Pooled Safety and Tolerability Analysis of Empagliflozin in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The aim of this analysis was to characterize the safety and tolerability of empagliflozin in patients with type 2 diabetes mellitus (T2DM) who were randomized to empagliflozin (10/25 mg) or placebo in clinical trials.
Methods: Pooled data from 20 trials were analyzed for patients with T2DM treated with empagliflozin 10 mg ($n = 4858$), empagliflozin 25 mg ($n = 5057$), or placebo ($n = 4904$). The dataset comprised 15 randomized phase I–III trials, an extension trial and dose escalation studies. Adverse events (AEs) were assessed descriptively in participants who took ≥ 1 dose of study drug. AE incidence rates per 100 patient-years were calculated to adjust for differences in drug exposure between trials.

Results: Total exposure was 16,480 and 7857 patient-years in the pooled empagliflozin 10/25 mg and placebo groups, respectively. The incidence of any AEs, AEs leading to treatment discontinuation, severe AEs, and serious AEs was similar across groups. The frequency of serious AEs requiring hospitalization was 18.6% for the empagliflozin 10/25 mg group and 21.3% for the placebo group. The empagliflozin 10/25 mg group was not associated with a higher rate of confirmed hypoglycemia versus placebo, except in patients co-administered insulin and/or a sulfonylurea (31.5% vs. 30.2%, respectively). The incidence of events consistent with urinary tract infections (UTI) was also similar for the empagliflozin 10/25 mg group versus placebo (9.27 vs. 9.70/100 patient-years, respectively). History of UTI was identified as a risk factor for UTI during treatment. Events consistent with genital infections occurred more frequently with empagliflozin 10/25 mg than placebo (3.54 vs. 0.95/100 patient-years, respectively). The frequency of AEs consistent with volume depletion was similar across groups, but higher with empagliflozin 10/25 mg than placebo in patients aged 75 to < 85 years and those on loop diuretics at baseline.
Conclusion: This comprehensive analysis confirms that both empagliflozin 10 mg and 25 mg are well tolerated in patients with T2DM, reinforcing the established clinical safety profile of empagliflozin.

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PLAIN LANGUAGE SUMMARY

Empagliflozin is approved to treat adults with type 2 diabetes mellitus (T2DM) insufficiently controlled by diet and exercise. It lowers blood glucose levels by inhibiting sodium-glucose co-transporter-2 (SGLT2), a protein involved in glucose reabsorption by the kidneys. By blocking SGLT2, glucose is removed in urine instead of being reabsorbed into the bloodstream. Numerous clinical studies have shown the effectiveness and safety of empagliflozin, but recent reports of two types of serious side effects [fractures and lower limb amputations (LLAs)] associated with another drug in the class, canagliflozin, has triggered a review of the risk associated with taking SGLT2 inhibitors. To examine the safety and tolerability of empagliflozin we pooled data from 20 clinical trials involving over 15,000 patients with T2DM who received either empagliflozin or placebo (control). We found that the risk of side effects was similar whether patients received empagliflozin or placebo. This included side effects that led to treatment being stopped as well as severe and serious side effects, including fractures and LLAs. Empagliflozin was not associated with a higher rate of hypoglycemia (low blood sugar) versus placebo, except in patients also treated with insulin and/or a sulfonylurea (31.5% vs. 30.2%, respectively). The risk of urinary tract infections was also similar for empagliflozin versus placebo (9.27 vs. 9.70/100 patient-years, respectively). However, genital infections, as anticipated, occurred more frequently in patients treated with empagliflozin than placebo (3.54 vs. 0.95/100 patient-years, respectively). Overall, this analysis confirms the results of previous studies showing that empagliflozin is well tolerated in patients with T2DM.

Key Summary Points

Why carry out this study?

Empagliflozin is a potent sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated for the treatment of type 2 diabetes mellitus (T2DM), including reduction of cardiovascular (CV) mortality in patients with T2DM and CV disease.

The clinical efficacy and safety profile of empagliflozin in T2DM has been well documented; however, new safety signals of increased lower limb amputations and fractures reported for another SGLT2 inhibitor have prompted a review of the risks associated with this drug class.

This study examined the safety and tolerability of empagliflozin in patients with T2DM using data pooled from 20 placebo-controlled clinical trials based on over 16,480 patient-years' exposure to empagliflozin.

What was learned from the study?

This updated pooled analysis confirmed that both empagliflozin 10 mg and 25 mg are well tolerated in patients with T2DM.

These results reinforce the findings of a favorable benefit–risk profile for empagliflozin from previous clinical trials in patients with T2DM, including trials establishing the effects of empagliflozin on CV and all-cause mortality.

INTRODUCTION

Empagliflozin, a potent and selective sodium-glucose co-transporter-2 (SGLT2) inhibitor, is indicated for the treatment of type 2 diabetes

mellitus (T2DM) including reduction of cardio-vascular (CV) mortality in patients with T2DM and CV disease. By blocking sodium-glucose co-transporters on proximal tubules, empagliflozin induces urinary glucose and sodium excretion which contribute to osmotic diuresis and reductions in plasma volume load [1–3]. The effects of SGLT2 inhibition on salt, water, and energy metabolism are thought to underlie the CV, renal, and metabolic benefits demonstrated by this drug class [4, 5]. Importantly, as this mechanism of action is independent of insulin modulation by β-cells, SGLT2 inhibitors are associated with a low risk of hypoglycemia [6].

The clinical efficacy and safety profile of empagliflozin in T2DM has been well docu-mented. Treatment with empagliflozin at daily doses of 10 or 25 mg, either as monotherapy or add-on therapy, has been demonstrated to improve glycemic control and to result in reductions in body weight and blood pressure, and was well tolerated in placebo-controlled phase III trials in patients with T2DM [7–14]. Moreover, in the EMPA-REG OUTCOME® trial, empagliflozin, when given in addition to stan-dard of care and compared with placebo, sig-nificantly reduced the risk of CV death by 38%, hospitalization for heart failure by 35%, improved clinically relevant kidney outcomes, and slowed the progression of kidney function decline in patients with T2DM and established CV disease [15, 16]. In the CANagliflozin car-dioVascular Assessment Study (CANVAS), the SGLT2 inhibitor canagliflozin has also been shown to lower the risk of CV events in patients with T2DM and elevated risk of CV disease versus placebo [17]. However, a new and important safety signal was reported in the trial: there was a twofold increased risk of lower limb amputations (LLAs; primarily of the toe or metatarsal) in patients in the canagliflozin-treated group, versus placebo {hazard ratio (HR) 1.97 [95% confidence interval (CI) 1.41, 2.75]} [17]. The CANVAS program also reported an increased risk of all fractures with canagliflozin versus placebo [HR 1.26 (95% CI 1.04, 1.52)] [17]. Such new findings have prompted a review of the risks of LLAs and fractures associated with other SGLT2 inhibitors, including empagliflozin and dapagliflozin. For example, in the

Dapagliflozin Effect on CardiovascuLAR Events (DECLARE–TIMI 58) and Dapagliflozin And Prevention of Adverse–outcomes in Heart Fail-ure (DAPA-HF) trials, dapagliflozin showed no increased risk of either LLAs or fractures versus placebo [18, 19].

