European Journal of Medical Research

RESEARCH

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The association between sodium–glucose cotransporter 2 inhibitors and contrast-associated acute kidney injury in patients with type 2 diabetes undergoing angiography: a propensity-matched study

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Abstract

Background Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have been proven to prevent decline in kidney function and failure. Whether SGLT2i affect the risk of contrast-associated acute kidney injury (CA-AKI) remains uncertain.

Methods Use of SGLT2i was assessed in consecutive diabetics undergoing coronary angiography (CA) or percutaneous coronary intervention (PCI) from January 2020 to May 2023 at a tertiary hospital in Chongqing, China. Propensity-matched analysis was used to adjust for baseline variables. CA-AKI was defined by the Acute Kidney Injury Network (AKIN) as creatinine increase ≥ 0.3 mg/dl (26.4 µmol/l), or a percentage increase in the serum creatinine level of ≥ 50%.

Results A total of 604 new users of SGLT2i, and 298 chronic users of SGLT2i were matched with non-users. New use of SGLT2i was not associated with an increased incidence of AKIN-defined CA-AKI (OR 1.60; 95% CI 0.97–2.63; $p = 0.065$), in-hospital new-onset dialysis (OR 0.50; 95% CI 0.09–2.73; $p = 0.422$), or death (OR 0.55; 95% CI 0.18–1.66; $p = 0.289$). However, it was associated with a minor (> 25%) creatinine elevation (OR 1.55; 95% CI 1.04–2.30; $p = 0.030$), a 0.3 mg/dl increase in creatinine (OR 1.66; 95% CI 1.01–2.75; $p = 0.048$), and CMSC-defined CA-AKI (OR 1.51; 95% CI 1.02–2.24; $p = 0.039$). By 90 days, there was no evidence creatinine elevation differed between the two groups ($p = 0.590$). Chronic use of SGLT2i was not associated with AKIN-defined CA-AKI (OR, 0.92; 95% CI 0.41–2.05; $p = 0.838$).

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Conclusions New use of SGLT2i during CA or PCI was not associated with an AKIN-defined CA-AKI, and it did not translate into new-onset dialysis or death during hospital stay. Chronic usage of SGLT2i did not affect creatinine. Further randomized clinical trials are warranted to confirm this finding.

Key learning points

What was known: Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have a renal protective effect; however, they cause an acute increase in the creatinine level and dip in glomerular filtration rate (GFR) upon treatment initiation.

This study adds: New use of SGLT2i during coronary angiography or percutaneous coronary intervention was associated with an acute increase in the creatinine level, but it did not translate into new-onset dialysis or death during hospital stay, causing a pseudo contrast-associated acute kidney injury, and the creatinine level seemed return to normal thereafter. Continuation of SGLT2i did not affect creatinine elevation.

Potential impact: Usage of SGLT2i may be safe during coronary angiography or percutaneous coronary intervention. Randomized controlled trials and other observational studies are needed to validate our observation.

Keywords Sodium–glucose cotransporter 2 inhibitor, Contrast-associated acute kidney injury, Diabetes mellitus, Coronary angiography, Percutaneous coronary intervention

Introduction

Coronary angiography (CA) and percutaneous coronary intervention (PCI) are widely used for the diagnosis and treatment of coronary heart disease (CHD), a disease that affects around 126 million individuals worldwide [1]. The iodine-based contrast medium used in these procedures can cause direct tubular toxicity, intra-renal vasoconstriction, and excessive production of reactive oxygen species, all of which can lead to contrast-associated acute kidney injury (CA-AKI) [2]. Between 4 and 10% of patients undergoing CA or PCI experience CA-AKI [3, 4]. CA-AKI is associated with increased short- and long-term mortality and end-stage renal events [5]. Several drugs, such as renin–angiotensin–aldosterone system blockers and metformin, may increase the incidence of CA-AKI, and some guideline recommendations withhold their use at the time of CA [6, 7].

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) reduce blood glucose by inhibiting its reabsorption in proximal tubules and by promoting urinary glucose excretion. SGLT2 inhibitors are listed as a first-line drug therapy for diabetes complicated with established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD) according to the ADA and KDIGO guideline [8, 9, 10]. In recent landmark trials, SGLT2i were found to not only reduce blood glucose, but also significantly reduce cardiovascular events, renal failure, and renal death in patients with T2D, chronic kidney disease, and heart failure [11]. However, SGLT2i inhibition increases sodium delivery to the juxtaglomerular apparatus, leading to afferent arteriolar vasoconstriction and a decrease in intraglomerular pressure, causing an acute increase in creatinine and dip in glomerular filtration rate (GFR) upon treatment initiation [12]. Whether SGLT2i affects the risk of CA-AKI is largely unknown. Here, we aimed to explore the effect of SGLT2i on the development of CA-AKI in patients with T2D undergoing CA or PCI using propensity score-matched retrospective data.

Materials and methods

Participants

All consecutive patients with T2D undergoing CA or PCI at Xinqiao Hospital, a tertiary teaching hospital, between January 1, 2020, and May 26, 2023, were considered for inclusion in the study. A total of 4014 patients were identified. Patients with lacking periprocedural creatinine data (defined as 31 days before the procedure and 4 days after the procedure), or with repeat admission were excluded ($n=1595$). A total of 2419 patients were included in the final analysis. New use of SGLT2i was defined as administration of an oral dose of SGLT2i after admission and before the CA procedure, and no prior history of SGLT2i use. Chronic use of SGLT2i was defined as regular use of SGLT2i before admission and not interrupted during hospital stay. The interval from new use of SGLT2i to CA is 2.84 (1.77, 4.04) days. The interval from chronic use of SGLT2i to CA is not available. The dose and type of SGLT2i prescribed was at the doctor's discretion. The Institutional Review Board of the Xinqiao Hospital approved the research protocol.

