Diabetes Epidemiology and Management 3 (2021) 100021

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Review

Epidemiology of acute kidney injury adverse events with SGLT2 inhibitors: A meta-analysis of observational cohort studies

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ARTICLE INFO

Article History:
Received 8 October 2021
Accepted 11 October 2021
Available online 12 October 2021

Keywords:
Acute kidney injury
Meta-analysis
Nephrotoxicity
RAAS inhibitors
Real-life
SGLT2 inhibitors

ABSTRACT

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) have proven long-term nephroprotective effects in large prospective cardiovascular and renal outcome placebo-controlled trials, which follow a initial transient dip of estimated glomerular filtration rate. Nevertheless, case reports of acute kidney injury (AKI) associated with SGLT2i therapy were reported, leading the US Food and Drug Administration to publish a warning in 2016. Of note, the incidence of AKI events was not increased and often reduced in outcome trials that compared SGLT2i treatment with placebo. However, patients in real-life might be at higher risk because of a more frailty profile and a less strict supervision. In a meta-analysis of 9 cohorts from 8 observational studies worldwide, the relative risk of AKI was significantly reduced (HR 0.61, 95% CI 0.55−0.67, I^2 = 70%) in SGLT2i users (725 AKI events/68,802 patients) compared with non-users (treated with other glucose-lowering agents, including incretin-based compounds: 977 AKI events/67,458 patients). In conclusion, observational studies in real-world conditions confirm the results reported in placebo-controlled outcome trials and show a reduction in AKI episodes in patients with type 2 diabetes treated with SGLT2is compared with those treated with other glucose-lowering agents. Overall, the renal safety of SGLT2is should be acknowledged by physicians, even if dehydration should be avoided.

Introduction

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) have been associated with both positive and negative effects on renal function. On the one hand, it is increasingly recognized that SGLT2is can exert remarkable nephroprotective effects among at risk patients because of the presence of type 2 diabetes, atherosclerotic cardiovascular disease, heart failure and/or chronic kidney disease (CKD) [1,2]. The primary renal outcome (a composite of sustained loss of estimated glomerular filtration rate or doubling of serum creatinine, end-stage renal disease or renal death) was significantly reduced by around 35−45% in almost all large prospective placebo-controlled randomized trials published so far as summarized in different meta-analyses [3−6]. However, SGLT2is have been associated with the occurrence of acute kidney injury (AKI) events described in several case reports [7−11]. AKI episodes are associated with a higher cardiovascular risk [12,13] and also with a greater risk of later chronic deterioration of kidney function [13,14]. The US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) in 2016 has collected over 100 cases of AKI for canagliflozin and dapagliflozin since their approval. The proportion of reports with AKI among reports with SGLT2is was almost three-fold higher compared to reports without these drugs (relative odds ratio 2.88, 95% CI 2.71−3.05, $p < 0.001$) [15]. In 2016, the FDA warned of the risk of AKI for canagliflozin and dapagliflozin [16] and required that AKI be listed as a potential side effect of SGLT2is along with cautious prescription of these drugs with other medications, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics, and non-steroidal anti-inflammatory drugs [17]. Of note, more reassuring data were recorded in the Japanese Adverse Drug Event Report database (JADER) (4322 adverse events of interest that involved SGLT2is between April 2014 and February 2019); indeed, the reporting odds ratio for SGLT2is versus other glucose-lowering drugs was calculated as 1.0 (95% CI 0.9−1.2) for acute renal failure [18].

Data collected in cardiovascular and renal outcome studies with different SGLT2is (canagliflozin, dapagliflozin, empagliflozin) were reassuring with no increase (on the contrary, a decrease), in the

Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.deman.2021.100021

incidence rate of AKI in patients treated with a SGLT2i compared with those treated with a placebo. This has been emphasized in several meta-analyses that reported statistically significant 25 to 35% reductions in AKI events in patients treated with SGLT2is compared to placebo [19–21]. However, some cardiovascular findings suggest that results from current randomized controlled trials (RCTs) may be less applicable to real-world patients and that further studies are required to support the concept of real-world cardiovascular event protection through SGLT2is [22]. As patients recruited in clinical trials are different compared to those treated in real-life and patients in clinical practice are exposed to a potential higher risk of AKI because of older age, presence of co-medications, less careful supervision and presence of other illnesses [23], it is of interest to compare the incidence of AKI adverse events in real-world conditions, including in a more frailty population.

The aim of this concise review is to summarize the effects of SGLT2is on the risk of AKI in large observational retrospective studies that compared SGLT2i users versus non users treated with other glucose-lowering agents and were carried out in different countries, on various populations, and with different SGLT2is.

