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Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: A time-updated propensity analysis

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Abstract

Purpose—To investigate the association of the thiazolidinediones (TZDs), rosiglitazone and pioglitazone, together and individually on the risk of cardiovascular outcomes and all-cause mortality, using time-updated propensity score adjusted analysis

Methods—We conducted a retrospective cohort study in a large vertically integrated health system in southeast Michigan. Cohort inclusion criteria included adult patients with diabetes treated with oral medications and followed longitudinally within the health system between January 1, 2000 and December 1, 2006. The primary outcome was fatal and non-fatal acute myocardial infarction. Secondary outcomes included hospitalizations for congestive heart failure, fatal and non-fatal cerebrovascular accidents and transient ischemic attacks, combined coronary heart disease events, and all-cause mortality.

Results—19,171 patients were included in this study. Use of TZDs (adjusted hazard ratio [aHR] with propensity adjustment [PA], 0.92; 95% confidence interval [CI] 0.73–1.17), rosiglitazone (aHR with PA, 1.06; 95% CI 0.66–1.70), and pioglitazone (aHR with PA, 0.91; 95% CI 0.69–1.21) was not associated with a higher risk of acute myocardial infarction. However, pioglitazone use was associated with a reduction in all-cause mortality (aHR with PA, 0.60; 95% CI 0.42–0.96). Compared with rosiglitazone, pioglitazone use was associated with a lower risk of all outcomes assessed, particularly congestive heart failure ($P = 0.013$) and combined coronary heart disease events ($P = 0.048$).

Conclusions—Our findings suggest that pioglitazone may have a more favorable risk profile when compared to rosiglitazone, arguing against a singular effect for TZDs on cardiovascular outcomes.

Keywords

Thiazolidinediones; Coronary Heart Disease; Congestive Heart Failure; Cerebrovascular Accident; Mortality

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INTRODUCTION

Rosiglitazone was approved by the FDA in 1999 for treatment of type 2 diabetes mellitus.¹ Troglitazone, an earlier drug in the same class was removed from the U.S. market in 2000 for liver toxicity.² However, the safety of rosiglitazone and of thiazolidinediones (TZDs) as a class for potentially increasing the risk of acute myocardial infarction (AMI) has just recently garnered widespread attention following a meta-analysis by Nissen and Wolski.^{3;4}

Reaction has been mixed,⁵ reflecting in part uncertainty in the evidence.^{6–9} A more recent meta-analysis by Singh et al. also showed a similar increased risk of AMI.¹⁰ However, interim analysis of a randomized trial designed to assess cardiovascular outcomes in diabetic patients on rosiglitazone did not show an increased risk of acute MI,^{11;12} and data from large observational studies has been equally unrevealing.^{13;14}

Most of the recently published studies of TZD use and cardiovascular risk have been meta-analyses;^{3;10;15–17} however, meta-analyses may not always provide an accurate estimate of treatment effects as measured in large clinical trials.¹⁸ To date, there is only one completed clinical trial designed to assess the effect of TZDs on cardiovascular outcomes. This trial demonstrated that pioglitazone use significantly decreased the secondary composite outcome of all-cause mortality, non-fatal AMI, and stroke compared to placebo.¹⁹ Two recent observational studies suggest that pioglitazone has a more favorable effect with respect to cardiovascular outcomes^{20;21} and all-cause mortality compared to rosiglitazone;²¹ however, one study was limited by the absence of an “untreated” comparator group,²⁰ and the other by the lack of a direct comparison of risks for pioglitazone and rosiglitazone exposure.²¹

Given the discrepant findings for TZDs and their widespread use,²² it is important to assess whether the risks and benefits associated with these medications are class-specific or drug-specific. To address this issue we examined the relationship of TZD use together (i.e., either rosiglitazone or pioglitazone) and as individual drugs on cardiovascular outcomes and all-cause mortality in a large cohort of patients with diabetes. Unlike previous approaches, our study design allowed us to estimate the effect of TZD use compared with those not so treated *and* to assess outcome differences between TZD treatments. We used time-updated propensity scores to adjust for potential confounders associated with treatment,^{23–26} and also unique to all studies to date, we used continuous metrics of medication exposure to both estimate and account for changes in medication use over time.²⁷

METHODS

Study Design, Setting, and Population

We conducted a retrospective cohort study in a large vertically integrated health system in southeast Michigan. This study was approved by the Institutional Review Boards at Henry Ford Health System and the Michigan Department of Community Health. The study was also in compliance with the health system’s Health Insurance Portability and Accountability Act policy. Reporting is in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.²⁸ Patients were both members of a large, health maintenance organization (HMO) in southeast Michigan and they received their care from a large, multi-specialty medical group. All patients had prescription coverage, with tiered co-payments based on the covering entity’s formulary. To be included in the cohort, patients had to meet the following eligibility criteria: age >18 years; at least one clinical encounter with a coded diagnosis of diabetes (international classification of diseases [ICD]-9 code 250.xx) between January 1, 2000 and December 1, 2006; and at least one prescription of an oral diabetes medication during this same time period. For patients meeting these criteria, the index date was the first date during the observation period that the

patient had a clinical encounter coded as diabetes or a fill of an oral diabetes medication. We required patients to have at least 12 months of continuous enrollment in the HMO prior to the index date, and at least 6 months of follow-up after the index date to be included in the analytic set. The latest date of observation was May 31, 2007.

