Observational Study

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# Effect of antidiabetic medication adherence on risk of all-cause mortality and cardiovascular diseases in type 2 diabetes patients

## Impact of antidiabetic adherence on cardiovascular disease

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**Abstract**

This retrospective cohort study aims to examine the association between adherence to thiazolidinedione (TZD) therapy and the risk of all-cause mortality and cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus, compared with utilization of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas (SUs), using real-world national data from the Korean National Health Insurance Service (2009–2018). Two matched cohorts were established: TZDs versus DPP-4 inhibitors (n = 7875) and TZDs versus SUs (n = 5837). Adherence was measured using the proportion of days covered during the first year, with high adherence defined as proportion of days covered ≥0.8. Outcomes included myocardial infarction, stroke, CV death, hospitalization for heart failure, major adverse CV events, and all-cause mortality. Cox proportional hazards models were applied using intention-to-treat and adherence-stratified analyses. At 12 months, DPP-4 inhibitor users demonstrated higher adherence and persistence compared to the TZD users, whereas adherence was comparable between TZD and SU users. In cohort 1, TZD therapy was associated with increased risks of stroke (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.01–1.23) and all-cause mortality (HR 1.10, 95% CI: 1.01–1.20) compared with DPP-4 inhibitors. In cohort 2, TZDs were associated with lower risks of myocardial infarction (HR 0.80, 95% CI: 0.65–0.99), major adverse CV events (HR 0.85, 95% CI: 0.76–0.95), hospitalization for heart failure (HR 0.86, 95% CI: 0.75–1.00), and all-cause mortality (HR 0.83, 95% CI: 0.74–0.93) compared with SUs. High adherence to TZDs was consistently associated with more favorable CV and survival outcomes, in comparison to SUs. In this nationwide cohort, TZD therapy, especially with high adherence, reduced CV risk and mortality compared with SUs and DPP-4 inhibitors, highlighting the importance of sustained TZD adherence for optimal long-term outcomes in routine clinical practice.

**Abbreviations:** CI = confidence interval, CV = cardiovascular, DPP-4 = dipeptidyl peptidase-4, HHF = hospitalization for heart failure, HR = hazard ratio, ICD-10 = International Classification of Diseases, 10th revision, MACE = major adverse cardiovascular events, MI = myocardial infarction, NHIS = National Health Insurance Service, PDC = proportion of days covered, SU = sulfonylurea, T2DM = type 2 diabetes mellitus, TZD = thiazolidinedione.

**Keywords:** adherence, antidiabetic medications, cardiovascular disease, mortality, type 2 diabetes

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder requiring multiple pharmacotherapies to manage the disease and associated complications.[1] It is associated with significant morbidity and mortality, primarily due to cardiovascular (CV) complications.[2] Effective T2DM management requires a multifaceted approach, including lifestyle modifications and pharmacological interventions, which often involve polypharmacy.[3,4] However, the success of these interventions is heavily dependent on adherence to prescribed medications, which can be complicated by the challenges associated with polypharmacy.[4]

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*The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.*

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Adherence to antidiabetic therapy is a key determinant of clinical outcomes. Large cohort studies and systematic reviews have consistently shown that higher adherence to glucose-lowering therapy is associated with better glycemic control, lower rates of microvascular and macrovascular complications, reduced hospitalizations, and lower all-cause mortality, whereas suboptimal adherence is common and linked to adverse outcomes and increased healthcare utilization.[3,5] Despite the well-established benefits of antidiabetic medications in T2DM, suboptimal adherence continues. Studies have shown that adherence rates to antidiabetic medications vary widely, ranging from 9.4% to 84.3% across different populations and treatment regimens.[6-8] Poor medication adherence can lead to suboptimal glycemic control, increased risk of complications, and higher mortality rates.[2] Moreover, suboptimal adherence is associated with higher healthcare utilization and costs, as well as reduced patient quality-of-life.[3]

Recent research has highlighted the importance of medication adherence in reducing major adverse cardiovascular events (MACE) and all-cause mortality in T2DM patients. A systematic review found better adherence to antidiabetic medications to be associated with lower rates of hospitalization and CV events.[3,9] Another study demonstrated that persistent adherence to antidiabetic medications and lifestyle recommendations significantly reduces the risk of MACE and mortality in patients with advanced atherosclerosis and T2DM.[2] Despite the recognized importance of medication adherence in the management of CV outcomes in patients with T2DM, few studies have examined how adherence to specific antidiabetic drug classes influences long-term CV outcomes and mortality, which warrants further investigation.

Thiazolidinediones (TZDs), specifically pioglitazone and rosiglitazone, are widely used in the management of T2DM, offering insulin-sensitizing effects. However, there are differential CV risks between these agents that warrant careful consideration. Pioglitazone, as evidenced by recent studies, has a more favorable CV profile, reducing the risk of stroke and myocardial infarction (MI).[10] In contrast, rosiglitazone has been associated with an increased risk of heart failure and other adverse CV events.[10] These heterogeneous findings underscore the need to better understand the real-world effectiveness and safety of TZDs, particularly in relation to medication adherence. Given that real-world adherence to TZDs varies substantially and may modify both therapeutic benefit and risk, adherence-stratified evaluations are essential for accurately interpreting their CV effects in routine clinical practice.[5]

Despite the growing literature on medication adherence in T2DM, relatively few studies have specifically examined the impact of adherence to individual antidiabetic drug classes, such as TZDs, on long-term CV outcomes and mortality, particularly in comparison with other commonly used agents like dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas (SUs). In addition, most prior work has focused on overall adherence rather than on class-specific adherence patterns. To address this gap, the present study used nationwide claims data from the Korean National Health Insurance Service (NHIS) to compare adherence and persistence with TZDs versus DPP-4 inhibitors and TZDs versus SUs, and to evaluate the association between adherence to these agents and risks of major CV events and all-cause mortality in patients with T2DM. Understanding this correlation is crucial for developing targeted interventions to improve adherence and, ultimately, patient outcomes in T2DM management.

## 2. Materials and methods

### 2.1. Data sources

We used patient data from the Korean NHIS database, which covers data from 98% of the population between January 2009 to December 2018.[11,12] A broad spectrum of variables was included in this database: sex, socioeconomic status, medical care history, medical care institutions, diagnosis code, surgery code, drug prescription name and dose, and date of prescription.

