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Primary cardiovascular preventive effect of thiazolidinedione in adults with type 2 diabetes: A nationwide cohort study in Korea

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ABSTRACT

Background: Thiazolidinediones (TZDs) are antidiabetic agents recognized for their effectiveness in secondary cardiovascular prevention; however, their role in primary prevention remains uncertain. This study evaluated the primary cardiovascular preventive effect of TZDs in patients with type 2 diabetes mellitus (T2DM).

Methods: Using the nationwide health claims database, we conducted a cohort study including 1,958,643 adults with T2DM and no prior history of cardiovascular disease. TZD users were compared with dipeptidyl peptidase-4 inhibitor (DPP-4i) users as active comparators. After 1:1 propensity score matching (PSM), major cardiovascular events—composite of myocardial infarction (MI), stroke, hospitalization for heart failure (HF), and all-cause mortality—were compared using Cox proportional hazards models.

Results: In the PSM cohort consisting of 47,536 TZD users and 47,536 DPP-4i users, TZD users were associated with a lower risk of major cardiovascular events (HR 0.85, 95% CI 0.82–0.88). TZD users had lower risks of MI (HR 0.72, 95% CI 0.64–0.82), stroke (HR 0.84, 95% CI 0.78–0.90), and all-cause mortality (HR 0.86, 95% CI 0.82–0.90), with no difference in HF hospitalizations.

Conclusions: TZD use was associated with a reduced risk of major cardiovascular events in T2DM patients, suggesting a potential role of TZDs in primary cardiovascular prevention.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by chronic hyperglycemia and insulin resistance. Cardiovascular disease (CVD) remains among the leading global causes of mortality and disability, disproportionately impacting individuals with T2DM[1,2]. Individuals with T2DM have substantially elevated risks of cardiovascular (CV) events, including ischemic stroke and myocardial infarction (MI). These risks are largely driven by mechanisms such as chronic hyperglycemia, endothelial dysfunction, thrombogenicity, oxidative stress, and systemic low-grade inflammation[2–5]. Considering the importance of CV prevention in patients with T2DM, clinical guidelines emphasize individualized use of appropriate glucose-lowering agents based not only on glycemic control but also on individual CV risk profiles, particularly for patients with T2DM at high CV risk[6].

Among these agents, thiazolidinediones (TZDs), a class of oral antidiabetic agents that act as insulin sensitizers by activating peroxisome proliferator-activated receptor-γ (PPAR-γ), have garnered attention for their pleiotropic vascular protective effects[7–10]. Substantial evidence supports the use of pioglitazone, the most widely used TZD, in reducing recurrent stroke and major adverse CV events, particularly in patients with established CVD[10–12]. This highlights its potential as an effective CV preventive agent. Lobeglitazone is a newer TZD developed in South Korea for the treatment of T2DM[13]. It acts as a high-affinity PPAR-γ agonist, with approximately 12-fold greater binding affinity compared with pioglitazone[14]. Experimental and clinical studies have suggested that lobeglitazone exerts anti-atherosclerotic effects similar to those of pioglitazone, including reduced plaque formation, attenuation of

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inflammation, and improvement in lipid profiles[15–18]. Given its pharmacologic similarity to other TZDs, lobeglitazone is considered to share class-related metabolic and vascular effects. Recent studies have suggested that both pioglitazone and lobeglitazone may reduce cardiovascular risk in patients with T2DM, particularly among those with ischemic stroke or carotid artery disease[19,20].

Nevertheless, most existing studies on TZDs have focused on secondary prevention in patients with established CVD, leaving a notable gap in evidence regarding their role in primary CV prevention. To address this crucial gap, we conducted a large-scale population-based cohort study using nationwide health screening and health insurance claims data from the National Health Insurance Service (NHIS) in South Korea. The objective of this study was to evaluate the effectiveness of TZDs (pioglitazone or lobeglitazone) in reducing major CV outcomes in adults with T2DM and no history of CVD, with a focus on primary prevention. As active comparators, we used dipeptidyl peptidase-4 inhibitors (DPP-4i), which are widely prescribed for T2DM and considered neutral for CV outcomes[21,22].

METHODS

Study design and population

We conducted a retrospective cohort study using data from the NHIS in South Korea. South Korea has a single-payer, mandatory, universal healthcare system organized through the NHIS. Consequently, the NHIS database includes comprehensive information on healthcare utilization, including hospital visits, diagnoses, procedures, and prescriptions, for all Korean citizens. During each hospital visit, diagnoses are recorded based on the International Classification of Diseases, 10th Revision (ICD-10) codes. The NHIS also provides a National Health Screening Program that offers free standardized examinations to all adults for public health promotion. These screenings include physical examinations, blood tests, and questionnaires on medical history and lifestyle[23]. Anonymized NHIS datasets are available to academic researchers upon submission and approval of the research proposal. The NHIS database has become increasingly recognized as an invaluable resource for epidemiological studies, health policy evaluations, and clinical research[24].

From the NHIS database, we identified adults aged ≥20 years who had undergone a national health-screening program between 2015 and 2016 and met the diagnostic criteria for T2DM. The presence of T2DM was determined if they met at least one of the following criteria at the baseline health screening: (1) a self-report on the prior diagnosis of T2DM, (2) current use of antidiabetic medications, or (3) a fasting blood glucose level ≥126 mg/dL. The index date was defined as the date of health screening in 2015–2016. As this study was conducted to investigate the long-term primary CV preventive role of TZD in patients with T2DM, we excluded individuals with a history of cardiovascular disease (angina pectoralis, MI, stroke, or transient ischemic attack), as well as those who had undergone procedures for peripheral artery disease, percutaneous coronary intervention, or coronary artery bypass graft surgery[25]. We also excluded individuals with type 1 diabetes mellitus, missing covariate data, or a follow-up duration of ≤90 days. The operational definitions for the exclusion criteria are provided in Table S1.

