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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

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Abstract

Aim: To examine the real-world cardiovascular effectiveness and safety associated with sodium-glucose co-transporter-2 (SGLT2) inhibitor compared with dipeptidyl peptidase-4 (DPP-4) inhibitor treatment in older adults with type 2 diabetes.

Materials and Methods: In this retrospective cohort study, older adults with type 2 diabetes (aged ≥65 years) were identified in the Korean National Health Insurance Service database from September 2014 to December 2016. In total, 408 506 new users of an SGLT2 inhibitor or DPP-4 inhibitor were propensity score matched. Cox regression was used to estimate the hazard ratios (HR) and 95% confidence interval (CI) for outcomes of interest: hospitalization for heart failure (HHF), all-cause death, myocardial infarction, stroke, diabetic ketoacidosis (DKA), bone fracture, severe hypoglycaemia, genital infection and urinary tract infection (UTI).

Results: Compared with DPP-4 inhibitors, new users of SGLT2 inhibitors had a lower risk of HHF (HR 0.86; 95% CI 0.76-0.97), all-cause death (HR 0.85; 95% CI 0.75-0.98) and stroke (HR 0.86; 95% CI 0.77-0.97), but a similar risk of myocardial infarction (HR 0.95; 95% CI 0.77-1.19). The risks of DKA, bone fracture and severe hypoglycaemia were similar between both groups, although genital infection (HR 2.44; 95% CI 2.22-2.67) and UTI (HR 1.05; 95% CI 1.00-21.11) were more frequent among new users of SGLT2 inhibitors compared with DPP-4 inhibitors.

Conclusion: Our findings suggest that initiation of SGLT2 inhibitors offers cardiovascular disease protection and can be used safely in older adults with type 2 diabetes.

KEYWORDS

aged, cardiovascular diseases, dipeptidyl-peptidase-4 inhibitor, drug-related side effects and adverse reactions, sodium-glucose co-transporter-2 inhibitor, type 2 diabetes

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1 | INTRODUCTION

Type 2 diabetes in the elderly population is recognized as a public health challenge. Increases in lifespan and the chronic natural course of type 2 diabetes contribute to the increased prevalence of diabetes. In Korea, nearly 30% of individuals aged 65 years or older have type 2 diabetes. Worldwide, the estimated number of people older than 65 years with diabetes is 135.6 million, and this is expected to increase to 276.2 million in 2045.[1,2]

Older adults with type 2 diabetes have a higher risk of cardiovascular disease (CVD) and mortality.[3] In addition, older adults are more prone to adverse drug reactions than younger adults because of multiple medication regimens (polypharmacy), co-morbidities and age-related changes in pharmacokinetics and pharmacodynamics.[4,5] Older adults with type 2 diabetes are at an increased risk of severe hypoglycaemia, which is associated with higher hospitalization and death rates.[6] Therefore, pharmacological therapies in older adults with type 2 diabetes should be carefully prescribed and monitored, taking into consideration the cardiovascular risks and potential for adverse drug reactions among this patient population, as well as the need to avoid hypoglycaemia.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a recently approved class of oral antidiabetic drugs that lower blood glucose concentration by increasing urinary glucose excretion via inhibition of SGLT2 in the proximal renal tubules.[7] SGLT2 inhibitors have received considerable attention because of their significant reduction of CVD events in addition to glucose-lowering effects, with minimal risk of hypoglycaemia.[8–10] Based on these characteristics, these drugs may be suitable treatment options in older adults with type 2 diabetes. However, clinicians also have concerns about the side effects of these drugs, which include diabetic ketoacidosis (DKA), genital infection, urinary tract infection (UTI) and bone fracture. Post hoc analyses of randomized controlled trials (RCTs) have examined the CVD benefits and safety of SGLT2 inhibitors in older adults with type 2 diabetes.[11,12] However, these RCTs are limited because of the comparatively small sample sizes and strict inclusion and exclusion criteria, which do not appropriately reflect elderly patients with type 2 diabetes at risk of a variety of serious co-morbidities. In addition, there is a lack of large-scale observational studies on CVD-related effects as well as the safety of SGLT2 inhibitors in older adults with type 2 diabetes. For these reasons, the currently available data are insufficient to support the recommendation of SGLT2 inhibitors to elderly patients with type 2 diabetes in routine clinical practice.

On the other hand, dipeptidyl peptidase (DPP)-4 inhibitors have been recommended as second-line agents for treatment of older adults with type 2 diabetes by several expert groups.[13] Previous studies in older adults with type 2 diabetes have shown the efficacy and safety of DPP-4 inhibitors with minimal hypoglycaemic events, no risk of bone fracture, and neutral risk of CV complications and mortality.[14] In addition, DPP-4 inhibitors are commonly prescribed in a similar manner to how SGLT2 inhibitors are prescribed for people with type 2 diabetes.[15,16] Therefore, DPP-4 inhibitors are a suitable active comparator to evaluate the effectiveness of SGLT2 inhibitors in older adults with type 2 diabetes in the clinical setting.

