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ORIGINAL RESEARCH

Thiazolidinedione Use and Cardiovascular Outcomes in Patients With Type 2 Diabetes Who Underwent Carotid Artery Revascularization

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BACKGROUND: Thiazolidinediones are oral antidiabetic agents known for their wide-ranging pleiotropic effects, potentially offering cardiovascular protection. Using a nationwide health claims database in Korea, we evaluated whether thiazolidinedione treatment was associated with long-term cardiovascular prognosis after carotid revascularization.

METHODS AND RESULTS: This retrospective cohort study included patients with type 2 diabetes who underwent carotid endarterectomy or stent insertion in Korea between 2009 and 2020. The use of medications, including thiazolidinediones, was determined from prescription records, identifying exposure to medications within 30 days following carotid revascularization. The primary outcome was the composite occurrence of stroke, myocardial infarction, and all-cause death following carotid revascularization. A multivariate Cox regression analysis was conducted to assess the primary outcomes. The cohort included 14 220 patients with type 2 diabetes who underwent carotid revascularization (2669 via carotid endarterectomy and 11 551 via carotid stent insertion). Among them, 1034 patients received thiazolidinedione treatment. Over a mean follow-up period of 4.13±3.14 years, 4087 patients experienced a primary outcome. Thiazolidinedione treatment was significantly associated with a reduced risk of primary outcomes (adjusted hazard ratio [HR], 0.81 [95% CI, 0.71–0.93]; *P*=0.002). The protective effect of thiazolidinediones was supported in a propensity score–matched analysis comparing thiazolidinedione users with nonusers (HR, 0.81 [95% CI, 0.68–0.95]; *P*=0.013).

CONCLUSIONS: Thiazolidinedione treatment following carotid revascularization was associated with favorable cardiovascular outcomes in patients with type 2 diabetes. Further research is needed to explore the cardioprotective roles of thiazolidinediones in this high-risk group.

Key Words: carotid artery ■ diabetes ■ myocardial infarction ■ stroke ■ thiazolidinediones

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The carotid arteries, located on each side of the neck, are the primary vessels supplying oxygenated blood to the brain. Atherosclerosis is relatively common among older individuals with multiple vascular risk factors. This condition, through hemodynamic impairment and artery-to-artery embolism, increases the risk of ischemic stroke in patients with carotid artery stenosis, accounting for ≈10% to 20% of all ischemic strokes.[1] Prior randomized controlled trials have established carotid revascularization, through either

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CLINICAL PERSPECTIVE

What Is New?

- In a large, nationwide cohort of patients with type 2 diabetes undergoing carotid endarterectomy or stenting, thiazolidinedione use was associated with lower rates of stroke, myocardial infarction, and all-cause death after carotid revascularization, highlighting their potential to prevent major adverse cardiovascular events in this high-risk population.
- Beyond glycemic control, these real-world findings suggest that thiazolidinediones may confer antiatherosclerotic and anti-inflammatory benefits to patients with severe carotid artery disease, thus further reducing their risk of recurrent cardiovascular and cerebrovascular events.

What Are the Clinical Implications?

- Incorporating thiazolidinediones into standard post–carotid revascularization treatment protocols may improve long-term vascular outcomes in patients with type 2 diabetes, although further prospective research is necessary to establish optimal patient selection and confirm overall safety.

Nonstandard Abbreviations and Acronyms

CAS	carotid artery stenting
CEA	carotid endarterectomy
HIRA	Health Insurance Review and Assessment
IRIS	Insulin Resistance Intervention After Stroke
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PSM	propensity score matching
T2D	type 2 diabetes

carotid endarterectomy (CEA) or carotid artery stenting (CAS), as an effective treatment for severe carotid stenosis, reducing the risk of ischemic stroke for both primary and secondary prevention.[2] However, individuals treated with carotid revascularization still have a substantially increased risk of future cardiovascular complications, attributed to concurrent comorbidities, systemic atherosclerosis, inadequate control of residual risk factors, and the possibility of carotid restenosis.[3] Hence, a comprehensive long-term cardiovascular preventive strategy is crucial for patients following carotid revascularization, particularly considering their subsequent cardiovascular risk.

Diabetes is a major vascular risk factor, associated with an increased prevalence and severity of carotid artery stenosis. It is a common comorbidity among patients who have undergone carotid revascularization and is associated with an increased risk of adverse complications compared with those without diabetes.[4] Thiazolidinediones, a class of oral glucose-lowering medications, are used in the treatment of type 2 diabetes (T2D). Beyond glycemic control, substantial experimental and clinical data support the beneficial role of thiazolidinediones on the cardiovascular system.[5] Indeed, thiazolidinediones have been shown to reduce recurrent cardiovascular events in patients with stroke and T2D.[6,7] Therefore, we hypothesized that thiazolidinedione treatment could potentially reduce subsequent cardiovascular complications in patients with T2D who have undergone carotid revascularization. To evaluate the relationship between thiazolidinedione treatment and prognosis after carotid revascularization, we conducted a retrospective cohort study using nationwide health insurance claims data from Korea.

