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Acute Kidney Injury with sodium-glucose linked cotransporter-2 inhibitors: a meta-analysis of cardiovascular outcome trials

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.13754

ABSTRACT

Three, multi-centre, large-scale, randomised, placebo-controlled trials of cardiovascular outcomes with sodium-glucose linked cotransporter-2 (SGLT2) inhibitors have each shown substantial reductions in hospitalisation for heart failure and progression of chronic kidney disease in patients with type 2 diabetes. However, safety concerns remain for this ostensibly paradigm-shifting drug class. In particular, the FDA has highlighted the risk of acute kidney injury (AKI), a condition associated with high morbidity and mortality. To investigate this further, we conducted a meta-analysis of the three trials to compare the frequency of AKI adverse event reports between patients treated with placebo and those who had received an SGLT2 inhibitor. Rather than an increase, we noted a consistent and robust reduction in the likelihood of AKI among those patients who had been randomised to receive an SGLT2 inhibitor (hazard ratio 0.66, 95% confidence intervals: 0.54 - 0.80). We further noted that the reports of AKI were similar in frequency to those of kidney disease progression. The caveats of the non-adjudicated reporting of AKI in the trials notwithstanding, these data suggest that SGLT2 inhibitors may protect vulnerable type 2 diabetic patients from AKI and that prospective studies to evaluate this additional aspect of kidney protection are warranted.

INTRODUCTON

In June 2016 the U.S. Food and Drug Administration (FDA) strengthened their warning regarding the risk of acute kidney injury (AKI) in patients with diabetes who were being treated with an SGLT2 inhibitor.[1] The announcement followed the reporting to the FDA of 101 confirmable cases of AKI from the approval of the first SGLT2 inhibitor, canagliflozin, in March 2013 up until October 2015. Ninety-six of the 101 patients required hospitalization, 22 were admitted to intensive care units and 15 required haemodialysis. And while the majority recovered, 11 were left with CKD and 4 died. Such adverse outcomes following AKI are largely consistent with data from other sources. In the SURDIAGENE Study, for instance, an episode of AKI was associated with an approximate 10-fold increase in death.[2]

The weight of the FDA's warnings were reinforced by the biological plausibility of SGLT2 inhibitor-mediated AKI. By inducing a glucosuric osmotic diuresis, this class of drug leads to volume contraction and a reduction in systemic blood pressure, both known risk factors for AKI. Beyond these systemic actions, however, SGLT2 inhibitors have been shown to also effect intra-renal haemodynamics. Most prominently, increased delivery of sodium to the distal nephron in the setting of SGLT2 inhibition leads to a reduction in glomerular hyperfiltration through tubuloglomerular feedback.

While this has been viewed as beneficial in the CKD setting, the attendant afferent arteriolar constriction leads to a diminution in postglomerular perfusion that should, in theory, increase the propensity of the tubule to ischaemic injury. Finally, as a consequence of both crystal-dependent and independent effects, the uricosuric action of SGLT2 inhibitors has also been proposed as a predisposing factor to AKI in the type 2 diabetes setting.[3]

While concerns over drug safety dominated discussion in the first years of SGLT2 inhibitor use, these have largely been supplanted by the positive effects seen in three large cardiovascular outcome trials (CVOTs). These trials, EMPA-REG Outcome,[4] CANVAS Program,[5] and DECLARE-TIMI 58[6] have not only shown reductions in hospitalisation for heart failure but have also convincingly demonstrated reductions in the rate of eGFR decline and in the proportion of patients reaching a composite kidney endpoint of a meaningful reduction in function (40% decrease in eGFR or doubling serum creatinine), end-stage kidney disease (ESKD) or renal death. The magnitude of the effect and its consistency across members of the drug class attest to the potential benefit of SGLT2 inhibitors in diabetic kidney disease. We are, however, reminded that while far less often the focus of attention, AKI is common, increasing in incidence and often deadly.[7,8] Given the possible offsetting of the benefits on CKD by the occurrence of AKI, we sought to examine the likelihood of the latter.