In this study, we compared the cardiovascular outcomes and adverse drug reactions between older adults with type 2 diabetes newly initiating an SGLT2 inhibitor or a DPP-4 inhibitor using the Korean National Health Insurance Service (NHIS) database.

2 | METHODS

2.1 | Data source and study design

We conducted a population-based, retrospective, observational cohort study using the Korean NHIS database, which provides a centralized repository of longitudinal data for 97% of the Korean population and is linked to the Korean National Death Registry.[17] The NHIS database includes information on demographic characteristics, socioeconomic status, and claims, such as diagnosis (International Classification of Diseases, 10th revision [ICD-10] code), drug prescriptions (Anatomical Therapeutic Chemical code) and medical procedures. Socioeconomic status is indirectly estimated using annual medical insurance premiums, which are determined based on income and assets. This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-EXP-17-510), which waived the requirement for informed consent because all patient data were de-identified.

2.2 | Patient cohort

People with type 2 diabetes were identified using the standard diagnosis codes (ICD-10) E11, E12, E13 and E14. The study comprised adults aged 65 years or older with type 2 diabetes who had newly started SGLT2 inhibitors or DPP-4 inhibitors. New users were defined as patients who were written a prescription (initial or add-on therapy) for any SGLT2 inhibitor (dapagliflozin, empagliflozin, ipragliflozin) or DPP-4 inhibitor (sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin, anagliptin, tenegliptin, gemigliptin, evogliptin) from 1 September 2014 (when SGLT2 inhibitors were first approved in Korea) to 31 December 2016, and who had not used either drug during the preceding 12 months. The index date was defined as the prescription date for new initiation of an SGLT2 inhibitor or DPP-4 inhibitor. Patients with type 1 diabetes (ICD-10 code: E10) or gestational diabetes (ICD-10 code: O24) were excluded. A flowchart of patient selection is shown in Figure S1. A total of 408 506 patients newly started with an SGLT2 inhibitor or DPP-4 inhibitor who met the eligibility criteria were identified. Of these, 15 703 were new users of SGLT2 inhibitors and 392 803 were new users of DPP-4 inhibitors. After 1:1 propensity score matching, 15 699 new users of the SGLT2 inhibitor and 15 699 new users of the DPP-4 inhibitor remained. We assessed baseline characteristics, which included age, sex, index year, household income, prescribed medication, co-morbidities and frailty within 1 year prior to the index date. Co-morbidities were recorded using ICD-10

TABLE 1 Baseline characteristics of older patients with type 2 diabetes in this study