A comprehensive analysis of pooled safety profile data for empagliflozin, published in 2016 and derived from clinical trials of more than 9000 patient-years' exposure to the drug, demonstrated that empagliflozin treatment was well tolerated and not associated with an increased risk of hypoglycemia compared with placebo, except in patients on background treatment with a sulfonylurea (SU) and/or insulin [20]. Furthermore, genital infection was reported to occur in a higher percentage of patients treated with empagliflozin versus pla-cebo [20], which was consistent with findings from previous trials. An update of this pooled analysis, published in 2017, involved in excess of 15,000 patient-years' exposure, and contin-ued to support the favorable benefit–risk profile of empagliflozin in patients with T2DM [21]. However, a weakness of this larger analysis was that one of its component trials (the EMPA-REG OUTCOME® trial) contributed to over 55% (n = 7020) of the empagliflozin- or placebo-treated patients to the overall analysis popula-tion (n = 12,620) [21].

We report here the findings from an addi-tional update on the pooled safety analysis of empagliflozin. This new analysis aims to further describe the safety and tolerability of empagli-flozin based on 16,480 patient-years' exposure to empagliflozin 10 mg or 25 mg in random-ized, controlled phase I–III trials.

METHODS

Patients

In this updated analysis, data were pooled from 20 trials (Table 1). This included the earlier dataset from 14 trials of 8 days' to 78 weeks' duration [7–14, 22–27], the 52-week extension trial to the phase III trials of empagliflozin as monotherapy, or as add-on to metformin, metformin plus an SU, and pioglitazone with or

Table 1 Overview of the clinical trials included in the pooled safety analysis

ClinicalTrials.gov identifier (BI study number)	Short title	Treatment duration	Dose escalation[a]
NCT00558571 (1245.4)	4 weeks' treatment in patients with T2DM	28 days	No
NCT00789035 (1245.9)	Dose finder versus placebo as monotherapy	12 weeks	No
NCT00749190 (1245.10)	Dose finder versus placebo as add-on therapy	12 weeks	No
NCT00885118 (1245.15)	Treatment of patients with T2DM in Japan	4 weeks	No
NCT01210001 (1245.19)	Efficacy on background TZD ± metformin	24 weeks	No
NCT01177813 (1245.20)	Efficacy in drug-naïve patients	24 weeks	No
NCT01159600 (metformin) (1245.23)	Efficacy on background metformin	24 weeks	No
NCT01159600 (metformin + SU) (1245.23)	Efficacy on background metformin ± SU	24 weeks	No
NCT01131676 (1245.25)	Safety cardiovascular outcome trial	Mean: 2.8 years	No
NCT02182830 (1245.29)	African American patients with T2DM and hypertension	24 weeks	Yes
NCT01011868 (1245.33)	Efficacy on background basal insulin	78 weeks	No
NCT01947855 (1245.35)	Japanese post-prandial glucose	4 weeks	No
NCT01164501 (1245.36)	Renal safety study	52 weeks	No
NCT01193218 (1245.38)	Japanese dose finder study plus extension	52 weeks	No
NCT01370005 (1245.48)	Efficacy in patients with T2DM and hypertension	12 weeks	No
NCT01306214 (1245.49)	Efficacy on background MDI insulin ± metformin	52 weeks	No
NCT02589639 (1245.107)	Empagliflozin add-on to insulin (Japan)	52 weeks	No
NCT01734785 (1275.9)	Empagliflozin add-on to linagliptin	24 weeks	No
NCT02453555 (1275.19)	Empagliflozin add-on to linagliptin (Japan)	52 weeks	Yes
NCT01649297 (1276.10)	Empagliflozin QD versus BID on background metformin	16 weeks	No

All trials were randomized, double-blind, and placebo-controlled in ambulatory patients with T2DM treated with empagliflozin 10 or 25 mg

BI Boehringer Ingelheim, *BID* twice daily, *MDI* multiple daily injections, *QD* once daily, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinedione

[a] In some trials, the investigators could decide to increase the dose of empagliflozin from 10 to 25 mg in a blinded manner during the trial

without metformin [28–31], and the CV outcomes trial EMPA-REG OUTCOME® [15]. It included all randomized, double-blind, placebo-controlled trials conducted in ambulatory patients with T2DM, including dose escalation trials and one extension trial of 52 weeks with

patients enrolled from three main trials [32–36]). Data were only included for patients treated with empagliflozin (10/25 mg) or placebo who were randomized using either a 1:1 or 1:1:1 schedule.

The procedures followed in all studies were in accordance with the ethical standards of the responsible institutional and/or national committees on human experimentation, and with the Helsinki Declaration of 1964, as revised in 2013. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All patients provided their written informed consent prior to participation.

Assessments and Data Analyses

Safety and tolerability were assessed as for the earlier analysis [21], on the basis of investigator-reported adverse events (AEs) that were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 preferred terms. The safety topics of interest were analyzed using MedDRA version 21.0 preferred terms. A severe AE was any AE adjudged by the investigator to be either incapacitating, causing inability to work, or to perform usual activities. A serious AE was any AE that resulted in death, was immediately life-threatening, resulted in persistent or marked disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason.

Similar to the previous analysis [21], safety topics of interest included events consistent with hypoglycemia (confirmed hypoglycemia was defined as a plasma glucose level of ≤ 3.9 mmol/l and/or requiring assistance), urinary tract infections, genital infections, volume depletion, diabetic ketoacidosis, urinary tract carcinogenicity, hepatic injury, bone fractures, acute pancreatitis, amputations, and decreased renal function. As LLAs were not systematically reported as separate AEs, the retrieval of these cases involved medical review of the narratives and concomitant therapy data. The present analysis also includes assessments of complicated urinary tract infections (UTIs) and complicated genital infections.

Analyses of AEs were descriptive and based on patients who received at least one dose of the study drug. Exposure-adjusted incidence rates were calculated per 100 patient-years as $100 \times n/T$ where n was the number of patients with the event and T was the total number of patient-years at risk of the event. Patient-years at risk was defined for patients with an event as the time from first dose to the onset of a first event, or for patients without an event, as the time from first dose to the last dose plus 7 days. For LLAs, an intent-to-treat analysis was performed based on cases reported from the first intake of study drug up to trial termination in patients treated with at least one dose of the study drug. Additionally, a time-to-first-event analysis was performed.

The primary analysis was of placebo compared with the pooled empagliflozin 10/25 mg population, as the safety and tolerability of the two empagliflozin doses were shown to be similar in previous analyses [20, 21]. Data from the individual empagliflozin 10 mg and 25 mg groups are also presented in the tables and figure, but exclude the dose-escalation trials.

RESULTS

Patient Disposition, Exposure and Baseline Characteristics

The analysis set included 10,177 patients treated with empagliflozin 10/25 mg and 4904 treated with placebo. Compared with the earlier pooled safety analysis of empagliflozin [21], the current dataset represents an approximate 20% increase in the number of patients analyzed overall (12,620 patients vs. 15,081 patients, respectively). In addition, the EMPA-REG OUTCOME® trial accounted for less than 50% of patients in the current analysis compared with earlier pooled safety analysis [21] (46.5% vs. 55.6%, respectively). However, patients aged ≥ 85 years old (0.2% of overall population) and those with an estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73 m^2 (0.8% of the overall population), were under-

