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SGLT2 inhibitor use and renal outcomes in low-risk population with diabetes mellitus and normal or low body mass index

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ABSTRACT

Introduction Recent post hoc analyses indicate that patients with normal or low body mass index (BMI) benefit from sodium-glucose cotransporter-2 (SGLT2) inhibitor use. We aimed to evaluate the effects of SGLT2 inhibitors on renal and patient outcomes in patients with diabetes and normal or low BMI.

Research design and methods This single-center retrospective cohort study included 5,842 adult patients with type 2 diabetes and BMI<23 kg/m^2 from 2016 to 2020. Patients were divided into control and SGLT2 inhibitor groups and matched using propensity scores. The primary outcome was the annual change in the estimated glomerular filtration rate (eGFR). Secondary outcomes included change in BMI, a composite renal outcome (eGFR decline of ≥40% from baseline or end-stage kidney disease), all-cause mortality, and cardiovascular disease (CVD).

Results Overall, 648 patients were selected for propensity score matching, of whom 216 (33.3%) were receiving SGLT2 inhibitors. The mean age and eGFR were 61.6 years and 84.7 mL/min/1.73 m^2, respectively. The median urine albumin-to-creatinine ratio was 11.6 mg/gCr. The control group showed relatively unchanged eGFR over time, whereas the SGLT2 inhibitor group showed an increase in eGFR over time (0.0 vs +0.3 mL/min/1.73 m^2/year, p=0.0398). SGLT2 inhibitor use was associated with a lower risk of mortality (HR 0.171, 95% CI 0.041 to 0.718, p=0.0159) and composite renal outcome (HR 0.223, 95% CI 0.052 to 0.952; p=0.0426), but not with the risk of CVD.

Conclusions SGLT2 inhibitor use may reduce the risk of eGFR decline and all-cause mortality even in low-risk patients with diabetes and normal or low BMI.

INTRODUCTION

The number of individuals with diabetes mellitus (DM) worldwide is expected to reach 738 million by 2045.[1] Approximately 50% of people with type 2 diabetes develop diabetic nephropathy—a major complication of DM[2]; approximately 20% of patients with diabetic nephropathy progress to end-stage kidney

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sodium-glucose cotransporter-2 (SGLT2) inhibitors have demonstrated significant renal and cardiovascular benefits in patients with type 2 diabetes mellitus (DM), particularly in those with obesity, proteinuria, reduced kidney function, or a high risk of cardiovascular disease.
⇒ However, their effects and safety in patients with normal or low body mass index (BMI), especially in low-risk populations, remain unclear.
⇒ Concerns about potential adverse effects, including excessive weight loss and the implications of the obesity paradox, have limited their use in this population.

WHAT THIS STUDY ADDS

⇒ This study provides evidence that SGLT2 inhibitor use is associated with improved renal function and a reduced risk of composite renal outcomes and all-cause mortality even in patients with type 2 DM and normal or low BMI.
⇒ Furthermore, SGLT2 inhibitor use did not lead to significant weight loss in this population and may prevent weight gain over time.
⇒ These findings suggest that SGLT2 inhibitors can be beneficial even in low-risk patients without obesity or overt renal impairment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians may consider prescribing SGLT2 inhibitors for renal protection and mortality reduction, even in patients with normal or low BMI and without overt proteinuria or significant renal dysfunction.
⇒ These findings alleviate previous concerns about the SGLT2 inhibitor use in patients with normal or low BMI and support their potential use in a broader population with diabetes.
⇒ Further research is needed to confirm the long-term benefit and elucidate the mechanisms underlying these effects in low-risk populations.

disease (ESKD) despite receiving treatment to slow its progression.[3] While sodium-glucose cotransporter-2 (SGLT2) inhibitors were developed as antihyperglycemic drugs, several large clinical trials have demonstrated that these drugs improve renal and cardiovascular outcomes beyond glycemic-lowering effects.[4–9]

Obesity causes glomerular hyperfiltration and damage,[10–12] and SGLT2 inhibitors alleviate glomerular hyperfiltration caused by obesity. Caloric loss by glycosuria can result in weight loss;[13–15] weight control is a recommended measure to control diabetes and prevent or slow the progression of diabetic nephropathy in patients with overweight or obesity.[16–18] Several randomized controlled trials observed that SGLT2 inhibitor use was associated with improved kidney and cardiovascular outcomes in patients with a body mass index (BMI) of 29–32 kg/m^2.[4–9] Therefore, SGLT2 inhibitors are undoubtedly beneficial in patients with overweight or obesity.

