Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of SGLT2 Inhibitors on Cardiovascular and Lower Limb Events in Patients with Type 2 Diabetes: A Nationwide Population-Based Study

Min Jin Lee[1,2,*], Ji Hyun Bae[1,2,*], Ah Reum Khang[1,2], Yang Ho Kang[1,2], Joo Yeon Kim[1,2], Su Hyun Kim[1,2], Soo Yong Lee[2,3], Seung Hun Woo[2,4], Minae Park[5], Sojeong Park[5], Dong Hee Kim[2], Dasol Kang[2], Sujin Park[2], Dongwon Yi[1,3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea; [2]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea; [3]Division of Cardiology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea; [4]Department of Orthopedic Surgery, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea; [5]Department of Data Science, Hanmi Pharm. Co., Ltd, Seoul, Republic of Korea

*These authors contributed equally to this work

Correspondence: Dongwon Yi, Division of Endocrinology and Metabolism, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan, 50612, Republic of Korea, Email drwonny@gmail.com

Purpose: The cardiovascular (CV) benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) are well established, but their effects on lower limb events (LLEs) remain inconclusive, with conflicting findings from clinical trials and real-world studies. This study aimed to assess the risks of CV and LLEs associated with SGLT2i compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in patients with type 2 diabetes.

Patients and Methods: The study included patients with type 2 diabetes who were newly prescribed SGLT2i or DPP-4i using data from the National Health Insurance Service in South Korea. A 1:1 propensity score matching method was used to assign 97,584 patients to the SGLT2i and DPP-4i groups. The study endpoints included all-cause mortality, CV events, and LLEs—a composite outcome encompassing diabetic foot or ulcer, amputation, debridement, graft transplantation or flap operation, and revascularization.

Results: Over a median follow-up of 2.74 years, the SGLT2i group had a lower incidence of all-cause mortality (hazard ratio [HR] 0.63, 95% CI 0.51–0.78), heart failure (HR 0.85, 95% CI 0.78–0.93), ischemic stroke (HR 0.77, 95% CI 0.67–0.88), and peripheral artery disease (HR 0.66, 95% CI 0.63–0.69) than the DPP-4i group. However, no significant difference was observed in the incidence of myocardial infarction (HR 1.06, 95% CI 0.87–1.28) or LLEs (HR 1.05, 95% CI 0.80–1.38) between the two groups.

Conclusion: In this nationwide, real-world study, SGLT2i use demonstrated a neutral effect on LLEs compared to DPP-4i in patients with type 2 diabetes. However, SGLT2i was associated with a lower risk of all-cause mortality, heart failure, ischemic stroke, and peripheral artery disease. These findings contribute to the ongoing debate on the safety of SGLT2i regarding LLEs and highlight their broader CV benefits, warranting further investigation into their long-term effects on lower limb complications.

Keywords: sodium-glucose transporter 2 inhibitors, cardiovascular diseases, lower extremity, peripheral arterial disease, diabetic foot, amputation, surgical

Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) lower blood glucose levels in patients with type 2 diabetes and reduce both mortality and the risk of cardiovascular (CV) diseases, primarily by decreasing the likelihood of hospitalization for heart failure and improving kidney outcomes.[1,2] However, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program found that canagliflozin nearly doubled the risk of lower-limb amputation, raising concerns about the safety of SGLT2i in this regard.[3] In contrast, other randomized controlled trials (RCTs) on canagliflozin, such as the Canagliflozin and

Received: 14 January 2025
Accepted: 22 March 2025
Published: 28 March 2025

Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, along with RCTs on other SGLT2i, did not demonstrate a significant increase in amputation risk.[4–6]

Studies assessing the risk of lower-limb amputation or complications associated with SGLT2i—drawing from various RCTs, real-world data, and meta-analyses—have yielded inconsistent results, making it difficult to draw definitive conclusions.[7–12] A meta-analysis of RCTs on SGLT2i suggested a link between lower-limb complications in patients with type 2 diabetes and reductions in weight and blood pressure (BP).[8] Aggressive BP-lowering targets can negatively impact distal limb perfusion, increasing the risk of adverse limb events.[13] However, intensive BP control is also associated with reduced CV morbidity and mortality.[14] SGLT2i lower the risk of CV events and heart failure hospitalization through mechanisms, such as diuresis, weight reduction, and BP reduction.[15] Nevertheless, studies comprehensively evaluating lower-limb complications in the context of CV outcome risk reduction associated with SGLT2i remain limited.

Moreover, most studies have focused primarily on lower-limb amputation, with insufficient investigation into other diabetes-associated complications, such as foot ulceration, debridement, graft transplantation, and revascularization—each of which significantly impacts the quality of life in patients with diabetes.[7–12] To address this gap, the present study defines a composite outcome of lower-limb events (LLEs), encompassing diabetic foot or ulcer and procedures or surgeries, such as amputation, debridement, graft transplantation, flap operations, and lower-limb revascularization.

This study aimed to examine the risk of CV events and LLEs associated with SGLT2i compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in patients with type 2 diabetes in a real-world setting.

Materials and Methods

Study Data Source

We utilized claims and health examination data from the Korean National Health Insurance Service (NHIS) spanning 2013 to 2020. The NHIS covers approximately 97% of medical expenses for the Korean population and maintains a comprehensive database to monitor claimed expenses and assess the appropriateness of treatments.[16] This database contains extensive hospital information, including disease diagnoses, medication prescriptions, surgical procedures, admission and discharge details, and medical costs.[16,17] Additionally, the NHIS maintains a health examination database for adults aged 18 years and older, with examinations conducted every 1 or 2 years. This database includes survey data on health status and behavior, as well as measurements of body weight, height, BP, and results from blood and urine laboratory tests.[17] As per its policy, the NHIS provides customized databases for academic research. For this study, we obtained permission from the NHIS to access data tailored to our research objectives and subsequently analyzed it. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (No. 05–2023-023). The requirement for informed consent was waived because the database was anonymized and de-identified.[16]

Study Population

This study included patients aged 18 years and older with type 2 diabetes who were newly prescribed SGLT2i or DPP-4i during the index period, based on NHIS records. The index period was defined as September 1, 2014—when SGLT2i were first approved in Korea—to August 31, 2018 (Supplementary Figure S1). During this period, dapagliflozin, empagliflozin, and ipragliflozin were the SGLT2i approved for use. Type 2 diabetes was identified using the ICD-10 codes E11–E14.