Assessing exposure to thiazolidinediones

We have previously assessed exposure to oral hypoglycemic medications and other classes of medication using pharmacy claims data.^{27;29} We calculated the following exposure categories: any TZD use (i.e., either rosiglitazone or pioglitazone use), rosiglitazone use, and pioglitazone use. Exposure was calculated as the days' supply of medication dispensed in a 6-month time block divided by the number of days.³⁰ For each individual we calculated a moving window of exposure for every day of observation (i.e., exposure over the preceding 6 months) starting 6-months after the index date. Therefore, each individual had a continuous measure of medication exposure for the aforementioned TZD categories for each day of follow-up. Individual exposure measures could vary daily and included periods of no exposure. The 6-month time interval was chosen based on the minimum duration of exposure in the meta-analysis by Nissen and Wolski.³

Outcome assessment

Outcomes were assessed without knowledge of individuals' medication exposure. We identified cardiovascular end-points from electronically maintained claims data, similar to that which has been reported elsewhere.^{13;20} These data included diagnosis and procedural codes for events which occurred both within and outside the health system. Cardiovascular outcomes were based on inpatient codes, whereas baseline cardiovascular status was derived from both inpatient and outpatient codes. Information regarding deaths (and cause of death) within the cohort was obtained by comparing the patient list with records maintained by the Division of Vital Records and Health Statistics, Michigan Department of Community Health. We also looked for missing or misidentified death records by additionally comparing the cohort list with death data maintained electronically by the health system and then reassessing state records for incorrectly entered patient identifiers; this identified an additional 141 deaths.

The primary outcome of this study was fatal and non-fatal acute myocardial infarction (AMI). Secondary outcomes included the following: hospitalizations for congestive heart failure (CHF); fatal and non-fatal cerebrovascular accidents (CVA) and transient ischemic attacks (TIA); combined coronary heart disease (CHD) events (i.e., fatal and non-fatal acute myocardial infarction; other acute coronary syndromes, including unstable angina; and coronary revascularization procedures); and all-cause mortality.

Covariates

Demographic data including age, sex, and race-ethnicity, laboratory data, and clinical data including pharmacy claims were maintained electronically by the health system. Race-ethnicity was usually patient self-identified, but on occasion could have been assigned by health care personnel. Household income was estimated using software which mapped the patient's address to a census block (Pitney Bowes MapInfo, Troy, NY). Individuals' household income was taken as the median household income for their census block using year 2000 data from the U.S. Census Bureau. Laboratory data abstracted included percent glycated hemoglobin (HbA1c); low density lipoprotein cholesterol (LDL); high density lipoprotein cholesterol (HDL); triglyceride levels; serum creatinine; and liver transaminases. Of the 19,171 patients examined, the following numbers were missing laboratory values for the study entirety: 222 (1.1%) for creatinine; 155 (0.8%) for HbA1c; 376 (2.0%) for SGPT; 2,148 (11.2%) for LDL; 1,951 (10.2%) for HDL; and 1,936 (10.1%) for triglycerides.

Baseline clinical status was based on diagnoses and procedures extending one year prior to the index date through 6 months after the index date for the following conditions: CHD, CHF, CVA and TIA, peripheral vascular occlusive disease (PVOD), chronic kidney disease (CKD), and end-staged renal disease (ESRD). We also used diagnosis and procedural codes to calculate an adaptation of the Charlson co-morbidity index as another estimate of baseline co-morbidity.³¹ Lastly, we abstracted prescription fills for other classes of oral diabetes medication (i.e., biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors), antihypertensive medications; lipid lowering agents; and insulin.

Statistical analysis

As TZDs are considered second-tier agents for the treatment of type 2 diabetes mellitus,³² patients with diabetes taking these medications are likely to differ from those not taking these medications in ways that may be associated with cardiovascular outcomes independent of the treatment itself. To account for the probability of taking these medications in our analyses we first performed a propensity analysis to estimate the probability of treatment. We built three separate propensity models for any TZD use, rosiglitazone use, and pioglitazone use. In constructing the propensity scores for rosiglitazone use and pioglitazone use we excluded individuals who had used pioglitazone and rosiglitazone, respectively. The following factors were considered on theoretic grounds to influence TZD use: use of other oral diabetes medication classes in the preceding 6 months (included as a count variable for the number of other classes); use of insulin in the preceding 6 months; renal function (i.e., dichotomized for a serum creatinine level less than and ≥ 1.5); liver function (i.e., serum glutamic pyruvic transaminase [SGPT] level); and level of glycemic control (i.e., HbA1c). Propensity models were fit using data from each day of observation for each individual in the cohort. We used PROC SURVEYLOGISTIC in SAS (SAS version 9.1, SAS Institute Inc, Cary, NC)³³ to account for clustering of covariate values within individuals. As new laboratory data was not available for every day of observation we used forward imputation for each lab value obtained after the diabetes index date. If this left an initial gap, we extrapolated forward any lab value obtained within the 12 months prior to the diabetes index date. If no such lab value was available, we imputed backwards the first available lab value. Parameter estimates from each model were then used to generate a propensity score for each day of follow-up for patients in the cohort, representing the propensity to be treated (i.e., with any TZD, rosiglitazone, or pioglitazone) in the preceding 6 months.