Ethics approval and informed consent

Due to the nature of a retrospective study based on fully anonymized data from the NHIS, this study was approved, and the requirement for informed consent was waived by the Institutional Review Board of Yongin Severance Hospital (9-2023-0156).

Covariates and medication exposure

The baseline characteristics of the study participants were derived from the index health screening and health claims data. Detailed information on the covariates is provided in Table S2. For each participant, exposure to medications, including antidiabetic agents, was assessed based on prescription records. Participants were considered exposed to oral medication if a prescription was covered for at least 1 day within 30 days prior to the index date. Patients exposed to TZD (lobeglitazone or pioglitazone) within 30 days of the index date were classified as TZD users. Similarly, we assessed exposure to other oral antidiabetic medications, such as insulin secretagogues (sulfonylureas or meglitinides), biguanides, DPP-4i, sodium-glucose cotransporter-2 inhibitors, and alpha-glucosidase inhibitors. Additionally, we assessed the use of statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) and oral antithrombotics. Oral antithrombotics included antiplatelet agents (aspirin, clopidogrel, ticlopidine, ticagrelor, prasugrel, triflusal, dipyridamole, and cilostazol) and anticoagulant agents (warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban). The use of non-oral antidiabetic agents, including insulin and glucagon-like peptide-1 receptor agonists, was assessed for at least one prescription within 90 days prior to the index date[19].

Study outcomes

The primary outcome was a composite of the development of MI, stroke, hospitalization for heart failure (HF), and all-cause mortality after the index date of health screening. Study patients were followed from the index date until the occurrence of the primary outcome, loss of participant eligibility due to death or emigration, or the study end date (December 31, 2023), whichever occurred first. Based on the health claims data, the development of stroke was identified as admission with a primary diagnosis of "I60-63," along with brain computed tomography or magnetic resonance imaging[26]. MI was defined as admission with a primary diagnosis of "I21-22"[27]. Hospitalization for HF was determined as admission with a primary diagnosis of "I50, I42, I11.0, I13.0, I13.2, I25.5"[28]. Mortality data were obtained through a linkage between the NHIS and Statistics Korea. Secondary outcomes included the

individual components of the primary outcome (stroke, MI, hospitalization for HF, all-cause mortality). In the secondary outcome analyses, events other than the outcomes of interest were treated as competing risks. Patients who experienced a competing event before the outcome of interest were censored at the date of the competing event.

Statistical analysis and propensity score matching

Categorical variables are presented as numbers (%) and continuous variables as mean ± standard deviation. To evaluate the effect of TZD, DPP-4i was selected as the active comparator group owing to their widespread clinical use in treating T2DM and their established neutral effect on the CV risk[29]. Among the study participants, we identified those treated with TZD or DPP-4i. Patients who received both or neither medication were excluded from the study. To minimize potential confounding due to the difference in characteristics between the TZD and DPP-4 users, we performed a 1:1 propensity score matching (PSM) using a nearest neighbor matching with a caliper width of <0.1. Propensity scores for receiving TZD or DPP-4i were calculated using a logistic regression model that included the following covariates: sex, age, household income, smoking status, alcohol consumption, physical activity, chronic kidney disease, atrial fibrillation, HF, systolic blood pressure, fasting glucose, body mass index, hemoglobin, low-density lipoprotein cholesterol, triglycerides, and concurrent medications. The covariate balance between the TZD and DPP-4i groups was assessed by calculating the standardized mean difference (SMD), with absolute SMD values <0.1 indicating adequate balance.

Following PSM, we compared the risk of the primary outcome between the TZD and DPP-4i groups. For the TZD and DPP-4i groups, we illustrated cumulative incidence curves for the primary outcomes. Differences between curves were evaluated using a log-rank test. Cox proportional hazard regression analysis was performed to calculate hazard ratios (HR) and 95% confidence intervals (CI) for TZD compared with DPP-4i. In addition to the main analysis of TZD vs DPP-4i groups, we separately conducted 1:1 PSM analyses for pioglitazone vs DPP-4i and lobeglitazone vs DPP-4i to assess the effect of these drugs individually. To explore the potential interactions between the effect of TZD and risk factors, we performed a subgroup analysis according to sex, age, and characteristics. Additional subgroup analyses were conducted according to prior TZD exposure during the pre-index period (between 12 and 6 months before the index date) and according to pioglitazone daily dose (≤15 mg vs. >15 mg).

For sensitivity analyses, we performed several additional analyses. First, we applied a multivariable Cox proportional hazards regression model to the entire pre-matched cohort (N = 1,958,643, Figure 1) to assess the association between TZD and the primary outcome. Second, we conducted a multivariable time-varying Cox regression analysis using the same cohort, in which exposure to TZDs and other oral antidiabetic agents during follow-up was treated as time-varying covariates. Third, to reduce potential exposure misclassification and to focus on patients with good adherence to medication, we redefined TZDs and DPP-4i users as those with ≥60 days of prescription exposure within the 90 days following the index health screening, followed by repeating the PSM and primary analysis.

RESULTS

Baseline characteristics

After applying the inclusion and exclusion criteria, 1,958,643 participants with T2DM and no prior cardiovascular disease were identified. A total of 49,323 patients were classified as TZD users without concurrent DPP-4i use, and 521,629 were classified as DPP-4i users without TZD use. After 1:1 PSM, 47,536 patients were selected from each of the TZD and DPP-4i groups (Figure 1). Baseline characteristics before and after PSM are presented in Table 1. Evaluating the balance of covariates between the TZD and DPP-4i groups after PSM by calculating the SMD, we found that all absolute SMD values were <0.1, indicating that the covariates were adequately balanced (Table 1).