Table 2 Demographics and baseline characteristics

	Placebo (n = 4904)	EMPA 10 mg (n = 4858)	EMPA 25 mg (n = 5057)	EMPA 10/25 mg (n = 10,177)
Male, n (%)	3119 (63.6)	3094 (63.7)	3249 (64.2)	6529 (64.2)
Age, years	60.5 (9.8)	60.3 (9.7)	60.4 (9.8)	60.3 (9.7)
Age groups, years (%)				
< 65	3197 (65.2)	3168 (65.2)	3293 (65.1)	6639 (65.2)
65 to < 75	1377 (28.1)	1390 (28.6)	1426 (28.2)	2887 (28.4)
75 to < 85	318 (6.5)	290 (6.0)	327 (6.5)	630 (6.2)
≥ 85	12 (0.2)	10 (0.2)	11 (0.2)	21 (0.2)
Race, n (%)				
White	3044 (62.1)	3256 (67.0)	3346 (66.2)	6602 (64.9)
Asian	1347 (27.5)	1252 (25.8)	1349 (26.7)	2601 (25.6)
Black/African–American	279 (5.7)	213 (4.4)	219 (4.3)	512 (5.0)
Other[a]	51 (1.0)	50 (1.0)	51 (1.0)	101 (1.0)
Missing	183 (3.7)	87 (1.8)	92 (1.8)	361 (3.5)
Region, n (%)				
Europe	1821 (37.1)	1939 (39.9)	2013 (39.8)	3952 (38.8)
North America	1057 (21.6)	1056 (21.7)	1083 (21.4)	2219 (21.8)
Latin America	474 (9.7)	503 (10.4)	505 (10.0)	1008 (9.9)
Africa/Middle East	132 (2.7)	129 (2.7)	141 (2.8)	270 (2.7)
Asia	1420 (29.0)	1231 (25.3)	1315 (26.0)	2728 (26.8)
Time since diabetes diagnosis, years, n (%)				
≤ 1	259 (5.3)	295 (6.1)	308 (6.1)	616 (6.1)
> 1 to ≤ 5	1077 (22.0)	1048 (21.6)	1100 (21.8)	2216 (21.8)
> 5	3553 (72.5)	3500 (72.0)	3633 (71.8)	7314 (71.9)
Missing	15 (0.3)	15 (0.3)	16 (0.3)	31 (0.3)
BMI, kg/m^{2b}	30.4 (5.5)	30.5 (5.5)	30.5 (5.5)	30.5 (5.6)
eGFR, ml/min/1.73 m^2, n (%)[c]				
≥ 90	1933 (39.4)	1998 (41.1)	2041 (40.4)	4177 (41.0)
≥ 60 to < 90	2123 (43.3)	2203 (45.3)	2155 (42.6)	4477 (44.0)
≥ 45 to < 60	519 (10.6)	464 (9.6)	535 (10.6)	1003 (9.9)
≥ 30 to < 45	277 (5.6)	182 (3.7)	262 (5.2)	445 (4.4)
< 30	52 (1.1)	10 (0.2)	61 (1.2)	71 (0.7)

Table 2 continued

	Placebo (*n* = 4904)	EMPA 10 mg (*n* = 4858)	EMPA 25 mg (*n* = 5057)	EMPA 10/25 mg (*n* = 10,177)
Missing	0	1 (< 0.1)	3 (0.1)	4 (< 0.1)

Data are mean (SD) unless otherwise indicated

BMI body mass index, *eGFR* estimated glomerular filtration rate, *EMPA* empagliflozin, *SD* standard deviation

[a] American Indian/Alaska Native/Hawaiian/Pacific Islander

[b] Placebo, *n* = 4883; EMPA 10 mg, *n* = 4838; EMPA 25 mg, *n* = 5038; EMPA 10/25 mg, *n* = 10,138

[c] Placebo, *n* = 4904; EMPA 10 mg, *n* = 4857; EMPA 25 mg, *n* = 5054; EMPA 10/25 mg, *n* = 10,173

Table 3 Incidence of adverse events

	Placebo (*n* = 4904)	EMPA 10 mg (*n* = 4858)	EMPA 25 mg (*n* = 5057)	EMPA 10/25 mg (*n* = 10,177)
≥ 1 AE	197.62	170.01	168.59	168.89
≥ 1 drug-related AE[a]	15.45	19.57	19.38	19.54
≥ 1 AE leading to discontinuation	7.40	6.57	6.38	6.43
≥ 1 severe AE[b]	10.43	8.80	9.51	9.04
≥ 1 serious AE[c]	18.61	15.29	16.07	15.52
Fatal	1.57	1.24	1.01	1.12

Data are the rate/100 patient-years. A patient may be counted in more than one seriousness criterion. MedDRA version used for reporting: 20.1

AE adverse event, *EMPA* empagliflozin, *MedDRA* Medical Dictionary for Regulatory Activities

[a] Investigator-defined

[b] An AE that is incapacitating or causing inability to work or perform usual activities

[c] An AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is deemed serious for any other reason

represented in the present sample, similar to the earlier analysis [21]. The total study drug exposure was 16,480 and 7857 patient-years in the empagliflozin 10/25 mg and placebo groups, respectively. Patient baseline demographics and clinical characteristics were well balanced across the treatment groups. These are summarized in Table 2.

General Safety

The overall pattern of AEs observed in the earlier pooled safety analysis [21] was also seen in this updated analysis, with incidences of severe AEs, serious AEs, fatal AEs and AEs leading to treatment discontinuation being similar between the empagliflozin and placebo groups (Table 3). The percentage of patients with a serious AE requiring hospitalization was similar for the empagliflozin and placebo groups (empagliflozin 10/25 mg: 18.6%; placebo: 21.3%) (Table 4). The most common serious AEs requiring hospitalization (based on MedDRA terms) were cardiac disorders (empagliflozin 10/25 mg: 5.7%; placebo: 7.1%), infections and infestations (empagliflozin 10/25 mg: 3.8%; placebo: 4.6%), and nervous system disorders

Table 4 Frequency of adverse events

	Placebo (*n* = 4904)	EMPA 10 mg (*n* = 4858)	EMPA 25 mg (*n* = 5057)	EMPA 10/25 mg (*n* = 10,177)
≥ 1 AE	3942 (80.4)	3740 (77.0)	3896 (77.0)	7805 (76.7)
≥ 1 drug-related AE[a]	1028 (21.0)	1247 (25.7)	1279 (25.3)	2571 (25.3)
≥ 1 AE leading to discontinuation	565 (11.5)	514 (10.6)	512 (10.1)	1033 (10.2)
≥ 1 severe AE[b]	747 (15.2)	651 (13.4)	718 (14.2)	1371 (13.5)
≥ 1 serious AE[c]	1204 (24.6)	1046 (21.5)	1104 (21.8)	2161 (21.2)
Fatal	125 (2.5)	101 (2.1)	84 (1.7)	186 (1.8)
Immediately life-threatening	53 (1.1)	54 (1.1)	64 (1.3)	118 (1.2)
Disability/incapacitation	29 (0.6)	20 (0.4)	27 (0.5)	47 (0.5)
Requiring hospitalization	1044 (21.3)	898 (18.5)	986 (19.5)	1891 (18.6)
Prolonged hospitalization	79 (1.6)	57 (1.2)	76 (1.5)	133 (1.3)
Congenital anomaly	0	0	0	0
Other	193 (3.9)	170 (3.5)	175 (3.5)	348 (3.4)

Data are *n* (%). A patient may be counted in more than one seriousness criterion. MedDRA version used for reporting: 20.1
AE adverse event, *EMPA* empagliflozin, *MedDRA* Medical Dictionary for Regulatory Activities
[a] Investigator-defined
[b] An AE that is incapacitating or causing inability to work or perform usual activities
[c] An AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is deemed serious for any other reason

(empagliflozin 10/25 mg: 2.8%; placebo: 3.1%) (Table 5). In contrast, AEs that were deemed by the study investigator to be drug-related were more common in patients treated with empagliflozin compared with the placebo group (empagliflozin 10/25 mg: 25.3%; placebo: 21.0%) (Table 4).