### 2.2. Study subjects

From the Korean NHIS database, we identified adults aged ≥20 years with at least 1 diagnosis of type 2 diabetes (International Classification of Diseases, 10th revision [ICD-10] codes E11–E14) who were newly prescribed TZDs, DPP-4 inhibitors, or SUs between January 1, 2009 and December 31, 2018. Patients with type 1 diabetes (ICD-10 code E10) or any prior prescription for the study drugs in the preceding year were excluded. After applying these criteria, 10,066 TZD initiators and 49,013 DPP-4 inhibitor initiators were eligible for cohort 1, while 5903 TZD initiators and 54,224 SU initiators were eligible for cohort 2. Following 1:1 propensity score matching, 7875 participants were retained in each arm of cohort 1 and 5837 in each arm of cohort 2. The index date was defined as the first prescription date for the respective study drugs (Fig. 1A, B). The distribution of individual agents within each class is presented in Table S1, Supplemental Digital Content, https://links.lww.com/MD/R539. In cohort 1, the majority of TZD users were on pioglitazone (80.9%), with rosiglitazone (11.1%) and lobeglitazone (8.0%) also used. In the DPP-4 inhibitor group, sitagliptin was the most common (50.8%). In cohort 2, pioglitazone (71.1%) was the most widely used TZD, while glimepiride was the dominant SU (84.9%). The study protocol was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-EXP-2019-517), which waived the requirement for informed consent due to the use of anonymized administrative data.

### 2.3. Outcomes

The primary outcomes of this study were medication adherence and persistence with TZD versus DPP-4 inhibitors and TZD versus SU at 12 months following the index date. The medication adherence was evaluated using proportion of days covered (PDC).[13] One-year PDC was calculated from the patients' prescription record, which contains information regarding the duration of a prescription (sum of total prescription days) of oral hypoglycemic agents.[14,15] Participants without at least 2 outpatient visits, which are essential for calculating the PDC, and those who were hospitalized for >90 days were excluded from the analysis.

Persistence was calculated as the number of days between the index date and the last day with the index medication on hand, based on the end of the last day of supply or the end of follow-up (i.e., 365 days), whichever occurred first. Discontinuation was defined as the absence of a subsequent prescription within a grace period of twice the number of days to the most recent prescription. Patients who used continuous medication for 365 days, allowing for permissible gaps, were considered persistent.

In addition to these primary outcomes, CV outcomes were observed during the follow-up. The CV outcomes of interest were all-cause mortality, CV mortality, hospitalization for heart failure (HHF; ICD-10 code I50), hospitalization with diagnosis of MI (ICD-10 codes I21 and I22), and stroke (ICD-10 codes I60-64). MACE was defined as the composite of MI, stroke, or CV mortality. All-cause mortality was defined by the death status in the NHIS database, which was linked to the National Death Registry using unique resident registration numbers. Each patient was followed up from the index date until the earliest occurrence of any study outcome, death, or the end of the study period (December 31, 2019).

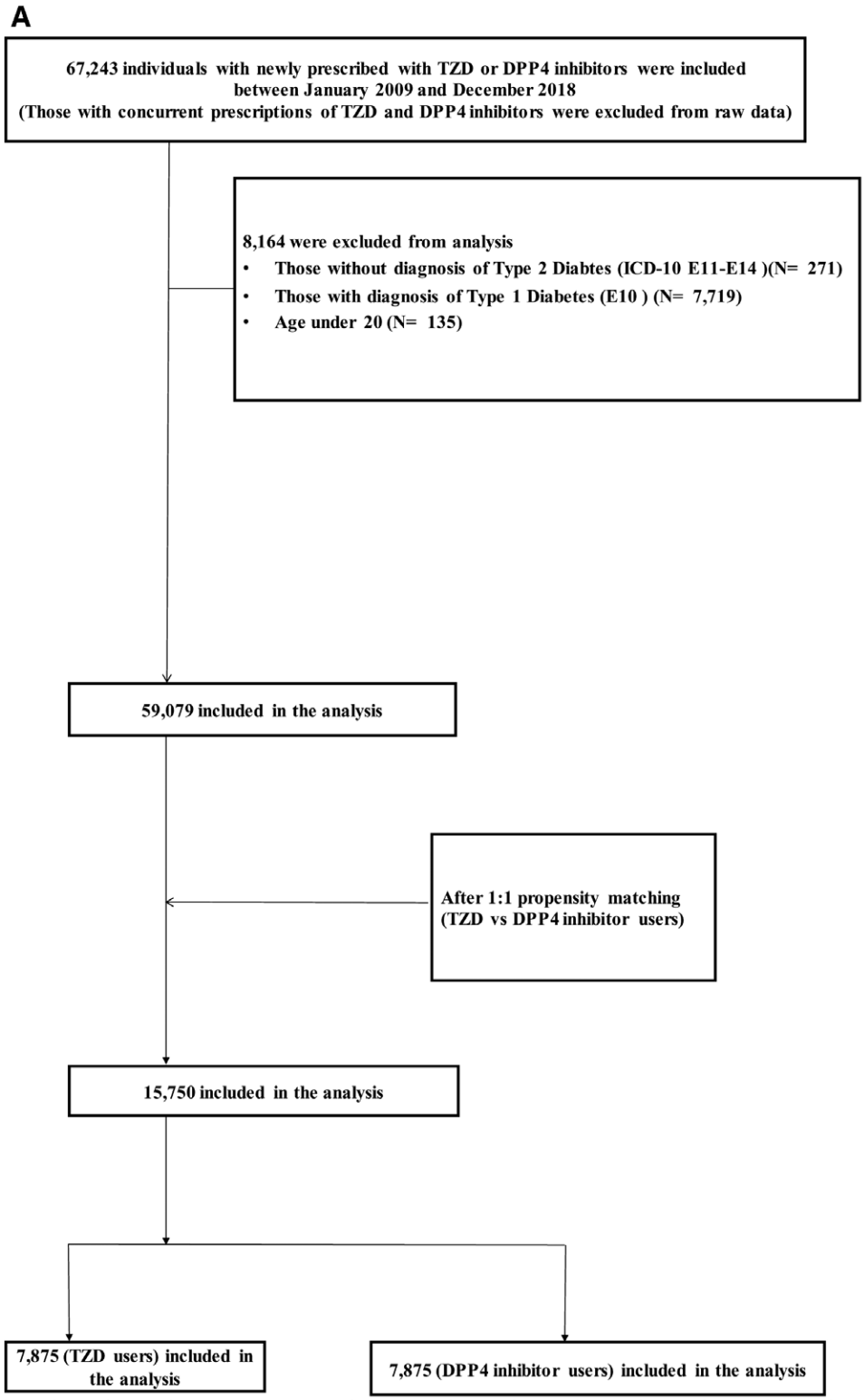


Figure 1. (A) Flow diagram for cohort 1. (B) Flow diagram for cohort 2. DPP-4 = dipeptidyl peptidase-4, ICD-10 = International Classification of Diseases, 10th revision, SU = sulfonylurea, TZD = thiazolidinedione.