Primary outcome

In the TZD and DPP-4i groups, each comprising 47,536 patients, the primary outcome occurred in 12,622 patients over a mean follow-up period of 7.52 ± 1.54 years. The cumulative incidence of the primary outcome was significantly lower in the TZD group than in the DPP-4i group (P < 0.001, Figure 2). In the Cox regression analysis (Table 2), TZD use was associated with a significantly lower risk of the primary outcome than DPP-4i use (HR 0.85, 95% CI 0.82–0.88).

We further performed 1:1 PSM analyses for two separate comparisons: pioglitazone vs DPP-4i groups and lobeglitazone vs DPP-4i groups. Baseline characteristics were well balanced in both comparisons, with all covariates achieving absolute SMD <0.1 after PSM (Tables S3, S4). Consistent with the main analysis of TZD vs DPP-4i, both pioglitazone (HR 0.85, 95% CI 0.82–0.89) and lobeglitazone (HR 0.86, 95% CI 0.79–0.93) were associated with significantly lower risks of the primary outcome compared with DPP-4i (Tables S5, S6). The cumulative incidence curves also demonstrated reduced event rates in both pioglitazone and lobeglitazone groups compared with DPP-4i group (Figures S1, S2).

Secondary outcomes

Secondary outcome analyses were conducted using cause-specific Cox regression models for individual outcomes (Table 2). Compared with the use of DPP-4i, TZD use was associated with a significantly lower risk of stroke (HR 0.84, 95% CI 0.78–0.90), MI (HR 0.72, 95% CI 0.64–0.82), and all-cause mortality (HR 0.86, 95% CI 0.82–0.90). The risk of

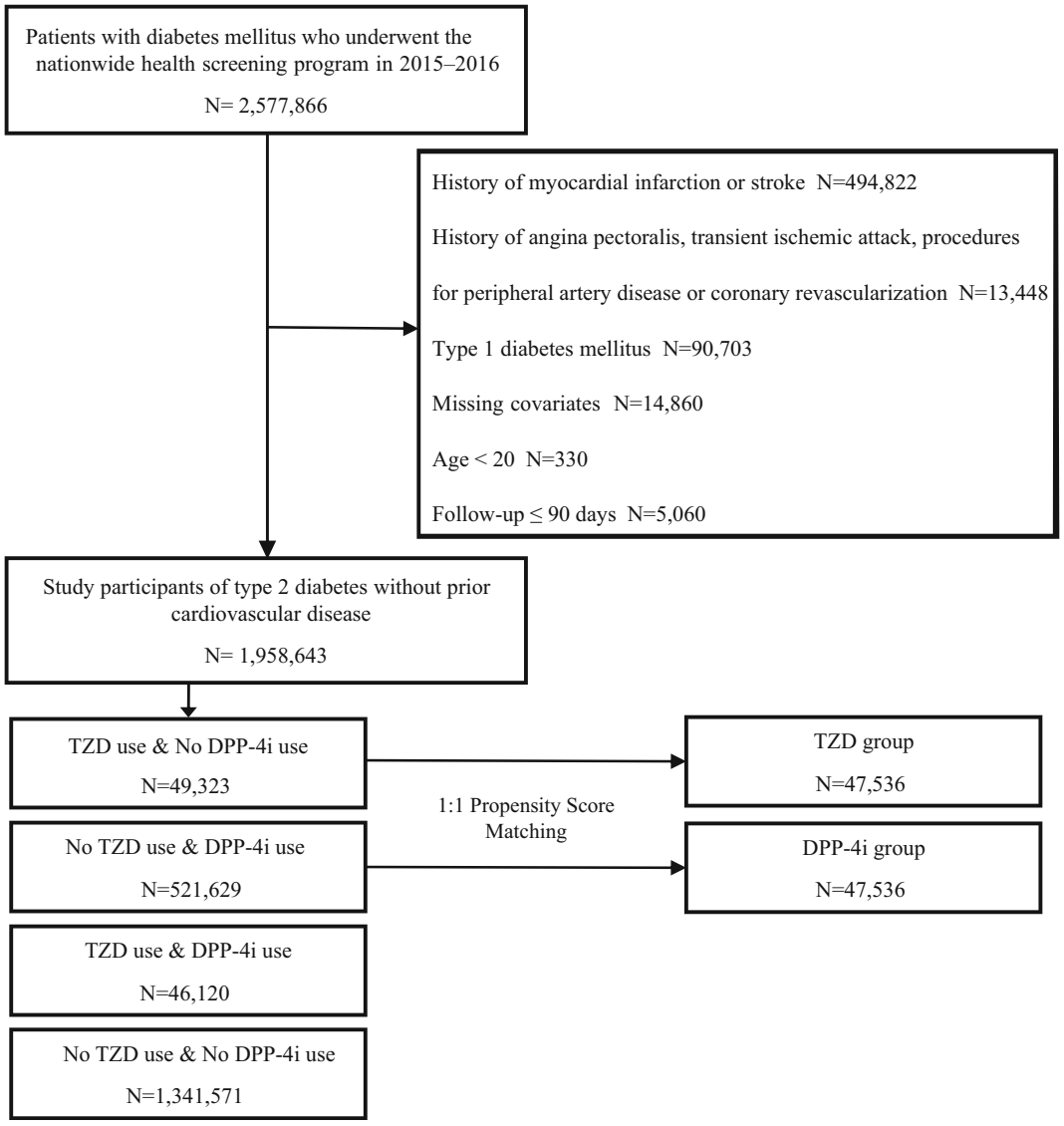

Figure 1 | Flowchart of the study participants and propensity score matching. DPP-4i, dipeptidyl peptidase-4 inhibitor; PSM, propensity score matching; TZD, thiazolidinedione.

hospitalization for HF did not differ significantly between the TZD and DPP-4i groups (HR 1.00, 95% CI 0.87–1.14).