The J-shaped relationship observed between weight and mortality in several diseases is known as the obesity paradox.[19–21] Although the validity and mechanisms of the obesity paradox are still debated, being underweight is also a known risk factor for mortality in patients with advanced chronic kidney disease (CKD).[22 23] Researchers question the benefits offered by SGLT2 inhibitors in patients with normal or low BMI. Post hoc analyses of previous clinical trials have shown that SGLT2 inhibitors are beneficial even in patients with normal or low BMI.[24–26] However, previous clinical trials focused on high-risk patients with proteinuria, decreased renal function, or a history of or high risk for cardiovascular disease (CVD). Given the increasingly widespread use of SGLT2 inhibitors in patients with DM, it is also important to investigate their effectiveness or safety in low-risk patients, particularly those with normal or low BMI. Therefore, we aimed to evaluate the effects of SGLT2 inhibitors on renal and patient outcomes in a low-risk population with Type 2 DM and normal or low BMI.

METHODS

Study design and participants

In this single-center retrospective cohort study, we included adult patients who visited the endocrinology outpatient department of the Samsung Medical Center for type 2 diabetes between January 1, 2016, and December 31, 2020. We screened 29,311 patients with type 2 diabetes and excluded the following individuals: those younger than 18 years of age (n=5); those with pre-existing CKD stage 4 or 5 (n=738); those with insufficient baseline information (n=2,842); those with fewer than two follow-up visits (n=6,617); and those with fewer than two post-follow-up laboratory tests (n=1,630). A total of 17,479 patients remained. Underweight was defined as BMI less than 18.5 kg/m^2 and normal weight was defined as BMI 18.5–22.9 kg/m^2, according to the WHO guidelines for the Asia-Pacific region.[27] After excluding patients with BMI 23 kg/m^2 or higher (n=11,637), 5,842 patients were included in the final analysis (online supplemental figure S1).

Exposure

The patients were categorized into SGLT2 inhibitor and control groups. The SGLT2 inhibitor group included patients who received SGLT2 inhibitors for the first time at Samsung Medical Center. The control group included patients who did not receive SGLT2 inhibitors during follow-up at the Samsung Medical Center.

Study variables

We extracted data from the Clinical Data Warehouse DARWIN-C of Samsung Medical Center. Comorbidities (hypertension, heart failure, ischemic heart disease, cerebrovascular disease, and cancer) were also recorded. The use of medications (ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB), loop diuretics, mineralocorticoid receptor antagonists, insulin, and oral hypoglycemic agents (OHAs)) was defined as receiving medication within 12 months prior to the start of follow-up. Values of systolic blood pressure, diastolic blood pressure, and laboratory examinations (serum creatinine, hemoglobin, blood urea nitrogen, hemoglobin A1c (HbA1c), and urine albumin-to-creatinine ratio (uACR)) at baseline were also obtained. The estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine levels using the CKD-Epidemiology Collaboration 2009 equation.[28]

Propensity score matching

SGLT2 inhibitor and control groups were propensity-score matched at a 1:2 ratio using the nearest neighbor search strategy based on sex, age, BMI, height, body weight, serum creatinine level, hemoglobin level, blood urea nitrogen level, eGFR, HbA1c, systolic blood pressure, diastolic blood pressure, medical history (hypertension, heart failure, ischemic heart disease, cerebrovascular disease, cancer), medication use (ACEi or ARB, loop diuretics, mineralocorticoid receptor antagonist), number of OHAs received, insulin use, and duration of DM (months). We excluded uACR from the matching variables since it had many missing values.

Outcomes

The primary outcome was the annual change in eGFR per year. Secondary outcomes were the change in BMI, a composite renal outcome (eGFR decline of ≥40% from baseline or ESKD), all-cause mortality and CVD. CVD was defined as a composite outcome of myocardial infarction and stroke. For CVD analyses, we excluded those with baseline ischemic heart disease or cerebrovascular disease.

Subgroup analysis

We conducted a subgroup analysis according to RAS inhibitor use (ACEi or ARB), uACR (≥30 mg/gCr or<30 mg/gCr), eGFR (≥90 mL/min/1.73 m^2

or<90 mL/min/1.73 m^2), and HbA1c (≥7.5% or <7.5%).