### 2.4. Statistical analysis

Categorical variables were described using frequencies and percentages, and continuous variables were described using mean ± standard deviation values. The propensity scores were matched in a 1:1 ratio using a caliper width equal to 0.25 of the standard deviation of the logits 20. The following potential risk factors related to the outcome and confounding variables associated with both treatment status (TZDs, DPP-4 inhibitors, or SUs) and outcome were included as propensity score covariates: age, sex, index year, household income, duration of diabetes, diabetic complications, other comorbidities, use of other glucose-lowering drugs, and use of other drugs. Before and after propensity score matching, the covariate balance was calculated as standardized differences; moreover, significant

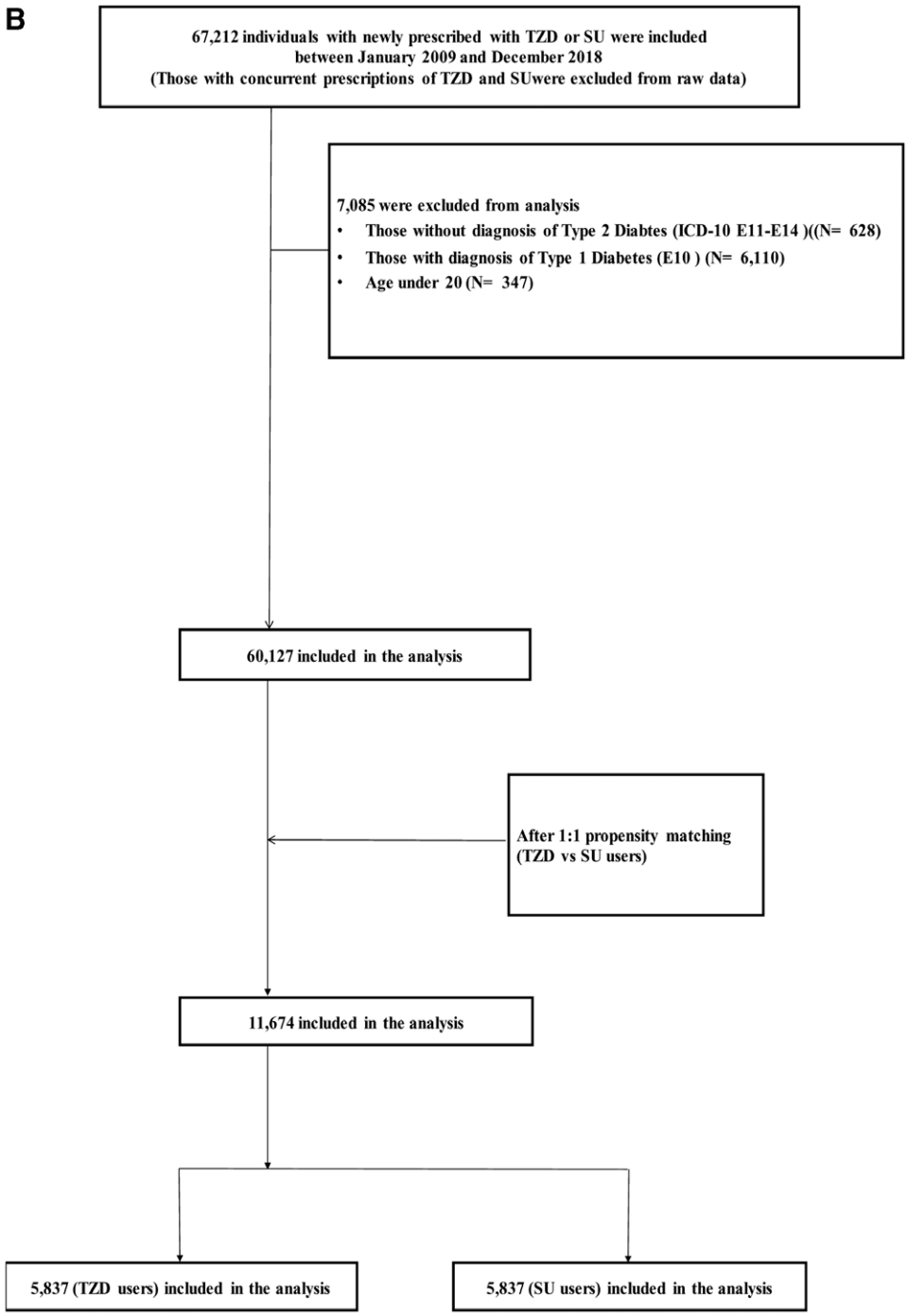


**Figure 1.** Continued

imbalances were defined as standardized differences of ≥10%.[16] Only the first occurrence of each outcome was included, and the crude incidence rate in each group was calculated as the number of incidence events divided by the total number of 100 person-years at risk. The time to the first event for TZDs versus DPP-4 inhibitors and TZD versus SUs was assessed using Kaplan–Meier plots and the log-rank test. Cox proportional hazard models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) values for each outcome. The primary analysis used an intention-to-treat approach, wherein all individuals were followed from the index date until the outcome of interest, death, or end of the study period, whichever occurred first. Analyses of all outcomes were then repeated in patient subgroups and stratified by adherence to examine whether the associations of TZDs and DPP-4 inhibitors, or TZDs and SUs, with CV outcomes differed. To test the stability of the findings, a sensitivity analysis using an as-treated approach was performed, wherein follow-up was censored at the discontinuation of the index treatment, outcome of interest, or death, whichever occurred first. All analyses were performed using Statistical Analysis System software (ver. 9.4, SAS Institute Inc., Cary), and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### *3.1. Study population*

The current study included a total of 1,19,206 patients: for cohort 1, there were 10,066 and 49,013 patients in the TZD and

DPP-4 inhibitor group, respectively, and for cohort 2, there were 5903 and 54,224 patients in the TZD and SU group, respectively (Fig. 1). In cohort 1, patients initiated on DPP-4 inhibitor had a shorter duration of diabetes (<3 years), lower rates of diabetic neuropathy, higher rates of hyperlipidemia, and similar rates of CV comorbidities prior to propensity matching. Usage of angiotensin-converting enzyme inhibitors, calcium channel blockers, and statins was more prevalent in the DPP-4 inhibitor group (Table S2, Supplemental Digital Content, https://links.lww.com/MD/R539). In cohort 2, patients initiated on SU were older and had lower rates of diabetic nephropathy, lower rates of hyperlipidemia, and similar rates of CV comorbidities. Usage of lipid-lowering drugs, including statins, was also lower in the SU group.