To evaluate the effectiveness of the propensity score adjustment, for each outcome (i.e., TZD use, rosiglitazone use, and pioglitazone use), we fit models to determine if adjustment for the propensity score resulted in making each covariate non-significant. Quintiles worked for all of the rosiglitazone use models. Deciles worked for the TZD use models. For the pioglitazone use models, propensity deciles rendered all covariates non-significant except insulin use ($p=0.008$). Therefore, insulin use was retained as a separate covariate in the pioglitazone models.

We used Cox proportional hazards models to examine the relationship between the three time-updated, continuous measures of TZD exposure (i.e., any TZD exposure, rosiglitazone exposure, and pioglitazone exposure) and outcomes. In these time-to-event analyses, follow-up for each individual started 6 months following their index date (i.e., to allow for an initial 6 months of medication exposure) and censoring for each analysis occurred at the first of the following events: the time of disenrollment from the health plan, the time the study outcome was met, or the end of the observation period. For the separate rosiglitazone and pioglitazone analyses, we excluded individuals ever exposed to pioglitazone and rosiglitazone, respectively. This was done to prevent comparing individuals on different TZDs contemporaneously and potentially falsely diminishing the effect of a given TZD exposure. Indicator variables representing propensity quantiles were used to control for the

likelihood of medication use. In addition to propensity scores and measures of medication exposure (i.e., any TZD use, rosiglitazone use alone, and pioglitazone use alone), the models included the following additional time-updated covariates: LDL levels, HDL levels, triglyceride levels, antihypertensive medication use, and lipid-lowering medication use. The proportional hazards models also adjusted for sociodemographic variables, including age, sex, race-ethnicity, marital status, and median household income; baseline clinical status for CHD, CHF, CVA/TIA, PVOD, ESRD, and CKD; and the Charlson co-morbidity index. In short, the hazard ratios reported for each TZD exposure category represent the relative likelihood for outcomes between no exposure and daily exposure over a 6-month time period.

To examine whether the associations for rosiglitazone use and pioglitazone use differed for any given outcome, we used the Wald test to assess for differences in the coefficients for these variables. Exposure variables for rosiglitazone use and pioglitazone use (i.e., possession ratios) were entered simultaneously in models for each separate outcome. These analyses comprised the entire cohort (n = 19,171) and adjusted for all other covariates including the propensity score for TZD use. As a post-hoc analysis, we also assessed whether TZD use, pioglitazone use, and rosiglitazone use was associated with a reduction in cardiovascular deaths (i.e., primary cause of death listed as an ICD-10 code of I00-I99) or non-cardiovascular deaths (i.e., all other ICD-10 codes).

We performed a number of additional analyses as a check of our findings. First, rather than use time-updated propensity scores, we repeated our analyses using time-updated covariates representing oral diabetes medication use (included as a count variable for the number of other classes); use of insulin; renal function (i.e., dichotomized for a serum creatinine level less than and ≥ 1.5); SGPT levels; HbA1c levels, LDL levels, HDL levels, triglyceride levels, antihypertensive medication use, and lipid-lowering medication use. We also repeated all analyses with TZD exposure (i.e., rosiglitazone, pioglitazone, or both) measured dichotomously. In this series of analyses, a person with a TZD fill was considered to be “exposed” from the time of the initial prescription fill until one of the study outcomes was reached. We then separately adjusted for the baseline covariates (i.e., CHD, CHF, CVA and TIA, PVOD, CKD, ESRD, and the Charlson co-morbidity index) and the time-updated variables mentioned above.

All analyses were performed with standard statistical software (SAS version 9.1, SAS Institute Inc, Cary, NC).³³ A P value of less than .05 was considered statistically significant.

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The funding source had no role in the design of the study, the collection of data, analysis, review of the manuscript for critical content, or the decision to publish.

RESULTS

We identified 19,171 patients that met our criteria of diabetes with at least one fill of oral diabetes medication between January 1, 2000 and December 1, 2006. These patients had a total of 78,442 patient-years of follow-up extending through at latest May 31, 2007. The characteristics of those patients are shown in Table 1. Of the 19,171 patients, 4,580 (23.9%) had at least 1 fill for a TZD; 1,056 (5.5%) had ≥ 1 fill of rosiglitazone but no pioglitazone fills; 3,217 (16.8%) had ≥ 1 fill of pioglitazone but no rosiglitazone fills; and 307 (1.6%) had ≥ 1 fill of rosiglitazone and pioglitazone. Baseline comparisons between individuals who used rosiglitazone alone, pioglitazone alone, and both pioglitazone and rosiglitazone during the observation period are also shown. Significant overall differences between groups were

noted in age, sex, race, marital status, biguanide use, meglitinide use, and insulin use; however, there were no significant differences in baseline co-morbidities.

