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Safety of Empagliflozin in Patients with Type 2 Diabetes and CKD: Pooled Analysis of Placebo-Controlled Clinical Trials

Running Title: Empagliflozin Safety in Chronic Kidney Disease

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Abstract

OBJECTIVE

To assess safety of empagliflozin in patients with type 2 diabetes and moderate-to-severe chronic kidney disease ([CKD] category G3–4) enrolled in clinical trials.

RESEARCH DESIGN AND METHODS

This analysis pooled data from 19 randomized, placebo-controlled, phase 1–4 clinical trials and one randomized, placebo-controlled extension study in which patients received empagliflozin 10 mg or 25 mg daily. Time to first occurrence of adverse events (AEs) was evaluated using Kaplan-Meier analysis and multivariable Cox regression models.

RESULTS

Among a total of 15,081 patients who received at least one study drug dose,1522, 722, and 123 individuals were classified as CKD categories G3A, G3B, and G4, respectively, at baseline. Demographics and clinical characteristics were similar between treatment groups across categories of CKD. Rates of serious AEs, AEs leading to discontinuation, and events of special interest (including lower limb amputations and acute renal failure [ARF]) were also similar between empagliflozin and placebo across CKD subgroups. In adjusted Cox regression analyses, risks for volume depletion and ARF were similar for empagliflozin and placebo in the combined group with (CKD categoriesy G3B-- and +G4) groups compared with and the G3A groups, . but withNotably lower observed risks (HR [95% CI]) were observed in both groups in the G3B+G4 group for hyperkalemia (0.59 [0.37–0.96], *P* = 0.0323; and 0.48 [0.26–0.91], *P* = 0.0243,

respectively) and edema (0.47 [0.33–0.68], $P < 0.0001$; and 0.44 [0.28–0.68], $P = 0.0002$, respectively).

CONCLUSIONS

Use of empagliflozin in patients with type 2 diabetes and advanced CKD raised no new safety concerns and may have beneficial effects on development of hyperkalemia and edema.

INTRODUCTION

Type 2 diabetes is the leading cause of chronic kidney disease (CKD) worldwide (1). CKD, characterized by the presence of albuminuria and/or a decline in glomerular filtration rate (GFR), develops in approximately 40% of patients with type 2 diabetes (2; 3). During the course of CKD in diabetes, the annual decline in estimated GFR (eGFR) varies greatly depending on the severity of CKD and risk factors such as hyperglycemia, hypertension, obesity, and smoking (4). CKD attributed to diabetes is the leading global cause of kidney failure requiring dialysis treatment or a kidney transplant (5). Both eGFR <60 mL/min/1.73 m^2 and albuminuria are independent predictors of cardiovascular events and mortality (6; 7), meaning that patients with diabetes and concomitant CKD are a particularly high-risk population.

Interventions to prevent or slow CKD progression are essential to reduce risks for serious complications (8). Empagliflozin, a selective sodium–glucose cotransporter 2 (SGLT2) inhibitor, has been shown to reduce onset and progression of CKD in patients with type 2 diabetes (8). Current US Food and Drug Administration prescribing information allows for empagliflozin to be used in patients with eGFR ≥30 mL/min/1.73 m^2 (9) (but labeling may vary from country to country). However, both kidney and cardiovascular benefits have been observed with empagliflozin in patients with heart failure and an eGFR as low as 20 mL/min/1.73 m^2~~;~~, irrespective of diabetes ~~status these patients had heart failure and reduced ejection fraction with or without type 2 diabetes~~ (10).

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), a cardiovascular outcome trial that included patients

with type 2 diabetes and established cardiovascular disease with eGFR ≥30 mL/min/1.73 m^2, empagliflozin added to the standard of care reduced cardiovascular death by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32%, compared with placebo (11); there was also a 39% reduction in incident or worsening nephropathy (12). Notably, the safety profile of empagliflozin in patients with CKD category G3 ~~CKD~~ (eGFR 30 to <60 mL/min/1.73 m^2) was consistent with that of the overall trial population (12), and observed rates of adverse events (AEs) of particular concern in this population, such as rates of urinary tract and genital infections, volume depletion, acute renal failure (ARF), hyperkalemia, hypoglycemia, bone fracture, and lower limb amputations, were not different from rates seen in patients receiving placebo (13).

A large pooled analysis of data from the empagliflozin clinical trial program has previously reported safety analyses (14). The present analysis reports safety data for AEs that are particularly relevant in this population ~~in patients~~ with type 2 diabetes and moderate-to-severe CKD (CKD categor~~iesy~~ G3–4) who were enrolled in these clinical trials~~; it includes patients with AEs that are of clinical importance in this population~~.

RESEARCH DESIGN AND METHODS

The pooled analysis included data from 19 randomized, placebo-controlled, phase 1–4 clinical trials (including EMPA-REG OUTCOME) and one extension study that ~~enrolled~~ included ~~patients~~participants from three of the 19 included trials (Supplementary Table 1). All trials enrolled patients with type 2 diabetes. The data pool comprised placebo-controlled trials in which ~~patients~~ participants received empagliflozin 10 mg or 25 mg

daily, including some that involved dose-escalation or up-titration from the 10 mg to the 25 mg dose. No studies of open-label treatment or active comparators were included.

Safety Assessment

Safety was assessed based on investigator-reported AEs that were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Serious AEs (SAEs) were defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or marked disability/incapacity, required or prolonged inpatient hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason. Hypoglycemia, including all confirmed hypoglycemic events (with a glucose value ≤70 mg/dL or where assistance was required), and other defined events of special interest were identified by a search of MedDRA preferred terms. As lower limb amputations were not usually captured in AE reports, the frequency of lower limb amputations was assessed based on a medical review of the pooled safety data and AE narratives (15).

Data Analyses

The eGFR was calculated from the serum creatinine (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation 2009). AEs were assessed in all ~~patients~~ participants who received at least one study drug dose. Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × *n*/T, where *n* was the number of ~~subjects~~ participants with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment received to the onset of the first event (for ~~patients~~ those with an event) or to the last dose ~~+~~plus 7 days (for ~~patients~~ those without an event). Time to first occurrence

of events consistent with edema, hyperkalemia, bone fracture, volume depletion, and ARF was evaluated by Kaplan-Meier analysis (~~a list of~~ MedDRA terms, ~~included for each outcome is shown in~~ Supplementary Table 2). Cox regression analyses were performed for hyperkalemia, edema, volume depletion, and ARF. The Cox regression models for time to first event included the following covariables: age, baseline body mass index, baseline HbA_{1c}, treatment, sex, baseline eGFR, and a treatment-by-baseline eGFR interaction term. To check for heterogeneity, the Cox regression models were repeated with EMPA-REG OUTCOME versus other trials as a categorical class variable in the model, and with the individual study as a random effect, both in addition to the standard parameterization used in the analysis.

Data and Resource Availability

The sponsor of the EMPA-REG OUTCOME trial (Boehringer Ingelheim) is committed to responsible sharing of clinical trial reports, related clinical documents, and patient-level clinical data. Researchers are invited to submit inquiries via the Vivli Center for Global Clinical Research website (https://vivli.org).

RESULTS

Analysis Population

In total, 15,081 patients were included in the pooled analysis population. Baseline eGFR was <60 mL/min/1.73 m^2 in 2,367 patients (1,519 who received empagliflozin 10/25 mg; 848 who received placebo). A total of 1,522, 722, and 123 individuals were classified as having CKD categories G3A (eGFR 45 to <60 mL/min/1.73 m^2), G3B (eGFR 30 to

<45 mL/min/1.73 m^2), and G4 (eGFR <30 mL/min/1.73 m^2), respectively~~, based on their baseline eGFR level.~~ . Total exposure in patient-years for the placebo and empagliflozin groups, respectively, was: CKD category G3A ~~(eGFR 45 to <60 mL/min/1.73 m^2)~~, 1,014 and 2,021; CKD category G3B ~~(eGFR 30 to <45 mL/min/1.73 m^2)~~, 503 and 850; CKD category G4 ~~(eGFR <30 mL/min/1.73 m^2)~~, 50 and 89. The proportion of patients with normoalbuminuria, microalbuminuria, or macroalbuminuria was similar across the empagliflozin (66.3%, 24.8%, and 7.7%, respectively) and placebo (64.5%, 25.6%, and 8.9%, respectively) treatment groups. Demographics and baseline characteristics were similar between patients with eGFR <60 mL/min/1.73 m^2 in the empagliflozin and placebo groups, across these CKD categories (Table 1).

Adverse Events

Rates of SAEs, AEs leading to discontinuation, and AEs of special interest (including lower limb amputations and ARF) were ~~generally~~ similar between empagliflozin and placebo across CKD subgroups (Table 2 and Supplementary Fig. 1). However, the overall frequency of genital infections was higher among those receiving empagliflozin compared with placebo. Notably, the ~~(but~~ incidence rates of genital infections were progressively lower across CKD categories 3A, 3B, and 4~~)~~. Unadjusted time to first occurrence of hyperkalemia, ARF, volume depletion, and bone fracture revealed no significant differences between treatment groups, while edema was less common in patients receiving empagliflozin than placebo (Fig. 1 and Supplementary Fig. 2). For~~In~~ adjusted Cox regression models~~analyses~~, the G4 group was too small for statistical analyses and was therefore combined~~pooled~~ with the G3B group (CKD categories~~y~~

G3B–G4). Ssimilar risks for volume depletion and ARF persisted for empagliflozin and placebo in the groups with eGFR <45 mL/min/1.73 m^2 (CKD categoriesy G3B–G4CKD categories G3B and+G4) and 45 to <60 mL/min/1.73 m^2 (CKD category G3A), but lower risks (hazard ratio [95% CI]), were observed with empagliflozin for hyperkalemia (0.59 [0.37–0.96], *P* = 0.0323; and 0.48 [0.26–0.91], *P* = 0.0243, respectively) and edema (0.47 [0.33–0.68], *P* < 0.0001; and 0.44 [0.28–0.68], *P* = 0.0002, respectively) compared with placebo (Supplementary Table 3). The G4 group was too small for statistical analysis and was therefore pooled with the G3B group for the adjusted analyses. Testing for heterogeneity across trials in these models showed only marginal differences with regard to the hazard ratios and their 95% CIs for the risks of volume depletion, ARF, hyperkalemia, and edema (Supplementary Tables 4 and 5).

CONCLUSIONS

This comprehensive safety analysis of a large pool of patients with advanced CKD who received empagliflozin in clinical trials found no overall differences in rates of SAEs, AEs leading to discontinuation, or events of special interest with empagliflozin treatment versus placebo, irrespective of baseline eGFR. An exception was genital infections, a well-recognized side effect of the SGLT2 inhibitor class (16-18), which- occurred more frequently in the empagliflozin than in the placebo group, but with lower incidence rates in advanced CKD categories. This is could be due at least in part to lesser urinary glucose excretion at lower levels of eGFR (19). Indeed, poorly controlled diabetes, typically accompanied by higher urinary glucose excretion, independently increases risk of genital infections in patients with T2D (20). Current prescribing information for

empagliflozin notes that a higher incidence of adverse reactions related to reduced renal function may be seen in patients with ~~impaired renal function~~CKD (9). However, while the risk of ARF was seen to increase with decreasing kidney function in both treatment groups, ~~observed~~ ARF rates were similar ~~overall~~ between empagliflozin and placebo across CKD subgroups. Notably, a meta-analysis of SGLT2 inhibitor studies, which included cardiovascular outcome trials and the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial that was conducted in patients with type 2 diabetes and CKD, demonstrated a 25% reduction in the risk of acute kidney injury (21).

The safety findings with empagliflozin in this pooled analysis may support the use of SGLT2 inhibitors in patients with type 2 diabetes and advanced CKD. In CREDENCE (22), canagliflozin showed consistent benefit across CKD subgroups. The Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD) trial (23) further demonstrated that dapagliflozin reduced risks of CKD outcomes, as well as heart failure events, cardiovascular death, and all-cause mortality, in a trial population of patients with CKD, a third of whom did not have type 2 diabetes. The American Diabetes Association (24) currently recommends that for patients with type 2 diabetes, CKD, and albuminuria, SGLT2 inhibitor therapy is preferred, but that either an SGLT2 inhibitor or a GLP-1 receptor agonist is suitable for patients with type 2 diabetes and CKD in the absence of albuminuria. The Kidney Disease: Improving Global Outcomes guidelines for diabetes and CKD (25) also recommend an SGLT2 inhibitor as first-line treatment in patients with CKD and type 2 diabetes who have eGFR ≥30 mL/min/1.73 m^2, regardless of the presence or absence

of albuminuria. However, the current label recommendations for eGFR levels at which SGLT2 inhibitors can be initiated or should be discontinued differ between different agents, and the labeling for each agent may differ between countries and regions. Of note, no new safety concerns were seen in the small group of patients with eGFR <30 mL/min/1.73m^2 included in this analysis, supporting the safety of SGLT2 inhibitors in advanced CKD. This aligns with findings from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) that included patients with heart failure and eGFR level as low as 20 mL/min/1.73m^2 (10). CKD was present in 53% of this trial population.

