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RESEARCH PAPER

Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial

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Abstract

Objective: The risks of cardio-renal complications of diabetes increase with age. In the EMPA-REG OUTCOME® trial, empagliflozin reduced cardiovascular (CV) mortality by 38% in patients with type 2 diabetes (T2D) and CV disease. Here we compare outcomes with empagliflozin in older patients in EMPA-REG OUTCOME.
Methods: Patients with T2D and CV disease were randomised to empagliflozin 10 or 25 mg, or placebo plus standard of care. In post hoc analyses, risks of 3-point major adverse CV events (3P-MACE: composite of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke), CV death, hospitalisation for heart failure, all-cause mortality, all-cause hospitalisation and incident/worsening nephropathy were evaluated for empagliflozin versus placebo by baseline age (<65, 65 to <75, ≥75 years). Adverse events (AEs) were analysed descriptively.
Results: Effect of empagliflozin on all outcomes was consistent across age categories ($P \geq 0.05$ for interactions) except 3P-MACE. The 3P-MACE hazard ratios (HRs) were 1.04 (95% confidence interval [CI] 0.84, 1.29), 0.74 (0.58, 0.93) and 0.68 (0.46, 1.00) in patients aged <65, 65 to <75, and ≥75 years, respectively ($P = 0.047$ for treatment-by-age group interaction). Corresponding CV death HRs were 0.72 (95% CI 0.52, 1.01), 0.54 (0.37, 0.79) and 0.55 (0.32, 0.94), respectively ($P = 0.484$ for treatment-by-age group interaction). Across age categories, empagliflozin AEs reflected its known safety profile. Rates of bone fractures, renal AEs and diabetic ketoacidosis were similar between empagliflozin and placebo across age categories.
Conclusions: In the EMPA-REG OUTCOME trial, empagliflozin reduced risks of CV mortality, heart failure and renal outcomes, supporting its cardio-renal benefits in older patients.

Keywords: *aged*, *cardiovascular disease*, *clinical trial*, *kidney diseases*, *type 2 diabetes*

Key Points

- Reductions in risks of cardio-renal outcomes with empagliflozin versus placebo were consistent across subgroups by baseline age.
- The known safety profile of empagliflozin was reflected across all baseline age categories.

- Hypoglycaemia, fracture, renal AE and diabetic ketoacidosis rates were similar for empagliflozin and placebo across age groups.

Introduction

Type 2 diabetes (T2D) in older people is increasingly recognised as a public health challenge [1]. In the United States, 22% of individuals 65 years or older have diabetes. Moreover, 21% of people with diabetes are 75 years or older [2]. Treatment of patients with diabetes aged ≥65 years requires particular care as comorbidities, polypharmacy and the complications of diabetes are more common in older individuals, and the risk of hypoglycaemia is higher [3,4]. Geriatric conditions such as falls and urinary incontinence also have the potential to impact diabetes self-management, as noted in the American Diabetes Association (ADA) guidelines for older adults [4]. Patients aged ≥65 years are also more prone to adverse events (AEs) than younger patients [5].

Empagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor used in the treatment of T2D. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin reduced the risk of the primary composite outcome of cardiovascular (CV) death, non-fatal myocardial infarction (MI) or non-fatal stroke (3-point major adverse CV events [3P-MACE]) compared with placebo (hazard ratio [HR] 0.86 [95% confidence interval (CI) 0.74, 0.99]). This was driven by a 38% reduction in risk of CV death (HR 0.62 [95% confidence interval (CI) 0.49, 0.77]) [6]. Further, empagliflozin reduced the risk of all-cause mortality (0.68 [95% CI 0.57, 0.82]), hospitalisation for heart failure (HR 0.65 [95% CI 0.50, 0.85]), all-cause hospitalisation (HR 0.89 [95% CI 0.82, 0.96]), and incident or worsening nephropathy (HR 0.61 [95% CI 0.53, 0.70]) [6–8].

