RESEARCH ARTICLE

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The Effect of Sodium–Glucose Co-Transporter-2 Inhibitors in Contrast-Induced Acute Kidney Injury: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Aims: Contrast-Induced Acute Kidney Injury (CI-AKI) is the third leading cause of hospital-acquired renal damage, associated with increased mortality and morbidity. Despite CI-AKI incidence decline, it remains a concern, especially during procedures like percutaneous coronary intervention, impacting the vulnerable elderly with compromised renal function. This study aimed at assessing the effect of Sodium–Glucose Transporter-2 Inhibitors in contrasting induced nephropathy.

Methods and Materials: Authors performed a systematic search of literature in Web of Science, Scopus, and PubMed with relevant keywords. Our eligibility criteria were defined based on the PICO framework. The pooled odds ratios were calculated using random effects model and Mantel-Haenszel method along with the 95% confidence intervals. For assessing the heterogeneity of the included studies, the I^2 (I square) test was used. R and RStudio were used for the statistical analysis.

Results: Overall, from 20 records, 5 studies were added for final analysis. Based on the pooled OR of the included studies, there was no significant association between exposure to SGLT2-type drugs and CI-AKI compared to the control groups [OR=0.86, 95%CI: 0.29 – 2.51, *p-value = 0.78*]. Based on the pooled mean eGFR of the included studies, there was a significant association between exposure to SGLT2-type drugs and lower levels of eGFR compared to the control groups [MD=-4.00, 95%CI: -7.75 – -0.24, *p-value = 0.04*].

Conclusion: In conclusion, we assessed the impact of Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) on Contrast-Induced Acute Kidney Injury (CI-AKI). No significant association between SGLT2i use and CI-AKI risk was found, but a notable link emerged between SGLT2-type drug exposure and lower Estimated Glomerular Filtration Rate (eGFR). Uncertainty persists on whether SGLT2i prevent or contribute to CI-AKI, with a suggestion to temporarily halt SGLT2i before contrast studies, particularly in certain patients.

Keywords: Contrast Induced Nephropathy, Kidney Injury, Sodium-Glucose Transporter-2 Inhibitors.

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INTRODUCTION

Contrast-Induced Acute Kidney Injury (CI-AKI) stands as the third most prevalent cause of hospital-acquired acute renal damage, linked to heightened mortality, morbidity, and enduring renal impairment. Diverse definitions of CI-AKI have been employed, contributing to variations in its reported incidence across studies. Recent standards, as per one study, define CI-AKI by criteria such as a serum creatinine increase of at least 0.3 mg/dL (or 26.5 mmol/L) within 48 hours post-contrast media exposure, a serum creatinine rise exceeding 1.5 times the baseline within 7 days following contrast administration, and a urinary volume below 0.5 mL/kg/h for at least 6 hours post-contrast exposure[1-3]. Acknowledging the limitations of serum creatinine, the KDIGO criteria have exhibited superior predictive value for long-term mortality and morbidity in individuals undergoing contrast media procedures[4-8]. Despite a decrease in CI-AKI incidence in recent decades, it remains a significant concern, particularly in patients undergoing procedures like percutaneous coronary intervention, especially in acute scenarios and the vulnerable elderly population with often compromised renal function. Diabetes mellitus is a significant contributor to the risk of contrast-induced acute kidney injury, with patients having diabetic nephropathy facing the greatest susceptibility to this complication. The latest approved categories of glucose-lowering drugs exhibit considerable advantages for renal health. Yet, it remains uncertain whether these medications could potentially decrease the occurrence of CI-AKI[9-13].

In this context, this review aimed to assess the most recent experimental and clinical studies investigating the beneficial effects of Sodium–Glucose Transporter-2 Inhibitors (SGLT2i) on contrast induced nephropathy and renal injury, focusing on their potential role in the prevention of CI-AKI.

MATERIALS & METHODS

This systematic review and meta-analysis study was conducted based on the Preferred Reporting Items for Systematic reviews And Meta-Analyses (PRISMA) guideline 2020[14].

