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Cardioprotective Effect of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients: A Multicenter Propensity Score Matched Study

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Introduction: Kidney transplantation (KT) improves the cardiovascular outcomes of patients with end-stage kidney disease. However, cardiovascular disease remains the leading cause of premature death and graft loss in KT recipients (KTRs) with diabetes. We evaluated the cardioprotective effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in KTRs with diabetes.

Methods: A total of 750 KTRs with diabetes were enrolled from 6 tertiary hospitals. Among them, 129 patients (17.2%) were prescribed SGLT2i. The primary outcome was the incidence of major adverse cardiovascular events (MACE), which comprised myocardial infarction (MI), death from cardiovascular causes, hospitalization for heart failure, and stroke. Multivariable Cox regression analysis and propensity score matching were used to investigate the effect of SGLT2i on clinical outcomes.

Results: In the matched cohort, MACE occurred in 5 patients (3.9%) in the SGLT2i group and 15 patients (11.8%) in the non-SGLT2i group, out of 127 patients in each group over 55.3 months. The incidence of MACE and MI was lower in the SGLT2i group than in the non-SGLT2i group ($P = 0.036$ and 0.008, respectively). In multivariate analysis, the SGLT2i group had a lower risk of MACE and MI than the non-SGLT2i group (adjusted hazard ratio [HR], 0.30 and 0.04; 95% confidence interval [CI], 0.10–0.88 and 0.004–0.40; $P = 0.028$ and 0.006, respectively). There was no difference in the incidence of urinary tract infection (UTI) between the 2 groups.

Conclusion: SGLT2i significantly decreased the risk of cardiovascular events in KTRs with diabetes, particularly lowering the incidence of MI and death from cardiovascular causes. SGLT2i can be used to reduce the burden of cardiovascular disease in KTRs with diabetes.

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KT is the treatment of choice for patients with end-stage kidney disease that can improve clinical and patient-reported outcomes.[1,2] KTRs have a higher survival rate than patients who undergo dialysis because of the decreased cardiovascular disease burden.[3,4] However, studies have reported that KTRs have a higher risk of cardiovascular mortality than the general population.[5,6] KTRs also have a high prevalence of cardiovascular risk factors, such as diabetes, hypertension, and dyslipidemia. In addition, the maintenance of immunosuppressants increases the risk of cardiovascular disease.[3,7-9]

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Despite the high risk of cardiovascular disease, this area remains understudied and undertreated in KTRs.[3] Numerous studies have failed to reduce the risk of cardiovascular disease, and there have been few drugs that have been shown to effectively lower the risk of cardiovascular disease that are applicable to KTRs.[10-12] Furthermore, KTRs are generally excluded from major cardiovascular outcome trials because of drug interactions with their immunosuppressants and balancing their graft preservation in KTRs.[13]

Recently, SGLT2i have emerged as effective agents for cardiovascular disease. They were originally designed to manage hyperglycemia by inhibiting renal glucose reabsorption, but they also exhibited potent protective effects on the heart and kidneys.[14,15] Their cardiovascular benefits include reduced cardiovascular death and hospitalization, which have been widely acknowledged in several landmark trials.[14-17]

The pathophysiologic mechanisms of cardiovascular protection by SGLT2i have been identified. SGLT2i has multifaceted protective mechanisms, such as natriuresis, modulation of the inflammatory pathways, and the preservation of endothelial function, which contributes to cardiovascular protection.[18-20] Considering these mechanisms, SGLT2i is expected to also have cardiovascular benefits in KTRs.

We have previously reported the protective effects and safety of SGLT2i on graft function in KTRs.[21] However, few studies have assessed the effect of SGLT2i on the development of cardiovascular disease after KT. This study aimed to evaluate the cardiovascular benefits and safety of SGLT2i in KTRs. This will facilitate optimal care for KTRs, thereby improving cardiovascular outcomes and reducing deaths with functioning grafts.

METHODS

Study Participants

This study retrospectively analyzed the multicenter KT cohort data. Among the 7196 KTRs who received the transplant before 2020 at 6 tertiary hospitals in Korea, those who had diabetes before KT or developed posttransplant diabetes mellitus were enrolled ($n = 2282$). Posttransplant diabetes mellitus was diagnosed according to the international consensus guidelines.[22] Among them, patients with a history of pancreas transplantation were excluded. Detailed information regarding the cohort is presented in our previous study.[21] Unlike the previous study, we used data from patients who underwent KT after 2015, a period when SGLT2i was available, rather than the entire KT cohort. This approach was intended to reduce lead time and selection biases caused by a prolonged interval between the date of transplantation and the initiation of SGLT2i treatment. Patients were excluded if they had heart failure, acute coronary syndrome, or stroke and had received percutaneous coronary intervention or coronary artery bypass surgery within 3 months before KT. We also excluded patients who had been prescribed SGLT2i for <90 days to avoid confounding effects. Finally, a total of 750 KTRs were analyzed using a propensity score matching adjusted for baseline characteristics (Figure 1).