METHODS

The data set used in this study is accessible from HIRA in Korea, but with restrictions to data availability. The use of the data set is available under permission from HIRA; therefore, public access to the data set is not available. Researchers can access the data only upon reasonable request and receiving approval from the inquiry committee of research support in HIRA (https://opendata.hira.or.kr/or/orb/useGdInfo.do).

Ethical Statement

This study was conducted in accordance with the Helsinki Declaration. Owing to the retrospective nature of this study and the use of fully anonymized data, the requirement for informed consent was waived by the Institutional Review Board of Yongin Severance Hospital (9-2023-0156). The research reported in this article adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study Design and Data Source

This retrospective cohort study used a population-based health claims database in South Korea. South Korea operates a government-mandated national health insurance program, which is mandatory for all residents. Health Insurance Review and Assessment (HIRA) is a government agency under the Ministry of Health and Welfare responsible for reviewing medical fee claims and assessing quality assessments of health care services. To support political and

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academic research, HIRA has established a health care claims database that includes hospital visits, diagnoses, procedures, medications, and demographic information of health insurance subscribers in Korea. At each hospital visit, diagnostic codes are recorded according to the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*), and information on procedures or medications is submitted to HIRA for insurance claims. The database is fully anonymized and accessible to approved researchers only.

Study Participants

Upon approval from HIRA, we collected health claims data for study participants who underwent CEA (O0226, O0227, O2066) or CAS (M6602) on the basis of the procedure-related claim codes from January 2009 to December 2020.[8] From this data set, we established a cohort of patients with T2D aged ≥18 years. The index date for each patient was defined as the date of carotid revascularization. T2D was identified by at least 1 claim for antidiabetic medications, along with a related diagnostic code (E11, E12, E13, or E14) before or on the index date.[7] Through an examination of HIRA claims data, study patients were followed up until the occurrence of the primary outcome, death, loss of eligibility for health insurance, or the study's end date (June 30, 2021). Patients who experienced outcomes too soon or had a short follow-up period (<30 days) were excluded from the analysis to omit early outcomes potentially resulting from the complications of the procedure itself. The initial 30 days after carotid revascularization served as a landmark period for determining thiazolidinedione treatment.

Outcomes

The primary outcome was the composite occurrence of stroke, myocardial infarction (MI), and all-cause death after the index date. The occurrence of stroke was identified by an admission lasting >3 days with a primary diagnosis of I60 to I63 accompanied by a brain computed tomography or magnetic resonance imaging scans. The occurrence of MI was identified by an admission with a primary diagnosis of I21. Previous studies using health claims data in Korea have validated the diagnostic accuracy of I60 to I63 for stroke and I21 for MI.[9] In cases with multiple outcomes, only the earliest event was considered. If death and stroke (or MI) occurred on the same day, the primary outcome was considered stroke (or MI). The secondary outcomes included the individual components of the primary outcome. Additionally, as a safety outcome measure, we established a subcohort of patients without prior diagnosis of heart failure (HF) before carotid revascularization. We then assessed the occurrence of HF during the follow-up period, identifying cases through health claim records with a primary or secondary diagnosis of I11.0, I13.0, I13.2, and I50.x.[7]

Covariates

Clinical characteristics including sex, age, health insurance type, type of carotid revascularization (CEA, CAS), symptomatic carotid stenosis, and comorbidities were assessed. The public health care system in Korea comprises a 2-tier system including National Health Insurance and the Medical Aid program. The Medical Aid program covers the near-poor, a low-income population. Symptomatic carotid stenosis was determined on the basis of the occurrence of ischemic stroke (I63), transient ischemic attack (G45), or retinal artery occlusion (H34.0–2) within the past 6 months before carotid revascularization. These events were identified through the presence of relevant diagnostic codes in the claims database.[10,11] The presence of the specific diagnostic and claims codes before or on the index date indicated the presence of hypertension, atrial fibrillation, coronary artery disease, renal disease, and malignancy. A detailed indication of the comorbidities is provided in the Supplemental Methods.

Treatment With Thiazolidinediones and Other Medications

In South Korea, cardiovascular and antidiabetic medications are prescribed by physicians. Prescription records (prescription date, name, dosage, and duration) are available in the HIRA claims database. Antidiabetic medications are classified as thiazolidinediones, sulfonylureas, or meglitinides (insulin stimulators), biguanides, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter-2 inhibitors, α-glucosidase inhibitors, glucagon-like peptide-1 antagonists, and insulin. During the study period, 2 thiazolidinediones (pioglitazone and lobeglitazone) were available in Korea.[12,13] As covariates, we assessed the use of thiazolidinediones, other classes of antidiabetic medications, oral antiplatelets (aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, triflusal, and cilostazol), oral anticoagulants (coumadin, rivaroxaban, apixaban, edoxaban, and dabigatran), and statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin). Based on prescription records, individuals who were exposed to the medication for at least 1 day within 30 days after carotid revascularization were classified as users of the medication.

