# SGLT2 inhibitors and contrast-associated acute kidney injury

Richard Solomon

University of Vermont Larner College of Medicine, Burlington, Vermont, United States

***Related article***
by Kültürsay et al.

**Correspondence to:**
Richard Solomon, MD, FASN, FACP, University of Vermont Larner College of Medicine, UHC 2309, 1 South Prospect St, Burlington, VT 05401, United States, phone: +802 847 35 72, e-mail: richard.solomon@uvmhealth.org



DOI: 10.33963/v.kp.98717

**Received:**
December 20, 2023

**Accepted:**
December 22, 2023

**Early publication date:**
December 28, 2023

The association of increases in serum creatinine with the administration of iodinated contrast has been known for over 70 years. In that time, we have refined the definition of serum creatinine rises based upon the Kidney Disease: Improving Global Outcomes criteria, renamed the association from contrast-induced nephropathy to contrast-associated acute kidney injury (CA-AKI), learned much about the risk factors and predictors of CA-AKI, the pathogenesis of the condition, and increasingly appreciated the short and long-term consequences of CA-AKI. However, we have progressed little in the area of prevention despite a multiplicity of efforts involving devices, pharmaceuticals, and other physiologic maneuvers [1]. The search for a preventive measure is littered with unsuccessful attempts that had worked in animal models and early (Phase II) clinical trials. However, when applied to large prospective randomized multicenter phase III registration trials, the interventions fared no better than the control group. One might argue that over time, we got better at managing this adverse effect and thus the control groups did better, raising the bar for an effective intervention. This, however, does not seem to be the case as the incidence of CA-AKI has not changed that much in the past 2 decades. So we are left with the current American College of Cardiology/American Heart Association guidelines which simply recommend "adequate hydration" and limiting the amount of contrast administered, particularly in patients deemed to be at increased risk of CA-AKI due to underlying chronic kidney disease [2].

We are now beginning a new chapter in the prevention of CA-AKI. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed for treating hyperglycemia, have been found to exert long-term benefits in the cardiovascular and renal systems. The mechanism(s) of these benefits is complex and not completely understood but does not seem to depend on any reduction in glycemia. Indeed, this class of medications is no longer considered a specialty-specific therapy but is increasingly being marketed to cardiologists and nephrologists for patients without diabetes.

In this issue of *Polish Heart Journal*, Kultursay and colleagues [3] used an existing database of patients with diabetes who were admitted with STEMI. Some patients had been taking SGLT2 inhibitors (SGLT2i) for at least 6 months while others had not. They first compared the incidence of CA-AKI (a 25% increase in serum creatinine over 48–72 hours) and found it was ~50% lower in the group that had been taking SGLT2i (9% vs. 18%). Recognizing that there were likely many differences between those taking and those not taking SGLT2i that might influence whether they suffered from CA-AKI, the authors used statistical techniques involving propensity matching to adjust for those variables that were different between the groups — age, sex, baseline creatinine, use of RAAS inhibitors, diabetic drugs, such as metformin. Although the benefit diminished somewhat (OR, 0.86), a significant benefit in the SGLT2 takers was still observed.

Similar observations have been made from the SGLT2-I AMI PROTECT registry which included 652 non-insulin-taking diabetes patients admitted with acute myocardial infarction, some (n = 111) taking an SGLT2i for longer than 3 months and others (n = 535) not taking. The overall incidence of CA-AKI

was 11.2%, 5.4% in SGLT2i takers vs. 13.1% in non-takers ($P = 0.022$) [4]. In a follow-up analysis, the reduction in CA-AKI was seen in both those with and without CKD (OR, 0.356; $P = 0.038$) [5]. Similar results from a single center in China support the protective effect of SGLT2 on CA-AKI when using propensity matching to address potential confounders [6].