Data collection

Patient demographic, clinical, and laboratory data as well as medications used before, during, and after the procedure and in-hospital outcomes were obtained from electronic medical records. These data included age, sex, body mass index (BMI), systolic or diastolic blood pressure (SBP or DBP), left ventricular ejection fraction (LVEF), and left ventricular end-diastolic diameter (LVEDD) from an echocardiogram, comorbid conditions (hypertension, previous myocardial infarction, PCI, chronic kidney disease, acute myocardial infarction), medication use (SGLT2i, ACE inhibitors/ARBs, statins, β-blockers, calcium channel blockers, and diuretics), and basic information of the PCI procedure (no. of diseased vessels, average stent implanted for each patient, left main lesion). In new use analysis, the median (IQR) dose of loop diuretic for both group is 20.00 (20.00, 20.00) mg after propensity matching. There is marginal difference between the two group ($p=0.049$). In chronic use analysis, the median (IQR) dose for both group is 20.00 (20.00, 20.00) mg after propensity matching. There is no difference between the two group ($p=0.148$). Laboratory data included serum creatinine levels before and after CA, as well as hemoglobin, low-density lipoprotein (LDL) cholesterol, glycated hemoglobin, fasting blood glucose levels, brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), which were measured in the hospital central laboratory on hospital admission and follow-up with consistent methodology. The estimated GFR (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Further, CA or PCI was performed according to the local clinical care guidelines [13]. As actual contrast volume was not routinely recorded in our center, the contrast volume category (>200 ml or ≤200 ml) reported was based on the number of vials opened (100 ml each). As some patients measured BNP and others NT-proBNP, abnormal BNP or NT-proBNP were reported according to age-stratified cut-off [14]. Mehran 2 CA-AKI risk score was calculated using preoperative variables [15].

Outcome endpoint

The primary outcome of this study was serum creatinine elevation, which was defined as an relative increase in serum creatinine of >25% from the baseline to peak value within 96 h after exposure to the contrast medium [16]. Various definitions, including CA-AKI defined by the Contrast Media Safety Committee of the European Society of Urogenital Radiology (CMSC) [17] and CA-AKI defined later by the Acute Kidney Injury Network (AKIN) [6], relative increase of >25% or >50%, and absolute increase in the serum creatinine level >0.3 mg/dl or >0.5 mg/dl were included as the exploratory endpoint within 96 h after exposure to the contrast medium [6]. Sensitivity analysis using 48 and 72 h definition. Baseline creatinine was collected within 1 month before the procedure. In patients who had multiple assessments of serum creatinine within 30 days before the procedure, the value closest to the time of the procedure was considered as the baseline value. Peak creatinine was defined as the highest value of creatinine within 96 h after the procedure, and it was used to define events. New-onset dialysis was defined as new, unplanned need for hemodialysis during the hospital stay of patients, due to worsening of renal function after CA or PCI. In-hospital death was obtained from the medical records. Creatinine within 90 days after the procedure was defined as the lowest value of creatinine after the measurement of 96-h peak creatinine and within 90 days after the procedure.

Statistical analysis

Propensity scoring was used to reduce potential confounding and selection bias between study arms. The propensity score was calculated for each patient by modeling the probability of receiving a SGLT2i. For new-onset user analysis, a multivariable logistic regression analysis model was generated to predict the probability of receiving a SGLT2i given the following set of covariates: age, sex, baseline levels of creatinine and fasting glucose, abnormal BNP/NT-proBNP, baseline systolic blood pressure, baseline left ventricular ejection fraction, baseline use of insulin, ACEI/ARB and diuretics, presence or absence of acute myocardial infarction, and contrast volume or stent used. For chronic use analysis, a multivariable logistic regression analysis model was generated to predict the probability of receiving a SGLT2i given the following set of covariates: age, sex, baseline levels of creatinine and LDL, medical history of hypertension PCI, and myocardial infarction, presence or absence of acute myocardial infarction, and contrast volume used. The values of glycated hemoglobin, although unbalanced, were not entered into the propensity model as more than half of the values were missing. A propensity score was calculated and used to match 604 new users of SGLT2i with non-users, and 298 chronic users of SGLT2i with non-users, at a ratio of 1:1 using the greedy matching algorithms. Patients without a corresponding match were excluded. Sensitivity analysis using inverse probability of treatment weighting were performed. Matching adequacy was confirmed by calculating the standardized differences in baseline variables among the matched subset, with a standardized difference of <25% suggesting adequate matching. After all propensity score matches were performed, the balance in baseline covariates was

assessed through Kruskal–Wallis test, and Chi-square tests were performed for continuous and categorical variables. All available data were analyzed without imputation of missing values. Categorical variables were described as frequencies (percentages), and continuous variables were described as means ± SDs, unless skewed, as medians (interquartile ranges). The change in continuous variables over time was determined using linear mixed models. A logistic regression model was used to determine the risk for events. All analyses were performed with the SAS software (Cary, North Carolina, SAS Institute, version 9.4). Statistical significance was defined as $p < 0.05$.

Results

Initial start on admission

New-onset use of SGLT2i occurred in 665 patients (Fig. 1). Baseline characteristics of SGLT2i users compared with non-users are described in Table 1. New-onset SGLT2i users had a higher prevalence of New York Heart Association (NYHA) IV, more abnormal BNP or NT-proBNP, worse cardiac systolic function, and worse glucose control; were more likely to use RAASi and diuretics, and experience acute myocardial infarction at baseline. The overall Mehran 2 score and number of disease vessels are different between groups.