Statistical Analysis

Categorical variables are presented as numbers (%) and continuous variables as mean±SD. For comparison between groups, categorical variables were compared using the χ^2 test, and continuous variables were compared using the independent *t* test. Cumulative incidence curves were generated on the basis of the use of thiazolidinediones, and differences between the curves were

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evaluated using a log-rank test. To identify risk factors for event outcomes, hazard ratios (HRs) and 95% CIs were calculated using a Cox proportional hazard regression model, adjusting for sex and variables with $P<0.10$ in the univariate analysis. The proportional hazard assumption for thiazolidinediones in the Cox regression model was evaluated by calculating the Schoenfeld residuals, which was satisfied. To explore potential interaction effects between thiazolidinedione use and characteristics, subgroup analyses were conducted based on sex, age, type of carotid revascularization, and symptomatic carotid stenosis. For the analysis of secondary outcome, separate Cox regression models were constructed for individual outcomes (stroke, MI, and all-cause death). These secondary outcome analyses were conducted using a cause-specific Cox regression approach, whereby patients who experienced another event outcome (acting as a competing risk) before the event of interest were censored at the time of the preceding competing event. As a measure of safety outcomes, we evaluated the risk of HF in relation to thiazolidinedione use by constructing a Cox regression model for HF.

To address potential biases due to uncontrolled confounding factors between thiazolidinedione users and nonusers, we conducted a sensitivity analysis using propensity score matching (PSM). Propensity scores, reflecting the probability of receiving thiazolidinediones, were calculated using a multivariable binary logistic regression model that included all collected covariates except the use of thiazolidinediones. Each patient treated with a thiazolidinedione was matched at a 1:3 ratio with those without thiazolidinediones using the nearest-neighbor method with a caliper width of 0.10 and without replacement. To access the balance, the standardized mean differences of each covariate between the groups were calculated before and after the PSM. An absolute standardized mean difference <0.1 was considered appropriate. Using the matched data set after PSM, we conducted a stratified Cox regression analysis for the primary outcome. Statistical analyses were performed using R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Inc., Cary, NC). Differences were considered significant at 2-sided P values <0.05.

RESULTS

Study Population and Characteristics

According to the HIRA database, 36 104 Korean patients underwent CEA or CAS between 2009 and 2020. Based on the inclusion and exclusion criteria, this study included 14 220 patients with T2D who underwent carotid revascularization (2669 with CEA and 11 551 with CAS; Figure 1). Male patients comprised 81.2% of the cohort, and the mean age at the time of carotid revascularization was 69.7±8.2 years (Table 1). There were 6121 patients with symptomatic carotid stenosis. Of these, 5992 had ischemic stroke, 851 had

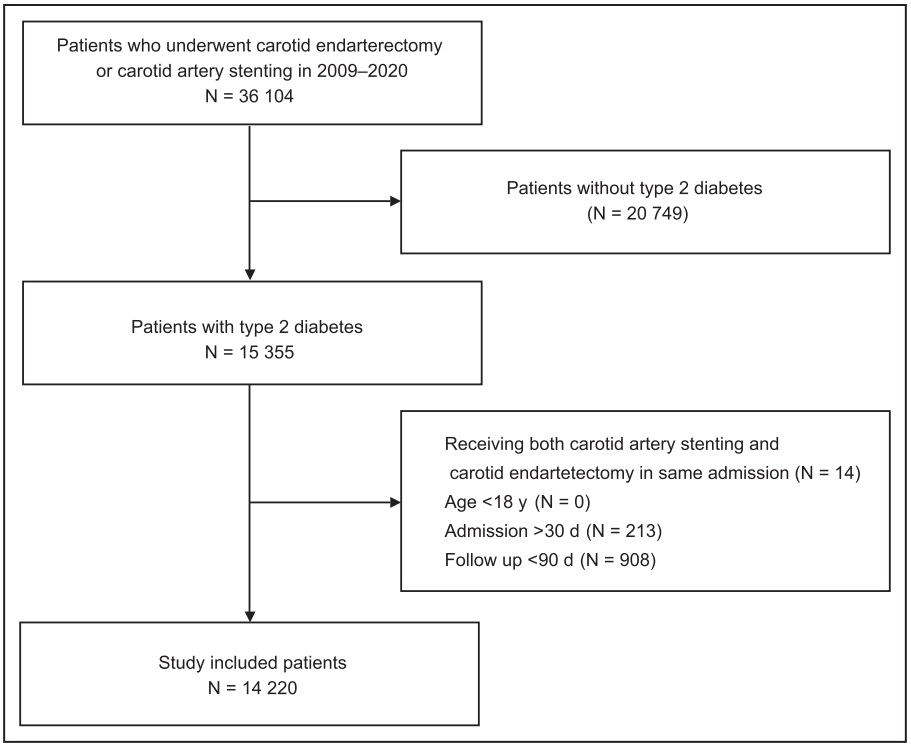


Figure 1. Inclusion and exclusion criteria for study patients from a nationwide health claim database in Korea.

