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Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitor and Thiazolidinedione Treatment on Risk of Stroke among Patients with Type 2 Diabetes Mellitus

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Background: Although cardiovascular outcome trials using sodium-glucose cotransporter-2 inhibitors (SGLT-2i) showed a reduction in risk of 3-point major adverse cardiovascular events (MACE), they did not demonstrate beneficial effects on stroke risk. Additionally, meta-analysis showed SGLT-2i potentially had an adverse effect on stroke risk. Contrarily, pioglitazone, a type of thiazolidinedione (TZD), has been shown to reduce recurrent stroke risk. Thus, we aimed to compare the effect of SGLT-2i and TZD on the risk of stroke in type 2 diabetes mellitus (T2DM) patients.
Methods: Using the Korean National Health Insurance Service data, we compared a 1:1 propensity score-matched cohort of patients who used SGLT-2i or TZD from January 2014 to December 2018. The primary outcome was stroke. The secondary outcomes were myocardial infarction (MI), cardiovascular death, 3-point MACE, and heart failure (HF).
Results: After propensity-matching, each group included 56,794 patients. Baseline characteristics were well balanced. During the follow-up, 862 patients were newly hospitalized for stroke. The incidence rate of stroke was 4.11 and 4.22 per 1,000 person-years for the TZD and SGLT-2i groups respectively. The hazard ratio (HR) of stroke was 1.054 (95% confidence interval [CI], 0.904 to 1.229) in the SGLT-2i group compared to the TZD group. There was no difference in the risk of MI, cardiovascular death, 3-point MACE between groups. Hospitalization for HF was significantly decreased in SGLT-2i-treated patients (HR, 0.645; 95% CI, 0.466 to 0.893). Results were consistent regardless of prior cardiovascular disease.
Conclusion: In this real-world data, the risk of stroke was comparable in T2DM patients treated with SGLT-2i or TZD.

Keywords: Sodium-glucose transporter 2 inhibitors; Stroke; Thiazolidinediones

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a potent risk factor for cardiovascular disease (CVD) [1] which is a common cause of death in patients with diabetes [2]. Asian populations show different characteristics of CVD when compared to Westerners; Asians have a greater prevalence of stroke than coronary heart disease whereas the pattern is reversed in western populations [3]. Thus, it is important to ascertain the impact of drugs used for diabetes on stroke especially in this population.

Current clinical guidelines recommend using sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with diabetes and atherosclerotic CVD [4,5] based on favourable outcomes in cardiovascular outcome trials. Although the treatment with SGLT-2i showed a reduced risk of 3-point major adverse cardiovascular events (MACE), there have been no randomized clinical trials (RCTs) using SGLT-2i showing a reduction in stroke risk [6-9]. In addition, a meta-analysis reported SGLT-2i treatment had adverse effects on stroke risk [10]. However, more recent meta-analyses incorporating addi-

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tional RCTs [11,12] have revealed that SGLT-2i does not increase the risk of stroke [12], suggesting that further investigation is needed regarding the association between SGLT-2i and stroke

Pioglitazone, a type of thiazolidinedione (TZD), has been shown to be able to reduce recurrent stroke risk in RCTs [13]. However, its benefit was not observed when pioglitazone was prescribed to patients without a previous stroke [13]. To date, no study has compared effects of SGLT-2i and TZD in terms of stroke prevention.

In this study, we aimed to compare the effect of SGLT-2i and TZD on the risk of stroke among Korean patients with T2DM. In addition, we evaluate the effect of each drug on other cardiovascular events including myocardial infarction (MI), cardiac death, heart failure (HF), and 3-point MACE.

METHODS

This was a retrospective cohort study using National Health Insurance Service (NHIS) database constructed by Korean NHIS. To access the NHIS database, a completed application form, a research proposal, and the applicant's Institutional Review Board approval document should be submitted to the Review Committee of Research Support in Korean NHIS. After NHIS review and approval, data are available in deidentified format. Anonymized and de-identified information were used for analyses. The present study was approved by the Institutional Review Board of Dongguk University Ilsan Hospital (No.: 2019-02-002-002). Written informed consent by the patients was waived due to a retrospective nature of our study. All procedures used in this study were performed in accordance with the Declaration of Helsinki.

The Korean NHIS is a single-payer healthcare system and mandatory for all residents of Korea [14]. The NHIS established a national health information database which includes each patient's demographic information, medical claims, medications, health check-up, and death information. Because the NHIS provides regular cost free health check-ups to all applicable examinees including employee subscribers, regional insurance subscriber, and medical aid beneficiaries, the results of regular health check-ups can be integrated with other medical information so that comprehensive and detailed analyses are possible. In addition to NHIS database, death records from the National Statistical Office were linked to individuals using unique personal identification to further examine the cause of death.