After propensity score matching, the study included 7875 and 5837 participants per group in cohort 1 (TZD vs DPP-4 inhibitors) and 2 (TZD vs SUs), respectively, with well-balanced baseline characteristics (Table 1). The mean age of cohort 1 was 59 years, and 44% of the patients were women. Approximately half had diabetes for ≥6 years, with 15%, 25%, and 10% having retinopathy, neuropathy, and nephropathy, respectively. Hypertension (61%) and hyperlipidemia (71%) were highly prevalent. Metformin (81%) and insulin (15%) were frequently prescribed along with statins (49%) and antiplatelet therapy (47%). In cohort 2, the mean age was 58 years (41% women). Approximately 40% had diabetes for ≥6 years, with 14%, 20%, and 11% having retinopathy, neuropathy, and nephropathy, respectively. Hypertension (58%) and hyperlipidemia (72%) were highly prevalent, while ischemic heart disease (14%), prior stroke (6%), and heart failure (3%) occurred less often. Concomitant therapies utilized metformin (74%), insulin (13%), statins (53%), and antiplatelet agents (42%).

### 3.2. Adherence and persistence

In cohort 1, at 12 months of follow-up, significant differences in adherence and persistence were observed between the TZD and DPP-4 inhibitor users (Table 2). Additionally, users of DPP-4 inhibitors demonstrated higher adherence than TZD users, which was reflected by a greater mean PDC (0.65 vs 0.58, $P < .001$) and a larger proportion achieving a PDC ≥ 0.8 (48.2% vs 39.8%, $P < .001$). Persistence was also longer for DPP-4 inhibitors, with an average of 232.6 days versus 216.1 days for TZDs ($P < .001$), and the risk of discontinuation was significantly higher among TZD users (HR 1.16, 95% CI: 1.11–1.20). In contrast, in cohort 2, the mean PDC values were slightly higher in SU users than in TZD users (0.63 vs 0.61, $P < .001$), but no significant differences were noted in persistence duration or discontinuation risk.

### 3.3. Cardiovascular outcomes

With respect to CV outcomes, TZD therapy demonstrated contrasting risk patterns depending on the comparator drug class (Tables 3 and 4). In cohort 1, compared with DPP-4 inhibitors, TZDs were associated with higher risks of stroke (HR 1.14, 95% CI: 1.01–1.23), CV death (HR 1.21, 95% CI: 1.00–1.45), and all-cause mortality (HR 1.10, 95% CI: 1.01–1.20), while risks of MI, MACE, and HHF were similar. Contrastingly, in cohort 2, TZDs were generally more favorable than SUs, with reduced risks of MI (HR 0.80, 95% CI: 0.65–0.99), MACE (HR 0.85, 95% CI: 0.76–0.95), HHF (HR 0.86, 95% CI: 0.75–1.00), and all-cause mortality (HR 0.83, 95% CI: 0.74–0.93), and no significant differences in risks of stroke or CV death. When outcomes were reexamined using the as-treated approach (Table S3, Supplemental Digital Content, https://links.lww.com/MD/R539), the direction of findings remained consistent, but HR generally attenuated toward nonsignificance.

Adherence-stratified analyses (Tables 5 and 6) demonstrated that the higher CV risks of TZDs relative to DPP-4 inhibitors in cohort 1 were attenuated among adherent patients (PDC ≥ 0.8), with HRs for all outcomes becoming nonsignificant. In cohort 2, adherence enhanced the cardioprotective associations of TZDs, in comparison with SUs, with significant reductions in risks of MI (HR 0.64; 95% CI: 0.45–0.93), stroke (HR 0.78; 95% CI: 0.64–0.97), CV death (HR 0.59; 95% CI: 0.40–0.88), MACE (HR 0.72; 95% CI: 0.60–0.86), and all-cause death (HR 0.74; 95% CI: 0.62–0.89) among adherent users (Fig. 2A, B). These findings underscore adherence as a key modifier of the comparative CV outcomes associated with TZD therapy.

## 4. Discussion

The present nationwide cohort study provides comprehensive evidence that adherence to antidiabetic medications, particularly TZDs, is associated with clinical outcomes among individuals with T2DM. Our findings highlight that patient adherence substantially influences the effectiveness of glucose-lowering therapies and long-term outcomes. Notably, compared to SU adherence, the adherence to TZDs was associated with favorable long-term outcomes, with a lower risk of CV events and mortality in individuals with T2DM. It also attenuated risks of stroke and CV death compared with DPP-4 inhibitors. Importantly, these results extend the previous evidence on the CV safety of TZDs by demonstrating that the degree of medication adherence significantly influences clinical outcomes. This highlights the need for improved strategies for long-term treatment persistence in the real world.

Medication adherence plays a pivotal role in determining long-term outcomes in individuals with T2DM, significantly influencing both all-cause mortality and the risk of macrovascular complications, such as CV disease. Numerous real-world studies and systematic reviews have demonstrated that individuals who consistently take their prescribed antidiabetic medications, achieving an adherence threshold of at least 80% of days covered, experience a 10% to 30% reduction of major CV events, such as MI, stroke, heart failure hospitalization, and all-cause mortality, compared to those with poor adherence.[3,8,9,17] This positive effect has been observed for various classes of antidiabetic drugs, especially sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and pioglitazone. Although TZDs – especially rosiglitazone – have remained a subject of considerable clinical interest, with respect to their impact on CV in patients with T2DM, accumulating evidence indicates otherwise. Pioglitazone exerts a neutral to modestly beneficial effect on MACE. A comprehensive meta-analysis of randomized controlled trials demonstrated that pioglitazone significantly reduced the risk of MACE by 14% and nonfatal stroke by 23% compared to regimens not including pioglitazone (odds ratio MACE: 0.86, 95% CI: 0.75–0.98; odds ratio for stroke: 0.77, 95% CI: 0.60–0.99).[10,18] Moreover, treatment with TZDs following carotid artery procedures was associated with a reduced incidence of stroke, MI, and mortality in patients with T2DM.[19] The excess stroke risk observed with TZDs in this study (cohort 1) may reflect lower adherence, residual rosiglitazone exposure, and the inclusion of an older real-world population with longer diabetes duration and greater comorbidity burden than typical trial cohorts.