During the index period, 2,057,721 patients with type 2 diabetes were newly prescribed SGLT2i or DPP-4i. From this cohort, we excluded patients who were younger than 18 years at the start of medication, had previously used SGLT2i or DPP-4i before the index date, had a prescription duration of less than 90 d, were prescribed both SGLT2i and DPP-4i simultaneously, lacked health check-up data, had end-stage renal disease, or were undergoing dialysis. After applying these exclusion criteria, 1,252,582 patients remained eligible for analysis. Patients were categorized into 99,391 SGLT2i users and 1,153,191 DPP-4i users (control group) for outcome comparisons. To ensure comparability, patients were matched 1:1 based on propensity scores, resulting in 48,792 patients in each group. A flowchart of the study cohort is shown in Figure 1.

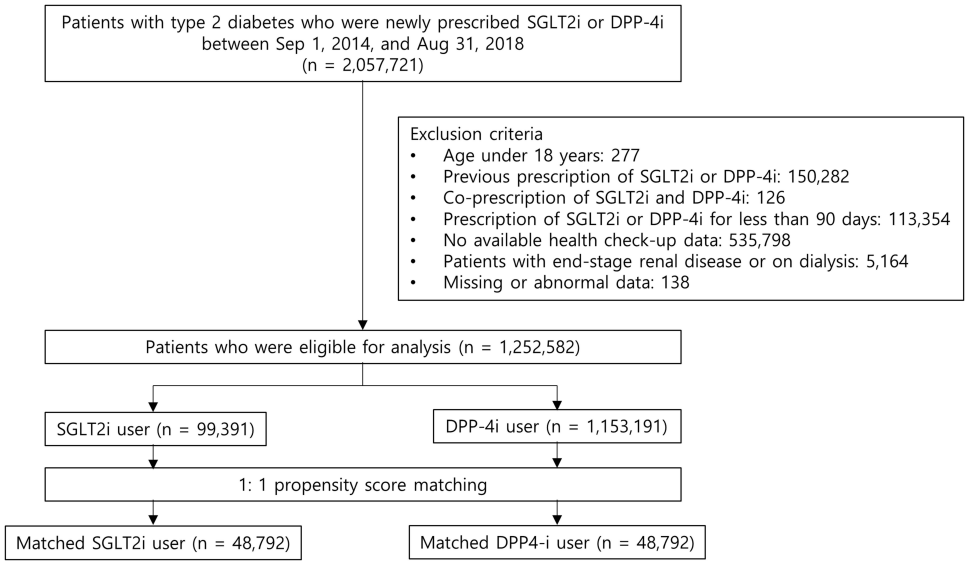

Figure 1 Flow chart of the study cohort.

Baseline Variables

We collected data on baseline covariates, including age, sex, body mass index (BMI), BP, laboratory findings, household income, smoking status, and alcohol consumption, using health check-up records. Low-income households were defined as those in the lowest income quintile. Smoking status was categorized as never smokers, ex-smokers, or current smokers based on lifetime smoking history. Alcohol consumption was assessed based on the average frequency of drinking per week. Individuals who consumed alcohol less than once per week were classified as non-drinkers, whereas those who consumed alcohol at least once per week were considered drinkers. Additionally, a history of CV disease or lower-limb complications, the presence of comorbidities, prior procedures or surgeries, and medication use were identified using diagnostic, procedural, and medication codes during the baseline assessment period, defined as the year preceding the index date. The specific diagnostic, procedural, and medication codes used to define the study cohort are provided in Supplementary Table S1.

End Points

The follow-up period extended from the index date until December 31, 2020, marking the end of the study period. An intention-to-treat approach was employed, tracking patients from the index date until the occurrence of an outcome, discontinuation or switching of the index drug, death, or the end of the study period, whichever occurred first.

As the NHIS database does not provide detailed information on the cause of death, all-cause mortality was assessed as an outcome. CV events were defined as the occurrence of heart failure, myocardial infarction, percutaneous coronary intervention (PCI), ischemic stroke, or peripheral artery disease (PAD). LLEs were evaluated as a composite outcome, including diabetic foot or ulcer, amputation, debridement, graft transplantation, flap operation, and lower-limb revascularization. Lower-limb revascularization encompassed both percutaneous transluminal angioplasty and bypass surgery. The analysis considered both the composite outcome of LLEs and each individual component separately.

Outcome occurrences were identified by examining NHIS admission and discharge records and verifying International Classification of Diseases 10th revision (ICD-10) codes for diagnoses during hospitalization to enhance accuracy. Additionally, domestic procedure codes for surgeries or interventions performed during hospitalization were reviewed. The relevant ICD-10 and domestic procedure codes associated with the study outcomes are provided in Supplementary Table S1.

Propensity Score Matching

One-to-one (1:1) PSM was conducted between the SGLT2i and DPP-4i groups using greedy nearest-neighbor matching to balance baseline characteristics and mitigate confounding variables. Matching covariates included the index year, age, sex, BMI, fasting plasma glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic BP, diastolic BP,

 https://doi.org/10.2147/DMSO.S515384

estimated glomerular filtration rate, household income, smoking status, alcohol consumption, history of CV disease, LLEs, comorbidities, and the use of hypoglycemic agents, antihypertensive drugs, diuretics, antiplatelet drugs, or lipid-lowering agents.

Statistical Analysis

Baseline characteristics of the two treatment groups are presented as mean ± standard deviation for continuous variables and were compared using Student's *t*-test. Categorical variables are expressed as numbers and percentages and were compared using the chi-square test. Following PSM analysis, an absolute standardized difference of < 0.1 between the two groups was considered indicative of negligible differences for each covariate.[18] The cumulative incidence of endpoints was estimated using the Kaplan–Meier method, and the Log rank test was applied to compare the two treatment groups. With the DPP-4i group as the control group, hazard ratios (HRs) for the SGLT2i group regarding the endpoints were calculated using Cox proportional hazards regression analysis. A subgroup analysis was conducted to compare LLE incidence across various clinical conditions that may influence prognosis. Furthermore, an interaction analysis was performed to assess heterogeneity. Additional sensitivity analyses were conducted to mitigate the potential for collider stratification bias arising from the exclusion criteria. Participants excluded due to factors influencing LLE risk were sequentially reintroduced into the cohort, and PSM was repeated. The HR for LLEs was then reassessed in these expanded cohorts. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

A total of 1,252,582 individuals were eligible for the study, with 99,391 in the SGLT2i group and 1,153,191 in the DPP-4i group. The baseline characteristics of the entire cohort differed between the two groups (Supplementary Table S2). Compared to the DPP-4i group, patients in the SGLT2i group were younger, had a higher prevalence of obesity, and exhibited a greater incidence of heart failure and myocardial infarction. Following 1:1 PSM, 48,792 individuals were assigned to each group. The baseline characteristics of both groups after PSM are presented in Table 1, demonstrating well-balanced characteristics with a standardized mean difference of < 0.1 between the two groups.