Safety Topics of Interest

Hypoglycemia
The frequency and incidence rate of hypoglycemic AEs were similar for empagliflozin and placebo in all-comers (empagliflozin 10/25 mg: 20.3%, 15.69 events per 100 patient-years; placebo: 21.3%, 16.32 events per 100 patient-years) (Table 6). However, a higher percentage of patients that used insulin and/or an SU at baseline in the empagliflozin 10/25 mg than placebo groups reported confirmed hypoglycemic AEs (empagliflozin 10/25 mg: 31.5%, 20.88 events per 100 patient-years; placebo: 30.2%, 20.36 per 100 patient-years) (Table 6).

Urinary Tract Infections
The frequency and incidence of events consistent with UTI was higher among females compared with males in all treatment groups, but was similar when comparing empagliflozin with placebo in both males and females [empagliflozin 10/25 mg: (females) 25.4%, 22.55 events per 100 patient-years, (males) 7.0%, 4.21 events per 100 patient-years; placebo: (females) 27.3%, 24.50 events per 100 patient-years, (males) 6.5%, 3.97 events per 100 patient-years] (Table 6). Excluding patients aged ≥ 85 years, the frequency and incidence of UTI increased with age in all treatment groups,

Table 5 Frequency of patients with serious adverse events requiring hospitalization

	Placebo (n = 4904)	EMPA 10 mg (n = 4858)	EMPA 25 mg (n = 5057)	EMPA 10/25 mg (n = 10,177)
Number of patients	1044 (21.3)	898 (18.5)	986 (19.5)	1891 (18.6)
SOC				
Infections and infestations	225 (4.6)	187 (3.8)	200 (4.0)	387 (3.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	45 (0.9)	65 (1.3)	75 (1.5)	142 (1.4)
Blood and lymphatic system disorders	18 (0.4)	16 (0.3)	14 (0.3)	30 (0.3)
Immune system disorders	4 (0.1)	3 (0.1)	4 (0.1)	7 (0.1)
Endocrine disorders	3 (0.1)	3 (0.1)	8 (0.2)	11 (0.1)
Metabolism and nutrition disorders	66 (1.3)	42 (0.9)	40 (0.8)	82 (0.8)
Psychiatric disorders	19 (0.4)	11 (0.2)	7 (0.1)	18 (0.2)
Nervous system disorders	152 (3.1)	136 (2.8)	153 (3.0)	289 (2.8)
Eye disorders	26 (0.5)	29 (0.6)	22 (0.4)	51 (0.5)
Ear and labyrinth disorders	17 (0.3)	7 (0.1)	16 (0.3)	23 (0.2)
Cardiac disorders	347 (7.1)	282 (5.8)	296 (5.9)	580 (5.7)
Vascular disorders	115 (2.3)	74 (1.5)	109 (2.2)	183 (1.8)
Respiratory, thoracic and mediastinal disorders	69 (1.4)	43 (0.9)	52 (1.0)	95 (0.9)
Gastrointestinal disorders	93 (1.9)	94 (1.9)	93 (1.8)	187 (1.8)
Hepatobiliary disorders	25 (0.5)	28 (0.6)	30 (0.6)	59 (0.6)
Skin and subcutaneous tissue disorders	28 (0.6)	20 (0.4)	34 (0.7)	54 (0.5)
Musculoskeletal and connective tissue disorders	98 (2.0)	79 (1.6)	81 (1.6)	160 (1.6)
Renal and urinary disorders	69 (1.4)	43 (0.9)	41 (0.8)	84 (0.8)
Pregnancy, puerperium and perinatal conditions	0	0	1 (< 0.1)	1 (< 0.1)
Reproductive system and breast disorders	10 (0.2)	18 (0.4)	19 (0.4)	37 (0.4)
Congenital, familial and genetic disorders	6 (0.1)	4 (0.1)	2 (< 0.1)	6 (0.1)
General disorders and administration site conditions	75 (1.5)	58 (1.2)	62 (1.2)	121 (1.2)
Investigations	18 (0.4)	8 (0.2)	15 (0.3)	23 (0.2)
Injury, poisoning and procedural complications	83 (1.7)	69 (1.4)	80 (1.6)	151 (1.5)
Surgical and medical procedures	15 (0.3)	14 (0.3)	16 (0.3)	30 (0.3)

Table 5 continued

	Placebo (n = 4904)	EMPA 10 mg (n = 4858)	EMPA 25 mg (n = 5057)	EMPA 10/25 mg (n = 10,177)
Social circumstances	0	1 (< 0.1)	0	1 (< 0.1)
Product issues	4 (0.1)	0	2 (< 0.1)	2 (< 0.1)

Data are *n* (%). A patient could have more than one event. MedDRA version used for reporting: 20.1

EMPA empagliflozin, *MedDRA* Medical Dictionary for Regulatory Activities, *SOC* System Organ Class

but, again, the frequency and incidence of UTI was similar when comparing empagliflozin with placebo in all age groups (Table 6). The majority of these events were non-serious, mild or moderate in intensity and led to treatment discontinuation in < 1% of treated patients in the empagliflozin 10/25 mg and placebo groups (Table 7). Similar proportions of patients (< 1%) with UTIs that either required or prolonged hospitalization were observed in the empagliflozin 10/25 mg and placebo groups (Table 7). Approximately one-third of patients in both the empagliflozin 10/25 mg and placebo groups with a history of chronic or recurrent UTIs had a UTI during treatment (Table 7). Similar proportions of patients in the empagliflozin 10/25 mg and placebo groups had complicated UTIs (0.9% vs. 1.2%, respectively; Table 7).

Genital Infections

The frequency and incidence of events consistent with genital infections was higher among females compared with males in all treatment groups, and was higher for empagliflozin than placebo in both males and females [empagliflozin 10/25 mg: (females) 8.5%, 6.33 events per 100 patient-years, (males) 3.9%, 2.30 events per 100 patient-years; placebo: (females) 2.2%, 1.58 events per 100 patient-years, (males) 1.1%, 0.66 events per 100 patient-years], and in all age groups (Table 6). As for UTIs, the majority of genital infections were non-serious, mild or moderate in intensity and led to treatment discontinuation in < 1% of patients in each of the treatment groups (Table 7). In addition, < 1% of patients across treatment groups had genital infections that required or

prolonged hospitalization (Table 7). The frequency of events consistent with genital infections was higher in patients with a history of chronic or recurrent genital infections compared with patients without such a history for both empagliflozin 10/25 mg and placebo (empagliflozin 10/25 mg: 22.7% vs. 5.4%; placebo: 7.9% vs. 1.5%, respectively) (Table 7). Moreover, complicated genital infection rates were consistently low and similar across groups (0.5% for both empagliflozin 10/25 mg and placebo) (Table 7).

Volume Depletion

A higher rate of volume depletion was reported in patients with hypotension at baseline versus without, in patients treated with diuretics or loop diuretics at baseline than without, and in patients taking angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) or antihypertensive drugs at baseline than without (Table 8). However, the frequency of events consistent with volume depletion was similar between patients treated with empagliflozin 10/25 mg and placebo in these subgroups, except for patients aged 75 to < 85 years (5.9% vs. 5.0%, respectively), and patients treated with loop diuretics at baseline (9.8% vs. 7.4%, respectively), where the frequency was higher for empagliflozin 10/25 mg compared with placebo (Table 8).