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Table 1. Characteristics of Study Patients

	Total (n=14 220)	Without thiazolidinedione (n=13 186)	With thiazolidinedione (n=1034)	*P* value
Type of revascularization				0.124
Carotid stent	11 551 (81.23)	10 692 (81.09)	859 (83.08)	
Carotid endarterectomy	2669 (18.77)	2494 (18.91)	175 (16.92)	
Sex, male	11 548 (81.21)	10 682 (81.01)	866 (83.75)	0.033
Age, y	69.66±8.25	69.73±8.26	68.76±8.14	<0.001
Symptomatic carotid stenosis*	6121 (43.05)	5696 (43.20)	425 (41.10)	0.201
Recent ischemic stroke	5992 (42.14)	5576 (42.29)	416 (40.23)	0.209
Recent transient ischemic attack	851 (5.98)	791 (6.00)	60 (5.80)	0.851
Recent retinal artery occlusion	168 (1.18)	150 (1.14)	18 (1.74)	0.114
Insurance type				0.861
Health insurance	13 160 (92.55)	12 205 (92.56)	955 (92.36)	
Medical aid	1060 (7.45)	981 (7.44)	79 (7.64)	
Comorbidity				
Hypertension	13 067 (91.89)	12 122 (91.93)	945 (91.39)	0.581
Atrial fibrillation	1530 (10.76)	1435 (10.88)	95 (9.19)	0.101
Renal disease	4279 (30.09)	3864 (29.30)	415 (40.14)	<0.001
Malignancy	1464 (10.30)	1378 (10.45)	86 (8.32)	0.034
Coronary artery disease	4815 (33.86)	4494 (34.08)	321 (31.04)	0.051
Medication				
Statin	13 005 (91.46)	12 035 (91.27)	970 (93.81)	0.006
Oral antiplatelet	14 175 (99.68)	13 144 (99.68)	1031 (99.71)	1.000
Oral anticoagulant	1050 (7.38)	987 (7.49)	63 (6.09)	0.113
Insulin	7171 (50.43)	6593 (50.00)	578 (55.90)	<0.001
GLP-1 agonist	24 (0.17)	21 (0.16)	3 (0.29)	0.553
Sulfonylurea or meglitinide	6932 (48.75)	6339 (48.07)	593 (57.35)	<0.001
Biguanide	10 481 (73.71)	9677 (73.39)	804 (77.76)	0.002
DPP-4 inhibitor	6355 (44.69)	5751 (43.61)	604 (58.41)	<0.001
SGLT2 inhibitor	478 (3.36)	439 (3.33)	39 (3.77)	0.502
α-Glucosidase inhibitor	1144 (8.05)	1090 (8.27)	54 (5.22)	0.001
Thiazolidinedione	1034 (7.27)	0	1034 (100.0)	
Pioglitazone	856 (6.02)	0	856 (82.79)	
Lobeglitazone	178 (1.25)	0	178 (17.21)	

Data are represented as n (%) or mean±SD. DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium–glucose cotransporter 2.

*Patients with symptomatic carotid stenosis could have concurrent ischemic stroke, transient ischemic stroke, and retinal artery occlusion within the past 6 mo.

transient ischemic attack, and 168 had retinal artery occlusion within the 6 months before carotid revascularization (Figure S1). The proportion of patients treated with thiazolidinediones was 7.3% (pioglitazone, 6.0%; and lobeglitazone, 1.3%).

Primary Outcomes

During the mean follow-up period of 4.13±3.14 years after carotid revascularization, 4087 patients experienced a primary outcome (composite of stroke, MI, and all-cause death). Of these, 1516 patients had a stroke, 424 patients had an MI, and 2147 patients experienced all-cause death. In thiazolidinedione users, the incidence rate of primary outcomes was 562.7 per 10 000 person-years, while in non-thiazolidinedione users, it was 706.1 per 10 000 person-years (Table 2). The comparison of cumulative incidence curves (Figure 2) revealed that those treated with thiazolidinediones had a significantly lower risk of the primary outcome than that of patients not treated with thiazolidinediones (P<0.001).

Association of Thiazolidinediones and Outcomes

We performed a Cox regression analysis to evaluate the risk factors associated with the primary outcome

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Table 2. Incidence of Outcomes According to the Use of Thiazolidinediones

Patient number by thiazolidinedione use	Cumulative follow-up duration (person-years)	Number of patients with event outcome				Incidence rate per 10 000 person-years (95% CI)*			
		Primary outcome	Stroke	Myocardial infarction	All-cause death	Primary outcome	Stroke	Myocardial infarction	All-cause death
Total (n=14 220)	58694.05	4087	1516	424	2147	696.3 (675.1–718.0)	258.3 (245.4–271.6)	72.2 (65.5–79.4)	365.8 (350.5–381.6)
Thiazolidinedione nonuser (n=13 186)	54695.40	3862	1431	405	2026	706.1 (684.0–728.7)	261.6 (248.2–275.5)	74.0 (67.0–81.6)	370.4 (354.5–386.9)
Thiazolidinedione user (n=1034)	3998.65	225	85	19	121	562.7 (491.6–641.2)	212.6 (169.8–262.8)	47.5 (28.6–74.2)	302.6 (251.1–361.6)

*95% CI for an incidence rate is calculated on the basis of the Poisson distribution.

