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Do Sodium-Glucose Cotransporter 2 Inhibitors Decrease the Risk of Contrast-Associated Acute Kidney Injury in Patients with Type II Diabetes Mellitus?

ABSTRACT

Background: The risk of contrast-associated acute kidney injury is relatively higher in patients with diabetes mellitus compared to non-diabetics. Recent trials have revealed the renoprotective effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors. We aimed to investigate the possible preventive effect of SGLT2 inhibitors against contrast-associated acute kidney injury in the diabetic population who underwent coronary angiography with a diagnosis of stable angina or acute coronary syndrome.

Methods: This was a cross-sectional and single-center study. We enrolled 345 patients with type II diabetes mellitus who were divided into 2 groups: using an SGLT2 inhibitor (group 1; n = 133) in addition to other antidiabetic medication and not using an SGLT2 inhibitor (group 2; n = 212). Both groups were compared in terms of contrast-associated acute kidney injury incidence. We also compared groups for the duration of hospitalization.

Results: Baseline characteristics (age, sex, risk factors and medications) and laboratory findings were similar between the 2 groups. The means of administered contrast volume were also similar (160.42 (± 70.31) mL vs. 158.72 (± 81.24) mL, P = 0.83) between groups 1 and 2, respectively. We found that contrast-associated acute kidney injury incidence was significantly higher in group 2 compared to group 1 (n = 56 (26.4%) vs. n = 12 (9.0%), P < 0.001). The duration of hospitalization was significantly longer in group 2 (3.25 (± 2.03) days) than in group 1 (2.54 (± 1.39) days) (P = 0.001).

Conclusion: We found that contrast-associated acute kidney injury was significantly lower, and the duration of hospitalization was significantly shorter in diabetic patients using SGLT2 inhibitors compared to non-users.

Keywords: Contrast-associated acute kidney injury, diabetes mellitus, SGLT2 inhibitor

ORIGINAL INVESTIGATION

INTRODUCTION

Contrast-associated acute kidney injury (CA-AKI) is a complication of angiographic procedures using intravascular iodinated contrast media (CM). Although CA-AKI is often regarded as a reversible event (in approximately 80% of cases), it portends a variety of short- and long-term adverse events, such as longer hospital stays and in-hospital mortality.[1,2] Contrast-associated acute kidney injury could also result in persistent worsening renal function or renal replacement therapy in a range between 0.7%-7%.[3] The risk of CA-AKI rises with particular baseline factors, such as preexisting renal impairment [estimated glomerular filtration rate (eGFR) <60 mL/min/m^2] and patients with renal transplant, heart failure with reduced ejection fraction (HFrEF), anemia or procedure-related blood loss, diabetes mellitus (DM), acute myocardial infarction, advanced age (>75 years), periprocedural hypotension, or use of an intra-aortic balloon pump. The risk of CA-AKI also rises with administration of a higher amount of CM.[4] An evidence-based approach is required for CA-AKI prevention, including hydration, administration of low/iso-osmolar CM, minimizing CM volume, pre-treatment with statins and *N*-acetylcysteine (with hydration), discontinuation of nephrotoxic drugs (such

Gizem Çabuk

Kutluhan Eren Hazır

Department of Cardiology, Tepecik Training and Research Hospital, İzmir, Türkiye

Corresponding author:
Gizem Çabuk
✉ giizemcelik@gmail.com

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as cisplatin, amphotericin, aminoglycosides, non-steroidal anti-inflammatory drugs) before CM exposure.[5]

As mentioned above, DM is accepted as a non-modifiable risk factor for CA-AKI development, particularly in patients with concomitant nephropathy. Diabetes itself may be the independent cause of CA-AKI after CM exposure by means of several mechanisms such as pronounced alterations in glomerular filtration rate (GFR), increased renal tubular transport and oxygen consumption, aggravation of medullary hypoxia, and enhanced generation of reactive oxygen species.[6]

Renoprotective effects of a new class of antidiabetic agents—sodium-glucose cotransporter 2 (SGLT2) inhibitors—have recently been demonstrated by several clinical trials.[7,8] Sodium-glucose cotransporter 2 inhibitors reduce composite renal outcomes (described as doubling of serum creatinine, development of macroalbuminuria, need for dialysis, and/or transplantation or kidney death) by 40%-70% in patients with type II DM.[7,8]

It is also known that patients who underwent urgent revascularization procedures due to acute coronary syndrome (ACS) have a higher risk for the development of CA-AKI compared to patients without ACS.[9] Our aim was to investigate the possible protective effect of SGLT2 inhibitors on the development of CA-AKI in a high-risk population with DM who underwent elective coronary angiography (CAG) and/or percutaneous coronary intervention (PCI) and patients with ACS who were treated medically or underwent PCI after CAG.