Diabetic Ketoacidosis

The frequency and incidence of diabetic ketoacidosis were similar for patients treated with empagliflozin and placebo (empagliflozin 10/25 mg: 0.1%, 0.04 events per 100 patient-

Table 6 Frequency and incidence rate of important identified risks

	Placebo (n = 4904)		EMPA 10 mg (n = 4858)		EMPA 25 mg (n = 5057)		EMPA 10/25 mg (n = 10,177)	
	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs
UTIs (BlcMQ)	691 (14.1)	9.70	684 (14.1)	9.45	675 (13.3)	9.04	1382 (13.6)	9.27
Sex								
Male	204/3119 (6.5)	3.97	225/3094 (7.3)	4.33	224/3249 (6.9)	4.11	455/6529 (7.0)	4.21
Female	487/1785 (27.3)	24.50	459/1764 (26.0)	22.43	451/1808 (24.9)	22.35	927/3648 (25.4)	22.55
Age, years								
< 65	401/3197 (12.5)	9.00	389/3168 (12.3)	8.58	360/3293 (10.9)	7.71	762/6639 (11.5)	8.16
65 to < 75	220/1377 (16.0)	10.35	216/1390 (15.5)	9.64	243/1426 (17.0)	10.59	466/2887 (16.1)	10.14
75 to < 85	69/318 (21.7)	13.39	79/290 (27.2)	17.38	71/327 (21.7)	14.72	153/630 (24.3)	16.13
≥ 85	1/12 (8.3)	4.61	0/10	–	1/11 (9.1)	4.48	1/21 (4.8)	2.98
Complicated UTIs (BlcMQ)	59 (1.2)	0.75	39 (0.8)	0.48	54 (1.1)	0.65	93 (0.9)	0.56
Genital infections (BlcMQ)	75 (1.5)	0.95	278 (5.7)	3.57	281 (5.6)	3.52	565 (5.6)	3.54
Sex								
Male	35/3119 (1.1)	0.66	139/3094 (4.5)	2.62	116/3249 (3.6)	2.07	255/6529 (3.9)	2.30
Female	40/1785 (2.2)	1.58	139/1764 (7.9)	5.61	165/1808 (9.1)	6.98	310/3648 (8.5)	6.33
Age, years								
< 65	50/3197 (1.6)	1.03	192/3168 (6.1)	4.01	192/3293 (5.8)	3.93	386/6639 (5.8)	3.93
65 to < 75	21/1377 (1.5)	0.88	69/1390 (5.0)	2.81	71/1426 (5.0)	2.82	144/2887 (5.0)	2.86
75 to < 85	4/318 (1.3)	0.68	17/290 (5.9)	3.21	17/327 (5.2)	3.13	34/630 (5.4)	3.13
≥ 85	0/12	–	0/10	–	1/11 (9.1)	4.35	1/21 (4.8)	2.92
Complicated genital infections (BlcMQ)	24 (0.5)	0.30	29 (0.6)	0.36	26 (0.5)	0.31	55 (0.5)	0.33
Hypoglycemia (narrow SMQ)	1045 (21.3)	16.32	1009 (20.8)	15.79	1053 (20.8)	16.02	2067 (20.3)	15.69
Confirmed hypoglycemic AEs	987 (20.1)		945 (19.5)		1000 (19.8)		1948 (19.1)	
Confirmed hypoglycemia[a] with baseline use of insulin and/or SU	915 (30.2)	20.36	889 (31.9)	20.92	942 (31.2)	20.84	1,833 (31.5)	20.88
Confirmed hypoglycemia without baseline use of insulin and/or SU	54 (2.9)	2.66	38 (1.8)	1.67	46 (2.3)	2.13	85 (2.0)	1.83

Table 6 continued

	Placebo (n = 4904)		EMPA 10 mg (n = 4858)		EMPA 25 mg (n = 5057)		EMPA 10/25 mg (n = 10,177)	
	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs
Diabetic ketoacidosis (narrow BIcMQ[b])	4 (0.1)	0.05	4 (0.1)	0.05	2 (< 0.1)	0.02	6 (0.1)	0.04
Urinary tract carcinogenicity[c] (BIcMQ)	9 (0.2)	0.11	10 (0.2)	0.12	13 (0.3)	0.16	23 (0.2)	0.14
Onset after 6 months' treatment	7 (0.2)	0.12	8 (0.2)	0.13	10 (0.3)	0.16	18 (0.3)	0.15
Liver injury (SMQ)	157 (3.2)	2.02	109 (2.2)	1.36	135 (2.7)	1.65	247 (2.4)	1.51
Bone fractures (BIcMQ)	134 (2.7)	1.72	121 (2.5)	1.52	107 (2.1)	1.30	233 (2.3)	1.42
Pancreatitis (SMQ)	11 (0.2)	0.14	8 (0.2)	0.10	7 (0.1)	0.08	15 (0.1)	0.09
Amputation risk (ITT population)	46 (0.9)	0.52	46 (0.9)	0.51	49 (1.0)	0.54	95 (0.9)	0.52
Minor	27 (0.6)	0.30	36 (0.7)	0.40	40 (0.8)	0.44	76 (0.8)	0.41
Major	19 (0.4)	0.21	10 (0.2)	0.11	9 (0.2)	0.10	19 (0.2)	0.10

AE adverse event, *BIcMQ* Boehringer Ingelheim customized MedDRA query, *EMPA* empagliflozin, *ITT* intent-to-treat, *MedDRA* Medical Dictionary for Regulatory Activities, *pt-yrs* patient-years, *SMQ* standardized MedDRA queries, *SU* sulfonylurea, *UTI* urinary tract infection

[a] Confirmed hypoglycemia was defined as plasma glucose ≤ 3.9 mmol/l and/or requiring assistance

[b] The lower number of events in the placebo group compared with the previously updated pooled safety analysis [21] is due to a change in definition resulting from a revision in MedDRA mapping between versions (i.e., the lowest level term 'diabetic ketosis' was mapped to the preferred term 'diabetic ketoacidosis' in version 18.0; however, this is no longer the case in version 21.0)

[c] Bladder and renal malignancies

Table 7 Frequency and incidence rate for UTIs and genital infections by seriousness, need for hospitalization, treatment discontinuation, history of chronic or recurrent infection, and complicated infection

	Placebo (n = 4904)		EMPA 10 mg (n = 4858)		EMPA 25 mg (n = 5057)		EMPA 10/25 mg (n = 10,177)	
	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs
UTIs (BIcMQ)[a]								
Serious UTIs	39 (0.8)	0.49	27 (0.6)	0.33	39 (0.8)	0.47	66 (0.6)	0.40
Requires or prolongs hospitalization	38 (0.8)	0.5	26 (0.5)	0.3	39 (0.8)	0.5	65 (0.6)	0.4
Treatment discontinued	15 (0.3)	0.19	27 (0.6)	0.33	25 (0.5)	0.30	52 (0.5)	0.31
History of chronic or recurrent UTI[b]								
Yes	100/277 (36.1)	32.46	98/280 (35.0)	28.58	102/313 (32.6)	28.41	205/615 (33.5)	28.82
No	573/4267 (13.4)	8.71	559/4221 (13.2)	8.39	550/4402 (12.5)	7.98	1126/8863 (12.7)	8.20
Complicated UTIs[c]	59 (1.2)	0.75	39 (0.8)	0.48	54 (1.1)	0.65	93 (0.9)	0.56
Genital infections (BIcMQ)[d]								
Serious genital infections	3 (0.1)	0.04	8 (0.2)	0.10	4 (0.1)	0.05	12 (0.1)	0.07
Requires or prolongs hospitalization	3 (0.1)	< 0.1	8 (0.2)	0.1	4 (0.1)	< 0.1	12 (0.1)	0.1
Treatment discontinued	2 (< 0.1)	0.03	26 (0.5)	0.32	21 (0.4)	0.25	47 (0.5)	0.28
History of chronic or recurrent genital infection[e]								
Yes	6/76 (7.9)	5.25	17/76 (22.4)	17.93	22/92 (23.9)	23.47	39/172 (22.7)	20.30
No	66/4468 (1.5)	0.88	243/4425 (5.5)	3.27	249/4623 (5.4)	3.25	498/9306 (5.4)	3.25