Subgroup analysis

Subgroup analyses were performed to assess the consistency of TZD effects across diverse clinical and demographic factors (Figure 3). TZD use was associated with a reduced risk of the primary outcome across most subgroups, with a consistent direction of effect. The lack of statistical significance in the atrial fibrillation subgroup may be attributable to the small number of patients in this group (N = 103), resulting in limited statistical power. Overall, these findings suggest that the cardiovascular benefits of TZDs are broadly consistent across diverse patient characteristics.

When the TZD group was stratified according to prior TZD exposure during the pre-index period of 12 to 6 months before the index date (Table S7), the association between TZD use and reduced risk of the primary outcome remained consistent in both groups (with prior TZD exposure [N = 41,178]: HR 0.84, 95% CI 0.81–0.87; without prior TZD exposure [N = 6,358]: HR 0.91, 95% CI 0.85–0.98).

In the separate matched cohort comparing pioglitazone with DPP-4i users (N = 38,567 per group), most pioglitazone users received a daily dose of ≤15 mg (88.7%). Compared with DPP-4i users, both ≤15 mg and >15 mg pioglitazone dose groups showed a lower risk of the primary outcome; however, a statistically significant reduction was observed only in the ≤15 mg group (Table S8).

Table 1 | Baseline characteristics before and after propensity score matching

	Before PSM			After PSM		
	TZD (–), DPP-4i (+)	TZD (+), DPP-4i (–)	Absolute SMD	TZD (–), DPP-4i (+)	TZD (+), DPP-4i (–)	Absolute SMD*
N	521,629	49,323		47,536	47,536	
Sex, male	299,629 (57.44)	28,860 (58.51)	0.0217	28,082 (59.08)	27,999 (58.90)	0.0035
Age	60.14 ± 10.49	61.75 ± 10.38	0.1544	61.65 ± 10.38	61.59 ± 10.70	0.0063
Household income			0.0148			0.0093
Q1	136,416 (26.15)	13,059 (26.48)		12,461 (26.21)	12,563 (26.43)	
Q2	120,262 (23.06)	11,089 (22.48)		10,856 (22.84)	10,700 (22.51)	
Q3	111,596 (21.39)	10,688 (21.67)		10,205 (21.47)	10,301 (21.67)	
Q4	153,355 (29.40)	14,487 (29.37)		14,014 (29.48)	13,972 (29.39)	
Smoking status			0.0159			0.0081
Non-smoking	294,731 (56.50)	28,059 (56.89)		26,666 (56.10)	26,848 (56.48)	
Past smoking	117,109 (22.45)	11,199 (22.71)		10,928 (22.99)	10,872 (22.87)	
Current smoking	109,789 (21.05)	10,065 (20.41)		9,942 (20.91)	9,816 (20.65)	
Alcohol consumption			0.0354			0.0084
Nondrinker (0 g/week)	330,416 (63.34)	30,577 (61.99)		29,293 (61.62)	29,440 (61.93)	
Mild drinker (0–104 g/week)	100,793 (19.32)	9,558 (19.38)		9,237 (19.43)	9,242 (19.44)	
Moderate drinker (105–209 g/week)	50,005 (9.59)	5,024 (10.19)		4,927 (10.36)	4,844 (10.19)	
Heavy drinker (≥210 g/week)	40,415 (7.75)	4,164 (8.44)		4,079 (8.58)	4,010 (8.44)	
Physical activity, METs-min/week			0.0409			0.0040
0	112,303 (21.53)	11,447 (23.21)		10,953 (23.04)	10,935 (23.00)	
1–499	144,033 (27.61)	13,378 (27.12)		12,850 (27.03)	12,926 (27.19)	
500–999	149,765 (28.71)	13,941 (28.26)		13,516 (28.43)	13,456 (28.31)	
≥1,000	115,528 (22.15)	10,557 (21.40)		10,217 (21.49)	10,219 (21.50)	
Chronic kidney disease	64,717 (12.41)	5,973 (12.11)	0.0090	5,819 (12.24)	5,789 (12.18)	0.0019
Atrial fibrillation	860 (0.16)	47 (0.10)	0.0193	57 (0.12)	46 (0.10)	0.0070
Heart failure	13,931 (2.67)	1,315 (2.67)	0.0003	1,242 (2.61)	1,263 (2.66)	0.0028
Systolic blood pressure, mmHg	127.06 ± 14.39	128.21 ± 14.46	0.0800	128.17 ± 14.41	128.10 ± 14.43	0.0053
Fasting glucose, mmol/L	7.96 ± 2.40	7.65 ± 2.42	0.1279	7.67 ± 2.15	7.68 ± 2.44	0.0036
Body mass index, kg/m^2	25.16 ± 3.41	26.20 ± 3.75	0.2903	26.14 ± 3.93	26.10 ± 3.69	0.0111
Hemoglobin, g/dL	13.94 ± 1.63	13.65 ± 1.66	0.1758	13.66 ± 1.70	13.68 ± 1.65	0.0097
LDL cholesterol, mmol/L	2.37 ± 0.95	2.50 ± 0.93	0.1441	2.45 ± 1.08	2.49 ± 0.92	0.0437
Triglyceride, mmol/L	1.72 ± 1.19	1.53 ± 1.08	0.1650	1.55 ± 1.08	1.54 ± 1.09	0.0051
Medication						
Statin	279,317 (53.55)	27,703 (56.17)	0.0527	26,976 (56.75)	26,637 (56.04)	0.0144
Oral antithrombotic	343,003 (65.76)	16,189 (32.82)	0.6977	16,548 (34.81)	16,176 (34.03)	0.0165
Sulfonylurea or meglitinide	231,137 (44.31)	28,404 (57.59)	0.2680	26,814 (56.41)	26,808 (56.40)	0.0003
Biguanide	483,069 (92.61)	37,948 (76.94)	0.4469	37,738 (79.39)	37,903 (79.74)	0.0086
SGLT2 inhibitor	2,831 (0.54)	276 (0.56)	0.0023	299 (0.63)	267 (0.56)	0.0088
Alpha-glucosidase inhibitor	3,106 (0.60)	443 (0.90)	0.0352	444 (0.93)	416 (0.88)	0.0062
Insulin	21,221 (4.07)	2,258 (4.58)	0.0120	2,255 (4.74)	2,191 (4.61)	0.0064
GLP-1 agonist	53 (0.01)	13 (0.01)	0.0061	13 (0.03)	11 (0.02)	0.0026
DPP-4i	521,629 (100.00)	0 (0.00)	–	47,536 (100.00)	0 (0.00)	–
TZD	0 (0.00)	49,323 (100.00)	–	0 (0.00)	47,536 (100.00)	–
Pioglitazone	–	39,781 (80.65)		–	38,277 (80.52)	
Lobeglitazone	–	9,542 (19.35)		–	9,259 (19.48)	