Patients with advanced CKD, especially those receiving renin-angiotensin system blockers, are prone to hyperkalemia. Notably, a lower risk for hyperkalemia was observed in patients receiving empagliflozin versus placebo in the present analysis. Dapagliflozin has also shown no signal for higher risk of hyperkalemia (26; 27). Moreover, hyperkalemia risk was mitigated by canagliflozin in the CREDENCE trial, and there were no meaningful effects of canagliflozin on serum potassium or related AEs across the Canagliflozin Cardiovascular Assessment Study (CANVAS) program (28; 29). This favorable effect of SGLT2 inhibitors on serum potassium in patients with type 2 diabetes and CKD might permit the broader use of drugs associated with hyperkalemia, such as mineralocorticoid-receptor antagonists (30; 31).

In the pooled data set analyzed for the current study, there was no association between empagliflozin and increased risk of bone fracture or lower limb amputations. The pattern for these events with empagliflozin was similar to that seen with placebo. Indeed, a similar risk of volume depletion and ARF was seen in the empagliflozin and

placebo groups in this analysis, but a reduction in the occurrence of edema was reported in patients receiving empagliflozin versus those in the placebo group. Like empagliflozin, no causal association between dapagliflozin and risk of fractures or LLA has been confirmed (26; 27). However, the CANVAS Program reported a two-fold increased risk of lower limb amputation and a 26% increased risk of bone fractures associated with canagliflozin (32). While this initially resulted in a black box warning to highlight the potentially increased risk of lower limb amputation for canagliflozin (18), these findings were not reproduced in the subsequent CREDENCE trial, and the black box warning has since been removed (33).

In this pooled safety analysis, we did not assess diabetic ketoacidosis by CKD subgroup as the incidence of this AE was too low. However, in a previous pooled analysis, overall observed rates of diabetic ketoacidosis were comparable across empagliflozin and placebo treatment groups (14). A similar result was seen in the DAPA-CKD trial, where diabetic ketoacidosis was not seen in any participant receiving dapagliflozin and was reported in only two receiving placebo (23).

Strengths of this analysis include the large sample size and inclusion only of patients randomized to double-blind treatment. The dataset was derived from placebo-controlled clinical trials at different stages of development, and it included patients in each of the low eGFR categories for analysis. Baseline characteristics were balanced between the different treatment groups and time on treatment was similar. Limitations of this pooled analysis arise from the varying durations, designs, and populations of the included studies. Additionally, by merging the patients treated with empagliflozin 10 mg or 25 mg into a single group, this analysis cannot elaborate on potential dose effects for AEs or

SAEs. In other studies, however, the safety profile was similar for both doses (14). There were two studies (contributing a total of 432 participants) in which the dose of empagliflozin was escalated from 10 to 25 mg daily (N=157 participants), or up-titrated from 10 to 25 mg -in patients with insufficient glycaemic control only (N=275 participants). Data from these participants are included in the EMPA 10/25 mg results. Renal impairment as exclusion criteria at baseline in both of these trials was defined as eGFR <45 ml/min/1.73m^2, compared to <30 ml/min/1.73m^2 in EMPA-REG OUTCOME. Findings regarding patients with CKD category G4 should be interpreted with caution owing to the small sample size. Finally, statistical analyses were not adjusted for multiple comparisons.

In conclusion, use of empagliflozin in patients with type 2 diabetes and advanced CKD raised no new safety concerns, and may have beneficial effects on development of hyperkalemia and edema. Dedicated SGLT2i trials investigating treatment effects in CKD populations may provide further data to confirm these observations, particularly in patients with CKD category 4 where limited data are currently available. Nevertheless, careful consideration of the current prescribing information for empagliflozin is recommended in this population. To build on the promising findings to date, a dedicated kidney disease outcome trial of empagliflozin versus placebo, enrolling over 6600 patients with and without diabetes, including those with low levels of kidney function with and without albuminuria, is under way (EMPA-KIDNEY; NCT03594110) (7).

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Characteristic	CKD Category					
	G3A (eGFR 45 to <60)		G3B (eGFR 30 to <45)		G4 (eGFR 15 to <30)	
	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg
N	519	1,003	277	445	52	71
Male, *n* (%)	358 (69.0)	653 (65.1)	167 (60.3)	277 (62.2)	30 (57.7)	41 (57.7)
Age, years, mean ± SD	67.1 ± 8.1	67.1 ± 7.5	67.9 ± 8.2	67.7 ± 8.7	63.7 ± 10.7	68.8 ± 9.1
Race, *n* (%)*						
White	369 (71.1)	730 (72.8)	195 (70.4)	308 (69.2)	24 (46.2)	47 (66.2)
Asian	118 (22.7)	210 (20.9)	70 (25.3)	109 (24.5)	28 (53.8)	22 (31.0)
Black/African American	29 (5.6)	52 (5.2)	8 (2.9)	24 (5.4)	0	1 (1.4)
Ethnicity, *n* (%)						
Not Hispanic/Latino	450 (86.7)	864 (86.1)	245 (88.4)	384 (86.3)	50 (96.2)	65 (91.5)
Hispanic/Latino	68 (13.1)	138 (13.8)	33 (11.6)	61 (13.7)	2 (3.8)	6 (8.5)
HbA_{1c}, % (mmol/mol), mean ± SD	8.0 ± 0.8 (64 ± 9)	8.01 ± 0.8 (64 ± 9)	8.1 ± 0.9 (65 ± 10)	8.1 ± 0.9 (65 ± 10)	8.1 ± 0.9 (65 ± 10)	7.95 ± 0.91 (63 ± 10)
Body mass index, kg/m^2, mean ± SD	30.6 ± 5.2	31.0 ± 5.5	31.1 ± 5.8	31.3 ± 5.6	30.9 ± 5.7	29.5 ± 4.9
Blood pressure, mmHg, mean ± SD‡						
Systolic	136.7 ± 18.7	135.9 ± 17.1	135.0 ± 17.7	137.4 ± 18.0	143.0 ± 23.9	137.5 ± 21.0
Diastolic	75.4 ± 10.2	75.5 ± 10.1	73.6 ± 10.2	74.0 ± 9.9	75.2 ± 12.4	72.6 ± 10.8
Heart failure, *n* (%)‡	51 (9.8)	114 (11.4)	31 (11.2)	53 (11.9)	8 (15.4)	7 (9.9)
Hypertension, *n* (%)	486 (93.6)	950 (94.7)	270 (97.5)	426 (95.7)	51 (98.1)	68 (95.8)
Concomitant medications, *n* (%)						
Metformin	352 (67.8)	662 (66.0)	118 (42.6)	198 (44.5)	9 (17.3)	35 (49.3)
Insulin	268 (51.6)	502 (50.0)	172 (62.1)	276 (62.0)	38 (73.1)	53 (74.6)
ACE inhibitors/ARBs	424 (81.7)	843 (84.0)	224 (80.9)	361 (81.1)	36 (69.2)	51 (71.8)
Loop diuretics	109 (21)	195 (19.4)	91 (32.9)	151 (33.9)	24 (46.2)	35 (49.3)
Statins	370 (71.3)	752 (75.0)	198 (71.5)	315 (70.8)	40 (76.9)	52 (73.2)
Aspirin	387 (74.6)	739 (73.7)	209 (75.5)	333 (74.8)	34 (65.4)	51 (71.8)

Table 1—Demographics and baseline characteristics of the pooled analysis population with eGFR <60 mL/min/1.73 m^2 (*N* = 2367)

*Race identified as other (American Indian/Alaska Native/Hawaiian/Pacific Islander), or race information not recorded, for seven patients in the CKD category G3A group.

†Baseline systolic BP/diastolic BP readings were missing for one patient in the empagliflozin 10 mg group.

‡A history of heart failure at baseline was identified by narrow SMQ 20000004.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in mL/min/1.73m^2); HbA_{1c}, glycated hemoglobin; PBO, placebo; SD, standard deviation.

Category	Placebo		Empagliflozin 10/25 mg	
	n/*N* (%)	Rate/100 p-y (95% CI)	*n*/*N* (%)	Rate/100 p-y (95% CI)
Serious AEs				
Overall	1,204/4,904 (24.6)	18.61 (17.57–19.69)	2,161/10,177 (21.2)	15.52 (14.88–16.19)
G3A	209/519 (40.3)	27.18 (23.62–31.12)	354/1,003 (35.3)	22.46 (20.19–24.93)
G3B	113/277 (40.8)	31.16 (25.69–37.46)	177/445 (39.8)	26.81 (23.00–31.06)
G4	13/52 (25.0)	29.93 (15.94–51.17)	28/71 (39.4)	41.31 (27.46–59.69)
AEs leading to treatment discontinuation				
Overall	565/4,904 (11.5)	7.40 (6.80–8.04)	1,033/10,177 (10.2)	6.43 (6.05–6.84)
G3A	100/519 (19.3)	10.37 (8.44–12.61)	179/1,003 (17.8)	9.26 (7.95–10.72)
G3B	62/277 (22.4)	13.10 (10.05–16.79)	113/445 (25.4)	14.17 (11.68–17.03)
G4	10/52 (19.2)	21.47 (10.30–39.47)	14/71 (19.7)	15.70 (8.59–26.35)
Hypoglycemia				
Overall	1,045//4,904 (21.3)	16.32 (15.35–17.34)	2,067/10,177 (20.3)	15.69 (15.02–16.38)
G3A	177/519 (34.1)	24.02 (20.62–27.83)	268/1,003 (26.7)	17.20 (15.21–19.39)
G3B	91/277 (32.9)	24.23 (19.51–29.75)	141/445 (31.7)	22.85 (19.24–26.95)
G4	23/52 (44.2)	67.50 (42.80–101.23)	24/71 (33.8)	39.34 (25.21–58.52)
Urinary tract infection				
Overall	691/4,904 (14.1)	9.70 (8.99–10.46)	1,382/10,177 (13.6)	9.27 (8.79–9.77)
G3A	84/519 (16.2)	9.18 (7.32–11.37)	200/1,003 (19.9)	11.36 (9.84–13.05)
G3B	62/277 (22.4)	13.69 (10.49–17.54)	101/445 (22.7)	13.98 (11.39–16.99)
G4	5/52 (9.6)	10.24 (3.32–23.89)	18/71 (25.4)	25.19 (14.93–39.81)
Genital infection				
Overall	75/4,904 (1.5)	0.85 (0.75–1.20)	565/10,177 (5.6)	3.54 (3.25–3.84)
G3A	8/519 (1.5)	0.79 (0.34–1.56)	54/1,003 (5.4)	2.75 (2.06–3.58)
G3B	2/277 (0.7)	0.39 (0.05–1.43)	15/445 (3.4)	1.78 (1.00–2.94)
G4	0/52 (0)	0	1/71 (1.4)	1.13 (0.03–6.28)

Volume depletion				
Overall	147/4,904 (3.0)	1.89 (1.60–2.23)	320/10,177 (3.1)	1.97 (1.76–2.20)
G3A	33/519 (6.4)	3.38 (2.32–4.74)	63/1,003 (6.2)	3.22 (2.48–4.12)
G3B	19/277 (6.9)	3.95 (2.38–6.17)	28/445 (6.3)	3.43 (2.28–4.95)
G4	6/52 (11.5)	12.04 (4.42–26.19)	7/71 (9.8)	8.22 (3.30–16.93)
Edema				
Overall	278/4,904 (5.7)	3.67 (3.25–4.12)	269/10,177 (2.6)	1.65 (1.46–1.86)
G3A	51/519 (9.8)	5.37 (4.00–7.06)	49/1003 (4.9)	2.48 (1.84–3.28)
G3B	38/277 (13.7)	8.12 (5.75–11.15)	36/445 (8.1)	4.42 (3.10–6.12)
G4	5/52 (9.6)	11.77 (3.82–27.47)	1/71 (1.4)	1.11 (0.03–6.18)
Bone fracture				
Overall	134/4,904 (2.7)	1.72 (1.44–2.04)	233/10,177 (2.3)	1.42 (1.25–1.62)
G3A	26/519 (5.0)	2.60 (1.79–3.81)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	12/277 (4.3)	2.40 (1.24–4.19)	20/445 (4.5)	2.40 (1.46–3.70)
G4	1/52 (1.9)	2.06 (0.05–11.49)	0/71 (0)	0
Falls				
Overall	87/4,904 (1.8)	1.11 (0.89–1.37)	197/10,177 (1.9)	1.20 (1.04–1.38)
G3A	17/519 (3.3)	1.70 (0.99–2.72)	30/1,003 (3.0)	1.50 (1.01–2.15)
G3B	10/277 (3.6)	2.01 (0.97–3.70)	11/445 (2.5)	1.30 (0.65–2.33)
G4	1/52 (1.9)	2.06 (0.05–11.49)	1/71 (1.4)	1.11 (0.03–6.18)
Hyperkalemia				
Overall	90/4,904 (1.8)	1.15 (0.92–1.41)	119/10,177 (1.2)	0.72 (0.60–0.86)
G3A	23/519 (4.4)	2.31 (1.47–3.47)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	18/277 (7.6)	3.73 (2.21–5.89)	15/445 (3.4)	1.78 (1.00–2.93)
G4	3/52 (0)	6.16 (1.27–17.99)	1/71 (1.4)	1.11 (0.03–6.21)
Acute renal failure				
Overall	169/4,904 (3.4)	2.18 (1.86–2.53)	291/10,177 (1.2)	1.78 (1.58–2.00)