Statistical analysis

Continuous variables are presented as mean±SD or median (IQR), and categorical variables are presented as numbers (percentages). Continuous variables were compared using an independent two-sample t-test or the Wilcoxon rank-sum test. Categorical variables were compared using the χ^2 test (or Fisher's exact test). The annual changes in eGFR were calculated as the average annualized change in eGFR from baseline to follow-up period. The comparison of annual changes in eGFR between the placebo group and SGLT2 inhibitor group was performed by Wilcoxon rank-sum test. Changes in BMI were analyzed using a mixed model with Šidák's correction for multiple comparisons. We presented the incidence rates of composite renal outcomes and all-cause mortality as the number of events per 1,000 person-years. We plotted the survival curve as a Kaplan-Meier curve and determined the differences between groups using the log-rank test. We used a Cox regression model to estimate the HRs and 95% CIs between groups. Even after propensity score matching, there was a significant difference in HbA1c between the two groups. Therefore, we estimated the HR adjusted for HbA1c. Because the traditional Cox regression model yielded extremely wide and unreliable CIs when analyzing the subgroups of composite renal outcome, we used Firth's penalized likelihood Cox regression model to overcome this limitation. Statistical significance was set at a two-sided p value of less than 0.05. Statistical analyses were performed using SAS V.9.4. (Cary, North Carolina, USA) and GraphPad Prism V.10.2.2. (GraphPad Software, Massachusetts, USA).

RESULTS

Baseline characteristics

Among 5,842 participants with a BMI less than 23 kg/m^2, we selected 648 participants using propensity score matching, of whom 216 (33.3%) were taking SGLT2 inhibitors. The baseline characteristics are shown in table 1. Before propensity score matching, patients receiving SGLT2 inhibitors were younger; had higher BMI, eGFR, and HbA1c levels; and received more RAS inhibitors than controls; however, uACRs remained similar. After propensity score matching, the SGLT2 inhibitor group had higher HbA1c concentrations than the control group (control vs SGLT2 inhibitor: 7.3% vs 7.5%, p=0.0141), and the other baseline characteristics were similar between the two groups. In the control and SGLT2 inhibitor groups, the mean ages were 61.5±11.8 and 61.8±10.0 years, median BMIs were 21.7 (20.7–22.4) and 21.8 (20.8–22.4) kg/m^2, and mean eGFRs were 84.8±18.9 and 84.5±18.0 mL/min/1.73 m^2, respectively. Of the 211 patients receiving RAS inhibitors, 144 (33.3%) and 67 (31.0%) were in the control and SGLT2 inhibitor groups, respectively (p=0.5533). We excluded uACRs from the matching process because of the large number of missing values; however, we observed no differences between the groups.

Changes in eGFR

The median follow-up duration for changes in eGFR were 5.0 (IQR 3.0–5.1) and 3.2 (IQR 2.8–5.0) years in the control and SGLT2 inhibitor groups, respectively. The eGFR remained relatively unchanged in the control group, whereas it increased over time in the SGLT2 group (control vs SGLT2 inhibitors: 0.0 mL/min/1.73 m^2/year vs +0.3 mL/min/1.73 m^2/year, p=0.0398) (table 2).

Change in BMI

The control and SGLT2 inhibitor groups showed differences in changes in BMI over time (figure 1): the control group showed an increase in BMI in year 1, which then decreased; the SGLT2 inhibitor group showed relatively unchanged BMI. Additionally, we observed that the SGLT2 inhibitor group had a lower BMI than the control group at years 1 and 2, but were similar after year 3.

Composite renal outcome, all-cause mortality and CVD

The incidence of composite renal outcome (eGFR decline of ≥40% from baseline or ESKD) was 11.24 per 1,000 person-years and 2.57 per 1,000 person-years in the control and SGLT2 inhibitor groups respectively. The number of composite renal outcome events was 16 (3.7%) versus 2 (0.9%) for eGFR decline of≥40% and 7 (1.6%) versus 0 for ESKD in the control and SGLT2 inhibitor groups, respectively. SGLT2 inhibitor use was associated with a lower risk for composite renal outcome (HR 0.223, 95% CI, 0.052 to 0.952; p=0.0426) (figure 2A).

The incidence of all-cause mortality was 1.09 per 1,000 person-year and 0.21 per 1,000 person-year in the control and SGLT2 inhibitor groups, respectively. SGLT2 inhibitor use was associated with a lower risk of mortality (HR 0.171, 95% CI, 0.041 to 0.718; p=0.0159) (figure 2B).

The incidence of CVD was 3.41 per 1,000 person-year and 3.87 per 1,000 person-year in the control and SGLT2 inhibitor groups, respectively. SGLT2 inhibitor use was not associated with a risk of CVD (HR 1.075, 95% CI, 0.274 to 4.212; p=0.9170) (figure 2C).

Subgroup analysis

Baseline uACR results were available for 253 and 132 patients in the control and SGLT2 inhibitor groups, respectively. The numbers of patients with uACR≥30 mg/gCr were 73 and 41 in the control and SGLT2 inhibitor groups, respectively. Table 2 shows changes in eGFR according to subgroups. The SGLT2 inhibitor group demonstrated a more positive eGFR slope than the control group in patients with uACR≥30 mg/gCr and in those with eGFR<90 mL/min/1.73 m2. Furthermore, in patients not taking ACEi or ARB and in those with HbA1c≥7.5%, the SGLT2 inhibitor group showed a more positive eGFR slope than the control group—although the difference was not statistically significant.

