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Empagliflozin in Patients With Type 2 Diabetes Undergoing On-Pump CABG: The POST-CABGDM Randomized Clinical Trial

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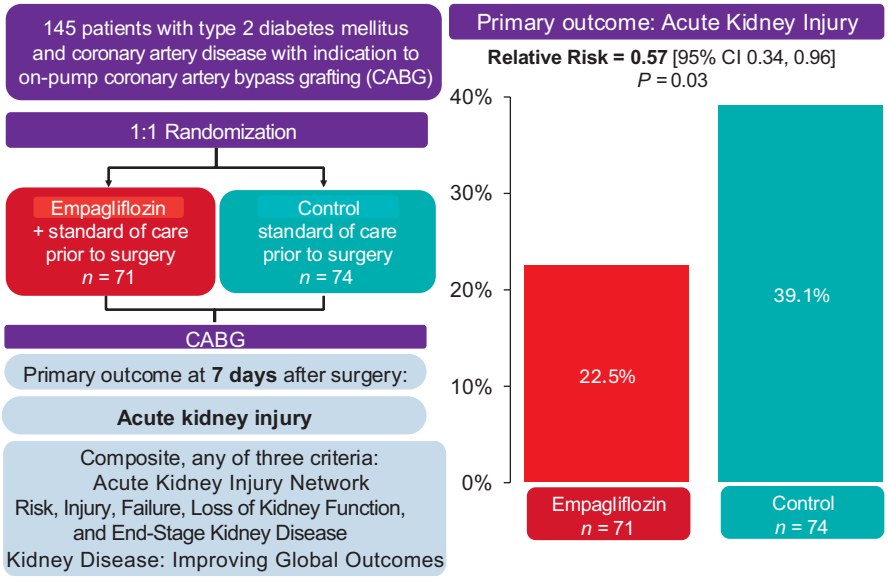

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To assess the efficacy and safety of empagliflozin in patients with type 2 diabetes mellitus undergoing coronary artery bypass grafting (CABG).
- **What is the specific question we wanted to answer?**
  Does initiating empagliflozin at least 3 months before on-pump CABG reduce the incidence of postoperative acute kidney injury (AKI)?
- **What did we find?**
  Among 145 participants ($n = 71$ empagliflozin plus standard care group; $n = 74$ standard care group), administration of empagliflozin prior to CABG reduced postoperative AKI (relative risk 0.57 [95% CI 0.34–0.96]; $P = 0.03$).
- **What are the implications of our findings?**
  The observed kidney protective effects of an SGLT2 inhibitor in this setting warrant confirmation in larger, adequately powered trials.

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OBJECTIVE

To evaluate the efficacy and safety of empagliflozin in patients with type 2 diabetes mellitus (T2DM) undergoing elective on-pump coronary artery bypass grafting (CABG).

RESEARCH DESIGN AND METHODS

Investigator-initiated, pragmatic, single-center, randomized, open-label trial with blinded outcome adjudication conducted in Brazil. A total of 145 patients with T2DM scheduled for elective on-pump CABG were randomized to receive empagliflozin 25 mg daily plus standard care (*n* = 71) for at least 3 months, which was discontinued 72 h before surgery, or to received standard care alone (*n* = 74). The primary outcome was postoperative acute kidney injury (AKI) within 7 days of surgery, defined by creatinine-based criteria (namely, Acute Kidney Injury Network; Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; or Kidney Disease: Improving Global Outcomes). Secondary outcomes included 30-day postoperative atrial fibrillation and type 5 myocardial infarction (MI). Safety outcomes were ketoacidosis, urinary tract infection, hospital-acquired pneumonia, and wound infection within 30 days after CABG.

RESULTS

AKI occurred in 22.5% of the empagliflozin group vs. 39.1% in the control group (relative risk [RR] 0.57 [95% CI 0.34–0.96]; *P* = 0.03). Rates of atrial fibrillation (15.4% vs. 13.5%; RR 1.15 [95% CI 0.52–2.53]; *P* = 0.73) and type 5 MI (1.4% vs. 4.1%; RR 0.35 [95% CI 0.04–3.26]; *P* = 0.62) were similar between groups. No statistically significant differences between groups were observed for safety events. Three deaths occurred, all in the control group.

CONCLUSIONS

Empagliflozin use before on-pump CABG in patients with T2DM was associated with a reduced incidence of postoperative AKI without an increase in safety events. These findings warrant confirmation in larger clinical trials.