Study population

In Korea, SGLT-2i was available from 2014, thus we included patients who were diagnosed with T2DM and treated with SGLT-2i or TZD from January 2013 to December 2018. T2DM was defined as the presence of International Classification of Diseases, 10th Revision (ICD-10) code (E11–14) according to a previous study [15]. A new user was defined as a patient who received any SGLT-2i (dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin) or TZD (pioglitazone or lobeglitazone) between January 2014 and December 2018 with a 1-year washout period. Among the new users, we only included those who were prescribed study drugs ≥90 days. Health information from January 2008 to December 2012 of enrolled patients was collected and integrated to determine the patient's baseline characteristics.

We identified 481,515 new users of SGLT-2i or TZD. Among them, we excluded the following patients: (1) those who were prescribed study drugs less than 90 days; (2) those who were prescribed SGLT-2i and TZD simultaneously; (3) those who were younger than 18 or older than 84 years; (4) those who were diagnosed with malignancy during the study period; (5) those who did not have a health check-up within one year prior to the index year; (6) those who had end stage renal disease; and (7) those who had outlier levels of low density lipoprotein (LDL)-cholesterol (>300 mg/dL). A total of 168,559 patients were identified, of which 71,530 used SGLT-2i and 97,029 used TZD. After propensity matching, a total of 113,588 patients were identified, 56,794 in each group (Fig. 1). The participants were followed until the outcome event, death, or December 31, 2018, whichever occurred first.

Demographic factors at baseline

During regular health checks, all participants were asked to fill out questionnaires including questions about smoking status, alcohol consumption, and physical activity. Current smokers were defined as those who smoked ≥100 cigarettes in their lifetime and continue to smoke. Heavy drinkers were defined as those who drank 5 or more days per week. Subjects were defined as physically active if they exercised vigorously ≥3 days a week or a moderately for ≥5 days. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

After at least 8 hours of fasting, venous sampling was done to examine fasting blood glucose (FBG), total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, LDL-cholesterol, aspartate aminotransferase (AST), alanine amino-

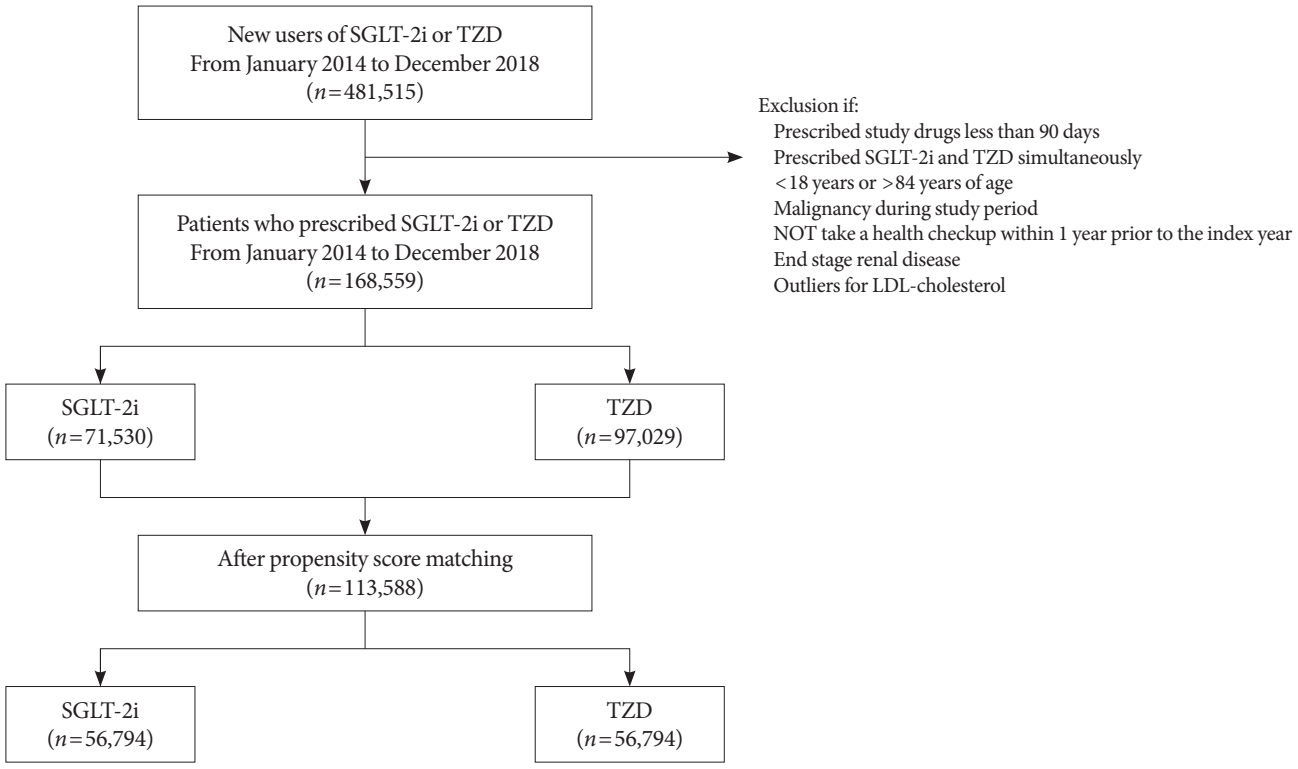

Fig. 1. Flow chart of study population. SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; LDL, low density lipoprotein.