Table 1 Baseline Characteristics of SGLT2 Inhibitors Vs DPP-4 Inhibitors After PSM

	SGLT2i	DPP-4i	ASD
Participants, n	48,792	48,792	
Index year, n (%)			
2014	3146 (6.45)	3182 (6.52)	0.0051
2015	8438 (17.29)	8318 (17.05)	
2016	13,481 (27.63)	13,405 (27.47)	
2017	15,949 (32.69)	16,036 (32.87)	
2018	7778 (15.94)	7851 (16.09)	
Age (years)	53.30 ± 10.65	53.29 ± 10.99	0.0011
<65	41,541 (85.14)	41,037 (84.11)	0.0257
≥65	7251 (14.86)	7755 (15.89)	
Sex			
Male	36,274 (74.34)	36,109 (74.01)	0.0079
Female	12,518 (25.66)	12,683 (25.99)	
BMI (kg/m^2)	27.42 ± 4.03	27.40 ± 4.17	0.0054
<25	13,414 (27.49)	14,073 (28.84)	0.0285
≥25	35,378 (72.51)	34,719 (71.16)	
FPG (mg/dL)	160.76 ± 57.44	161.08 ± 57.08	0.0056
Triglycerides[a] (mg/dL)	214.41 ± 204.55	215.13 ± 202.01	0.0035

(*Continued*)

Table 1 (Continued).

	SGLT2i	DPP-4i	ASD
HDL cholesterol (mg/dL)	49.75 ± 13.16	50.10 ± 38.66	0.0196
LDL cholesterol (mg/dL)	107.38 ± 42.82	107.89 ± 44.40	0.0117
Systolic BP (mmHg)	129.35 ± 15.03	129.31 ± 15.18	0.0031
Diastolic BP (mmHg)	80.59 ± 10.37	80.60 ± 10.46	0.0009
eGFR (mL/min/1.73 m^2)	92.33 ± 28.34	92.41 ± 27.26	0.0029
Low income	7,765 (15.91)	7,657 (15.69)	0.006
Smoker			
Never	18,399 (37.71)	18,553 (38.02)	0.0039
Ex-	13,631 (27.94)	13,484 (27.64)	
Current	16,762 (34.35)	16,755 (34.34)	
Alcohol consumption			
Nondrinker	7119 (14.59)	7128 (14.61)	0.0005
Drinker	41,673 (85.41)	41,664 (85.39)	
CV disease			
Heart failure	2891 (5.93)	2833 (5.81)	0.0053
Myocardial infarction	753 (1.54)	744 (1.52)	0.0017
PCI	496 (1.02)	505 (1.04)	0.0021
Ischemic stroke	1373 (2.81)	1309 (2.68)	0.0073
PAD	1552 (3.18)	1588 (3.25)	0.0049
Lower limb events			
Diabetic foot or ulcer	214 (0.44)	197 (0.4)	0.0053
Amputation	5 (0.01)	3 (0.01)	0.0052
Revascularization	26 (0.05)	21 (0.04)	0.0045
Other comorbidities			
Diabetic neuropathy	5086 (10.42)	5112 (10.48)	0.0017
Hypertension	28,822 (59.07)	28,734 (58.89)	0.0037
Dyslipidemia	37,477 (76.81)	37,451 (76.76)	0.0012
Chronic kidney disease	578 (1.18)	555 (1.14)	0.0039
Malignancy	1689 (3.46)	1729 (3.54)	0.0042
Hypoglycemic medications			
Sulfonylurea	14,569 (29.86)	14,656 (30.04)	0.0038
Metformin	25,656 (52.58)	25,554 (52.37)	0.0043
Thiazolidinedione	4134 (8.47)	4100 (8.4)	0.0027
Alpha glucosidase inhibitors	1413 (2.9)	1443 (2.96)	0.0035
GLP-1 receptor agonists	4 (0.01)	1 (0)	0.0094
Insulin or 3 ≥ OHA	16,454 (33.7)	16,406 (33.6)	0.0025
Antihypertensive drugs			
ACEi or ARB	18,812 (38.56)	18,743 (38.41)	0.0029
Beta-blockers	4719 (9.67)	4687 (9.61)	0.0023
Calcium channel blockers	14,608 (29.94)	14,563 (29.85)	0.002
Diuretics			
MRA	503 (1.03)	476 (0.98)	0.0058
Thiazide diuretics	7741 (15.87)	7829 (16.05)	0.0049
Loop diuretics	427 (0.88)	411 (0.84)	0.0034
Antiplatelet drugs	5276 (10.81)	5259 (10.78)	0.0011
Lipid-lowering agents	22,411 (45.93)	22,435 (45.98)	0.001

Notes: Data are mean ± SD or n (%). [a]Logarithmic transformation was performed for the comparison.
Abbreviations: ASD, Absolute standardized difference; BMI, body mass index; FPG, fasting plasma, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; eGFR, estimated glomerular filtration rate; CV, cardiovascular; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; GLP-1, glucagon-like peptide-1; OHA, oral hypoglycemic agents; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonist.

https://doi.org/10.2147/DMSO.S515384

Endpoints

The median follow-up period was 2.74 years (interquartile range [IQR] 1.02–3.89), with 2.54 years (IQR 0.85–3.73) in the SGLT2i group and 2.92 years (IQR 1.25–4.04) in the DPP-4i group. The cumulative incidence of CV events and LLEs is depicted in Figure 2. Kaplan–Meier analysis showed a significantly lower cumulative incidence of all-cause mortality, heart failure, ischemic stroke, and PAD in the SGLT2i group than the DPP-4i group (log-rank, all $P < 0.0001$). However, there were no significant differences in the cumulative incidence of myocardial infarction, PCI, or LLEs between the two groups (log-rank, $P = 0.31$, $P = 0.26$, and $P = 0.9$, respectively).

The risk of occurrence for CV events and LLEs is presented in Table 2. The all-cause mortality rate was significantly lower in the SGLT2i group (HR 0.63, 95% CI 0.51–0.78, $P < 0.0001$). Compared to the DPP-4i group, the SGLT2i group had lower incidence rates of heart failure (10.49 vs 12.84 per 1000 person-years; HR 0.85, 95% CI 0.78–0.93, $P = 0.0006$), ischemic stroke (3.91 vs 5.13 per 1000 person-years; HR 0.77, 95% CI 0.67–0.88, $P < 0.0001$), and PAD (7.09 vs 9.08 per 1000 person-years; HR 0.66, 95% CI 0.63–0.69, $P < 0.0001$). However, no significant differences were observed between the SGLT2i and DPP-4i groups in the incidence rates of myocardial infarction (HR 1.06, 95% CI 0.87–1.28, $P = 0.5602$) or PCI (HR 1.05, 95% CI 0.91–1.21, $P = 0.4689$). Similarly, no significant difference was found in the occurrence of LLEs between the two groups (HR 1.05, 95% CI 0.80–1.38, $P = 0.727$), nor in the individual components of LLE.