Table 7 continued

	Placebo (n = 4904)		EMPA 10 mg (n = 4858)		EMPA 25 mg (n = 5057)		EMPA 10/25 mg (n = 10,177)	
	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs	n (%)	Rate/100 pt-yrs
Complicated genital infections[f]	24 (0.5)	0.30	29 (0.6)	0.36	26 (0.5)	0.31	55 (0.5)	0.33

Data are n (%) except where indicated

AE adverse event, BIcMQ Boehringer Ingelheim customized MedDRA query, EMPA empagliflozin, MedDRA Medical Dictionary for Regulatory Activities, pt-yrs patient-years, UTI urinary tract infection

[a] Based on pre-defined MedDRA preferred terms, of which UTI, asymptomatic bacteriuria, and cystitis were the most frequent

[b] Number of patients with UTIs/number of treated patients in subgroup (number of patients with UTIs as % of number of treated patients in subgroup)

[c] All upper UTIs reported as serious or non-serious AEs and all lower UTIs reported as serious AEs

[d] Based on pre-defined MedDRA preferred terms, of which balanoposthitis, vulvovaginal mycotic infection, and vulvovaginal candidiasis were the most frequent

[e] Number of patients with genital infections/number of treated patients in subgroup (number of patients with genital infections as % of number of treated patients in subgroup)

[f] Events related to abscesses of external genital organs, endometritis, adnexitis, prostatitis, orchiepididymitis, pelvic infections, and serious AEs of vulvovaginitis and balanoposthitis

years; placebo: 0.1%, 0.05 events per 100 patient-years) (Table 6). Of four patients in the placebo group with diabetic ketoacidosis, none discontinued treatment and symptoms eventually resolved in all patients. Of six patients in the empagliflozin 10/25 mg group who experienced diabetic ketoacidosis, two discontinued treatment and symptoms resolved in five patients (the status of one patient was unknown).

Urinary Tract Carcinogenicity

The frequency and incidence of events consistent with urinary tract carcinogenicity (bladder and renal malignancies) with an onset of at least 6 months from the start of treatment were similar for the empagliflozin 10/25 mg and placebo groups (empagliflozin 10/25 mg: 0.3%, 0.15 events per 100 patient-years; placebo: 0.2%, 0.12 events per 100 patient-years) (Table 6).

Liver Injury

The frequency and incidence of events consistent with hepatic injury were similar for the empagliflozin and placebo groups (empagliflozin 10/25 mg: 2.4%, 1.51 events per 100 patient-years; placebo: 3.2%, 2.02 events per 100 patient-years) (Table 6). Elevations in alanine aminotransferase and/or aspartate aminotransferase ≥ 5 times the upper limit of normal were more frequent with empagliflozin 10/25 mg versus placebo (0.4% vs. 0.2%, respectively) (Table 9).

Bone Fractures

The frequency and incidence of bone fractures were similar for the empagliflozin 10/25 mg and placebo groups (empagliflozin 10/25 mg: 2.3%, 1.42 events per 100 patient-years; placebo: 2.7%, 1.72 events per 100 patient-years) (Table 6).

Pancreatitis

The frequency and incidence of pancreatitis, including acute pancreatitis, were similar for the empagliflozin 10/25 mg and placebo groups (empagliflozin 10/25 mg: 0.1%, 0.09 events per

Table 8 Frequencies for volume depletion by age, hypotension at baseline, and concomitant drugs at baseline

	Placebo (*n* = 4904)	EMPA 10 mg (*n* = 4858)	EMPA 25 mg (*n* = 5057)	EMPA 10/25 mg (*n* = 10,177)
Volume depletion[a] (BIcMQ)	147 (3.0)	150 (3.1)	169 (3.3)	320 (3.1)
Age (years)				
< 65	62/3197 (1.9)	59/3168 (1.9)	73/3293 (2.2)	132/6639 (2.0)
65 to < 75	67/1377 (4.9)	73/1390 (5.3)	75/1426 (5.3)	149/2887 (5.2)
75 to < 85	16/318 (5.0)	18/290 (6.2)	19/327 (5.8)	37/630 (5.9)
≥ 85	2/12 (16.7)	0/10	2/11 (18.2)	2/21 (9.5)
Hypotension at baseline				
Yes	17/244 (7.0)	15/254 (5.9)	9/276 (3.3)	24/542 (4.4)
No	130/4602 (2.8)	135/4548 (3.0)	160/4727 (3.4)	296/9525 (3.1)
Use of diuretics at baseline				
Yes	83/1660 (5.0)	79/1602 (4.9)	96/1703 (5.6)	175/3349 (5.2)
No	64/3244 (2.0)	71/3256 (2.2)	73/3354 (2.2)	145/6828 (2.1)
Use of loop diuretics at baseline				
Yes	36/488 (7.4)	42/415 (10.1)	47/489 (9.6)	89/909 (9.8)
No	111/4416 (2.5)	108/4443 (2.4)	122/4568 (2.7)	231/9268 (2.5)
Use of ACE inhibitor/ARB at baseline				
Yes	121/3256 (3.7)	126/3261 (3.9)	142/3360 (4.2)	269/6733 (4.0)
No	26/1648 (1.6)	24/1597 (1.5)	27/1697 (1.6)	51/3444 (1.5)
Use of antihypertensive drugs at baseline				
Yes	140/3922 (3.6)	142/3857 (3.7)	158/3986 (4.0)	301/7996 (3.8)
No	7/982 (0.7)	8/1001 (0.8)	11/1071 (1.0)	19/2181 (0.9)

Data are *n* (%) except where indicated. Percentages are calculated using the total number of patients per treatment as the denominator

ACE angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker, *BIcMQ* Boehringer Ingelheim customized MedDRA query, *EMPA* empagliflozin, *MedDRA* Medical Dictionary for Regulatory Activities

[a] Based on pre-defined MedDRA preferred terms, of which hypotension, syncope, and dehydration were the most frequent

100 patient-years; placebo: 0.2%, 0.14 events per 100 patient-years) (Table 6).