The risk:benefit of empagliflozin in older patients has yet to be fully explored. We investigated the potential effect of age on the reduction in CV outcomes, renal outcomes and mortality with empagliflozin versus placebo, and on the drug's safety and tolerability profile, in the EMPA-REG OUTCOME trial. Given the increasing burden placed on health systems by hospitalisations of older patients with diabetes, we also assessed rates of hospitalisation in the empagliflozin and placebo groups.

Methods

Trial design

Briefly, patients with T2D (with glycated haemoglobin [HbA1c] 7.0–9.0% [53–75 mmol/mol)] for drug-naïve patients and 7.0–10.0% [53–86 mmol/mol] for those on stable glucose-lowering therapy), established CV disease and estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 were randomised to receive empagliflozin 10 mg, empagliflozin 25 mg or placebo in addition to standard of care. Background glucose-lowering therapy was to remain unchanged for the first 12 weeks of treatment. After week 12, investigators were encouraged to adjust glucose-lowering therapy to achieve glycaemic control according to local guidelines. Investigators were encouraged to treat CV risk factors according to local guidelines throughout the trial. The trial was to continue until ≥691 patients experienced an adjudicated event included in the primary outcome (3P-MACE). Patients who prematurely discontinued study medication continued to be followed for the ascertainment of CV outcomes, AEs and vital status.

The EMPA-REG OUTCOME trial was registered with ClinicalTrials.gov (NCT01131676) and carried out in compliance with the protocol and the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. An independent ethics committee or institutional review board approved the clinical protocol at each participating centre. All patients provided signed and dated informed consent.

Outcomes

CV outcome events and deaths were prospectively adjudicated by Clinical Events Committees [6]. Outcomes were analysed in subgroups by baseline age (<65 years, 65 to <75 years, ≥75 years); there was a particular focus on older patients with the subgroup of patients ≥75 years chosen to be clinically relevant in reflecting the advancing age of the population with diabetes [2]. The analysed outcomes were: 3P-MACE; CV death; fatal or non-fatal stroke; fatal or non-fatal MI; hospitalisation for heart failure; composite of heart failure hospitalisation or CV death; all-cause hospitalisation (defined as hospitalisation due to any AE); all-cause mortality; time to first event of incident or worsening nephropathy (defined as progression to macroalbuminuria [urine albumin-to-creatinine ratio >300 mg/g]), doubling of serum creatinine accompanied by eGFR (Modification of Diet in Renal Disease [MDRD] formula) ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy or death due to renal disease) and components of incident or worsening nephropathy. We analysed HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, uric acid and eGFR (MDRD) over time in these three age groups.

The safety and tolerability of empagliflozin in these age groups were assessed based on AEs (coded according to preferred terms in the Medical Dictionary for Regulatory Activities version 18.0) reported by the investigator that occurred during treatment or ≤7 days after the last dose of

a study drug, except for cancer, which was based on events up to trial termination.

Analyses

All analyses were post hoc and so *P*-values should be interpreted as explorative. The analyses were performed in patients who received ≥1 dose of study drug. Differences between empagliflozin pooled and placebo in the risk of an outcome were assessed using a Cox proportional hazards model based on events observed from randomisation to the end of the study. The following variables were included in the Cox regression model: sex, baseline body mass index category, baseline HbA1c category, baseline eGFR category, geographical region, treatment, age groups and treatment-by-age groups interaction. Proportionality checks were performed on all patients by visual inspection of log(−log [survival function]) against the log of time by treatment group. The interaction of treatment with log of time and Schoenfeld residuals was investigated.

