Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

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OBJECTIVE

To assess the 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 1 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, 1,522, 722, and 123 were classified as having G3A, G3B, and G4 CKD, respectively, at baseline. Demographic and clinical characteristics were similar between treatment groups across CKD categories. 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 and G4 and the G3A group. Notably lower risks were observed in both groups for hyperkalemia (hazard ratio 0.59 [95% CI 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 the development of hyperkalemia and edema.

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

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filtration rate, develops in ~40% of patients with type 2 diabetes (2,3). During the course of CKD in diabetes, the annual decline in estimated glomerular filtration rate (eGFR) varies greatly depending on the severity of CKD and the presence of 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 U.S. Food and Drug Administration prescribing information allows for empagliflozin to be used in patients with an 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 an 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 1 extension study that included participants from 3 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 uptitration from the 10 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 the total patient-years at risk for 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 BMI, 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 through 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 or 25 mg; 848 who received placebo). A total of 1,522, 722, and 123 patients 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 for the placebo and empagliflozin groups, respectively, was 1,014 and 2,021 patient-years in CKD category

G3A, 503 and 850 patient-years in CKD category G3B, and 50 and 89 patient-years in CKD category G4. 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. Demographic 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).

AEs

Rates of SAEs and AEs leading to discontinuation were similar between the empagliflozin and placebo treatment groups across the overall cohort and CKD subgroups (Table 2 and Supplementary Fig. 1). SAE incidence rates were numerically higher in the G4 category for empagliflozin versus placebo (41.31 vs. 29.93 per 100 patient-years). However, numbers of patients in this group were low (51 and 71 patients, respectively), with wide CIs that should therefore be interpreted with caution.

Events of special interest (including lower limb amputations and ARF) were similar between empagliflozin and placebo across CKD subgroups and overall (Table 2 and Supplementary Fig. 1). An exception was the frequency of genital infections, which 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. In contrast, most other AEs were more frequent among those with worsening CKD categories. Unadjusted time to first occurrence of ARF, volume depletion, and bone fracture revealed no significant differences between treatment groups, while edema was less common in patients receiving empagliflozin versus 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

Table 1—Demographic and baseline characteristics of the pooled analysis population with eGFR <60 mL/min/1.73 m^2 (*N* = 2,367)

	CKD category and study treatment					
	G3A		G3B		G4	
Characteristic	Placebo	EMPA 10/25 mg	Placebo	EMPA 10/25 mg	Placebo	EMPA 10/25 mg
Patients, *n*	519	1,003	277	445	52	71
Male sex, *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 or African American	29 (5.6)	52 (5.2)	8 (2.9)	24 (5.4)	0	1 (1.4)
Ethnicity, *n* (%)						
Not Hispanic or Latino	450 (86.7)	864 (86.1)	245 (88.4)	384 (86.3)	50 (96.2)	65 (91.5)
Hispanic or Latino	68 (13.1)	138 (13.8)	33 (11.6)	61 (13.7)	2 (3.8)	6 (8.5)
HbA_{1c}, mean ± SD						
%	8.0 ± 0.8	8.01 ± 0.8	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	7.95 ± 0.91
mmol/mol	64 ± 9	64 ± 9	65 ± 10	65 ± 10	65 ± 10	63 ± 10
BMI (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)

CKD categories by eGFR: G3A, 45 to <60 mL/min/1.73 m^2; G3B, 30 to <45 mL/min/1.73 m^2; G4, 15 to <30 mL/min/1.73 m^2. ARB, angiotensin receptor blocker; EMPA 10/25, empagliflozin 10 or 25 mg. *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/diastolic blood pressure readings were missing for one patient in the empagliflozin 10 mg group. ‡A history of heart failure at baseline was identified by narrow standardized MedDRA query 20000004.