(Table 3). Patients treated with thiazolidinediones had a lower risk of the primary outcome (adjusted HR, 0.81 [95% CI, 0.71–0.93]; *P*=0.002). In a separate analysis comparing lobeglitazone and pioglitazone with no thiazolidinedione treatment, the adjusted HRs for the primary outcome of pioglitazone and lobeglitazone were 0.80 (95% CI, 0.69–0.92), and 0.91 (95% CI, 0.64–1.28), respectively. Subgroup analyses based on sex, age, type of carotid revascularization, and symptomatic carotid stenosis (Figure 3) revealed no significant interaction effects between thiazolidinedione treatment and these factors. In secondary outcome analysis for individual outcomes of stroke, MI, and all-cause death (Figure 4), thiazolidinedione treatment was associated with a reduced risk of stroke, MI, and all-cause death; however, statistical significance was achieved only for MI (adjusted HR, 0.62 [95% CI, 0.39–0.98]; *P*=0.039). In the safety outcome analysis for HF, no significant difference in the development of HF was observed between thiazolidinedione users and nonusers (Table S1).

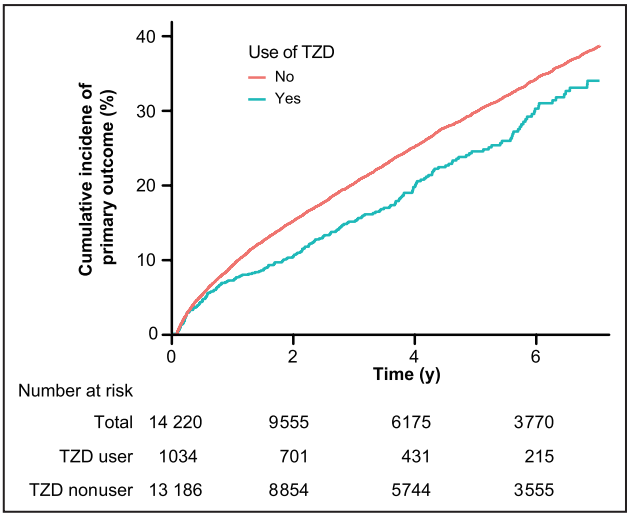


Figure 2. Cumulative incidence curves for the primary outcome on the basis of treatment with thiazolidinedione.
TZD indicates thiazolidinedione.

Sensitivity Analysis Using PSM

In the sensitivity analysis, following a 1:3 PSM sampling based on thiazolidinedione use, we included 1031 patients treated with thiazolidinedione and 3093 patients not treated with thiazolidinediones (Table S2). The absolute standardized mean difference of all covariates between the groups was <0.1, indicating a good balance in their distribution. Stratified Cox regression analysis, conducted on the PSM samples, revealed that patients treated with thiazolidinediones had a lower risk of the primary outcome than that of patients not treated with thiazolidinediones (HR, 0.81 [95% CI, 0.68–0.95]; *P*=0.013). Considering that the observed benefit in thiazolidinedione users may be due to stricter glucose control from additional oral antidiabetic medications rather than a class effect of thiazolidinediones, we performed an additional PSM analysis to balance the number of oral antidiabetic medication classes between the thiazolidinedione and non-thiazolidinedione groups, with both groups having a median of 3 (interquartile range, 2–3). The result consistently indicated a lower risk for the thiazolidinedione group (HR, 0.71 [95% CI, 0.57–0.87]; *P*<0.001).

DISCUSSION

Using a population-based cohort, we evaluated the long-term cardiovascular outcomes of treatment with thiazolidinediones after carotid revascularization in patients with T2D. We observed a significant reduction in cardiovascular events with thiazolidinedione treatment after carotid revascularization. These results were further supported by a sensitivity analysis comparing the groups treated with and without thiazolidinediones using PSM. No significant interaction was observed between the beneficial effect of thiazolidinediones and sex, age, type of carotid revascularization, and symptomatic carotid stenosis in the subgroup analysis. The results of this study suggest that thiazolidinediones, originally developed as antidiabetic medications for

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Table 3. Univariate and Multivariate Cox Regression for the Primary Outcome