Table 1 Baseline characteristics of the participants before and after propensity score matching

Variables	Before PSM			After PSM (1:2)		
	Control (n=5,538)	SGLT2 inhibitor (n=304)	P value	Control (n=432)	SGLT2 inhibitor (n=216)	P value
Age, years	64.4±11.0	61.2±10.2	<0.001	61.5±11.8	61.8±10.0	0.730
Female	2,708 (48.9)	130 (42.8)	0.037	203 (47.0)	90 (41.7)	0.199
BMI, kg/m^2	21.4 (20.1–22.2)	21.9 (21.0–22.5)	<0.001	21.7 (20.7–22.4)	21.8 (20.8–22.4)	0.816
Height, cm	162.5±8.7	164.6±8.6	<0.001	164.1±9.2	164.5±8.7	0.567
Body weight, kg	55.5±7.5	58.3±6.8	<0.001	57.8±7.2	58.2±7.0	0.562
Systolic BP, mm Hg	125.7±17.4	124.7±17.9	0.329	125.3±18.1	125.8±17.6	0.700
Diastolic BP, mm Hg	73.2±11.6	69.5±13.1	<0.001	71.0±11.3	71.3±13.3	0.737
Comorbidities						
Hypertension	2,323 (41.9)	147 (48.4)	0.028	224 (51.9)	107 (49.5)	0.578
Heart failure	284 (5.1)	19 (6.3)	0.391	27 (6.3)	11 (5.1)	0.554
Ischemic heart disease	112 (2.0)	21 (6.9)	<0.001	26 (6.0)	9 (4.2)	0.326
Cerebrovascular disease	1,062 (19.2)	58 (19.1)	0.966	86 (19.9)	40 (18.5)	0.674
Cancer	450 (8.1)	20 (6.6)	0.334	28 (6.5)	15 (6.9)	0.823
Laboratory findings						
Serum Cr, mg/dL	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.190	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.478
eGFR, mL/min/1.73 m^2	81.1±18.7	85.7±18.1	<0.001	84.8±18.9	84.5±18.0	0.844
BUN, mg/dL	15.4 (12.5–19.1)	15.5 (12.5–19.7)	0.749	15.3 (12.4–19.0)	15.2 (12.5–19.6)	0.898
Hb, g/L	132 (121–144)	134 (124–145)	0.034	132 (121–144)	134 (124–146)	0.099
HbA1c, %	6.7 (6.2–7.5)	7.8 (7.1–8.7)	<0.001	7.3 (6.6–8.4)	7.5 (7.0–8.3)	0.014
uACR, mg/gCr	11.9 (5.8–44.2)	12.7 (5.7–38.6)	0.634	11.7 (5.3–42.4)	11.4 (5.3–40.0)	0.252
Medications						
RAS inhibitors	1,347 (24.3)	103 (33.9)	<0.001	144 (33.3)	67 (31.0)	0.553
Loop diuretics	575 (10.4)	29 (9.5)	0.638	41 (9.5)	21 (9.7)	0.925
MRA	282 (5.1)	20 (6.6)	0.254	28 (6.5)	12 (5.6)	0.644
Insulin	1,436 (25.9)	139 (45.7)	<0.001	185 (42.8)	97 (44.9)	0.614
Number of OHAs	2.0 (1.0–2.0)	3.0 (2.0–3.0)	<0.0001	2.0 (2.0–3.0)	2.5 (2.0–3.0)	0.758
DM duration, months	47.8 (0.0–130.0)	98.0 (23.8–173.7)	<0.001	101.4±83.6	101.5±82.4	0.989

Continuous variables were expressed as mean±SD or median (IQR). Categorical variables were presented as numbers (percentages).
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; MRA, mineralocorticoid receptor antagonist; OHAs, oral hypoglycemic agents; PSM, propensity score matching; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2; uACR, urine albumin-to-creatinine ratio.

Figure 3 shows the HRs for composite renal outcome and mortality according to the subgroups. We observed no significant difference in the risk for composite renal outcomes between the groups in each subgroup. We also observed no significant interactions according to subgroups in the risk for all-cause mortality. However, those with HbA1c≥7.5% tended to benefit more from the SGLT2 inhibitors (p for interaction 0.079).