transferase (ALT), gamma-glutamyl transferase (GGT), and creatinine levels. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Proteinuria was defined as 1+ or more by dipstick test for proteinuria.

Baseline comorbidities

If individuals had an ICD-10 code for hypertension (I10–13, I15) concurrent with either antihypertensive medications or systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg at health check-up, they were defined as having hypertension. The ICD-10 code of dyslipidemia (E78) concurrent with administration of lipid-lowering agents or a total cholesterol level ≥240 mg/dL was used for the diagnosis of dyslipidemia.

Subjects with any diagnostic codes for stroke (I60–I64), MI (I21–I23), or unstable angina (I20) were defined as having each disease respectively. Peripheral artery disease was diagnosed when patients had ≥2 outpatient diagnoses or ≥1 inpatient diagnosis of ICD-10 codes I70 and I73 as in previous studies [16]. If patients had any of these four diseases, they were defined as having prior CVD.

HF was diagnosed if patients had ≥2 outpatient diagnoses or ≥1 inpatient diagnosis of the ICD-10 codes for HF (I11.0, I13.0, I13.2, I50) concurrent with relevant medications including spironolactone, loop diuretics (furosemide, torsemide), beta blockers (carvedilol, bisoprolol, nebivolol, metoprolol), or sacubitril/valsartan.

Outcome

The primary outcome of this study was hospitalization with a main diagnosis of stroke (ICD-10: I60–I64). Secondary outcomes included hospitalized MI, hospitalized HF, cardiovascular death, and 3-point MACE (non-fatal MI, non-fatal stroke, and cardiovascular death). Detailed operational definitions of the outcomes are described in Supplementary Table 1.

Subgroup

Analyses of outcomes were repeated across multiple subgroups (age, sex, prior CVD, prior stroke, and eGFR level). For the age, patients were categorized as <65 or ≥65 years old. For the eGFR, patients were classified into eGFR <60 or ≥60 mL/

min/1.73 m^2. At a $P<0.05$ we considered there to be no statistical difference in the effect of treatments between subgroups.

Statistical analyses

To minimize differences between the two treatment groups, we conducted a propensity score matched analysis. First, we chose covariates (age, sex, stroke, MI, peripheral artery disease, unstable angina, hypertension, dyslipidemia, HF, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, statin, antiplatelet, anticoagulant, smoking, drinking, proteinuria, weight, height, waist circumference, systolic blood pressure, diastolic blood pressure, hemoglobin, fasting blood sugar, HDL-cholesterol, LDL-cholesterol, triglyceride, aspartate aminotransferase, alanine aminotransferase, GGT, and eGFR) to be used and assessed the predicted probability of SGLT-2i users versus TZD users using a logistic regression model. Second, we performed matching for the two groups in a 1:1 ratio using a greedy method within a caliper of 0.1. Lastly, we evaluated matching quality using absolute standardized difference (ASD) in mean between the two groups. An ASD of less than 0.1 was considered a negligible difference in each covariate [17].

After propensity score matching, the cumulative incidence of outcomes according to treatment group was compared using Kaplan-Meier curves and log-rank tests. If there were more than two incidents in one patient, only the outcome of the first incident was included. The incidence rate of outcomes was expressed as the number of events per 1,000 person-years. Cox proportional hazards regression analyses were used to calculate the hazard ratio (HR) for outcomes according to the treatment.

In this study, patients were censored if they switched study drugs (e.g., from SGLT-2i to TZD or from TZD to SGLT-2i) before events occur. Without regard to treatment continuation, the analyses used an intention-to-treat approach in which patients were followed until the outcome event, death, or December 31, 2018, whichever occurred first.

In addition to the primary analysis, we performed two sensitivity analyses. First, the outcome results were adjusted for multiple covariates on top of the propensity score matching. Covariates used for adjustment included age, sex, BMI, alcohol, smoking, hypertension, dyslipidemia, FBG, proteinuria, HF, MI, stroke, systolic blood pressure, diastolic blood pressure, log of HDL-cholesterol, log of LDL-cholesterol, log of triglyceride, eGFR, and medication that could affect CVD outcome (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, statin, anticoagulant, and antiplatelet). The second sensitivity analysis was performed incorporating patients who were prescribed study drugs at least once. Propensity score matching was applied in the second sensitivity analysis and final sample size was 148,862 (74,431 patients in each treatment group). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). *P* values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 71,530 patients of SGLT-2i and 97,029 patients of TZD were identified. Prior to propensity matching, SGLT-2i users were younger and more obese than those who used TZD (Supplementary Table 2). They also had higher levels of AST, ALT, and GGT. Additionally, level of triglycerides and the proportion of dyslipidemia were higher in SGLT-2i users compared to TZD users. TZD users had a higher proportion of participants with decreased renal function (eGFR <60 mL/min/1.73 m^2) compared to SGLT-2i users.