Type 2 diabetes mellitus (T2DM) is a risk factor for coronary artery disease (CAD). It is associated with diffuse, complex, and multivessel CAD. Coronary artery bypass

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graft (CABG) surgery is the preferred revascularization strategy for patients with T2DM (1). CABG is the most commonly performed cardiac surgery worldwide (2), and nearly half of the surgeries are performed on individuals with T2DM (3). Complications after CABG include death, myocardial infarction (MI), stroke, surgical site infection, and acute kidney injury (AKI). AKI is common after cardiac surgery, and T2DM and the use of cardiopulmonary bypass (on-pump) are known risk factors for developing this complication (4).

Perioperative AKI is associated with an increased risk of MI (5), heart failure (HF) (6), progression to end-stage chronic kidney disease (CKD) (7), and death. None of the therapies used for kidney protection in the outpatient setting for patients with T2DM and at risk for kidney disease have been shown to effectively reduce the incidence of AKI in patients undergoing CABG (8).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) have shown protective effects on kidney and cardiovascular outcomes in patients with T2DM, HF, and CKD (9). SGLT2 inhibition may also positively influence the biological processes involved in post-CABG kidney injury by mitigating inflammation pathways, reducing oxidative stress, alleviating kidney cortical hypoxia and ischemia, and avoiding kidney venous hypertension during hypervolemia (10,11). In animal models of AKI, SGLT2is reduced inflammatory biomarkers and protected against renal damage (12–15). Furthermore, in a meta-analysis, chronic use of SGLT2is was associated with a reduced risk of AKI compared with placebo and other glucose-lowering therapies (16).

Therefore, we designed the Empagliflozin in Type 2 Diabetes Undergoing On-Pump CABG (POST-CABGDM) trial, a randomized, open-label trial with blinded adjudication of outcomes to evaluate the efficacy of adding empagliflozin to the standard of care in patients with T2DM undergoing on-pump CABG for the prevention of AKI.

RESEARCH DESIGN AND METHODS

Trial Design and Population

The POST-CABGDM was a single-center, investigator-initiated, pragmatic, randomized, open-label, proof-of-concept trial with blinded outcome adjudication conducted at Instituto do Coracao, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. The trial was registered with ClinicalTrials.gov (identifier NCT04523064). The local ethics committee approved the trial protocol, and all patients provided written informed consent. The trial was conducted in accordance with the Good Clinical Practice guidelines and is reported following the Consolidated Standards of Reporting Trials 2010 statement for parallel-group randomized clinical trials (17).

Patients aged 18 years or older with T2DM and angiographically confirmed multivessel CAD with planned coronary revascularization using on-pump CABG were eligible for the trial. Exclusion criteria were prior use of any SGLT2i, an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (Calculated with the Chronic Kidney Disease–Epidemiology Collaboration formula), chronic dialysis, and the need for urgent coronary revascularization. The list of inclusion and exclusion criteria is provided in the Supplementary Materials.

Randomization, Allocation Concealment, and Blinding

Eligible patients were randomized and assigned in a 1:1 ratio to receive open-label empagliflozin 25 mg before CABG in addition to standard care (empagliflozin group) or standard care alone (control group). Randomization was performed by an automated system (Research Electronic Data Capture), stratified by age (<65 vs. ≥ 65 years) and eGFR (≤ 45 vs. >45 mL/min/1.73 m^2), with variable block sizes. Health care personnel, patients, and clinicians were aware of the treatment group assignment.

Interventions and Procedures

All patients referred for CABG receive comprehensive perioperative medical management to minimize perioperative complications. Clinical care involves, but is not limited to, the optimization of secondary prevention medications, blood pressure management, and glycemic control. Patients with T2DM are expected to achieve an HbA_{1c} $\leq 8\%$. The trial protocol specified only the addition of empagliflozin to the standard of care for patients randomized to the intervention group. All other trial procedures were integrated into routine care and conducted by health care personnel.

Empagliflozin 25 mg/day was administered orally for a minimum of 3 months prior to CABG and continued until 72 h before surgery, following the US Food and Drug Administration guidance to stop SGLT2is 3 to 4 days before a scheduled surgery. β-Blockers and renin-angiotensin system inhibitors were continued until the day of surgery. Care in the intensive care unit (ICU) was provided as standard-of-care treatment of critical illness, with aspects of care determined exclusively by the ICU health care team. Serum creatinine was expected to be measured daily during the ICU stay and according to clinical indications during hospitalization. As part of routine care, patients who underwent CABG were followed up for at least 1 month after hospital discharge.