Among the 19,171 individuals with which to analyze the relationship between TZD exposure and outcomes during follow-up, 1,315 (6.9%) had ≥ 1 AMI; 2,725 (14.2%) had ≥ 1 hospitalization for CHF; 1,826 (9.5%) had ≥ 1 CVA/TIA; 2,302 (12.0%) met the combined CHD outcome; and 1,547 (8.1%) died. Thiazolidinedione use was associated with a significantly increased risk of CHF hospitalization (adjusted hazard ratio [aHR] with propensity adjustment [PA], 1.24; 95% confidence interval [CI] 1.07–1.44), but a significantly lower risk of all-cause mortality (aHR with PA, 0.69; 95% CI 0.52–0.90) when compared with those patients with diabetes not using TZDs (Table 2). Thiazolidinedione use was not associated with an increased risk of the primary outcome, AMI (aHR with PA, 0.92; 95% CI 0.73–1.17), nor was TZD use associated with CVA/TIA (aHR with PA, 0.97; 95% CI 0.79–1.20) or combined CHD events (aHR with PA, 0.92; 95% CI 0.77–1.10).

After excluding individuals who had used pioglitazone, data were available on 15,647 patients with diabetes. Among these 15,647 individuals, 1,056 (6.7%) had used rosiglitazone at least once during the observation period; 1,040 (6.6%) had ≥ 1 AMI; 2,120 (13.5%) had ≥ 1 hospitalization for CHF; 1,433 (9.2%) had ≥ 1 CVA/TIA; 1,817 (11.6%) met the combined CHD outcome; and 1,314 (8.4%) died. The relationship between rosiglitazone exposure and outcomes is shown in Table 3. The only significant relationship observed was a positive association between rosiglitazone exposure and an increased risk of CHF hospitalization (aHR with PA, 1.65; 95% CI 1.25–2.19) when compared with those patients not using rosiglitazone. No significant relationship was seen between rosiglitazone exposure and AMI (aHR with PA, 1.06; 95% CI 0.66–1.70), nor was a significant relationship seen between rosiglitazone exposure and CVA/TIA, combined CHD events, or all-cause mortality.

After excluding individuals who had used rosiglitazone, data were available on 17,808 patients with diabetes. Among these 17,808 individuals, 3,217 (18.1%) had used pioglitazone at least once during the observation period; 1,208 (6.8%) had ≥ 1 AMI; 2,463 (13.8%) had ≥ 1 hospitalization for CHF; 1,657 (9.3%) had ≥ 1 CVA/TIA; 2,099 (11.8%) met the combined CHD outcome; and 1,341 (7.5%) died. The relationship between pioglitazone exposure and outcomes is shown in Table 4. A significant positive relationship between pioglitazone exposure and CHF hospitalization was seen on the adjusted analysis (aHR, 1.25; 95% CI 1.05–1.50) but not the propensity analysis (aHR with PA, 1.14; 95% CI 0.96–1.37) when compared with those patients not using pioglitazone. Pioglitazone use was not significantly associated with the primary outcome, AMI (aHR with PA, 0.91; 95% CI 0.69–1.21), nor was it associated with CVA/TIA or combined CHD events. Pioglitazone use was associated with a significant reduction in all-cause mortality (aHR with PA, 0.60; 95% CI 0.42–0.96).

We explicitly tested whether rosiglitazone and pioglitazone differed in relation to the outcomes examined (Table 5). Pioglitazone use was associated with a lower risk for all outcomes when compared with rosiglitazone use. However, this difference only reached statistical significance for CHF hospitalizations ($P = 0.013$) and combined CHD events ($P = 0.048$), suggesting that pioglitazone was less likely to provoke a CHF exacerbation and more likely to reduce combined CHD events when compared with rosiglitazone. Although only pioglitazone use was associated with a significantly reduced risk of all-cause mortality (Table 4), this reduction was not statistically different from that seen for rosiglitazone ($P = 0.26$). Post-hoc analysis showed that TZDs were associated with similar reductions in cardiovascular deaths (aHR with PA, 0.70; 95% CI 0.48–1.01) and non-cardiovascular deaths (aHR with PA, 0.67; 95% CI 0.45–1.01) when compared with study individuals not

using TZDs. Analysis of pioglitazone use also showed similar reductions in cardiovascular deaths (aHR with PA, 0.61; 95% CI 0.37–0.98) and non-cardiovascular deaths (aHR with PA, 0.61; 95% CI 0.36–1.04) when compared with individuals not taking pioglitazone, but only the former association reached statistical significance.

As a check of our findings we repeated our regression analysis using time-updated covariates in lieu of the propensity analysis (Table E1 in the online repository). This gave similar results, suggesting that pioglitazone is associated with a lower risk of CHF and combined CHD events when compared with rosiglitazone. The only exception was that pioglitazone use was now also associated with a lower risk of AMI when compared with no TZD use (aHR 0.62; 95% CI 0.41–0.94).

Repeating the analysis with TZD exposure defined dichotomously (i.e. “exposed” vs. “not exposed”) from the time of the first fill suggested that both rosiglitazone and pioglitazone were significant risk factors for all of the outcomes assessed (Table E2). These relationships persisted after adjustment for the baseline comorbidities (Table E3). However, after accounting for other potential time-updated confounders (i.e., other diabetes medication use; renal function; liver function; glycemic control; lipid control, and antihypertensive and lipid-lowering medication use), effect estimates were similar to those found using continuous measures of medication exposure (Table E4). We again found that pioglitazone was associated with a lower risk of CHF and combined CHD events when compared with rosiglitazone. Pioglitazone was no longer associated with a significant reduction in all-cause mortality (aHR 1.07; 95% CI 0.90–1.25), but was associated with a significantly increased risk of CHF when compared with no TZD use (aHR 1.14; 95% CI 1.02–1.29). Rosiglitazone use was associated with a statistically significant increased risk of CHF (aHR 1.53; 95% CI 1.26–1.85), CVA/TIA (aHR 1.36; 95% CI 1.08–1.72), combined CHD events (aHR 1.34; 95% CI 1.08–1.65), and all-cause mortality (aHR 1.35; 95% CI 1.07–1.71) when compared with no TZD use.