After propensity matching, each group included 56,794 patients. Mean age was 57.2 years; approximately 58% were men; 19.3% had prior CVD. The mean BMI of matched cohorts was 26.3 kg/m^2 and FBG was 151.4 mg/dL. Patients (92.4%) had eGFR ≥60 mL/min/1.73 m^2 and 12.3% showed proteinuria. Overall, baseline characteristics of matched cohorts were well-balanced with ASD ≤0.1 for all variables (Table 1, Supplementary Fig. 1).

The distribution of specific SGLT-2i and TZD compounds are described in Supplementary Table 3. Dapagliflozin and pioglitazone account for the major portion of SGLT-2i and TZD prescriptions respectively.

Risk of hospitalization for stroke between SGLT-2i vs. TZD

For the primary analysis, the mean duration of follow-up time was 655.6 days for the TZD group and 674.3 days for the SGLT-2i group. During the follow-up, 862 patients were newly hospitalized for stroke (419 TZD, 443 SGLT-2i) (Supplementary Table 4). Time intervals between drug initiation and stroke outcome were 1.80±1.17 years in the TZD group and 1.85±1.03 years in the SGLT-2i group. The incidence rate of stroke was 4.11 and 4.22 per 1,000 person-years for the TZD and SGLT-2i groups respectively. Cumulative incidence of hospi-

Table 1. Baseline characteristics of study population after propensity matching

Characteristic	SGLT-2i (*n*=56,794)	TZD (*n*=56,794)	ASD
Men	32,690 (57.6)	33,112 (58.3)	0.0151
Age, yr	56.68±10.54	57.79±10.52	0.0296
≥65	13,502 (23.8)	14,240 (25.1)	
<65	43,292 (76.2)	42,554 (74.9)	
Prior CVD	10,987 (19.3)	10,961 (19.3)	0.0012
Stroke	5,462 (9.6)	5,619 (9.9)	0.0091
MI	2,199 (3.9)	2,150 (3.8)	0.0045
PAD	1,292 (2.3)	1,305 (2.3)	0.0015
Unstable angina	4,524 (8)	4,409 (7.8)	0.0076
Comorbidities			
Hypertension	39,588 (69.7)	39,423 (69.4)	0.0063
Dyslipidemia	37,333 (65.7)	37,098 (65.3)	0.0086
HF	3,626 (6.4)	3,469 (6.1)	0.0114
Medication use			
ARB	33,584 (59.1)	33,343 (58.7)	0.0086
ACEi	6,712 (11.8)	6,719 (11.8)	0.0004
BB	19,414 (34.2)	19,186 (33.8)	0.0085
Statin	36,138 (63.6)	35,952 (63.3)	0.0068
Anti-platelet	28,897 (50.9)	29,120 (51.3)	0.0079
Anti-coagulant	1,285 (2.3)	1,258 (2.2)	0.0032
Current smoker	13,165 (23.2)	13,210 (23.3)	0.0019
Heavy drinker	2,458 (4.3)	2,491 (4.4)	0.0028
Physically active	12,461 (21.9)	12,415 (21.9)	0.0020
Height, cm	163.59±9.12	163.52±9.41	0.0081
Weight, kg	70.95±13.16	70.38±13.49	0.0424
BMI, kg/m^2	26.41±3.78	26.2±3.76	0.0614
≥25	35,791 (63.0)	34,100 (60.0)	
<25	21,003 (37.0)	22,694 (40.0)	
WC, cm	88.18±9.42	88±9.52	0.0260
Men, ≥90; women, ≥80	33,907 (59.7)	33,181 (58.4)	
Men, <90; women, <80	22,887 (40.3)	23,613 (41.6)	
SBP, mm Hg	126.94±14.57	126.97±14.34	0.0019
DBP, mm Hg	77.72±9.66	77.64±9.54	0.0088
FBG, mg/dL	151.13±52.1	151.72±50.23	0.0112
Log triglycerides	4.92±0.52	4.91±0.52	0.0153
Log HDL-cholesterol	3.89±0.24	3.89±0.24	0.0024
Log LDL-cholesterol	4.47±0.45	4.47±0.45	0.0021
Log AST	3.29±0.46	3.29±0.45	0.0092
Log ALT	3.34±0.58	3.33±0.57	0.0209
Log GGT	3.58±0.72	3.57±0.73	0.0127
Haemoglobin, g/dL	14.44±1.62	14.39±1.56	0.0346
eGFR, mL/min/1.73 m^2	89.59±25.17	89.13±29.19	0.0171
≥60	52,838 (93.0)	52,128 (91.8)	
<60	3,956 (7.0)	4,666 (8.2)	
Proteinuria	6,964 (12.3)	6,961 (12.3)	0.0002