Sensitivity analysis

To adjust for differences in the start of follow-up and follow-up duration, we performed propensity score matching at a 1:2 ratio among patients with follow-up start years of 2016, 2017, 2018, 2019, and 2020, and then combined them for analysis. A total of 480 patients were matched, of whom 183 (38.1%) were taking SGLT2 inhibitors. The baseline characteristics of patients stratified according to the start of follow-up are shown in online supplemental table S1. All variables were well matched between groups. The median follow-up duration for changes in eGFR were 3.7 (IQR 2.4–5.2) and 3.8 (IQR 2.4–5.2) years in the control and SGLT2 inhibitor groups, respectively. The eGFR decreased in the control group, whereas it increased over time in the SGLT2 group (control vs SGLT2 inhibitors: −0.3 mL/min/1.73 m^2/year vs +0.3 mL/min/1.73 m^2/year, p=0.01). SGLT2 inhibitor use was associated with a lower risk of composite renal

Table 2 Changes in eGFR according to the use of SGLT2 inhibitors

	Control	SGLT2 inhibitor	P value
Total (n=648)	0.0 (–1.8, 1.2)	0.3 (–1.5, 2.1)	0.040
Use of ACEi or ARB			
Yes (n=211)	–0.3 (–2.0, 1.0)	0.3 (–1.9, 2.6)	0.257
No (n=437)	0.0 (–1.6, 1.2)	0.3 (–1.4, 1.7)	0.097
uACR			
≥30 mg/gCr (n=114)	0.1 (–1.8, 0.9)	1.0 (–1.0, 2.4)	0.041
<30 mg/gCr (n=271)	0.0 (–1.4, 1.2)	0.4 (–1.5, 1.7)	0.245
eGFR			
≥90 mL/min/1.73 m^2 (n=286)	–0.3 (–1.5, 0.7)	–0.3 (–1.5, 1.0)	0.531
<90 mL/min/1.73 m^2 (n=362)	0.2 (–1.8, 1.8)	1.0 (–1.4, 3.2)	0.021
Hemoglobin A1c			
≥7.5% (n=310)	–0.3 (–2.2, 0.8)	–0.1 (–2.0, 2.4)	0.080
<7.5% (n=338)	0.1 (–1.5, 1.3)	0.4 (–0.9, 1.8)	0.218

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, Hemoglobin A1c; SGLT2, sodium-glucose cotransporter-2; uACR, urine albumin-to-creatinine ratio.

outcomes (HR 0.235, 95% CI, 0.070 to 0.788; p=0.0190) and a lower risk of mortality (HR 0.242, 95% CI, 0.057 to 0.705; p=0.0218), but not with the risk of CVD (HR 0.627, 95% CI 0.122 to 3.232; p=0.5770) (online supplemental figure S2).

DISCUSSION

In this study, we investigated the effects of SGLT2 inhibitors on renal and patient outcomes in patients with type 2 DM and normal or low BMI. We found that patients with type 2 DM and normal or low BMI who received SGLT2