Subgroup Analysis

For LLEs, we conducted a subgroup analysis to evaluate the influence of potential confounding factors, including age, CV disease status, presence of diabetic neuropathy, and the use of diuretics or beta-blockers. The results are presented in Figure 3. Most of these factors did not significantly alter the effect of SGLT2i on LLEs. However, in women or in those without hypertension, SGLT2i appeared to have a more favorable effect (P for interaction = 0.0096 and P for interaction = 0.0313, respectively). Despite this, the HRs themselves were not statistically significant (HR 0.43, 95% CI 0.11–1.66; HR 0.67, 95% CI 0.27–1.63).

Additionally, we conducted a subgroup analysis based on treatment duration, categorized as <1 year, 1–2.5 years, 2.5–4 years, and ≥4 years (Supplementary Table S3). However, treatment duration did not significantly influence the efficacy of SGLT2i on LLEs (P for interaction = 0.4532).

Further sensitivity analyses are provided in Supplementary Table S4. First, we included 113,354 participants with an SGLT2i or DPP-4i prescription for fewer than 90 d to reassess LLE risk. After PSM, 100,193 participants were assigned to each group (SGLT2i vs DPP-4i). In this cohort, the HR for LLEs with SGLT2i use compared to DPP-4i was 0.88 (95% CI 0.74–1.06, $P = 0.1804$), indicating no statistically significant difference. Second, we expanded the analysis to include 535,798 participants who lacked health check-up data. As key health check-up variables (eg, BMI, fasting plasma glucose, lipid profiles, blood pressure, eGFR, household income, smoking status, and alcohol consumption) were unavailable, adjustments were made using a modified set of covariates, including age, sex, index year, history of CV disease, LLEs, comorbidities, and medication use. After PSM, 141,116 participants were assigned to each group. In this analysis, the HR for LLEs associated with SGLT2i use compared to DPP-4i was 0.84 (95% CI 0.72–0.97, $P = 0.0185$), indicating a statistically significant reduction in LLEs in the SGLT2i group.

Discussion

In this large-scale, real-world study of patients with type 2 diabetes, we demonstrated that initiating SGLT2i, compared to DPP-4i, had a neutral effect on LLEs and their individual outcomes. However, SGLT2i use significantly reduced the risks of all-cause mortality, heart failure, ischemic stroke, and PAD. In contrast, the SGLT2i group did not exhibit a reduction in the risks of myocardial infarction or PCI compared to the DPP-4i group.

SGLT2i is recommended as the preferred glucose-lowering medication for reducing CV and kidney disease risk in patients with type 2 diabetes, as evidenced by its benefits in CV outcome trials.[19,20] SGLT2i exert pleiotropic effects on cardiorenal protection by improving myocardial structure and function, restoring intraglomerular pressure through increased angiotensin activity, and inducing vasodilatory and anti-inflammatory effects.[21,22] These mechanisms help validate CV outcome trials and provide insights into their potential mechanisms.[21,22] Recent meta-analyses of 15 large-scale trials, encompassing approximately 100,000 patients with heart failure, type 2 diabetes, chronic kidney disease, and

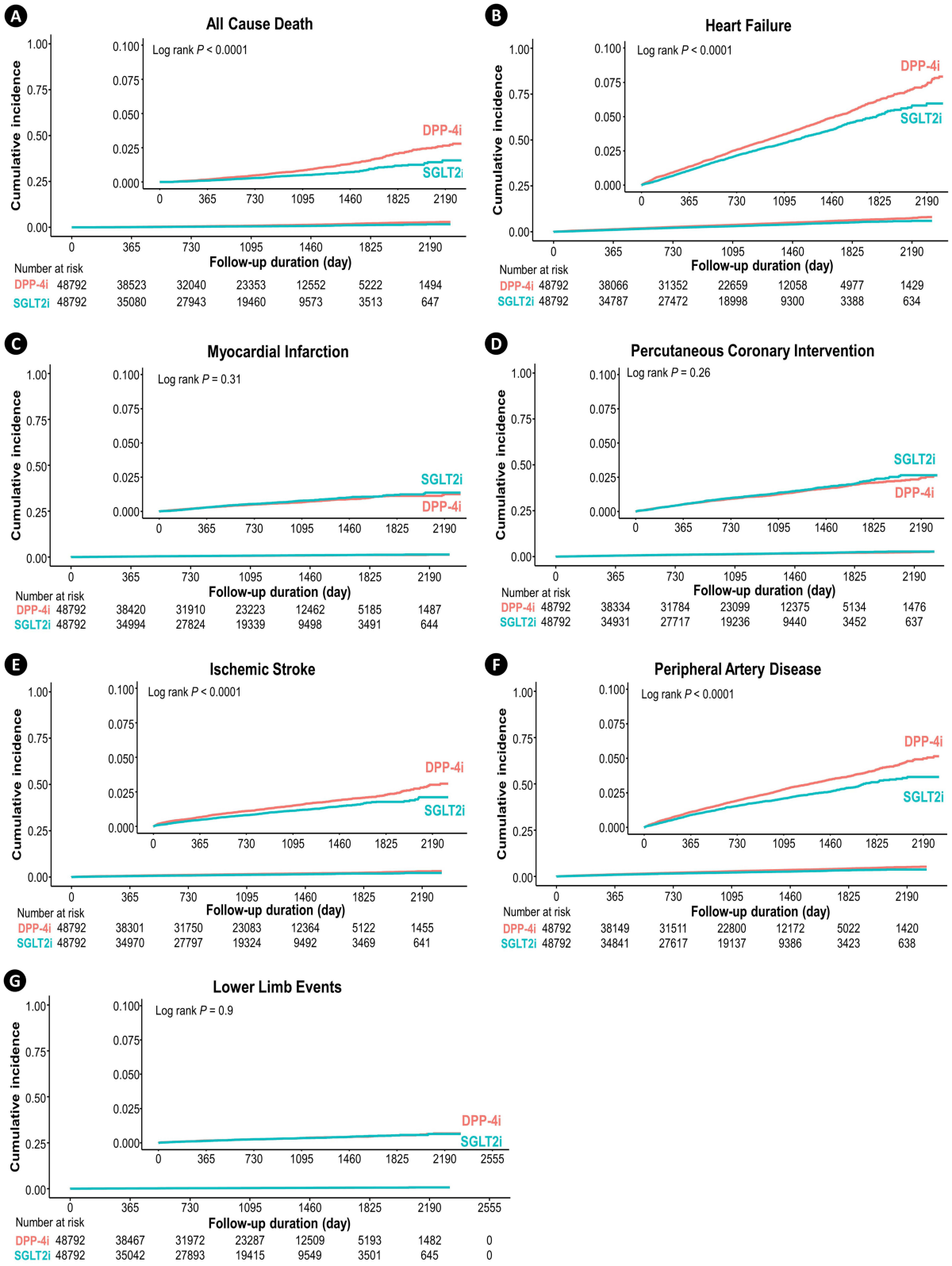

Figure 2 Kaplan-Meier curves of endpoints in new users of SGLT2 inhibitors vs DPP-4 inhibitors. (**A**) Cumulative incidence for the all-cause death. (**B**) Cumulative incidence for the heart failure. (**C**) Cumulative incidence for the myocardial infarction. (**D**) Cumulative incidence for the percutaneous coronary intervention. (**E**) Cumulative incidence for the ischemic stroke. (**F**) Cumulative incidence for the peripheral artery disease. (**G**) Cumulative incidence for the lower limb events.