Despite these benefits, real-world adherence rates are often suboptimal and decline over time. Studies employing prescription claims data often identify that approximately 50% to 60% of patients are adherent.[3,5,9,20] Moreover, comparative real-world studies have highlighted significant variability in adherence and persistence across antidiabetic medication classes. While adherence rates are generally the highest for metformin, TZDs have demonstrated comparable or slightly better adherence than SUs, though somewhat

**Table 1**

**Baseline characteristics of study participants after PSM.**

| | Cohort 1 | | | | | Cohort 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TZDs (N = 7875) | | DPP-4 inhibitors (N = 7875) | | SMD | TZDs (N = 5837) | | SUs (N = 5837) | | SMD |
| Mean (SD) age | 59.3 | (12.4) | 59.4 | (12.3) | 0.01 | 57.6 | (12.3) | 57.8 | (12.3) | 0.01 |
| Women | 3474 | (44.1) | 3511 | (44.6) | 0.01 | 2419 | (41.4) | 2465 | (42.2) | 0.02 |
| Index yr | | | | | | | | | | |
| 2009 | 2884 | (36.6) | 2621 | (33.3) | 0.07 | 2545 | (43.6) | 2573 | (44.1) | 0.01 |
| 2010 | 1271 | (16.1) | 1132 | (14.4) | 0.05 | 326 | (5.6) | 306 | (5.2) | 0.02 |
| 2011 | 657 | (8.3) | 646 | (8.2) | 0.01 | 166 | (2.8) | 179 | (3.1) | 0.01 |
| 2012 | 521 | (6.6) | 545 | (6.9) | 0.01 | 169 | (2.9) | 176 | (3.0) | 0.01 |
| 2013 | 488 | (6.2) | 570 | (7.2) | 0.04 | 196 | (3.4) | 190 | (3.3) | 0.01 |
| 2014 | 540 | (6.9) | 553 | (7.0) | 0.01 | 363 | (6.2) | 344 | (5.9) | 0.01 |
| 2015 | 494 | (6.3) | 529 | (6.7) | 0.02 | 448 | (7.7) | 449 | (7.7) | 0.00 |
| 2016 | 391 | (5.0) | 451 | (5.7) | 0.03 | 510 | (8.7) | 500 | (8.6) | 0.01 |
| 2017 | 315 | (4.0) | 440 | (5.6) | 0.07 | 536 | (9.2) | 554 | (9.5) | 0.01 |
| 2018 | 314 | (4.0) | 388 | (4.9) | 0.05 | 578 | (9.9) | 566 | (9.7) | 0.01 |
| Household income | | | | | | | | | | |
| Low | 1615 | (20.5) | 1615 | (20.5) | 0.00 | 1274 | (21.8) | 1269 | (21.7) | 0.00 |
| Intermediate | 2463 | (31.3) | 2428 | (30.8) | 0.01 | 1871 | (32.1) | 1943 | (33.3) | 0.03 |
| High | 3024 | (38.4) | 3059 | (38.8) | 0.01 | 2354 | (40.3) | 2287 | (39.2) | 0.02 |
| Missing | 773 | (9.8) | 773 | (9.8) | 0.00 | 338 | (5.8) | 338 | (5.8) | 0.00 |
| Duration of diabetes, yr | | | | | | | | | | |
| <3 | 2109 | (26.8) | 2134 | (27.1) | 0.01 | 1965 | (33.7) | 2015 | (34.5) | 0.02 |
| 3–5 | 1831 | (23.3) | 1750 | (22.2) | 0.02 | 1501 | (25.7) | 1461 | (25.0) | 0.02 |
| ≥6 | 3935 | (50.0) | 3991 | (50.7) | 0.01 | 2371 | (40.6) | 2361 | (40.4) | 0.00 |
| Diabetes complications | | | | | | | | | | |
| Diabetic retinopathy | 1217 | (15.5) | 1203 | (15.3) | 0.00 | 826 | (14.2) | 840 | (14.4) | 0.01 |
| Diabetic neuropathy | 1947 | (24.7) | 1833 | (23.3) | 0.03 | 1154 | (19.8) | 1139 | (19.5) | 0.01 |
| Diabetic nephropathy | 771 | (9.8) | 780 | (9.9) | 0.00 | 630 | (10.8) | 625 | (10.7) | 0.00 |
| Hypoglycemia | 112 | (1.4) | 111 | (1.4) | 0.00 | 43 | (0.7) | 46 | (0.8) | 0.01 |
| Diabetic ketoacidosis | 23 | (0.3) | 21 | (0.3) | 0.00 | 22 | (0.4) | 22 | (0.4) | 0.00 |
| Hyperosmolar hyperglycemic nonketotic syndrome | 78 | (1.0) | 71 | (0.9) | 0.01 | 40 | (0.7) | 33 | (0.6) | 0.02 |
| Diabetes with peripheral circulatory disorders | 47 | (0.6) | 58 | (0.7) | 0.02 | 37 | (0.6) | 35 | (0.6) | 0.00 |
| Lower extremity amputation | 8 | (0.1) | 10 | (0.1) | 0.01 | 2 | (0.0) | 2 | (0.0) | 0.00 |
| Other comorbidities | | | | | | | | | | |
| Hypertension | 4831 | (61.3) | 4859 | (61.7) | 0.01 | 3369 | (57.7) | 3396 | (58.2) | 0.01 |
| Hyperlipidemia | 5485 | (69.7) | 5575 | (70.8) | 0.02 | 4273 | (73.2) | 4172 | (71.5) | 0.04 |
| Ischemic heart disease | 1295 | (16.4) | 1316 | (16.7) | 0.01 | 825 | (14.1) | 804 | (13.8) | 0.01 |
| Stable angina | 252 | (3.2) | 263 | (3.3) | 0.01 | 170 | (2.9) | 161 | (2.8) | 0.01 |
| Previous cardiac procedure (CABG or PTCA or Stent) | 67 | (0.9) | 99 | (1.3) | 0.04 | 38 | (0.7) | 44 | (0.8) | 0.01 |
| Ischemic stroke | 524 | (6.7) | 506 | (6.4) | 0.01 | 333 | (5.7) | 347 | (5.9) | 0.01 |
| Hemorrhagic stroke | 48 | (0.6) | 53 | (0.7) | 0.01 | 31 | (0.5) | 41 | (0.7) | 0.02 |
| TIA | 185 | (2.3) | 186 | (2.4) | 0.00 | 119 | (2.0) | 116 | (2.0) | 0.00 |
| Congestive Heart failure | 271 | (3.4) | 270 | (3.4) | 0.00 | 165 | (2.8) | 182 | (3.1) | 0.02 |
| Peripheral vascular disease or surgery | 5 | (0.1) | 9 | (0.1) | 0.02 | 3 | (0.1) | 5 | (0.1) | 0.01 |
| Atrial fibrillation | 119 | (1.5) | 133 | (1.7) | 0.01 | 77 | (1.3) | 107 | (1.8) | 0.04 |
| Chronic kidney disease | 158 | (2.0) | 126 | (1.6) | 0.03 | 105 | (1.8) | 112 | (1.9) | 0.01 |
| Chronic kidney disease stage 3–4 | 17 | (0.2) | 16 | (0.2) | 0.00 | 16 | (0.3) | 19 | (0.3) | 0.01 |
| Liver disease | 3285 | (41.7) | 3329 | (42.3) | 0.01 | 2438 | (41.8) | 2409 | (41.3) | 0.01 |
| Use of antidiabetic drugs | | | | | | | | | | |
| Metformin | 6370 | (80.9) | 6535 | (83.0) | 0.05 | 4297 | (73.6) | 4294 | (73.6) | 0.00 |
| Sulfonylureas 2nd generation | 5177 | (65.7) | 4902 | (62.2) | 0.07 | | | | | |
| Dipeptidyl peptidase-4 inhibitors | | | | | | 1651 | (28.3) | 1620 | (27.8) | 0.01 |
| GLP-1 receptor agonists | 2 | (0.0) | 1 | (0.0) | 0.01 | 2 | (0.0) | 1 | (0.0) | 0.01 |
| Meglitinides | 330 | (4.2) | 333 | (4.2) | 0.00 | 169 | (2.9) | 160 | (2.7) | 0.01 |
| Insulin | 1215 | (15.4) | 1233 | (15.7) | 0.01 | 782 | (13.4) | 769 | (13.2) | 0.01 |
| α-Glucosidase inhibitors | 1523 | (19.3) | 1356 | (17.2) | 0.05 | 417 | (7.1) | 407 | (7.0) | 0.01 |
| Sodium-glucose cotransporter-2 inhibitors | 46 | (0.6) | 42 | (0.5) | 0.01 | 69 | (1.2) | 75 | (1.3) | 0.01 |
| Use of other drugs | | | | | | | | | | |
| ACE inhibitor | 525 | (6.7) | 472 | (6.0) | 0.03 | 316 | (5.4) | 336 | (5.8) | 0.01 |
| ARB | 3168 | (40.2) | 3166 | (40.2) | 0.00 | 2113 | (36.2) | 2092 | (35.8) | 0.01 |
| β-Blocker | 1150 | (14.6) | 1161 | (14.7) | 0.00 | 718 | (12.3) | 745 | (12.8) | 0.01 |
| Calcium channel blocker | 2262 | (28.7) | 2174 | (27.6) | 0.02 | 1375 | (23.6) | 1412 | (24.2) | 0.01 |
| Thiazides | 922 | (11.7) | 898 | (11.4) | 0.01 | 581 | (10.0) | 586 | (10.0) | 0.00 |
| Loop diuretics | 575 | (7.3) | 567 | (7.2) | 0.00 | 319 | (5.5) | 352 | (6.0) | 0.02 |
| Statin | 3833 | (48.7) | 3890 | (49.4) | 0.01 | 3103 | (53.2) | 3058 | (52.4) | 0.02 |
| Other lipid-lowering drugs, excluding statins | 876 | (11.1) | 890 | (11.3) | 0.01 | 694 | (11.9) | 679 | (11.6) | 0.01 |
| Antiplatelet | 3687 | (46.8) | 3634 | (46.1) | 0.01 | 2448 | (41.9) | 2455 | (42.1) | 0.00 |
| Anticoagulants | 81 | (1.0) | 98 | (1.2) | 0.02 | 56 | (1.0) | 71 | (1.2) | 0.02 |

DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, PSM = propensity score matching, SMD = standardized mean difference, SU = sulfonylurea, TZD = thiazolidinedione.

**Table 2**

**Adherence and persistence at 12-month follow-up.**

| | Cohort 1 | | | Cohort 2 | | |
|---|---|---|---|---|---|---|
| | TZDs (N = 7875) | DPP-4 inhibitors (N = 7875) | *P* value | TZDs (N = 5837) | SUs (N = 5837) | *P* value |
| Adherence | | | | | | |
| PDC, mean ± SD | 0.58 ± 0.34 | 0.65 ± 0.32 | <.001 | 0.61 ± 0.33 | 0.63 ± 0.32 | <.001 |
| PDC ≥ 0.8, n (%) | 3135 (39.8) | 3798 (48.2) | <.001 | 2023 (34.7) | 2044 (35.0) | .698 |
| Persistence | | | | | | |
| Days of persistence, mean ± SD | 216.1 ± 134.1 | 232.6 ± 134.1 | <.001 | 228.6 ± 133.2 | 225.4 ± 135.5 | .197 |
| HR (95% CI) for discontinuation | 1.16 (1.11–1.20) | 1.00 (Reference) | <.001 | 0.99 (0.95–1.04) | 1.00 (Reference) | .721 |

DPP-4 = dipeptidyl peptidase-4, HR = hazard ratio, PDC = proportion of days covered, SD = standard deviation, SU = sulfonylurea, TZD = thiazolidinedione.

**Table 3**

**Risk of cardiovascular outcomes and mortality for cohort 1.**

| | TZDs (N = 7875) | | | DPP-4 inhibitors (N = 7875) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total follow-up (yr) | Number of events | Event rate (100 PY) | Total follow-up (yr) | Number of events | Event rate (100 PY) | HR (95% CI) | *P* value |
| MI | 58,135 | 270 | 0.46 | 55,801 | 255 | 0.46 | 1.02 (0.86–1.21) | .848 |
| Stroke | 56,046 | 850 | 1.52 | 54,133 | 741 | 1.37 | 1.14 (1.01–1.23) | .032 |
| CV death | 59,080 | 255 | 0.43 | 56,680 | 200 | 0.35 | 1.21 (1.00–1.45) | .048 |
| MACE | 55,349 | 1113 | 2.01 | 53,409 | 1021 | 1.91 | 1.06 (0.97–1.15) | .206 |
| HHF | 57,377 | 617 | 1.08 | 55,129 | 602 | 1.09 | 0.97 (0.87–1.09) | .660 |
| All-cause death | 59,080 | 1137 | 1.92 | 56,680 | 981 | 1.73 | 1.10 (1.01–1.20) | .027 |

CI = confidence interval, CV = cardiovascular, DPP-4 = dipeptidyl peptidase-4, HHF = hospitalization for heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, MI = myocardial infarction, TZD = thiazolidinedione.