Using propensity score, 604 SGLT2i users were successfully matched to non-users (sFigure 1a). There were no statistically significant clinical differences between SGLT2i users and non-users (Table 1). As shown in Table 2, in the propensity-matched cohort, no differences in the incidence of AKIN-defined CA-AKI (7.0% vs. 4.5%, odds ratio [OR] 1.60, 95% confidence interval [CI] 0.97 to 2.63, $p = 0.065$), severe creatinine elevation (> 50%), 0.5 mg/dl increase in creatinine, new-onset dialysis, and in-hospital death were observed between patients treated with SGLT2i and those not. However, patients treated with SGLT2i had a significantly higher incidence of creatinine elevation (creatinine increase of > 25%, 11.1% vs. 7.5%, OR 1.55, 95% CI 1.04 to 2.30, $p = 0.030$), 0.3 mg/dl increase in creatinine (OR 1.66, 95% CI 1.01 to 2.75, $p = 0.048$), and CMSC-defined CA-AKI (OR 1.51, 95% CI 1.02 to 2.24, $p = 0.039$). Similar results were found in the unadjusted analysis (Table 2), in sensitivity analysis using 48 or 72 h definition of CA-AKI (sTable 1), and in analysis using inverse probability of treatment weighting

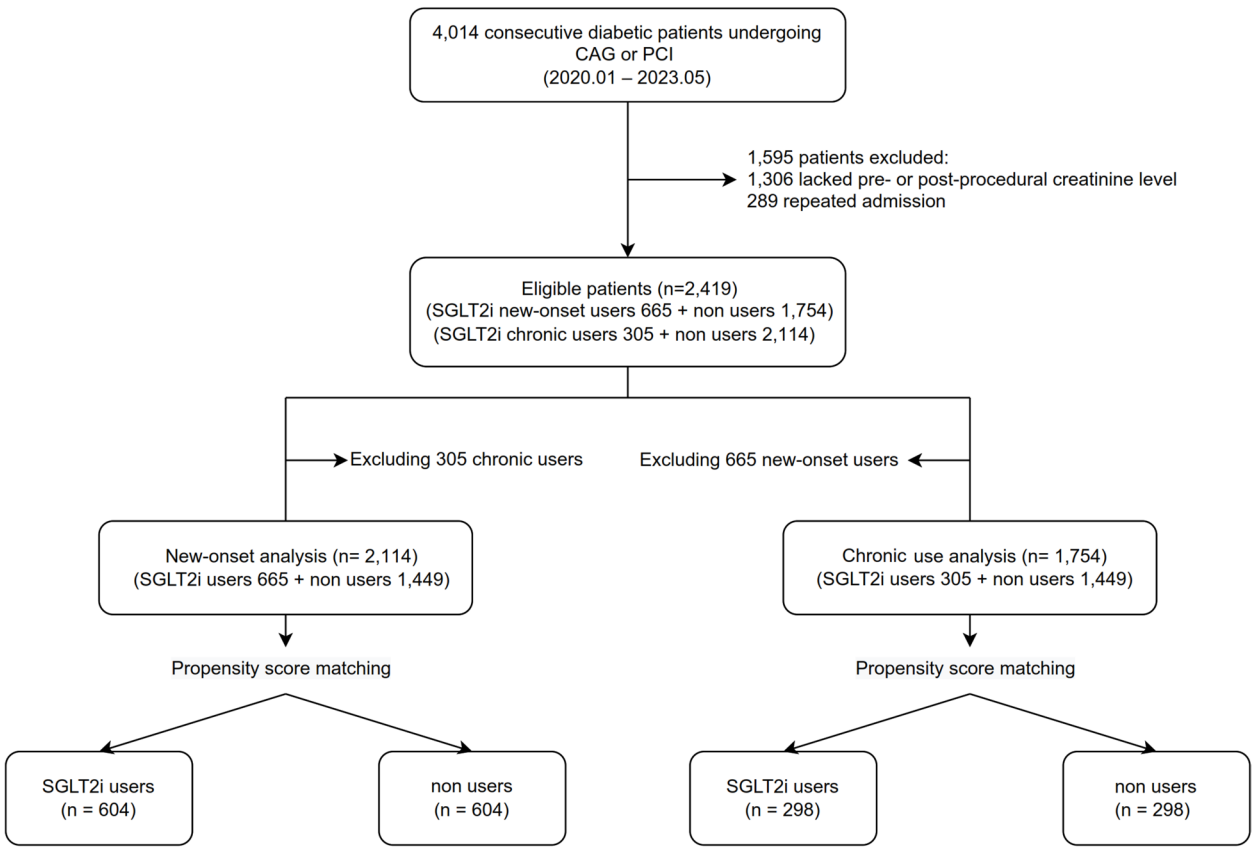

Fig. 1 Cohort formation

Table 1 Baseline characteristics of study participants in new-onset analysis

	Before matching				After matching		
	SGLT2i (*N* = 665)	Non-users (*n* = 1449)	N.Missing	*p* value	SGLT2i (*N* = 604)	Non-users (*n* = 604)	*p* value
Age (years)	63.48 (10.45)	64.37 (10.65)		0.092	63.56 (10.51)	63.92 (10.89)	0.638
Female (%)	190 (28.57)	441 (30.43)		0.385	175 (28.97)	167 (27.65)	0.609
NYHA IV	26 (3.91)	29 (2.00)		**0.010**	25 (4.14)	22 (3.64)	0.655
Previous MI (%)	58 (8.72)	105 (7.25)		0.238	52 (8.61)	42 (6.95)	0.283
Previous PCI (%)	161 (24.21)	328 (22.64)		0.425	148 (24.50)	132 (21.85)	0.275
Chronic kidney disease (%)	109 (16.39)	255 (17.60)		0.495	100 (16.56)	89 (14.74)	0.384
Proteinuria (%)	208 (31.28)	458 (31.61)	108 (5.11)	0.624	191 (31.62)	202 (33.44)	0.483
Hypertension (%)	459 (69.02)	1026 (70.81)		0.405	422 (69.87)	437 (72.35)	0.341
Creatinine (μmol/l)	79.20 (67.00, 97.10)	79.00 (66.40, 98.50)		0.673	78.75 (66.65, 96.40)	78.65 (65.65, 95.65)	0.674
eGFR (ml/min1.73m^2)	79.72 (22.14)	76.92 (25.20)		0.091	79.74 (22.13)	79.93 (22.23)	0.851
Fasting blood glucose (mmol/l)	8.71 (3.55)	8.24 (3.31)	64 (3.03)	**< 0.001**	8.71 (3.54)	8.64 (3.65)	0.248
LDL (mmol/l)	2.08 (0.73)	2.04 (0.81)	67 (3.17)	0.057	2.09 (0.74)	2.11 (0.86)	0.878
Hemoglobin (g/l)	134.18 (19.73)	132.43 (19.41)	6 (0.28)	0.086	134.20 (19.49)	133.32 (19.14)	0.368
BMI (kg/m^2)	25.20 (3.20)	25.15 (3.09)	17 (0.80)	0.616	25.26 (3.25)	25.26 (3.08)	0.954