Variables	Crude HR (95% CI), *P* value	Adjusted HR (95% CI),* *P* value
Type of revascularization		
Carotid stent	Ref	Ref
Carotid endarterectomy	0.74 (0.68–0.80), <0.001	0.72 (0.66–0.78), <0.001
Sex, male	1.06 (0.98–1.15), 0.151	1.22 (1.12–1.32), <0.001
Age	1.05 (1.05–1.06), <0.001	1.05 (1.04–1.05), <0.001
Symptomatic carotid stenosis	1.33 (1.25–1.41), <0.001	1.32 (1.24–1.40), <0.001
Insurance type		
Health insurance	Ref	Ref
Medical aid	1.42 (1.27–1.58), <0.001	1.44 (1.30–1.61), <0.001
Comorbidity		
Hypertension	1.45 (1.27–1.64), <0.001	1.23 (1.08–1.40), 0.002
Atrial fibrillation	1.53 (1.39–1.67), <0.001	1.26 (1.14–1.40), <0.001
Renal disease	1.33 (1.25–1.42), <0.001	1.19 (1.11–1.28), <0.001
Malignancy	1.46 (1.33–1.61), <0.001	1.25 (1.14–1.38), <0.001
Coronary artery disease	1.12 (1.05–1.19), <0.001	1.09 (1.02–1.16), 0.015
Medication		
Statin	0.87 (0.79–0.95), 0.003	0.87 (0.79–0.95), 0.004
Oral antiplatelet	0.78 (0.48–1.27), 0.317	–
Oral anticoagulant	1.41 (1.27–1.57), <0.001	1.17 (1.03–1.32), 0.014
Insulin	1.29 (1.21–1.37), <0.001	1.39 (1.31–1.48), <0.001
GLP-1 agonist	0.67 (0.17–2.66), 0.566	–
Sulfonylurea or meglitinide	1.07 (1.00–1.13), 0.042	1.06 (1.00–1.13), 0.064
Biguanide	0.74 (0.69–0.79), <0.001	0.80 (0.74–0.85), <0.001
DPP-4 inhibitor	1.02 (0.96–1.09), 0.454	–
SGLT2 inhibitor	0.99 (0.78–1.25), 0.905	–
α-Glucosidase inhibitor	1.10 (1.00–1.21), 0.051	1.06 (0.96–1.17), 0.250
Thiazolidinedione	0.79 (0.69–0.91), <0.001	0.81 (0.71–0.93), 0.002

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium–glucose cotransporter.

*Adjusted for sex and variables with *P*<0.10 in the univariate Cox regression for the primary outcome (type of revascularization; age; symptomatic carotid stenosis; insurance type; hypertension; atrial fibrillation; renal disease; malignancy; coronary artery disease; and use of statins, oral anticoagulants, insulin, sulfonylurea or meglitinide, biguanide, α-glucosidase inhibitor, thiazolidinedione).

T2D, have the potential to prevent future cardiovascular events in those treated with carotid revascularization for severe carotid stenosis.

Thiazolidinediones are synthetic agonists of peroxisome proliferator-activated receptor-γ, a transcription factor mainly responsible for regulating adipogenesis, and lipid/glucose metabolism.[14] Activation of peroxisome proliferator-activated receptor-γ results in insulin sensitization and lowers blood glucose through several metabolic pathways by increasing insulin-mediated glucose uptake in skeletal muscle, suppressing hepatic glucose production, and improving the secretory response of insulin in pancreatic β cells.[15] Beyond their metabolic effects, thiazolidinediones can exert multiple antiatherosclerotic effects by improving endothelial function, reducing intimal hyperplasia, decreasing systemic blood pressure, inhibiting neutrophil recruitment, increasing cholesterol removal from the human macrophage foam cells, suppressing the inflammatory signaling pathway, reducing the proliferation and migration of vascular smooth muscle, restoring collateral blood flow through angiogenesis, decreasing arterial stiffness, and stabilizing atherosclerotic plaques.[16–19] Peroxisome proliferator-activated receptor-γ agonists can also attenuate platelet activation and the release of proinflammatory/procoagulant mediators.[20] These anti-inflammatory and antithrombotic properties of thiazolidinediones may impact the development and progression of atherosclerosis.[21]

Growing clinical evidence also supports the protective role of thiazolidinediones in atherosclerosis-driven vascular events, including coronary, cerebral, and peripheral artery diseases.[5] Thiazolidinediones have shown a significant reduction in neointimal tissue proliferation, in-stent restenosis, and target lesion revascularization after coronary stent implantation.[22,23] Studies in patients with coronary artery disease have documented a decrease in coronary artery inflammation, stabilization of coronary plaque, and reduction of coronary atheroma volume with pioglitazone treatment.[24,25] The antiatherosclerotic effect of pioglitazone has also been shown in femoral and carotid artery diseases.[26] In the context of carotid artery atherosclerosis, treatment with pioglitazone has been shown to reduce carotid intima-media thickness and attenuate atherosclerotic plaque inflammation, independent of glycemic control.[16,27,28] We hypothesize that the antiatherosclerotic and anti-inflammatory roles of thiazolidinediones in the cardiovascular system could contribute to the reduction in cardiovascular events in this study's population, who underwent carotid revascularization.