Search strategy: Two authors performed a systematic search of literature in the following electronic databases: Web of Science, Scopus, and PubMed. No time limitation was defined and all English studies from the beginning until December 2023 were included. The relevant Medical Subject Heading (MeSH) terms and related keywords were used in combination to build the search strategy; ("Sodium-Glucose Transport Protein 2" OR "SGLT2") and ("Kidney injury" OR "Contrast Induced Nephropathy").

Eligibility criteria: Our eligibility criteria were defined based on the PICO framework: (P) Population: patients with diabetes mellitus. (I) use of SGLT2-inhibitor drugs. (C) CI-AKI and eGFR. (O) Not applicable. Those studies that did not include a control group, were grey literature, lacked individual data, or were not in English, were excluded.

Data extraction and outcome measures: A standardized Excel sheet was prepared for data extraction. Two independent authors performed the data extraction based on the aforementioned data extraction sheet. Disagreement between these two authors, regarding inclusion, exclusion or data extraction, was discussed and resolved by a third author. The data extraction sheet included the following study characteristics: first author's name, year of publication, country, study design, number of CI-AKI cases in the SGLT group, number CI-AKI cases in the control group, total number of cases in the SGLT group, total number of cases in the control group, mean/sd of eGFR in the SGLT group, and mean/sd of eGFR in the control group.

Data synthesis and Statistical Analysis: We used R (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio, Inc., Boston, MA) for the statistical analysis and creating the figures. The pooled odds ratios were calculated using random effects model and Mantel-Haenszel method along with the 95% confidence intervals. For assessing the heterogeneity of the included studies, the I^2 (I square) test was used. The Mantel-Haenszel method and random effects model was used for pooling the effect sizes. For testing the overall significance of the random model, z-test was performed Potential publication bias was graphically assessed by creating funnel plots for each of the aforementioned groups.

RESULTS

Our initial search retrieved 20 articles from PubMed, Scopus, and Web of Science, from which 4 duplicates were removed. After screening the title and abstract of 16 records, 10 full texts were retrieved, among which 5 studies **(Figure 1)** were included based on our eligibility criteria[15-19]. More detail regarding the study characteristics of the included studies is summarized in **(Table 1)**.

Based on the pooled OR of the included studies **(Figure 2)**, there was no significant association between exposure to SGLT2-type drugs and CI-AKI compared to the control groups [OR=0.86, 95%CI: 0.29 – 2.51, *p-value = 0.78*]. The heterogeneity of the included studies was graphically assessed by funnel plot **(Figure 3)**.

Based on the pooled mean eGFR of the included studies **(Figure 4)**, there was a significant association between exposure to SGLT2-type drugs and lower levels of eGFR compared to the control groups [MD=-4.00, 95%CI: -7.75 – -0.24, *p-value = 0.04*]. The heterogeneity of the included studies was graphically assessed by funnel plot **(Figure 5)**.