Systolic BP (mmHg)	128.47 (22.06)	130.50 (21.36)	18 (0.85)	**0.045**	128.52 (21.81)	128.92 (21.57)	0.697
Diastolic BP (mmHg)	73.96 (13.43)	73.85 (13.54)	24 (1.14)	0.695	73.92 (13.42)	73.97 (14.30)	0.780
Abnormal BNP or NT-proBNP	206 (30.98)	312 (21.53)	54 (2.55)	**< 0.001**	188 (31.13)	181 (29.97)	0.662
Mehran 2 score	3.00 (2.00, 5.00)	3.00 (1.00, 4.00)	138 (6.53)	**< 0.001**	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	0.193
Echocardiography							
LVEF (%)	57.88 (11.47)	60.71 (9.51)	76 (3.60)	**< 0.001**	57.76 (11.57)	57.95 (11.04)	0.925
LVEDD (mm)	47.86 (6.92)	46.68 (5.34)	30 (1.42)	**0.007**	47.85 (6.93)	47.96 (6.25)	0.291
Medication (%)							
Insulin	311 (46.77)	634 (43.75)		0.196	283 (46.85)	278 (46.03)	0.773
RAASi	426 (64.06)	824 (56.87)		**< 0.001**	393 (65.07)	384 (63.58)	0.589
Diuretics	215 (32.33)	323 (22.29)		**< 0.001**	197 (32.62)	205 (33.94)	0.625
β-blocker	471 (70.83)	1023 (70.60)		0.915	432 (71.52)	438 (72.52)	0.701
Current hospitalization (%)							
AMI	150 (22.56)	254 (17.53)		**0.006**	128 (21.19)	128 (21.19)	1.000
Contrast volume > 200 ml	249 (37.44)	483 (33.33)	14 (0.66)	0.078	224 (37.09)	227 (37.58)	0.858
Left main	37 (5.56)	97 (6.69)		0.322	35 (5.79)	42 (6.95)	0.410
No. of diseased vessels				**0.020**			0.378
1	115 (17.29)	331 (22.84)			105 (17.38)	124 (20.53)	
2	199 (29.92)	438 (30.23)			178 (29.47)	184 (30.46)	
3	324 (48.72)	628 (43.34)			295 (48.84)	276 (45.70)	
Stent implanted	1.00 (1.23)	0.96 (1.11)		0.987	0.99 (1.26)	1.01 (1.10)	0.193

Bold indicates a *p* value less than 0.05

AMI: acute myocardial infarction; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention

(sTable 2 and sFigure 2). When we examined the occurrence of AKIN-defined CA-AKI in different patient subgroups, interaction existed with respect to the baseline kidney function (chronic kidney disease and GFR) and abnormal BNP/ NT-proBNP. No difference in outcomes was observed in any other subgroup (Fig. 2).

The geometric mean of the creatinine level was increased by 3.06% (95% CI 1.32 to 4.82%) on average within 4 days after the procedure in the SGLT2i group ($p = 0.001$), while the least-squares mean level of eGFR was decreased by − 2.02 (95% CI − 3.11 to − 0.93) ml/min 1.73 m^2, $p < 0.001$ (Fig. 3). Both biomarkers seemed return to normal within 90 days (for creatinine, geometric mean ratio 0.99, 95% CI 0.96 to 1.02, $p = 0.569$ and for eGFR difference between groups, 0.98 (95% − 1.19 to 2.67), $p = 0.452$. Full recovery of kidney function within

Table 2 Unmatched and propensity-matched in-hospital outcome of patients in new-onset analysis