https://doi.org/10.2147/DMSO.S515384

Table 2 Risk of Occurrence for Cardiovascular and Lower Limb Events: SGLT2 Inhibitors vs DPP-4 Inhibitors

Outcome	SGLT2i		DPP-4i (Reference)		HR (95% CI)	P
	No. (%)	Rate/1000 person-yr	No. (%)	Rate/1000 person-yr		
All cause death	218 (0.45)	1.81	462 (0.95)	3.34	*0.63 (0.51–0.78)*	<0.0001
Heart failure	1245 (2.55)	10.49	1739 (3.56)	12.84	*0.85 (0.78–0.93)*	0.0006
Myocardial infarction	305 (0.63)	2.54	318 (0.65)	2.31	1.06 (0.87–1.28)	0.5602
PCI	558 (1.14)	4.67	594 (1.22)	4.33	1.05 (0.91–1.21)	0.4689
Ischemic stroke	468 (0.96)	3.91	703 (1.44)	5.13	*0.77 (0.67–0.88)*	0.0002
PAD	845 (1.73)	7.09	1235 (2.53)	9.08	*0.66 (0.63–0.69)*	<0.0001
Lower limb events	140 (0.29)	1.16	160 (0.33)	1.16	1.05 (0.8–1.38)	0.727
Diabetic foot or ulcer	79 (0.16)	0.66	110 (0.23)	0.80	0.86 (0.62–1.21)	0.395
Amputation	28 (0.06)	0.23	30 (0.06)	0.22	0.87 (0.48–1.58)	0.6476
Debridement	30 (0.06)	0.25	46 (0.09)	0.33	0.9 (0.54–1.51)	0.6915
Graft transplantation or flap operation	11 (0.02)	0.09	11 (0.02)	0.08	0.75 (0.26–2.16)	0.5943
Revascularization	70 (0.14)	0.58	68 (0.14)	0.49	1.24 (0.81–1.92)	0.3242

Note: Italicized values indicate statistical significance.
Abbreviations: HR, hazard ratio; CI, confidence interval; PCI, percutaneous coronary intervention; PAD, peripheral artery disease.

atherosclerotic CV disease, have further confirmed that SGLT2i reduce heart failure events and CV death, demonstrating consistent benefits across diverse patient populations.[23] Additionally, several real-world studies have shown that SGLT2i use is associated with a reduction in hospitalizations for heart failure and all-cause mortality in patients with type 2

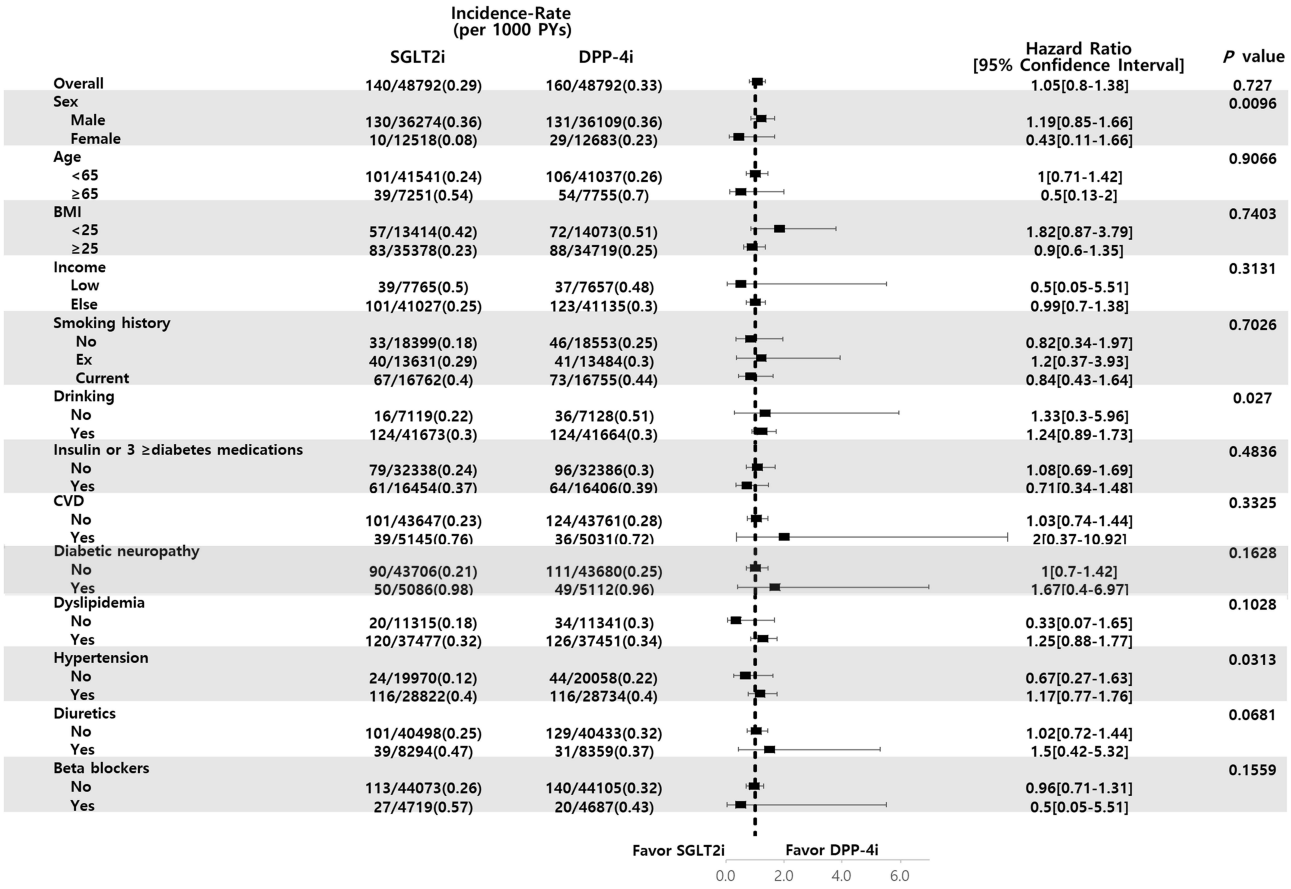

Figure 3 Subgroup analyses of lower limb events: SGLT2 inhibitor vs DPP-4 inhibitor.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease.