G3A	48/519 (9.2)	4.92 (3.63–6.53)	86/1,003 (8.6)	4.44 (3.55–5.48)
G3B	37/277 (13.3)	7.85 (5.53–10.83)	57/445 (12.8)	7.22 (5.47–9.35)
G4	6/52 (11.5)	13.87 (5.09–30.19)	9/71 (12.7)	10.85 (4.96–20.59)
Lower limb amputation				
Overall	46/4,904 (0.9)	0.52 (0.38–0.69)	95/10,177 (0.1)	0.52 (0.42–0.63)
G3A	11/519 (2.1)	0.92 (0.46–1.65)	17/1,003 (1.7)	0.74 (0.43–1.18)
G3B	7/277 (2.5)	1.22 (0.49–2.51)	10/445 (2.2)	0.95 (0.46–1.75)
G4	0/52 (0)	0	4/71 (5.6)	3.59 (0.98–9.20)

Table 2—Patients with at least one adverse event by CKD category at baseline

Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × *n*/T, where *n* was the number of participants with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (mL/min/1.73 m^2) calculated using the CKD-EPI equation. CKD categories by eGFR (mL/min/1.73 m^2): G3A, 45 to <60; G3B, 30 to <45; G4, 15 to <30. Frequencies *n*/*N* = patients with ≥1 event/all patients who received ≥1 dose of study drug.

*Data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial only. No amputations were reported for the four patients with missing baseline eGFR values.

AE, adverse event; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; p-y, patient-years.

CKD category	G3A	G3A	G3B	G3B	G4	G4
eGFR (mL/min/1.73m²)	45 to <60	45 to <60	30 to <45	30 to <45	15 to <30	15 to <30
Study treatment	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg
N	519	1,003	277	445	52	71
Male, *n* (%)	358 (69.0)	653 (65.1)	167 (60.3)	277 (62.2)	30 (57.7)	41 (57.7)
Age, years, mean ±SD	67.1 ±8.1	67.1 ±7.5	67.9 ±8.2	67.7 ±8.7	63.7 ±10.7	68.8 ±9.1
Race, *n* (%)*						

White	369 (71.1)	730 (72.8)	195 (70.4)	308 (69.2)	24 (46.2)	47 (66.2)
Asian	118 (22.7)	210 (20.9)	70 (25.3)	109 (24.5)	28 (53.8)	22 (31.0)
Black/African American	29 (5.6)	52 (5.2)	8 (2.9)	24 (5.4)	0	1 (1.4)
Ethnicity, *n* (%)						
Not Hispanic/Latino	450 (86.7)	864 (86.1)	245 (88.4)	384 (86.3)	50 (96.2)	65 (91.5)
Hispanic/Latino	68 (13.1)	138 (13.8)	33 (11.6)	61 (13.7)	2 (3.8)	6 (8.5)
HbA_{1c}, % (mmol/mol), mean ±SD	8.0 ±0.8 (64 ±9)	8.01 ±0.8 (64 ±9)	8.1 ±0.9 (65 ±10)	8.1 ±0.9 (65 ±10)	8.1 ±0.9 (65 ±10)	7.95 ±0.91 (63 ±10)
Body mass index, kg/m², mean ±SD	30.6 ±5.2	31.0 ±5.5	31.1 ±5.8	31.3 ±5.6	30.9 ±5.7	29.5 ±4.9
Blood pressure, mmHg, mean ±SD†						
Systolic	136.7 ±18.7	135.9 ±17.1	135.0 ±17.7	137.4 ±18.0	143.0 ±23.9	137.5 ±21.0
Diastolic	75.4 ±10.2	75.5 ±10.1	73.6 ±10.2	74.0 ±9.9	75.2 ±12.4	72.6 ±10.8
Heart failure, *n* (%)‡	51 (9.8)	114 (11.4)	31 (11.2)	53 (11.9)	8 (15.4)	7 (9.9)
Hypertension, *n* (%)	486 (93.6)	950 (94.7)	270 (97.5)	426 (95.7)	51 (98.1)	68 (95.8)
Concomitant medications, *n* (%)						
Metformin	352 (67.8)	662 (66.0)	118 (42.6)	198 (44.5)	9 (17.3)	35 (49.3)
Insulin	268 (51.6)	502 (50.0)	172 (62.1)	276 (62.0)	38 (73.1)	53 (74.6)
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Statins	370 (71.3)	752 (75.0)	198 (71.5)	315 (70.8)	40 (76.9)	52 (73.2)
Aspirin	387 (74.6)	739 (73.7)	209 (75.5)	333 (74.8)	34 (65.4)	51 (71.8)

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†Baseline systolic BP/diastolic BP readings were missing for one patient in the empagliflozin 10 mg group.

‡A history of heart failure at baseline was identified by narrow SMQ 20000004.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in mL/min/1.73m²); HbA_{1c}, glycated hemoglobin; PBO, placebo; SD, standard deviation.

Category	Placebo	Placebo	EMPA 10/25 mg	EMPA 10/25 mg
	n/*N* (%)	Rate/100 p-y (95% CI)	*n*/*N* (%)	Rate/100 p-y (95% CI)
Serious AEs				
Overall	1,204/4,904 (24.6)	18.61 (17.57–19.69)	2,161/10,177 (21.2)	15.52 (14.88–16.19)
G3A	209/519 (40.3)	27.18 (23.62–31.12)	354/1,003 (35.3)	22.46 (20.19–24.93)
G3B	113/277 (40.8)	31.16 (25.69–37.46)	177/445 (39.8)	26.81 (23.00–31.06)
G4	13/52 (25.0)	29.93 (15.94–51.17)	28/71 (39.4)	41.31 (27.46–59.69)
AEs leading to treatment discontinuation				
Overall	565/4,904 (11.5)	7.40 (6.80–8.04)	1,033/10,177 (10.2)	6.43 (6.05–6.84)
G3A	100/519 (19.3)	10.37 (8.44–12.61)	179/1,003 (17.8)	9.26 (7.95–10.72)
G3B	62/277 (22.4)	13.10 (10.05–16.79)	113/445 (25.4)	14.17 (11.68–17.03)
G4	10/52 (19.2)	21.47 (10.30–39.47)	14/71 (19.7)	15.70 (8.59–26.35)
Hypoglycemia				
Overall	1,045//4,904 (21.3)	16.32 (15.35–17.34)	2,067/10,177 (20.3)	15.69 (15.02–16.38)
G3A	177/519(34.1)	24.02 (20.62–27.83)	268/1,003 (26.7)	17.20 (15.21–19.39)
G3B	91/277 (32.9)	24.23 (19.51–29.75)	141/445 (31.7)	22.85 (19.24–26.95)
G4	23/52 (44.2)	67.50 (42.80–101.23)	24/71 (33.8)	39.34 (25.21–58.52)
Urinary tract infection				
Overall	691/4,904 (14.1)	9.70 (8.99–10.46)	1,382/10,177 (13.6)	9.27 (8.79–9.77)
G3A	84/519 (16.2)	9.18 (7.32–11.37)	200/1,003 (19.9)	11.36 (9.84–13.05)
G3B	62/277 (22.4)	13.69 (10.49–17.54)	101/445 (22.7)	13.98 (11.39–16.99)
G4	5/52 (9.6)	10.24 (3.32–23.89)	18/71 (25.4)	25.19 (14.93–39.81)
Genital infection				
Overall	75/4,904 (1.5)	0.85 (0.75–1.20)	565/10,177 (5.6)	3.54 (3.25–3.84)
G3A	8/519 (1.5)	0.79 (0.34–1.56)	54/1,003 (5.4)	2.75 (2.06–3.58)

G3B	2/277 (0.7)	0.39 (0.05–1.43)	15/445 (3.4)	1.78 (1.00–2.94)
G4	0/52 (0)	0	1/71 (1.4)	1.13 (0.03–6.28)
Volume depletion				
Overall	147/4,904 (3.0)	1.89 (1.60–2.23)	320/10,177 (3.1)	1.97 (1.76–2.20)
G3A	33/519 (6.4)	3.38 (2.32–4.74)	63/1,003 (6.2)	3.22 (2.48–4.12)
G3B	19/277 (6.9)	3.95 (2.38–6.17)	28/445 (6.3)	3.43 (2.28–4.95)
G4	6/52 (11.5)	12.04 (4.42–26.19)	7/71 (9.8)	8.22 (3.30–16.93)
Edema				
Overall	278/4,904 (5.7)	3.67 (3.25–4.12)	269/10,177 (2.6)	1.65 (1.46–1.86)
G3A	51/519 (9.8)	5.37 (4.00–7.06)	49/1003 (4.9)	2.48 (1.84–3.28)
G3B	38/277 (13.7)	8.12 (5.75–11.15)	36/445 (8.1)	4.42 (3.10–6.12)
G4	5/52 (9.6)	11.77 (3.82–27.47)	1/71 (1.4)	1.11 (0.03–6.18)
Bone fracture				
Overall	134/4,904 (2.7)	1.72 (1.44–2.04)	233/10,177 (2.3)	1.42 (1.25–1.62)
G3A	26/519 (5.0)	2.60 (1.79–3.81)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	12/277 (4.3)	2.40 (1.24–4.19)	20/445 (4.5)	2.40 (1.46–3.70)
G4	1/52 (1.9)	2.06 (0.05–11.49)	0/71 (0)	0
Falls				
Overall	87/4,904 (1.8)	1.11 (0.89–1.37)	197/10,177 (1.9)	1.20 (1.04–1.38)
G3A	17/519 (3.3)	1.70 (0.99–2.72)	30/1,003 (3.0)	1.50 (1.01–2.15)
G3B	10/277 (3.6)	2.01 (0.97–3.70)	11/445 (2.5)	1.30 (0.65–2.33)
G4	1/52 (1.9)	2.06 (0.05–11.49)	1/71 (1.4)	1.11 (0.03–6.18)
Hyperkalemia				
Overall	90/4,904 (1.8)	1.15 (0.92–1.41)	119/10,177 (1.2)	0.72 (0.60–0.86)
G3A	23/519 (4.4)	2.31 (1.47–3.47)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	18/277 (7.6)	3.73 (2.21–5.89)	15/445 (3.4)	1.78 (1.00–2.93)

G4	3/52 (0)	6.16 (1.27–17.99)	1/71 (1.4)	1.11 (0.03–6.21)
Acute renal failure				
Overall	169/4,904 (3.4)	2.18 (1.86–2.53)	291/10,177 (1.2)	1.78 (1.58–2.00)
G3A	48/519 (9.2)	4.92 (3.63–6.53)	86/1,003 (8.6)	4.44 (3.55–5.48)
G3B	37/277 (13.3)	7.85 (5.53–10.83)	57/445 (12.8)	7.22 (5.47–9.35)
G4	6/52 (11.5)	13.87 (5.09–30.19)	9/71 (12.7)	10.85 (4.96–20.59)
Lower limb amputation				
Overall	46/4,904 (0.9)	0.52 (0.38–0.69)	95/10,177 (0.1)	0.52 (0.42–0.63)
G3A	11/519 (2.1)	0.92 (0.46–1.65)	17/1,003 (1.7)	0.74 (0.43–1.18)
G3B	7/277 (2.5)	1.22 (0.49–2.51)	10/445 (2.2)	0.95 (0.46–1.75)
G4	0/52 (0)	0	4/71 (5.6)	3.59 (0.98–9.20)

Table 2—Patients with at least one adverse event by CKD category at baseline

Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × *n*/T, where *n* was the number of participants with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (mL/min/1.73 m^2) calculated using the CKD-EPI equation. CKD categories by eGFR (mL/min/1.73 m^2): G3A, 45 to <60; G3B, 30 to <45; G4, 15 to <30. Frequencies *n*/*N* = patients with ≥1 event/all patients who received ≥1 dose of study drug.

*Data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial only. No amputations were reported for the four patients with missing baseline eGFR values.

AE, adverse event; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; p-y, patient-years.