	Unmatched outcome				Propensity-matched outcome			
	SGLT2i (*N* = 665)	Non-users (*n* = 1449)	OR (95% CI)	*p* value	SGLT2i (*N* = 604)	Non-users (*n* = 604)	OR (95% CI)	*p* value
Serum creatinine change within 96 h								
CA-AKI$_{AKIN}$	49 (7.4)	78 (5.4)	1.40 (0.97, 2.02)	0.075	42 (7.0)	27 (4.5)	1.60 (0.97, 2.63)	0.065
> 50% ↑	13 (2.0)	23 (1.6)	1.24 (0.62, 2.46)	0.545	11 (1.8)	11 (1.8)	1.00 (0.43, 2.32)	1.000
> 25% ↑	76 (11.4)	85 (5.9)	2.07 (1.50, 2.86)	< 0.001	67 (11.1)	45 (7.5)	1.55 (1.04, 2.30)	0.030
> 0.5 mg/dl ↑	114 (2.1)	42 (2.9)	0.72 (0.39, 1.33)	0.294	11 (1.8)	12 (2.0)	0.92 (0.40, 2.09)	0.833
> 0.3 mg/dl ↑	49 (7.4)	75 (5.2)	1.46 (1.00, 2.12)	0.048	42 (7.0)	26 (4.3)	1.66 (1.01, 2.75)	0.048
CA-AKI$_{CMSC}$	76 (11.4)	94 (6.5)	1.86 (1.35, 2.56)	< 0.001	67 (11.1)	46 (7.6)	1.51 (1.02, 2.24)	0.039
New-onset dialysis	2 (0.3)	19 (1.3)	0.23 (0.05, 0.98)	0.047	2 (0.3)	4 (0.7)	0.50 (0.09, 2.73)	0.422
In-hospital death	6 (0.9)	19 (1.3)	0.69 (0.27, 1.72)	0.422	5 (0.8)	9 (1.5)	0.55 (0.18, 1.66)	0.289

CA-AKI$_{CMSC}$: contrast-associated acute kidney injury was defined by the Contrast Media Safety Committee of the European Society of Urogenital Radiology as an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 μmol/l). CA-AKI$_{AKIN}$: contrast-associated acute kidney injury was defined by the Acute Kidney Injury Network using ≥ 0.3 mg/dl (26.4 μmol/l), or a percentage increase in the serum creatinine level of ≥ 50% (1.5-fold from baseline)

90 days after the procedure was similar between the two groups (55.3% vs 50.5%; overall $p = 0.590$) (Table 3).

Chronic users of SGLT2i

A total of 305 patients were taking SGLT2i prior to hospital admission. Characteristics of the study population are listed in Table 4. Compared to non-users, patients with chronic SGLT2i treatment were younger; had a higher prevalence of previous MI and PCI; were less likely to use insulin at baseline and be current MI patients; and had better glucose control, higher hemoglobin and eGFR, less proteinuria, and lower SBP, BMI, LDL and Mehran 2 score. The propensity-matched cohorts showed an improved balance. The factors, blood glucose, hemoglobin, proteinuria, BMI, BP and insulin usage were not entered into the model as they reflected the effect of SGLT2i rather than bias between groups [18, 19]. Patients with prior SGLT2i treatment had a similar incidence of AKIN-defined CA-AKI (4.0% vs. 4.4%, OR 0.92, 95% CI 0.41 to 2.05, $p = 0.838$); and no differences in the incidence of CMSC-defined CA-AKI, creatinine elevation, severe creatinine elevation (> 50%), 0.3 or 0.5 mg/dl increase in creatinine, new-onset dialysis, and in-hospital death were observed between the two groups. Similar results were found in the unadjusted analysis (Table 5).

Discussion

In the present study, we evaluated administration and continuation of SGLT2i in diabetic patients hospitalized for CA or PCI. Administration of these drugs on admission was associated with a spike in creatinine and a dip in eGFR, leading to a pseudo CA-AKI that did not satisfy more rigorous definitions, and the creatinine level returned to the pre-procedure level within 3 months. Continuation of SGLT2i did not affect CA-AKI. These findings are particularly important to provide safety evidence of administration and continuation of SGLT2i around the time of contrast exposure.

In 1999, CA-AKI was first defined by the Contrast Media Safety Committee of the European Society of Urogenital Radiology, as an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 μmol/l) within 3 days following intravascular administration of a contrast medium [17]. Later, the Acute Kidney Injury Network suggested using ≥ 0.3 mg/dl (26.4 μmol/l), or a percentage increase in serum creatinine level of ≥ 50% (1.5-fold from baseline) [6]. More recent studies suggested that an absolute increase in serum creatinine from 0.5 to 0.75 mg/dl is a better threshold than a relative increase in serum creatinine for the diagnosis of CA-AKI [20, 21]. When initial SGLT2i just before contrast exposure, our results support the latter that a more rigid definition should be used for clinically meaningful CA-AKI, as an increase in creatinine is a mix of true AKI and the drug effect. In fact, the acute and reversible dip in eGFR observed soon after SGLT2i administration most likely reflects their action of protective mechanism. SGLT2i causes glucosuria, inhibits sodium reabsorption in the proximal tubule, leads to afferent arteriolar vasoconstriction, and causes reduction in glomerular hyperperfusion and hyperfiltration [22]. SGLT2i also improve tubular oxygenation and metabolism and reduce renal inflammation and fibrosis [23]. Other beneficial effects of SGLT2i include less intra-renal congestion-tamponade [24], and reduced venous congestion and increased renal blood flow [25]. Post hoc analysis of large clinical trials has shown that such an eGFR dip did not modify the benefit to the