Lower Limb Amputation Risk
In the current pooled safety analysis LLAs, including minor (at the ankle or below) and major (above the ankle) amputations, occurred in 95 and 46 patients in the intent-to-treat analysis who were treated with empagliflozin 10/25 mg and placebo, respectively. There was no difference in the overall incidence rate of LLAs between the empagliflozin 10/25 mg and placebo groups (0.52 vs. 0.52 cases per 100 patient-years, respectively) (Table 6). The degree of amputation was less often major in the

Table 9 Elevations in liver enzymes and bilirubin[a]

	Placebo (*n* = 4904)	EMPA 10 mg (*n* = 4858)	EMPA 25 mg (*n* = 5057)	EMPA 10/25 mg (*n* = 10,177)
ALT and/or AST ≥ 3 × ULN	65 (1.3)	50 (1.0)	45 (0.9)	99 (1.0)
ALT and/or AST ≥ 5 × ULN	11 (0.2)	18 (0.4)	21 (0.4)	40 (0.4)
ALT and/or AST ≥ 3 × ULN with total bilirubin ≥ 2 × ULN[b]	2 (< 0.1)	5 (0.1)	5 (0.1)	10 (0.1)

Data are *n* (%) in patients who received at least one dose of study drug

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *EMPA* empagliflozin, *ULN* upper limit of normal

[a] Patients are presented regardless of baseline elevations

[b] Patients with ALT and/or AST ≥ 3 × ULN with concomitant or subsequent total bilirubin ≥ 2 × ULN in a 30-day period after ALT and/or AST elevation

Table 10 Frequency and incidence rate of user-defined renal impairment events

	Placebo (*n* = 4904)		EMPA 10 mg (*n* = 4858)		EMPA 25 mg (*n* = 5057)		EMPA 10/25 mg (*n* = 10,177)	
	n (%)	Rate/100 pt-yrs	*n* (%)	Rate/100 pt-yrs	*n* (%)	Rate/100 pt-yrs	*n* (%)	Rate/100 pt-yrs
Renal impairment	169 (3.4)	2.18	139 (2.9)	1.75	152 (3.0)	1.86	291 (2.9)	1.78
Acute kidney injury[a]	44 (0.9)	0.56	29 (0.6)	0.36	28 (0.6)	0.34	57 (0.6)	0.34
Renal impairment by baseline eGFR (CKD-EPI), ml/min/1.73 m², *n* (%)								
≥ 90	15/1933 (0.8)	0.57	12/1998 (0.6)	0.43	10/2041 (0.5)	0.35	22/4177 (0.5)	0.39
60 to < 90	63/2123 (3.0)	1.73	57/2203 (2.6)	1.48	60/2155 (2.8)	1.56	117/4477 (2.6)	1.50
45 to < 60	48/519 (9.2)	4.92	46/464 (9.9)	4.80	40/535 (7.5)	4.09	86/1003 (8.6)	4.44
30 to < 45	37/277 (13.4)	7.85	21/182 (11.5)	5.83	36/262 (13.7)	8.38	57/445 (12.8)	7.22
< 30	6/52 (11.5)	13.87	3/10 (30.0)	20.63	6/61 (9.8)	8.77	9/71 (12.7)	10.85

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, *eGFR* estimated glomerular filtration rate, *EMPA* empagliflozin, *MedDRA* Medical Dictionary for Regulatory Activities, *pt-yrs* patient-years

[a] Based on the MedDRA preferred term

empagliflozin 10/25 mg group than in the placebo group (0.10 vs. 0.21 cases per 100 patient-years, respectively), and more often minor in the empagliflozin 10/25 mg group than in the placebo group (0.41 vs. 0.30 cases per 100 patient-years, respectively) (Table 6). In addition, analysis of the EMPA-REG OUTCOME® trial, from which the majority of the cases of amputation were reported, showed that the proportion of patients with LLA was similar between the treatment groups, and that empagliflozin was not associated with an increased risk of LLA versus placebo in the trial [21, 37].

Renal Impairment

The frequency and incidence of renal impairment events, including acute kidney injury, were similar for the empagliflozin and placebo groups (empagliflozin 10/25 mg: 2.9%, 1.78 events per 100 patient-years; placebo: 2.4%, 2.18 events per 100 patient-years) (Table 10). In particular, the overall frequency of events across treatment groups, assessed by baseline eGFR range, was similar, including in patients with a reduced eGFR of ≥ 30 to < 45 ml/min/1.73 m² (empagliflozin 10/25 mg: 12.8%; placebo: 13.4%) and < 30 ml/min/1.73 m² (empagliflozin 10/25 mg: 12.7%; placebo: 11.5%). Kaplan–Meier
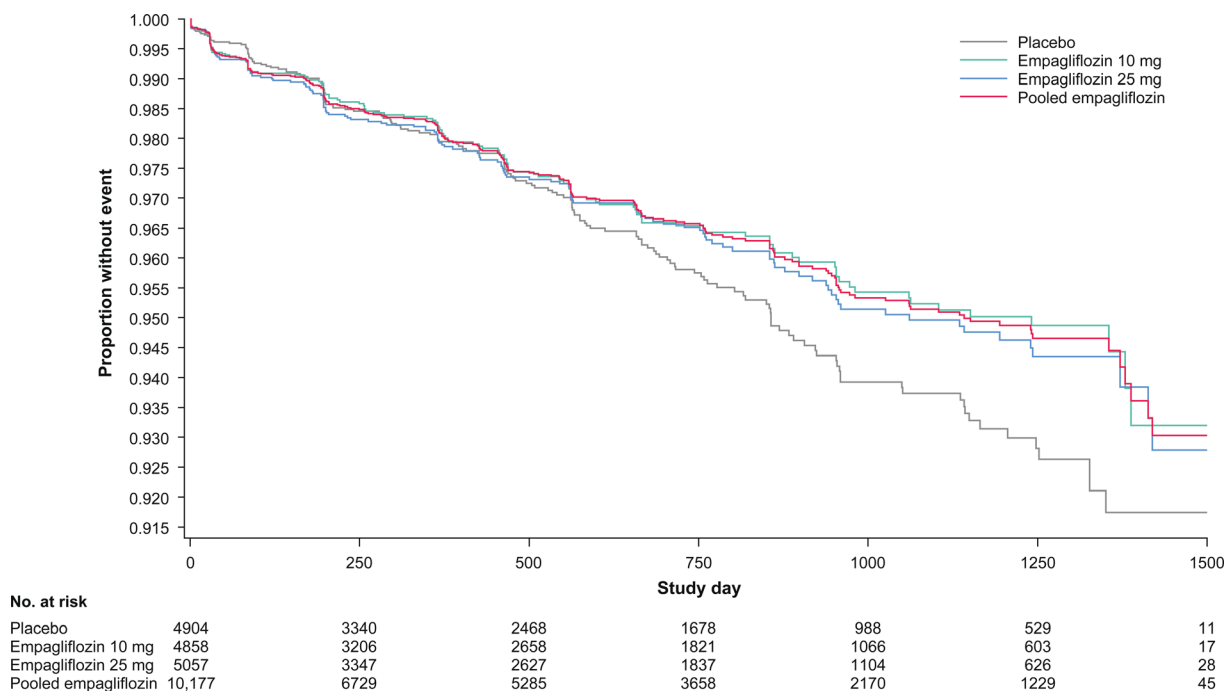
Fig. 1 Kaplan–Meier estimates of time to onset of first event suggestive of renal impairment

estimates of time to first renal impairment event for patients treated with empagliflozin compared with placebo are shown in Fig. 1.

DISCUSSION

In the EMPA-REG OUTCOME® trial in patients with T2DM and established CV disease, empagliflozin reduced the risk of CV death by 38% compared with placebo [15]. Patients treated with empagliflozin also experienced a 32% reduction in the risk of all-cause mortality, a 35% reduction in the risk of hospitalization for heart failure, and a 39% reduction in the risk of incident or worsening nephropathy [15, 16, 38]. In addition, empagliflozin has been estimated to increase life expectancy by an average of 1–4.5 years (depending on age), compared with placebo [39].

