Review Article

Risk of Acute Kidney Injury with Sodium-Glucose Cotransporter-2 Inhibitors in Elderly and Very Elderly Adults Compared to the General Adult Population

by Kenina E. Silvera, 2024 PharmD Candidate, Michael W. Nagy, PharmD, BCACP

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are used to treat type 2 diabetes mellitus (T2DM) by inhibiting the reabsorption of filtered glucose in the proximal convoluted tubules of the kidney, promoting urinary excretion of glucose. The five SGLT2 inhibitors approved by the FDA are: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin.[1] Some of these agents have additionally gained approval for the use in other disease states, including heart failure and chronic kidney disease (CKD).

Question

In the general adult population, elderly adults, and very elderly adults, what is the risk of acute kidney injury (AKI) with sodium-glucose cotransporter-2 (SGLT2) inhibitors versus placebo?

While these agents largely have shown long-term benefits of kidney protection, there has been controversy regarding the risk for AKI, which is defined by the Kidney Disease Improving Global Outcomes (KDIGO) guideline as an increase in serum creatinine (SCr) by ≥0.3 mg/dL within 48 hours, or an increase in SCr ≥1.5 times baseline presumed within 7 days.[2]

The concern for AKI rose after an increased number of reports to the FDA adverse event report system, with 101

TABLE 1. Published Meta-Analyses on the Association Between SGLT2 Inhibitors and the Risk of AKI Versus Placebo

Authors	Study Population	Baseline Age, Years	Studies Included in AKI Calculations	Patients Analyzed with AKI Results, n	Results on Risk of AKI, Ratio (95% CI)
Donnan et al.[7]	Patients with T2DM	NR	Bailey et al.[14] (2012) Bailey et al.[15] (2013) Cefalu et al.[16] Kohan et al.[17] Leiter et al.[18] Malodonado-Lutomirsky et al.[19] Softeland et al.[20] EMPA-REG Outcome[21]	10,651	RR 0.59 (0.39-0.89)
Gilbert et al.[8]	Patients with T2DM	NR	EMPA-REG Outcome[21] CANVAS[22] DECLARE-TIMI 58[23]	28,490	HR 0.66 (0.54-0.80)
Salah et al.[9]	Patients hospitalized with AHF or within 3 days of discharge with AHF	Mean: 69.9	SOLOIST-WHF[24] EMPULSE[25]	1,740	OR 0.76 (0.50-1.16)
Kaze et al.[10]	Patients with DKD	Median: 65.2	CANVAS[22] CREDENCE[26] EMPA-REG Outcome[21]	15,744	RR 0.85 (0.66-1.11)
Rigato et al.[11]	Elderly patients with T2DM	NR	DECLARE-TIMI 58*[23] DAPA-CKD[27] CREDENCE[26] Leiter et al.*[28] EMPA-REG Outcome*[21]	Age ≥ 65: 15,344 Age > 75: 1,819	Age ≥ 65: RR 0.73 (0.62-0.87) Age > 75: RR 0.59 (0.37-0.94)

*AKI = acute kidney injury, T2DM = type 2 diabetes mellitus, AHF = acute heart failure, DKD = diabetic kidney disease, NR = not reported, HR = hazard ratio, OR = odds ratio, RR = risk ratio, * = included in calculations for patients > 75*

confirmable cases from March 2013 to October 2015 regarding AKI following SGLT2 inhibitor initiation, some requiring hospitalization and dialysis.[3] About half of the cases occurred within 1 month of SGLT2 inhibitor initiation, with most patients improving with cessation of the agent. Some patients were dehydrated, hypotensive, or taking other agents that can have renal effects. Mechanistically, this concern for AKI is plausible, particularly due to the possibility for osmotic diuresis and volume depletion, which if not prevented have the potential to induce AKI. Additionally, increased sodium delivery to the macula densa leads to increased afferent arteriole constriction and decreased GFR, which could lead to renal ischemic injury.[4,5] While a modest eGFR "dip" of 3-5 mL/min/1.73 m^2 on average with initiation of an SGLT2 inhibitor is common, the class of agents has consistently demonstrated long-term renal protection, similar to that in renin-angiotensin-aldosterone-system inhibitors.[4,5] However, these potential mechanisms of AKI could be particularly concerning in elderly (≥65 years) and very elderly (≥75 years) patients, who are at a greater baseline risk of AKI due to physiologic changes in the aging kidney, use of concomitant nephrotoxic medications, and being more susceptible to volume depletion.[6]

Literature Review / Evidence Summary

A literature search was performed using PubMed with the following terms or their combinations: "acute kidney injury," "AKI," "SGLT2," "elderly," and "safety."