**Table 4**

**Risk of cardiovascular outcomes and mortality for cohort 2.**

| | TZDs (N = 5837) | | | SUs (N = 5837) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total follow-up (yr) | Number of events | Event rate (100 PY) | Total follow-up (yr) | Number of events | Event rate (100 PY) | HR (95% CI) | *P* value |
| MI | 39,610 | 149 | 0.38 | 39,222 | 184 | 0.47 | 0.80 (0.65–0.99) | .045 |
| Stroke | 38,613 | 447 | 1.16 | 38,077 | 496 | 1.30 | 0.89 (0.78–1.01) | .072 |
| CV death | 40,205 | 136 | 0.34 | 39,960 | 142 | 0.36 | 0.95 (0.75–1.20) | .669 |
| MACE | 38,129 | 593 | 1.56 | 37,526 | 687 | 1.83 | 0.85 (0.76–0.95) | .004 |
| HHF | 39,323 | 339 | 0.86 | 38,994 | 389 | 1.00 | 0.86 (0.75–1.00) | .047 |
| All-cause death | 40,205 | 567 | 1.41 | 39,960 | 676 | 1.69 | 0.83 (0.74–0.93) | .001 |

CI = confidence interval, CV = cardiovascular, HHF = hospitalization for heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, MI = myocardial infarction, SU = sulfonylurea, TZD = thiazolidinedione.

lower rates than DPP-4 inhibitors,[5,20] which is consistent with findings of our study. Persistence with TZDs, measured as the duration of continuous therapy or absence of major refill gaps, typically falls in the range of 46% to 76% at 1 year; it is similar to or modestly lower than that with DPP-4 inhibitors and higher than that with injectables, such as insulin or glucagon-like peptide-1 receptor agonists,[5,17,20] Adverse effects, patient demographics, medication complexity, and safety concerns affect adherence and persistence rates over time.[17] In this nationwide cohort study, TZD use, especially with good adherence, was associated with notably lower risks of MACE, MI, HHF, and all-cause mortality than SUs. However, the benefit of TZD therapy appears modest when compared to DPP-4 inhibitors, which may be due, in part, to the relatively short follow-up period in our cohort. A longer follow-up period is likely needed to fully capture the long-term benefits of TZDs on CV events and mortality.[21] While the risk of heart failure associated with TZDs remains a consideration, mandating clinical vigilance (especially in susceptible populations), real-world data provide important insights. These findings emphasize the need for tailored interventions to support long-term TZD use and maximize the clinical benefits of TZD treatment.

This study provides novel insights by demonstrating that medication adherence significantly modifies the CV effects of TZDs in routine practice. Although previous research has established general links between antidiabetic drug adherence and improved outcomes, few studies have evaluated adherence-stratified risks across specific drug classes. In our nationwide cohort, high adherence to TZDs was associated with substantially reduced risks of MI, stroke, CV death, and all-cause mortality compared to SUs, whereas low adherence attenuated these benefits. Notably, adherence mitigated the excess stroke and mortality risks observed when TZDs were compared with DPP-4 inhibitors. Collectively, these results demonstrate that adherence is not only a determinant of glycemic control, but also a critical modifier of comparative CV safety, thereby highlighting the need for adherence-focused strategies to optimize long-term outcomes in T2DM.

This study had several limitations. First, as with all observational analyses, residual confounding from unmeasured factors, such as lifestyle behaviors, socioeconomic conditions,

**Table 5**

**Risk of cardiovascular outcomes and mortality by adherence for cohort 1.**

| | TZDs | | | DPP-4 inhibitors | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total follow-up (yr) | Number of events | Event rate (100 PY) | Total follow-up (yr) | Number of events | Event rate (100 PY) | HR (95% CI) | *P* value |
| Adherence(+) | | | | | | | | |
| MI | 20,154 | 88 | 0.44 | 22,481 | 84 | 0.37 | 1.18 (0.87–1.59) | .279 |
| Stroke | 19,665 | 246 | 1.25 | 21,966 | 264 | 1.20 | 1.05 (0.88–1.25) | .610 |
| CV death | 20,473 | 77 | 0.38 | 22,729 | 78 | 0.34 | 1.08 (0.79–1.48) | .629 |
| MACE | 19,405 | 342 | 1.76 | 21,760 | 367 | 1.69 | 1.05 (0.91–1.22) | .488 |
| HHF | 19,965 | 199 | 1.00 | 22,244 | 210 | 0.94 | 1.03 (0.85–1.25) | .742 |
| All-cause death | 20,473 | 364 | 1.78 | 22,729 | 353 | 1.55 | 1.23 (0.97–1.30) | .113 |
| Adherence(–) | | | | | | | | |
| MI | 29,222 | 129 | 0.44 | 24,584 | 122 | 0.50 | 0.89 (0.69–1.13) | .338 |
| Stroke | 28,171 | 437 | 1.55 | 24,019 | 309 | 1.29 | 1.21 (1.05–1.40) | .011 |
| CV death | 29,548 | 137 | 0.46 | 24,982 | 93 | 0.37 | 1.24 (0.96–1.62) | .105 |
| MACE | 27,936 | 573 | 2.05 | 23,679 | 452 | 1.91 | 1.08 (0.95–1.22) | .247 |
| HHF | 28,796 | 312 | 1.08 | 24,296 | 283 | 1.16 | 0.93 (0.79–1.09) | .361 |
| All-cause death | 29,548 | 661 | 2.24 | 24,982 | 511 | 2.05 | 1.10 (0.98–1.23) | .125 |

CI = confidence interval, CV = cardiovascular, DPP-4 = dipeptidyl peptidase-4, HHF = hospitalization for heart failure, HR = hazard ratio, ITT = intent-to-treat, MACE = major adverse cardiovascular events, MI = myocardial infarction, TZD = thiazolidinedione.

**Table 6**

**Risk of cardiovascular outcomes and mortality by adherence for cohort 2.**

| | TZDs | | | SUs | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total follow-up (yr) | Number of events | Event rate (100 PY) | Total follow-up (yr) | Number of events | Event rate (100 PY) | HR (95% CI) | *P* value |
| Adherence(+) | | | | | | | | |
| MI | 14,804 | 45 | 0.30 | 16,909 | 79 | 0.47 | 0.64 (0.45–0.93) | .020 |
| Stroke | 14,507 | 149 | 1.03 | 16,528 | 216 | 1.31 | 0.78 (0.64–0.97) | .025 |
| CV death | 15,000 | 38 | 0.25 | 17,219 | 74 | 0.43 | 0.59 (0.40–0.88) | .009 |
| MACE | 14,328 | 197 | 1.37 | 16,283 | 312 | 1.92 | 0.72 (0.60–0.86) | <.001 |
| HHF | 14,728 | 144 | 0.98 | 16,869 | 156 | 0.92 | 0.84 (0.66–1.08) | .173 |
| All-cause death | 15,000 | 198 | 1.32 | 17,219 | 309 | 1.79 | 0.74 (0.62–0.89) | <.001 |
| Adherence(–) | | | | | | | | |
| MI | 18,549 | 67 | 0.36 | 15,918 | 73 | 0.46 | 0.78 (0.56–1.09) | .150 |
| Stroke | 18,107 | 200 | 1.10 | 15,564 | 179 | 1.15 | 0.96 (0.79–1.18) | .701 |
| CV death | 18,746 | 80 | 0.43 | 16,176 | 51 | 0.32 | 1.33 (0.94–1.89) | .110 |
| MACE | 17,933 | 277 | 1.54 | 15,370 | 256 | 1.67 | 0.93 (0.78–1.10) | .393 |
| HHF | 18,330 | 167 | 0.91 | 15,770 | 164 | 1.04 | 0.86 (0.70–1.07) | .185 |
| All-cause death | 18,746 | 312 | 1.66 | 16,176 | 312 | 1.93 | 0.86 (0.73–1.00) | .056 |