Study Outcomes

The primary outcome was the occurrence of AKI during the first week after CABG. AKI was defined as meeting at least one stage 1 criterion from any of the following three AKI definitions: (1) Kidney Disease: Improving Global Outcomes (KDIGO) (18); (2) Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) (19); or (3) Acute Kidney Injury Network (AKIN) (20). Baseline creatinine values were defined as the most recent measurement prior to surgery. Detailed definitions of outcomes for AKI are provided in Supplementary Table 1. The primary outcome was assessed for each AKI criterion by an independent committee composed of three physicians unaware of randomized treatment assignments, with baseline serum creatinine level defined as the most recent value obtained before the surgical procedure.

There were two prespecified secondary outcomes: occurrence of atrial fibrillation and type 5 MI (definitions are listed in Supplementary Table 2). Secondary outcomes were evaluated during the hospitalization for the surgical procedure and up to 30 days after the surgery date. Ketoacidosis, urinary tract infection, hospital-acquired pneumonia, wound infection, need for ICU readmission, and need for continuous intravenous (IV) insulin were prespecified safety events and were also monitored during the study.

Statistical Analysis

We estimated that a sample size of 144 patients would provide the trial with at least 75% power to detect an effect size of 0.5 (21) if 40% of patients undergoing

CABG would meet at least one of the three AKI criteria, with a two-sided α of 5%. All analyses were conducted in the modified intention-to-treat population, excluding patients who were randomized to treatment arm and who did not undergo the planned surgery. Continuous variables are presented as means with SDs or medians with interquartile ranges (IQRs); categorical variables are presented as frequencies and proportions. All primary and secondary binary outcomes were analyzed unadjusted, with intervention effects reported as relative risks (RRs) and absolute risk differences along with their corresponding 95% CIs. Between-group differences were compared using a two-tailed χ^2 test or Fisher exact test, as appropriate. Changes in serum creatinine levels during study follow-up were analyzed using a mixed model for repeated measures, adjusted for baseline values. Mean estimated serum creatinine levels for trial groups were plotted with corresponding 95% CIs, with between-group mean differences and 95% CIs calculated for each trial time point.

Four post hoc analyses were conducted to evaluate the empagliflozin effect on patient-centered exploratory outcomes: *1*) 30-day mortality, defined as all-cause death within 30 days after surgery; *2*) occurrence of stroke during the 30 days after surgery; *3*) ICU-free days; and *4*) hospital-free days. ICU- and hospital-free days were defined as the number of calendar days spent not in the ICU and hospital, respectively, within 30 days after surgery. Patients who died within 30 days were assigned the worst possible score (0, on an ordinal scale from 0 to 30, with higher values indicating more positive outcomes), with between-group comparisons performed using the Wilcoxon rank-sum test and median absolute differences calculated using the Hodges-Lehmann method. An additional analysis was conducted using serum creatinine values at enrollment as the baseline for defining AKI to account for minor eGFR fluctuations related to initiation or discontinuation of empagliflozin.

A two-sided P value < 0.05 was considered to indicate statistical significance. No adjustment was performed for multiple comparisons; thus, the interpretation of P values and 95% CIs for all secondary outcomes and post hoc analyses should not be used to infer definite treatment effects. All analyses were conducted using R software, version 4.2.1 or higher (R Foundation for Statistical Computing).

RESULTS

Trial Population and Interventions

Between September 2020 and October 2023, 371 patients with T2DM and an indication for CABG were screened, and 154 were deemed eligible for this trial and randomized, 76 to the empagliflozin group and 78 to the control group. Among the 154 randomized participants, 145 underwent surgery (n = 71 in the empagliflozin group and 74 in the control group) and were included in the modified intention-to-treat analysis (Supplementary Fig. 1). In nine participants (n = 5 in the empagliflozin group and 4 in the control group), the CABG procedure was performed off-pump due to intraoperative technical decisions.