	Before propensity score matching			After propensity score matching		
	SGLT2i (N = 15 703)	DPP-4i (N = 392 803)	Standardized difference	SGLT2i (N = 15 699)	DPP-4i (N = 15 699)	Standardized difference
Mean (SD) age	71.9 (5.5)	73.8 (6.2)	32.2	71.9 (5.5)	71.8 (5.5)	0.9
Women	9031 (57.5)	214 011 (54.5)	6.1	9027 (57.5)	9021 (57.5)	0.1
Index year						
2014	2017 (12.8)	45 187 (11.5)	4.1	2017 (12.8)	2047 (13.0)	0.6
2015	5610 (35.7)	178 015 (45.3)	19.6	5609 (35.7)	5626 (35.8)	0.2
2016	8076 (51.4)	169 601 (43.2)	16.6	8073 (51.4)	8026 (51.1)	0.6
Household income						
Low	3069 (19.5)	74 156 (18.9)	1.7	3067 (19.5)	3074 (19.6)	0.1
Intermediate	4182 (26.6)	103 103 (26.2)	0.9	4182 (26.6)	4105 (26.1)	1.1
High	6961 (44.3)	176 963 (45.1)	1.5	6959 (44.3)	7080 (45.1)	1.6
Missing	1491 (9.5)	38 581 (9.8)	1.1	1491 (9.5)	1440 (9.2)	1.1
Drugs						
Metformin	11 173 (71.2)	256 048 (65.2)	12.8	11 169 (71.1)	11 430 (72.8)	3.7
Sulphonylurea	8132 (51.8)	217 388 (55.3)	7.1	8129 (51.8)	8242 (52.5)	1.4
Thiazolidinedione	2063 (13.1)	35 349 (9.0)	13.2	2061 (13.1)	2083 (13.3)	0.4
Glucagon-like peptide-1 agonist	21 (0.1)	74 (0.0)	4.2	17 (0.1)	19 (0.1)	0.4
Meglitinide	241 (1.5)	8623 (2.2)	4.9	241 (1.5)	229 (1.5)	0.6
Alpha glucosidase inhibitor	1427 (9.1)	37 105 (9.4)	1.2	1427 (9.1)	1376 (8.8)	1.1
Insulin	2864 (18.2)	96 106 (24.5)	15.2	2861 (18.2)	2739 (17.4)	2.0
Low dose acetylic salicylic acid	6008 (38.3)	156 626 (39.9)	3.3	6008 (38.3)	5965 (38.0)	0.6
Statin	10 532 (67.1)	238 806 (60.8)	13.1	10 528 (67.1)	10 457 (66.6)	1.0
ACE inhibitors	794 (5.1)	19 757 (5.0)	0.1	794 (5.1)	766 (4.9)	0.8
ARB	9413 (59.9)	226 663 (57.7)	4.6	9409 (59.9)	9426 (60.0)	0.2
Dihydropyridines	4885 (31.1)	141 224 (36.0)	10.3	4884 (31.1)	4909 (31.3)	0.3
Low ceiling diuretics	2180 (13.9)	52 826 (13.4)	1.3	2180 (13.9)	2144 (13.7)	0.7
Beta blockers	4037 (25.7)	102 775 (26.2)	1.0	4035 (25.7)	3931 (25.0)	1.5
Non-hydropyridines	834 (5.3)	19 691 (5.0)	1.3	834 (5.3)	836 (5.3)	0.1
High ceiling diuretics	1738 (11.1)	62 372 (15.9)	14.1	1737 (11.1)	1675 (10.7)	1.3
Aldosterone antagonists	750 (4.8)	22 151 (5.6)	3.9	750 (4.8)	733 (4.7)	0.5
Warfarin	284 (1.8)	9272 (2.4)	3.9	284 (1.8)	238 (1.5)	2.3
Receptor P2Y12 antagonists	2722 (17.3)	65 467 (16.7)	1.8	2722 (17.3)	2664 (17.0)	1.0
Co-morbidities						
Cardiovascular disease	7213 (45.9)	177 345 (45.1)	1.6	7212 (45.9)	6945 (44.2)	3.4
Myocardial infarction	619 (3.9)	15 937 (4.1)	0.6	619 (3.9)	605 (3.9)	0.5
PCI with stent	417 (2.7)	8173 (2.1)	3.8	417 (2.7)	404 (2.6)	0.5
Unstable angina	1381 (8.8)	28 642 (7.3)	5.5	1381 (8.8)	1338 (8.5)	1.0
Angina pectoris	4089 (26.0)	91 366 (23.3)	6.5	4088 (26.0)	4004 (25.5)	1.2
Heart failure	1774 (11.3)	46 397 (11.8)	1.6	1773 (11.3)	1703 (10.8)	1.4
Atrial fibrillation	805 (5.1)	20 806 (5.3)	0.8	805 (5.1)	734 (4.7)	2.1
Stroke	3079 (19.6)	86 723 (22.1)	6.1	3079 (19.6)	3055 (19.5)	0.4

TABLE 1 (Continued)

	Before propensity score matching			After propensity score matching		
	SGLT2i (N = 15 703)	DPP-4i (N = 392 803)	Standardized difference	SGLT2i (N = 15 699)	DPP-4i (N = 15 699)	Standardized difference
Peripheral artery disease	47 (0.3)	2444 (0.6)	4.8	47 (0.3)	43 (0.3)	0.5
Chronic kidney disease	436 (2.8)	24 683 (6.3)	16.9	436 (2.8)	449 (2.9)	0.5
Diabetic neuropathy	4907 (31.2)	115 191 (29.3)	4.2	4905 (31.2)	4790 (30.5)	1.6
Diabetic retinopathy	5271 (33.6)	123 571 (31.5)	4.5	5268 (33.6)	5169 (32.9)	1.3
Diabetic nephropathy	2757 (17.6)	65 249 (16.6)	2.5	2754 (17.5)	2713 (17.3)	0.7
Severe hypoglycaemia	566 (3.6)	19 102 (4.9)	6.3	566 (3.6)	519 (3.3)	1.6
Keto−/lactate acidosis	148 (0.9)	3755 (1.0)	0.1	148 (0.9)	133 (0.8)	1.0
Cancer	2312 (14.7)	65 174 (16.6)	5.1	2311 (14.7)	2304 (14.7)	0.1
Frailty (yes)	638 (4.1)	30 727 (7.8)	16.0	638 (4.1)	682 (4.3)	1.4

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4i, dipeptidyl peptidase-4 inhibitor; PCI, percutaneous coronary intervention; SGLT2i, sodium-glucose co-transporter-2 inhibitor.
Note: Data are presented as mean ± standard deviation or number (%).

codes (Table S1) and frailty was defined as at least one hospital admission for 3 or more consecutive days.[18–20]

2.3 | Study outcomes

Cardiovascular outcomes of hospitalization for heart failure (HHF), all-cause death, a composite of these endpoints (all-cause death or HHF), myocardial infarction (MI) and stroke were evaluated. Cardiovascular outcomes were defined using primary discharge diagnosis codes (Table S1). Safety endpoints were assessed as occurrence of DKA, bone fracture, genital infection, severe hypoglycaemia and UTI. Safety endpoints were defined using diagnosis codes from inpatient and outpatient claim data, except that for DKA (inpatients only).