diabetes.[24–31] In this study, DPP-4i was selected as an active comparator due to its widespread use in clinical practice and its well-documented neutral effect on CV diseases in CV outcome trials.[32] Consistent with previous real-world studies using DPP-4i comparators, our findings indicate that SGLT2i, compared to DPP-4i, provides significant benefits in reducing hospitalizations for heart failure and all-cause mortality.[27–31]

However, SGLT2i has not demonstrated a significant benefit in reducing the risk of myocardial infarction or stroke in several CV outcome trials, including the EMPA-REG OUTCOME trial, DECLARE-TIMI 58 trial, and CANVAS trial.[3,6,33] Additionally, numerous meta-analyses have reported conflicting data on this matter.[1,24,25,30,34–42] In the CVD-REAL 2 multinational cohort study, which included 386,000 matched patients from over 2.4 million individuals with type 2 diabetes, DPP-4i was used as an active comparator.[30] The results indicated significantly lower risks of heart failure and death, as well as moderately lower risks of myocardial infarction and stroke in clinical practice, based on pooled data from 13 countries in a weighted meta-analysis.[30] However, the effect of SGLT2i on myocardial infarction and stroke varied across countries. Specifically, data from South Korea did not show a significant benefit of SGLT2i over DPP-4i in reducing the risk of myocardial infarction (HR 0.92, 95% CI 0.79–1.07) but did indicate a significant benefit for stroke (HR 0.83, 95% CI 0.77–0.91).[30] Our study, based on Korean insurance data, similarly found no statistically significant benefit of SGLT2i for myocardial infarction or coronary revascularization (HR 1.06, 95% CI 0.87–1.28, and HR 1.05, 95% CI 0.91–1.21, respectively) but did demonstrate a significant benefit for ischemic stroke (HR 0.77, 95% CI 0.67–0.88). The similarity between the CVD-REAL 2 study findings in South Korea and our results supports the relevance of our data. Additionally, a real-world study based on Korean insurance data compared the effects of SGLT2i with thiazolidinediones (TZD) on stroke, finding a comparable risk of stroke between patients with type 2 diabetes treated with either medication.[43] This study by Lee et al suggested a potential benefit of SGLT2i for stroke, considering that pioglitazone, a TZD, has been shown to reduce the risk of recurrent stroke in RCTs.[44] These findings highlight the need for further research on the effects of SGLT2i on myocardial infarction and stroke.

Concerns regarding lower-limb amputation raised by the CANVAS trial were not observed in other SGLT2i CV outcome trials.[3–6] A meta-analysis investigating the impact of SGLT2i on lower-limb complications noted a slightly increased risk of amputation and PAD with canagliflozin treatment, potentially linked to reductions in weight and BP.[8] Similar to the association between thiazide diuretics and an increased amputation risk in patients with type 2 diabetes compared to other antihypertensive agents, it has been suggested that more frequent volume depletion in the canagliflozin group may cause circulatory failure in the distal peripheral arteries, leading to adverse events.[45,46] In a real-world cohort study using three US nationwide databases, adults aged 65 years or older with baseline CV disease had a higher amputation rate with canagliflozin than that with glucagon-like peptide-1 receptor agonists.[7]

Conversely, a sub-analysis of the EMPA-REG OUTCOME study showed no increased risk of lower-limb amputation with empagliflozin in patients with type 2 diabetes and PAD.[47] Similarly, a study by Park et al, using South Korea's national health insurance data, found that SGLT2i neither increased nor decreased the risk of amputation compared to DPP-4i, regardless of patients' vulnerability to amputation due to CV disease or diuretic use.[12] Furthermore, a study using Taiwan's health insurance data—conducted during a period when only dapagliflozin and empagliflozin were available—revealed that SGLT2i, compared to DPP-4i, reduced the risk of lower limb ischemia or amputation in patients with type 2 diabetes and PAD.[11] This effect was attributed to the vascular benefits of SGLT2i, including reduced oxidative stress in endothelial cells and enhanced vasorelaxation, which improve atherosclerosis and benefit PAD.[48–50] In the present study, a sensitivity analysis that included individuals without health check-up data demonstrated a statistically significant reduction in LLE risk with SGLT2i use (HR 0.84 95% CI 0.72–0.97, $P = 0.0185$). While this finding aligns with results from the Taiwan study, the potential influence of unmeasured confounders cannot be excluded. For instance, renal function (eGFR) was unavailable in this analysis. Given that SGLT2i use during the study period was typically restricted to patients with eGFR ≥45 mL/min/1.73m², whereas DPP-4i was prescribed regardless of renal function, the DPP-4i group may have included a higher proportion of individuals with lower renal function, potentially contributing to the observed difference in LLE risk. Additionally, individuals who did not attend health check-ups may represent a population with lower socioeconomic status, which could predispose them to a higher risk of LLEs. These factors warrant further investigation to clarify the impact of SGLT2i on lower-limb outcomes.

Controversial findings from real-world studies on the risk of lower-limb amputation with SGLT2i may be attributed to the lower incidence of adverse events in the general population, which reduces the statistical power of these studies to detect significant differences.[51] Therefore, our study investigated LLEs as a composite outcome, encompassing not only amputation but also diabetic foot or ulcers, debridement, graft transplantation or flap operations, and revascularization. Nonetheless, the incidence rate of LLEs remained relatively low in both the SGLT2i and DPP-4i groups, at 1.16 per 1000 person-years. Notably, we observed a significantly lower risk of PAD in the SGLT2i group, even though we were unable to demonstrate either a beneficial or harmful effect of SGLT2i on LLEs compared to DPP-4i. The positive impact of SGLT2i on PAD in our study may be attributed to early improvements in heart failure and renal outcomes, both of which are known risk factors for PAD.[52,53] Conversely, no significant difference was found in LLEs, highlighting the need for further research on the long-term benefits of SGLT2i in PAD progression and related outcomes, such as lower limb revascularization, diabetic foot or ulcers, and amputation. Additionally, while our study did not demonstrate the benefit of SGLT2i in reducing the risk of myocardial infarction or coronary revascularization, it did show a protective effect against stroke and PAD. Further research is warranted to explore these contrasting results in atherosclerotic diseases in more detail.