[Figure legend]

Figure 1—Kaplan-Meier estimates of time to first event of (*A*) hyperkalemia, (*B*) volume depletion, (*C*) edema, and (*D*) ARF in patients with eGFR <45 mL/min/1.73 m^2 (left-hand side) and 45 to <60 mL/min/1.73 m^2 (right-hand side).

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. ARF, acute renal failure; eGFR, estimated glomerular filtration rate.

Safety of Empagliflozin in Patients with Type 2 Diabetes and CKD: Pooled Analysis of Placebo-Controlled Clinical Trials

Running Title: Empagliflozin Safety in Chronic Kidney Disease

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Clinical Trial Registry.

ClinicalTrials.gov identifiers for the clinical trials included in the pooled analysis are: NCT00885118, NCT00789035, NCT00558571, NCT00749190, NCT01011868, NCT01193218, NCT01210001, NCT01177813, NCT01159600, NCT01289990, NCT01131676, NCT01164501, NCT01370005, NCT01306214, NCT01649297, NCT01947855, and NCT02589639.

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Abstract

OBJECTIVE

To assess safety of empagliflozin in patients with type 2 diabetes and moderate-to-severe chronic kidney disease ([CKD] category G3–4) enrolled in clinical trials.

RESEARCH DESIGN AND METHODS

This analysis pooled data from 19 randomized, placebo-controlled, phase 1–4 clinical trials and one randomized, placebo-controlled extension study in which patients received empagliflozin 10 mg or 25 mg daily. Time to first occurrence of adverse events (AEs) was evaluated using Kaplan-Meier analysis and multivariable Cox regression models.

RESULTS

Among a total of 15,081 patients who received at least one study drug dose,1522, 722, and 123 individuals were classified as CKD categories G3A, G3B, and G4, respectively, at baseline. Demographics and clinical characteristics were similar between treatment groups across categories of CKD. Rates of serious AEs, AEs leading to discontinuation, and events of special interest (including lower limb amputations and acute renal failure [ARF]) were also similar between empagliflozin and placebo across CKD subgroups. In adjusted Cox regression analyses, risks for volume depletion and ARF were similar for empagliflozin and placebo in the combined group with CKD categories G3B–G4 and the G3A group. Notably lower risks (HR [95% CI]) were observed in both groups for hyperkalemia (0.59 [0.37–0.96], $P = 0.0323$; and 0.48 [0.26–0.91], $P = 0.0243$, respectively) and edema (0.47 [0.33–0.68], $P < 0.0001$; and 0.44 [0.28–0.68], $P = 0.0002$, respectively).

CONCLUSIONS

Use of empagliflozin in patients with type 2 diabetes and advanced CKD raised no new safety concerns and may have beneficial effects on development of hyperkalemia and edema.

INTRODUCTION

Type 2 diabetes is the leading cause of chronic kidney disease (CKD) worldwide (1). CKD, characterized by the presence of albuminuria and/or a decline in glomerular filtration rate (GFR), develops in approximately 40% of patients with type 2 diabetes (2; 3). During the course of CKD in diabetes, the annual decline in estimated GFR (eGFR) varies greatly depending on the severity of CKD and risk factors such as hyperglycemia, hypertension, obesity, and smoking (4). CKD attributed to diabetes is the leading global cause of kidney failure requiring dialysis treatment or a kidney transplant (5). Both eGFR <60 mL/min/1.73 m^2 and albuminuria are independent predictors of cardiovascular events and mortality (6; 7), meaning that patients with diabetes and concomitant CKD are a particularly high-risk population.

Interventions to prevent or slow CKD progression are essential to reduce risks for serious complications (8). Empagliflozin, a selective sodium–glucose cotransporter 2 (SGLT2) inhibitor, has been shown to reduce onset and progression of CKD in patients with type 2 diabetes (8). Current US Food and Drug Administration prescribing information allows for empagliflozin to be used in patients with eGFR ≥30 mL/min/1.73 m^2 (9) (but labeling may vary from country to country). However, both kidney and cardiovascular benefits have been observed with empagliflozin in patients with heart failure and an eGFR as low as 20 mL/min/1.73 m^2, irrespective of diabetes status (10).

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), a cardiovascular outcome trial that included patients with type 2 diabetes and established cardiovascular disease with eGFR

≥30 mL/min/1.73 m^2, empagliflozin added to the standard of care reduced cardiovascular death by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32%, compared with placebo (11); there was also a 39% reduction in incident or worsening nephropathy (12). Notably, the safety profile of empagliflozin in patients with CKD category G3 (eGFR 30 to <60 mL/min/1.73 m^2) was consistent with that of the overall trial population (12), and observed rates of adverse events (AEs) of particular concern in this population, such as rates of urinary tract and genital infections, volume depletion, acute renal failure (ARF), hyperkalemia, hypoglycemia, bone fracture, and lower limb amputations, were not different from rates seen in patients receiving placebo (13).

A large pooled analysis of data from the empagliflozin clinical trial program has previously reported safety analyses (14). The present analysis reports safety data for AEs that are particularly relevant in this population with type 2 diabetes and moderate-to-severe CKD (CKD categories G3–4) who were enrolled in these clinical trials.

RESEARCH DESIGN AND METHODS

The pooled analysis included data from 19 randomized, placebo-controlled, phase 1–4 clinical trials (including EMPA-REG OUTCOME) and one extension study that included participants from three of the 19 included trials (Supplementary Table 1). All trials enrolled patients with type 2 diabetes. The data pool comprised placebo-controlled trials in which participants received empagliflozin 10 mg or 25 mg daily, including some that involved dose-escalation or up-titration from the 10 mg to the 25 mg dose. No studies of open-label treatment or active comparators were included.

Safety Assessment

Safety was assessed based on investigator-reported AEs that were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Serious AEs (SAEs) were defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or marked disability/incapacity, required or prolonged inpatient hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason. Hypoglycemia, including all confirmed hypoglycemic events (with a glucose value ≤70 mg/dL or where assistance was required), and other defined events of special interest were identified by a search of MedDRA preferred terms. As lower limb amputations were not usually captured in AE reports, the frequency of lower limb amputations was assessed based on a medical review of the pooled safety data and AE narratives (15).

Data Analyses

The eGFR was calculated from the serum creatinine (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation 2009). AEs were assessed in all participants who received at least one study drug dose. Exposure-adjusted incidence rates were calculated per 100 patient-years as $100 \times n/T$, where n was the number of participants with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment received to the onset of the first event (for those with an event) or to the last dose plus 7 days (for those without an event). Time to first occurrence of events consistent with edema, hyperkalemia, bone fracture, volume depletion, and ARF was evaluated by Kaplan-Meier analysis (MedDRA terms, Supplementary Table 2). Cox regression analyses were performed for hyperkalemia, edema, volume depletion, and ARF. The Cox

regression models for time to first event included the following covariables: age, baseline body mass index, baseline HbA_{1c}, treatment, sex, baseline eGFR, and a treatment-by-baseline eGFR interaction term. To check for heterogeneity, the Cox regression models were repeated with EMPA-REG OUTCOME versus other trials as a categorical class variable in the model, and with the individual study as a random effect, both in addition to the standard parameterization used in the analysis.

Data and Resource Availability

The sponsor of the EMPA-REG OUTCOME trial (Boehringer Ingelheim) is committed to responsible sharing of clinical trial reports, related clinical documents, and patient-level clinical data. Researchers are invited to submit inquiries via the Vivli Center for Global Clinical Research website (https://vivli.org).

RESULTS

Analysis Population

In total, 15,081 patients were included in the pooled analysis population. Baseline eGFR was <60 mL/min/1.73 m^2 in 2,367 patients (1,519 who received empagliflozin 10/25 mg; 848 who received placebo). A total of 1,522, 722, and 123 individuals were classified as having CKD categories G3A (eGFR 45 to <60 mL/min/1.73 m^2), G3B (eGFR 30 to <45 mL/min/1.73 m^2), and G4 (eGFR <30 mL/min/1.73 m^2), respectively. Total exposure in patient-years for the placebo and empagliflozin groups, respectively, was: CKD category G3A, 1,014 and 2,021; CKD category G3B, 503 and 850; CKD category G4, 50 and 89. The proportion of patients with normoalbuminuria, microalbuminuria, or

macroalbuminuria was similar across the empagliflozin (66.3%, 24.8%, and 7.7%, respectively) and placebo (64.5%, 25.6%, and 8.9%, respectively) treatment groups. Demographics and baseline characteristics were similar between patients with eGFR <60 mL/min/1.73 m^2 in the empagliflozin and placebo groups, across these CKD categories (Table 1).

Adverse Events

Rates of SAEs, AEs leading to discontinuation, and AEs of special interest (including lower limb amputations and ARF) were similar between empagliflozin and placebo across CKD subgroups (Table 2 and Supplementary Fig. 1). However, the overall frequency of genital infections was higher among those receiving empagliflozin compared with placebo. Notably, the incidence rates of genital infections were progressively lower across CKD categories 3A, 3B, and 4. Unadjusted time to first occurrence of hyperkalemia, ARF, volume depletion, and bone fracture revealed no significant differences between treatment groups, while edema was less common in patients receiving empagliflozin than placebo (Fig. 1 and Supplementary Fig. 2). For adjusted Cox regression models, the G4 group was too small for statistical analyses and was therefore combined with the G3B group (CKD categories G3B–G4). Similar risks for volume depletion and ARF persisted for empagliflozin and placebo in the groups with eGFR <45 mL/min/1.73 m^2 (CKD categories G3B–G4) and 45 to <60 mL/min/1.73 m^2 (CKD category G3A), but lower risks (hazard ratio [95% CI]), were observed with empagliflozin for hyperkalemia (0.59 [0.37–0.96], P = 0.0323; and 0.48 [0.26–0.91], P = 0.0243, respectively) and edema (0.47 [0.33–0.68], P < 0.0001; and

0.44 [0.28–0.68], *P* = 0.0002, respectively) compared with placebo (Supplementary Table 3). Testing for heterogeneity across trials in these models showed only marginal differences with regard to the hazard ratios and their 95% CIs for the risks of volume depletion, ARF, hyperkalemia, and edema (Supplementary Tables 4 and 5).

CONCLUSIONS

This comprehensive safety analysis of a large pool of patients with advanced CKD who received empagliflozin in clinical trials found no overall differences in rates of SAEs, AEs leading to discontinuation, or events of special interest with empagliflozin treatment versus placebo, irrespective of baseline eGFR. An exception was genital infections, a well-recognized side effect of the SGLT2 inhibitor class (16-18), which occurred more frequently in the empagliflozin than in the placebo group, but with lower incidence rates in advanced CKD categories. This could be due at least in part to lesser urinary glucose excretion at lower levels of eGFR (19). Indeed, poorly controlled diabetes, typically accompanied by higher urinary glucose excretion, independently increases risk of genital infections in patients with T2D (20). Current prescribing information for empagliflozin notes that a higher incidence of adverse reactions related to reduced renal function may be seen in patients with CKD (9). However, while the risk of ARF was seen to increase with decreasing kidney function in both treatment groups, ARF rates were similar between empagliflozin and placebo across CKD subgroups. Notably, a meta-analysis of SGLT2 inhibitor studies, which included cardiovascular outcome trials and the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial that was conducted in patients with

type 2 diabetes and CKD, demonstrated a 25% reduction in the risk of acute kidney injury (21).

The safety findings with empagliflozin in this pooled analysis may support the use of SGLT2 inhibitors in patients with type 2 diabetes and advanced CKD. In CREDENCE (22), canagliflozin showed consistent benefit across CKD subgroups. The Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD) trial (23) further demonstrated that dapagliflozin reduced risks of CKD outcomes, as well as heart failure events, cardiovascular death, and all-cause mortality, in a trial population of patients with CKD, a third of whom did not have type 2 diabetes. The American Diabetes Association (24) currently recommends that for patients with type 2 diabetes, CKD, and albuminuria, SGLT2 inhibitor therapy is preferred, but that either an SGLT2 inhibitor or a GLP-1 receptor agonist is suitable for patients with type 2 diabetes and CKD in the absence of albuminuria. The Kidney Disease: Improving Global Outcomes guidelines for diabetes and CKD (25) also recommend an SGLT2 inhibitor as first-line treatment in patients with CKD and type 2 diabetes who have eGFR ≥30 mL/min/1.73 m^2, regardless of the presence or absence of albuminuria. However, the current label recommendations for eGFR levels at which SGLT2 inhibitors can be initiated or should be discontinued differ between different agents, and the labeling for each agent may differ between countries and regions. Of note, no new safety concerns were seen in the small group of patients with eGFR <30 mL/min/1.73m^2 included in this analysis, supporting the safety of SGLT2 inhibitors in advanced CKD. This aligns with findings from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-

Reduced) that included patients with heart failure and eGFR level as low as 20 mL/min/1.73m^2 (10). CKD was present in 53% of this trial population.