2.4 | Statistical analysis

Baseline characteristics were analysed using descriptive statistics. Continuous variables were described as mean with standard deviation (SD) and categorical variables as frequency and percentage. The differences between SGLT2 inhibitor and DPP-4 inhibitor groups were adjusted via propensity score matching with a 1:1 ratio, using the nearest neighbour technique with a caliper of 0.25 SD on the probability scale.[21] We set age, sex, index year, household income, prescribed medication, co-morbidities and frailty as confounding variables then used them to calculate propensity scores. The adequacy of matching was assessed by evaluating postmatch standardized differences in individual characteristics (Table 1). A non-negligible imbalance was considered if a standardized difference of greater than 10% occurred between the two groups postmatch.

The incidence rate for each outcome was calculated as the number of events divided by the total number of person-years at risk. The time from initiation of an SGLT2 inhibitor or DPP-4 inhibitor to first event was assessed using Kaplan–Maier plots and the log-rank test. Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for each outcome. We further investigated heterogeneity among studies by conducting subgroup analyses. Interaction terms were used to evaluate whether the occurrence of outcomes would change by factor across subgroups. We primarily used an intent-to-treat approach, in which patients were followed from the index date until the outcome of interest, death, or end of the study period, whichever came first.

All analyses were performed using SAS software (v. 9.4, SAS Institute Inc., Cary, NC, USA) and survival curves were calculated using the R 'survival' package (v. 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

In total, 408 506 individuals were included in the cohort during the study period. After propensity score matching, 15 699 pairs were identified (Figure S1). The baseline characteristics for new users of SGLT2 inhibitors and DPP-4 inhibitors were well-matched, with a standardized difference of less than 4% for all variables (Table 1). The mean follow-up period was 384.7 ± 246.3 days.

Initiation of an SGLT2 inhibitor was associated with lower risks of HHF (HR 0.86; 95% CI 0.76-0.97; P = .017), all-cause death (HR 0.85; 95% CI 0.75-0.98; P = .024), a composite of HHF or death (HR 0.86; 95% CI 0.78-0.94; P = .002) and stroke (HR 0.86; 95% CI 0.77-0.97; P = .010) compared with initiation of a DPP-4 inhibitor, but had no effect upon the risk of MI (Figure 1, Table 2). Similar results were observed in the on-treatment analyses (Table S2).

As for safety outcomes, the incidences of DKA, bone fracture and severe hypoglycaemia were balanced between patients