A test of interaction between treatment and age category (<65 years, 65 to <75 years, ≥75 years) was applied to assess the homogeneity of the treatment effect by subgroup of age category; the categorisation of age was not pre-specified. Interaction *P*-values, with no adjustment for multiple testing, are presented. Data from patients who did not have an event were censored on the last day they were known to be free of the outcome. Cumulative incidence function estimates were corrected for death as a competing risk. Kaplan–Meier estimates are presented for all-cause mortality and incident or worsening nephropathy. Changes in HbA1c, blood pressure, weight, uric acid and eGFR with empagliflozin 10 mg, empagliflozin 25 mg and placebo were assessed using a mixed model repeated measures analysis using all data obtained until study end. AEs were assessed descriptively.

Results

Study patients

A total of 7020 patients were treated in the EMPA-REG OUTCOME trial, of whom 55.5%, 35.3% and 9.3% were aged <65 years, 65 to <75 years and ≥ 75 years at baseline, respectively. In total, 97.0% of patients completed the study, with 25.4% of patients prematurely discontinuing study medication, and final vital status available for 99.2% of patients [6].

Baseline characteristics

Baseline characteristics were balanced between the empagliflozin and placebo groups within each age subgroup (Appendix S1, Supplementary data, available in *Age and Ageing* online). With increasing age, SBP was higher; HbA1c, weight, DBP and eGFR were lower; greater proportions of patients had been diagnosed with diabetes for >10 years; and greater proportions had coronary artery disease, heart failure, or were taking loop diuretics (Appendix S1, Supplementary data, available in *Age and Ageing* online).

CV outcomes

The reductions in risk of CV death, hospitalisation for heart failure, heart failure hospitalisation or CV death and all-cause hospitalisation with empagliflozin versus placebo in the three age categories (<65 years, 65 to <75 years and ≥ 75 years) were similar to the overall trial population ($P = 0.484$, $P = 0.488$, $P = 0.240$ and $P = 0.638$ for treatment-by-age group interaction, respectively) (Figure 1). In the two oldest age groups, reductions in the risks of these outcomes with empagliflozin versus placebo were sustained throughout the trial (Figure 2 and Appendices S2, S3 and S4, Supplementary data, available in *Age and Ageing* online). Analyses by age showed heterogeneity in the reduction in the risk of 3P-MACE with empagliflozin versus placebo ($P = 0.047$ for interaction) (Figure 1). As in the overall trial population, there was no difference in the risk of MI (fatal or non-fatal) or stroke (fatal or non-fatal) with empagliflozin versus placebo across age categories ($P = 0.258$ and $P = 0.142$ for interaction, respectively) (Appendix S5, Supplementary data, available in *Age and Ageing* online).

All-cause mortality

The reduction in risk of all-cause mortality with empagliflozin versus placebo was also similar in the three age categories compared with the overall trial population ($P = 0.836$ for treatment-by-age group interaction) (Figure 1). In the older age groups, the reduction in the risk of all-cause mortality with empagliflozin versus placebo was sustained throughout the trial (Appendix S6, Supplementary data, available in *Age and Ageing* online).

Renal outcomes

The reduction in risk of incident or worsening nephropathy (Figure 1 and Appendix, Supplementary data, available in *Age and Ageing* online) and progression to macroalbuminuria (Appendix S8, Supplementary data, available in *Age and Ageing* online) with empagliflozin versus placebo in the three age categories were consistent with the general trial population ($P = 0.733$ and $P = 0.741$ for treatment-by-age group interaction, respectively). HRs were not calculated for the other components of the incident or worsening nephropathy due to the low number of patients with events in ≥1 age category (Appendix S8, Supplementary data, available in *Age and Ageing* online). Three (0.1%) patients in the empagliflozin group and none in the placebo group died from renal disease.