Values are presented as number (%) or mean±standard deviation.
SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; ASD, absolute standardized difference; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease; HF, heart failure; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BB, beta blocker; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate.

talization for stroke was not significantly different between groups (log-rank test, P=0.505) (Fig. 2). The HR of hospitalization for stroke was 1.054 (95% confidence interval [CI], 0.904 to 1.229) in the SGLT-2i group compared to the TZD group (Fig. 3). Risk of ischemic or haemorrhagic stroke was respectively evaluated and no differences between groups were observed (Figs. 2 and 3, Supplementary Table 4).

The results remained consistent after sensitivity analysis which adjusted for multiple covariates that could affect outcomes (Supplementary Fig. 2). Another sensitivity analysis was performed for those who were prescribed study drugs at least once; there was no difference in hospitalization for total stroke, ischemic stroke, or haemorrhagic stroke between two groups (Supplementary Figs. 3 and 4).

Hospitalized MI, hospitalized HF, cardiovascular death, and 3-point MACE

The cumulative incidence plots for each outcome are described in Supplementary Fig. 5. The incidence rate of hospitalized MI in the TZD and SGLT-2i groups was 1.57 and 1.72 per 1,000 person-years respectively (Supplementary Table 4). Risk of hospitalized MI was not different between the two treatment groups (HR, 1.068; 95% CI, 0.831 to 1.373) (Fig. 3). The incidence rates of cardiovascular death were 1.70 and 1.75 per

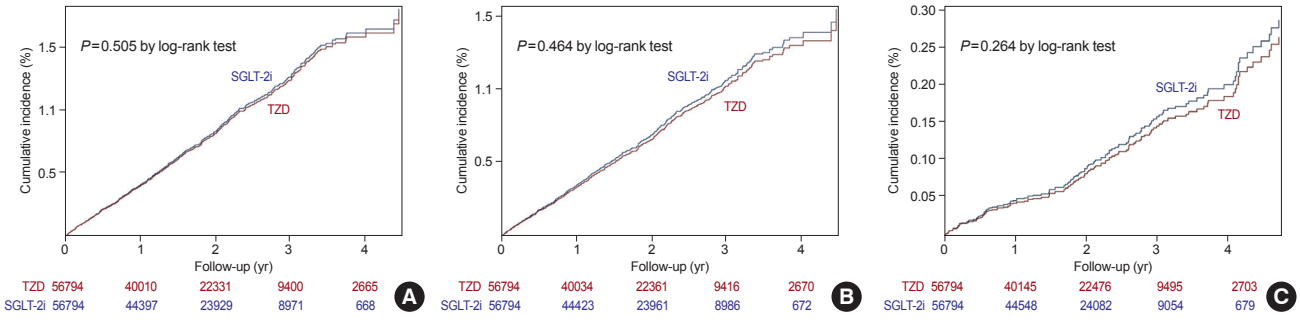

Fig. 2. Cumulative incidence of stroke in sodium-glucose cotransporter-2 inhibitor (SGLT-2i) and thiazolidinedione (TZD) groups. Cumulative incidence and number at risk of (A) total stroke, (B) ischemic stroke, and (C) hemorrhagic stroke in SGLT-2i-treated and TZD-treated groups.

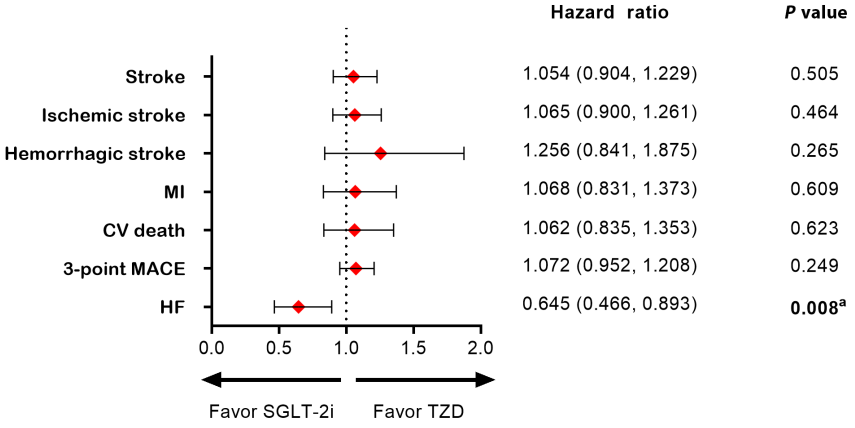

Fig. 3. Risk of cardiovascular outcomes in sodium-glucose cotransporter-2 inhibitor (SGLT-2i) and thiazolidinedione (TZD) groups. Hazard ratio and 95% confidence interval for cardiovascular outcomes. MI, myocardial infarction; CV, cardiovascular; MACE, major adverse cardiovascular events; HF, heart failure. [a]Bold denotes statistical significance at the $P<0.05$ level.