Four meta-analyses in the general adult population concluded no increased risk of AKI with SGLT2 inhibitors, with two meta-analyses concluding a decreased risk of AKI, which is shown in Table 1.[7-10] Though the meta-analysis by Donnan et al. showed a decreased risk of AKI (RR 0.59; 95% CI: 0.39-0.89), evidence for decreased risk is heavily weighted by the EMPA-REG Outcome trial, and the pooled estimate is considered non-significant with removal of this trial (RR 0.48; 95% CI: 0.14-1.64).[7] The meta-analysis by Gilbert et al. similarly showed a decreased risk of AKI, also including the EMPA-REG Outcome trial, though weighting of each trial was not reported.[8] Salah et al. analyzed safety outcomes of starting SGLT2 inhibitors in patients hospitalized with acute heart failure or within three days of discharge, with an average patient age of 70 years, showing no increased risk of AKI with SGLT2 inhibitors versus placebo (OR 0.76; 95% CI: 0.50-1.16).[9] This result in a population particularly vulnerable to AKI with an older average age further contributes to the safety profile of SGLT2 inhibitors.

Rigato et al. specifically analyzed the safety profile of SGLT2 inhibitors in elderly patients with T2DM, showing decreased risk of AKI with SGLT2 inhibitors in patients ≥65 years (RR 0.73; 95% CI: 0.62-0.87).[11] Adults older than age 75 accounted for < 10% of the meta-analysis population, with 1,819 patients older than 75 out of a total population of 19,986 patients. Though the three randomized controlled trials (RCTs) that reported rates of AKI for patients older than 75 individually showed no significant difference in rates of AKI between SGLT2 inhibitors and placebo, when pooled, a decreased risk of AKI with SGLT2 inhibitors was found (RR 0.59; 95% CI: 0.37-0.94).[11] The authors did note that RCTs typically do not stratify adverse effects by age, and the data obtained from supplement and post-hoc analysis was often incomplete and fragmented.[11] Notably, every meta-analysis was limited due to AKI in RCTs largely being reported as an adverse effect rather than a primary or secondary outcome. This means data on AKI may not have been systematically collected with variations in reporting between trials.

The 2023 American Diabetes Association Standards of Care in Diabetes guideline states that though there was initial concern for risk of AKI with SGLT2 inhibitors, this has not been found to be true in RCTs of patients with or without advanced kidney disease, regardless of use of diuretics or other medication that may reduce GFR.[12] The 2022 KDIGO Diabetes Management in CKD guideline states that despite the theoretical concern for AKI with SGLT2 inhibitors, clinical trials have shown a decreased incidence of AKI with SGLT2 inhibitor initiation.[13] However, in patients with tenuous volume status, the KDIGO guideline also states that it may be reasonable to reduce the dose of diuretics with SGLT2 inhibitor initiation out of an abundance of caution, with follow-up arranged to monitor. To prevent premature discontinuation of SGLT2 inhibitors, an acute decrease of less than 30% in eGFR should be tolerated. If there is a decline in eGFR of greater than 30%, volume status should be optimized, any other nephrotoxic agents should be discontinued, and alternative etiologies for AKI should be evaluated.[13]

Evidence-Based Answer

Despite earlier FDA warnings, SGLT2 inhibitors are not associated with an increased risk of AKI in adult, elderly, and very elderly populations (strength of recommendation = A, based on multiple, consistent, patient-oriented meta-analysis of high-quality studies). More data is needed to explore the potential for decreased risk of AKI with SGLT2 inhibitors, with rates of AKI studied as a primary or secondary outcome.

Kenina Silvera is a 2024 Doctor of Pharmacy Candidate at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Michael Nagy is an Assistant Professor at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI.

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