METHODS

Study Design

This was a cross-sectional and single-center study. This study was carried out in accordance with the conditions of the Declaration of Helsinki and approved by our local ethical committee. Informed consent was obtained from all participants.

Study Population

We enrolled patients with DM (type II DM) (n=345) who had refractory angina pectoris despite optimal medical therapy and a diagnosis of ACS between April 2022 and February 2023. Patients with type I DM and non-diabetic patients were excluded. We defined 2 study groups as patients who were using an SGLT2 inhibitor (empagliflozin or dapagliflozin) for at least 6 months, confirmed by electronic medical records, until the date of CAG (including the day of CAG) in addition to other anti-diabetic medication (group 1, n=133) and patients not using an SGLT2 inhibitor (group 2, n=212). We further divided these 2 groups into sub-groups: patients who underwent elective angiography with a diagnosis of stable angina and those who had urgent angiography due to ACS (Figure 1). All subjects were monitored throughout their hospital stay and observed for the occurrence of CA-AKI development for up to 72 hours.

Patients with a history of HFrEF (left ventricular EF < 40%), preprocedural eGFR <30 mL/min/m^2 and acute renal failure or end-stage renal failure requiring dialysis, CM exposure within 15 days, anemia (Hb <10g/dL), abnormal thyroid hormone levels, active infectious disease (including coronavirus disease 2019), cardiogenic shock and/or the use of an intra-aortic balloon pump, and excessive exposure to CM (>500 mL) during percutaneous intervention were excluded from the study. Pregnant patients, patients using nephrotoxic drugs (e.g., amphotericin, aminoglycosides, cisplatin, non-steroidal anti-inflammatory drugs, furosemide), or patients who underwent repeated CAG in-hospital (due to complications such as stent thrombosis or for the purpose of complete revascularization) and patients treated by coronary artery bypass grafting surgery were also excluded from the study.

Laboratory Measurements

Serum creatinine levels were measured by Jaffe assay (IDMS traceable calibration) with Beckman Coulter AU5800 (Beckman Coulter, Inc. Diagnostics Division Headquarters 250 South Kraemer Boulevard Brea, CA, USA) before angiography and after 48-72 hours. eGFR was calculated using the Levey-modified modification of diet in renal disease (MDRD) formula: (186.3 × serum creatinine [mg/dL]$^{-1.154}$ × age [years]$^{-0.203}$ × (0.742 if female).[10] Contrast-associated acute kidney injury was defined (which is widely accepted criteria in the literature) by an increase in serum creatinine of ≥0.5 mg/dL or an absolute increase of ≥25% from baseline 72 hours after CM exposure.

Coronary Angiography

All coronary angiography procedures were performed via the femoral/radial approach, and all patients received intravenous isotonic saline infusion (0.9% NaCl, 1.5 mL/kg/h) starting at the beginning of angiography and continuing for at least 12 hours after the procedure. Patients with ST elevation myocardial infarction (STEMI) were immediately taken to the catheter laboratory for PCI, while patients with non-STEMI (NSTEMI) or unstable angina pectoris underwent coronary angiography within 24 hours after admission according to recommendations of recent guidelines.[11] We used a non-ionic and low osmolality contrast agent (Optiray© [Ioversol]) and administered it manually to all patients, and the amount used was recorded at the end of each intervention.

Statistical Analysis

Statistical Package for Social Sciences 21.0 (SPSS, Chicago, Ill, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was applied to determine the normal

HIGHLIGHTS

- We found that contrast-associated acute kidney injury (CA-AKI) incidence was significantly lower in patients using an sodium-glucose cotransporter 2 (SGLT2) inhibitor compared to non-users.
- Another important finding of our study was the difference in duration of hospitalization in the study groups; it was significantly shorter in patients using an SGLT2 inhibitor.
- We think this study is going to strengthen the evidence of another renal-protective effect of SGLT2 inhibitors.

