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Empagliflozin and incidence of events consistent with acute kidney injury: Pooled safety analysis in >15 000 individuals

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1. Background

Chronic kidney disease (CKD) is a common comorbidity that will develop in about 40% of patients with type 2 diabetes (T2D).[1] Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are key treatment options for patients with T2D to reduce the risk for cardiovascular (CV) disease, heart failure (HF) and kidney disease. More recently, beneficial effects with SGLT2i in patients with HF and CKD have also been demonstrated, independent of prevalence of T2D.[2-5]

SGLT2i have been shown to acutely decrease estimated glomerular filtration rate (eGFR), often referred to as an 'initial eGFR dip'.[6-8] Although largely considered a haemodynamic and reversible effect, there has been concern that SGLT2i potentially predispose patients to acute kidney injury (AKI) due to reduction in intraglomerular pressure, induction of kidney medullary hypoxic injury or hypovolaemia.[9] This may be of particular concern in patients who have impaired kidney function, are elderly or receiving loop diuretic medication.

In the EMPA-REG OUTCOME trial, treatment with empagliflozin was not associated with an increased risk of AKI, even in the patient subgroup with eGFR levels <60 mL/min/1.73m^2 at baseline.[8] While patients were more likely to experience an 'eGFR dip' of >10% with empagliflozin, CV and kidney outcomes were consistent.[10]

We analysed pooled safety data sets in the global empagliflozin clinical trial program to investigate the incidence of investigator-reported acute kidney events, focusing on patient groups at risk of acute kidney events overall and during the first 30 days after treatment initiation.

Methods

2.1 Pooled data set

We analysed pooled safety data from 20 trials (Table S1) all in patients with T2D who were randomized to receive empagliflozin or matching placebo. Where studies included other empagliflozin doses, only patients who received empagliflozin 10/25

mg were included; dose escalation from 10 mg to 25 mg empagliflozin was used in some cases (Table S1). Safety topics of interest were analysed using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 preferred terms. AKI was assessed using investigator-reported AEs and captured by the MedDRA preferred term 'acute kidney injury'. AKD is a broader umbrella term that includes AKI events, but also includes events that were haemodynamically driven (Table S2). AKD was assessed using investigator-reported AEs (without adjudication) coded as 'acute renal failure' according to the narrow standardized MedDRA query (see Table S2).

2.2 Analyses

Descriptive analyses were performed based on all patients treated with ≥1 dose of trial drug (placebo or empagliflozin). Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 × n/T, where n was the number of patients 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 to the onset of the first event (for patients with an event) or to the last dose +7 days (for patients without an event). Time to first occurrence of AKI or AKD was evaluated by Kaplan–Meier analysis.

RESULTS

3.1 Studied population

A total of 15081 patients were included with a combined total empagliflozin exposure in patient-years of 16480 and 7857 for the empagliflozin 10/25 mg and placebo groups, respectively. The studied population was 64% male with a mean age of 60.5 years in the placebo group and 60.3 years in the empagliflozin 10/25 mg group (Table S3). Mean (standard deviation) eGFR at baseline in the placebo group was 80.9 (21.0) mL/min/1.73m^2 compared with 82.3 (20.2) mL/min/1.73m^2 in the empagliflozin group. At baseline, 25.6% of the placebo group and 24.8% of the

empagliflozin group had microalbuminuria, while 8.9% of the placebo group and 7.7% of the empagliflozin group had macroalbuminuria.

3.2 AKI and AKD

The incidence of AKI and AKD events were numerically lower in the the empagliflozin vs placebo group (Figure 1 and Table 1). Information on acute dialysis was only available for the EMPA-REG OUTCOME trial, and the majority of AKI events in this pooled group were from EMPA-REG OUTCOME (placebo, n = 37; empagliflozin 10 mg, n = 26; empagliflozin 25 mg, n = 19).[8] Similarly, the majority of AKD events in the pooled group were from EMPA-REG OUTCOME (placebo, n = 155; empagliflozin 10 mg, n = 121; empagliflozin 25 mg, n = 125).[8]

Although no formal statistical analyses were used to compare the groups, the overall AKI risk with empagliflozin and placebo appeared similar. AKI events increased with decreasing kidney function, but the overall incidence rate with empagliflozin was numerically lower than with placebo across all subgroups of baseline eGFR (Table S4). Further, the incidence of AKI events remained numerically lower with empagliflozin across all baseline categories by urine albumin:creatinine ratio, history of HF and baseline use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), diuretics or loop diuretics for empagliflozin vs. placebo. The incidence of AKD events was also seen to increase with decreasing kidney function (Table S5) but remained similar between treatments across various baseline subgroups (Figure S1).

There were no differences between the treatment groups in the number of AKI outcomes that occurred within the first 30 days of treatment initiation (five events [0.1%], 1.25/100 patient-years [placebo], vs. six events [0.1%], 0.72/100 patient-years [empagliflozin 10/25 mg]), or in the number of AKD events occurring over this period

(18 events [0.4%], 4.50/100 patient-years [placebo], vs. 49 events [0.5%], 5.91/100 patient-years [empagliflozin]; Table S5).

4 DISCUSSION

In this post-hoc, pooled analysis of >15000 patients from the global empagliflozin clinical trial program, risk for AKI and AKD with empagliflozin was comparable to placebo, including in patients with impaired kidney function or chronic HF. In patients receiving medications associated with potential AKI risk (e.g., ACE inhibitors/ARBs, NSAIDs, diuretics and loop diuretics), risk was generally higher compared with those not receiving any of these drugs but was comparable for empagliflozin versus placebo.