The mean age of participants was 61.9 years (±8.2), of whom 33.1% were female. Among the participants, 137 (94.5%) had hypertension, and 74 (51%) had a history of prior MI. The overall uptake of guideline-directed medical therapy for CAD was high, with 137 (94.5%), 139 (95.9%), and 127 (87.6%) patients using aspirin, a high-potency statin, and renin-angiotensin system inhibitors, respectively. A total of 127 participants (87.6%) had a three-vessel disease, and 115 (79.3%) received three or more grafts, with the surgical procedure occurring a median of 91 days after randomization to study arm (IQR = 82, 104) in the empagliflozin group and 89 days (IQR = 82, 104) in the control group (Supplementary Fig. 2). Detailed baseline, anatomic, and procedural characteristics are reported in Table 1.

Empagliflozin was administered to all randomized participants in the intervention group who underwent CABG from randomization until 72 h before the scheduled surgery, except for a single participant (1.4%) whose medication was discontinued because of the development of a side effect (skin reaction) prior to surgery. No patients in the control group received any SGLT2i before the procedure. Serum creatinine values were available for >95% of participants from randomization to day 3 after the CABG procedure (Supplementary Table 3 and Supplementary Fig. 3).

Primary, Secondary and Exploratory Outcomes

Within the first 7 days after surgery, AKI developed in 16 patients (22.5%) in the empagliflozin group and in 29 patients (39.1%) in the control group (absolute difference, −16.7% [95% CI −31.4% to −1.9%]; RR 0.58 [95% CI 0.34, 0.96]; P = 0.03). The number of patients who met the AKIN and KDIGO criteria was the same as for the composite AKI primary outcome, whereas fewer patients met the RIFLE criterion: 9 (12.7%) in the empagliflozin group and 13 (17.6%) in the control group. In both groups, serum creatinine levels declined immediately after the procedure. Mean serum creatinine levels throughout the study follow-up according to study group are shown in Fig. 1. The relationship between baseline and peak serum creatinine levels during follow-up for each participant is shown in Supplementary Fig. 4. Among AKI staging criteria, only one case (in the control group) developed stage 3 criteria; most patients met AKI stage 1 criteria (n = 13 patients in the empagliflozin group and 24 patients in the control group).

At 30 days after surgery, there were no between-group significant differences for the secondary outcomes of atrial fibrillation (RR 1.15 [95% CI 0.52, 2.53]; P = 0.73) and type 5 MI (RR 0.35 [95% CI 0.04, 3.26]; P = 0.62). There was only one case of in-hospital death, and two death events occurring after hospital discharge within 30 days after surgery. Detailed narratives of all death events occurring in the study are provided in Supplementary Table 4. Sensitivity analyses using the per-protocol population and defining AKI based on creatinine level at randomization as the baseline yielded similar results to the primary analysis (Supplementary Tables 5 and 6, respectively). The results for the exploratory outcome of ICU-free days at day 30 after surgery were similar in the trial groups: 27 days (IQR = 26, 28) in the empagliflozin group and 28 (IQR = 26, 28) in the control group (absolute difference, 0 days [95% CI 0, 0]; P = 0.87). The median hospital-free days at day 30 was higher in the empagliflozin group (n = 22 days; IQR = 17.5, 22) versus the control group (n = 21 days; IQR = 9, 22; absolute difference, 1 day [95% CI 0, 2]; P = 0.04] (Supplementary Figs. 5 and 6). Data for primary, secondary, and exploratory outcomes are reported in Table 2.

Safety

The use of empagliflozin before surgery did not result in a statistically significant