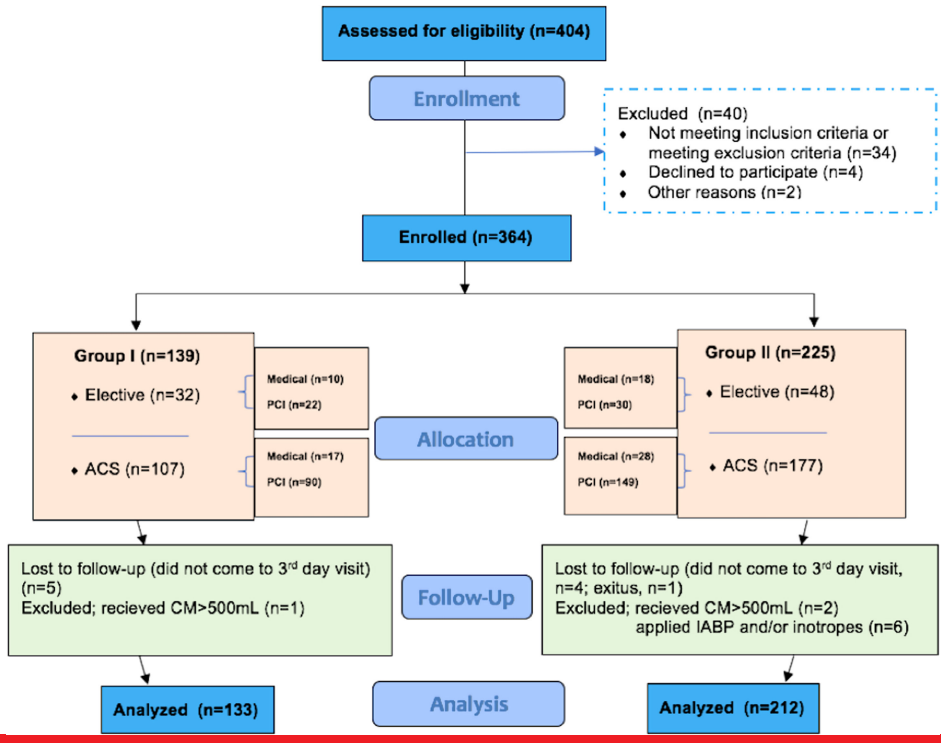

Figure 1. Consort flow diagram of the study. ACS, acute coronary syndrome; CM, contrast media; IABP, intra-aortic balloon pump.

distribution of variables. Categorical variables were demonstrated as number and percentage; continuous variables were demonstrated as mean (± SD) when normally distributed, while nonparametric variables were shown as median and the percentiles. Categorical variables were analyzed using the chi-square test or by Fisher's exact test, as appropriate. In order to minimize selection bias, we matched patients using SGLT2 inhibitors to control subjects by performing nearest neighbor propensity score matching algorithm. The Student's *t*-test was used to compare parameters which were normally distributed, while the Mann–Whitney *U*-test was used for non-normally distributed parameters. We tested the significance of the difference in creatinine and eGFR values before and after coronary angiography with Wilcoxon signed-rank test for both groups and subgroups. Possible confounders were controlled with binary logistic regression analysis, and we found the odds ratio of using an SGLT2 inhibitor adjusted for the other covariates (including confounders). All statistical testing was based on a 2-sided $\alpha = .05$ significance level.

RESULTS

A total of 345 patients with type II DM were included in this trial. Baseline characteristics [age: 61.68 ± 9.91 vs. 63.58 ± 9.85, female: (n = 50 (37.6%) vs. n = 81 (38.2%)), risk factors and medications] and laboratory findings (including baseline creatinine and eGFR values) were similar between the 2 groups (Table 1). Coronary angiography indications and the parameters related to the angiography procedure were shown in Table 2. While the majority of patients in both groups underwent percutaneous coronary intervention (108 of 133 patients (81.2%) in group 1 vs. 171 of 212 patients [80.7%] in group 2, $P = 1.00$), the remaining patients were managed medically after coronary angiography. The means of administered contrast volume were similar (158.72 ± 81.24 vs. 160.42 ± 70.3, $P = .83$) between groups 1 and 2, respectively.