Patients with advanced CKD, especially those receiving renin-angiotensin system blockers, are prone to hyperkalemia. Notably, a lower risk for hyperkalemia was observed in patients receiving empagliflozin versus placebo in the present analysis. Dapagliflozin has also shown no signal for higher risk of hyperkalemia (26; 27). Moreover, hyperkalemia risk was mitigated by canagliflozin in the CREDENCE trial, and there were no meaningful effects of canagliflozin on serum potassium or related AEs across the Canagliflozin Cardiovascular Assessment Study (CANVAS) program (28; 29). This favorable effect of SGLT2 inhibitors on serum potassium in patients with type 2 diabetes and CKD might permit the broader use of drugs associated with hyperkalemia, such as mineralocorticoid-receptor antagonists (30; 31).

In the pooled data set analyzed for the current study, there was no association between empagliflozin and increased risk of bone fracture or lower limb amputations. The pattern for these events with empagliflozin was similar to that seen with placebo. Indeed, a similar risk of volume depletion and ARF was seen in the empagliflozin and placebo groups in this analysis, but a reduction in the occurrence of edema was reported in patients receiving empagliflozin versus those in the placebo group. Like empagliflozin, no causal association between dapagliflozin and risk of fractures or LLA has been confirmed (26; 27). However, the CANVAS Program reported a two-fold increased risk of lower limb amputation and a 26% increased risk of bone fractures associated with canagliflozin (32). While this initially resulted in a black box warning to highlight the potentially increased risk of lower limb amputation for canagliflozin (18),

these findings were not reproduced in the subsequent CREDENCE trial, and the black box warning has since been removed (33).

In this pooled safety analysis, we did not assess diabetic ketoacidosis by CKD subgroup as the incidence of this AE was too low. However, in a previous pooled analysis, overall observed rates of diabetic ketoacidosis were comparable across empagliflozin and placebo treatment groups (14). A similar result was seen in the DAPA-CKD trial, where diabetic ketoacidosis was not seen in any participant receiving dapagliflozin and was reported in only two receiving placebo (23).

Strengths of this analysis include the large sample size and inclusion only of patients randomized to double-blind treatment. The dataset was derived from placebo-controlled clinical trials at different stages of development, and it included patients in each of the low eGFR categories for analysis. Baseline characteristics were balanced between the different treatment groups and time on treatment was similar. Limitations of this pooled analysis arise from the varying durations, designs, and populations of the included studies. Additionally, by merging the patients treated with empagliflozin 10 mg or 25 mg into a single group, this analysis cannot elaborate on potential dose effects for AEs or SAEs. In other studies, however, the safety profile was similar for both doses (14). There were two studies (contributing a total of 432 participants) in which the dose of empagliflozin was escalated from 10 to 25 mg daily (N=157 participants), or up-titrated from 10 to 25 mg in patients with insufficient glycaemic control only (N=275 participants). Data from these participants are included in the EMPA 10/25 mg results. Renal impairment as exclusion criteria at baseline in both of these trials was defined as eGFR <45 ml/min/1.73m^2, compared to <30 ml/min/1.73m^2 in EMPA-REG OUTCOME.

Findings regarding patients with CKD category G4 should be interpreted with caution owing to the small sample size. Finally, statistical analyses were not adjusted for multiple comparisons.

In conclusion, use of empagliflozin in patients with type 2 diabetes and advanced CKD raised no new safety concerns, and may have beneficial effects on development of hyperkalemia and edema. Dedicated SGLT2i trials investigating treatment effects in CKD populations may provide further data to confirm these observations, particularly in patients with CKD category 4 where limited data are currently available. Nevertheless, careful consideration of the current prescribing information for empagliflozin is recommended in this population. To build on the promising findings to date, a dedicated kidney disease outcome trial of empagliflozin versus placebo, enrolling over 6600 patients with and without diabetes, including those with low levels of kidney function with and without albuminuria, is under way (EMPA-KIDNEY; NCT03594110) (7).

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CKD category	G3A	G3A	G3B	G3B	G4	G4
eGFR (mL/min/1.73m²)	45 to <60	45 to <60	30 to <45	30 to <45	15 to <30	15 to <30
Study treatment	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg	PBO	EMPA 10/25 mg
N	519	1,003	277	445	52	71
Male, *n* (%)	358 (69.0)	653 (65.1)	167 (60.3)	277 (62.2)	30 (57.7)	41 (57.7)
Age, years, mean ±SD	67.1 ±8.1	67.1 ±7.5	67.9 ±8.2	67.7 ±8.7	63.7 ±10.7	68.8 ±9.1
Race, *n* (%)*						
White	369 (71.1)	730 (72.8)	195 (70.4)	308 (69.2)	24 (46.2)	47 (66.2)
Asian	118 (22.7)	210 (20.9)	70 (25.3)	109 (24.5)	28 (53.8)	22 (31.0)
Black/African American	29 (5.6)	52 (5.2)	8 (2.9)	24 (5.4)	0	1 (1.4)
Ethnicity, *n* (%)						
Not Hispanic/Latino	450 (86.7)	864 (86.1)	245 (88.4)	384 (86.3)	50 (96.2)	65 (91.5)
Hispanic/Latino	68 (13.1)	138 (13.8)	33 (11.6)	61 (13.7)	2 (3.8)	6 (8.5)
HbA_{1c}, % (mmol/mol), mean ±SD	8.0 ±0.8 (64 ±9)	8.01 ±0.8 (64 ±9)	8.1 ±0.9 (65 ±10)	8.1 ±0.9 (65 ±10)	8.1 ±0.9 (65 ±10)	7.95 ±0.91 (63 ±10)
Body mass index, kg/m², mean ±SD	30.6 ±5.2	31.0 ±5.5	31.1 ±5.8	31.3 ±5.6	30.9 ±5.7	29.5 ±4.9
Blood pressure, mmHg, mean ±SD†						
Systolic	136.7 ±18.7	135.9 ±17.1	135.0 ±17.7	137.4 ±18.0	143.0 ±23.9	137.5 ±21.0
Diastolic	75.4 ±10.2	75.5 ±10.1	73.6 ±10.2	74.0 ±9.9	75.2 ±12.4	72.6 ±10.8
Heart failure, *n* (%)‡	51 (9.8)	114 (11.4)	31 (11.2)	53 (11.9)	8 (15.4)	7 (9.9)
Hypertension, *n* (%)	486 (93.6)	950 (94.7)	270 (97.5)	426 (95.7)	51 (98.1)	68 (95.8)
Concomitant medications, *n* (%)						
Metformin	352 (67.8)	662 (66.0)	118 (42.6)	198 (44.5)	9 (17.3)	35 (49.3)
Insulin	268 (51.6)	502 (50.0)	172 (62.1)	276 (62.0)	38 (73.1)	53 (74.6)
ACE inhibitors/ARBs	424 (81.7)	843 (84.0)	224 (80.9)	361 (81.1)	36 (69.2)	51 (71.8)
Loop diuretics	109 (21)	195 (19.4)	91 (32.9)	151 (33.9)	24 (46.2)	35 (49.3)
Statins	370 (71.3)	752 (75.0)	198 (71.5)	315 (70.8)	40 (76.9)	52 (73.2)
Aspirin	387 (74.6)	739 (73.7)	209 (75.5)	333 (74.8)	34 (65.4)	51 (71.8)

Table 1—Demographics and baseline characteristics of the pooled analysis population with eGFR <60 mL/min/1.73 m² (*N* = 2367)

*Race identified as other (American Indian/Alaska Native/Hawaiian/Pacific Islander), or race information not recorded, for seven patients in the CKD category G3A group.

†Baseline systolic BP/diastolic BP readings were missing for one patient in the empagliflozin 10 mg group.

‡A history of heart failure at baseline was identified by narrow SMQ 20000004.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in mL/min/1.73m²); HbA_{1c}, glycated hemoglobin; PBO, placebo; SD, standard deviation.

Category	Placebo	Placebo	EMPA 10/25 mg	EMPA 10/25 mg
	n/*N* (%)	Rate/100 p-y (95% CI)	*n*/*N* (%)	Rate/100 p-y (95% CI)
Serious AEs				
Overall	1,204/4,904 (24.6)	18.61 (17.57–19.69)	2,161/10,177 (21.2)	15.52 (14.88–16.19)
G3A	209/519 (40.3)	27.18 (23.62–31.12)	354/1,003 (35.3)	22.46 (20.19–24.93)
G3B	113/277 (40.8)	31.16 (25.69–37.46)	177/445 (39.8)	26.81 (23.00–31.06)
G4	13/52 (25.0)	29.93 (15.94–51.17)	28/71 (39.4)	41.31 (27.46–59.69)
AEs leading to treatment discontinuation				
Overall	565/4,904 (11.5)	7.40 (6.80–8.04)	1,033/10,177 (10.2)	6.43 (6.05–6.84)
G3A	100/519 (19.3)	10.37 (8.44–12.61)	179/1,003 (17.8)	9.26 (7.95–10.72)
G3B	62/277 (22.4)	13.10 (10.05–16.79)	113/445 (25.4)	14.17 (11.68–17.03)
G4	10/52 (19.2)	21.47 (10.30–39.47)	14/71 (19.7)	15.70 (8.59–26.35)
Hypoglycemia				
Overall	1,045//4,904 (21.3)	16.32 (15.35–17.34)	2,067/10,177 (20.3)	15.69 (15.02–16.38)
G3A	177/519(34.1)	24.02 (20.62–27.83)	268/1,003 (26.7)	17.20 (15.21–19.39)
G3B	91/277 (32.9)	24.23 (19.51–29.75)	141/445 (31.7)	22.85 (19.24–26.95)
G4	23/52 (44.2)	67.50 (42.80–101.23)	24/71 (33.8)	39.34 (25.21–58.52)
Urinary tract infection				
Overall	691/4,904 (14.1)	9.70 (8.99–10.46)	1,382/10,177 (13.6)	9.27 (8.79–9.77)
G3A	84/519 (16.2)	9.18 (7.32–11.37)	200/1,003 (19.9)	11.36 (9.84–13.05)
G3B	62/277 (22.4)	13.69 (10.49–17.54)	101/445 (22.7)	13.98 (11.39–16.99)
G4	5/52 (9.6)	10.24 (3.32–23.89)	18/71 (25.4)	25.19 (14.93–39.81)
Genital infection				
Overall	75/4,904 (1.5)	0.85 (0.75–1.20)	565/10,177 (5.6)	3.54 (3.25–3.84)
G3A	8/519 (1.5)	0.79 (0.34–1.56)	54/1,003 (5.4)	2.75 (2.06–3.58)

G3B	2/277 (0.7)	0.39 (0.05–1.43)	15/445 (3.4)	1.78 (1.00–2.94)
G4	0/52 (0)	0	1/71 (1.4)	1.13 (0.03–6.28)
Volume depletion				
Overall	147/4,904 (3.0)	1.89 (1.60–2.23)	320/10,177 (3.1)	1.97 (1.76–2.20)
G3A	33/519 (6.4)	3.38 (2.32–4.74)	63/1,003 (6.2)	3.22 (2.48–4.12)
G3B	19/277 (6.9)	3.95 (2.38–6.17)	28/445 (6.3)	3.43 (2.28–4.95)
G4	6/52 (11.5)	12.04 (4.42–26.19)	7/71 (9.8)	8.22 (3.30–16.93)
Edema				
Overall	278/4,904 (5.7)	3.67 (3.25–4.12)	269/10,177 (2.6)	1.65 (1.46–1.86)
G3A	51/519 (9.8)	5.37 (4.00–7.06)	49/1003 (4.9)	2.48 (1.84–3.28)
G3B	38/277 (13.7)	8.12 (5.75–11.15)	36/445 (8.1)	4.42 (3.10–6.12)
G4	5/52 (9.6)	11.77 (3.82–27.47)	1/71 (1.4)	1.11 (0.03–6.18)
Bone fracture				
Overall	134/4,904 (2.7)	1.72 (1.44–2.04)	233/10,177 (2.3)	1.42 (1.25–1.62)
G3A	26/519 (5.0)	2.60 (1.79–3.81)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	12/277 (4.3)	2.40 (1.24–4.19)	20/445 (4.5)	2.40 (1.46–3.70)
G4	1/52 (1.9)	2.06 (0.05–11.49)	0/71 (0)	0
Falls				
Overall	87/4,904 (1.8)	1.11 (0.89–1.37)	197/10,177 (1.9)	1.20 (1.04–1.38)
G3A	17/519 (3.3)	1.70 (0.99–2.72)	30/1,003 (3.0)	1.50 (1.01–2.15)
G3B	10/277 (3.6)	2.01 (0.97–3.70)	11/445 (2.5)	1.30 (0.65–2.33)
G4	1/52 (1.9)	2.06 (0.05–11.49)	1/71 (1.4)	1.11 (0.03–6.18)
Hyperkalemia				
Overall	90/4,904 (1.8)	1.15 (0.92–1.41)	119/10,177 (1.2)	0.72 (0.60–0.86)
G3A	23/519 (4.4)	2.31 (1.47–3.47)	37/1,003 (3.7)	1.86 (1.31–2.56)
G3B	18/277 (7.6)	3.73 (2.21–5.89)	15/445 (3.4)	1.78 (1.00–2.93)

G4	3/52 (0)	6.16 (1.27–17.99)	1/71 (1.4)	1.11 (0.03–6.21)
Acute renal failure				
Overall	169/4,904 (3.4)	2.18 (1.86–2.53)	291/10,177 (1.2)	1.78 (1.58–2.00)
G3A	48/519 (9.2)	4.92 (3.63–6.53)	86/1,003 (8.6)	4.44 (3.55–5.48)
G3B	37/277 (13.3)	7.85 (5.53–10.83)	57/445 (12.8)	7.22 (5.47–9.35)
G4	6/52 (11.5)	13.87 (5.09–30.19)	9/71 (12.7)	10.85 (4.96–20.59)
Lower limb amputation				
Overall	46/4,904 (0.9)	0.52 (0.38–0.69)	95/10,177 (0.1)	0.52 (0.42–0.63)
G3A	11/519 (2.1)	0.92 (0.46–1.65)	17/1,003 (1.7)	0.74 (0.43–1.18)
G3B	7/277 (2.5)	1.22 (0.49–2.51)	10/445 (2.2)	0.95 (0.46–1.75)
G4	0/52 (0)	0	4/71 (5.6)	3.59 (0.98–9.20)

Table 2—Patients with at least one adverse event by CKD category at baseline

Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × *n*/T, where *n* was the number of participants with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (mL/min/1.73 m^2) calculated using the CKD-EPI equation. CKD categories by eGFR (mL/min/1.73 m^2): G3A, 45 to <60; G3B, 30 to <45; G4, 15 to <30. Frequencies *n*/*N* = patients with ≥1 event/all patients who received ≥1 dose of study drug.