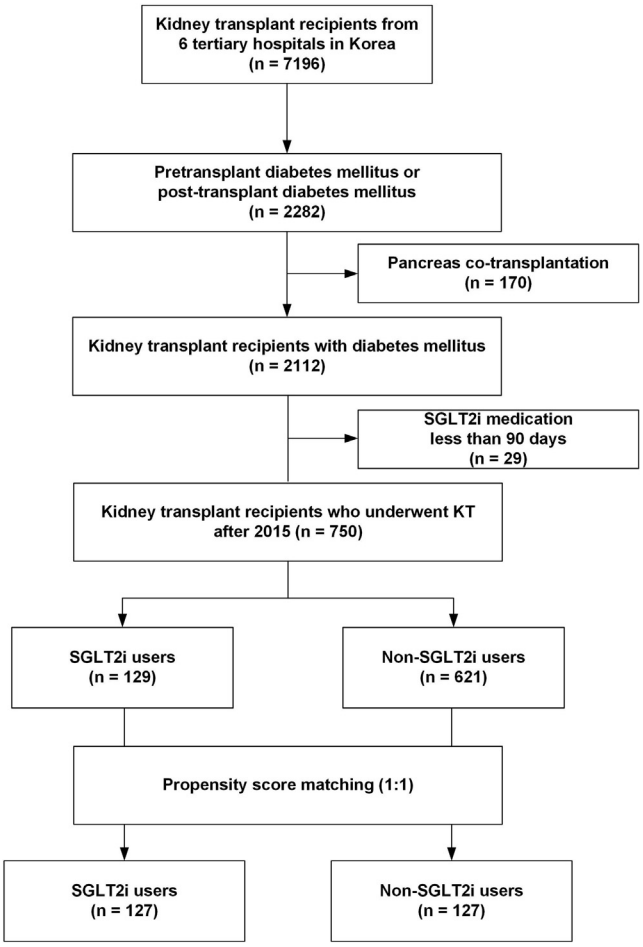

Figure 1. Flow diagram of the study participants. KT, kidney transplantation; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Data Collection

The baseline characteristics, which included age, natal sex, body mass index, cause of end-stage kidney disease, pretransplant dialysis type and duration, and comorbidities, as well as donor information, were collected at the time of KT. Follow-up laboratory data, including serum creatinine and HbA1c levels, were collected at 3 and 12 months after KT. Data regarding hospitalization for cardiovascular disease, death and cause of death, and data from the last follow-up were obtained retrospectively from the electronic medical records. Adverse events included UTI, including

bacterial and fungal infections, and euglycemic ketoacidosis. UTI was determined by the result of a urine culture. Euglycemic ketoacidosis was defined as a state of metabolic acidosis with pH <7.3, ketonuria, and blood glucose <250 mg/dl.[23]

Outcomes

The primary outcome was MACE, consisting of MI, death from cardiovascular causes, hospitalization for heart failure, or stroke in the propensity score matched group. Each component of the primary outcome was further analyzed separately as the secondary outcomes. The start time for the survival analyses was established as when the patient began taking antidiabetic medication after KT.

Statistical Analysis

The normal distribution of variables was analyzed using the Shapiro-Wilk test. Continuous variables were expressed as the median (interquartile range [IQR]), and the categorical variables were expressed as numbers (percentage, %). The Mann-Whitney *U* test was used to determine the differences between continuous variables, and the χ^2 test or Fisher exact test was used for the categorical variables. Time-to-event data were evaluated using cumulative incidence curves with the log-rank test and Cox proportional hazards regression models. Univariate and multivariate Cox regression models for the primary and secondary outcomes were used to calculate the HRs, 95% CIs, and *P*-values. In the multivariable Cox proportional hazard regression models, confounding variables of the KTRs and donor baseline characteristics were adjusted as follows: Model 1: unadjusted; Model 2: adjusted for age, sex, and body mass index; Model 3: adjusted for model 2 variables, donor type; and Model 4: adjusted for model 3 variables, ABO incompatibility, mean HbA1c levels for 1 year after KT, metformin use, dipeptidyl peptidase 4 inhibitor use, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use. The proportional hazards assumption was assessed using statistical test and graphical diagnostics based on the scaled Schoenfeld residuals. All the variables including SGLT2i use met the proportional hazards assumption. A Cox regression analysis for death from cardiovascular causes could not be performed because there were no incidents among the SGLT2i group. Additionally, to equalize the differences in baseline characteristics between the SGLT2i users and SGLT2i nonusers, propensity score matching was performed using nearest-neighbor 1:1, 1:2, or 1:3 matching. The matching variables were age, sex, body mass index, donor type, ABO-incompatibility, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and 1-year mean HbA1c level. Subgroup analysis by age, sex, body mass index, mean HbA1c levels for 1 year after KT, donor type, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and type of SGLT2i were performed for the composite outcome using the Cox proportional hazards model. Statistical analysis was performed using R Studio software (version 3.6.2; The R Foundation for Statistical Computing, Vienna, Austria). A *P*-value < 0.05 was considered statistically significant for all analyses.

RESULTS

Baseline Characteristics

Among the 750 KTRs, the median age was 55.0 years (IQR, 47.0–61.0 years), and 69.6% were men (Supplementary Table S1). The median follow-up duration was 56.3 months (IQR, 44.1–70.3 months), and of the patients, 129 (17.2%) used SGLT2i. The median time to initiate SGLT2i use was 13.4 months (IQR, 2.4–30.1 months) after KT. The body mass index was significantly higher in the SGLT2i group than in the non-SGLT2i group (25.4 kg/m^2 [IQR, 22.1–27.5] vs. 23.8 kg/m^2 [IQR, 21.5–26.1]; $P < 0.001$). The rate of posttransplant diabetes mellitus was 20.2% in the SGLT2i group and 15.3% in the non-SGLT2i group; the rates were not different. Other variables also did not differ between the 2 groups.