Potential mechanisms of benefit are beyond this editorial. Suffice it to say that all pathologic mechanisms thought to account for CA-AKI, including mitochondrial injury causing direct nephrotoxicity, vasoconstriction causing ischemia, and generation of reactive oxygen intermediates reducing NO levels, are all favorably affected by SGLT2i treatment in *in vitro* and animal studies [7].

How enthusiastic should we be about these observations? While there is no question that we need an effective prevention for CA-AKI, we are a long way from establishing a role for SGLT2i.

First, no matter how exhaustive the adjustment for confounding variables, such as with propensity matching, residual confounding cannot be eliminated. This is why, "evidence-based medicine" relies on prospective, randomized trials where the number of events and number of patients are high enough that one expects (hopes) the randomization process to adjust for all confounders.

Second, we have no data on the pharmacodynamics of this potential benefit. The patients described in the study had been on SGLT2i for a minimum of 6 months. There were variable doses observed. The other observational studies, likewise, included only patients on SGLT2i for months. Would there still be a benefit if the SGLT2i was given 30 minutes or even 24 hours before exposure to contrast? Is the benefit better at high dose vs. low dose of SGLT2i?

These are questions that will hopefully be answered by future prospective randomized trials. At least one such trial is underway using a single low dose of SGTL2i administered for 5 days before elective percutaneous coronary intervention or coronary angiogram in high-risk patients (NCT04806633).

In conclusion, the observational data presented in this article is potentially another feather in the cap of SGLT2i. The risk of acute kidney injury may indeed be diminished in those taking this class of medications. However, I would not interpret the data to suggest that administering an SGLT2i immediately before to exposure to contrast is beneficial. That is a very slippery path that has not been navigated successfully by many other interventions despite the best of intentions.

## *Article information*

**Conflict of interest:** None declared.

**Funding:** None.



## REFERENCES

1. Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol. 2014; 113(10): 1753–1764, doi: 10.1016/j.amjcard.2014.02.034, indexed in Pubmed: 24792742.
2. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022; 79(2): e21–e129, doi: 10.1016/j.jacc.2021.09.006, indexed in Pubmed: 34895950.
3. Kültürsay B, Yılmaz C, Güven B, et al. Potential renoprotective effect of SGLT2 inhibitors against contrast-induced AKI in diabetic STEMI patients undergoing primary PCI. Pol Heart J. 2024; 82(1): 29–36, doi: 10.33963/v.kp.98260, indexed in Pubmed: 38230461.
4. Paolisso P, Bergamaschi L, Gragnano F, et al. Outcomes in diabetic patients treated with SGLT2-Inhibitors with acute myocardial infarction undergoing PCI: The SGLT2-I AMI PROTECT Registry. Pharmacol Res. 2023; 187: 106597, doi: 10.1016/j.phrs.2022.106597, indexed in Pubmed: 36470546.
5. Paolisso P, Bergamaschi L, Cesaro A, et al. Impact of SGLT2-inhibitors on contrast-induced acute kidney injury in diabetic patients with acute myocardial infarction with and without chronic kidney disease: Insight from SGLT2-I AMI PROTECT registry. Diabetes Res Clin Pract. 2023; 202: 110766, doi: 10.1016/j.diabres.2023.110766, indexed in Pubmed: 37276980.
6. Hua R, Ding N, Guo H, et al. Contrast-induced acute kidney injury in patients on SGLT2 inhibitors undergoing percutaneous coronary interventions: a propensity-matched analysis. Front Cardiovasc Med. 2022; 9: 918167, doi: 10.3389/fcvm.2022.918167, indexed in Pubmed: 35795364.
7. Nusca A, Piccirillo F, Viscusi MM, et al. Contrast-induced acute kidney injury in diabetic patients and SGLT-2 inhibitors: A preventive opportunity or promoting element? J Cardiovasc Pharmacol. 2022; 80(5): 661–671, doi: 10.1097/FJC.0000000000001329, indexed in Pubmed: 35881892.