Metabolic and haemodynamic parameters

There were greater reductions in HbA1c in the empagliflozin versus placebo group in patients aged <65 years than ≥65 years (Appendix S9, Supplementary data, available

	Empagliflozin	Placebo	HR (95% CI)	Treatment by age group interaction
	Patients with events, n/ patients analysed, N (%)			
3P-MACE				
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)	
Age at baseline, years				
<65	251/2596 (9.7)	121/1297 (9.3)	1.04 (0.84, 1.29)	*P*=0.047
65 to <75	182/1667 (10.9)	115/808 (14.2)	0.74 (0.58, 0.93)	
≥75	57/424 (13.4)	46/228 (20.2)	0.68 (0.46, 1.00)	
CV death				
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
Age at baseline, years				
<65	85/2596 (3.3)	59/1297 (4.5)	0.72 (0.52, 1.01)	*P*=0.484
65 to <75	59/1667 (3.5)	51/808 (6.3)	0.54 (0.37, 0.79)	
≥75	28/424 (6.6)	27/228 (11.8)	0.55 (0.32, 0.94)	
Hospitalisation for heart failure				
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)	
Age at baseline, years				
<65	54/2596 (2.1)	37/1297 (2.9)	0.73 (0.48, 1.10)	*P*=0.488
65 to <75	57/1667 (3.4)	40/808 (5.0)	0.66 (0.44, 1.00)	
≥75	15/424 (3.5)	18/228 (7.9)	0.45 (0.22, 0.89)	
Heart failure hospitalisation or CV death				
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
Age at baseline, years				
<65	127/2596 (4.9)	81/1297 (6.2)	0.78 (0.59, 1.03)	*P*=0.240
65 to <75	101/1667 (6.1)	79/808 (9.8)	0.59 (0.44, 0.80)	
≥75	37/424 (8.7)	38/228 (16.7)	0.52 (0.33, 0.82)	
All-cause mortality				
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)	
Age at baseline, years				
<65	112/2596 (4.3)	78/1297 (6.0)	0.72 (0.54, 0.96)	*P*=0.836
65 to <75	107/1667 (6.4)	74/808 (9.2)	0.68 (0.51, 0.92)	
≥75	50/424 (11.8)	42/228 (18.4)	0.61 (0.41, 0.93)	
All-cause hospitalisation				
All patients	1725/4687 (36.8)	925/2333 (39.6)	0.89 (0.82, 0.96)	
Age at baseline, years				
<65	851/2596 (32.8)	450/1297 (34.7)	0.92 (0.82, 1.03)	*P*=0.638
65 to <75	683/1667 (41.0)	362/808 (44.8)	0.85 (0.74, 0.96)	
≥75	191/424 (45.0)	113/228 (49.6)	0.88 (0.70, 1.11)	
Incident or worsening nephropathy				
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	
Age at baseline, years				
<65	277/2306 (12.0)	208/1148 (18.1)	0.61 (0.51, 0.73)	*P*=0.733
65 to <75	191/1459 (13.1)	126/700 (18.0)	0.65 (0.52, 0.81)	
≥75	57/359 (15.9)	54/213 (25.4)	0.54 (0.37, 0.79)	