Table 1—Baseline, angiographic and procedure characteristics

Characteristic	Empagliflozin group (*n* = 71)	Control group (*n* = 74)
Age, mean (SD), years	62.1 (7.9)	61.8 (8.5)
Female sex at birth, *n* (%)	20 (28.2)	28 (37.9)
Race, *n* (%)		
Black	5 (7.0)	8 (10.8)
Multiracial	10 (14.1)	5 (6.8)
White	56 (78.9)	61 (82.4)
Medical history, *n* (%)		
Hypertension	67 (94.3)	70 (94.5)
Diabetes mellitus		
Duration >10 years	42 (59.1)	42 (56.7)
Insulin dependent	28 (39.4)	27 (36.4)
Prior MI	34 (47.8)	40 (54.0)
Prior stroke	5 (7.0)	6 (8)
HF	30 (42.2)	31 (41.9)
Peripheral artery disease	7 (9.8)	9 (12.1)
History of tobacco use, *n* (%)	37 (52.1)	41 (55.4)
Concomitant medications, *n* (%)		
Aspirin	67 (94.4)	70 (94.5)
Clopidogrel	15 (21.1)	15 (20.2)
High potency statin*	70 (98.5)	69 (93.2)
ACE inhibitor or ARB	59 (83.1)	68 (91.9)
Diuretic†	23 (32.4)	29 (39.2)
β-Blocker	67 (94.3)	68 (91.8)
Metformin	62 (87.3)	66 (89.1)
Serum creatinine level, median (IQR), mg/dL	1.01 (0.8, 1.1)	1.04 (0.8, 1.1)
eGFR‡, median (IQR), mL/min/1.73 m^2	76 (63, 88)	72 (60, 89)
Left ventricular ejection fraction, median (IQR), %	57 (50, 60)	58 (52, 62)
≤50%, *n* (%)	24 (33.8)	18 (24.3)
HbA_{1c}, median (IQR), %		
At enrollment	7.5 (6.4, 8.5)	7.7 (6.5, 8.4)
Prior to surgery	6.5 (6.0, 7.0)	6.8 (6.1, 7.3)
Hemoglobin, median (IQR), g/dL		
At enrollment	14.0 (13.0, 14.8)	13.8 (12.7, 15.1)
Prior to surgery	14.3 (13.4, 15.1)	13.6 (12.5, 14.8)
LDL cholesterol, median (IQR), mg/dL	85 (63, 106)	83 (61, 101)
HDL cholesterol, median (IQR), mg/dL	41 (33, 47)	40 (33, 46)
Logistic EuroSCORE II, median (IQR), %	0.94 (0.71, 1.56)	1.06 (0.77, 1.51)
Anatomic and procedural characteristics		
Three-vessel disease, *n* (%)	63 (88.7)	64 (86.5)
Time to surgery, median (IQR), days	91 (82, 104)	89 (82, 104)
CBP duration§, median (IQR), min	90 (73, 105)	92 (79, 108)
Grafts, *n* (%)		
2	13 (18.3)	17 (22.9)
3	35 (49.2)	36 (48.6)
≥4	23 (32.3)	21 (28.3)

ARB, angiotensin receptor blocker; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation score. *Defined as the use of atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. †Use of loop diuretics or thiazides. ‡Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. §Data for 66 patients undergoing on-pump CABG in the empagliflozin group and 70 patients in the control group.

increase in safety events during the follow-up period (Table 3). However, continuous IV insulin was used more frequently among participants in the empagliflozin group (*n* = 49 patients [69%]) compared with those in the control group (*n* = 42 patients [56.8%]) (*P* = 0.12). A total of 22 patients developed sternal wound infections, with 10 (14.1%) in the empagliflozin group and 12 (16.2%) in the control group. Very few instances of urinary tract infection were observed; there were three cases in the empagliflozin group (4.2%) and three cases in the control group (4.1%). No cases of ketoacidosis were observed.