AKI in observational studies

We identified eight retrospective studies (one with two cohorts) that compared the risk of AKI in patients treated with SGLT2is compared to different active comparators: metformin, dipeptidyl peptidase-4(DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, any other glucose-lowering drug. They were carried out in different countries, in Europe, North America and Asia. Most of them used the propensity-score matching to compare the two groups. The numbers of patients included in each group ranged from less than 1000 to around 20,000 across studies and the follow-up was also highly variable from 90 days to over 450 days [24–32]. The definition of AKI differed between studies. Some Authors used usual ICD ("International Classification of Diseases") score to define hospitalization for AKI (yet, with some differences between scores considered across studies: ICD-9 and/or ICD-10). Others used the definition recommended by the KDIGO (for "Kidney Disease: Improving Global Outcomes") 2012 guidelines based on laboratory data (increase in serum creatinine by > 0.3 mg/dL within 48 h or increase in serum creatinine by >1.5 times baseline value) [33]. (Table 1). Results are expressed as hazard ratio, odds ratio or risk ratio depending on the considered study. Overall, there was a reduction in the risk of developing AKI among SGLT2i users versus non-users (all mean values < 1), but with a large range between 0.4 and 0.94. When considering the 95% CI, the reduction was statistically significant in 5 studies, non-significant in 3 studies and unknown in 1 study (Table 1).

In a meta-analysis of 9 cohorts from 8 observational studies worldwide (North America, Europe, Asia), the relative risk of AKI was significantly reduced (HR 0.61, 95% CI 0.55–0.67, $p < 0.0001$) in SGLT2i users (725 AKI events/68,802 patients) compared with non-users (treated with other glucose-lowering agents, including incretin-based compounds: 977 AKI events/67,458 patients), yet with a cetain degree of between-study heterogeneity ($I^2 = 70\%$) (Fig. 1).

Two large-scale observational studies, the multinational CVD-REAL 3 [34] and a Scandinavian study [35] reported a significant reduction in serious adverse events among SGLT2 users versus non-users, but unfortunately did not specifically reports AKI episodes [36], and thus their results could not be incorporated in the meta-analysis.

Discussion

Published results of observational studies show that the incidence of AKI episodes is not increased but rather numerically decreased (and significantly in over half of the 9 studies). These

Table 1
Summary of observational studies that compared the risk of AKI in SGLT2i users versus non-users. All SGLT2is were considered except in Lin et al. 2019 who specifically evaluated dapagliflozin and empagliflozin.

Reference	Country	Comparator	Follow-up	AKI definition	N patients SGLT2i vs comparator	N AKI events SGT2i vs comparator	Relative risk (*)
Nadkarni et al. 2017 [28]	United States (2 cohorts)	oGLDs	450 days 14 months	KDIGO 2012 definition	1207 vs 1207	26 vs 55	0.5 (0.3–0.8)
					372 vs 372	14 vs 36	0.4 (0.2–0.7)
Ueda et al. 2018 [30]	Sweden Danemark	GLP-1 RAs	270 days	AKI according to ICD-10 code	17,213 vs 17,213	34 vs 62	0.69 (0.45–1.05)
Cahn et al. 2019 [31]	Israel	DPP-4is	24 weeks	Hospitalization for AKI according to ICD-9 code	6418 vs 5604	23 vs 78	0.26 (0.16–0.42)
Lin et al. 2019 [29]	Taiwan	oGLDs	18 months	Hospitalization for AKI according to ICD-10 code	7624 vs 7624	77 vs 129	0.65 (0.49–0.86)
Iskander et al. 2020 [27]	Canada	DPP-4is	90 days	KDIGO 2012 definition	19,611 vs 19,775	216 vs 275	0.79 (0.64–0.98)
Rampersad et al. 2020 [26]	Canada	oGDLs	0.9 vs 0.7 years	Hospitalization for AKI according to ICD-10 or 9 code or KDIGO 2012 definition	4778 vs 4778	47 vs 70	0.64 (0.40–1.03)
Shen et al. 2021 [25]	China	DPP-4is	90 days	KDIGO 2012 definition	1615 vs 921	254 vs 226	0.86 (NA)
Fralick et al. 2021 [24]	United States	Metformin	147 vs 213 days	Hospitalization for AKI according to ICD-10 or 9 code	9964 vs 9964	34 vs 46	0.94 (0.60–1.47)

AKI: acute kidney injury. DPP-4is: dipeptidyl peptidase-4 inhibitors. GLP-1 RAs: glucagon-like peptide-1 receptor agonists. oGDLs: other glucose-lowering drugs. NA: not available.
(*) Relative risk expressed by hazard ratio, odds ratio or risk ratio across studies.
ICD: International Classification of Diseases.
KDIGO (Kidney Disease: Improving Global Outcomes) 2012 definition: increase in serum creatinine by >0.3 mg/dL within 48 h or increase in serum creatinine by >1.5 times baseline value in the prior 7 days.