To correct for variables that differed in baseline characteristics between groups, propensity score matching was performed. Table 1 displays the baseline characteristics of the 1:1 propensity score-matched group. After propensity score matching, no variables in the baseline characteristics, including age, sex, and body mass index, differed between the SGLT2i and non-SGLT2i groups. Supplementary Table S2 shows the pre- and post-match standardized mean differences of the covariates used for propensity score matching and confirms that all variables are well-balanced.

The SGLT2i group had higher metformin use and the non-SGLT2i group had higher dipeptidyl peptidase 4 inhibitor use, both in the overall patients and the propensity score matched population (Table 2).

Cardiovascular Protective Effects of SGLT2i in all KTRs

The incidence of outcomes in the total patient population is shown in Supplementary Table S3, and cardiovascular outcomes (MACE) occurred in 84 patients (11.2%). The incidence was significantly lower in the SGLT2i group than that of the non-SGLT2i group (4.7% vs. 12.6%; $P = 0.015$). When analyzed separately for each MACE component, the incidence of MI and death from cardiovascular causes was significantly lower in the SGLT2i group than in the non-SGLT2i

Table 1. Baseline characteristics before and after propensity score matching

	Before matching			After matching		
Variable	SGLT2i group (n = 129)	Non-SGLT2i group (n = 621)	P	SGLT2i group (n = 127)	Non-SGLT2i group (n = 127)	P
Age, yr	54.0 (47.0–60.0)	55.0 (47.0–62.0)	0.331	54.0 (46.0–60.0)	55.0 (47.0–60.0)	0.830
Sex, male, n (%)	89 (69.0)	433 (69.7)	0.952	87 (68.5)	92 (72.4)	0.582
Body mass index, kg/m^2	25.4 (22.1–27.5)	23.8 (21.5–26.1)	<0.001	25.3 (22.0–27.4)	25.2 (23.1– 27.7)	0.893
Posttransplant diabetes mellitus, n (%)	26 (20.2)	95 (15.3)	0.172	25 (19.7)	18 (14.2)	0.242
Pretransplant dialysis vintage, yr	0.6 (0.1–3.5)	0.5 (0–5.8)	0.676	0.6 (0.1–3.4)	0.6 (0–5.0)	0.803
Pretransplant comorbidities, n (%)						
Hypertension	108 (83.7)	490 (78.9)	0.264	106 (83.5)	101 (79.5)	0.518
Dyslipidemia	14 (10.9)	52 (8.4)	0.463	14 (11.0)	14 (11.0)	1.000
Ischemic heart disease	18 (14.0)	73 (11.8)	0.584	17 (13.4)	16 (12.6)	1.000
Donor age, yr	52.0 (40.0–59.0)	50.0 (41.0–58.0)	0.553	52.0 (40.0–59.0)	51.0 (41.0–59.0)	0.871
Donor sex, male, n (%)	50 (38.8)	200 (32.2)	0.179	50 (39.4)	36 (28.3)	0.174
Donor type, n (%)			0.199			0.758
Deceased	25 (19.4)	169 (27.2)		25 (19.7)	29 (22.8)	
Living-related	50 (38.8)	228 (36.7)		49 (38.6)	50 (39.4)	
Living-unrelated	54 (41.9)	219 (35.3)		53 (41.7)	48 (37.8)	
ABO-incompatibility, n (%)	28 (21.7)	127 (20.5)	0.841	28 (22.0)	23 (18.1)	0.531
Tacrolimus, n (%)	113 (87.6)	533 (84.6)	0.384	112 (88.2)	109 (85.8)	0.576
Cyclosporine, n (%)	18 (14.0)	96 (15.5)	0.665	17 (13.4)	19 (15.0)	0.719
ACEi or ARB use, n (%)	46 (35.7)	210 (33.8)	0.765	45 (35.4)	48 (37.8)	0.794
3-mo mean Scr, mg/dl	1.1 (1.0–1.4)	1.1 (0.9–1.3)	0.069	1.1 (1.0–1.4)	1.2 (0.9–1.3)	0.275
3-mo mean HbA1c, %	7.1 (6.3–8.1)	6.9 (6.1–7.8)	0.113	7.1 (6.3–8.1)	7.1 (6.2–8.1)	0.785
1-yr mean Scr, mg/dl	1.2 (1.0–1.3)	1.1 (0.9–1.4)	0.397	1.2 (1.0–1.3)	1.2 (0.9–1.4)	0.481
1-yr mean HbA1c, %	7.1 (6.4–7.8)	7.0 (6.5–8.0)	0.399	7.0 (6.5– 8.0)	7.3 (6.6– 7.9)	0.836

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; KT, kidney transplantation; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

group (MI: 1.6% vs. 8.9%, $P = 0.008$; death from cardiovascular causes: 0 vs. 3.2%, $P = 0.034$). The incidence of hospitalizations for heart failure and stroke did not differ between the groups.