DISCUSSION

Given the recent widely publicized meta-analyses suggesting that rosiglitazone may increase the risk of acute myocardial infarction and cardiovascular death,^{3;10} it would not be surprising if clinicians altered or avoided prescribing TZDs. Recent history has seen similar controversies regarding other commonly prescribed medications, most notably the non-steroidal anti-inflammatory cyclooxygenase-2 inhibitors, whose use was also associated with an increased risk of cardiovascular events.³⁴ However, even among these medications it was not clearly established whether this was a class or drug-specific effect.^{35–40}

Controversy regarding the methodology used in current rosiglitazone meta-analyses notwithstanding,^{6;8} there is credible evidence from one large trial specifically designed to assess cardiovascular outcomes that pioglitazone treatment reduced the composite outcome of all-cause mortality, non-fatal myocardial infarction, and stroke by 16% as compared to placebo (HR 0.84, 95% CI 0.72–0.98). The risk reduction for all cause mortality alone was more modest (HR 0.96, 95% CI 0.78–1.18).¹⁹ A recent meta-analysis of pioglitazone also demonstrated a reduced risk of the composite outcome of death, myocardial infarction, and stroke (HR 0.82, 95% CI 0.72–0.94).⁴¹ In addition, a population-based study of older patients with diabetes from Ontario, Canada by Lipscombe et al. showed a significant positive relationship between rosiglitazone use and the risk of CHF, AMI, and death, whereas no significant relationship was observed between these outcomes and current pioglitazone use.²¹ Rosiglitazone and pioglitazone have also been shown to have disparate effects on lipid metabolism.^{42;43} Together these findings suggest that there may be differences between current TZDs on cardiovascular outcomes and death. While our data

does not exclude the estimated increased risk of all-cause mortality reported by Lipscombe and colleagues for rosiglitazone use (i.e. the point estimate falls within our confidence interval), we do demonstrate a reduction in all-cause mortality associated with pioglitazone use which was not shown in the Canadian study. This could be the result of greater numbers of pioglitazone users in our cohort. Our study also suggests that pioglitazone may have a more favorable risk profile with regard to congestive heart failure and combined coronary heart events when compared with rosiglitazone.

The relationship between TZD use and congestive heart failure has now been demonstrated in a number of studies,^{15–17;44;45} and TZDs are not recommended for use in individuals with class III or IV New York Heart Association CHF.^{46;47} The association is felt to be the result of increased fluid retention and expansion of plasma volume by TZDs;⁴⁸ however, the underlying mechanism for this volume expansion is not fully known.⁴⁶ To our knowledge, ours is the first study to demonstrate a significant difference between rosiglitazone and pioglitazone on congestive heart failure. However, a recent meta-analysis by Lago and colleagues also suggested a difference between pioglitazone (risk ratio [RR] 1.32; 95% CI 1.04–1.68) and rosiglitazone (RR 2.41; 95% CI 1.61–3.61) on CHF events, but this did not reach statistical significance ($P = 0.07$).¹⁷

It is important to note that we did not find an increased risk of our primary outcome, myocardial infarction, in either the rosiglitazone or pioglitazone users. However, as we had less exclusive rosiglitazone users ($n = 1,056$) than originally anticipated, we were likely underpowered to detect (or exclude) an effect for rosiglitazone of the magnitude described by Nissen and Wolski (RR 1.43),³ Singh and colleagues (RR 1.42).¹⁰ In contrast, we had many more exclusive pioglitazone users ($n = 3,217$) in our study population. As a result, the confidence intervals for the relationship between pioglitazone use and AMI (aHR with PA, 0.91; 95% CI 0.69–1.21) were narrower and excluded the effect size reported for rosiglitazone. Therefore, it seems unlikely that pioglitazone has the relationship with AMI reported for rosiglitazone in these other studies.

This study must be interpreted in light of its limitations. Since we primarily relied on pharmacy claims data for one carrier, medications obtained from alternative sources (e.g., dual insurance coverage) may have been missed. Previous analyses by our group for another condition showed that very few medications are filled via other coverage.⁴⁹ Similar to others,³ we assumed that 6-months of TZD exposure was sufficient to observe associated outcomes. However, the critical duration of exposure is not currently known.

As an observational study, treatment groups may have differed in important ways that were not accounted for in our regression models. We used propensity-scores to account for factors associated with treatment, so as to minimize confounding when these predictors are also directly or indirectly related to outcomes. This approach has been shown to be effective for balancing observed covariates²⁵ and may produce estimates close to those seen in randomized controlled trials.²⁶ Because we had a long period of observation, we used a time-updated propensity score to account for changes that may affect treatment over time. However, it is not clear that this approach or other propensity adjustments are superior to standard multivariable regression models.⁵⁰ In fact, we obtained similar estimates when repeating our analyses using time updated covariates rather than propensity scores.