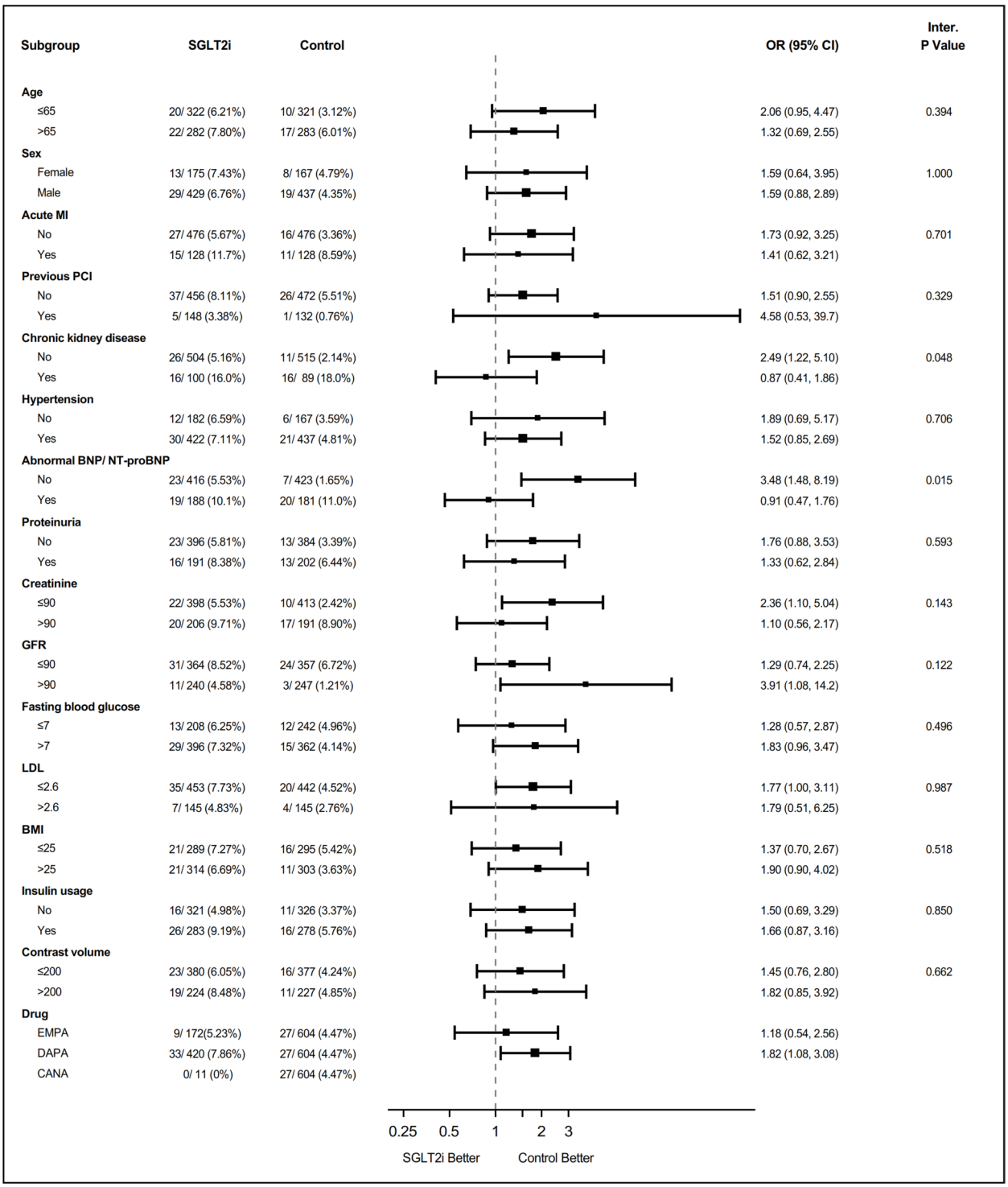

Fig. 2 Subgroup analysis in new-onset analysis

cardiovascular system and kidneys [26, 27]. Moreover, full recovery of kidney function within 30 days after an AKI event occurred more frequently after treatment with SGLT2i [28]. It should be mentioned that a large eGFR dip (> 30%), although a very rare event, slightly increases the risk for kidney-related adverse events [29].

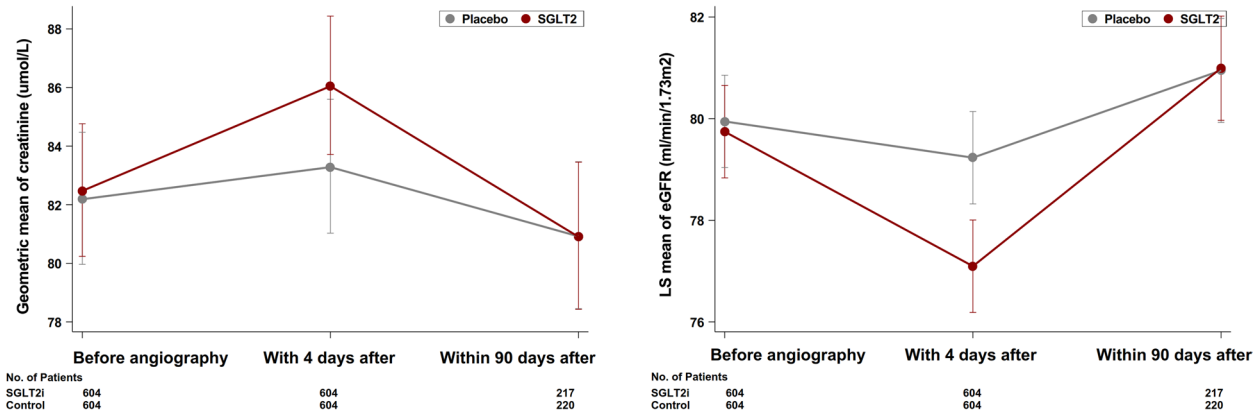

Fig. 3 Effects on creatinine and estimated gfr in new-onset analysis. **A** shows the effects of SGLT2i and non-users on the creatinine level. **B** shows the estimated GFR level. The I bars indicate the 95% confidence interval in (**A**) and the standard error in (**B**)

Table 3 Long-term kidney function in new-onset analysis. Change in the creatinine level from pre-procedure to within 90 days postangiography

	SGLT2i	Non-users	*p* value
> 25% (no recovery)	15/217 (6.9)	16/220 (7.3)	0.590
0 to 25% (partial recovery)	82/217 (37.8)	93/220 (42.3)	
≤ 0% (full recovery)	120/217 (55.3)	111/220 (50.5)	

CA-AKI is considered an important cause of hospital-acquired renal failure [30]. However, in most cases, CA-AKI manifests as mild transient impairment of renal function; creatinine typically rises within the first 48 h after contrast medium administration, peaks at 3–5 days, and returns near to baseline or to a new baseline within 1–3 weeks [31]. Although irreversible loss of renal function occurs in rare cases, it subsequently progresses to chronic kidney disease and dialysis [32]. Our results showed that the creatinine level might return to baseline within 3 months, reflecting that non-nephrotoxicity drives this process.