METHODS

Search strategy

Using the methods proposed in the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA),[9] this analysis focussed on the reports of AKI in all randomised, placebo-controlled CVOTs of SGLT2 inhibitors that had been conducted up until February, 2019. This search yielded findings that were identical to a recently published PRISMA-based meta-analysis of cardiovascular and renal outcomes up until September 2018,[10] yielding three trials: EMPA-REG Outcome,[11,12] CANVAS,[5,13] and DECLARE-TIMI 58.[6] The occurrence of AKI was reported as an adverse event in the publications of all three trials.

Data analysis

AKI was reported as an adverse event/serious adverse event at the discretion of study investigators using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term: acute kidney injury. Given the differences in the manner in which the frequency of AKI was reported in the various trials, the hazard ratio (HR) was chosen as the most appropriate estimate of treatment effect. The analysis was then performed on the logarithm of the HR, extracting the treatment effect estimate and standard error depending on what was reported in the trials, as detailed below.

DECLARE-TIMI 58 reported the HR and 95% confidence interval. Extraction proceeded by taking the logs of the HR and confidence limits. The standard error for the log-HR was then obtained by solving for s in the following formula which is derived from the standard confidence interval formula:

$$(\mathrm{UCL} - \mathrm{LCL}) = 2(1.96)s$$

The EMPA-REG OUTCOME trial reported the number of events and hazard (rate per 100 patient-years) for the treatment groups for each of two eGFR strata, <60 and ≥60 ml/min/1.73 m^2. These needed to be combined across strata and was done by estimating the patient years associated with each hazard. If ρ is the hazard, d is the number of events and T is the total patient years, the hazard can be estimated by the formula:

$$\rho = \frac{d}{T}$$

Thus, given the hazard and number of events, the patient years were estimated by solving for T in the preceding formula. Once the patient years were estimated for each stratum and treatment, number of events and the patient years could be summed across strata for each treatment group. The hazards for each group were then estimated using the same formula and subsequently the HR and log-HR so that if the

number of events in the active and placebo groups are represented by d_A and d_P respectively, the standard error for log-HR is estimated by the formula:

$$s = \sqrt{\frac{1}{d_A} + \frac{1}{d_P}}$$

The sponsor of the CANVAS study provided the actual numbers of events and patient-years at risk for the canagliflozin and placebo-treated groups (personal communication, George Capuano PhD, Janssen Research & Development, Raritan, NJ). Thus, the same formulae used with EMPA-REG OUTCOME were used with the CANVAS data to arrive at the necessary estimates.

The final analysis that employed a random-effect model was performed in R version 3.5.2 (2018-12-20)[14] with the metafor (Version: 2.0-0) package for conducting meta-analyses.[15]

RESULTS

Although the trials reported their findings using different measures, the frequency of AKI and CKD progression events were similar as was the magnitude of difference between SGLT2 inhibitor and placebo-treated groups (Table 1). Meta-analysis of the three major CVOTs with SGLT2 inhibitors showed an overall reduction in the risk of AKI with a HR of 0.66 (95% confidence intervals: 0.54 0.80, Figure 1). In two of the trials, DECLARE-TIMI 58 and EMPA-REG Outcome, the upper bound of the 95% confidence interval was less than 1. No heterogeneity was evident among the three trials.

DISCUSSION

In direct contrast to earlier concerns, this meta-analysis of three large placebo-controlled CVOTs shows a robust and consistent reduction in AKI across three members of the SGLT2 inhibitor class. The analysis further shows that across these trials, AKI events were similar in frequency to those associated with CKD progression.

The present analysis has several limitations. Most notably, AKI was reported as an adverse event and as such was not subject to the rigorous adjudication of the primary and secondary outcomes. Differences in the manner by which the data were reported in each of trials is also noteworthy. Counterbalancing these caveats, however, are the magnitude and consistency of the observed effect of SGLT2 inhibition in each of the trials.