Data are presented as numbers (%) or mean ± standard deviation. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; MET, metabolic equivalent of task; PSM, propensity score matching; Q, quartile; SGLT2, sodium-glucose co-transporter-2; SMD, standardized mean difference; TZD, thiazolidinedione. *All absolute SMD values were <0.1 in the propensity score-matched cohort.

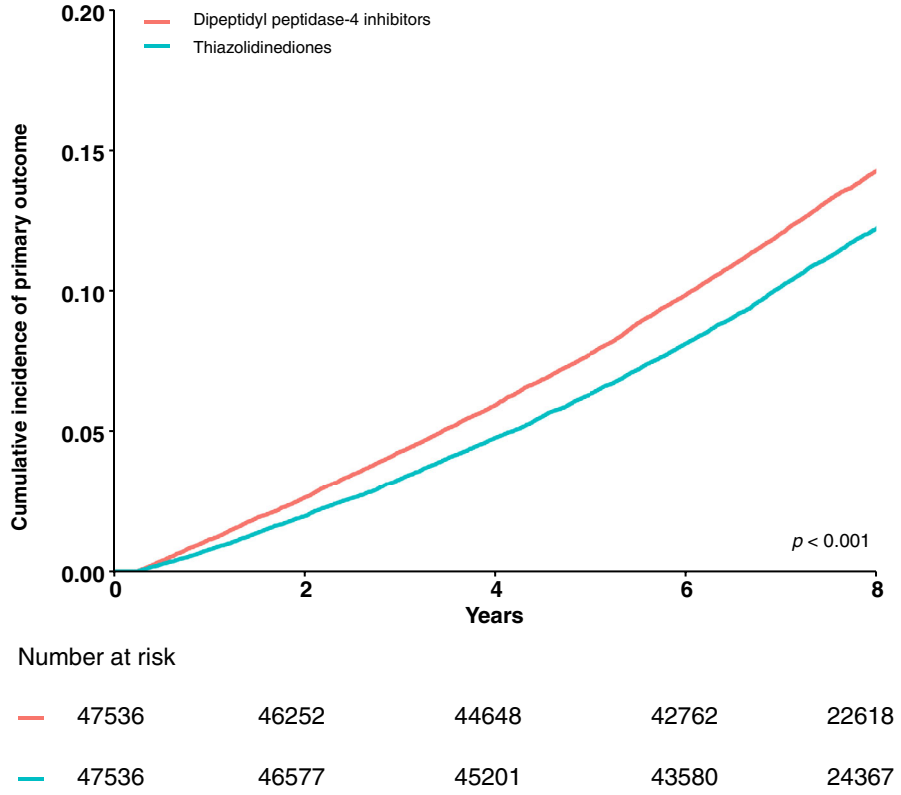

Figure 2 | Cumulative incidence curves for the primary outcome between the TZD and DPP-4i groups. DPP-4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione. *P*-value is derived using the log-rank test.

Table 2 | Association between TZD use and cardiovascular outcomes vs DPP-4i use after propensity score matching

Study outcome	Number of patients with the outcome		HR [95% CI]	*p*-value
	DPP-4i group (*N* = 47,536)	TZD group (*N* = 47,536)		
Primary outcome*	6,761	5,861	0.85 [0.82–0.88]	<0.001
Secondary outcomes				
Stroke	1,571	1,341	0.84 [0.78–0.90]	<0.001
Myocardial infarction	596	438	0.72 [0.64–0.82]	<0.001
Hospitalization for heart failure	416	424	1.00 [0.87–1.14]	0.978
All-cause mortality	4,178	3,658	0.86 [0.82–0.90]	<0.001

Data are presented as HR [95% CI] for TZD compared with DPP-4i, derived from Cox regression analysis. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; TZD, thiazolidinedione. *Composite of stroke, myocardial infarction, hospitalization for heart failure, and all-cause mortality.

Sensitivity analysis

Several sensitivity analyses were performed to assess the robustness of the primary findings.