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

	Placebo		EMPA 10/25 mg	
Category	*n*/*N* (%)	Rate, 100 patient-years (95% CI)	*n*/*N* (%)	Rate, 100 patient-years (95% CI)
SAEs				
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 (6)	6.16 (1.27–17.99)	1/71 (1.4)	1.11 (0.03–6.21)
ARF				
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)

Continued on p. 1449

Table 2—Continued

Category	Placebo		EMPA 10/25 mg	
	n/*N* (%)	Rate, 100 patient-years (95% CI)	*n*/*N* (%)	Rate, 100 patient-years (95% CI)
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)

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 the total patient-years at risk for 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 plus 7 days (for those without an event). The eGFR was calculated using the CKD-EPI equation. CKD categories by eGFR: G3A, 45 to <60 mL/min/1.73 m^2; G3B, 30 to <45 mL/min/1.73 m^2; G4, 15 to <30 mL/min/1.73 m^2. Frequencies *n*/*N* = patients with one or more events of all patients who received one or more doses of study drug. EMPA 10/25, empagliflozin 10 or 25 mg. *Data from the EMPA-REG OUTCOME trial only. No amputations were reported for the four patients with missing baseline eGFR values.

persisted with adjustment 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 were observed with empagliflozin for hyperkalemia (hazard ratio [HR] 0.59 [95% CI 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 showed nominal differences with regard to the HRs and 95% CIs for the risks of volume depletion, ARF, hyperkalemia, and edema (Supplementary Tables 4 and 5). Even though the EMPA-REG OUTCOME trial versus other trials showed a statistically significant different trial effect for volume depletion ($P < 0.001$) and edema ($P = 0.005$), which can give a hint that there might be trial-specific heterogeneity, the HRs were essentially identical compared with the original Cox regression model or with the additional trial frailty term model including study as a random effect (for eGFR 45 < 60 mL/min/1.73 m^2 for volume depletion: HR 0.90 [original model] vs. 0.90 [EMPA-REG OUTCOME trial vs. other] and 0.91 [frailty term model with trial as random effect]; for edema: 0.47 vs. 0.47 and 0.47, respectively).

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 adverse effect of the SGLT2 inhibitor class (16–18), which occurred more frequently in the empagliflozin group versus the placebo group but with lower incidence rates in advanced CKD categories. This could be due to, at least in part, lesser urinary glucose excretion at lower levels of eGFR (19). Indeed, poorly controlled diabetes, typically accompanied by higher urinary glucose excretion, independently increases the risk of genital infections in patients with type 2 diabetes (20). Current prescribing information for empagliflozin notes that a higher incidence of AEs related to reduced renal function may be seen in patients with CKD (9). However, while ARF and other AEs were more common with decreasing kidney function in both treatment groups, observed rates were similar between empagliflozin and placebo in all CKD categories. 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, one-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 glucagon-like peptide 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 recommended an SGLT2 inhibitor as first-line treatment in patients with CKD and type 2 diabetes who have an 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 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/1.73 m^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