CI = confidence interval, CV = cardiovascular, HHF = hospitalization for heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, MI = myocardial infarction, SU = sulfonylurea, TZD = thiazolidinedione.

and patient beliefs, cannot be fully excluded. Adherence was estimated using prescription refill information, which does not confirm actual medication ingestion or account for precise dosing. The study relied on administrative diagnostic codes, introducing the potential for disease misclassification, although the Korean registry validations suggest reasonable accuracy. Additionally, limited clinical details (e.g., glycemic control, renal function, and laboratory values) restrict the adjustment for some relevant biological confounders, which are crucial for directly assessing the effects of the studied agents on glycemic control and the findings may not be generalizable to countries with different healthcare structures or patient populations. Finally, TZDs, SUs, and DPP-4 inhibitors were primarily used as add-on therapies in most patients, and the complexity of polypharmacy may introduce residual confounding, making it difficult to isolate the effects of individual glucose-lowering agents. While we employed propensity score matching to balance baseline characteristics and medication use, this remains a limitation. Despite these limitations, a large-scale population-based approach and a consistent analytical methodology enhance the reliability and relevance of the results.

## 5. Conclusion

In this nationwide cohort study, higher adherence to TZD therapy was associated with more favorable CV outcomes and lower all-cause mortality compared with SU, whereas comparisons with DPP-4 inhibitors yielded mixed results. Although these findings suggest a potential benefit of sustained TZD adherence in routine clinical practice, they should be interpreted cautiously given the retrospective study design and acknowledged limitations. Nonetheless, as optimal diabetes management requires pharmacological therapy alongside lifestyle modification, strategies to improve long-term medication adherence may contribute to meaningful reductions in major adverse CV events and all-cause mortality in individuals with T2DM.

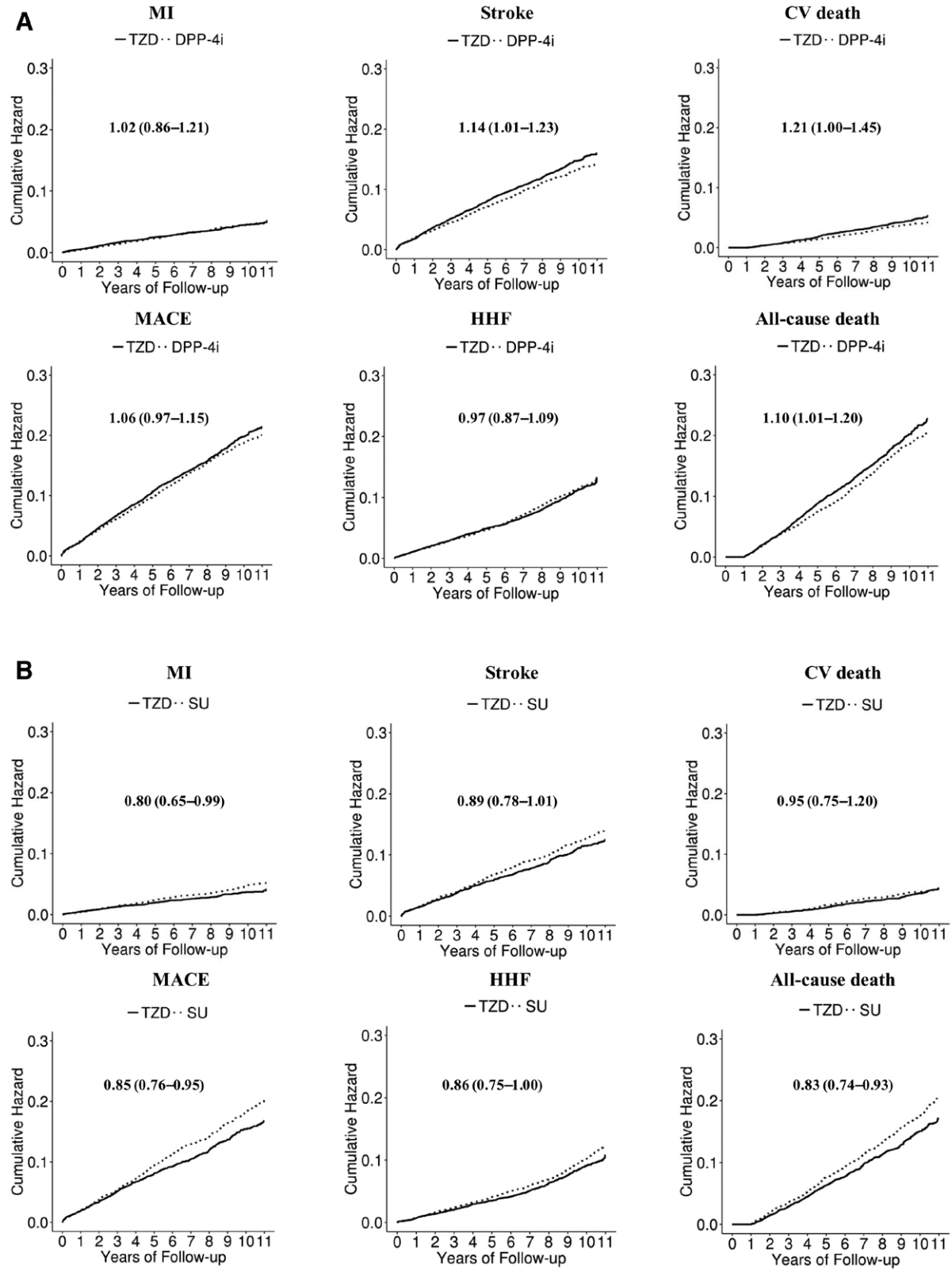


Figure 2. (A) Comparison of cumulative incidence for all cardiovascular outcomes in cohort 1. (B) Comparison of cumulative incidence for all cardiovascular outcomes in cohort. DPP-4 = dipeptidyl peptidase-4, SU = sulfonylurea, TZD = thiazolidinedione.

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