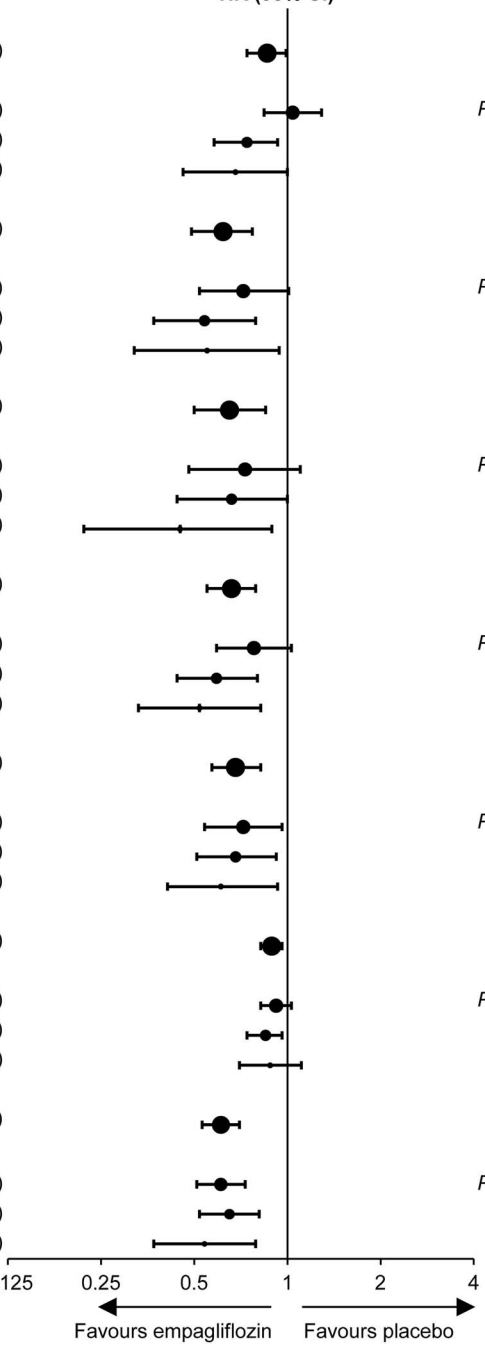

Figure 1. CV outcomes, all-cause mortality, all-cause hospitalisation and incident for worsening nephropathy by baseline age. Cox regression analysis in patients treated with ≥1 dose of study drug. Interaction *P*-value is for the test of homogeneity of treatment group difference among subgroups (test for treatment by subgroup interaction) with no adjustment for multiple tests. 3P-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

in *Age and Ageing* online). Reductions in SBP with empagliflozin versus placebo were similar in patients aged <65 and 65 to <75 years, and smaller in patients aged ≥75 years (Appendix S10, Supplementary data, available in *Age and Ageing* online). Similar reductions in DBP, weight and uric acid were observed with empagliflozin versus placebo across age categories (Appendices S11–13, Supplementary data, available in *Age and Ageing* online).