1,000 person-years for the TZD and SGLT-2i groups respectively. Incidence rates for those who presented with 3-point MACE were 6.90 and 7.23 per 1,000 person-years for TZD and SGLT-2i treatments respectively. Neither cardiovascular death nor 3-point MACE showed any significant difference between the two groups (Fig. 3). Over a follow-up time of 207,695 person-years, 135 of those in the TZD group and 87 of those in the SGLT-2i group had incidents of HF hospitalization (incidence rate, 1.32 per 1,000 person-years for TZD; incidence rate, 0.83 per 1,000 person-years for SGLT-2i). SGLT-2i was associated with 35% lower risk of hospitalization for HF than TZD (Fig. 3).

In the sensitivity analyses, the results were similar in that only the risk of hospitalization for HF was significantly lower in SGLT-2i group than TZD group (adjusted analysis [HR, 0.429; 95% CI, 0.190 to 0.970], patients with drugs at least once [HR, 0.719; 95% CI, 0.566 to 0.913]) (Supplementary Figs. 2 and 4).

Subgroup analyses

Stratified analyses were conducted according to subgroups of age, sex, prior CVD, and eGFR level. No variables could modulate the risk profile (Fig. 4). In patients with prior stroke, the TZD-treated group tended to be associated with a lower risk of MI. However, the effect size was modest and statistical significance was not observed (P interaction=0.068).

DISCUSSION

In this nationwide study with real-world data, we found that there is no difference in the risk of stroke incidence between TZD and SGLT-2i treated patients. In addition, there was no