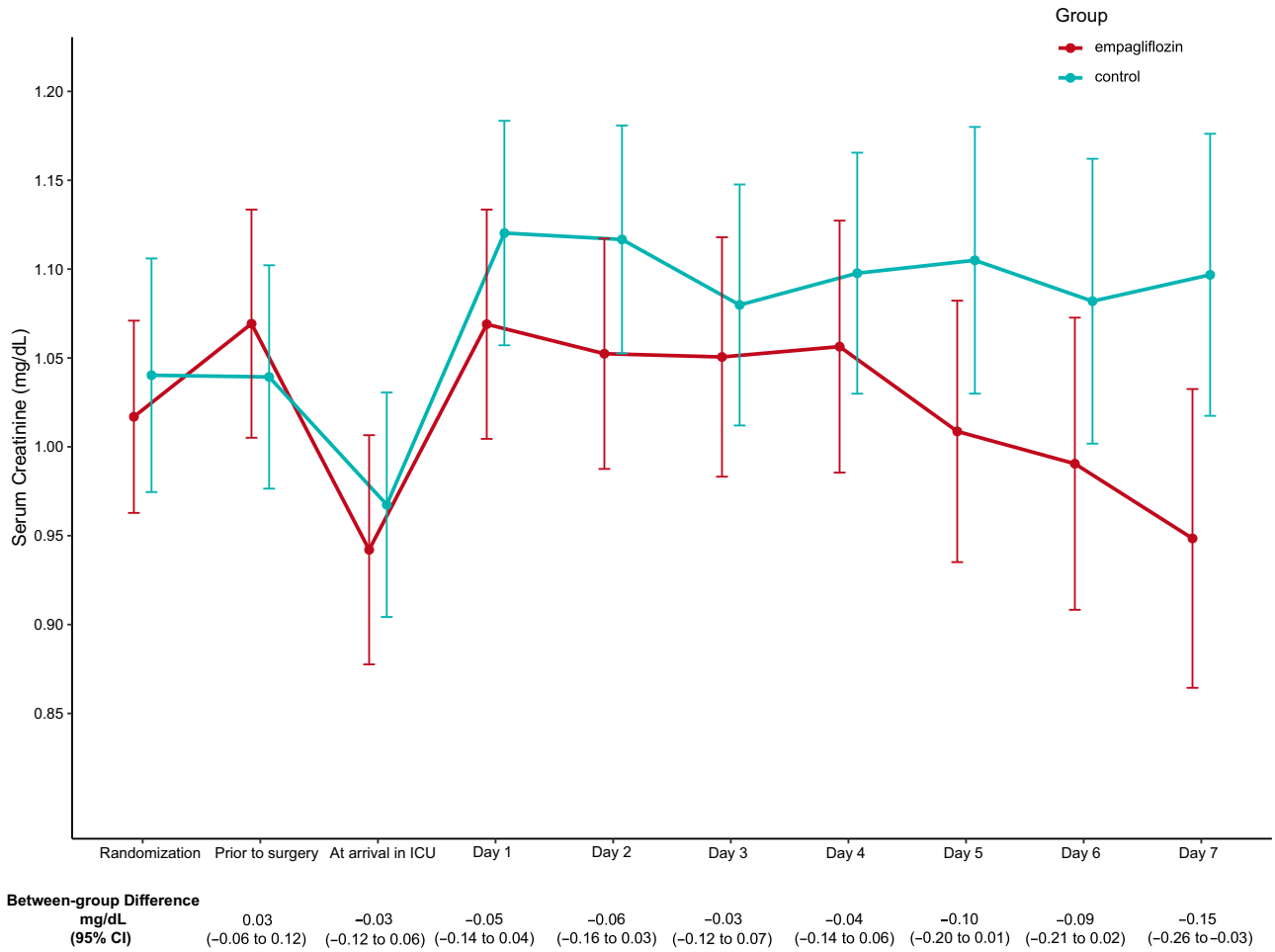

Figure 1—Changes in serum creatinine during study follow-up. The mean estimated serum creatinine levels for the empagliflozin and control groups during study follow-up. Mean values for trial groups and between-group differences (empagliflozin minus control) were estimated using a linear mixed model for repeated measures, adjusted for baseline creatinine levels. The coordinates of the estimated serum creatinine values for the empagliflozin group (red circles) were slightly shifted to the left to facilitate visualization. Vertical bars represent 95% CIs. To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

CONCLUSIONS

In this pragmatic, single-center, randomized, open-label clinical trial, the use of empagliflozin prior to on-pump CABG for patients with T2DM resulted in a significantly lower incidence of AKI compared with the standard of care. Administering empagliflozin before surgery, with preoperative cessation 72 h before surgery, did not lead to a statistically significant increase in infections (namely, pneumonia, urinary tract, or sternal wound infection) or need for ICU readmission, and no instances of ketoacidosis were observed. Although the use of empagliflozin was associated with an increase in 1 day alive and out of hospital, no significant effects were observed for all-cause mortality, all secondary outcomes, and the number of days that patients were alive and not admitted to the ICU. Nephroprotective effects of empagliflozin were not observed for more severe AKI (stage 2 or higher).

Several factors are associated with AKI occurring after on-pump CABG, including hypoperfusion, fluid balance, excess sympathetic activation, ischemia-reperfusion injury, oxidative stress, and inflammation (22). Current knowledge suggests that SGLT2is modulate several biological processes that might confer kidney protection in this context, such as improved kidney oxygenation, reduced kidney sympathetic nerve activity, decreased cellular stress, and suppression of proinflammatory pathways (10,23). Given the intricate relationship between pathogenesis and protection mechanisms, it is challenging to ascertain the exact mechanisms driving the nephroprotective effects observed in our study. However, it does not appear to be related to better glycemic control. Preoperative HbA_{1c} values were similar between groups, and the need for continuous IV insulin was numerically higher in the empagliflozin group. Similarly, the precise mechanisms underlying the cardiovascular and kidney benefits observed in large, randomized outcome trials of SGLT2is are still to be determined, but they are also independent of glucose control. Importantly, because empagliflozin was discontinued 72 h prior to surgery—corresponding to approximately six half-lives of the drug—there appears to be carryover protection against kidney injury, because no meaningful drug activity was expected when surgery commenced. We chose to stop empagliflozin before surgery because preoperative cessation of SGLT2is was recommended during the trial design and is still endorsed by the American Diabetes Association Standards of Care (24,25). It was only after we began enrollment that evidence emerged