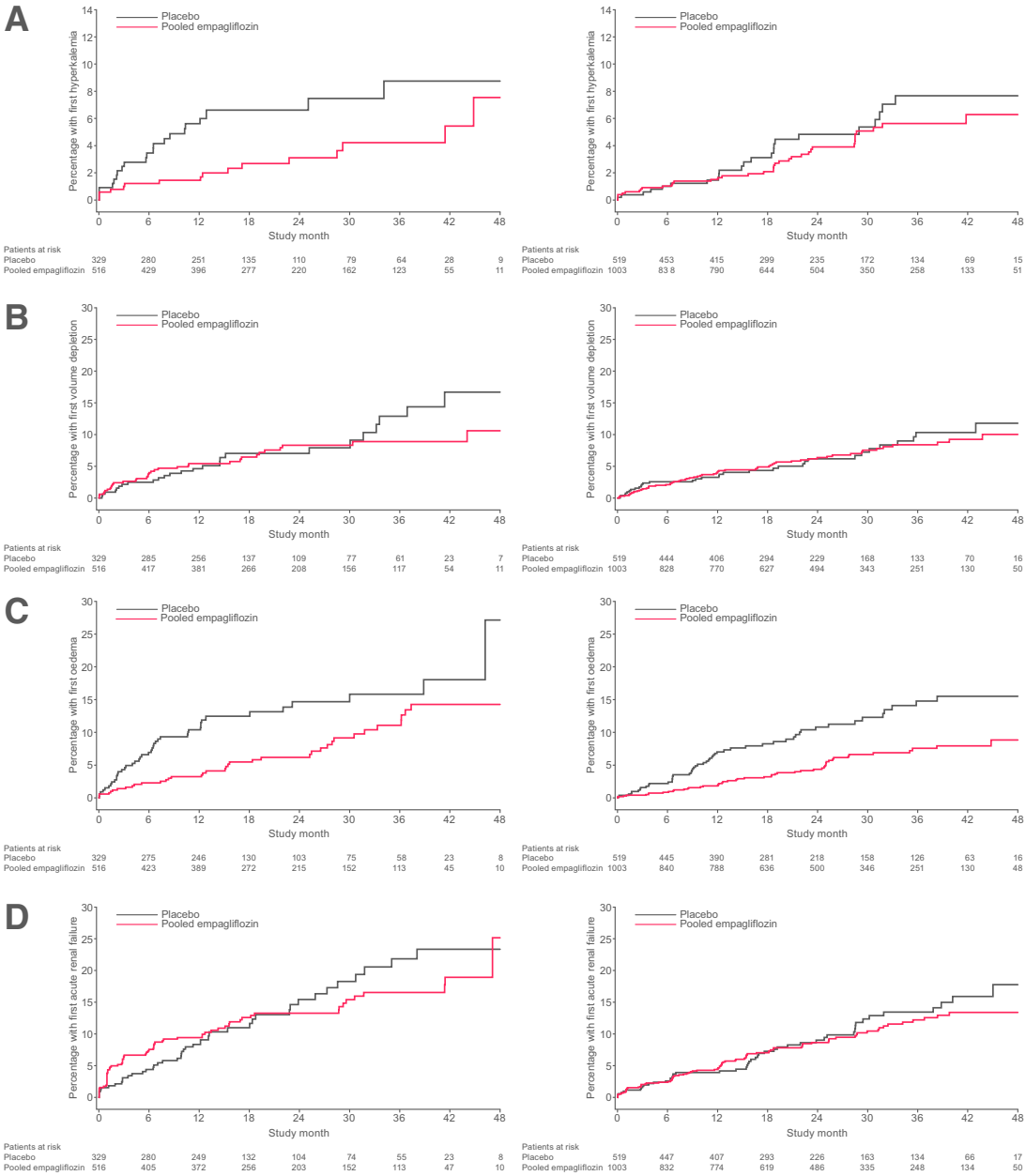

Figure 1—Kaplan-Meier estimates of time to first event of hyperkalemia (*A*), volume depletion (*B*), edema (*C*), and ARF (*D*) in patients with eGFR <45 mL/min/1.73 m^2 (left) and 45 to <60 mL/min/1.73 m^2 (right). eGFR was calculated using the CKD-EPI equation.

patients with heart failure and eGFR level as low as 20 mL/min/1.73 m^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 lower limb amputations has been confirmed (26,27). However, the CANVAS program reported a twofold 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 because 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 of only patients randomly assigned to double-blind treatment. The data set 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 arose from the varying durations, designs, and populations of the included studies. However, this limitation applies to all pooled analyses, including meta-analyses. In turn, it is generally accepted that the increased number of trials/individuals in pooled analyses outweigh the limitations mentioned above. 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 (NCT02182830: 157 participants) or uptitrated from 10 to 25 mg in patients with insufficient glycemic control only (NCT02453555: 275 participants). Data from these participants are included in the EMPA-REG OUTCOME 10 and 25 mg results. Renal impairment as an exclusion criterion at baseline in both these trials was defined as eGFR <45 mL/min/1.73 m^2 compared with <30 mL/min/1.73 m^2 in EMPA-REG OUTCOME. Findings regarding patients with CKD category G4 should be interpreted with caution because of 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 SGLT2 inhibitor trials investigating treatment effects in patients with CKD may provide further data to confirm these observations, particularly in those with CKD category G4 where data are currently limited. 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 >6,600 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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