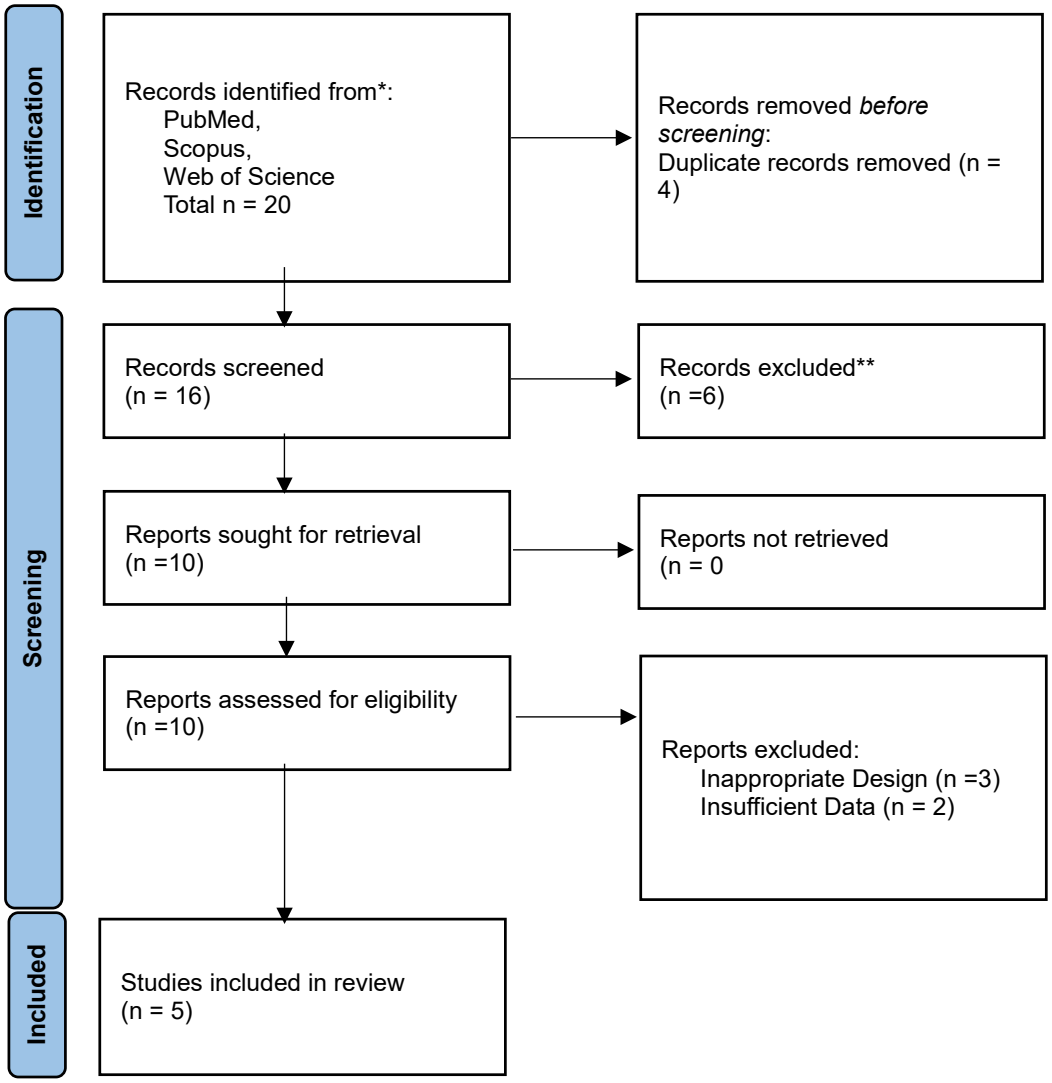

Figure 1: PRISMA flowchart of the included studies.

Table 1. Characteristics of the Included Studies.

				eGFR						CI-AKI			
Author	**Year**	**Design**	**Country**	**mean**	**SD**	**n**	**mean**	**SD**	**n**	**event**	**N**	**event**	**N**
Santos-Gallego et al.(19)	2020	Observational Retrospective Study	USA	75.1	23.3	52	78.9	21.1	52	-	-	-	-
Hua et al. (18)	2022	Case-Control Study	China	95.79	25.87	242	100.11	26.47	242	12	242	28	242
Feitosa et al. (17)	2023	Randomized Pilot Study	Brazil	62.1	22.5	22	68.2	17.7	20	3	22	2	20
Paolisso et al. (15)	2023	Rerospective Cohort Study	Italy	-	-	-	-	-	-	6	111	29	221
Ozkan et al. (16)	2023	Rerospective Cohort Study	Turkey	68.28	63.45	208	66.48	63.14	104	64	208	14	104