In group 1, 61 patients (45.9%) were using dapagliflozin, and 72 patients (54.1%) were using empagliflozin. We found that CA-AKI incidence was significantly higher in group 2 compared to group 1 (n = 56 [26.4%] vs. n = 12 [9.0%], $P < .001$) (Table 3). The number of CA-AKI cases in group 2 using empagliflozin was 7 and it was 5 for patients using dapagliflozin; however, this finding could be coincidental due to the limited number of patients and endpoints. Therefore, we did not perform a statistical analysis for this finding, and we could not speculate on a difference in terms of prevention from CA-AKI between these 2 molecules.

We also analyzed creatinine and eGFR values before and after coronary angiography for both groups. While these 2 parameters significantly changed in group 2, they did not change significantly in group 1 (Table 3).

In group 2, 3 patients died in-hospital (one of them received dialysis) and 3 other patients needed dialysis due to contrast nephropathy (their renal functions recovered in-hospital). In group 1, none of the patients needed dialysis and we did not observe any mortality. Another important finding of our study was the difference in duration of hospitalization between the study groups: It was significantly longer in group 2 (3.25 ± 2.03 days) than in group 1 (2.54 ± 1.39 days) ($P = .001$) (Table 2).

Table 1. Baseline Characteristics of Study Population

Parameter	Group 1 (n = 133)	Group 2 (n = 212)	P
Age, years	61.68 (± 9.91)	63.58 (±9.85)	.08
Sex (female), n,%	50 (37.6)	81 (38.2)	.92
BMI, kg/m^2	23.56 (20.12-28.34)	24.13 (20.33-29.45)	.77
Hypertension, n,%	95 (71.4)	151 (71.2)	.98
Glucose, mg/dL	187.99 (±64.51)	200.09 (±85.23)	.16
Urea, mg/dL	39.52 (±12.27)	41.56 (±19.60)	.28
Creatinine, mg/dL	1.00 (0.90-1.10)	1.00 (0.85-1.10)	.06
eGFR, mL/min/1.73 m^2	71.44 (57.04-86.22)	66.08 (52.23-84.16)	.14
Hemoglobin, g/dL	13.62 (±1.77)	13.38 (±1.44)	.18
WBC, ×10^9/L	11.52 (±2.98)	10.33 (±3.58)	.61
Platelet, ×10^3/µL	249.93 (±72.00)	258.87 (±79.31)	.29
Total cholesterol, mg/dL	192.64 (±65.26)	200.22 (±71.25)	.22
LDL, mg/dL	121.70 (±42.31)	116.21 (±42.13)	.26
HDL, mg/dL	41.62 (±9.46)	41.74 (±11.86)	.92
Triglyceride, mg/dL	188.63 (±130.41)	174.86 (±147.68)	.39
HbA1c, %	7.65 (±2.47)	7.71 (±2.68)	.12
LVEF, %	48.38 (±10.56)	48.42 (±10.30)	.96
Medications, n (%)			
ACE inhibitor	61 (45.9)	81 (38.2)	.16
ARB	23 (17.3)	39 (18.5)	.78
Beta blocker	70 (52.6)	106 (50.0)	.63
Calcium canal blocker	23 (17.3)	52 (24.5)	.09
Diuretic	38 (28.6)	53 (25.0)	.46
Statins	51 (38.3)	77 (36.3)	.70
Metformin	82 (61.7)	133 (62.7)	.46
Insulin	39 (29.3)	67 (31.6)	.65
Thiazolidinedion	14 (10.5)	25 (11.8)	.71
Sulfonilurea	23 (17.3)	44 (20.8)	.43
DPP4 inh	63 (47.4)	83 (49.2)	.13
Dapagliflozin	-	61 (45.9)	-
Empagliflozin	-	72 (54.1)	-

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DPP4, dipeptidyl-peptidase 4; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c, HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction, WBC; white blood cell.