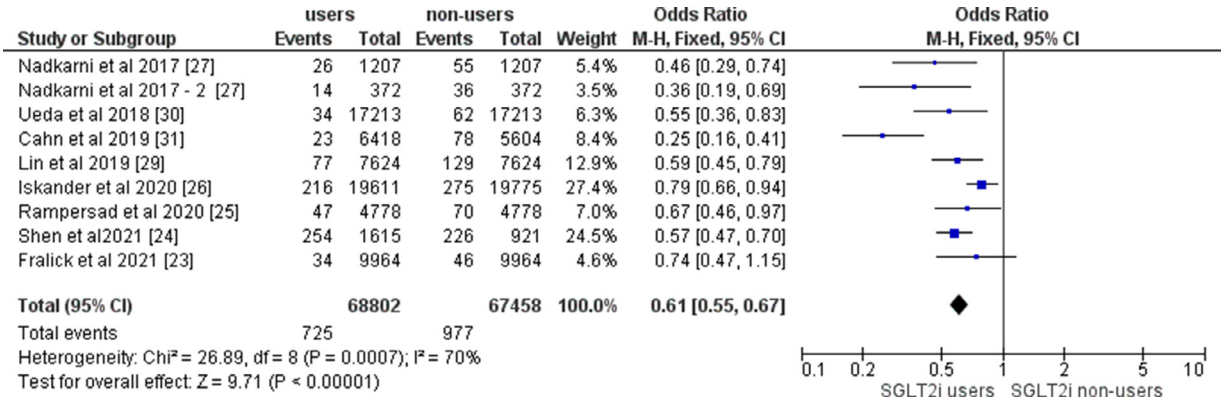

Fig. 1. Meta-analysis of observational studies (9 cohorts in 8 studies) that compared the risk of AKI in SGLT2i users versus non-users.

results are reassuring, after the FAERS alarming reports [15] and the warning published in 2016 by the US FDA [16]. It has been hypothesized [37] that the early onset of AKI events with SGLT2is in post marketing reports probably reflected the acute changes in estimated glomerular filtration rate attributable to the known renal haemodynamic effects of SGLT2 inhibition, to some extend close to those well known for RAAS inhibitors [38]. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting is challenging and exposed of potential reporting biases [39]. Of note, a re-examination of US FAERS data, combined with Japan observations, indicated that the signal of AKI with SGLT2is tends to be reduced in patients with the concomitant use of a RAAS inhibitor, yet a conclusion that requires further confirmation [40].

In a previous meta-analysis of 4 observational studies with 5 cohorts (n = 83,934), 777 AKI events were reported. The odds of suffering AKI were reduced in patients receiving SGLT2is (OR 0.40 [95% CI 0.33−0.48], $p < 0.001$). In another recent systematic review [41], a renal benefit of SGLT2i exposure was noticed in 4 cohorts from 3 observational studies published in 2017−2019 [28,30,31], although the confidence intervals were wide and all crossed unity, suggesting that these studies may be underpowered with a too short follow-up. Limitations of these retrospective observational studies are immortal time bias, the reliance on non-adjudicated safety endpoints, discrepant inclusion criteria and baseline glucose-lowering therapy between studies, varying follow-up times in different studies, and a lack of information on the severity of AKI [42].

The reduction in the risk of AKI among SGLT2i users observed in observational real-life studies appears to be rather similar as that previously reported in RCTs. In phase 3 RCTs that were published before cardiovascular and renal outcome trials, AKI episodes were reported in 10 trials (7 versus placebo and 3 versus an active comparator). The number of adverse events was very low in these trials and pooled estimate was non-significant (relative risk 0.48; 95% CI 0.14 −1.64) [43]. The number of AKI episodes was much greater in the prospective outcome trials because of a larger enrolled population and a longer follow-up. When considering the safety results with canagliflozin, dapagliflozin and empagliflozin in cardiovascular/renal outcome trials, several meta-analyses reported statistically significant 25 to 35% reductions in AKI events in patients treated with SGLT2is compared to placebo: hazard ratio 0.66 (95% confidence interval [CI] 0.54−0.80) [19], risk ratio 0.75; 95% CI 0.66−0.85) [20], hazard ratio 0.74; 95% CI 0.64−0.85 [21]. Post-hoc analyses of major outcome trials confirmed positive results with SGLT2is: in DECLARE-TIMI 58 when focusing on elderly patients (commonly recognized to be at higher risk of AKI) [44] and in the two landmark studies carried out in patients with CKD and albuminuria, CREDENCE with canagliflozin 100 mg [45] and DAPA-CKD with dapagliflozin 10 mg [46].