When an unexpected and seemingly contradictory finding is discovered, biological plausibility and data from other sources may add weight to the possibility of the association being real rather than a chance occurrence.[16] Given the importance of ischemia as a pivotal pathogenetic factor in AKI, it is notable that 25 years ago Körner et al. [17] reported improvement in kidney oxygenation with the use of phlorizin, hypothesizing that with SGLT1/2 inhibition, the diminution in inward Na^+ transport would mean that less needed to be extruded. Unlike Na^+ entry in to the cell, its export is an

energy and O_2 consuming process undertaken predominantly by the cell's Na^+/K^+ ATPase.[17] Consistent with this, a more recent study have shown that animals treated with the SGLT2 inhibitor, dapagliflozin, are comparatively resistant to ischemia perfusion injury,[18] and that tubular cells exposed to an hypoxic environment were more to likely remain viable when co-incubated with this SGLT2 inhibitor. Reinforcing the role of a diminished requirement for Na^+/K^+ ATPase in the proximal tubule when SGLT-mediated inward Na^+ transported is inhibited, kidney cortex pO_2 was notably higher in animals that had received phlorizin.[19]

The reduction in AKI presented in the current meta-analysis of CVOTs is consistent with so-called, real world evidence. In a propensity matched analysis of two large health care databases in the U.S., the hazard ratio for AKI was approximately halved in SGLT2 inhibitor users compared with non-users.[20] Given the contrasting findings between meta-analyses of small, short-term primarily glucose-lowering efficacy studies and larger CVOTs, we did not consider the former in our analysis. This inconsistency between small glucose-lowering and large cardiovascular outcome trials was especially apparent with another class of glucose lowering drugs, the di-peptidyl peptidase inhibitor where the former showed highly favourable odds ratios for MACE, myocardial infarction, stroke and mortality[21] that were not seen in the much larger and longer CVOTs[22-24] Despite these caveats, two recent meta-analyses combined a series of

small trials along with EMPA-REG Outcome but did not include either DECLARE-TIMI 58 or the CANVAS Program. In the most recent of these, published in February 2019, Donnan et al. combined 7 small trials each with 0 to 3 AKI events with EMPA-REG Outcome, finding a significant reduction in AKI that was no longer apparent when the EMPA-REG Outcome trial was excluded.[25] The second of these, a Cochrane meta-analysis published in September 2018, concluded that SGLT2 inhibitors have little or no effect on the risk of acute kidney injury (AKI) in people with diabetes and CKD (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2).[26] Accordingly, the current meta-analysis, by focussing exclusively on all three large, long term cardiovascular outcome trials, EMPA-REG Outcome, DECLARE-TIMI 58 and the CANVAS Program, provides additional information regarding AKI risk in patients with type 2 diabetes.

In contrast to the intense focus on CKD and ESKD comparatively little attention has been paid to AKI despite its known association as an independent risk factor for cardiovascular disease, heart failure as well as subsequent higher rates of CKD, ESKD and death.[27] Indeed, review of the literature, however, suggests that CKD/ESKD and AKI are twin epidemics.[8] Not only are their incidences similar at 343/10^6 person-years and 295/10^6 person-years for ESKD and AKI, respectively but so are their mortality rates at 24% and >28.[8] Consistent with these epidemiological data, the present

analysis of CVOTs, also found similar frequencies for AKI and the chronic kidney composite outcome of substantial GFR loss, ESKD and kidney death in all three trials. Moreover, while rates of ESKD continue to rise at ~1%/ year, the trajectory for future AKI is much steeper at >7% year, likely reflecting a rise in invasive procedures, imaging, an ageing population and the increasing prevalence of diabetes, itself an independent risk factor for AKI.[28]

The present report highlights the differences in adverse events reporting in the clinical trial setting and those received by the FDA Adverse Event Reporting System (FAERS). The latter provides an important tool that may draw attention to safety concerns of a marketed product. However, as described on the its website, the FAERS has several limitations.[29] These include the fact that unlike the clinical trial setting, reports to FAERS are voluntary, do not require a causal relationship with the product to be established, and are likely be influenced by the time a product has been marketed.

In summary, this meta-analysis of CVOTs does not indicate an increase in AKI with SGLT2 inhibitors but the opposite and may, accordingly, allay some concerns that might have otherwise precluded the use of this drug class. The caveats of this non-adjudicated adverse event notwithstanding, the magnitude of the reduction, the consistency across three members of the drug class along with the incidence, morbidity

and mortality associated with AKI all suggest the need for a dedicated, randomized controlled trials of SGLT2 usage for its prevention in at-risk populations.

AUTHOR CONTRIBUTIONS

Both authors, RG and KT, conducted the literature search, drafted the figure, conceived and executed the study design, data collection, data analysis, data interpretation and writing. Both authors contributed equally.