Table 2. Angiography Indications, Parameters Related to Angiography, and the Duration of Hospitalization in the Study Groups

	Group 1 (n = 133)	Group 2 (n = 212)	P
Angiography indication, n (%)			
Elective	27 (20.3)	44 (20.8)	.88
USAP	18 (13.5)	35 (16.5)	.67
NSTEMI	31 (23.3)	57 (26.9)	.16
STEMI	57 (42.9)	76 (35.8)	.06
PCI	108 (81.2)	171 (80.7)	.90
Contrast volume, mL	158.72 (±81.24)	160.42 (±70.31)	.83
Duration of hospitalization, day	3.25 (±2.03)	2.54 (±1.39)	<.001*

*Indicates statistical significance. NSTEMI, non-ST elevated myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevated myocardial infarction; USAP, unstable angina pectoris.

Table 3. Comparison of Renal Functions and Contrast-Associated Acute Kidney Injury Incidences of Study Groups

	Creatinine (basal), mg/dL	Creatinine (48-72 hours), mg/dL	P
Group 1 (n = 133)	1.00 (0.90-1.10)	1.00 (0.90-1.15)	.23
Group 2 (n = 212)	1.00 (0.85-1.10)	1.15 (0.90-1.40)	**<.001***
	eGFR (basal), mL/min/1.73 m^2	**eGFR (48-72 h),** mL/min/1.73 m^2	
Group 1 (n = 133)	71.44 (57.04-86.22)	69.39 (61.31-77.51)	.92
Group 2 (n = 212)	66.08 (52.23-84.16)	61.15 (44.59-75.96)	**<.001***
CA-AKI, n%	Group 1 (n = 133) 12 (9.0)	Group 2 (n = 212) 56 (26.4)	<.001*

*Indicates statistical significance. CA-AKI, contrast-associated acute kidney injury; eGFR, estimated glomerular filtration rate.

We also analyzed results separately according to CAG indication and baseline left ventricular ejection fraction (LVEF). We found that CA-AKI incidence was similar between the 2 groups in patients who underwent elective angiography; whereas it was significantly higher in group 2 compared to group 1 in patients with ACS (Table 4). When the results were analyzed according to LVEF, CA-AKI incidences were higher in group 2 compared to group 1 for both patient groups with normal baseline LV systolic functions (LVEF ≥ 50%) and with reduced or mildly reduced (LVEF < 50%) baseline LV systolic functions (Table 4). We also took into account all possible confounders for all subgroup analyses and compared baseline characteristics such as age, sex, basal creatinine and hemoglobin levels, amount of CM, left ventricular ejection fraction, hypertension, and basal eGFR. After adjustment of these variables, we found the predictive value of using an SGLT2 inhibitor for prevention of CA-AKI [OR 0.376; (0.172-0.598, 95% CI), $P = .022$] (Table 5). We also performed a subgroup analysis for patients with eGFR <60 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2 separately. While CA-AKI incidence was significantly lower in group 1 in patients with low eGFR (2 of 36 patients in group 1 [5.6%] vs. 29 of 77 patients in group 2 [37.7%], $P < .001$); P-value was equivalent to the level of significance for patients with eGFR ≥60 mL/min/1.73 m^2 (8 of 97 patients in group 1 [8.2%] vs. 27 of 135 patients in group 2 [20.0%], $P = .05$).

DISCUSSION

We found that the incidence of CA-AKI incidence was significantly lower in patients with DM using SGLT2 inhibitors than in those not using this medication. This finding might suggest a new renoprotective effect of SGLT2 inhibitors, as several

Table 4. Contrast-Associated Acute Kidney Injury Incidences According to Coronary Angiography Indication and Baseline Left Ventricular Ejection Fraction

	Group 1 CA-AKI Incidence, n (%)	Group 2 CA-AKI Incidence, n (%)	*P*
CAG indication			
Elective (group 1, n = 27) (group 2, n = 44)	2 (7.4)	9 (20.5)	.14
Acute coronary syndrome (group 1, n = 106) (group 2, n = 168)	10 (9.4)	47 (28.0)	**<0.001***
LVEF			
LVEF < 50% (group 1, n = 60) (group 2, n = 93)	10 (16.7)	33 (35.5)	**0.01***
LVEF ≥ 50% (group 1, n = 73) (group 2, n = 119)	2 (2.7)	23 (19.3)	0.001*

*Indicates statistical significance. CAG, coronary angiography; CA-AKI, contrast-associated acute kidney injury; LVEF, left ventricular ejection fraction.

recent trials have revealed. The renoprotective effects such as renal outcomes of SGLT2 inhibitors have already been demonstrated in patients with heart failure, DM (± nephropathy), or coronary heart disease by recent randomized controlled trials.[12-14]