The overall number of kidney-related events consistent with AKD or AKI within the first 30 days after treatment initiation was low and generally comparable between treatment groups. While there were more reports of kidney impairment in the first 30 days of treatment, no initiation of kidney replacement therapy was reported during this period, suggesting that this may reflect the “eGFR dip” known with empagliflozin and other SGLT2is and is probably of low clinical relevance.

Clinical interpretation of these findings may be limited by the clinical trial setting, and while these findings are consistent with real-world evidence to date,[11] confirmation by further analysis of patients in real-world clinical settings may be required. Monitoring of kidney function in line with local prescribing information and with consideration of factors that may predispose patients to AKI may be advisable when initiating SGLT2i. Only a low number of AKI and AKD events were reported (101 and 67, respectively) and these were based on investigator reports without any formal adjudication. In clinical settings such as the emergency room, AKI and AKD diagnosis via Kidney Disease Improving Global Outcomes (KDIGO) guidelines is often difficult to obtain,[12] and different definitions of AKD exist; for example, this analysis did not use the KDIGO definition. As AKI tends to be under-reported, the results presented here

likely represent a conservative estimate, but this should be comparable between treatment arms. No adjudication process implemented for renal events in this analysis, though as all trials were placebo-controlled, no bias is expected to be introduced by the absence of an adjudication process. Although the analysis population included a preponderance of male patients this phenomenon is common amongst clinical trials and not specific to the empagliflozin trial program and was balanced between treatment arms.

This comprehensive analysis indicates that empagliflozin was not associated with increased risk of AKI or acute kidney failure compared with placebo treatment. These results are supported by observational studies in propensity-score-matched cohorts and meta-analyses, which reported that SGLT2i use reduced the risk of AKI events.[13,14]

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CONFLICT OF INTEREST

RA is supported by research grants from NIH 5R01HL126903 and VA 5I01 CX001753 and has served as a consultant for Boehringer Ingelheim, Bayer, Akebia, AstraZeneca, Reata, Relypsa, Chinook and Janssen. DCW has acted as a consultant and/or received honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp,

Mitsubishi Tanabe, Mundipharma and Vifor Fresenius. KD has no conflicts to declare. CW has received personal fees from Boehringer Ingelheim; and has received personal fees from Akebia, AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Gilead, Merck Sharpe Dohme, Mundipharma, Sanofi-Genzyme and Vifor Fresenius outside the submitted work. SJH, AE, IR and DS are employees of Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

RA, SJH and CW reviewed and edited the initial research proposal, reviewed the data and analysis, and reviewed/edited the manuscript. SJH, DW and KD reviewed/edited the initial research proposal and the manuscript. AE conducted the statistical analysis and reviewed/edited the manuscript. DS reviewed the data and analysis, and reviewed/edited the manuscript.

Data Disclosure

All included trials are registered with ClinicalTrials.gov

Identifiers: NCT00885118, Pooled analysis; NCT IDs for the source clinical trials on ClinicalTrials.gov are

NCT00885118, NCT00789035, NCT00558571, NCT00749190, NCT0085118, NCT01011868, NCT01193218, NCT01210001, NCT01177813, NCT01159600, NCT01131676, NCT02182830, NCT01164501, NCT01370005, NCT01306214, NCT01649297, NCT01947855, NCT02589639, NCT02453555,

DATA AVAILABILITY STATEMENT

The sponsor of this analysis, Boehringer Ingelheim, is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical data. Researchers should use the https://vivli.org/ link to request access to study data and the Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

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Figure legend

FIGURE 1 (A) Acute kidney injury and (B) acute kidney disease events with empagliflozin versus placebo in the overall pooled analysis

TABLE 1 Incidence rates for AKI: subgroup analysis

	Placebo		EMPA 10/25 mg	
	n/N (%)	**Rate/100 patient-years**	**n/N (%)**	**Rate/100 patient-years**
All patients	44/4904 (0.9)	0.56	57/10 177 (0.6)	0.34
eGFR, mL/min/1.73m^2				
≥90	3/1933 (0.2)	0.11	6/4177 (0.1)	0.11
60 to <90	16/2123 (0.8)	0.43	20/4477 (0.4)	0.25
45 to <60	15/519 (2.9)	1.48	19/1003 (1.9)	0.94
30 to <45	8/277 (2.9)	1.60	9/445 (2.0)	1.06
<30	2/52 (3.8)	3.92	3/71 (4.2)	3.33
UACR, mg/g				
<30	24/3161 (0.8)	0.48	27/6571 (0.4)	0.26
≥30 to 300	11/1256 (0.9)	0.51	18/2522 (0.7)	0.40
>300	9/435 (2.1)	1.27	11/785 (1.4)	0.75
Heart failure				
Yes	7/285 (2.5)	1.24	11/521 (2.1)	0.98
No	37/4619 (0.8)	0.50	46/9656 (0.5)	0.30
ACE inhibitor/ARB				
Yes	36/3256 (1.1)	0.63	47/6733 (0.7)	0.39
No	8/1648 (0.5)	0.37	10/3444 (0.3)	0.22
NSAID				
Yes	7/422 (1.7)	1.18	12/798 (1.5)	0.92
No	37/4482 (0.8)	0.51	45/9379 (0.5)	0.29
Diuretic				
Yes	28/1660 (1.7)	0.93	42/3349 (1.3)	0.67
No	16/3244 (0.5)	0.33	15/6828 (0.2)	0.15
Loop diuretic				
Yes	18/488 (3.7)	1.88	17/909 (1.9)	0.91
No	26/4416 (0.6)	0.37	40/9268 (0.4)	0.27

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate (CKD-EPI); EMPA, empagliflozin; NSAID, non-steroidal anti-inflammatory drug, UACR, urine albumin-creatinine ratio.

Figure 1