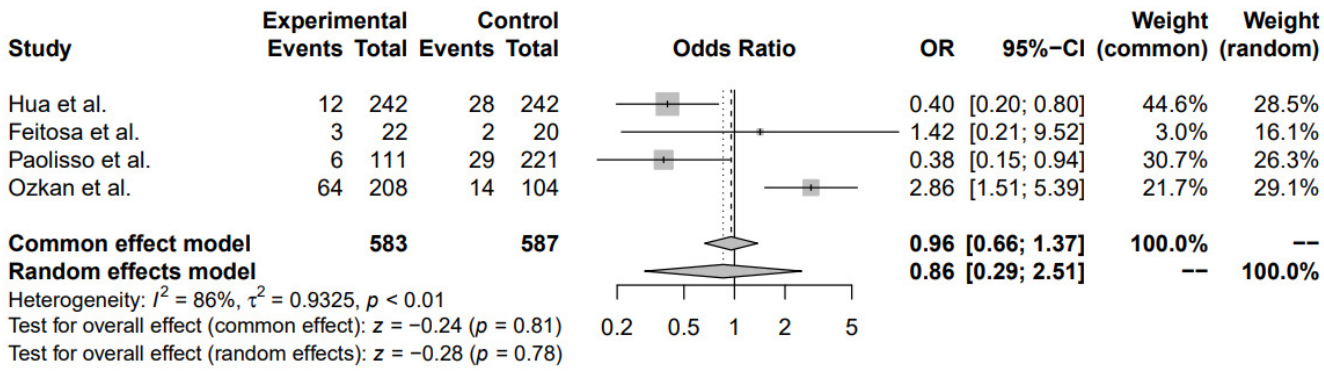

Figure 2: The forest plot of CI-AKI among the included studies.

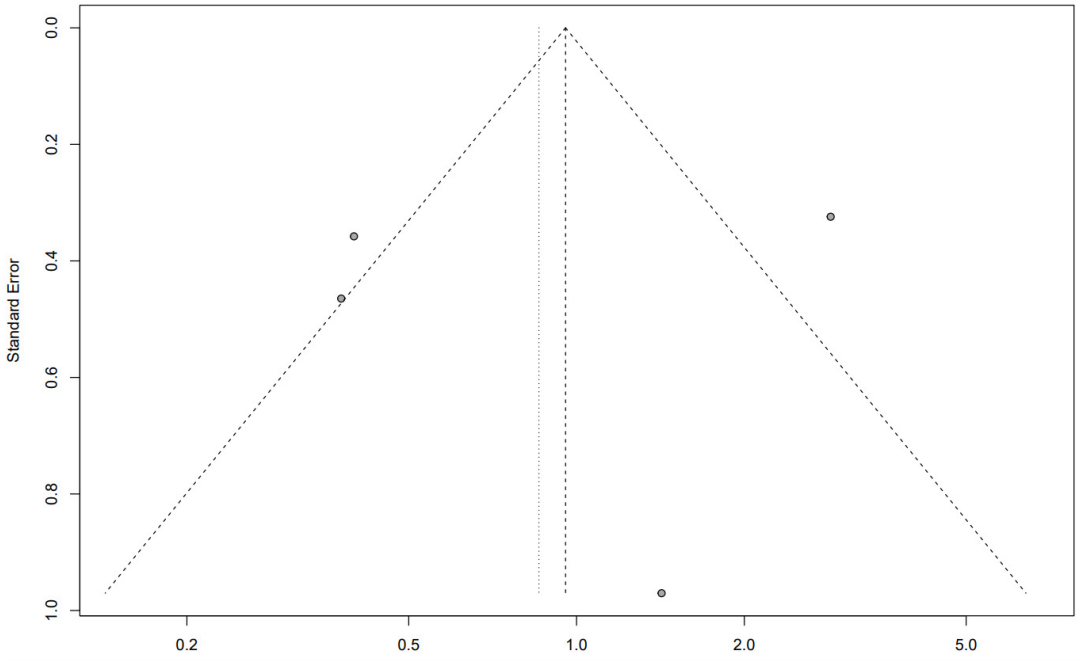

Figure 3: Funnel plot of CI-AKI assessment among the included studies.