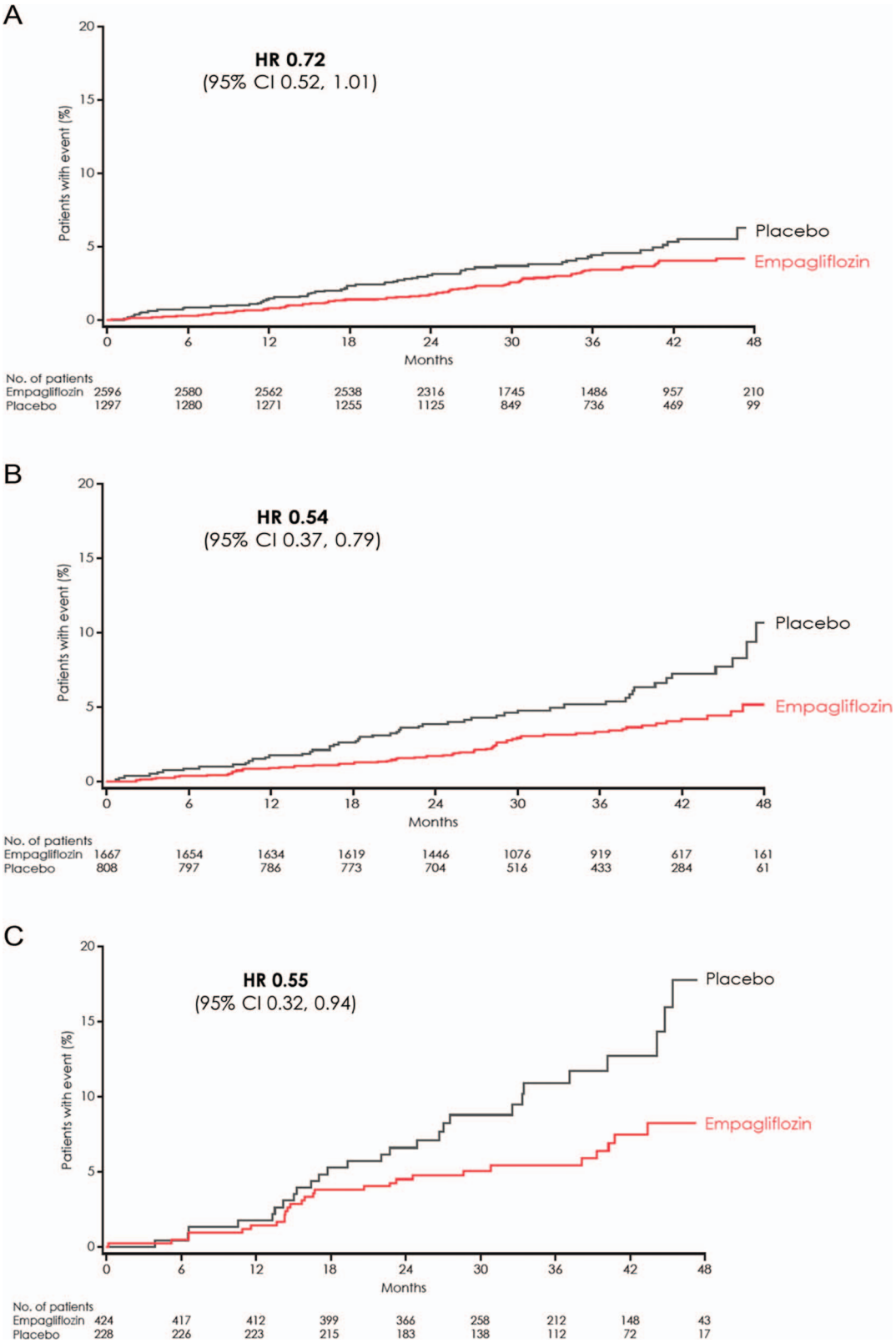

Figure 2. Time to CV death by age at baseline. (A) <65 years, (B) 65 to <75 years, and (C) ≥75 years. Cumulative incidence function in patients treated with ≥1 dose of study drug. HR and 95% CI are based on Cox regression analyses. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table 1. AEs in subgroups by age at baseline.

	<65 years		65 to <75 years		≥75 years	
	Placebo (*N* = 1297)	Empagliflozin (*N* = 2596)	Placebo (*N* = 808)	Empagliflozin (*N* = 1667)	Placebo (*N* = 228)	Empagliflozin (*N* = 424)
AE	1174 (90.5)	2314 (89.1)	750 (92.8)	1531 (91.8)	215 (94.3)	385 (90.8)
Serious AE	464 (35.8)	899 (34.6)	391 (48.4)	694 (41.6)	133 (58.3)	196 (46.2)
Death	45 (3.5)	78 (3.0)	46 (5.7)	73 (4.4)	28 (12.3)	25 (5.9)
AE leading to discontinuation of study drug	200 (15.4)	374 (14.4)	188 (23.3)	336 (20.2)	65 (28.5)	103 (24.3)
Confirmed hypoglycaemic AE[a]	342 (26.4)	706 (27.2)	246 (30.4)	480 (28.8)	62 (27.2)	117 (27.6)
Requiring assistance	18 (1.4)	29 (1.1)	13 (1.6)	26 (1.6)	5 (2.2)	8 (1.9)
AE consistent with UTI[b]	203 (15.7)	400 (15.4)	165 (20.4)	331 (19.9)	55 (24.1)	111 (26.2)
Complicated UTI[c]	18 (1.4)	31 (1.2)	18 (2.2)	38 (2.3)	5 (2.2)	13 (3.1)
AE consistent with genital infection[d]	23 (1.8)	181 (7.0)	17 (2.1)	97 (5.8)	2 (0.9)	23 (5.4)
AE consistent with volume depletion[e]	45 (3.5)	95 (3.7)	57 (7.1)	115 (6.9)	13 (5.7)	29 (6.8)
Acute renal failure[f]	75 (5.8)	119 (4.6)	61 (7.5)	103 (6.2)	19 (8.3)	24 (5.7)
Acute kidney injury	16 (1.2)	16 (0.6)	14 (1.7)	19 (1.1)	7 (3.1)	10 (2.4)
Diabetic ketoacidosis[g]	1 (0.1)	2 (0.1)	0	2 (0.1)	0	0
Thromboembolic events[f]	6 (0.5)	14 (0.5)	13 (1.6)	15 (0.9)	1 (0.4)	1 (0.2)
Bone fracture[h]	45 (3.5)	81 (3.1)	35 (4.3)	76 (4.6)	11 (4.8)	22 (5.2)
Cancer[i]	25 (1.9)	78 (3.0)	52 (6.4)	113 (6.8)	26 (11.4)	36 (8.5)