The cumulative incidence of cardiovascular outcomes is presented in Supplementary Figure S1. The MACE cumulative incidence rate of MI and death from cardiovascular causes was significantly lower in the SGLT2i group than in the non-SGLT2i group (all $P < 0.05$; Supplementary Figure S1A–S1C). The HR for the effect of SGLT2i on cardiovascular outcomes is presented in Supplementary Table S4. SGLT2i consistently had protective effects on MACE and MI after controlling for the various factors. The HR for MACE was 0.37 (95% CI, 0.16–0.87; $P = 0.022$), and the HR for MI was 0.15 (95% CI, 0.04–0.62; $P = 0.009$). However, the risk of stroke and hospitalization for heart failure remained unchanged in the SGLT2i group.

Cardiovascular Protective Effects of SGLT2i in the Propensity Score Matching Groups

In the matched population, the occurrence of MACE was significantly lower in the SGLT2i group in comparison to the non-SGLT2i group, with a difference of 3.9% versus 11.8%, respectively ($P = 0.036$) (Table 3). The occurrence of MI and death from any cause was considerably lower in the SGLT2i group (all $P < 0.05$).

Table 2. Information about used antidiabetic medications after kidney transplantation

All patients	Total (n = 750)	SGLT2i group (n = 129)	Non-SGLT2i group (n = 621)	P
Metformin, n (%)	518 (69.1)	112 (86.8)	406 (65.4)	<0.001
Sulfonylurea, n (%)	264 (35.2)	55 (42.6)	209 (33.7)	0.052
DPP4i, n (%)	458 (61.1)	57 (44.2)	401 (64.6)	<0.001
Insulin, n (%)	428 (57.1)	77 (59.7)	351 (56.5)	0.508
PSM patients	Total (n = 254)	SGLT2i group (n = 127)	Non-SGLT2i group (n = 127)	P
Metformin, n (%)	199 (78.3)	110 (86.6)	89 (70.1)	0.002
Sulfonylurea, n (%)	102 (40.2)	54 (42.5)	48 (37.8)	0.443
DPP4i, n (%)	137 (53.9)	57 (44.9)	80 (63.0)	0.004
Insulin, n (%)	149 (58.7)	76 (59.8)	73 (57.5)	0.702

DPP4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; PSM, propensity score matching.

Table 3. Clinical outcomes in the propensity score matching groups

Variables, *n* (%)	Total (*n* = 254)	SGLT2i group (*n* = 127)	Non-SGLT2i group (*n* = 127)	*P*
Major adverse cardiovascular event	20 (7.9)	5 (3.9)	15 (11.8)	0.036
Myocardial infarction	12 (4.7)	1 (0.8)	11 (8.7)	0.008
Stroke	5 (2.0)	3 (2.4)	2 (1.6)	1.000
Hospitalizations for heart failure	4 (1.6)	1 (0.8)	3 (2.4)	0.614
Death from cardiovascular causes	4 (1.6)	0 (0)	4 (3.1)	0.131
Death from any cause	14 (5.5)	1 (0.8)	13 (10.2)	0.001

SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Figure 2 displays the cumulative incidence of cardiovascular outcomes in the propensity score-matched groups. The matched SGLT2i group exhibited a significantly lower cumulative incidence rate of MACE and MI than the matched non-SGLT2i group ($P < 0.05$; Figure 2a and b). The HRs for the effect of SGLT2i on cardiovascular outcomes are presented in Table 4. SGLT2i consistently had a protective effect on MACE and MI. In the 1:1 propensity score-matched KTRs, SGLT2i showed cardiovascular benefits with an adjusted HR of 0.30 (95% CI, 0.10–0.88; $P = 0.028$) for MACE and an adjusted HR of 0.04 (95% CI, 0.004–0.40; $P = 0.006$) for MI.

To verify the reliability of these results, a multivariable Cox regression analysis was performed using nearest-neighbor 1:2 and 1:3 propensity score matching groups (Table 4). SGTL2i usage was independently associated with a lower risk of both MACE and MI in all of the matching groups after adjusting for confounding factors.

Adverse events including the incidence of UTI and euglycemic ketoacidosis were compared between propensity score matched SGLT2i and non-SGLT2i groups (Table 5). The incidence of all UTIs and bacterial UTIs did not differ between the 2 groups. The incidence of fungal UTIs was higher in the SGLT2i group, although it was still rare in both groups. There were no cases of euglycemic ketoacidosis in either group. Of the 129 patients taking SGLT2i, 18 (14.0%) discontinued SGLT2i during follow-up.

Cardiovascular Protective Effects of SGLT2i Subgroups

Figure 3 displays the HRs that depict the impact of SGLT2i on MACE according to subgroup. SGLT2i had a cardiovascular protective effect against MACE, particularly in patients aged <60 years, males, those with a higher body mass index, and KTRs with well-controlled glucose levels. The cardiovascular benefits of SGLT2i were not influenced by the type of SGLT2i used or the use of renin-angiotensin-aldosterone system inhibitors.

DISCUSSION

This study investigated the cardiovascular protective effects of SGLT2i in a specific cohort-patients with diabetes who underwent KT. The outcome of this study highlights the potential benefits of SGLT2i use in a group of patients with a combination of cardiovascular risk factors because of maintenance immunosuppressant therapy and diabetes. KTRs are in a functional single kidney state, and the effects of SGLT2i have not previously been well-studied within this population. The cardiovascular protective effects of SGLT2i in KTRs were confirmed through multifaceted analyses that were adjusted for the various confounders and performed on a matched population. These findings suggest that KTRs with diabetes should be treated with SGTL2i more aggressively, especially those with an increased risk for cardiovascular events.