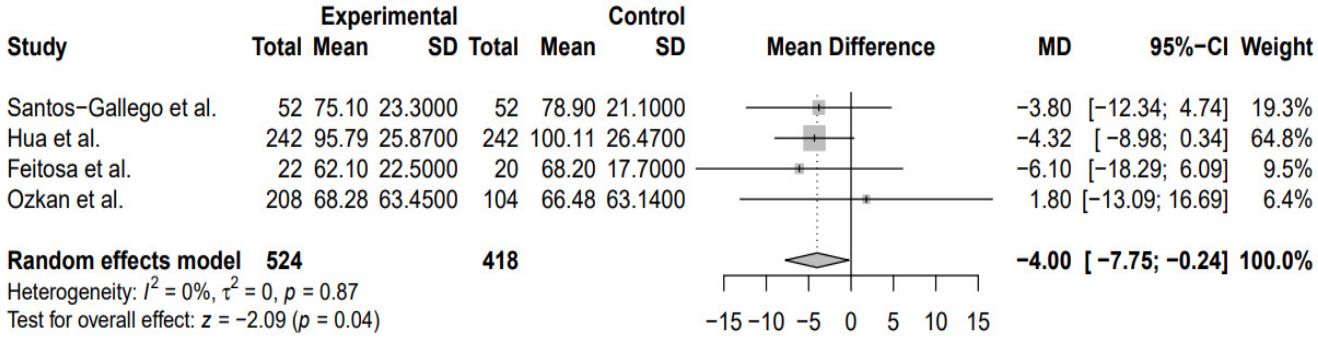

Figure 4: Funnel plot of eGFR assessment among the included studies.

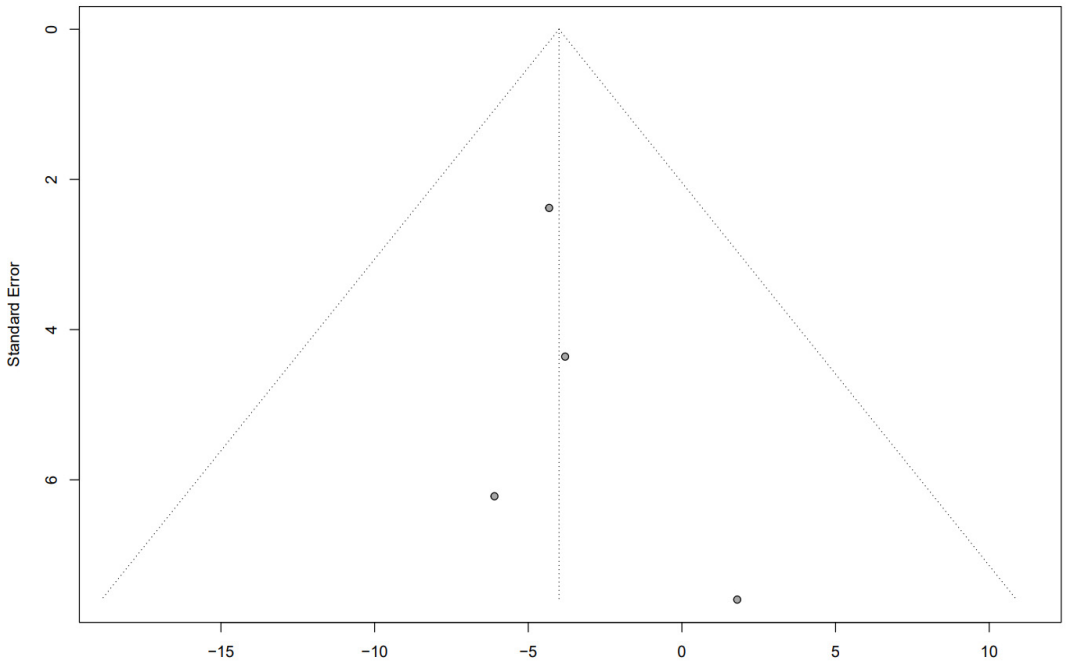

Figure 5: The forest plot of mean eGFR among the included studies.