This analysis of pooled safety data for empagliflozin was of an expanded dataset previously used to investigate the safety and tolerability of empagliflozin in patients with T2DM [21]. Whereas the earlier analysis was based on more than 15,000 patient-years' exposure to empagliflozin [21], the present

expanded dataset was based on more than 16,480 patient-years' exposure.

Following this earlier analysis [21], the present analysis showed a consistent AE profile and further continued to show that empagliflozin has a good safety profile and is well tolerated in patients with T2DM. In addition, the risk of hypoglycemia was similar for empagliflozin compared with placebo, except when co-administered with insulin and/or an SU.

Due to their mechanism of action, SGLT2 inhibitors cause transient increases in urine volume [1, 2], leading to acknowledgement of its potential for volume depletion and hypotension, particularly in the elderly population. The present analyses showed that the risk of volume depletion for empagliflozin compared with placebo was numerically increased in patients aged 75 to < 85 years, and in patients with concomitant use of loop diuretics, but not in patients with concomitant use of other diuretics, ACE inhibitors/ARBs, or other antihypertensive drugs.

Similarly, UTIs and genital infections are both identified risks associated with SGLT2 inhibitor use, with increases in urinary glucose concentration a potential exacerbating factor

[40]. The present data continue to support previous findings that there is no empagliflozin-specific increased risk of UTIs when compared with placebo. Furthermore, the notion that increased urinary glucose concentration and excretion might predispose to UTIs may be counterbalanced with the hypothesis that increased urinary flow due to osmotic diuresis may reduce or balance the potential impact of increased urinary glucose concentration. The risk of genital infection was elevated for empagliflozin compared with placebo, but excess events associated with empagliflozin were predominantly mild or moderate in intensity and seldom led to treatment discontinuation. There was no increased risk of complicated UTIs or complicated genital infections associated with empagliflozin compared with placebo.

The risk of diabetic ketoacidosis, a serious complication associated with diabetes that arises when the body produces high levels of ketones, may be increased by the use of SGLT2 inhibitors [41]. No imbalance in diabetic ketoacidosis has been reported in clinical trials [15, 17, 18], and there was a similar frequency in the present data for patients treated with empagliflozin compared with placebo. Despite this, in 2015, the US Food and Drug Administration issued a safety announcement of the potential for an increased risk of diabetic ketoacidosis with SGLT2 inhibitor treatment [42]. This was the result of post-marketing reports, coupled with a potential mechanism of action of SGLT2 inhibitors involving the metabolic shift towards lipid utilization, leading to increased ketone body production, particularly during prolonged fasting [43]. As a result, the labels for all SGLT2 inhibitors were updated with a warning of this complication [44].

Recently, based on a number of post-marketing reports, the labels for SGLT2 inhibitors were also updated with an adverse reaction of Fournier's gangrene, which is a rare but serious urological condition, characterized by a progressive necrotizing infection that affects the external genitalia or the perineum [45]. No cases of Fournier's gangrene have been reported in clinical trials with empagliflozin. Six cases of Fournier's gangrene were recorded in the DECLARE-TIMI 58 trial, one in the dapagliflozin group and five in the placebo group [18].

Previously, a concern of bladder cancer relating to SGLT2 inhibitor use was raised, particularly in relation to dapagliflozin [46, 47]. However, this risk was not confirmed in the DECLARE–TIMI 58 trial, a large placebo-controlled CV outcome trial [18]. There was also no increased risk of urinary tract cancer in the present analysis. In addition, an analysis of patients with at least 6 months' drug exposure in EMPA-REG OUTCOME® was undertaken to assess the risk of bladder cancer [48]. The incidence, with an onset after 6 months' cumulative exposure to the study drug, was reported in 10/4406 patients (0.2%) in the empagliflozin 10/25 mg group and 4/2187 patients (0.2%) in the placebo group. The authors concluded that, based on the totality of the data, no imbalance in bladder cancer cases between empagliflozin and placebo was observed in EMPA-REG OUTCOME® [48].

The CANVAS program reported an increased risk of fractures and LLAs with canagliflozin use, with LLAs consistent for minor and major amputations [17]. In 2017, regulators reviewed available data for possible associations between SGLT2 inhibitors and LLAs. They concluded that canagliflozin may increase the risk of LLA, and the US Food and Drug Administration issued a boxed warning to the canagliflozin label describing the increased risk of leg and foot amputations [49]. In the current analysis, there was no evidence of an association between empagliflozin use and LLAs. The overall frequency of amputations was the same for empagliflozin compared with placebo. In addition, the EMPA-REG OUTCOME® trial found that the proportion of patients with an LLA was similar between the empagliflozin and placebo groups [21]. Similarly, the DECLARE-TIMI 58 trial of over 17,000 patients found no increased risk of amputations between dapagliflozin and placebo [18]. A meta-analysis of the CANVAS program, EMPA-REG OUTCOME® and DECLARE-TIMI 58 trials showed that the increased risk of amputations and fractures in the CANVAS program contributed moderate to high percentages of the total variation across the three trials that was due to heterogeneity ($I^2 = 79.1\%$ for amputations and $I^2 = 42.1\%$ for fractures) [5]. In the recent CREDENCE study in

4401 patients with diabetes and albuminuric chronic kidney disease receiving canagliflozin or placebo on top of standard of care, there was no significant difference in the rates of amputation reported (HR 1.11 [95% CI 0.79, 1.56]) [50].

Other potential risks associated with SGLT2 inhibitor use, including liver injury, bone fracture, and pancreatitis, all occurred at a similar frequency for patients treated with empagliflozin and placebo. The events related to renal impairment for patients with reduced eGFR were similar for patients treated with empagliflozin compared with placebo.

Strengths of this analysis include the large sample size and patient exposure. Weaknesses include that the studies were of varying durations and that differences between groups were not compared using modeled analyses.

CONCLUSION

This pooled analysis, based on over 16,480 patient-years' exposure to empagliflozin in placebo-controlled trials, confirms previous knowledge of the tolerability of empagliflozin 10 and 25 mg in patients with T2DM. Empagliflozin was not associated with a higher rate of confirmed hypoglycemic events compared with placebo, except when co-administered with insulin and/or an SU. In both the placebo and empagliflozin groups, there was a higher rate of volume depletion in patients with baseline hypotension versus normotension, and in patients taking diuretics, loop diuretics, ACE inhibitors/ARBs, or antihypertensive drugs, compared with patients not taking these medications. The frequency and incidence rates of events consistent with volume depletion were similar between patients treated with empagliflozin and placebo, except for patients aged 75 to < 85, and for patients treated with loop diuretics at baseline, where the frequency was higher for empagliflozin compared with placebo. Genital infections, but not UTIs, were more frequent in patients treated with empagliflozin than placebo. There was no difference in the incidence of LLA in the pooled empagliflozin group versus placebo. The incidences of bone fractures, urinary tract

carcinogenicity, renal impairment, liver injury, pancreatitis, and diabetic ketoacidosis were not increased with empagliflozin compared with placebo in clinical trials. Further information on the safety and tolerability profile of empagliflozin will be provided by post-marketing surveillance and ongoing clinical trials. Overall, this analysis shows that empagliflozin is a well-tolerated SGLT2 inhibitor that reduces all-cause mortality in patients with T2DM and established CV disease while displaying a favorable benefit-risk profile.

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Data Availability. The sponsor of the clinical trials (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. The datasets analyzed during the current study are available in the Boehringer Ingelheim repository (https://trials.boehringer-ingelheim.com/). Researchers are invited to submit inquiries via the Boehringer Ingelheim website.

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