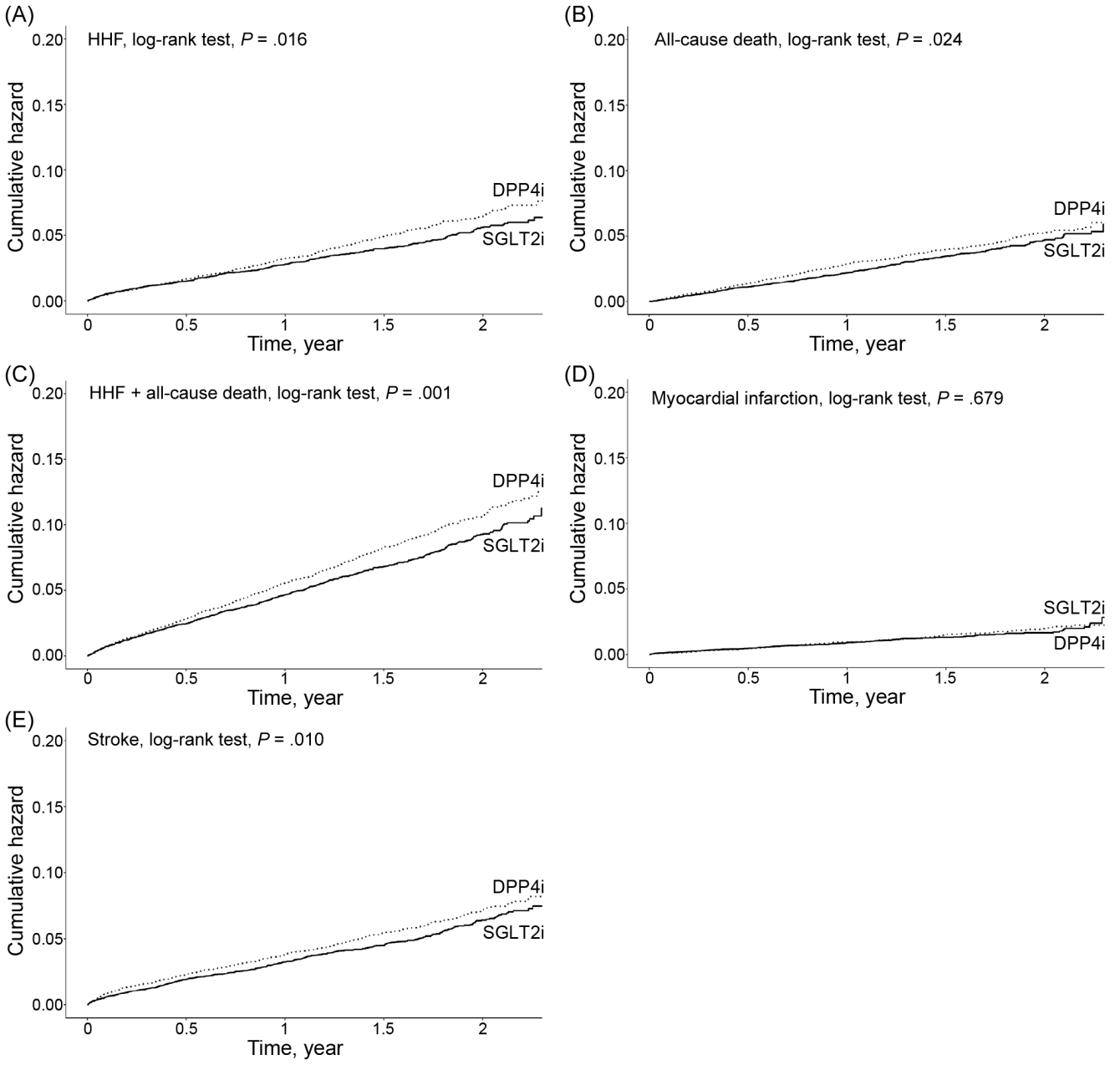


FIGURE 1 Cumulative incidence of cardiovascular outcomes with SGLT2 inhibitors versus DPP-4 inhibitors. DPP-4i, dipeptidyl-peptidase-4 inhibitor; HHF, hospitalization for heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor. A, hospitalization for heart failure, B, all-cause death, C, hospitalization for heart failure plus all-cause death, D, myocardial infarction, E, stroke

newly initiated on SGLT2 inhibitors and DPP-4 inhibitors (Figure 2, Table 2). However, initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a higher risk of genital infection and UTI (HR 2.44; 95% CI 2.22-2.67; $P < .001$; HR 1.05; 95% CI 1.00-1.11; $P = .047$, respectively). In on-treatment analyses, initiation of an SGLT2 inhibitor was associated with lower risks of bone fracture and severe hypoglycaemia, as well as a higher risk of genital infection, compared with a DPP-4 inhibitor (Table S2).

In subgroup analysis, patients were divided into elderly (aged <75 years) and very elderly (aged ≥75 years) age groups (Figure 3). Although analyses of the two subgroups directionally favoured the use of SGLT2 inhibitors over DPP-4 inhibitors for HHF, all-cause death, a composite of HHF or all-cause death and stroke, these effects were predominantly observed in elderly but not very elderly patients, with significant treatment-by-age group interactions. However, safety outcomes showed similar results across age groups. In subgroup analyses of CVD presence at baseline, protective effects of SGLT2 inhibitors on all CV outcomes except for MI were observed in patients with prior CVD but not in patients without prior CVD (all, P for interaction <.001) (Figure S2).

TABLE 2 Risk of cardiovascular outcomes and adverse events associated with SGLT2 inhibitors versus DPP-4 inhibitors

	Event rate (per 100 PY)		HR (95% CI)	*P*-value
	SGLT2i	DPP-4i		
HHF	2.82	3.28	0.86 (0.76-0.97)	.017
All-cause death	2.30	2.69	0.85 (0.75-0.98)	.024
HHF + all-cause death	4.72	5.51	0.86 (0.78-0.94)	.002
Myocardial infarction	0.94	0.98	0.95 (0.77-1.19)	.679
Stroke	3.30	3.82	0.86 (0.77-0.97)	.010
DKA	0.26	0.27	0.96 (0.63-1.46)	.853
Bone fracture	8.87	9.31	0.95 (0.88-1.02)	.155
Severe hypoglycaemia	2.40	2.56	0.93 (0.81-1.07)	.295
Genital infection	9.93	4.01	2.44 (2.22-2.67)	<.001
UTI	20.37	19.17	1.05 (1.00-1.11)	.047

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalization for heart failure; HR, hazard ratio; PY, person-years; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UTI; urinary tract infection.

4 | DISCUSSION

In a large population cohort of older adults with type 2 diabetes, initiation of SGLT2 inhibitor treatment was associated with significantly lower risk for HHF, all-cause death and stroke compared with initiation of a DPP-4 inhibitor. Although the risks of genital infection and UTI were higher with SGLT2 inhibitors versus DPP-4 inhibitors, SGLT2 inhibitors were tolerable therapeutic agents for older adults with type 2 diabetes.