SGLT2i primarily targets the renal proximal tubules to inhibit glucose and sodium reabsorption. Although it was initially developed for glycemic control in diabetes, its effects extend beyond glucose management. SGLT2i triggers natriuresis, diuresis, and weight loss. Consequently, they cause a decrease in tubuloglomerular feedback and have renoprotective effects; we demonstrated this in KTRs with diabetes in our previous study.[21] Furthermore, the beneficial effects of SGLT2i to prevent cardiovascular diseases have been acknowledged, and extensive research has been conducted in a variety of areas with promising results.

Our findings are in agreement with other research that has examined the cardiovascular protective effects of SGLT2i in patients with diabetes. Large randomized clinical trials, such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 Program, have provided considerable evidence for the advantages of SGLT2i in reducing cardiovascular events in patients with diabetes.[24–26] However, these studies primarily focused on general patients with diabetes regardless of KT history; therefore, the majority of the enrolled patients were not transplant recipients, which limits the applicability of the results to KT recipients. Our study confirmed that even in KTRs with diabetes, SGLT2i use reduced the risk of MACE, specifically decreasing the incidence of MI and cardiovascular death. Therefore, our results support the results of previous trials, and enhance the generalizability of those studies, and suggest the possible extensive use of SGLT2i in patients with KT.

The pathophysiologic mechanism of the cardiovascular protective effects of SGLT2i has been reported from various perspectives. First, SGLT2i has both natriuretic and diuretic effects, but they are milder than those of other diuretics. This property induces a

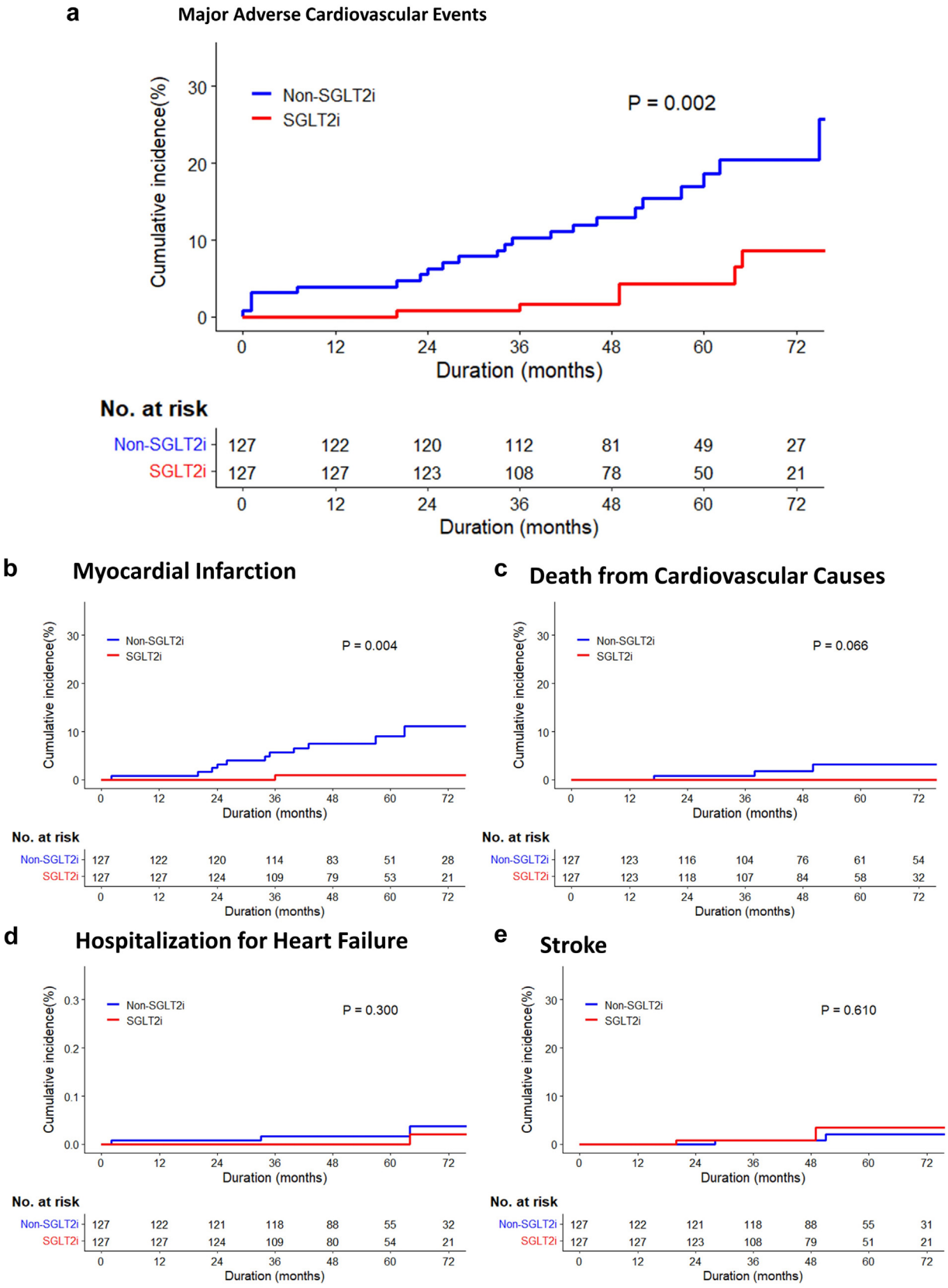

Figure 2. Cumulative incidence curves for outcomes in nearest-neighbor 1:1 propensity score matching groups. (a) Major adverse cardiovascular events. (b) Myocardial infarction. (c) Death from cardiovascular causes. (d) Hospitalization for heart failure. (e) Stroke.