DISCUSSION

Our systematic review and meta-analysis study was designed to assess the effect of SGLT2-inhibitor drugs on the Contrast Induced Nephropathy (CI-AKI). Based on the pooled results, the analysis of studies did not reveal a significant association between the use of SGLT2-inhibitor drugs and the risk of CI-AKI compared to control groups. However, a significant finding was a significant association between the exposure to SGLT2-type drugs and lower levels of Estimated Glomerular Filtration Rate (eGFR) compared to control groups.

The development of Contrast-Induced Acute Kidney Injury (CI-AKI) involves a range of pathophysiological mechanisms, with hemodynamic changes, inflammation, and oxidative stress playing crucial roles. These factors can be further exacerbated in the context of abnormal glycemic control. Acute hyperglycemia is linked to reduced endothelial-mediated vasodilation, exacerbating medullary hypoxia due to lower nitric oxide availability[7,20-22]. Additionally, it can trigger inflammation and the synthesis of reactive oxygen species, heightening the risk of contrast-induced injury in renal tubular cells. Notably, a diabetic condition, particularly abnormal glycemic values before Contrast Media (CM) administration, has been identified as a predictor of CI-AKI. In this context, SGLT2 inhibitors have the potential to mitigate this complication by optimizing glycemic control, thereby counteracting the adverse renal effects associated with chronic and acute hyperglycemia[23-25].

Moreover, contrast-induced acute kidney injury is commonly characterized by a sudden decline in renal function following the administration of iodinated contrast media. However, it is essential to recognize that, beyond contrast-induced hemodynamic abnormalities and cytotoxicity, the risk of acute kidney injury is significantly influenced by individual patient characteristics and the presence of concurrent contributing factors, such as underlying medical conditions and medications[8,26,27]. As a result, the term “contrast-associated” has been proposed as an alternative to “contrast-induced.” Among the various patient characteristics, baseline renal function is particularly crucial, as lower Estimated Glomerular Filtration Rate levels are associated with an increased risk of CI-AKI. SGLT2 inhibitors may have the potential to enhance renal outcomes and possibly delay the progression of chronic kidney disease in individuals with type 2 diabetes mellitus; thus, they could indirectly mitigate the risk of CI-AKI by improving baseline renal function in this patients[28-30]. Notably, most randomized and observational studies have not demonstrated an increased incidence of AKI associated with SGLT2 inhibitors, irrespective of the causative exposure[31-34].

Chronic Kidney Disease and heart failure pose significant health challenges globally, leading to substantial morbidity and mortality, despite the availability of pharmacological interventions. Originally designed as glucose-lowering agents, sodium-glucose co-transporter 2 inhibitors have demonstrated cardiovascular and renal benefits in patients with type 2 diabetes[35-37]. Subsequent dedicated trials aimed to assess the cardiovascular and kidney protective effects of SGLT2 inhibitors in individuals with CKD or heart failure. The outcomes of these trials and subsequent in-depth analyses have revealed consistent benefits across various patient subgroups. These advantages extend to individuals with or without type 2 diabetes, those at different CKD stages, and patients experiencing heart failure with preserved or reduced ejection fraction. Notably, post-hoc analyses have indicated that SGLT2 inhibitors can reduce the risk of anemia and hyperkalemia in CKD patients. In terms of safety, SGLT2 inhibitors are generally well tolerated, with no observed increased risk of hypoglycemia in patients with CKD or heart failure without diabetes. Importantly, these inhibitors do not elevate the risk of acute kidney injury. Consequently, SGLT2 inhibitors represent an exciting and novel therapeutic option for clinicians managing patients with CKD and heart failure[38-41].