*Data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial only. No amputations were reported for the four patients with missing baseline eGFR values.

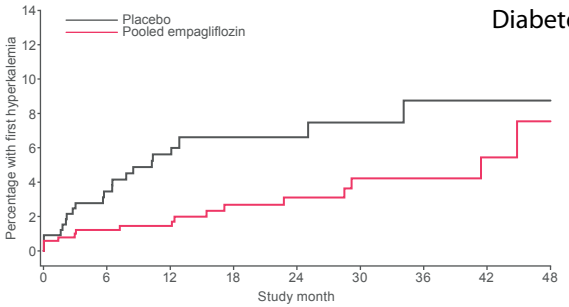
AE, adverse event; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; p-y, patient-years.

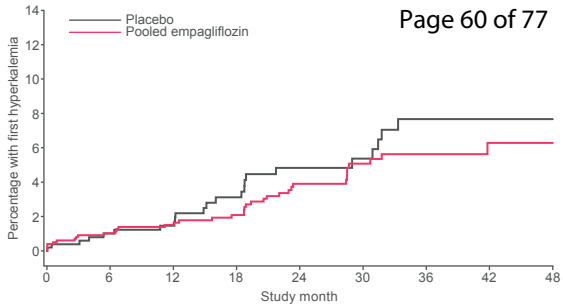
[Figure legend]

Figure 1—Kaplan-Meier estimates of time to first event of (*A*) hyperkalemia, (*B*) volume depletion, (*C*) edema, and (*D*) ARF in patients with eGFR <45 mL/min/1.73 m^2 (left-hand side) and 45 to <60 mL/min/1.73 m^2 (right-hand side).

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. ARF, acute renal failure; eGFR, estimated glomerular filtration rate.

a)

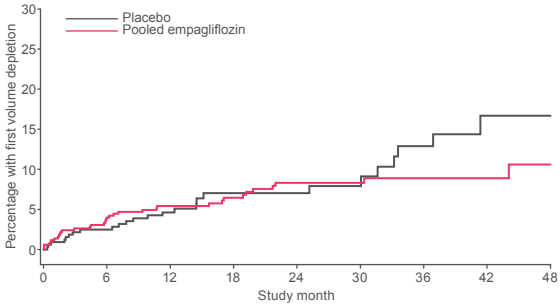


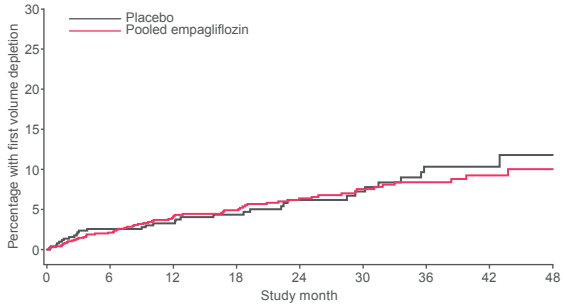


Patients at risk									
Placebo	329	280	251	135	110	79	64	28	9
Pooled empagliflozin	516	429	396	277	220	162	123	55	11

Patients at risk									
Placebo	519	453	415	299	235	172	134	69	15
Pooled empagliflozin	1003	83 8	790	644	504	350	258	133	51

b)

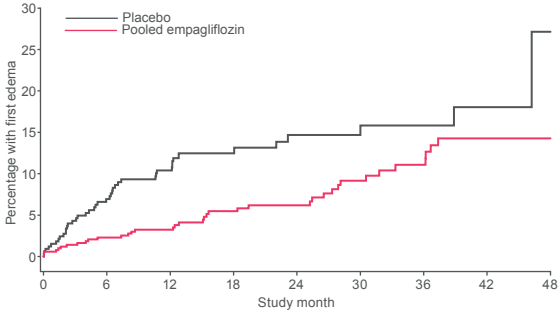


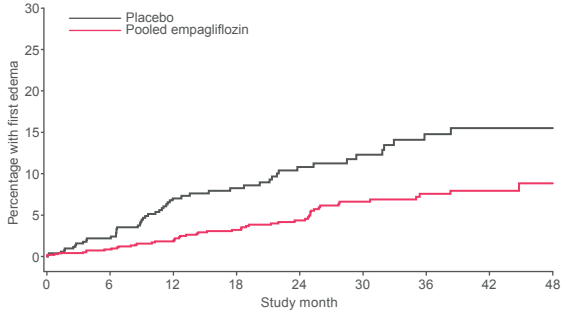


Patients at risk									
Placebo	329	285	256	137	109	77	61	23	7
Pooled empagliflozin	516	417	381	266	208	156	117	54	11

Patients at risk									
Placebo	519	444	406	294	229	168	133	70	16
Pooled empagliflozin	1003	828	770	627	494	343	251	130	50

c)

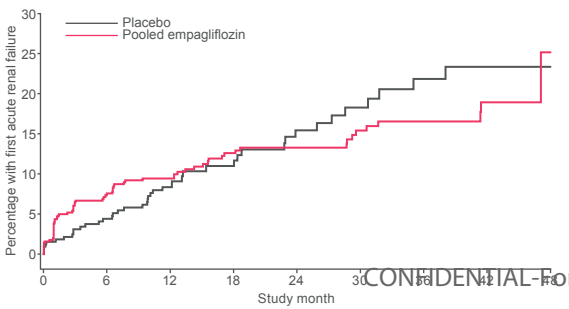


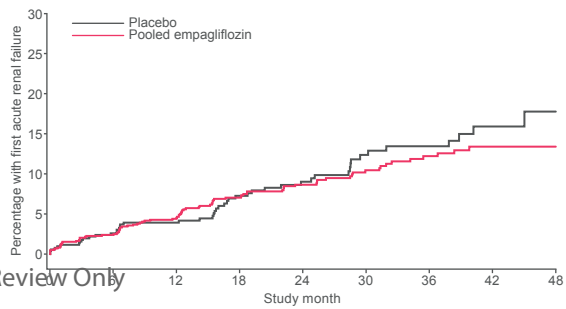


Patients at risk									
Placebo	329	275	246	130	103	75	58	23	8
Pooled empagliflozin	516	423	389	272	215	152	113	45	10

Patients at risk									
Placebo	519	445	390	281	218	158	126	63	16
Pooled empagliflozin	1003	840	788	636	500	346	251	130	48

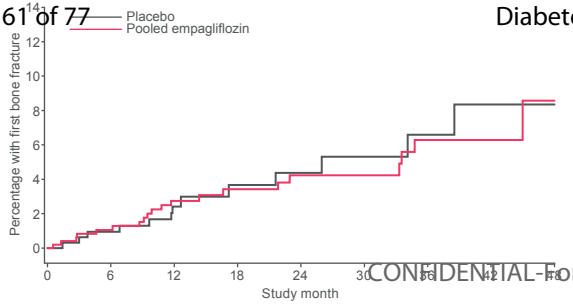
d)

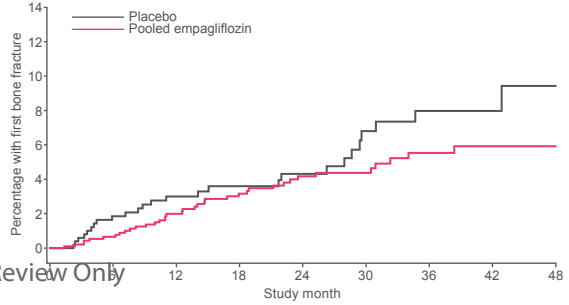




Patients at risk									
Placebo	329	280	249	132	104	74	55	23	8
Pooled empagliflozin	516	405	372	256	203	152	113	47	10

Patients at risk									
Placebo	519	447	407	293	226	163	134	66	17
Pooled empagliflozin	1003	832	774	619	486	335	248	134	50



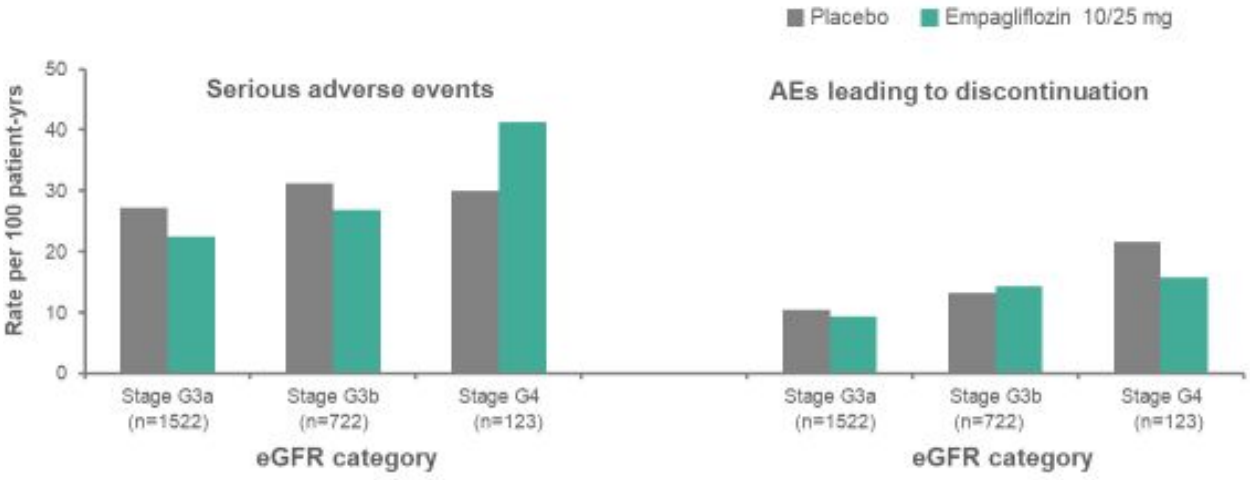


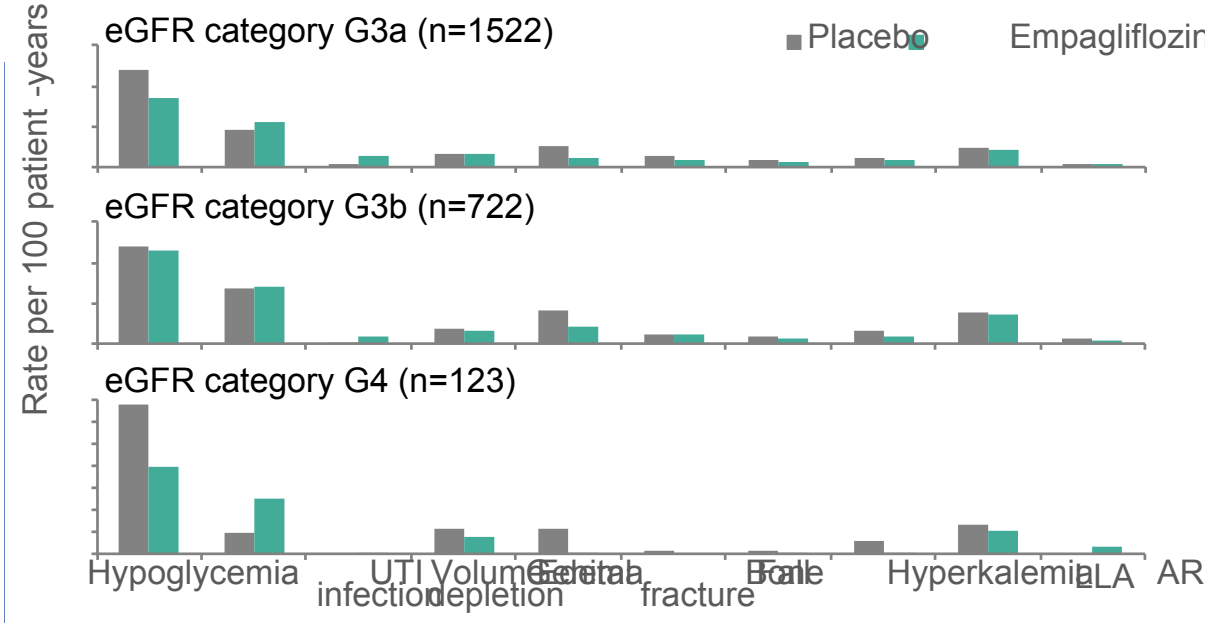
Patients at risk									
Placebo	329	287	258	142	115	82	67	28	8
Pooled empagliflozin	516	429	391	274	217	161	121	54	11

Patients at risk									
Placebo	519	448	408	299	243	172	137	71	17
Pooled empagliflozin	1003	841	787	636	502	354	257	136	49

Supplemental Material

Supplementary Figure 1—Rate of adverse events.