Table 4. Multivariable Cox regression analysis of outcomes in the propensity score matching groups with different matching ratios

	Major adverse cardiovascular events			Myocardial infarction			Hospitalizations for heart failure			Stroke		
PSM ratio	aHR[a]	95% CI	*P*	aHR[a]	95% CI	*P*	aHR[a]	95% CI	*P*	aHR*	95% CI	*P*
1:1	0.30	0.10–0.88	0.028	0.04	0.004–0.40	0.006	0.21	0.02–2.76	0.238	1.92	0.31–12.03	0.487
1:2	0.27	0.10–0.73	0.010	0.07	0.01–0.58	0.013	0.14	0.01–1.92	0.141	0.81	0.18–3.70	0.789
1:3	0.32	0.13–0.82	0.018	0.08	0.01–0.61	0.015	0.54	0.06–4.85	0.584	1.22	0.31–4.88	0.774

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor; PSM, propensity score matching.
[a]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO-incompatibility, post-transplant 1-year mean HbA1c (%), metformin use, DPP4i use, and ACEi or ARB use.

higher electrolyte-free water clearance, and the reduction of interstitial fluid volume is greater than the reduction of blood volume.[27] This allows for improved control of congestion without compromising arterial filling and perfusion. Second, the volume contraction by SGLT2i contributes to a lower blood pressure and a reduced left ventricular filling pressure.[28,29] This reduces the workload on the heart and helps prevent hypertensive heart disease. Third, SGLT2i may act as an antagonist of renal sympathetic nerve activity and help treat heart failure.[20] Fourth, SGLT2i therapy augments erythropoiesis and increases hematocrit.[18] In patients with diabetes mellitus, glucose uptake via SGLT2 is increased, which results in increased ATP consumption. To meet the increased ATP demand, oxygen consumption is increased in the proximal tubular epithelial cells. This results in local hypoxia and the release of inflammatory cytokines, which decreases the secretion of erythropoietin. Elevated hematocrit levels with SGLT2i use may be associated with a decreased incidence of MACE.[20,30,31]

In the subgroup analysis, the cardiovascular protective effects of SGLT2i were greater in the KTRs with good glycemic control. SGLT2i reduced the incidence of cardiovascular events regardless of baseline glycated hemoglobin and glucose control in patients with diabetes and chronic kidney disease.[32,33] However, several meta-analyses that included patients with established cardiovascular disease reported that intensive glucose control was associated with a reduced risk of MACE.[34–36] Our results suggest that both selecting the appropriate drug and maintaining glucose control are important to reduce cardiovascular complications in KTRs with a high risk of cardiovascular disease.

Table 5. Incidence of urinary tract infection

	SGLT2i group (*n* = 127)		Non-SGLT2i group (*n* = 127)			
Type of UTI	*n*	Events/100 patient-yr	*n*	Events/100 patient-yr	RR	95% CI
All	12	1.73	45	0.96	1.81	0.96–3.41
Bacteria	11	1.64	45	0.96	1.71	0.91–3.24
Fungus	2	0.09	1	0.01	11.75	1.07–129.59

CI, confidence interval; RR, relative risk; SGLT2i, sodium-glucose cotransporter 2 inhibitors; UTI, urinary tract infection.

In this study, the effects of SGLT2i were notable in patients with a younger age and a higher body mass index. It is unknown why the 2 groups, which have opposite patterns in terms of cardiovascular risk, showed a greater effect of SGLT2i. Larger-scale prospective studies will be able to identify the patient groups that would benefit the most from SGLT2i treatment. Nevertheless, our results provide evidence that SGLT2i could be prescribed for KTRs with either a relatively higher- or lower risk for cardiovascular disease. In addition, the cardioprotective effects of SGLT2i use did not differ with the concomitant use of renin-angiotensin-aldosterone system inhibitors or by the SGLT2i type; therefore, this should be considered when prescribing SGLT2i.

The strength of this study is that it demonstrates the cardioprotective effects of SGLT2i in a cohort of KTRs with diabetes, which has not been previously reported in this population. However, there are several limitations to this study. First, this is a retrospective observational study; therefore, we cannot establish a clear causal relationship and determine the pathophysiological mechanism. Second, there may be confounding factors that we did not identify, even though we adjusted for several variables and used propensity score-matched groups. Third, there may be a selection bias because SGLT2i were prescribed at the discretion of each clinician rather than by the consistent criteria for use. However, based on the characteristics of the patient population, it is suggested that SGLT2i was used in well-nourished patients with a high body mass index to expect weight loss effects. Fourth, because this study was not conducted as a randomized trial, there exists a potential for immortal time bias. To address this concern, our analyses were specifically focused on patients who underwent KT after the year 2015, coinciding with the introduction of SGLT2i. Our findings also need to be validated in forthcoming extensive randomized controlled to establish the efficacy of SGLT2i in KTRs and contribute to the development of guidelines.