First, using the entire cohort of participants with T2DM and no history of cardiovascular disease before PSM (*N* = 1,958,643), we constructed a multivariable Cox regression model for the primary outcome, adjusted for TZD, DPP-4i, and all the baseline covariates used in the PSM calculation (Table S9). This yielded consistent findings, with TZD use demonstrating a lower risk of the primary outcome (adjusted HR 0.89, 95% CI 0.87–0.91).

Secondly, we performed a multivariable time-varying Cox regression analyses in the same cohort of participants with T2DM and no history of cardiovascular disease (*N* = 1,958,643), in which exposure to oral antidiabetic medications, including TZDs, during follow-up was treated as

Subgroup	Number of patients in the subgroup	Number of patients in DPP-4i group	Number of patients in TZD group	HR [95% CI]*	p-value
Sex					
Male	56,081	28,082	27,999	0.83 [0.83-0.87]	<0.001
Female	38,991	19,454	19,537	0.88 [0.83-0.93]	<0.001
Age at index date					
Age < 65 years	58,239	28,906	29,333	0.91 [0.86-0.97]	0.003
Age ≥ 65 years	36,833	18,630	18,203	0.82 [0.79-0.86]	<0.001
Household income					
Q1–2	46,580	23,317	23,263	0.87 [0.83-0.92]	<0.001
Q3–4	48,492	24,219	24,273	0.83 [0.79-0.87]	<0.001
Smoking status					
non-smoking/past smoking	75,314	37,594	37,720	0.83 [0.80-0.87]	<0.001
Current smoking	19,758	9,942	9,816	0.91 [0.85-0.98]	0.012
Alcohol consumption					
Nondrinker (0 g/week)	58,733	29,293	29,440	0.82 [0.79-0.86]	<0.001
Drinker (>0 g/week)	36,339	18,243	18,096	0.90 [0.85-0.96]	0.002
Physical activity, METs-min/week					
<500	47,664	23,803	23,861	0.86 [0.82-0.90]	<0.001
≥500	47,408	23,733	23,675	0.84 [0.79-0.88]	<0.001
Chronic kidney disease					
Yes	11,608	5,819	5,789	0.77 [0.72-0.83]	<0.001
No	83,464	41,717	41,747	0.87 [0.83-0.90]	<0.001
Atrial fibrillation					
Yes	103	57	46	0.81 [0.45-1.43]	0.467
No	94,969	47,479	47,490	0.85 [0.82-0.88]	<0.001
Heart failure					
Yes	2,505	1,242	1,263	0.69 [0.58-0.81]	<0.001
No	92,567	46,294	46,273	0.86 [0.83-0.89]	<0.001
Systolic blood pressure, mmHg					
<140 mmHg	76,074	38,027	38,047	0.85 [0.81-0.88]	<0.001
≥140 mmHg	18,998	9,509	9,489	0.86 [0.80-0.92]	<0.001
Fasting glucose, mmol/L					
<7 mmol/L	41,533	19,830	21,703	0.80 [0.76-0.84]	<0.001
≥7 mmol/L	53,539	27,706	25,833	0.89 [0.85-0.93]	<0.001
Body mass index, kg/m²					
<25 kg/m²	38,704	19,589	19,115	0.85 [0.81-0.90]	<0.001
≥25 kg/m²	56,368	27,947	28,421	0.85 [0.81-0.89]	<0.001

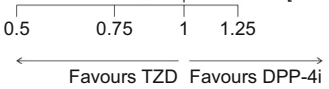

Figure 3 | Subgroup analysis of the effects of TZD versus DPP-4i on the risk of primary outcome. *Data are presented as HR [95% CI] for TZD compared with DPP-4i, derived from Cox regression analysis for the primary outcome. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; MET, metabolic equivalent of task; TZD, thiazolidinedione; Q, quartile.

time-varying covariates. The results remained consistent with the main analysis, (Table S10), showing a significantly lower risk associated with TZD use (adjusted HR 0.81, 95% CI 0.75–0.87).

Finally, we redefined TZD and DPP-4i users based on more stringent medication exposure definition (≥60 days of medication use within 90 days following the index health screening). After 1:1 PSM (43,716 TZD users and 43,716 DPP-4i users) and subsequent Cox regression analysis (Table S11), the association between TZD use and a lower risk of the primary outcome compared with the DPP-4i group remained consistent (adjusted HR 0.84, 95% CI 0.81–0.88).

DISCUSSION

In this nationwide cohort study, we investigated the CV protective effects of TZDs in patients with T2DM without a history of CVD, focusing on primary prevention. Compared with DPP-4i, which are generally known to be neutral in terms of CV risk, treatment with TZD was associated with a substantially lower incidence of the primary outcome–a composite of stroke, MI, hospitalization for HF, and all-cause mortality. This primary preventive effect was consistently observed with both pioglitazone and lobeglitazone. In the secondary outcome analyses, TZD treatment markedly reduced the risk of stroke, MI, and all-cause mortality. Nevertheless, there was no difference in

the risk of hospitalization for HF, thereby indicating that the CV preventive effects of TZD are mainly attributable to their anti-atherosclerotic properties rather than to direct effects on the heart. These findings provide evidence supporting the role of TZDs as potential candidates for the primary prevention of stroke and atherosclerotic CV events in T2DM populations, even in those without an established CVD.