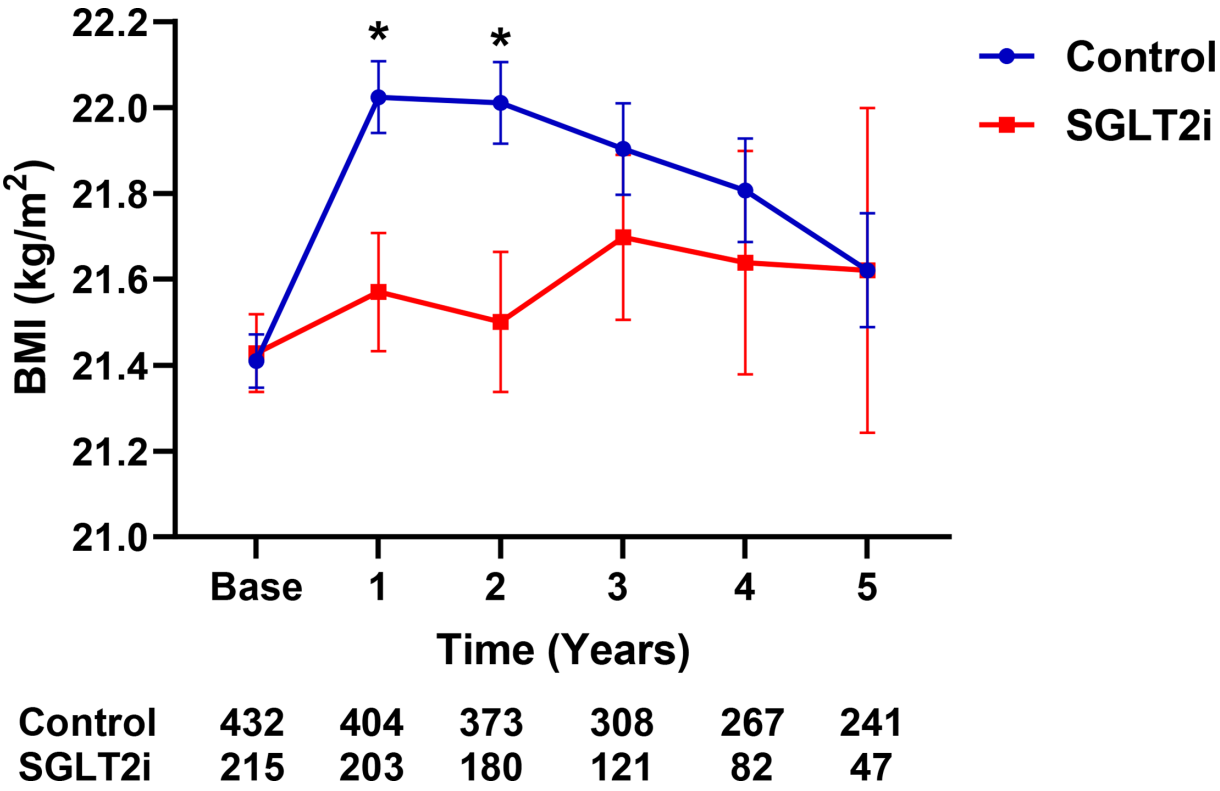

Figure 1 Changes in BMI according to SGLT2 inhibitor use. The control group showed an increase in BMI during the first year, which decreased thereafter. In contrast, the SGLT2 inhibitor group showed no significant changes over time. BMI, body mass index; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

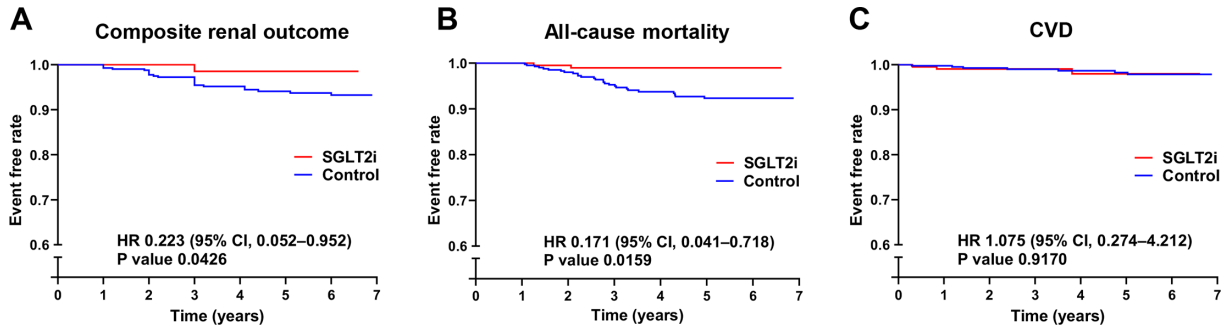

Figure 2 Event-free rates of composite renal outcome (eGFR decline of ≥40% or ESKD), all-cause mortality and cardiovascular disease according to SGLT2 inhibitor use. (A) Composite renal outcome (eGFR decline of ≥40% or ESKD) (B) all-cause mortality (C) cardiovascular disease. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SGLT2, sodium-glucose cotransporter-2.

inhibitors showed an improvement in renal function compared with the control group. In addition, SGLT2 inhibitor use was associated with a lower risk of composite renal outcomes and all-cause mortality.

In our study, the control group showed an initial increase in BMI, whereas the SGLT2 inhibitor group maintained their BMI. Meta-analysis has demonstrated that SGLT2 inhibitors reduce the body weight of patients with obesity.[14 29 30] Researchers are concerned that SGLT2 inhibitors may worsen the outcomes of patients with normal or low BMI—as hypothesized in the obesity paradox.[19] Our study showed that SGLT2 inhibitors did not cause significant weight loss in patients with normal or low BMI. These results are consistent with those of a recent Japanese postmarketing surveillance study, which showed that the weight loss effect of SGLT2 inhibitors was attenuated in patients with lower BMI.[31] Moreover, we found that patients who did not receive SGLT2 inhibitors gained weight during the first 2 years of follow-up—suggesting that SGLT2 inhibitors may prevent weight gain in patients with type 2 DM who have normal or low BMI.