Several randomized clinical trials have highlighted the cardiovascular protective effects of thiazolidinediones. In the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial (5238

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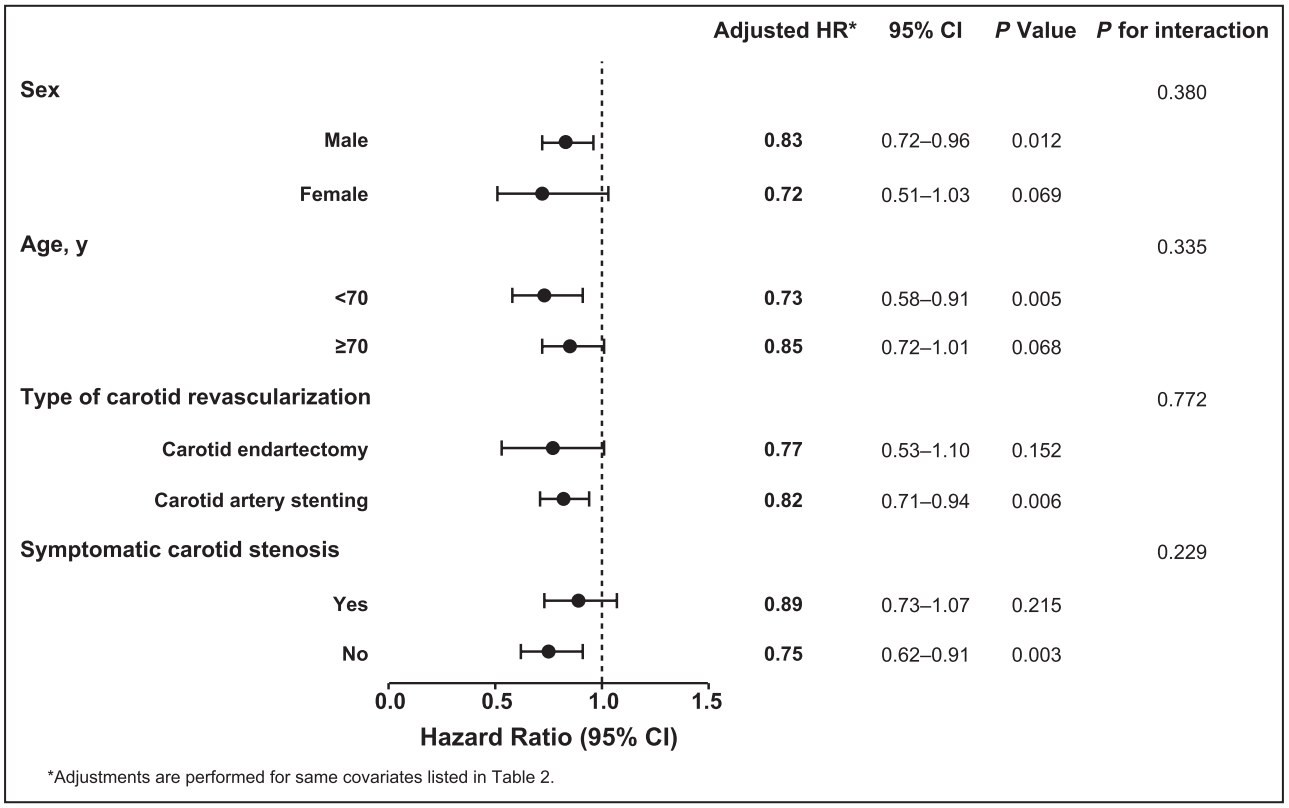


Figure 3. Subgroup analysis of the effect of thiazolidinediones on the basis of patient characteristics.
HR indicates hazard ratio.

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patients with T2D with macrovascular disease) showed a 16% reduction in the composite risk of all-cause death, nonfatal MI, and stroke with pioglitazone.[29] Similarly, the IRIS (Insulin Resistance Intervention After Stroke) trial reported that pioglitazone reduces the incidence of stroke/MI by 29%, stroke alone by 27%, and acute coronary syndrome by 27%.[30,31] Furthermore, a meta-analysis encompassing 5 randomized controlled trials including patients with diabetes revealed that pioglitazone is associated with a reduced risk of major adverse cardiovascular events (relative risk, 0.83 [95% CI, 0.72–0.97]).[32] While there is no prospective clinical trial focusing on cardiovascular outcomes with lobeglitazone yet, a retrospective cohort study in Korea has demonstrated that lobeglitazone possesses a secondary cardiovascular preventive effect similar to that of pioglitazone in patients with ischemic stroke with T2D.[7]

Despite their potent glucose-lowering and pleiotropic effects, thiazolidinediones have been limited in clinical practice due to safety concerns.[33] Pioglitazone, the most commonly used thiazolidinedione, has been associated with a higher incidence of hospitalization for HF. However, pioglitazone-related HF mainly occurs in patients with underlying heart disease, and no corresponding increase in mortality rate or worsening of cardiac function has been noted.[34] The mechanism behind thiazolidinedione-associated HF is considered to be related to increased plasma volume rather than direct detrimental effects on cardiac function.[35,36] Since sufficient evidence indicates that careful administration of pioglitazone, considering its potential risks and benefits, may contribute to the prevention of subsequent cardiovascular outcomes in high-risk patients. In the present study, which focused on patients who underwent carotid revascularization, the use of thiazolidinediones did not appear to be associated with the occurrence of HF. However, further research is necessary to elucidate the implications and safety of thiazolidinediones in these patient groups, particularly among those considered to be at high risk for HF.