Data are *n* (%) of patients treated with ≥1 dose of study drug in whom ≥1 such AE was reported. Events that occurred during treatment or ≤7 days after the last dose of study drug are presented, except for cancer, for which events up to trial termination are reported. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI, urinary tract infection. [a]Plasma glucose ≤70 mg/dl and/or requiring assistance. [b]Based on 79 MedDRA preferred terms. [c]Pyelonephritis, urosepsis or serious AE consistent with UTI. [d]Based on 88 MedDRA preferred terms. [e]Based on eight MedDRA preferred terms. [f]Based on one standardised MedDRA query. [g]Based on four MedDRA preferred terms. [h]Based on 62 MedDRA preferred terms. [i]Based on 1539 MedDRA preferred terms.

Safety and tolerability

AEs by age category are presented in Table 1. The proportions of patients with confirmed hypoglycaemic AEs and hypoglycaemic AEs requiring assistance were similar in patients treated with empagliflozin and placebo in all age categories. Greater proportions of patients treated with empagliflozin than placebo had AEs consistent with genital infections in all age categories. AEs consistent with urinary tract infections (UTIs) were more common in older patients, but were not more common in patients treated with empagliflozin than placebo. Diabetic ketoacidosis AEs were reported in four (0.1%) patients treated with empagliflozin (two patients aged <65 years, two patients aged 65 to <75 years), and one (<0.1%) patient in the placebo group. The proportion of patients with acute renal failure (including acute kidney injury) was lower in the empagliflozin group than the placebo group in all age categories. Events consistent with volume depletion were reported in a greater proportion of patients treated with empagliflozin than placebo in patients aged ≥75 years (6.8% versus 5.7%) but occurred at a similar frequency with empagliflozin and placebo in other age groups. The proportion of patients with bone fractures was similar between empagliflozin and placebo in all age categories.

Overall, there was no increase of malignancies with empagliflozin compared with placebo, and there was no specific subtype of cancer where a significant imbalance was observed. The proportion of patients with cancer AEs reported during the trial was greater with empagliflozin (3.0%) than placebo (1.9%) in patients aged <65 years, similar with empagliflozin (6.8%) and placebo (6.4%) in patients aged 65 to <75 years, and lower with empagliflozin (8.5%) than placebo (11.4%) in patients aged ≥75 years.

In all age categories, there was an initial decrease in eGFR with empagliflozin, followed by long-term stabilisation of renal function, contrasted by a steady decline in eGFR in the placebo group (Appendix S14, Supplementary data, available in *Age and Ageing* online).

Discussion

In the EMPA-REG OUTCOME trial, empagliflozin, given in addition to standard of care, reduced the risk of CV and all-cause death, hospitalisation for heart failure, all-cause hospitalisation and incident or worsening nephropathy in older patients with T2D and established CV disease. These benefits occurred in a population, in which the majority was taking anti-hypertensive therapies, lipid-lowering therapies and anti-platelet therapy at baseline.