In conclusion, this study provides evidence that SGLT2i significantly reduces the risk of MACE in KTRs with diabetes. Furthermore, this reduction is

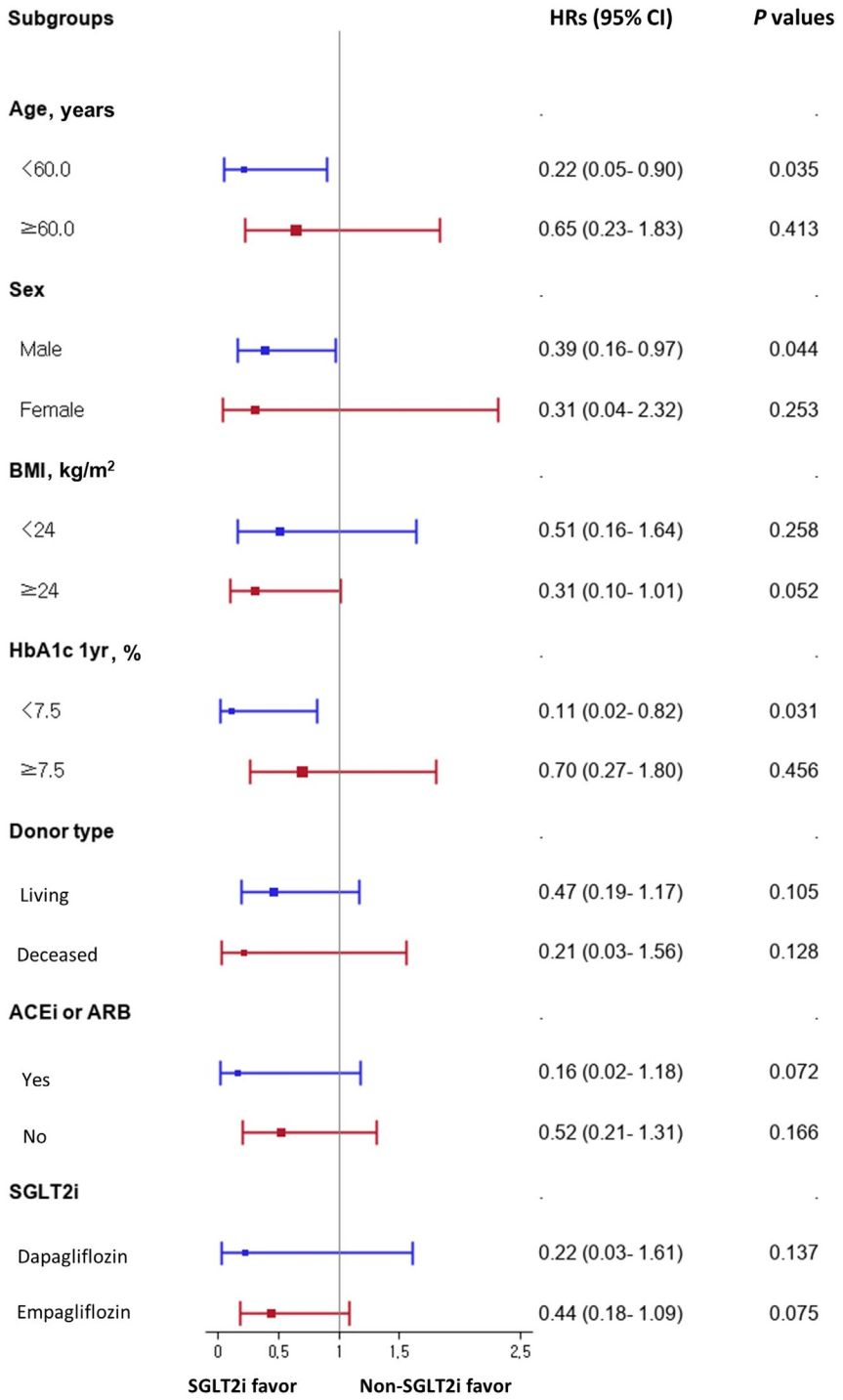

Figure 3. Hazard ratios for major adverse cardiovascular events in the subgroups. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

especially pronounced for the incidence of death from cardiovascular causes and MI. SGLT2i can be used to reduce the burden of cardiovascular disease in KTRs with diabetes. These findings highlight the potential of SGLT2i as a valuable treatment option to reduce the burden of cardiovascular disease among KTRs with diabetes. Future prospective randomized controlled trials are required to confirm the cardiovascular effects and safety of SGLT2i in KTRs.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Cumulative incidence curves for the outcomes. (A) Major adverse cardiovascular events. (B) Myocardial infarction. (C) Death from cardiovascular causes. (D) Hospitalization for heart failure. (E) Stroke.

Table S1. Baseline characteristics of all patients in the study.

Table S2. Balance of covariates used for propensity score matching.

Table S3. Incidence of clinical outcomes in all patients.

Table S4. Cox regression analysis of the outcomes.