To date, there have been two post hoc analyses examining the effect of age on cardiovascular outcomes during trials of SGLT2 inhibitors. First, according to a post hoc analysis performed for the EMPA-REG OUTCOME study, which included 2475 patients aged 65 to 75 years and 652 patients aged 75 years or older, empagliflozin reduced the risks of HHF, cardiovascular death and all-cause mortality compared with placebo across all age groups but did not affect MI or stroke.[11] The post hoc analysis conducted as part of the DECLARE-TIMI 58 study included 6811 patients aged 65 to 75 years and 1096 patients aged 75 years or older and found that dapagliflozin reduced the risk of HHF compared with placebo but did not reduce the risk of cardiovascular death, all-cause death, MI or stroke.[12] Although previous cardiovascular outcome trials provide strong evidence of the importance of treatment choice in type 2 diabetes management, RCTs have limitations because they do not fully reflect routine clinical practice, especially for older adults. Older adults are a heterogeneous group, with high variability in clinical metrics depending on the capacity for work, self-care, degree of frailty and overall dependency.[22] Furthermore, older adults have many barriers to participating in RCTs, so such studies may be affected by selection bias because they do not include frailer, older patients.[23] Therefore, in the current study, we surveyed data that reflected routine clinical practice and provided evidence about cardiovascular outcomes and the safety of SGLT2 inhibitors in older adults with diverse general conditions and a broad spectrum of CV risk. In addition, we chose DPP-4 inhibitors as an active comparator because they are commonly used in clinical practice to treat older adults in a manner similar to SGLT2 inhibitor use.

Previous observational studies of CV outcomes of SGLT2 inhibitors, such as the CVD-REAL study, a large multinational observational study, compared SGLT2 inhibitors with a group of unspecified glucose-lowering drugs; these studies did not provide comparative information for the CV effects of SGLT-2 inhibitors versus the specific antidiabetic drug options.[24–30] Therefore, our study, which directly compares SGLT2 inhibitors and DPP-4 inhibitors, may provide evidence that helps clinicians improve treatment decisions for elderly patients with type 2 diabetes. Heart failure is prevalent in older adults with diabetes and is associated with high mortality.[31] We confirmed that new use of an SGLT2 inhibitor yielded superior results compared with a DPP-4 inhibitor in older adults in terms of incident HHF and all-cause mortality, a result that is consistent with other recent real-world studies in general populations with type 2 diabetes across many countries.[20,32–37] Three of these studies, which performed subgroup analysis stratified by age (<65 vs. ≥65 years), showed that SGLT2 inhibitors were still associated with a lower risk of HHF or CVD compared with DPP-4 inhibitors in older adults.[32,35,36] However, the results for MI and stroke are conflicting. Some studies have shown that SGLT2 inhibitors are superior to DPP-4 inhibitors,[35,37] while others have reported a similar risk of MI or stroke between the two groups.[20,34,36] We found that initiation of an SGLT2 inhibitor reduced stroke by 14% compared with initiation of a DPP-4 inhibitor, but did not have a significant effect upon MI in older adults.

We found heterogeneity in reduction of cardiovascular outcomes after initiation of an SGLT2 inhibitor versus a DPP-4 inhibitor according to age group. Reduced risk of cardiovascular outcomes with SGLT2 inhibitor use were not evident in patients aged 75 years or older. Therefore, the protective effects of SGLT2 inhibitors against CVD may be diminished in very elderly patients (aged ≥75 years). Combined co-morbidities, such as impaired renal function and