Recent post hoc analyses of the Canagliflozin Cardiovascular Assessment Study (CANVAS), Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) clinical trials found that SGLT2 inhibitor use offered renal and cardiovascular benefits regardless of BMI.[24–26] The CANVAS trial enrolled patients with type 2 diabetes and a history of or high risk for CVD[32]; the EMPA-REG OUTCOME trial enrolled patients with type 2 diabetes and CVD;[4] and the DAPA-CKD trial enrolled patients with eGFR 25–75 mL/min/1.73 m^2 or uACR 200–5,000 mg/gCr with or without type 2 diabetes.[7] These trials demonstrated that SGLT2 inhibitors improve renal and cardiovascular outcomes in high-risk populations. Our study indicates that SGLT2 inhibitor use was associated with improved renal function and decreased all-cause mortality, even in patients with well-maintained renal function, no or low-grade albuminuria, and less CVD. Hyperfiltration in early diabetes is well known to occur regardless of obesity status.[33 34] Therefore, SGLT2 inhibitors may alleviate the injury caused by hyperfiltration in patients with diabetes and normal or low BMI. Furthermore, inflammation plays an important role in the development and progression of diabetic kidney disease and related complications.[35 36] Given that SGLT2 inhibitors have anti-inflammatory properties,[37] they may provide significant benefits even for patients with diabetes and normal or low BMI.

The effect of SGLT2 inhibitors was not affected by RAS inhibitor use, consistent with previous studies. Previous clinical trials have shown no differences in the efficacy of SGLT2 inhibitors regardless of RAS inhibitor use.[4 32 38] In patients with CKD or overt proteinuria, SGLT2 inhibitors have shown the renal and mortality benefits of SGLT2 inhibitors in addition to the effects of RAS inhibitors.[6–8 39] Post hoc analyses of BMI in previous clinical trials did not address differences in outcomes based on RAS inhibitor use.[24–26] Similarly, the impact of SGLT2 inhibitor use was not affected by proteinuria or GFR. On the other hand, the use of SGLT2 inhibitors tended to be associated with a lower HR of mortality in the group with HbA1c≥7.5%, although it is not clear whether this is an effect of additional glycemic control with SGLT2 inhibitors or an effect of SGLT2 inhibitors independent of glycemic control. This result suggests that SGLT2 inhibitors can be considered first when additional glycemic control is needed in patients with low or normal BMI.

We defined normal or low BMI as a value below 23 kg/m^2. Overweight is defined as a BMI of 25 kg/m^2 or higher in Caucasian populations. However, based on studies showing increased morbidity and mortality at BMIs above a lower cut-off level than 25 kg/m^2 in Asia-Pacific populations,[27 40] the WHO defines a BMI of≥23 kg/m^2 as overweight for this demographic. In a post hoc analysis of participants in the EMPA-REG OUTCOME trial that focused on the Asian population, those with BMI<24 kg/m^2 had pronounced benefits of SGLT2 inhibitor use.[25] Additionally, the subgroup analysis of the Asian population in the DAPA-CKD trial demonstrated pronounced benefits of SGLT2 inhibitor use in those with BMI<23 kg/m^2.[26] The findings of the present study corroborate those