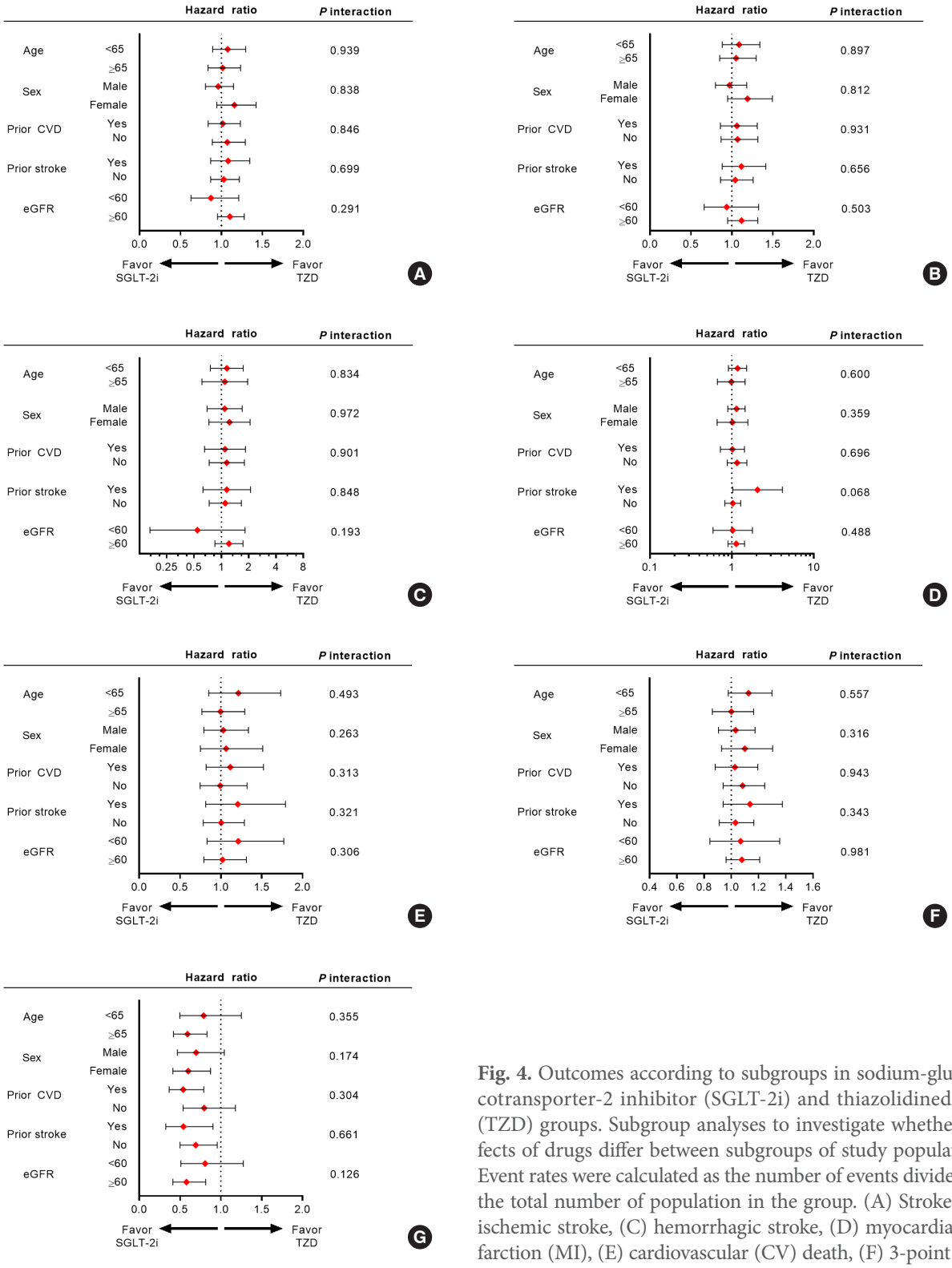

Fig. 4. Outcomes according to subgroups in sodium-glucose cotransporter-2 inhibitor (SGLT-2i) and thiazolidinedione (TZD) groups. Subgroup analyses to investigate whether effects of drugs differ between subgroups of study population. Event rates were calculated as the number of events divided by the total number of population in the group. (A) Stroke, (B) ischemic stroke, (C) hemorrhagic stroke, (D) myocardial infarction (MI), (E) cardiovascular (CV) death, (F) 3-point major adverse cardiovascular events (MACE), and (G) heart failure (HF). CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

difference in the risk of other cardiovascular outcomes between the groups except for hospitalization due to HF. Risk of hospitalization for HF was significantly lower in the SGLT-2i treated group than TZD treated group. Notably, there were no differences between those with prior CVD and those without.

To date, four large RCTs have investigated the effect of SGLT-2i on cardiovascular outcomes. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial first demonstrated the cardiovascular risk reduction effect of SGLT-2i [8]. Treatment with empagliflozin showed a 14% reduction of composite cardiovascular outcome versus placebo. However, it did not reduce non-fatal stroke (HR, 1.24; 95% CI, 0.92 to 1.64). Likewise, other trials using SGLT-2i did not demonstrate a benefit for decreasing stroke risk [6,7,9].

Although having a singular primary endpoint is ideal for clinical trials, this would require extremely large numbers of patients with long-term follow-ups. This makes ruling out the potential adverse effects of novel anti-diabetic medications in a timely manner impossible [18]. In that regard, taking a composite cardiovascular outcome is a pragmatic approach. Unfortunately, it can lead to undesirable results because each component does not have the same pathophysiological mechanism and heterogeneity of components exists [18]. Indeed, a meta-analysis that evaluated the effect of glucagon-like peptide 1 receptor agonists (GLP1-RAs) on individual components of cardiovascular outcomes reported that GLP1-RAs reduced the risk of stroke while not affecting the risk of MI [19]. In addition, stroke is a heterogeneous group of diseases and classified into two major types, ischemic and haemorrhagic [20]. Additionally, ischemic stroke can be categorized into at least five subtypes: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of other determined aetiology, and stroke of undetermined etiology [21], which makes it impossible to analyse stroke outcomes in total. Indeed, risk factors for the incidence of stroke vary according to subtype [22,23].

Reduction in the risk of MACE among SGLT-2i users was mainly attributed from the reduction in risk of cardiovascular death [10]. Considering that the risk of MI and stroke was not meaningfully reduced [7-9], decreased cardiovascular death is presumably due to the decrease of death after HF which was mediated by haemodynamic effect of SGLT-2i. In addition, benefit observed incredibly early in the study suggested haemodynamic effect of SGLT-2i rather than anti-atherosclerotic effect in terms of reducing CVD [24]. To the contrary, TZD is a peroxisome proliferator-activated receptor gamma (PPARγ) agonist which has been shown to improve insulin sensitivity. A large body of evidence suggests a strong association between insulin resistance and atherosclerosis [25,26]. Treatment with PPARγ agonists improved insulin sensitivity and inhibited the development of atherosclerosis in experimental models [27], demonstrating the potential anti-atherogenic effects. Pioglitazone was shown to reduce cardiovascular composite outcomes [28] through consistent benefit across the endpoints of MI and stroke. In addition, treatment with pioglitazone prevented cardiovascular events in patients without diabetes who had a recent ischemic stroke or transient ischemic stroke [29]. Of note, recent studies have reported beneficial effects of SGLT-2i not related to the haemodynamic mechanisms including systemic metabolic effects, hormonal effects, and direct vascular effects [24]. It is also important to link potential renal benefits [7,30] and CVD as renal dysfunction is an independent risk for CVD [31]. Thus, we cannot exclude the possibility that more prolonged administration of SGLT-2i might produce a more robust effect on atherosclerotic CVD.