We identified outcomes using methods and criteria similar to those used elsewhere.^{13;51;52} Nevertheless, because we relied on claims data, we did not have information on some potentially important factors, such as aspirin use, body mass index, and smoking status.

Similar to others,²¹ we did not adjust for multiple comparisons in our analyses. However, the consistency in our results with regard to a risk reduction for pioglitazone use on multiple

cardiovascular outcomes and all-cause mortality *and* in the differences observed between pioglitazone use and rosiglitazone use suggests that our reported findings were not spurious.

In addition, there were differences in the rates of pioglitazone and rosiglitazone use; however no overall differences were observed in baseline comorbidities. These differences in TZD use likely represent selection based on insurance formularies rather than underlying disease status or concomitant conditions. Regardless, we adjusted for underlying demographic variables, other diabetes and non-diabetes medication use, glycemic and lipid control, and the presence of baseline co-morbidities in our regression models.

Despite these limitations, this study had many features not included together in other studies to date. First, we were able to assess the relationship between both rosiglitazone use *and* pioglitazone use on multiple outcomes in a population-based sample of individuals with diabetes. As individuals were followed longitudinally, we were able to perform a time-to-event analysis. Lastly, we were able to estimate and account for varying medication use (i.e., exposure), which is often overlooked even in clinical trials.^{53;54} When we reanalyzed our data considering TZD exposure dichotomously, we initially obtained very different results. However, when we accounted for the variables likely affected by less than optimal use (e.g., glycemic control, lipid levels, and the need for additional diabetes medications) we found similar results to those observed when accounting for changing levels of medication exposure.

In summary, our study suggests that pioglitazone use does not increase the risk of myocardial infarction, but may reduce all-cause mortality, including cardiovascular deaths. When compared with rosiglitazone, pioglitazone use appears to have a more favorable profile, resulting in fewer congestive heart failure hospitalizations and coronary heart disease events. While the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial may establish the cardiovascular risk or benefit of rosiglitazone treatment, our study suggests that more research is needed to assess its relative benefit to pioglitazone, since the latter appears to be a dominant alternative for the outcomes assessed here.

Key points

- In this study, pioglitazone use appeared to protect against all-cause mortality and was not associated with an increased risk of acute myocardial infarction.
- As previously described, rosiglitazone use was associated with an increased risk of congestive heart failure hospitalization.
- When compared with rosiglitazone, pioglitazone use appeared to have a more favorable cardiovascular risk profile, particularly for congestive heart failure hospitalizations and coronary heart disease events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of patients with diabetes and at least one oral hypoglycemic medication fill between January 1, 2000 and December 1, 2006 (N=19,171).

Characteristic	All patients (N=19,171)	Patients treated with a thiazolidinedione during the observation period			Overall P-value *	Comparison of rosiglitazone alone and pioglitazone alone groups P-value [†]
		Rosiglitazone alone (n=1,056)	Pioglitazone alone (n=3,217)	Both rosiglitazone and pioglitazone (n=307)		
Age in years – mean ± SD	58.3 ± 13.0	59.0 ± 12.6	57.0 ± 12.0	57.3 ± 12.1	<0.001	<0.001
Female – No. (%)	9,688 (50.5)	545 (51.6)	1549 (48.2)	174 (56.7)	0.005	0.051
Race – No. (%)	--	--	--	--	<0.001	<0.001
African-American	7,988 (41.7)	509 (48.2)	1338 (41.6)	115 (37.5)		
White	9,962 (52.0)	477 (45.2)	1688 (52.5)	176 (57.3)		
Other/unknown	1,221 (6.3)	70 (6.6)	191 (5.9)	16 (5.2)		
Married – No. (%)	12,112 (63.2)	651 (63.0)	2140 (67.7)	206 (68.0)	0.019	0.006
Oral diabetes medication use (≥1 fill during observation period) – No. (%) [‡]	--	--	--	--	--	--
Thiazolidinedione class	4,580 (23.9)	--	--	--	--	--
Rosiglitazone alone	1,056 (5.5)	1,056 (100)	--	--	--	--
Pioglitazone alone	3,217 (16.8)	--	3,217 (100)	--	--	--
Both rosiglitazone and pioglitazone	307 (1.6)	--	--	307 (100)	--	--
Biguanide class	14,673 (76.5)	803 (76.0)	2633 (81.8)	251 (81.8)	<0.001	<0.001
Sulfonylurea class	13,564 (70.8)	816 (77.3)	2519 (78.3)	247 (80.5)	0.480	0.483
Alpha-glucosidase class	350 (1.8)	34 (3.2)	120 (3.7)	15 (4.9)	0.386	0.440
Meglitinide class	225 (1.2)	26 (2.5)	68 (2.1)	14 (4.6)	0.025	0.503
Insulin use (≥1 fill during observation period) – No. (%) [‡]	5,844 (30.5)	451 (42.7)	1517 (47.2)	175 (57.0)	<0.001	0.012
Antihypertensive medication use (≥1 fill during observation period) – No. (%) [‡]	16,856 (87.9)	974 (92.2)	2988 (92.9)	286 (93.2)	0.750	0.483
Lipid lowering medication use (≥1 fill during observation period) – No. (%) [‡]	13,615 (71.0)	825 (78.1)	2563 (79.7)	258 (84.0)	0.076	0.282
Baseline clinical diagnoses – No. (%) [§]	--	--	--	--	--	--