Pioglitazone is the most widely used TZD and can effectively improve insulin resistance and reduce blood glucose levels. Substantial clinical evidence supports the secondary preventive effects of pioglitazone in patients with T2DM with prior CVD[30,31]. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, a prospective randomized controlled trial including 5,238 patients with T2DM presenting with extensive macrovascular disease, the use of pioglitazone modestly but significantly reduced the composite of all-cause mortality, non-fatal MI, and stroke compared with placebo (HR 0.84, 95% CI, 0.72–0.98; $P = 0.027$)[10]. Although reductions in stroke incidence were not statistically significant among the overall study population, post hoc analyses revealed a significant reduction in recurrent CVD among patients with prior stroke[11]. Considering the more pronounced CV benefit observed with pioglitazone in patients with prior stroke, the Insulin Resistance Intervention After Stroke (IRIS) trial evaluated the risk of stroke or MI among patients with insulin resistance and recent ischemic stroke or transient ischemic attack[32]. According to the findings of the IRIS trial, the use of pioglitazone significantly reduced the development of stroke or MI (HR 0.76, 95% CI, 0.62–0.93; $P = 0.007$) compared with that in placebo[12]. A meta-analysis of 10 randomized controlled trials has further confirmed that pioglitazone effectively reduces the risk of recurrent major adverse CV events (risk ratio [RR] 0.74, 95% CI 0.60–0.92), stroke (RR 0.77, 95% CI 0.64–0.93), or MI (RR 0.81, 95% CI 0.68–0.96) in patients with clinical manifest vascular disease[33]. Real-world evidence also supports the secondary preventive role of pioglitazone in stroke survivors with T2DM[34,35]. Lobeglitazone is a novel TZD class antidiabetic agent with a more potent PPAR-γ agonist activity, developed as a glucose-lowering agent and approved in South Korea[13]. Despite the limited clinical evidence available for lobeglitazone compared with pioglitazone, observational studies suggest that lobeglitazone also offers secondary CV preventive effects comparable to those of pioglitazone in patients with ischemic stroke or carotid artery stenosis[19,20].

Multiple mechanisms have been proposed to clarify the CV protective effect of pioglitazone against stroke and CV events in individuals with T2DM or insulin resistance[36]. TZDs, including pioglitazone, function as PPAR-γ agonists. By activating PPAR-γ, pioglitazone enhances insulin sensitivity, modulates inflammatory pathways, reduces oxidative stress, and improves endothelial dysfunction—all of which are central to the pathogenesis of atherosclerosis and CV events[37,38]. By reducing oxidative damage and preserving vascular integrity, TZDs help prevent atherosclerotic plaque rupture, a key cause of acute atherosclerotic CVD, including ischemic stroke and MI[10,12,39]. Chronic inflammation is a major contributor to the pathogenesis of both T2DM and CVD, as it exacerbates endothelial dysfunction and promotes atherosclerosis. Activation of PPAR-γ exerts anti-inflammatory effects by reducing cytokines, such as tumor necrosis factor-α and interleukin-6[40]. Furthermore, PPAR-γ activation promotes the expression of nitric oxide synthase, resulting in improved endothelial function, vasodilation, and vascular health[41]. PPAR-γ also plays a crucial role in anti-atherosclerosis by promoting cholesterol efflux from macrophages, thereby preventing the buildup of cholesterol in the arterial walls[42]. In addition to pioglitazone, lobeglitazone, a novel TZD with higher affinity for PPAR-γ, has demonstrated similar anti-atherosclerotic and anti-inflammatory effects[18,43].

Considering the established secondary preventive and multiple pleiotropic effects of TZD beyond their glucose-lowering properties, it is biologically plausible that TZDs could confer primary preventive effects in patients with T2DM without established CVD. Nonetheless, evidence for the primary preventive effect of TZD remains controversial. To date, no randomized clinical trials have specifically focused on the primary CV preventive effects of TZDs. A meta-analysis of randomized controlled trials comparing pioglitazone with any control revealed that the CV preventive benefit was only observed in patients with a history of established CVD and not in those without CVD[44]. Among retrospective studies, there were conflicting findings on the primary preventive role of TZD. Two retrospective Asian cohort studies with T2DM without established CVD found that pioglitazone use was associated with a reduced risk of new-onset ischemic stroke[45,46]. In contrast, a study based on the National Health Insurance Research Database of Taiwan demonstrated that patients with T2DM taking metformin developed ischemic heart disease more frequently following the addition of pioglitazone[47]. The withdrawal of rosiglitazone owing to concerns regarding the increased risk of MI and CV mortality adds weight to doubts about the primary CV preventive effect of TZDs[48].

Several methodological factors may account for the inconsistencies in previous findings pertaining to the primary preventive effects of TZDs, including variations in study populations, outcome definitions, and control group selection. Given that TZDs are known to possess anti-atherosclerotic properties, the definition of outcomes, particularly whether atherosclerotic CVD was considered a primary outcome, may have markedly impacted the study findings. Defining the control group simply as patients not using TZDs may inadvertently reflect less intensive or suboptimal glycemic management, potentially obscuring the true effects of TZDs. Considering that patients with T2DM frequently receive multiple classes of glucose-lowering agents, concurrent medications can act as confounding factors in CV outcome analyses. To address these challenges in observational study design, we employed PSM to balance covariates and adopted an active comparator design, which compares the drug of interest with another commonly used agent for the same

indication, rather than with no treatment[49]. Because DPP-4i are widely prescribed as glucose-lowering agents to treat T2DM and have demonstrated neutral CV effects in multiple studies, we selected DPP-4i as an active comparator of TZD[29]. DPP-4i are frequently used as comparators in epidemiological studies evaluating CV outcomes in T2DM populations. After controlling baseline characteristics and concurrent use of other antidiabetic medications through PSM, we found that TZD-treated patients had a significantly lower risk of CV events than those treated with DPP-4i. The primary CV preventive effect was consistently observed with both pioglitazone and lobeglitazone, suggesting a potential class effect of TZD mediated via PPAR-γ activation.

