.4	16 (2.4) / 2.0	11 (1.8) / 1.4	10 (1.5) / 1.2	5 (1.0) / 0.9	7 (1.4) / 1.2

AE, adverse event; py, patient-years; UTI, urinary tract infection.
[a]Hypoglycaemic adverse events with plasma glucose ≤70 mg/dl or requiring assistance.

HFrEF trials.[11,12,21] This finding is in contrast with the fact that the benefit of neurohormonal inhibitors/modulators, including ACEi, ARB, ARNi, beta-blockers and MRA, and of ivabradine and dapagliflozin have been shown to be consistent across age and that older patients seem to benefit from these therapies as much as younger ones.[4,8,13,22–25] This was also true for empagliflozin in the present analysis. Evidence on the benefit of HF therapies in the elderly, provided by the present and previous studies, may thus allow an improvement in prescription rates of life-saving therapies in these patients.

Third, older HF patients have a significant burden of comorbidities.[6] This is particularly true for non-cardiovascular comorbidities that seem to increase linearly with age.[26] Comorbidities may explain the lower prescription rates of guideline-directed therapies as well as the higher incidence of AEs and serious AEs with age, also observed herein in both treatment arms. It is important to stress, however, that despite the higher rates of AEs, the use of guideline-recommended therapies and SGLT2i provide a net benefit in older patients that is consistent with that observed in younger patients.

Age has long been associated with worse outcomes in HF,[4–8,13] with older patients considered more vulnerable due to the effects of ageing on the cardiovascular system and the accumulation of comorbidities. In the present study, we did not observe a graded increase in the risk of cardiovascular death or HF hospitalization with advancing age in the placebo arm; event rates were actually lower in the middle-age group compared to younger patients but did not differ between the youngest and the oldest group. A similar trend in cardiovascular outcomes, with lower events in the middle-age group, was also observed in some recent clinical trials and registries,[4,7,27] in which patients were receiving good background therapy and age was taken as a trichotomous variable, as was also the case herein. Such a trend was further observed for in-hospital mortality in two nationwide registries.[28,29] In one of these latter registries, there was actually an inverse relationship between age and 30-day HF readmission, with younger patients having higher readmission rates than older ones.[28] The lower use of guideline-recommended therapies may theoretically account at least in part for the worse outcomes in elderly HF patients observed by previous studies. In OPTIMIZE-HF, older patients were characterized by both worse outcomes and a lower use of guideline-recommended therapies,[22] while in the V-HeFT study, increasing age (up to 75 years) was not associated with worse survival in HF patients who received optimal therapy.[30] Yet in contrast, in the present study, patients in the youngest group had lower LVEF, higher rate of HF hospitalization within the preceding year and lower use of CRT and these findings may partly explain the observed higher rate of HF hospitalization in this group during follow-up in the placebo arm compared with middle-aged patients.

Empagliflozin improves renal outcomes in patients with diabetes, regardless of the presence of HF, and in patients with HFrEF, regardless of the presence of diabetes.[12,31] These reno-protective effects are particularly relevant for elderly HF patients, in whom age-related renal function worsening may be accelerated by HF and comorbidities.[32] The reno-protective effect of empagliflozin was observed both in younger and in older HFrEF patients, as the

effects of the drug compared with placebo on the slope of change in eGFR and the renal composite outcome of end-stage kidney disease or sustained profound eGFR decrease were consistent across the three age groups. The benefits of empagliflozin did not come at the costs of worse tolerability, with AEs not being increased with empagliflozin versus placebo, even in the elderly.

Patient-reported health status and quality of life represents an important aspect of HF and a major treatment target.[33] Evidence on the effect of ageing on health status in patients with HF is controversial. In DAPA-HF and one other observational study, KCCQ tended to improve with increasing age, as older patients seemed to have less severe symptoms.[13,34] In PARADIGM-HF, in contrast, age was inversely correlated with KCCQ scores in physical and social activity limitations.[35] In the present analysis, KCCQ-CSS did not differ among age groups at baseline. Regarding the effects of HF therapies on patients' self-reported health status, in DAPA-HF, the effect of dapagliflozin on KCCQ was consistent across age groups.[13] In PARADIGM-HF, the improvement in combined KCCQ physical and social activity score seen with sacubitril/valsartan was comparable to a difference of 9 years of ageing.[35] In a previous analysis of the EMPEROR-Reduced trial, empagliflozin reduced the risk of cardiovascular death or HF hospitalization regardless of patients' baseline KCCQ-CSS, improving outcomes even in patients in the worst KCCQ-CSS tertile.[36] In addition, the drug improved significantly KCCQ-CSS, total summary score and overall summary score compared with placebo.[36] In the present analysis, we further expand these findings showing that the benefit of empagliflozin on KCCQ-CSS is consistent across the spectrum of age, including patients in the oldest age group. Taken together, the potentially impaired health status of the elderly does not affect their response to empagliflozin in cardiovascular or renal outcomes, while it is expected to improve with this treatment.

The present study represents a secondary analysis of a large randomized controlled trial and as such, its findings should be interpreted with caution. However, it should be stressed that the results observed in the different age groups were in accordance with those in the whole study population.

In conclusion, in the present secondary analysis of a large randomized clinical trial, the efficacy and safety of empagliflozin compared to placebo in improving cardiovascular and renal outcomes in HFrEF patients are consistent across the spectrum of age, including patients aged 75 or older. This finding is particularly important for elderly HF patients and especially those who currently receive limited prescription and titration of neurohormonal inhibitors or other guideline-recommended therapies.

Supplementary Information

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

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