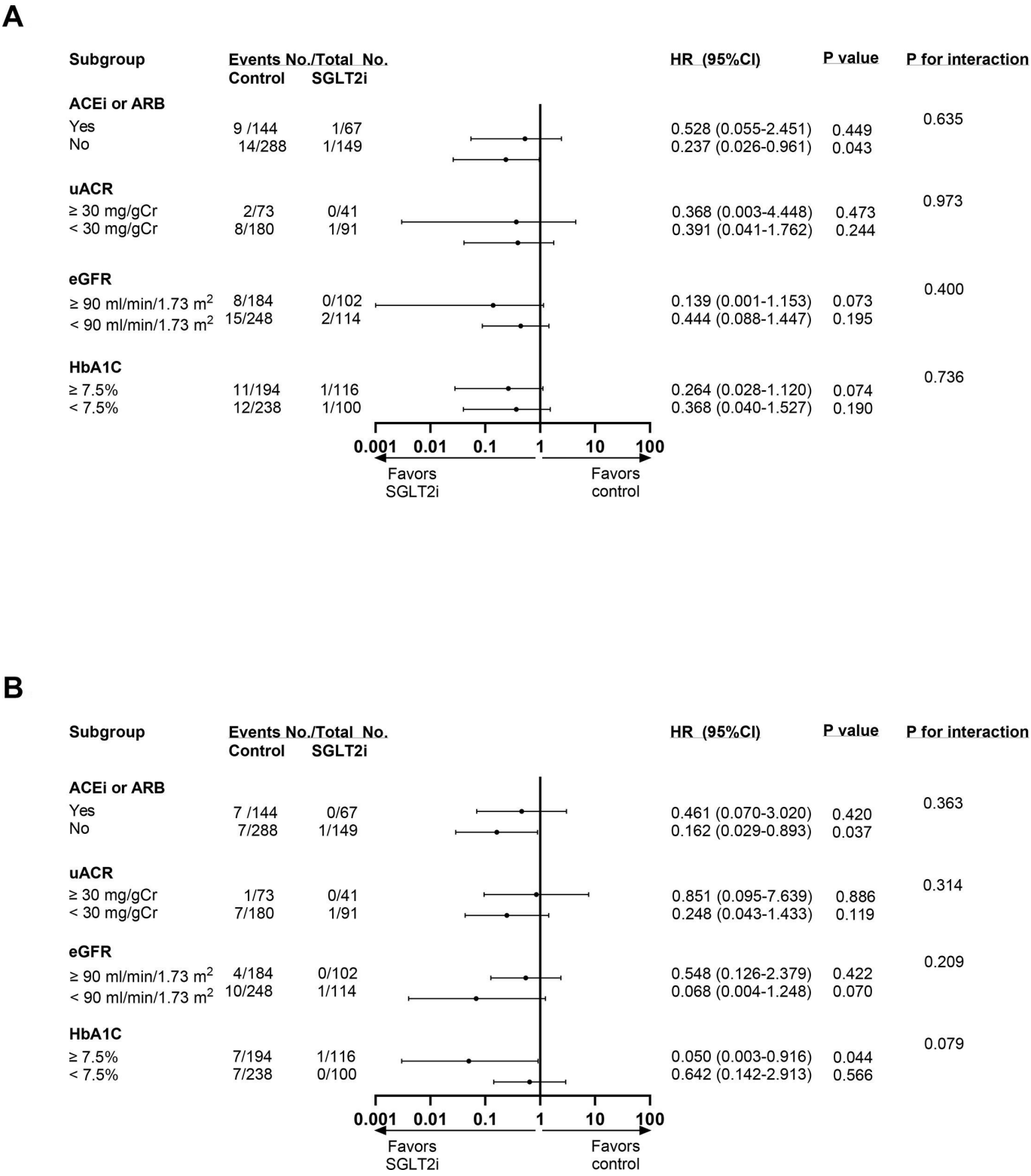

Figure 3 Subgroup analysis for composite renal outcome (eGFR decline of ≥40% or ESKD) and all-cause mortality according to SGLT2 inhibitor use. (A) Composite renal outcome (eGFR decline of ≥40% or ESKD). (B) All-cause mortality. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransporter-2; uACR, urine albumin-creatinine ratio.

of the aforementioned clinical trials, showing that SGLT2 inhibitor use offers renal and mortality benefits in a relatively low-risk population of East Asians with a normal or low BMI of<23 kg/m^2.

This study had some limitations. First, this was a single-center, retrospective observational study. Due to the retrospective nature of our study, inconsistencies or incompleteness in data collection may exist, and the

presence of unmeasured confounders cannot be ruled out. Consequently, fully eliminating confounding factors is challenging even after propensity score matching. In particular, studies on drug use are prone to selection bias or indication bias unless conducted as randomized controlled trials. In our center, SGLT2 inhibitors were likely to be prescribed to patients with normal or low BMI because of poor glycemic control despite conventional oral hypoglycemic or insulin therapy, rather than because of proteinuria. Propensity score matching revealed differences in HbA1c only; however, the residual confounding factors, especially regarding the decision to use SGLT2 inhibitors, cannot be disregarded. Second, the small number of events makes the reliability of the results questionable, reflecting the low-risk nature of our study population. In addition, the relatively small sample size and limited follow-up period may have contributed to the low event rate, potentially weakening the reliability of the findings and making it more difficult to reveal true differences in effects. However, despite questions about the reliability of the effect size, our study shows that even low-risk patients with normal or low BMI may benefit from the use of SGLT2 inhibitors. Third, this study included a South Korean population, so the results cannot be generalized to other ethnic groups. Fourth, our study included a heterogeneous population, with some individuals with CVD or reduced renal function. Nevertheless, the study predominantly included a low-risk population with relatively good kidney function and no or low-grade proteinuria. Therefore, we believe that our study may offer insights regarding the indication of SGLT2 inhibitors in low-risk individuals with normal or low BMI in clinical settings.

In conclusion, SGLT2 inhibitor use was associated with a lower risk of eGFR decline and composite renal outcome in patients with Type 2 DM and normal or low BMI. Furthermore, SGLT2 inhibitor use was associated with a lower risk of mortality. These results suggest that SGLT2 inhibitors are not harmful in low-risk patients with type 2 DM and normal or low BMI and may provide renal and mortality benefits.

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Contributors JJ conceptualized this study. YSL and JJ designed this study. GP, YSL, and JJ analyzed the data. YSL, KL, HRJ, JEL, WH, and JJ interpreted the data. YSL drafted the manuscript. YSL and JJ revised the manuscript for intellectual content. HRJ, JEL, and WH supervised the study. All the authors have read and approved the final version of this manuscript. JJ is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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