FUNDING

Funding was provided by the Canada Research Chairs Fund and the St. Michael's Hospital Foundation.

REFERENCES

1. Administration USFaD. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). 2016. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM506772.pdf (accessed March 16, 2019 2019).

2. Monseu M, Gand E, Saulnier PJ, et al. Acute Kidney Injury Predicts Major Adverse Outcomes in Diabetes: Synergic Impact With Low Glomerular Filtration Rate and Albuminuria. Diabetes Care 2015; 38(12): 2333-40.

3. Hahn K, Ejaz AA, Kanbay M, Lanaspa MA, Johnson RJ. Acute kidney injury from SGLT2 inhibitors: potential mechanisms. Nat Rev Nephrol 2016; 12(12): 711-2.

4. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373(22): 2117-28.

5. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377(7): 644-57.

6. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2018.

7. Sawhney S, Fraser SD. Epidemiology of AKI: Utilizing Large Databases to Determine the Burden of AKI. Adv Chronic Kidney Dis 2017; 24(4): 194-204.

8. Hsu CY. Where is the epidemic in kidney disease? J Am Soc Nephrol 2010; 21(10): 1607-11.

9. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015; 162(11): 777-84.

10. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2018.

11. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015.

12. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016.

13. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. The lancet Diabetes & endocrinology 2018; 6(9): 691-704.

14. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2018. https://www.R-project.org/ (accessed March 19, 2019 2019).

15. Vechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 2010; 36: 1-48.

16. Gilbert RE. SGLT2 inhibitors: β blockers for the kidney? The lancet Diabetes & endocrinology 2016; 4(10): 814.

17. Korner A, Eklof AC, Celsi G, Aperia A. Increased renal metabolism in diabetes. Mechanism and functional implications. Diabetes 1994; 43(5): 629-33.

18. Chang Y, Choi H, Jeong J, et al. Dapagliflozin, SGLT2 Inhibitor, Attenuates Renal Ischemia-Reperfusion Injury. PLoS One 2016; 11(7): e0158810.

19. O'Neill J, Fasching A, Pihl L, Patinha D, Franzen S, Palm F. Acute SGLT inhibition normalizes O2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol 2015; 309(3): F227-34.

20. Nadkarni GN, Ferrandino R, Chang A, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care 2017.

21. Monami M, Ahren B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013; 15(2): 112-20.

22. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med 2013.

23. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular

and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 2019; 321(1): 69-79.

24. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2015; 373(3): 232-42.

25. Donnan JR, Grandy CA, Chibrikov E, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. BMJ Open 2019; 9(1): e022577.

26. Lo C, Toyama T, Wang Y, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. Cochrane Database Syst Rev 2018; 9: CD011798.

27. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012; 81(5): 442-8.

28. James MT, Grams ME, Woodward M, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. Am J Kidney Dis 2015; 66(4): 602-12.

29. FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). 2019. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm (accessed April 17, 2019).

Table 1. Frequency of AKI and CKD events in DECLARE, EMPA-REG Outcome and CANVAS Program cardiovascular outcome trials.

	SGLT2i	Placebo
DECLARE AKI	1.5 [e]	2.0 [e]
DECLARE CKD[a]	1.5 [e]	2.8 [e]
EMPA REG AKI (low GFR[b])	2.1 [e]	3.6 [e]
EMPA REG AKI (higher GFR[c])	0.5 [e]	0.9 [e]
EMPA REG CKD[d]	1.7 [e]	3.1 [e]
CANVAS AKI	3.0 [f]	4.1 [f]
CANVAS CKD[a]	5.5 [f]	9.0 [f]

[a] ⩾40% reduction in eGFR to <60 ml/min/1.73 m^2, ESRD or death from renal cause

[b] eGFR <60 ml/min/1.73 m^2

[c] eGFR ⩾60 ml/min/1.73 m^2

[d] doubling of serum creatinine accompanied by eGFR ⩽45 ml/min/1.73 m^2, ESRD or death from renal disease

[e] reported as % with event

[f] reported as number/1000 patient years

Figure 1. Meta-analysis of frequency of AKI events in three CVOTs with SGLT2 inhibitors.