Our study addresses a crucial gap by demonstrating a protective role of TZD in primary prevention settings. However, concerns regarding the adverse effects of TZDs, including weight gain, fluid retention, HF, bone fractures, and cancer risk, remain notable considerations in clinical decision-making. The potential for developing these adverse effects is the primary factor limiting the clinical use of TZDs despite their notable benefits in CV prevention. In particular, HF is a well-recognized and serious complication associated with TZD use[50]. The DREAM trial reported that rosiglitazone was associated with an increased risk of HF[51], and the PROactive study revealed a higher incidence of serious HF with pioglitazone, without a corresponding increase in mortality or morbidity[52]. Importantly, risks within the TZD class appear to vary. Rosiglitazone has been associated with a higher risk of stroke, HF, and mortality than pioglitazone[53], potentially due to differences in its vasodilatory properties and sodium retention mechanisms[50,54].

In the current study, TZD use was not significantly associated with hospitalization due to HF compared with DPP-4i use. However, this finding should be interpreted with caution. In real-world clinical practice, TZDs are often avoided in patients perceived to be at higher risk of HF, and such clinical considerations may not be fully captured in claims-based data. Therefore, treatment-selection bias may have resulted in the TZD group representing a relatively lower-risk population, potentially contributing to the observed null association. Accordingly, our findings should not be interpreted as evidence that TZDs are safe with respect to HF risk across all patient populations. Rather, they suggest that, among patients with T2DM who are not at high risk of HF, TZD use may be considered in appropriately selected patients. Additional studies are warranted to further clarify the relationship between TZD use and HF outcomes in higher-risk populations.

This study has several strengths, including the use of a large nationally representative cohort and rigorous exclusion criteria to ensure a primary prevention focus. The Korean NHIS database, comprising comprehensive nationwide health claims data combined with health screening records, enabled the analysis of a large T2DM population with detailed covariate data, including blood pressure, life-styles, household income, and laboratory measurements. We employed rigorous statistical methods, including an active comparator design and PSM, and demonstrated the robustness of our findings through subgroup and sensitivity analyses. Nonetheless, this study has several limitations that need to be acknowledged. Given the retrospective nature of this study, the possibility of residual confounding due to unmeasured variables cannot be entirely excluded. Although the diagnostic validity of health claims data in Korea is known to be high, there is still a possibility of misclassification[24,55]. Additionally, some key clinical variables, such as hemoglobin A1C levels and duration of T2DM, were unavailable, as the NHIS database was primarily constructed for administrative rather than research purposes. To partially address this limitation, we accounted for multiple related clinical and treatment variables, including fasting glucose levels, insulin use, and the use of various glucose-lowering medications, which may reflect both glycemic control and treatment intensity. Furthermore, our findings remained consistent in time-varying analyses in which oral antidiabetic medication use was dynamically updated during follow-up. This consistency suggests that the observed association is robust to changes in treatment over time. Nevertheless, residual confounding due to unmeasured factors, particularly HbA1c and diabetes duration, remains an important limitation of this study. Finally, because the study population consisted exclusively of Korean adults, the generalizability of our findings to other ethnic and geographic populations may be limited.

In conclusion, our study provides important real-world evidence supporting the potential role of TZDs for primary CV prevention in patients with T2DM. These findings suggest that TZDs may offer meaningful CV benefits with appropriate patient selection. Future randomized controlled trials, particularly focusing on long-term outcomes, are warranted to better guide clinical decision-making and promote the safe and tailored use of TZDs in appropriately selected patients, balancing their potential benefits against associated risks.

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DISCLOSURE

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Approval of the research protocol: The study protocol was approved by the Institutional Review Board of Yongin Severance Hospital (9-2023-0156).
Informed consent: Due to the nature of this retrospective study based on fully anonymized data from the NHIS, individual patients could not be identified; therefore, the requirement for informed consent was waived.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

AUTHOR CONTRIBUTIONS

YC and JK conceptualized the study. JY and JJ performed the acquisition, analysis, and interpretation of data. YC, MB and JJ drafted the article. MB, JY and JK provided critical revision of the article for important intellectual content. JK obtained funding. All authors participated in reviewing, editing, and providing approval for the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The dataset used in this study was obtained from the NHIS in South Korea, which was provided for research purposes related to this study. The data set is confidential and its use is restricted to this study. Therefore, public access to this dataset is not available. To access the data, researchers must submit a completed application form, research proposal, and valid institutional review board approval documents, all of which are evaluated by the National Health Insurance Sharing Service's Inquiry Committee for Research Support (https://nhiss.nhis.or.kr/bd/ab/bdaba 000eng.do).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cumulative incidence curves for the primary outcome between pioglitazone and DPP-4i users after propensity matching.

Figure S2. Cumulative incidence curves for the primary outcome between lobeglitazone and DPP-4i users after propensity score matching.

Table S1. Operational definitions of exclusion criteria used in the present study.

Table S2. Definitions of collected patient characteristics in this study.

Table S3. Baseline characteristics before and after propensity score matching between DPP-4i vs pioglitazone.

Table S4. Baseline characteristics before and after propensity score matching between DPP-4i vs lobeglitazone.

Table S5. Association between pioglitazone use and cardiovascular outcomes vs DPP-4i use after propensity score matching.

Table S6. Association between lobeglitazone use and cardiovascular outcomes vs DPP-4i use after propensity score matching.

Table S7. Association between TZD use and the primary outcome according to prior TZD exposure.

Table S8. Association between pioglitazone dose and the risk of the primary outcome.

Table S9. Sensitivity analysis using the entire cohort: association of thiazolidinedione with primary outcome in Cox regression model.

Table S10. Time-varying associations of oral antidiabetic medications, including TZD, with the primary outcome.

Table S11. Sensitivity analysis of the association between TZD and DPP-4i use using an alternative medication exposure definition (≥60 days within 90 days).