Growing evidence indicating favorable cardiovascular and renal outcomes with SGLT2 inhibitors has sparked particular interest among scientists. Multifactorial mechanisms have been described in the literature to explain the renal protective effects of SGLT2 inhibitors: (a) reducing proximal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula densa which activates tubulo-glomerular feedback and leads to efferent arteriolar vasodilation and decreasing glomerular hyperfiltration; (b) it is a well-known fact that the reabsorption of electrolyte and organic solutes in the proximal tubule requires much energy.[15,16] Therefore, the proximal tubule is responsible for the largest amount of oxygen consumption in the kidney. Because of increased SGLT-2 expression in patients with DM, glucose and sodium reabsorption increase as well as the oxygen demand of tubular cells. Therefore, the proximal tubule is susceptible to hypoxia in patients with DM. Sodium-glucose cotransporter 2 inhibition reduces sodium and glucose reabsorption in the proximal tubule, thereby reducing the workload for proximal tubular cells as well as hypoxia. These could lead to improved tubular cell structural integrity and function, c) Other effects of SGLT2 inhibitors such as reducing arterial stiffness and serum uric acid levels, regulating the systemic and renal neurohormonal systems, anti-inflammatory, antifibrotic effects, and reducing oxidative stress may also slow down the progression of renal disease.[17-22]

Table 5. Binary Logistic Regression Analysis Results

		95% CI OR		
Variables	**OR**	**Lower**	**Upper**	***P***
Age	1.050	1.013	1.088	.008*
Sex	0.782	0.544	1.023	.060
Basal creatinine	0.871	0.71	1.23	.071
Basal eGFR	1.040	1.002	1.079	.039*
Hemoglobin	1.270	1.027	1.571	.026*
Amount of CM	1.006	1.002	1.011	.002*
LVEF	0.963	0.936	0.991	.010*
Hypertension	1.050	1.013	1.088	.008
Using an SGLT2 inhibitor	0.376	0.172	0.598	**.022***

*Indicates statistical significance.
CM, contrast medium; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio, SGLT2; sodium-glucose cotransporter 2.

Several pathogenetic factors have been found to be related to the development of CA-AKI. These include increased secretion of vasoactive amines (such as angiotensin, endothelin, etc.) after contrast exposure, which may be responsible for reduced nitric oxide synthesis, enhanced oxidative stress, and the secretion of proinflammatory cytokines. Interstitial inflammation due to complementary system activation and tubular obstruction have been proposed as underlying mechanisms for the development of CA-AKI.[23] Furthermore, the upregulation of SGLT2 in the proximal renal tubules due to hyperglycemia and hyperinsulinemia is well-known in patients with DM. Enhanced action of SGLT2 has been found to be linked to enhanced oxidative stress, mitochondrial dysfunction, and inflammation even without hyperglisemia.[24] Therefore, these deleterious effects, which may contribute to the development of CA-AKI, could be mitigated by SGLT2 inhibitors. We enrolled patients who had been using an SGLT2 inhibitor for at least 6 months (excluding patients who started using an SGLT2 inhibitor in the last 6 months) because it was shown that these agents may exhibit beneficial renoprotective effects after a 6-month period. This was done in order to avoid the GFR decreasing effect of SGLT2 inhibitors in the first days of starting the drug.[25]

Some preventive strategies have been studied to avoid the development of CA-AKI, such as volume expansion with oral and/or intravenous isotonic saline, *N*-acetylcysteine + isotonic saline, statins, reducing the amount of CM, and using low/iso-osmolar contrast agents. In our study groups, all patients were given intravenous saline infusion as a standard protocol of our institution, and there were no statistically significant differences in terms of statin use and amount/type of CM between the 2 groups. The factors affecting the risk of CA-AKI, such as heart failure, advanced age, hypotension, and baseline eGFR, were also similar between the study groups (Table 1 and 2). Therefore, we could analyze the independent effect of SGLT2 inhibitors on the prevention of CA-AKI.

Another important finding of our study was the shorter hospital stay in patients using SGLT2 inhibitors due to a lower incidence of CA-AKI. This finding might be speculated as a cost-effectiveness of this medication in patients with DM

and ACS. However, this should be studied prospectively in a larger population to claim that kind of cost-effective benefit.