On the contrary, the specific pharmacological impacts of SGLT2 inhibitors could potentially contribute to the occurrence of contrast-induced acute kidney injury. SGLT2i-induced osmotic diuresis and natriuretic may lead to intravascular volume depletion and dehydration, playing a significant role in this context[42-46]. Additionally, individuals taking SGLT2i are likely to use other drug classes, such as diuretics and ACE inhibitors, which may enhance the effects of volume depletion and renal vasculature. However, the combined effects of these factors have not been thoroughly investigated. In an experimental study conducted by Griffin et al., the concurrent administration of empagliflozin and intravenous bumetanide was associated with increased blood volume depletion. Interestingly, no elevated kidney damage was observed with this combination, and even a reduced release of urinary kidney injury molecule-1 was noted in patients receiving both SGLT2i and diuretics compared to those on diuretics alone. Similarly, in the DECLARE–TIMI 58 trial, AKI occurred less frequently with dapagliflozin, regardless of baseline blood pressure or diuretic use. In the DAPA-HF trial, the renal safety of SGLT2i was not compromised by concomitant high doses of diuretics, despite reports of higher volume depletion in patients receiving both agents and high-dose diuretics[47-51]. Consequently, mean creatinine values and the incidence of renal adverse events did not exhibit significant differences between patients on long-term dapagliflozin with and without diuretics. Moreover, several studies have investigated the potential synergistic effects of SGLT2i and ACE inhibitors/angiotensin receptor blockers in diabetic and non-diabetic nephropathy, without raising concerns about the safety of this combination for renal outcomes. A recent meta-analysis, encompassing large, randomized trials, reported greater efficacy in lowering composite kidney outcomes with the combination therapy of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACEi/ARB) and SGLT2i compared to

ACEi/ARB monotherapy in patients with type 2 diabetes. Notably, an experimental study has recently reported the SGLT2i-mediated down regulation of the renal expression of angiotensin II type-2 receptor in a rat model, potentially contributing to the Reno protective effects of SGLT2i in the context of concomitant use of ACEi/ARB[52-56].

In summary, the potential of Sodium-Glucose Co-Transporter 2 Inhibitors to either prevent or contribute to the development of Contrast-Induced Acute Kidney Injury remains uncertain, and there are several gaps in our current understanding of this topic. While the overall data on the risk of acute kidney injury is reassuring, some suggest temporarily discontinuing SGLT2i before undergoing radio contrast studies as a preventive measure for CI-AKI. However, this approach may be justified only in patients showing signs of volume contraction, sepsis, or active decompensating disease. Furthermore, parenchymal injury resulting from SGLT2i administration appears to be confined to tubular involvement, as indicated by specific urine biomarkers like neutrophil gelatinase–associated lipocalin or kidney injury molecule 1. Notably, these biomarkers have not been assessed as predictors of CI-AKI in patients using SGLT2i, prompting some authors to recommend their measurement to investigate the actual occurrence of hypoxic tubular injury in diabetic patients on SGLT2i. Ultimately, specific evidence-based guidelines are currently lacking, underscoring the urgent need for further research in this area.

CONCLUSION

Our systematic review and meta-analysis aimed to evaluate the impact of Sodium-Glucose Co-Transporter 2 Inhibitors on Contrast-Induced Acute Kidney Injury. The analysis did not reveal a significant association between SGLT2i use and CI-AKI risk compared to control groups. However, a notable finding was a significant association between exposure to SGLT2-type drugs and lower estimated glomerular filtration rate levels compared to control groups. The uncertainty regarding whether SGLT2i prevent or contribute to CI-AKI persists, with several knowledge gaps. Figure 3 outlines the potential renal and systemic effects of SGLT2i that may play a role in CI-AKI development. While overall data on AKI risk is reassuring, some suggest temporarily discontinuing SGLT2i before contrast studies as a preventive measure, particularly in patients with signs of volume contraction, sepsis, or active disease. Parenchymal injury from SGLT2i seems limited to tubular involvement, indicated by specific biomarkers. However, these biomarkers haven't been evaluated as CI-AKI predictors in SGLT2i users, prompting some to recommend their measurement for assessing hypoxic tubular injury in diabetic patients on SGLT2i. The lack of specific evidence-based guidelines underscores the urgent need for further research in this area.

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