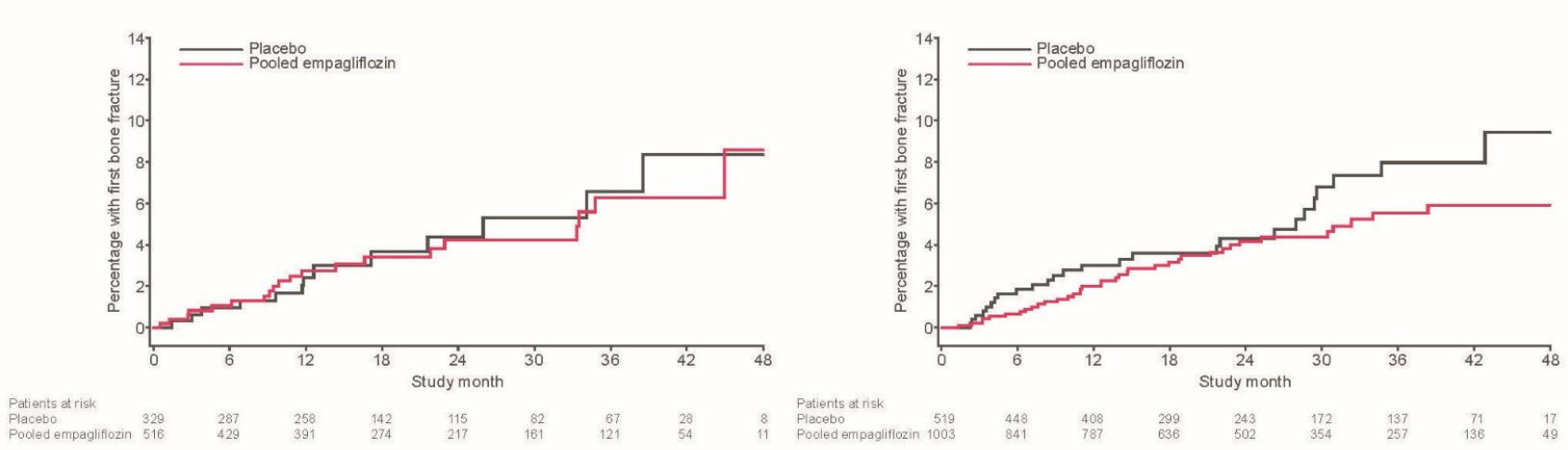
Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × *n*/T, where *n* was the number of subjects with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (mL/min/1.73m^2) calculated using the Chronic Kidney Disease Epidemiology

Collaboration (CKD-EPI) equation. eGFR categories (mL/min/1.73 m^2): G3A, 45 to <60; G3B, 30 to <45; G4, 15 to <30.

AE, adverse event; ARF, acute renal failure; LLA, lower limb amputation; UTI, urinary tract infection.

Supplementary Figure 2—Kaplan-Meier estimates of time to first event of bone fracture in patients with (*A*) eGFR <45 and (*B*) 45 to <60 mL/min/1.73 m^2.

A **B**



eGFR (mL/min/1.73 m^2) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. eGFR, estimated glomerular filtration rate.

Supplementary Table 1—Randomized, placebo-controlled trials included in the pooled analysis

Study	Reference	Population	Intervention	Comparator	Clinical phase	Duration	Primary endpoint	Number of patients (% of overall pool)		
								Placebo	Empagliflozin 10/25 mg	Total patients
1245.4	Heise et al. 2013 (31)	Patients with type 2 diabetes	EMPA 10, 25, or 100 mg qd	PBO	1	4 weeks	Safety	16 (0.3)	32 (0.3)	48 (0.3)
1245.9	Ferrannini et al. 2013 (32)	Patients with type 2 diabetes	EMPA 5, 10, or 25 mg qd Met	PBO	2b	12 weeks	Change in HbA_{1c}	82 (1.7)	163 (1.6)	245 (1.6)
1245.10	Rosenstock et al. 2013 (33)	Patients with type 2 diabetes not controlled on Met	Met plus EMPA 1, 5, 10, 25, or 50 mg qd	Met plus PBO Met plus sitagliptin 100 mg qd	2b	78 weeks	Change in HbA_{1c}	71 (1.4)	141 (1.4)	212 (1.4)
1245.15	Kanada et al. 2013 (34)	Japanese patients with type 2 diabetes	EMPA 1, 5, 10, or 25 mg qd	PBO	2	4 weeks	Change in UGE, FPG, and 8-point glucose profile	21 (0.4)	39 (0.4)	60 (0.4)
EMPA-REG PIO, EMPA-REG EXTEND PIO 1245.19 (plus extn)	Kovacs et al. 2014, 2015 (35,36)	Patients with type 2 diabetes	Pioglitazone with or without Met plus EMPA 10 or 25 mg qd PBO	Pioglitazone with or without Met plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA_{1c}	165 (3.4)	333 (3.3)	498 (3.3)
EMPA-REG MONO, EMPA-REG EXTEND MONO 1245.20 (plus extn)	Roden et al. 2013, 2015 (37,38)	Drug-naïve patients with type 2 diabetes	EMPA 10 or 25 mg qd	Sitagliptin 100 mg qd PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA_{1c}	229 (4.7)	447 (4.4)	676 (4.2)

EMPA-REG MET, EMPA-REG EXTEND MET 1245.23 (Met only) (plus extn)	Häring et al. 2014, Merker et al. 2015 (39,40)	Patients with type 2 diabetes not controlled on Met	Met plus EMPA 10 or 25 mg qd	Met plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA_{1c}	206 (4.2)	431 (4.2)	637 (4.2)
EMPA-REG METSU, EMPA-REG EXTEND METSU 1245.23 (Met+SU) (plus extn)	Häring et al. 2013 (41,42)	Patients with type 2 diabetes not controlled on Met plus SU	Met plus SU plus EMPA 10 or 25 mg qd	Met plus SU plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA_{1c}	225 (4.6)	441 (43)	666 (4.4)
EMPA-REG OUTCOME 1245.25	Zinman et al. 2015 (11)	Patients with type 2 diabetes at high cardiovascular risk	EMPA 10 or 25 mg qd	PBO	3	Event-driven	3P-MACE	2,333 (47.6)	4,687 (46.1)	7,020 (46.5)
1245.29	Ferdinand et al. 2019 (43)							77 (1.6)	80 (0.8)	157 (1.0)
EMPA-REG BASAL 1245.33	Rosenstock et al. 2015 (44)	Patients with type 2 diabetes not controlled on basal insulin	Basal insulin plus EMPA 10 or 25 mg qd	Basal insulin plus PBO	2b	78 weeks	Change in HbA_{1c}	170 (3.5)	324 (3.2)	494 (3.3)
1245.35	Nishimura et al. 2015 (45)	Japanese patients with type 2 diabetes (either drug-naïve or treated with 1 oral antidiabetic agent)	EMPA 10 or 25 mg qd	PBO	3	28 days	Change in $AUC_{1–4h}$ for PPG	21 (0.4)	39 (0.4)	60 (0.4)
EMPA-REG RENAL 1245.36	Barnett et al. 2014 (8)	Patients with type 2 diabetes and CKD category 2-4 not controlled on	Background antidiabetic agent plus	Background antidiabetic agent plus PBO	3	52 weeks	Change in HbA_{1c}	319 (6.5)	419 (4.1)	738 (4.9)

		existing antidiabetic medication	EMPA 10 or 25 mg qd							
1245.38	Kadowaki et al. 2015 (46)	Japanese patients with type 2 diabetes	EMPA 5, 10, 25, or 50 mg qd	PBO	2	52 weeks	Change in HbA_{1c}	109 (2.2)	218 (2.1)	327 (2.2)
EMPA-REG BP 1245.48	Tikkanen et al. 2015 (47)	Patients with type 2 diabetes and hypertension	EMPA 10 or 25 mg qd	PBO	3	12 weeks	Change in HbA_{1c}, change in SBP	272 (5.5)	552 (5.4)	824 (5.5)
EMPA-REG MDI 1245.49	Rosenstock et al. 2014 (48)	Obese patients with type 2 diabetes not controlled on MDI of insulin plus Met	MDI of insulin plus Met plus EMPA 10 or 25 mg qd	MDI of insulin plus Met plus PBO	3	52 weeks	Change in HbA_{1c}	188 (3.8)	375 (3.7)	563 (3.7)
1245.107	NCT02589639	Japanese patients with type 2 diabetes with insufficient glycemic control	EMPA 10 or 25 mg qd	PBO	4	52 weeks	Change in HbA_{1c}	90 (1.8)	176 (1.7)	266 (1.8)
1275.9	Søfteland et al. 2017 (49)	Patients with type 2 diabetes and insufficient glycemic control with linagliptin 5 mg qd on Met background therapy	EMPA 10 or 25 mg qd and linagliptin high dose or linagliptin low dose	Linagliptin 5 mg qd	3	24 weeks	Change in HbA_{1c}	110 (2.2)	222 (2.2)	332 (2.2)
1275.19	Kawamori et al. 2018 (50)	Japanese patients with type 2 diabetes	Linagliptin 5 mg + EMPA 10 mg or 25 mg bid	Linagliptin 5 mg qd	3	52 weeks	Change in HbA_{1c}	93 (1.9)	182 (1.8)	275 (1.8)

1276.10	NCT01649297	Patients with type 2 diabetes and insufficient glycemic control	Met + EMPA qd or bid	Met + PBO	3	24 weeks	Change in HbA_{1c}	107 (2.2)	876 (8.6)	983 (6.5)
Total								**4,904 (100.0)**	**15,081 (100.0)**	**15,081 (100.0)**

3P-MACE, 3-point major cardiovascular adverse events; $AUC_{1–4h}$ for PPG, area under the glucose concentration-time curve 3 h after breakfast; bid, twice daily; CKD, chronic kidney disease; EMPA, empagliflozin; extn, extension; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; MDI, multiple daily injections Met, metformin; PBO, placebo; PPG, post-prandial glucose; qd, once daily; SBP, systolic blood pressure; SU, sulfonylurea; UGE, urinary glucose excretion.