Considering that pioglitazone was reported to reduce the risk of recurrent stroke, comparable results between TZD and SGLT-2i in terms of stroke prevention seem to be counterintuitive. This might be due to different baseline characteristics of the study population between ours and previous trials. Notably, TZD reduced recurrent stroke in patients with T2DM, while TZD had no effect on first stroke in a previous study [13]. Likewise, another study showing risk reduction of composite cardiovascular outcome using TZD was also performed in patients who had a recent ischemic stroke or TIA [29]. On the contrary, only ~10% of patients in our study had a previous history of stroke, which might have blunted the beneficial effect of TZD on stroke. Whether the cardiovascular benefits observed in anti-diabetic drugs are only relevant for secondary prevention is a matter of debate [32]. It is important to note that there is no plausible explanation why a preventative therapy would work only in secondary prevention. Indeed, recent meta-analyses of GLP1-RA and SGLT-2i did not show any heterogeneity for the effect of drugs on MACE between the primary and secondary prevention cohorts [11,33]. However, heterogeneity of treatment effects by stroke history was not observed in our study, suggesting that the low prevalence of stroke might not be the cause. Another possible explanation might be the difference in dosage of TZD. In previous studies, patients received pioglitazone at the maximum tolerated dose

of 45 mg [13,29], while the recommended dose for pioglitazone was 15 or 30 mg in Korea. Further investigation is needed to see whether the effect of pioglitazone on stroke is different according to its dosage.

There are several limitations that should be considered in this study. First, because of the retrospective and observational nature of the claim database, there may be unmeasured confounding factors that could influence outcomes. For example, we could not include glycosylated hemoglobin (HbA1c) levels into the propensity-matching model because nationwide standard health check-ups in Korea do not measure HbA1c levels. In addition, there was no information regarding duration of diabetes, which could affect the risk of vascular complication. We could not take into account glycemic control during the follow-up period, which was another limitation of this study. Second, we should consider innate limitations of the propensity score matching method used in this study. It reduced sample size because matches could not be found for some patients [34]. Indeed, the sample size of this study was diminished from 168,559 at pre-matching to 113,588 at post-matching. In addition, imbalances might be inevitable regarding certain variables due to a small number of observation [34]. Third, we could not categorize ischemic stroke according to its subtypes because the NHIS database does not include information on stroke subclassification. However, even with detailed information, it is difficult to properly determine the stroke subtype. A previous study reported that neurologists specializing in stroke showed only moderate inter-rater reliability [35] to classify strokes into subtypes. Thus, to address this issue, a well-designed prospective study using advanced imaging technology is required. Fourth, we only compared two drugs which had shown beneficial effects on CVD, TZD, and SGLT-2i; if there had been additional neutral comparators, such as dipeptidyl peptidase-4 inhibitors, the effect would have been more obvious. In addition, comparison to other commonly used antidiabetic drug classes including sulfonylurea, insulin and GLP1-RAs might have also been informative. Fifth, in Korea, the percentage of the SGLT-2i prescription was low in 2014, the year of its first launch, which made the number of patients at risk in 2018 small. Thus, the mean duration of follow-up of our study was also short. A long-term follow-up period is needed for future studies. Lastly, because this study was conducted using Korean population, the result might not be applied to other populations. Despite these limitations, to our knowledge, this is the first study to directly compared the effect of SGLT-2i and TZD in terms of stroke outcomes using a large nationwide database. We believe that our results can be used as a scientific basis for decision-making regarding the usage of anti-diabetic drugs.

In summary, this nationwide study with real-world data found that the risk of stroke was comparable in patients with T2DM treated with either SGLT-2i or TZD. Except for hospitalization due to HF, other cardiovascular outcomes including MI, cardiovascular death, and 3-point MACE were not different between groups. Thus, TZD may be another good option for reducing CVD in patients with T2DM, especially those who are at risk of atherosclerotic CVD. In addition, given the opposing effects of TZD and SGLT-2i on body weight, combination or sequential therapy of these two drugs deserves more attention.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0160.

CONFLICTS OF INTEREST

Hyewon Nam, Hoseob Kim, and Dae-Sung Kyoung are employees of Hanmi Pharm. Co. Ltd. Data analysis was provided by Hanmi Pharmaceutical Corporation, Seoul, Korea. They were not involved in the writing process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design: S.E.L., K.A.K.
Acquisition, analysis, or interpretation of data: H.N., H.K., D.S.K.
Drafting the work or revising: S.E.L., H.S.C., K.A.K.
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