Characteristic	All patients (N=19,171)	Patients treated with a thiazolidinedione during the observation period			Overall P-value [*]	Comparison of rosiglitazone alone and pioglitazone alone groups P-value [†]
		Rosiglitazone alone (n=1,056)	Pioglitazone alone (n=3,217)	Both rosiglitazone and pioglitazone (n=307)		
Coronary heart disease ^{//}	1,389 (7.2)	95 (9.0)	247 (7.7)	27 (8.8)	0.349	0.171
Congestive heart failure	1,713 (8.9)	103 (9.7)	245 (7.6)	25 (8.1)	0.088	0.028
Cerebrovascular accidents or transient ischemic attacks	1,412 (7.4)	68 (6.4)	216 (6.7)	24 (7.8)	0.697	0.756
Peripheral vascular occlusive disease	1,009 (5.3)	66 (6.2)	155 (4.8)	22 (7.2)	0.064	0.068
Chronic kidney disease	622 (3.2)	48 (4.5)	106 (3.3)	15 (4.9)	0.090	0.059
End-staged renal disease	101 (0.5)	5 (0.5)	23 (0.7)	4 (1.3)	0.301	0.399

SD denotes standard deviation

^{*} For the comparison of the three groups treated with thiazolidinedione during the observation period (i.e., rosiglitazone alone, pioglitazone alone, and both rosiglitazone and pioglitazone)

[†] Comparison of rosiglitazone alone (n=1,056) and pioglitazone alone (n=3,217) groups.

[‡] The observation period refers to the time between the index date and the date of censoring. The index date is the first diagnosis of diabetes or the first fill of an oral diabetes medication between January 1, 2000 and December 1, 2006. The last day of any follow-up was May 31, 2007.

[§] Diagnoses occurring between 1 year prior to index date through the 6 months following the index date.

^{//} Includes a previous diagnosis of myocardial infarction, other acute coronary syndromes, and coronary revascularization procedures 1 year prior to 6 months following the index date.

Table 2

Relationship between thiazolidinedione use and outcomes among patients with diabetes treated with oral diabetes medications (n = 19,171).*

Outcomes	Thiazolidinedione treated individuals vs. others		
	HR (95% CI)	aHR (95% CI) [†]	aHR with propensity adjustment (95% CI) [‡]
Acute myocardial infarction [§]	0.89 (0.71–1.12)	0.99 (0.78–1.25)	0.92 (0.73–1.17)
Congestive heart failure hospitalization	1.25 (1.08–1.43)**	1.33 (1.15–1.54) ^{††}	1.24 (1.07–1.44)**
Cerebrovascular accident or transient ischemic attack [§]	0.86 (0.70–1.05)	1.05 (0.85–1.29)	0.97 (0.79–1.20)
Combined coronary heart disease ^{//}	0.99 (0.83–1.17)	0.97 (0.81–1.15)	0.92 (0.77–1.10)
All-cause mortality	0.54 (0.41–0.70) ^{††}	0.73 (0.56–0.95) [¶]	0.69 (0.52–0.90)**

HR denotes hazard ratio; aHR, adjusted hazard ratio; and CI, confidence interval.

* Includes individuals with either pioglitazone or rosiglitazone fills during the observation period.

[†] Adjusted for patient age, sex, marital status, race-ethnicity, median household income, Charlson co-morbidity index, high-density lipoprotein levels, low-density lipoprotein values, triglyceride values, anti-hypertensive medication use in the preceding 6 months, lipid lowering medication use in the preceding 6 months, and separate variables for each of the following baseline clinical history: coronary heart disease, congestive heart failure, cerebrovascular accidents or transient ischemic attacks, peripheral vascular occlusive disease, chronic kidney disease, and end-staged renal disease.

[‡] Adjusted for all previous variables plus the propensity score modeling the probability of being treated with a thiazolidinedione.

[§] Includes both fatal and non-fatal events.

^{//} Includes fatal and non-fatal acute myocardial infarction; other acute coronary syndromes, including unstable angina; and coronary revascularization procedures.

[¶] P<0.05

** P<0.01

^{††} P<0.001

Table 3

Relationship between rosiglitazone use and outcomes among patients with diabetes treated with oral diabetes medications (n = 15,647).*

Outcomes	Rosiglitazone treated individuals vs. others		
	HR (95% CI)	aHR (95% CI) [†]	aHR with propensity adjustment (95% CI) [‡]
Acute myocardial infarction [§]	1.05 (0.66–1.68)	1.12 (0.70–1.80)	1.06 (0.66–1.70)
Congestive heart failure hospitalization	1.66 (1.26–2.19)**	1.73 (1.31–2.29)**	1.65 (1.25–2.19) [¶]
Cerebrovascular accident or transient ischemic attack [§]	1.09 (0.72–1.65)	1.27 (0.84–1.94)	1.20 (0.79–1.82)
Combined coronary heart disease ^{//}	1.19 (0.89–1.60)	1.26 (0.94–1.68)	1.22 (0.91–1.63)
All-cause mortality	0.85 (0.54–1.35)	0.96 (0.60–1.56)	0.91 (0.57–1.48)

HR denotes hazard ratio; aHR, adjusted hazard ratio; and CI, confidence interval.