This large-scale, real-world study demonstrated that SGLT2i had a neutral effect on LLEs compared to DPP-4i. To the best of our knowledge, this is the first study to comprehensively examine LLEs—defined as a composite of diabetic foot or ulcer, amputation, debridement, graft transplantation or flap operation, and lower-limb revascularization—alongside CV outcomes in patients with type 2 diabetes treated with SGLT2i. Although our study has notable strengths, it also has some limitations. First, while concerns regarding lower-limb complications have primarily been associated with canagliflozin, this drug is not available in Korea.[3,7,8] Consequently, none of the patients in the SGLT2i group received canagliflozin. Additionally, as our data did not allow for differentiation between individual agents within the SGLT2 inhibitor class, it remained unclear whether the observed effects apply to the class as a whole or vary among specific agents. Second, although we used PSM to adjust for potential confounding variables between the SGLT2i and DPP-4i groups, the possibility of residual confounding due to unmeasured or uncontrolled factors cannot be excluded. This inherent limitation of observational studies arises from reliance on health insurance databases, which may lack comprehensive exposure data. Third, the accuracy of diagnostic codes for baseline comorbidities may be affected by miscoding or misclassification. To mitigate this, we prioritized hospitalization diagnoses by cross-referencing admission and discharge records from the KNHIS and verified ICD-10 codes and domestic procedural classifications for in-hospital diagnoses. These measures likely improved diagnostic accuracy. Fourth, the health examination data included only fasting plasma glucose levels and lacked information on hemoglobin A1C levels and diabetes duration. To address this, we adjusted for relevant variables, such as the presence of diabetes-related complications and the number of prescribed hypoglycemic agents, including insulin, which serve as surrogate markers of diabetes severity and duration. Although residual confounding remains possible, these adjustments likely mitigated some bias. Nonetheless, the absence of direct data necessitates a cautious interpretation of our findings. Fifth, patients with chronic kidney disease were relatively underrepresented in this study, comprising only 1.18% of the SGLT2i group and 1.14% of the DPP-4i group in the PSM cohort. Given that chronic kidney disease is a significant risk factor for LLEs in type 2 diabetes, further research is warranted to investigate the impact of SGLT2i on lower-limb complications in patients with impaired renal function.

Conclusion

In conclusion, the initiation of SGLT2i in patients with type 2 diabetes, compared to the initiation of DPP-4i, demonstrated a neutral effect on LLEs while reducing the risks of all-cause mortality, heart failure, ischemic stroke, and PAD in a real-world setting. These findings highlight the need for further research on the long-term benefits of SGLT2i in PAD progression and related outcomes, including lower-limb revascularization, diabetic foot or ulcers, and amputation.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (no. 05-2023-023). The requirement for informed consent was waived because the database was anonymized and de-identified.

Acknowledgments

We would like to thank the employees of the Korean NHIS for granting us access to the claims and health examination data and for handling the data, which enabled us to conduct this study.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by a 2023 research grant from Pusan National University Yangsan Hospital.

Disclosure

The authors report no conflicts of interest in this work.

References

1. McGuire DK, Shih WJ, Cosentino F. et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148–158. doi:10.1001/jamacardio.2020.4511
2. Jung CH, Jang JE, Park J-Y. A novel therapeutic agent for type 2 diabetes mellitus: SGLT2 Inhibitor. *Diabetes Metab J*. 2014;38(4):261–273. doi:10.4093/dmj.2014.38.4.261
3. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657. doi:10.1056/NEJMoa1611925
4. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295–2306. doi:10.1056/NEJMoa1811744
5. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME Trial. *Diabetes Care*. 2018;41(1):e4–e5. doi:10.2337/dc17-1551
6. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357. doi:10.1056/NEJMoa1812389
7. Fralick M, Kim SC, Schneeweiss S, Everett BM, Glynn RJ, Patorno E. Risk of amputation with canagliflozin across categories of age and cardiovascular risk in three US nationwide databases: cohort study. *BMJ*. 2020;370:m2812.
8. Lin C, Zhu X, Cai X, et al. SGLT2 inhibitors and lower limb complications: an updated meta-analysis. *Cardiovasc Diabetol*. 2021;20(1):91. doi:10.1186/s12933-021-01276-9
9. Adimadhyam S, Lee TA, Calip GS, Smith Marsh DE, Layden BT, Schumock GT. Risk of amputations associated with SGLT2 inhibitors compared to DPP-4 inhibitors: a propensity-matched cohort study. *Diabetes Obes Metab*. 2018;20(12):2792–2799. doi:10.1111/dom.13459
10. Heyward J, Mansour O, Olson L, Singh S, Alexander GC. Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: a systematic review and meta-analysis. *PLoS One*. 2020;15(6):e0234065. doi:10.1371/journal.pone.0234065
11. Lee HF, Chen SW, Liu JR, et al. Major adverse cardiovascular and limb events in patients with diabetes and concomitant peripheral artery disease treated with sodium glucose cotransporter 2 inhibitor versus dipeptidyl peptidase-4 inhibitor. *Cardiovasc Diabetol*. 2020;19(1):160. doi:10.1186/s12933-020-01118-0
12. Park S, Jeong HE, Bea S, et al. Safety of sodium-glucose co-transporter-2 inhibitors on amputation across categories of baseline cardiovascular disease and diuretics use in patients with type 2 diabetes. *Diabetes Obes Metab*. 2023;25(11):3248–3258. doi:10.1111/dom.15221
13. Itoga NK, Tawfik DS, Lee CK, Maruyama S, Leeper NJ, Chang TI. Association of blood pressure measurements with peripheral artery disease events. *Circulation*. 2018;138(17):1805–1814. doi:10.1161/CIRCULATIONAHA.118.033348
14. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–2116.
15. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *Heart*. 2021;107(13):1032–1038. doi:10.1136/heartjnl-2020-318060
16. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the national health information database of the national health insurance service in south Korea. *Int J Epidemiol*. 2017;46(3):799–800. doi:10.1093/ije/dyw253
17. Lee YH, Han K, Ko SH, Ko KS, Lee KU. Data analytic process of a nationwide population-based study using national health information database established by national health insurance service. *Diabetes Metab J*. 2016;40(1):79–82. doi:10.4093/dmj.2016.40.1.79
18. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107. doi:10.1002/sim.3697
19. Committee ADAPP. 9. pharmacologic approaches to glycemic treatment: standards of care in diabetes—2024. *Diabetes Care*. 2023;47(Supplement_1):S158–S178.
20. Moon JS, Kang S, Choi JH, et al. 2023 clinical practice guidelines for diabetes management in Korea: full version recommendation of the Korean Diabetes Association. *Diabetes Metab J*. 2024;48(4):546–708. doi:10.4093/dmj.2024.0249
21. Goldberg Lee R. The Pleiotropic Effects of SGLT2 Inhibitors. *JACC*. 2021;77(3):256–258. doi:10.1016/j.jacc.2020.11.029