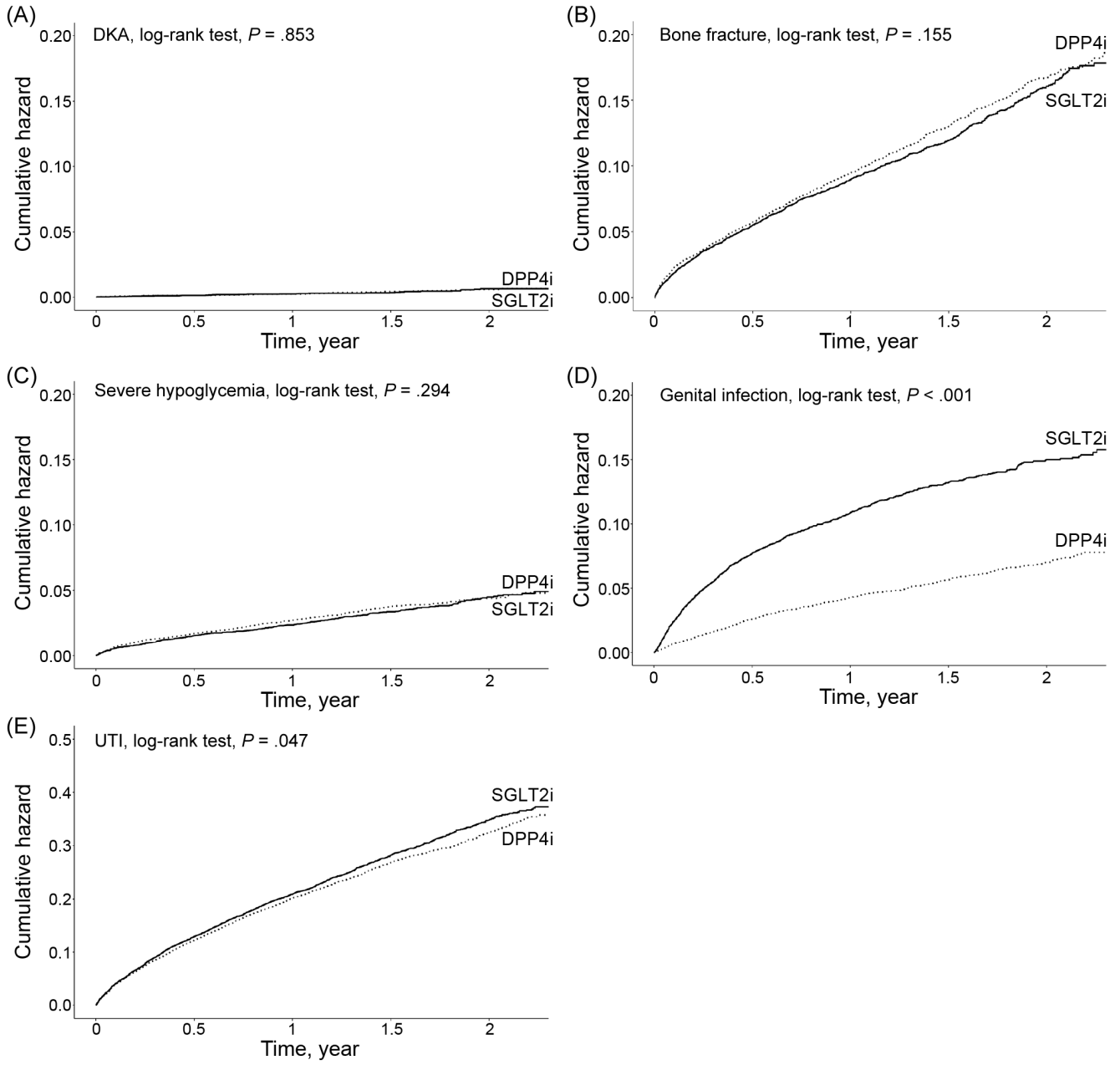


FIGURE 2 Cumulative incidence of adverse events with SGLT2 inhibitors versus DPP-4 inhibitors. DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl-peptidase-4 inhibitor; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UTI, urinary tract infection. A, diabetic ketoacidosis (DKA), B, bone fracture, C, severe hypoglycemia, D, genital infection, E, urinary tract infection (UTI)

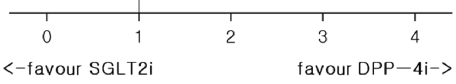
polypharmacy in very elderly adults, may have influenced these findings.[38] Prospective cohort studies are needed to confirm our findings.

The safety data for SGLT2 inhibitors observed in the current study were similar to those reported by previous RCTs and retrospective cohort studies. Among the older adults, there were no differences in the risk of DKA, bone fracture or severe hypoglycaemia between patients newly initiated on an SGLT2 inhibitor or on a DPP-4 inhibitor, but SGLT2 inhibitor use was associated with a 2.44-fold increase in the risk of genital infection and a mild increase in the risk of UTI compared with DPP-4 inhibitor use across age groups, which is consistent with previous studies.[39,40] A recent Canadian, older population-based study did not report an increased risk of UTI with SGLT2 inhibitors compared with DPP-4 inhibitors, although there was an increased risk of genital mycotic infection (2.47-fold within 30 days).[41] Because this study compared incident genital mycotic infection and UTI within 120 days of initial use of an SGLT2 inhibitor and a DPP-4 inhibitor, it was limited with respect to capturing the occurrence of all events, and therefore may not be consistent with our findings.