Some heterogeneity was observed in the reduction in risk of 3P-MACE with empagliflozin versus placebo analysed by age ($P = 0.047$ for interaction), which may be related to the composite nature of this endpoint. In

the overall population, the superiority of empagliflozin on 3P-MACE was driven by a significant reduction in death from CV causes [6], and there was a consistent benefit of empagliflozin versus placebo on death from CV causes across all age subgroups. The CV benefits of empagliflozin were reflected in the 2018 update to the consensus statement of the ADA and the European Association for the Study of Diabetes, which recommends glucose-lowering therapy with a proven CV benefit such as an SGLT2 inhibitor or glucagon-like peptide-1 receptor agonist for patients with clinical CV disease [9].

In all age groups, an initial decrease in eGFR was observed with empagliflozin, followed by stability over long-term treatment, compared with a steady decline in eGFR in the placebo group. This is reminiscent of the pattern observed with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [10, 11] and likely reflects the haemodynamic effects of empagliflozin [8].

In the EMPA-REG OUTCOME trial, the safety profile in older individuals was consistent with the known safety profile of empagliflozin [12]. Greater proportions of patients treated with empagliflozin than placebo had events consistent with genital infections in all age categories. Patients aged >60 years are known to be more susceptible to UTIs [13]. In EMPA-REG OUTCOME, events consistent with UTIs were more common in patients aged ≥65 years than in younger patients and appeared to increase with age, with the highest incidence in patients aged ≥75 years. This was also the case for complicated UTIs, volume depletion, acute kidney injury and the incidence of AEs leading to discontinuation of the study drug, which suggests age-dependent effects for this study population.

Patients with T2D aged ≥65 years are at greater risk of hypoglycaemia for several reasons, including greater use of insulin therapy, progressive renal dysfunction with reduced insulin clearance and abnormal counter-regulation [3, 4]. Thus it is reassuring to note that in EMPA-REG OUTCOME, the proportions of patients with confirmed hypoglycaemia and hypoglycaemia requiring assistance were similar with empagliflozin and placebo across age categories.

Older patients are also at higher risk of volume depletion, likely due to increased comorbidities, use of medications with hypotensive effects, altered thirst response and changes in water and sodium balance that occur with ageing [14]. In the EMPA-REG OUTCOME trial, the proportion of patients with events consistent with volume depletion was higher in patients aged ≥65 years. The frequency of these events was greater with empagliflozin than placebo in patients aged ≥75 years, but similar in those aged <75 years, consistent with previous data [15]. Reductions in SBP with empagliflozin versus placebo appeared to be smaller in patients aged ≥75 years.

Older age is associated with an increased risk of bone fractures [16] and an increased risk of bone fracture is listed as a side effect of the SGLT2 inhibitor canagliflozin [17]. In the EMPA-REG OUTCOME trial, the proportion of patients with bone fractures was similar with empagliflozin versus placebo across all-age subgroups.

Limitations of our exploratory analyses include that only 9% of patients were aged ≥75 years. Nevertheless, there were 652 patients aged ≥75 years and 2475 patients aged 65 to <75 years, providing sufficient data for comparison of empagliflozin and placebo. Statistical limitations of the study were the increased possibility of type I errors due to multiple testing, and inadequate statistical power for the interaction tests due to the small sample size of the ≥75 cohort and the low number of events. Patients' frailty status, a potentially important risk factor for adverse outcomes in older patients with diabetes [18,19], was not characterised.

In conclusion, empagliflozin given in addition to standard of care reduced the risk of CV and all-cause death, hospitalisation for heart failure, all-cause hospitalisation, and incident or worsening nephropathy versus placebo in older patients with T2D and established CV disease. In subgroup analyses, there was some heterogeneity for the primary composite outcome of 3P-MACE. However, there was a consistent benefit of empagliflozin versus placebo on death from CV causes across all subgroups. No new safety concerns were identified in patients aged ≥65 years. These data highlight the therapeutic potential of empagliflozin in older patients with T2D.

Supplementary data: Supplementary data are available in *Age and Ageing* online.

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