This study has several strengths and limitations. The population-based claim database in Korea allowed us to collect data from a relatively large number of patients with T2D who underwent carotid revascularization with long-term follow up. The diagnostic accuracy of cardiovascular events in Korean health claims data is known to be relatively good,[9] and prescription records are reported to HIRA. Therefore, we could verify each patient's use of antidiabetic and common cardiovascular drugs, such as antiplatelet agents and statins. To reduce potential bias due to differences in the underlying baseline characteristics, we performed

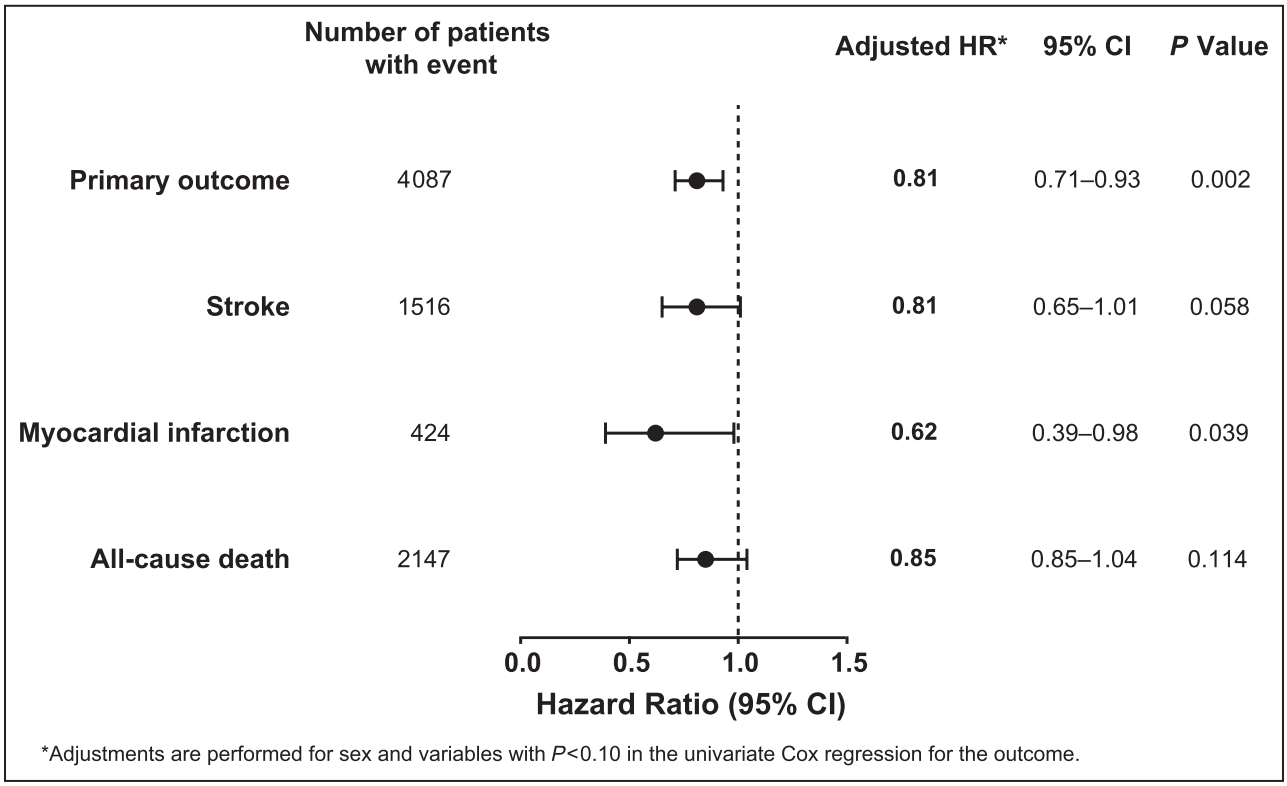


Figure 4. Analysis of secondary outcomes on the basis of treatment with thiazolidinedione.
HR indicates hazard ratio.

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sensitivity analyses using PSM. When comparing before and after PSM, we found that balancing between the 2 groups improved, and results after PSM revealed consistent findings. However, we should also acknowledge the limitations inherent to a retrospective study based on health insurance claims data. Because the claims database was not constructed for clinical study purposes, it lacked important clinical information such as the baseline and postprocedural degree of carotid artery stenosis and laboratory data on serum glucose levels and hemoglobin A_{1c}. Additionally, it was not possible to ascertain whether strokes occurring during the follow-up period were ipsilateral to the site of carotid revascularization. Considering the known HF risk of thiazolidinediones, physicians may have been more cautious in prescribing them to high-risk patients, potentially introducing selection bias. Moreover, this study included only the Korean population. Although we adjusted for multiple covariates and performed sensitivity analyses between thiazolidinedione users and nonusers, owing to the limitations of this retrospective observational study, a randomized study is needed to confirm the effect of thiazolidinediones after carotid revascularization.

In conclusion, thiazolidinedione treatment after carotid revascularization was associated with fewer subsequent cardiovascular events in patients with T2D. Thus, thiazolidinediones may provide a novel approach for the prevention and treatment of carotid artery stenosis in patients with T2D.

ARTICLE INFORMATION

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Supplemental Material

Figure S1
Tables S1–S2
Data S1

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