Modified STROBE Statement

REFERENCES

1. Viklicky O, Novotny M, Hruba P. Future developments in kidney transplantation. *Curr Opin Organ Transplant*. 2020;25:92–98. https://doi.org/10.1097/MOT.0000000000000722
2. Butt Z, Yount SE, Caicedo JC, Abecassis MM, Cella D. Quality of life assessment in renal transplant: review and future directions. *Clin Transpl*. 2008;22:292–303. https://doi.org/10.1111/j.1399-0012.2007.00784.x
3. Rangaswami J, Mathew RO, Parasuraman R, et al. Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. *Nephrol Dial Transplant*. 2019;34:760–773. https://doi.org/10.1093/ndt/gfz053
4. Vijayan S, Ho QY, Koh CH, et al. Cardiac evaluation for end-stage kidney disease patients on the transplant waitlist: a single-center cohort study. *Korean J Transplant*. 2022;36:187–196. https://doi.org/10.4285/kjt.22.0029
5. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295. https://doi.org/10.1056/NEJMoa041365
6. Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, van Es LA. Patient survival after renal transplantation; more than 25 years follow-up. *Nephrol Dial Transplant*. 1997;12:1672–1679. https://doi.org/10.1093/ndt/12.8.1672
7. Liefeldt L, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int*. 2010;23:1191–1204. https://doi.org/10.1111/j.1432-2277.2010.01159.x
8. Kasiske BL, Anjum S, Shah R, et al. Hypertension after kidney transplantation. *Am J Kidney Dis*. 2004;43:1071–1081. https://doi.org/10.1053/j.ajkd.2004.03.013
9. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant*. 2003;3:178–185. https://doi.org/10.1034/j.1600-6143.2003.00010.x
10. Holdaas H, Fellström B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024–2031. https://doi.org/10.1016/S0140-6736(03)13638-0
11. Dad T, Tighiouart H, Joseph A, et al. Aspirin use and incident cardiovascular disease, kidney failure, and death in stable kidney transplant recipients: a post hoc analysis of the folic acid for vascular outcome reduction in transplantation (FAVORIT) trial. *Am J Kidney Dis*. 2016;68:277–286. https://doi.org/10.1053/j.ajkd.2016.01.019
12. Paoletti E, Bellino D, Marsano L, Cassottana P, Rolla D, Ratto E. Effects of ACE inhibitors on long-term outcome of renal transplant recipients: a randomized controlled trial. *Transplantation*. 2013;95:889–895. https://doi.org/10.1097/TP.0b013e3182827a43
13. Rossignol P, Agarwal R, Canaud B, et al. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J*. 2019;40:880–886. https://doi.org/10.1093/eurheartj/ehx209
14. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424. https://doi.org/10.1056/NEJMoa2022190
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. https://doi.org/10.1056/NEJMoa2024816
16. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461. https://doi.org/10.1056/NEJMoa2107038
17. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303
18. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. *Circulation*. 2019;139:1985–1987. https://doi.org/10.1161/CIRCULATIONAHA.118.038881
19. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108–2117. https://doi.org/10.1007/s00125-018-4670-7
20. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis.

Circulation. 2022;146:1383–1405. https://doi.org/10.1161/CIRCULATIONAHA.122.061732

21. Lim JH, Kwon S, Jeon Y, et al. The efficacy and safety of SGLT2 inhibitor in diabetic kidney transplant recipients. *Transplantation*. 2022;106:e404–e412. https://doi.org/10.1097/TP.0000000000004228
22. Sharif A, Hecking M, de Vries AP, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant*. 2014;14:1992–2000. https://doi.org/10.1111/ajt.12850
23. Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: etiologies, evaluation, and management. *Am J Emerg Med*. 2021;44:157–160. https://doi.org/10.1016/j.ajem.2021.02.015
24. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. https://doi.org/10.1056/NEJMoa1504720
25. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. https://doi.org/10.1056/NEJMoa1611925
26. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357. https://doi.org/10.1056/NEJMoa1812389
27. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab*. 2018;20:479–487. https://doi.org/10.1111/dom.13126
28. Omar M, Jensen J, Frederiksen PH, et al. Effect of empagliflozin on hemodynamics in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2020;76:2740–2751. https://doi.org/10.1016/j.jacc.2020.10.005
29. Piperidou A, Sarafidis P, Boutou A, et al. The effect of SGLT-2 inhibitors on albuminuria and proteinuria in diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens*. 2019;37:1334–1343. https://doi.org/10.1097/HJH.0000000000002050
30. Docherty KF, Curtain JP, Anand IS, et al. Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail*. 2021;23:617–628. https://doi.org/10.1002/ejhf.2132
31. Kanbay M, Tapoi L, Ureche C, et al. Effect of sodium-glucose cotransporter 2 inhibitors on hemoglobin and hematocrit levels in type 2 diabetes: a systematic review and meta-analysis. *Int Urol Nephrol*. 2022;54:827–841. https://doi.org/10.1007/s11255-021-02943-2
32. Persson F, Rossing P, Vart P, et al. Efficacy and safety of dapagliflozin by baseline glycemic status: a prespecified analysis from the DAPA-CKD trial. *Diabetes Care*. 2021;44:1894–1897. https://doi.org/10.2337/dc21-0300
33. Charytan DM, Mahaffey KW, Jardine MJ, et al. Cardiorenal protective effects of canagliflozin in CREDENCE according to glucose lowering. *BMJ Open Diabetes Res Care*. 2023;11. https://doi.org/10.1136/bmjdrc-2022-003270
34. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009;52:2288–2298. https://doi.org/10.1007/s00125-009-1470-0
35. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med*. 2009;151:394–403. https://doi.org/10.7326/0003-4819-151-6-200909150-00137
36. Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis*. 2009;19:604–612. https://doi.org/10.1016/j.numecd.2009.03.021