Table 2—Primary, secondary, and exploratory outcomes

Outcome	Empagliflozin group (n = 71)	Control group (n = 74)	Absolute difference, % or days (95% CI)	RR (95% CI)	P value
Primary outcome at 7 days					
AKI, n (%)	16 (22.5)	29 (39.1)	−16.7 (−31.4 to −1.9)	0.57 (0.34, 0.96)	0.03
AKIN	16 (22.5)	29 (39.1)			
KDIGO	16 (22.5)	29 (39.1)			
RIFLE	9 (12.7)	13 (17.6)	−9.5 (−32.0 to −13.0)	0.72 (0.33, 1.58)	0.41
Secondary outcomes at 30 days					
Atrial fibrillation, n (%)	11 (15.4)	10 (13.5)	2.0 (−9.4 to 13.4)	1.15 (0.52, 2.53)	0.73
Type 5 MI, n (%)	1 (1.4)	3 (4.1)	−2.6 (−7.9 to 2.6)	0.35 (0.04, 3.26)	0.62
Exploratory outcomes at 30 days					
All-cause mortality, n (%)	0 (0)	3 (4.0)	−4.0 (−8.5 to 0.4)	–	0.25
Stroke, n (%)	1 (1.4)	2 (2.7)	−1.3 (−5.9 to 3.3)	0.52 (0.05, 5.62)	1.00
KDIGO AKI stage, n (%)					
1	13 (18.3)	24 (32.4)	−14.1 (−28.1 to −0.1)	0.56 (0.31, 1.02)	0.05
2	3 (4.2)	4 (5.4)	−1.2 (−8.1 to 5.8)	0.78 (0.18, 3.36)	1.00
3	0 (0)	1 (1.4)	−1.4 (−4.0 to 1.3)	NA	1.00
Days free, median (IQR)*			Days (95% CI)†		
ICU	27 (26, 28)	28 (26, 28)	0 (0, 0)	NA	0.87
Hospital	22 (17.5, 22)	21 (9, 22)	1 (0, 2)	NA	0.04

95% CIs were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; RIFLE, risk, injury, failure, loss, end-stage renal disease. *Days free was defined as the number of days alive and free of each component. †Absolute difference (empagliflozin minus control) was derived from the Hodges-Lehmann estimator, which represents the median of all pairwise comparisons between trial groups. Higher values indicate a more favorable outcome.

supporting the safety of this drug class in hospitalized patients with acute HF (26), or COVID-19 (27), and in those with critical illness and acute organ dysfunction (28).

Our findings are consistent with those of prior studies involving this drug class. In a meta-analysis of large randomized trials (each with >1,000 participants), which combined data from 90,413 patients with diabetes at high cardiovascular risk, CKD, or HF (with and without diabetes), the use of SGLT2is reduced the incidence of AKI by 23% compared with placebo (RR 0.77; 95% CI 0.70, 0.84) (9). Additionally, kidney events were lower with the use of SGLT2is in trials conducted in populations with acute illnesses, such as patients hospitalized with COVID-19 (27) and critically ill individuals with acute organ dysfunction (28).

SGLT2is are first-line therapy in European and American guidelines for patients with cardiovascular disease and T2DM to reduce cardiovascular risk independent of blood glucose control (29,30). However, patients with planned cardiac surgery or revascularization procedures at the time of enrollment were excluded from most of the randomized clinical trials that support this recommendation (31–33). Therefore, our study provides complementary evidence about this drug class among those in the high-risk spectrum of CAD, for whom empagliflozin appeared safe and demonstrated a protective effect against mild kidney injury.