Currently, very few studies are focusing on the relation between SGLT2i with CA-AKI; one abstract including 52 patients in each group reported that chronic treatment with SGLT2i induced an improvement in diabetic patients undergoing PCI [33]. In our population, most patients were new users of SGLT2i. Among the 298 chronic users, SGLT2i was not associated with an increase in CA-AKI.

Although the subgroup analysis lost the power to detect the true difference and may be influenced by multiple comparisons, we observed that SGLT2i was associated with less risk of CA-AKI in patients with impaired renal function compared with those who had relatively better renal function. This was not caused by less contrast use in these patients; the contrast volume was similar between CKD and non-CKD (data not shown). Previous study found the eGFR dip caused by SGLT2i was milder when baseline eGFR was lower [34]. Our study showed similar results, as the spike in creatinine was milder when renal function was worse. In subgroup analysis, the interaction between SGLT2i usage and baseline creatinine/ GFR were similar to that of CKD, although not significantly different. We observed that SGLT2i was not associated with an increased risk of CA-AKI in patients with abnormal BNP/NT-proBNP levels. BNP/NT-proBNP levels are influenced by other conditions such as CKD [35]. The eGFR dip was deeper in heart failure patients [36]. Our analysis showed that SGLT2i may not cause CA-AKI in heart failure patients.

However, there are some limitations to this study. First, this was a single-centre post hoc analysis of medical record data. Although propensity score matching was used to minimize the differences in baseline characteristics, it was an observational study rather than a randomized controlled interventional trial; thus, the results must be regarded as hypothesis generation and exploration and require validation in other studies. Some important data, such as the exact volume of contrast used, are missing. The contrast volume category was based on the number of vials opened, which was not associated with contrast volume in some situation.

Table 4 Baseline characteristics of study participants in chronic use analysis

	Before matching				After matching		
	SGLT2i (*N* = 305)	Non-users (*n* = 1449)	N.Missing	*p* value	SGLT2i (*N* = 298)	Non-users (*n* = 298)	*p* value
Age (years)	61.04 (10.71)	64.37 (10.65)		**< 0.001**	60.86 (10.67)	60.60 (11.39)	0.672
Female (%)	81 (26.56)	441 (30.43)		0.178	79 (26.51)	74 (24.83)	0.639
NYHA IV	6 (1.97)	29 (2.00)		0.969	6 (2.01)	4 (1.34)	0.524
Previous MI (%)	41 (13.44)	105 (7.25)		**< 0.001**	40 (13.42)	47 (15.77)	0.417
Previous PCI (%)	99 (32.46)	328 (22.64)		**< 0.001**	96 (32.21)	82 (27.52)	0.210
Chronic kidney disease (%)	48 (15.74)	255 (17.60)		0.435	48 (16.11)	32 (10.74)	0.055
Proteinuria (%)	65 (21.31)	458 (31.61)	90 (5.13)	**< 0.001**	64 (21.48)	79 (26.51)	0.118
Hypertension (%)	212 (69.51)	1026 (70.81)		0.651	206 (69.13)	211 (70.81)	0.655
Creatinine (μmol/l)	78.10 (65.40, 95.90)	79.00 (66.40, 98.50)		0.228	77.80 (64.90, 95.90)	75.75 (63.60, 91.20)	0.185
eGFR	82.46 (21.46)	76.92 (25.20)		**0.002**	82.72 (21.55)	85.34 (21.45)	0.145
Fasting blood glucose (mmol/l)	7.23 (2.59)	8.24 (3.31)	59 (3.36)	**< 0.001**	7.26 (2.61)	8.05 (3.01)	**0.001**
LDL (mmol/l)	1.96 (0.79)	2.04 (0.81)	63 (3.59)	**< 0.001**	1.96 (0.78)	2.03 (0.81)	0.340
Hemoglobin (g/l)	138.67 (17.34)	132.43 (19.41)	5 (0.29)	**< 0.001**	138.65 (17.38)	135.79 (18.94)	0.082
BMI	24.72 (2.97)	25.15 (3.09)	16 (0.91)	**0.024**	24.73 (2.98)	25.33 (2.88)	**0.006**
Systolic BP (mmHg)	122.87 (19.62)	130.50 (21.36)	17 (0.97)	**< 0.001**	123.09 (19.57)	129.41 (19.69)	**< 0.001**
Diastolic BP (mmHg)	72.91 (13.25)	73.85 (13.54)	22 (1.25)	0.131	73.13 (13.27)	75.33 (13.51)	**0.031**
Abnormal BNP or NT-proBNP	63 (20.66)	312 (21.53)	49 (2.79)	0.720	61 (20.47)	53 (17.79)	0.415
mehran 2 score	2.00 (1.00, 3.00)	3.00 (1.00, 4.00)	114 (6.50)	**< 0.001**	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	0.004
Echocardiography							
LVEF (%)	59.80 (9.76)	60.71 (9.51)	59 (3.36)	0.209	59.87 (9.80)	60.84 (9.83)	0.332
LVEDD (mm)	46.98 (6.13)	46.68 (5.34)	26 (1.48)	0.829	46.89 (6.09)	46.53 (4.93)	0.980
Medication (%)							
Insulin	96 (31.48)	634 (43.75)		**< 0.001**	94 (31.54)	124 (41.61)	**0.011**
ACEI/ARB	174 (57.05)	824 (56.87)		0.953	168 (56.38)	176 (59.06)	0.507
Diuretics	74 (24.26)	323 (22.29)		0.455	72 (24.16)	55 (18.46)	0.089
β-blocker	219 (71.80)	1023 (70.60)		0.675	213 (71.48)	227 (76.17)	0.192
Current hospitalization (%)							
AMI	37 (12.13)	254 (17.53)		**0.021**	35 (11.74)	48 (16.11)	0.124
Contrast volume > 200 ml	113 (37.05)	483 (33.33)	12 (0.68)	0.250	109 (36.58)	113 (37.92)	0.735
Left main	15 (4.92)	97 (6.69)		0.249	14 (4.70)	17 (5.70)	0.580
No. of diseased vessels				0.220			0.378
1	55 (18.03)	331 (22.84)			54 (18.12)	68 (22.82)	
2	93 (30.49)	438 (30.23)			92 (30.87)	94 (31.54)	
3	142 (46.56)	628 (43.34)			137 (45.97)	126 (42.28)	
Stent implanted	0.98 (1.53)	0.96 (1.11)		0.220	0.98 (1.54)	0.90 (1.01)	0.638