To the best of our knowledge, this is the largest population-based study of older adults with type 2 diabetes to show an association between initiation of an SGLT2 inhibitor or DPP-4 inhibitor and

(A)

Outcomes	Event rate	HR (95% CI)	*P*-value	*P* for Interaction
HHF				
<75	2.3	0.79 (0.66—0.93)	.006	<.001
≥75	5.1	0.95 (0.79—1.14)	.582	
all−cause death				
<75	1.5	0.72 (0.58—0.89)	.002	<.001
≥75	5.1	0.93 (0.77—1.11)	.422	
HHF + all−cause death				
<75	3.6	0.77 (0.67—0.88)	<.001	<.001
≥75	9.2	0.93 (0.81—1.06)	.283	
Myocardial infarction				
<75	0.8	0.74 (0.55—0.99)	.041	<.001
≥75	1.4	1.42 (1.00—2.00)	.049	
Stroke				
<75	2.8	0.78 (0.67—0.91)	.002	<.001
≥75	5.5	0.95 (0.79—1.13)	.566	



(B)

Outcomes	Event rate	HR (95% CI)	*P*-value	*P* for Interaction
DKA				
<75	0.2	1.06 (0.62—1.82)	.825	<.001
≥75	0.4	0.84 (0.43—1.63)	.604	
Bone fracture				
<75	7.9	0.90 (0.82—0.99)	.031	<.001
≥75	12.3	1.01 (0.90—1.14)	.850	
Severe hypoglycaemia				
<75	2.2	0.97 (0.81—1.15)	.693	<.001
≥75	3.4	0.85 (0.68—1.07)	.157	
Genital infection				
<75	7.4	2.49 (2.24—2.76)	<.001	<.001
≥75	5.2	2.65 (2.16—3.24)	<.001	
UTI				
<75	18.3	1.03 (0.97—1.10)	.305	<.001
≥75	23.7	1.09 (0.99—1.19)	.068	

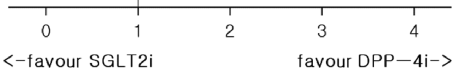


FIGURE 3 Subgroup analysis of HRs for cardiovascular outcomes and adverse events with SGLT2 inhibitors versus DPP-4 inhibitors by age group. A, CV outcomes; B, adverse events. CI, confidence interval; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl-peptidase-4 inhibitor; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UTI, urinary tract infection

cardiovascular events, as well as adverse events. Our large sample size of very elderly (aged ≥75 years) adults (n = 8950) permitted a more robust evaluation of the effectiveness and safety of SGLT2 inhibitors in very elderly patients with type 2 diabetes.

The database used for this study is nationwide and features a real-world design that allows generalization to routine care settings. In addition, we used an active drug comparator, new-user design and propensity score matching with control of common confounding variables to improve the robustness of the study findings.[42]

There are limitations, indicating that our results should be interpreted with caution. First, we defined cardiovascular outcomes and

safety profiles according to ICD-10 diagnostic codes, which introduces the possibility of outcome misclassification. Recent Korean studies that compared diagnoses from claim databases with medical records observed overall accuracy rates of 72.3% for diabetes, 92.0% for MI and 90.5% for ischaemic stroke.[43,44] There was a possibility of non-differential misclassification, which biased the risk ratio towards the null. Second, this database has insufficient information regarding cause of death, and all-cause death was assessed instead of cardiovascular death. However, a large portion of causes of death in this cohort was expected to be attributed to cardiovascular causes with type 2 diabetes.[8,9,45] Third, there is a possibility of residual confounding by unmeasured or uncontrolled confounders because this is an observational study that collected exposure information from a health insurance database. In particular, there is no information available about diabetes duration and HbA1c, which are related to diabetes severity and glucose control status. However, we carefully adjusted associated variables, such as the presence of diabetic microvascular and macrovascular complications, prescriptions for other hypoglycaemic agents including insulin as a proxy for diabetes duration and HbA1c using a propensity score matching method. Fourth, the phenomenon of volume depletion, which may occur in older adults who are prescribed SGLT2 inhibitors, could not be evaluated in this study because it was difficult to identify this factor using a claims database. Finally, the study had a comparatively short follow-up length. Further studies are needed to compare the long-term effects of SGLT2 inhibitors in older patients with type 2 diabetes.

In summary, in real-world clinical practice, in older adults with type 2 diabetes, initiation of an SGLT2 inhibitor was associated with significantly lower risks of HHF, all-cause death and stroke compared with initiation of a DPP-4 inhibitor. There were no new safety issues associated with the use of SGLT2 inhibitors in older adults. Although our safety outcomes are consistent with other studies, the beneficial cardiovascular effects of new SGLT2 inhibitor treatment were reduced in very elderly adults (aged ≥75 years). More clinical trial data on effectiveness and safety, especially for very elderly adults, are needed.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest with NHIS.

AUTHOR CONTRIBUTIONS

All authors participated in study design, discussed the results and reviewed the manuscript. KHH, SJH and DJK made substantial contributions to the conception and design of the study. KHH, SJH and NL contributed to data collection and statistical analyses. SJH wrote the manuscript. DJK is the guarantor of this work, had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly as the access of National Health Insurance Service (NHIS) data is available only at the NHIS center, Wonju, Korea. The contact information for the NHIS center of Korea is as follows: +82-33-736-2431~3 (Tel) and https://nhiss.nhis.or.kr (website).

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