AKI after cardiac surgery is a health issue associated with a range of adverse outcomes: progression to CKD, low quality of life, end-stage kidney disease, and all-cause mortality (34,35). The long-term association of AKI with patient-centered outcomes underscores the importance of preventing AKI during this vulnerable period. Despite this established association, there is a lack of therapies with proven efficacy to prevent this complication. The adoption of supportive measures and the infusion of amino acids reduce the incidence of AKI among patients undergoing cardiac surgery (36,37). These are potential strategies to mitigate this complication, because several other interventions have failed to demonstrate efficacy in

Table 3—Safety outcomes

Safety outcome after CABG at 30 days	Empagliflozin group (n = 71), n (%)	Control group (n = 74), n (%)	RR (95% CI)	P value
Need for continuous IV insulin	49 (69.0)	42 (56.8)	1.22 (0.94, 1.57)	0.12
Sternal wound infection	10 (14.1)	12 (16.2)	0.87 (0.40, 1.88)	0.72
Hospital-acquired pneumonia	6 (8.5)	4 (5.4)	1.56 (0.46, 5.31)	0.53
ICU readmission	2 (2.8)	5 (6.8)	0.42 (0.94, 2.08)	0.44
Urinary tract infection	3 (4.2)	3 (4.1)	1.04 (0.22, 4.99)	1.00
Ketoacidosis	0 (0)	0 (0)	NA	NA

NA, not applicable.

preventing AKI (35). The POST-CABGDM study observed a novel effect of preoperative empagliflozin administration in preventing kidney events, further supporting the nephroprotective effect of this drug class. Although the kidney protective effects observed in our study were primarily driven by reductions in mild AKI, it is important to note that even mild AKI is linked to worse clinical outcomes compared with patients who do not develop AKI (38).

These findings warrant further investigation in larger randomized clinical trials testing this hypothesis. The ongoing Empagliflozin to Prevent Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Graft Surgery trial will assess whether SGLT2is can reduce postoperative atrial fibrillation (39), and the Evaluating the Effect of Perioperative Empagliflozin trial is evaluating whether starting empagliflozin 5 days before surgery and continuing for 7 days postoperatively lowers the risk of major adverse kidney events (namely, ≥25% decrease in eGFR, need for kidney replacement therapy, or all-cause mortality) (40). These trials will provide important insights into the risk-benefit profile of SGLT2is in the CABG setting.

Study Strengths and Limitations

To our knowledge, this is the first trial to present efficacy and safety data about the specific preoperative use of an SGLT2i in patients with T2DM and CAD undergoing on-pump CABG. Moreover, we were able to embed trial activities into the existing practice while maintaining high-quality standards for adhesion to study intervention and outcomes ascertainment. Roughly 50% of screened patients were randomized, and no patient was lost to follow-up within 30 days after the CABG procedure.

Several limitations need to be considered. First, this is an open-label trial, and AKI was the only outcome adjudicated by blinded reviewers. Second, it was conducted in a single tertiary referral center that performs a large volume of cardiac surgeries annually, which might limit the generalizability of our findings. However, the observed incidence of AKI and 30-day mortality were similar to those reported in this population (4,38). Third, we acknowledge that the primary outcome was based solely on serum creatinine values because urine output after the first day of surgery is not routinely collected in our institution. This limitation may have influenced our findings due to variations in fluid status during the perioperative period or the discontinuation of empagliflozin prior to surgery in the intervention group. However, both study groups exhibited similar trends in serum creatinine levels immediately after surgery, and the post hoc analysis using creatinine level at randomization as the baseline yielded results consistent with our primary analysis. Fourth, due to our pragmatic design, biomarkers of AKI and physiological markers related to the metabolic effects of SGLT2 inhibition were unavailable. The lack of a comprehensive biomarker profile for AKI, along with the preoperative discontinuation of empagliflozin, limits our ability to fully understand the mechanisms underlying the observed kidney protection or whether these effects would persist if empagliflozin had been continued throughout the perioperative period. However, it is important to emphasize that the POST-CABGDM trial was not designed to explore mechanistic pathways. Finally, given the wide CIs across all study outcomes, the observed effect sizes require confirmation in larger studies.

Conclusion

Among patients with T2DM undergoing on-pump CABG, the preoperative addition of empagliflozin to standard care was associated with a lower incidence of AKI within the first 7 days after surgery, without difference in safety events. These findings justify larger studies investigating the nephroprotective effects of SGLT2is in the preoperative setting of cardiac surgery.

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