Supplementary Table 2—MedDRA preferred terms

ARF	Acute renal failure (narrow SMQ) -> see table below for preferred term listing

ARF	Acute kidney injury	10069339
	Acute phosphate nephropathy	10069688
	Anuria	10002847
	Azotemia	10003885
	Continuous hemodiafiltration	10066338
	Dialysis	10061105
	Fetal renal impairment	10078987
	Hemodialysis	10018875
	Hemofiltration	10053090
	Hyponatriuria	10077515
	Neonatal anuria	10049778
	Nephropathy toxic	10029155
	Oliguria	10030302
	Peritoneal dialysis	10034660
	Prerenal failure	10072370
	Renal failure	10038435
	Renal failure neonatal	10038447
	Renal impairment	10062237
	Renal impairment neonatal	10049776

Bone fracture	Acetabulum fracture	10000397
	Ankle fracture	10002544
	Atypical femur fracture	10070884
	Atypical fracture	10072395
	Avulsion fracture	10066184
	Bone fissure	10064210
	Bone fragmentation	10064211
	Cervical vertebral fracture	10049946
	Chance fracture	10073162
	Clavicle fracture	10009245
	Closed fracture manipulation	10009506
	Comminuted fracture	10052614
	Complicated fracture	10010149
	Compression fracture	10010214
	Craniofacial fracture	10077603
	Elevation skull fracture	10014487
	Epiphyseal fracture	10053962
	External fixation of fracture	10015741
	Facial bones fracture	10016042
	Femoral neck fracture	10016450
	Femur fracture	10016454
	Fibula fracture	10016667
	Flail chest	10016747
	Foot fracture	10016970
	Forearm fracture	10016997
	Fracture	10017076
	Fracture debridement	10057147
	Fracture displacement	10053206
	Fracture infection	10079813
	Fracture of clavicle due to birth trauma	10017107
	Fracture pain	10072132
	Fracture reduction	10057609
	Fracture treatment	10061959
	Fractured coccyx	10049164
	Fractured ischium	10017290
	Fractured maxilla elevation	10017296
	Fractured sacrum	10017308
	Fractured skull depressed	10017310
	Fractured zygomatic arch elevation	10059362
	Greenstick fracture	10018720
	Hand fracture	10019114
	Hip fracture	10020100
	Humerus fracture	10020462
	Ilium fracture	10021343

	Impacted fracture	10066386
	Internal fixation of fracture	10022576
	Intramedullary rod insertion	10069066
	Jaw fracture	10023149
	Limb fracture	10074551
	Lisfranc fracture	10078749
	Lower limb fracture	10061599
	Lumbar vertebral fracture	10049947
	Metaphyseal corner fracture	10079667
	Multiple fractures	10028200
	Open fracture	10030527
	Open reduction of fracture	10030682
	Osteochondral fracture	10073853
	Osteophyte fracture	10080550
	Osteoporotic fracture	10031290
	Patella fracture	10034122
	Pathological fracture	10034156
	Pelvic fracture	10061161
	Periprosthetic fracture	10069135
	Pubis fracture	10070286
	Radius fracture	10037802
	Rib fracture	10039117
	Sacroiliac fracture	10074362
	Scapula fracture	10039579
	Skull fracture	10061365
	Skull fractured base	10040960
	Spinal compression fracture	10041541
	Spinal fracture	10041569
	Spinal fusion fracture	10074807
	Sternal fracture	10042015
	Stress fracture	10042212
	Subchondral insufficiency fracture	10079864
	Surgical fixation of rib fracture	10077270
	Thoracic vertebral fracture	10049948
	Tibia fracture	10043827
	Torus fracture	10066094
	Traumatic fracture	10049514
	Ulna fracture	10045375
	Upper limb fracture	10061394
	Wrist fracture	10048049
	Skeletal traction	10040782

Edema	Edema defined by preferred terms Fluid overload, Fluid retention, Generalized edema, Edema, Edema peripheral, and Peripheral swelling

Hyperkalemia	Hyperkalemia defined by preferred terms Hyperkalemia and Blood potassium increased

Volume decreased	Blood pressure ambulatory decreased	10005731
	Blood pressure decreased	10005734
	Blood pressure diastolic decreased	10005737
	Blood pressure orthostatic decreased	10053356
	Blood pressure systolic decreased	10005758
	Circulatory collapse	10009192
	Dehydration	10012174
	Diastolic hypotension	10066077
	Hypotension	10021097
	Hypovolemia	10021137
	Hypovolemic shock	10021138
	Mean arterial pressure decreased	10026983
	Orthostatic hypotension	10031127
	Presyncope	10036653
	Syncope	10042772

ARF, acute renal failure; MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table 3—Multivariable Cox regression for time to first key safety endpoint events by baseline eGFR group

	eGFR <45 mL/min/1.73 m^2 *n* = 349, PBO; *n* = 554, EMPA 10/25 mg	eGFR 45 to <60 mL/min/1.73 m^2 *n* = 618, PBO; *n* = 1207, EMPA 10/25 mg
Hyperkalemia	0.48 (0.26–0.91)	0.59 (0.37–0.96)
Volume depletion	0.83 (0.50–1.39)	0.91 (0.61–1.35)
ARF	0.75 (0.35–1.64)	0.61 (0.31–1.20)
Edema	0.44 (0.28–0.69)	0.47 (0.33–0.68)

All values are hazard ratio (95% CI). Cox regression models include age, baseline BMI, baseline HbA_{1c}, sex, baseline eGFR, and treatment-by-baseline eGFR interaction term.

AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; HbA_{1c}, glycated hemoglobin; PBO, placebo.

Supplementary Table 4—Patients in the pooled by contributing study and eGFR (CKD−EPI):

A) eGFR 45 to <60 ml/min/1.73m^2 (Cat 3A)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		2 (0.3)	0	3 (0.5)	3 (0.2)	5 (0.3)
1245.10		4 (0.6)	1 (0.2)	5 (0.8)	6 (0.5)	10 (0.5)
1245.15		0	0	0	0	0
1245.19		17 (2.8)	18 (3.2)	14 (2.2)	32 (2.7)	49 (2.7)
1245.20		12 (1.9)	12 (2.1)	10 (1.6)	22 (1.8)	34 (1.9)
1245.23	(Met only)	10 (1.6)	8 (1.4)	11 (1.7)	19 (1.6)	29 (1.6)
1245.23	(Met+SU)	20 (3.2)	13 (2.3)	15 (2.4)	28 (2.3)	48 (2.6)
1245.25		418 (67.6)	420 (74.2)	411 (64.5)	831 (68.8)	1249 (68.4)
1245.29		1 (0.2)	0	0	1 (0.1)	2 (0.1)
1245.33		16 (2.6)	19 (3.4)	24 (3.8)	43 (3.6)	59 (3.2)
1245.35		0	1 (0.2)	0	1 (0.1)	1 (0.1)
1245.36		78 (12.6)	8 (1.4)	87 (13.7)	95 (7.9)	173 (9.5)
1245.38		2 (0.3)	4 (0.7)	1 (0.2)	5 (0.4)	7 (0.4)
1245.48		11 (1.8)	13 (2.3)	20 (3.1)	33 (2.7)	44 (2.4)
1245.49		8 (1.3)	13 (2.3)	7 (1.1)	20 (1.7)	28 (1.5)
1245.107		10 (1.6)	5 (0.9)	9 (1.4)	14 (1.2)	24 (1.3)
1275.9		2 (0.3)	2 (0.4)	1 (0.2)	3 (0.2)	5 (0.3)
1275.19		4 (0.6)	0	0	3 (0.2)	7 (0.4)
1276.10		3 (0.5)	29 (5.1)	19 (3.0)	48 (4.0)	51 (2.8)
Total		**618 (100.0)**	**566 (100.0)**	**637 (100.0)**	**1207 (100.0)**	**1825 (100.0)**

B) eGFR 30 to <45 ml/min/1.73m^2 (Cat 3B)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		0	0	0	0	0
1245.10		0	0	1 (0.3)	1 (0.2)	1 (0.1)
1245.15		0	0	0	0	0
1245.19		1 (0.3)	2 (1.0)	2 (0.7)	4 (0.8)	5 (0.6)
1245.20		1 (0.3)	1 (0.5)	0	1 (0.2)	2 (0.3)
1245.23	(Met only)	2 (0.7)	1 (0.5)	3 (1.0)	4 (0.8)	6 (0.8)
1245.23	(Met+SU)	2 (0.7)	6 (3.1)	2 (0.7)	8 (1.6)	10 (1.3)
1245.25		183 (61.8)	178 (91.8)	182 (62.3)	360 (73.9)	543 (69.3)

1245.29	2 (0.7)	0	0	1 (0.2)	3 (0.4)
1245.33	8 (2.7)	4 (2.1)	6 (2.1)	10 (2.1)	18 (2.3)
1245.35	0	0	0	0	0
1245.36	96 (32.4)	0	90 (30.8)	90 (18.5)	186 (23.8)
1245.38	0	0	0	0	0
1245.48	0	0	1 (0.3)	1 (0.2)	1 (0.1)
1245.49	0	0	0	0	0
1245.107	1 (0.3)	0	1 (0.3)	1 (0.2)	2 (0.3)
1275.9	0	0	0	0	0
1275.19	0	0	0	0	0
1276.10	0	2 (1.0)	4 (1.4)	6 (1.2)	6 (0.8)
Total	**296 (100.0)**	**194 (100.0)**	**292 (100.0)**	**487 (100.0)**	**783 (100.0)**

C) eGFR <30 ml/min/1.73m^2 (Cat 4)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		0	0	0	0	0
1245.10		0	0	0	0	0
1245.15		0	0	0	0	0
1245.19		0	0	0	0	0
1245.20		0	0	0	0	0
1245.23	(Met only)	0	0	0	0	0
1245.23	(Met+SU)	0	0	0	0	0
1245.25		6 (11.3)	7 (77.8)	14 (24.1)	21 (31.3)	27 (22.5)
1245.29		0	0	0	0	0
1245.33		1 (1.9)	2 (22.2)	1 (1.7)	3 (4.5)	4 (3.3)
1245.35		0	0	0	0	0
1245.36		46 (86.8)	0	42 (72.4)	42 (62.7)	88 (73.3)
1245.38		0	0	0	0	0
1245.48		0	0	1 (1.7)	1 (1.5)	1 (0.8)
1245.49		0	0	0	0	0
1245.107		0	0	0	0	0
1275.9		0	0	0	0	0
1275.19		0	0	0	0	0
1276.10		0	0	0	0	0
Total		**53 (100.0)**	**9 (100.0)**	**58 (100.0)**	**67 (100.0)**	**120 (100.0)**

eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; Met, metformin; SU, sulfonylurea.

Supplementary Table 5a—Cox regression for time to first outcome by eGFR category: EMPA-REG OUTCOME (study 1245.25) vs. Other and eGFR*treatment interaction term

	eGFR Cat 3A HR (95%CI), p-value	**eGFR Cat3B + Cat4** HR (95%CI), p-value
Hyperkalemia	0.59 (0.37, 0.95), p=0.0306	0.48 (0.25, 0.90), p=0.0217
Based on a Cox regression model with terms for age (p=0.1771), baseline BMI (p=0.1164), baseline HbA1c (p=0.4184), sex (p=0.6583), 1245.25 vs other SAF−43 trial (p=0.1404) and treatment by baseline eGFR interaction (p=0.4341), treatment (p=0.0007), baseline eGFR (p<0.0001).		
Volume depletion	0.90 (0.61, 1.34), p=0.6166	0.79 (0.48, 1.32), p=0.3742
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p=0.0213), baseline HbA1c (p=0.1080), sex (p=0.7494),1245.25 vs other SAF−43 trial (p<0.0001), treatment (p=0.7048), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.2183).		
AKI	0.61 (0.31, 1.19), p=0.1482	0.74, (0.34, 1.61), p=0.4435
Based on a Cox regression model with terms for age (p=0.0731), baseline BMI (p=0.0203), baseline HbA1c (p=0.3657), sex (p=0.5883), 1245.25 vs other SAF−43 trial (p=0.2354), treatment (p=0.0320), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.9086).		
Edema	0.47 (0.33, 0.68), p<0.0001	0.43 (0.27, 0.66), p<0.0001
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p<0.0001), baseline HbA1c (p=0.0841), sex (p=0.1373), 1245.25 vs other SAF−43 trial (p=0.0052), treatment (p<0.0001), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.9387).		

Note: 4 patients were excluded from all outcomes as the subgroup variable was missing.

Supplementary Table 5b—Frailty model for time to first outcome by eGFR category including study as random effect and eGFR*treatment interaction term

	eGFR Cat 3A HR (95%CI), P-value	**eGFR Cat3B + Cat4** HR (95%CI), P-value
Hyperkalemia	0.59 (0.37, 0.96), P=0.0318	0.48 (0.26, 0.91), P=0.0244
Comparison with placebo based on a Cox regression model with terms for age (p=0.1369), baseline BMI (p=0.1222), baseline HbA1c (p=0.4051), sex (p=0.7238), treatment (p=0.0008), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.4585) and trial number (random effect) (p=0.2205).		
Volume depletion	0.91 (0.61, 1.35), p=0.6268	0.82 (0.49, 1.36), p=0.4362
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p=0.0301), baseline HbA1c (p=0.0812), sex (p=0.7463), treatment (p=0.7815), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.2391) and trial number (random effect) (p<0.0001).		
AKI	0.61 (0.31, 1.20), p=0.1496	0.75 (0.35, 1.64), p=0.4747
Based on a Cox regression model with terms for age (p=0.0557), baseline BMI (p=0.0191), baseline HbA1c (p=0.3751), sex (p=0.6495), treatment (p=0.0346), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.8889) and trial number (random effect) (p=0.2325).		
Edema	0.47 (0.33, 0.68), p<0.0001	0.43, (0.28, 0.67), p=0.0002
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p<0.0001), baseline HbA1c (p=0.0734), sex (p=0.1459), treatment (p<0.0001), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.9540) and trial number (random effect) (p=0.0127).		

Note: 4 patients were excluded from all outcomes as the subgroup variable was missing.