While CA-AKI incidence was significantly lower in group 1 in patients with ACS, CA-AKI incidences were similar between groups in patients who underwent elective angiography. This finding might be due to the limited number of events in the stable angina subgroup (Table 4). Several factors may be responsible for kidney protection with SGLT2 inhibitors. Firstly, SGLT2 inhibition increases nitric oxide–dependent vasodilation, reducing ischemia–reperfusion injury, which could protect against AKI.[26] Other reported beneficial effects include suppression of kidney fibrosis, decreased peritubular hemorrhage and fibrosis, reduced hypoxia, and increased renal vascular endothelial growth factor A expression in response to ischemia–reperfusion injury, which could preserve intrarenal perfusion and attenuate ischemic injury.[27]

There are limited data investigating SGLT2 inhibitors in CA-AKI prevention; nevertheless, in a propensity match analysis, it was shown that SGLT2 inhibitor usage was found to be an independent protective factor for the occurrence of CA-AKI in patients with DM who had undergone elective CAG.[28] In a recent multicenter registry, it was shown in a cohort with ACS that the rate of CA-AKI was significantly lower in patients with DM who were using an SGLT2 inhibitor compared to non-users.[29] This trial was published while we were analyzing our findings, and we found similar results. We also analyzed the duration of hospitalization in addition to their findings. In a retrospective study, they also found that the use of SGLT2 inhibitors significantly reduced the risk of CA-AKI [odds ratio (OR): 0.41, 95% CI: 0.142–0.966, $P = .004$] in patients with non-ST elevation myocardial infarction.[30] The most likely mechanism leading to CA-AKI is a sustained reduction in renal plasma flow, especially to the outer medulla.[31] SGLT2 inhibitors cause natriuresis, glycosuria, and subsequently diuresis.[32] These effects may help clear CM, decrease the concentration of CM in the tubule lumen and vasa recta, and counteract the activation of neurohormonal systems that lead to medullary vasoconstriction.[33] While SGLT2 inhibitors may intensify outer medullary hypoxia by enhancing solute delivery for distal tubular reabsorption, one may speculate that perhaps chronic sub-lethal intensification of medullary hypoxia might provide hypoxia-tolerance during an acute hypoxic insult (ischemia-preconditioning).[34] However, this hypothesis needs further investigation and is beyond the scope of this paper.

Study Limitations

Although we showed that SGLT2 inhibitors might decrease the incidence of CA-AKI, our study had some limitations. Due to the cross-sectional design of our study, we could not investigate the prognostic value of SGLT2 inhibitors in this particular population. We had a relatively small sample size and a limited number of events (CA-AKI) due to being a single-center study. We could not include patients using canagliflozin because it has not been refunded in our country yet; therefore, our findings might not be generalized to all types of SGLT2 inhibitors. Lastly, we did not measure BNP levels and look for microalbuminuria in our study groups; as a matter of fact, Yıldız et al[35] found that brain natriuretic peptide (BNP) levels and the absence/presence of microalbuminuria were not related to the risk of CA-AKI in patients with ACS who underwent coronary angiography.

CONCLUSION

We found that in a high-risk patient population who had type II DM, CA-AKI incidence was lower and duration of hospitalization was shorter in patients using SGLT2 inhibitors in addition to other anti-diabetic therapy compared to non-users.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tepecik Training and Research Hospital, İzmir, Türkiye (Date: 15 March 2022/No. 2022/03-33). The chairperson of the ethics committee was Dilek Y. Ciftdogan, Professor Doctor.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Finn WF. The clinical and renal consequences of contrast-induced nephropathy. *Nephrol Dial Transplant*. 2006;21(6):i2-10. [CrossRef]
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103(5):368-375. [CrossRef]
3. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36(5):1542-1548. [CrossRef]
4. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl*. 2006;(100):S11-S15. [CrossRef]
5. Sholy H, Zukermann R, Soni A, Nikolsky E. Contrast induced nephropathy: an update on diagnosis, predictors, implications and preventive strategies. *Minerva Med*. 2012;103(6):465-486.
6. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? *BioMed Res Int*. 2013;2013:123589. [CrossRef]
7. 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):644-657. [CrossRef]

8. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(1):22-31. [CrossRef]
9. Matějka J, Varvařovský I, Rozsíval V, et al. Heart failure is the strongest predictor of acute kidney injury in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Kardiol Pol*. 2016;74(1):18-24. [CrossRef]
10. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-735. [CrossRef]
11. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42(14):1289-1367. [CrossRef]
12. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. [CrossRef]
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. [CrossRef]
14. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in Type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. [CrossRef]
15. Vallon V, Gerasimova M, Rose MA, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. *Am J Physiol Ren Physiol*. 2014;306(2): 194-204.
16. Gilbert RE. SGLT2 inhibitors: beta blockers for the kidney? *Lancet Diabetes Endocrinol*. 2016;4(10):814. [CrossRef]
17. Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. *J Clin Med Res*. 2016;8(12):844-847. [CrossRef]
18. Chilton R, Tikkanen I, Cannon CP, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metab*. 2015;17(12):1180-1193. [CrossRef]
19. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. [CrossRef]
20. Cherney DZ, Perkins BA, Soleymanlou N, et al. Sodium glucose cotransport-2 inhibition and intrarenal RAS activity in people with type 1 diabetes. *Kidney Int*. 2014;86(5):1057-1058. [CrossRef]
21. Jordan J, Tank J, Heusser K, et al. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. *J Am Soc Hypertens*. 2017;11(9):604-612. [CrossRef]
22. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(4):422-434. [CrossRef]
23. Ruparelia N, Digby JE, Jefferson A, et al. Myocardial infarction causes inflammation and leukocyte recruitment at remote sites in the myocardium and in the renal glomerulus. *Inflamm Res*. 2013;62(5):515-525. [CrossRef]
24. Maeda S, Matsui T, Takeuchi M, Yamagishi S. Sodium-glucose cotransporter 2- mediated oxidative stress augments advanced glycation end products-induced tubular cell apoptosis. *Diabetes Metab Res Rev*. 2013;29(5):406-412. [CrossRef]
25. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomized trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617. [CrossRef]
26. Durante W, Behnammanesh G, Peyton KJ. Effects of sodium-glucose co-transporter 2 inhibitors on vascular cell function and arterial remodeling. *Int J Mol Sci*. 2021;22(16):8786. [CrossRef]
27. Nishiyama A, Kitada K. Possible renoprotective mechanisms of SGLT2 inhibitors. *Front Med (Lausanne)*. 2023;10:1115413. [CrossRef]
28. Hua R, Ding N, Guo H, Wu Y, Yuan Z, Li T. Contrast-induced acute kidney injury in patients on SGLT2 inhibitors undergoing percutaneous coronary interventions: A propensity-matched analysis. *Front Cardiovasc Med*. 2022;9:918167. [CrossRef]
29. 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. [CrossRef]
30. Özkan U, Gürdoğan M. The effect of SGLT2 inhibitors on the development of contrast-induced nephropathy in diabetic patients with non-ST segment elevation myocardial infarction. *Medicina (Kaunas)*. 2023;59(3):505. [CrossRef]
31. Gassanov N, Nia AM, Caglayan E, Er F. Remote ischemic preconditioning and renoprotection: from myth to a novel therapeutic option? *J Am Soc Nephrol*. 2014;25(2):216-224. [CrossRef]
32. Kubica J, Kubica A, Grzelakowska K, et al. Inhibitors of sodium-glucose transport protein 2: A new multidirectional therapeutic option for heart failure patients. *Cardiol J*. 2023;30(1):143-149. [CrossRef]
33. Maioli M, Toso A, Leoncini M, et al. Bioimpedance-guided hydration for the prevention of contrast-induced kidney injury: the Hydra Study. *J Am Coll Cardiol*. 2018;71(25):2880-2889. [CrossRef]
34. Szalat A, Perlman A, Muszkat M, Khamaisi M, Abassi Z, Heyman SN. Can SGLT2 inhibitors cause acute renal failure? Plausible role for altered glomerular hemodynamics and medullary hypoxia. *Drug Saf*. 2018;41(3):239-252. [CrossRef]
35. Yildiz E, Köse M, Yürüyen G, et al. Relationship between brain natriuretic peptide, microalbuminuria, and contrast-induced nephropathy in patients with acute coronary syndrome. *Anatol J Cardiol*. 2014;14(6):505-510. [CrossRef]