* Analysis excludes individuals with pioglitazone fills during the observation period.

[†] Adjusted for patient age, sex, marital status, race-ethnicity, median household income, Charlson co-morbidity index, high-density lipoprotein levels, low-density lipoprotein values, triglyceride values, anti-hypertensive medication use in the preceding 6 months, lipid lowering medication use in the preceding 6 months, and separate variables for each of the following baseline clinical history: coronary heart disease, congestive heart failure, cerebrovascular accidents or transient ischemic attacks, peripheral vascular occlusive disease, chronic kidney disease, and end-staged renal disease.

[‡] Adjusted for all previous variables plus the propensity score modeling the probability of being treated with rosiglitazone.

[§] Includes both fatal and non-fatal events

^{//} Includes fatal and non-fatal acute myocardial infarction; other acute coronary syndromes, including unstable angina; and coronary revascularization procedures.

[¶] P<0.01

** P<0.001

Table 4

Relationship between pioglitazone use and outcomes among patients with diabetes treated with oral diabetes medications (n = 17,808).*

Outcomes	Pioglitazone treated individuals vs. others		
	HR (95% CI)	aHR (95% CI) [†]	aHR with propensity adjustment (95% CI) [‡]
Acute myocardial infarction [§]	0.87 (0.67–1.14)	0.99 (0.75–1.31)	0.91 (0.69–1.21)
Congestive heart failure hospitalization	1.12 (0.95–1.34)	1.25 (1.05–1.50) [¶]	1.14 (0.96–1.37)
Cerebrovascular accident or transient ischemic attack [§]	0.82 (0.65–1.04)	1.03 (0.80–1.32)	0.93 (0.72–1.20)
Combined coronary heart disease ^{//}	0.91 (0.74–1.11)	0.91 (0.73–1.12)	0.86 (0.69–1.06)
All-cause mortality	0.46 (0.33–0.65) ^{††}	0.65 (0.46–0.93) [¶]	0.60 (0.42–0.96) ^{**}

HR denotes hazard ratio; aHR, adjusted hazard ratio; and CI, confidence interval.

* Analysis excludes individuals with rosiglitazone fills during the observation period.

[†] Adjusted for patient age, sex, marital status, race-ethnicity, median household income, Charlson co-morbidity index, high-density lipoprotein levels, low-density lipoprotein values, triglyceride values, anti-hypertensive medication use in the preceding 6 months, lipid lowering medication use in the preceding 6 months, and separate variables for each of the following baseline clinical history: coronary heart disease, congestive heart failure, cerebrovascular accidents or transient ischemic attacks, peripheral vascular occlusive disease, chronic kidney disease, and end-staged renal disease.

[‡] Adjusted for all previous variables plus the propensity score modeling the probability of being treated with pioglitazone.

[§] Includes both fatal and non-fatal events.

^{//} Includes fatal and non-fatal acute myocardial infarction; other acute coronary syndromes, including unstable angina; and coronary revascularization procedures.

[¶] P<0.05

^{**} P<0.01

^{††} P<0.001

Table 5

Differences between pioglitazone use and rosiglitazone use on outcomes among patients with diabetes treated with oral diabetes medications (n = 19,171).*

Outcomes	Rosiglitazone use compared with no thiazolidinedione use – aHR with propensity adjustment (95% CI) [†]	Pioglitazone use compared with no thiazolidinedione use – aHR with propensity adjustment (95% CI) [†]	Wald test for equivalence between coefficients for rosiglitazone use and pioglitazone use P value [‡]
Acute myocardial infarction [§]	1.00 (0.64–1.58)	0.90 (0.69–1.18)	0.686
Congestive heart failure hospitalization	1.66 (1.28–2.15) **	1.13 (0.95–1.34)	0.013
Cerebrovascular accident or transient ischemic attack [§]	1.20 (0.82–1.77)	0.91 (0.71–1.17)	0.224
Combined coronary heart disease ^{//}	1.22 (0.89–1.67)	0.84 (0.69–1.04)	0.048
All-cause mortality	0.87(0.54–1.39)	0.63 (0.45–0.87) [¶]	0.263

aHR denotes adjusted hazard ratio and CI, confidence interval.

* Models comprise the entire cohort, including individuals with either pioglitazone or – rosiglitazone fills during the observation period.

[†] Adjusted for patient age, sex, marital status, race-ethnicity, median household income, Charlson co-morbidity index, high-density lipoprotein levels, low-density lipoprotein values, triglyceride values, anti-hypertensive medication use in the preceding 6 months, lipid lowering medication use in the preceding 6 months, and separate variables for each of the following baseline clinical history: coronary heart disease, congestive heart failure, cerebrovascular accidents or transient ischemic attacks, peripheral vascular occlusive disease, chronic kidney disease, and end-staged renal disease. Models also adjusted for the propensity score representing the probability of thiazolidinedione treatment.

[‡] P values < 0.05 represent a statistically significant difference between the estimated effect of rosiglitazone use and pioglitazone use.

[§] Includes both fatal and non-fatal events.

^{//} Includes fatal and non-fatal acute myocardial infarction; other acute coronary syndromes, including unstable angina; and coronary revascularization procedures.

[¶] P<0.01

** P<0.001