In a network meta-analysis of 18 trials with a total of 2051 AKI events (range: 1−300) among 156,690 patients with type 2 diabetes, SGLT2is were associated with a lower risk of AKI compared with placebo (OR 0.76; 95% CI, 0.66- 0.88), whereas both DPP-4 inhibitors and GLP-1 receptor agonists had neutral effects on risk of AKI. Even more interesting from a clinical point of view, SGLT2is were significantly associated with a lower risk in AKI than both DPP-4 inhibitors (OR 0.68; 95% CI 0.54−0.86). and GLP-1 receptor agonists (OR 0.79; 95% CI 0.65−0.97) [47].

In the warning by the FDA in 2016 regarding a possible increased risk of AKI with SGLT2is, caution was recommended about the combination with RAAS inhibitors [16]. RAAS inhibitors are recognized to be potentially associated with AKI, yet the degree of increased risk varies between patient groups depending on individual characteristics as shown in a population-based cohort study [48]. From a haemodynamic point of view, a combination of pre-glomerular arteriole constriction through SGLT2is and post-glomerular arteriole dilation under RAAS inhibition would be expected to cause an increased risk of AKI [49]. However, a large majority (> 75%) of patients recruited in the cardiovascular and renal outcome trials received RAAS inhibitors, yet a reduction rather than an increase in AKI events was reported in patients treated with an SGLT2i compared to those treated with a placebo [19−21]. Similarly, in the observational studies considered in the present meta-analysis, most patients receiving an SGLT2i were also treated with a RAAS inhibitor (range between 60.7% and 82.3%, except in two cohorts where the percentages were 25.5% and 43.7%). A subgroup analysis of data from the EMPA-REG OUTCOME trial by baseline background medications found a slightly increased risk of AKI in patients on RAAS inhibitors compared to patients not taking these drugs, but the risk of AKI with RAAS inhibitor use tended to be lower in patients also taking empagliflozin [50]. Thus, the combined therapy with SGLT2is and RAAS inhibitors appears safe from a renal point of view, at least in the absence of haemodynamic instability [51,52].

Despite almost 50 quantitative systematic reviews published on the safety of SGLT2is (a majority of them being of rather low methodological quality), clinicians are still left uncertain of the risks of important adverse effects [53,54]. Nevertheless, it is increasing obvious that none of the gliflozins were associated with a statistically significant increased risk of AKI [55]. This is an important message for the clinicians considering the diuretic effects of SGLT2is [56] and the increased risk of AKI reported with other diuretics [57], in particular when they were associated with RAAS inhibitors in patients potentially exposed to volume depletion [58]. One limitation of the published observational studies was the rather short (< 1 year, except 1-2 years in 3 studies) follow-up. However, in case reports of AKI, the adverse events occurred within the first few weeks-months after the initiation of SGLT2i therapy [7−11]. Another limitation is the use of

different definitions of AKI between studies [36], yet the results appear consistent what ever the definition used (Table 1).

Thus, as findings of observational studies confirm results of RCTs, the renal safety of SGLT2is regarding the risk of AKI is reassuring [59,60]. Furthermore, considering the overall safety of this pharmacological class, even in patients with mild to moderate CKD [61], combined with a potent nephroprotective effects in at risk patients [1,2], SGLT2is should be considered as a major breakthrough in the management of patients with type 2 diabetes, especially in those at risk of developing diabetic kidney disease [62,63], but also in non-diabetic individuals with renal disease [64].

Conclusion

Despite the warning published by the US FDA in 2016 about a potential risk of AKI when prescribing SGLT2is and the report of some clinical cases of AKI after the initiation of a gliflozin therapy, large observational real-life retrospective studies confirm the reassuring results reported in both phase 3 and cardiovasular/renal outcomes placebo-controlled trials. Overall, instead of increasing the risk of AKI, SGLT2is reduce such a risk in most instances. This does no exclude that AKI may occur among SGLT2i users in some particular circumstances, especially when dehydration is present, an adverse event that is also well known by physicians with RAAS inhibitors, generally being both preventable and treatable.

Disclosures

The Authors declare the following conflicts of interest in relation to the content of this article. P. Delanaye has received lecturer/advisor fees from AstraZeneca. A.J. Scheen has received lecturer/advisor fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme. He also worked as clinical investigator in three cardiovascular outcome trials with SGLT2is (EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58).

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