Bold indicates a *p* value less than 0.05

AMI: acute myocardial infarction; BMI: body mass index; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention

Other data; for example, serum creatinine was not checked in a systematic fashion, and not all patients had their serum creatinine level checked before and within the 96-h window that corresponded with peak serum creatinine elevation in patients with CA-AKI. The upcoming clinical trial of dapagliflozin to prevent the incidence of contrast-induced nephropathy after heart catheterization and PCI (NCT04806633) will

Table 5 Unmatched and propensity-matched in-hospital outcome of patients in chronic use analysis

	Unmatched outcome				Propensity-matched outcome			
	SGLT2i ($N=305$)	Non-users ($n=1449$)	OR (95 CI)	*p* value	SGLT2i ($N=298$)	Non-users ($n=298$)	OR (95 CI)	*p* value
Serum creatinine change within 96 h								
CA-AKI$_{AKIN}$	12 (3.9)	78 (5.4)	0.72 (0.39, 1.34)	0.300	12 (4.0)	13 (4.4)	0.92 (0.41, 2.05)	0.838
> 50% ↑	3 (1.0)	23 (1.6)	0.62 (0.18, 2.06)	0.432	3 (1.0)	5 (1.7)	0.60 (0.14, 2.52)	0.481
> 25% ↑	14 (4.6)	85 (5.9)	0.77 (0.43, 1.38)	0.382	14 (4.7)	18 (6.0)	0.77 (0.37, 1.57)	0.468
> 0.5 mg/dl ↑	4 (1.3)	42 (2.9)	0.45 (0.16, 1.25)	0.125	4 (1.3)	5 (1.7)	0.80 (0.21, 3.00)	0.738
> 0.3 mg/dl ↑	11 (3.6)	75 (5.2)	0.69 (0.36, 1.31)	0.251	11 (3.7)	11 (3.7)	1.00 (0.43, 2.34)	1.000
CA-AKI$_{CMSC}$	14 (4.6)	94 (6.5)	0.69 (0.39, 1.23)	0.213	14 (4.7)	19 (6.4)	0.72 (0.36, 1.47)	0.372
New-onset dialysis	0 (0)	19 (1.3)			0 (0)	3 (1.0)		
In-hospital death	3 (1.0)	19 (1.3)	0.75 (0.22, 2.54)	0.642	3 (1.0)	0 (0)		

CA-AKI$_{CMSC}$: contrast-associated acute kidney injury was defined by the Contrast Media Safety Committee of the European Society of Urogenital Radiology as an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 μmol/l). CA-AKI$_{AKIN}$: Contrast-associated acute kidney injury was defined by the Acute Kidney Injury Network using ≥ 0.3 mg/dl (26.4 μmol/l), or a percentage increase in the serum creatinine level of ≥ 50% (1.5-fold from baseline)

provide relevant evidence. Second, administrative identification of new SGLT2i use may not be reflected in the electronic medical record (EMR), thus being wrongly diagnosed as a new SGLT2i user when the patient was actually a chronic SGLT2i user, as a chronic SGLT2i user showed neutral effect for CA-AKI from our analysis; the "true" effect of new SGLT2i on creatinine spike could be even larger. Third, we could not measure kidney injury biomarkers, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and monocyte chemoattractant protein-1, which may provide an extra tool to judge real CA-AKI besides creatinine [37, 38]. Finally, we could not measure the long-term cardiovascular and renal outcomes, which may provide evidence to prove the effect of SGLT2i administration based on a long-term follow-up.

Our data provide evidence that as to CA-AKI risk, administration of SGLT2i is safe just before the time of contrast exposure, and in situation when SGLT2i has been already used before hospitalization, it should not be routinely withheld when contrast use is needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02214-7.

Supplementary Material 1.

Acknowledgements
None.

Author contributions
J.L, B.N, M.J, and J.J. contributed to the design and conduct of the study and interpretation of the data. J.L. and H.Y. contributed to the analysis and interpretation of data. J.L., C.A., M.J, and B.N drafted the manuscript. All authors critically revised the manuscript and gave their final approval. J.J. and J.L. had full access to all data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

Funding
This work is supported by innovation leading talents of Chongqing talent plan (J.J), university seeding foundation (JW L), and excellent talent program of Xinqiao hospital (2023XKYC011, JW L).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Institutional Review Board of the Xinqiao Hospital approved the research protocol. The study was performed in accordance with Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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Received: 3 March 2024 Accepted: 9 December 2024
Published online: 24 December 2024

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