22. Vallianou NG, Geladari E, Kazazis CE. SGLT-2 inhibitors: their pleiotropic properties. *Diabetes Metab Syndr*. 2017;11(4):311–315.
23. Usman MS, Bhatt DL, Hameed I, et al. Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2024;12(7):447–461. doi:10.1016/S2213-8587(24)00102-5
24. Persson F, Nyström T, Jørgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. *Diabetes Obes Metab*. 2018;20(2):344–351. doi:10.1111/dom.13077
25. Patorno E, Goldfine AB, Schneeweiss S, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. *BMJ*. 2018;360(k119):360.
26. Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(1):28–36. doi:10.1111/dom.13477
27. Gautam S, Agiro A, Barron J, Power T, Weisman H, White J. Heart failure hospitalization risk associated with use of two classes of oral antidiabetic medications: an observational, real-world analysis. *Cardiovasc Diabetol*. 2017;16(1):93. doi:10.1186/s12933-017-0575-x
28. Patorno E, Pawar A, Franklin JM, et al. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. *Circulation*. 2019;139 (25):2822–2830. doi:10.1161/CIRCULATIONAHA.118.039177
29. Pasternak B, Wintzell V, Melbye M, et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. *BMJ*. 2020;369(m1186). doi:10.1136/bmj.m1186.
30. Kohsaka S, Lam CSP, Kim DJ, et al. Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study. *Lancet Diabetes Endocrinol*. 2020;8(7):606–615. doi:10.1016/S2213-8587(20)30130-3
31. Han SJ, Ha KH, Lee N, Kim DJ. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a nationwide population-based study. *Diabetes Obes Metab*. 2021;23(3):682–691. doi:10.1111/dom.14261
32. Mannucci E, Mosenzon O, Avogaro A. Analyses of results from cardiovascular safety trials with DPP-4 inhibitors: cardiovascular outcomes, predefined safety outcomes, and pooled analysis and meta-analysis. *Diabetes Care*. 2016;39(Supplement_2):S196–S204. doi:10.2337/dcS15-3024
33. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373 (22):2117–2128. doi:10.1056/NEJMoa1504720
34. Bhattarai M, Salih M, Regmi M, et al. Association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in patients with type 2 diabetes and other risk factors for cardiovascular disease: a meta-analysis. *JAMA Network Open*. 2022;5(1):e2142078. doi:10.1001/jamanetworkopen.2021.42078
35. Yu J, Li J, Leaver PJ, et al. Effects of canagliflozin on myocardial infarction: a post hoc analysis of the CANVAS programme and CREDENCE trial. *Cardiovasc Res*. 2022;118(4):1103–1114. doi:10.1093/cvr/cvab128
36. Huang X, Dannya E, Liu X, Yu Y, Tian P, Li Z. Effect of sodium-glucose cotransporter-2 inhibitors on myocardial infarction incidence: a systematic review and meta-analysis of randomized controlled trials and cohort studies. *Diabetes Obes Metab*. 2024;26(3):1040–1049. doi:10.1111/dom.15405
37. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. *Cardiovasc Diabetol*. 2016;15(1):37. doi:10.1186/s12933-016-0356-y
38. Guo M, Ding J, Li J, et al. SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20(8):1977–1982. doi:10.1111/dom.13295
39. Wu JH, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2016;4(5):411–419. doi:10.1016/S2213-8587(16)00052-8
40. Tsai WH, Chuang SM, Liu SC, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):15364. doi:10.1038/s41598-021-94945-4
41. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31–39. doi:10.1016/S0140-6736(18)32590-X
42. Pioli MR, Ritter AMV, Modolo R. Unsweetening the Heart: possible Pleiotropic Effects of SGLT2 Inhibitors on cardio and cerebrovascular alterations in resistant hypertensive subjects. *Am J Hypertens*. 2018;31(3):274–280. doi:10.1093/ajh/hpx204
43. Lee SE, Nam H, Choi HS, Kim H, Kyoung DS, Kim KA. Comparative effects of sodium-glucose cotransporter 2 inhibitor and thiazolidinedione treatment on risk of stroke among patients with type 2 diabetes mellitus. *Diabetes Metab J*. 2022;46(4):567–577. doi:10.4093/dmj.2021.0160
44. Wilcox R, Bousser MG, Betteridge DJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone clinical trial in macrovascular events 04). *Stroke*. 2007;38(3):865–873. doi:10.1161/01.STR.0000257974.06317.49
45. Tanaka A, Node K. Increased amputation risk with canagliflozin treatment: behind the large cardiovascular benefit? *Cardiovasc Diabetol*. 2017;16 (1):129. doi:10.1186/s12933-017-0611-x
46. Chatterjee S, Bandyopadhyay D, Ghosh RK, et al. SGLT-2 inhibitors and peripheral artery disease: a statistical hoax or reality? *Curr Probl Cardiol*. 2019;44(7):207–222. doi:10.1016/j.cpcardiol.2018.06.004
47. Verma S, Mazer CD, Al-Omran M, et al. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation*. 2018;137(4):405–407. doi:10.1161/CIRCULATIONAHA.117.032031
48. Lin B, Koibuchi N, Hasegawa Y, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol*. 2014;13(1):148. doi:10.1186/s12933-014-0148-1
49. Gaspari T, Spizzo I, Liu H, et al. Dapagliflozin attenuates human vascular endothelial cell activation and induces vasorelaxation: a potential mechanism for inhibition of atherogenesis. *Diab Vasc Dis Res*. 2018;15(1):64–73. doi:10.1177/1479164117733626
50. Sugiyama S, Jinnouchi H, Kurinami N, et al. The SGLT2 inhibitor dapagliflozin significantly improves the peripheral microvascular endothelial function in patients with uncontrolled type 2 diabetes mellitus. *Intern Med*. 2018;57(15):2147–2156. doi:10.2169/internalmedicine.0701-17
51. Tkáč I, Kozárová M, Stančáková Yaluri A, Javorský M. Treatment with sodium-glucose cotransporter 2 inhibitors and risk of lower-limb amputations. *Diabetes Obes Metab*. 2024;26(10):4803–4805. doi:10.1111/dom.15775

52. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110(6):738–743. doi:10.1161/01.CIR.0000137913.26087.F0
53. Inglis SC, Hermis A, Shehab S, Newton PJ, Lal S, Davidson PM. Peripheral arterial disease and chronic heart failure: a dangerous mix. *Heart Fail Rev*. 2013;18(4):457–464. doi:10.1007/s10741-012-9331-1