Risk of Cardiovascular Events and All-Cause Mortality in Patients Treated With Thiazolidinediones in a Managed-Care Population

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Background—This study directly compares risk of acute myocardial infarction (AMI), acute heart failure (AHF), or all-cause death among pioglitazone- and rosiglitazone-treated patients in a managed-care population.

Methods and Results—Patients ≥18 years of age, newly initiated on rosiglitazone or pioglitazone between January 1, 2001, and December 12, 2005, were included. The date of the first pharmacy claim for rosiglitazone or pioglitazone was defined as index date. Patients were excluded if they had <1 year continuous eligibility preindex or a preindex insulin claim. Primary outcome measure was time to composite event of AMI, AHF or death among pioglitazone- and rosiglitazone-treated patients. The National Death Index database was accessed to obtain date of death for patients who died during the study period. Propensity score matching was used to control for potential confounders. The Cox proportional hazards model was used to evaluate effects of exposure to rosiglitazone and pioglitazone on time to event. A total of 36 628 patients (58% male; mean age, 54 years) were identified. Of the rosiglitazone-treated patients, 602 (4.16%) had an AMI, AHF, or death compared with 599 (4.14%) propensity score–matched pioglitazone-treated patients. No significant difference was observed between matched groups for risk of composite event (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15; \( P=0.666 \)) when patients were followed from index date until end of study period, termination of enrollment status, or diagnosis of AMI/AHF/death.

Conclusions—In this retrospective cohort study directly comparing rosiglitazone and pioglitazone with a propensity score–matched population that includes mortality data, no significant differences were found in the risk of AMI, AHF or death. (Circ Cardiovasc Qual Outcomes. 2010;3:538-545.)

Key Words: cardiovascular disease ■ diabetes mellitus ■ myocardial infarction ■ heart failure ■ mortality ■ thiazolidinediones ■ rosiglitazone ■ pioglitazone

Diabetes mellitus (DM) is a chronic disease of growing prevalence and is currently the sixth leading cause of death in the United States.1 Currently, there are 2 thiazolidinediones (TZDs), rosiglitazone (Avandia, GlaxoSmithKline)2 and pioglitazone (Actos, Takeda),3 approved in the United States for treatment of type 2 diabetes mellitus (T2DM). These drugs treat T2DM by reducing insulin resistance; however, they have differing effects on lipid levels.4,5 Prior evidence suggests that treatment with pioglitazone results in significant improvements in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides; whereas treatment with rosiglitazone is associated with an increase in LDL-C and high-density lipoprotein cholesterol (HDL-C).5 Both T2DM and elevated LDL-C are considered primary cardiovascular (CV) risk factors for acute myocardial infarction (AMI).6,7 The association of rosiglitazone with increased risk of AMI is controversial.7 Furthermore, fluid retention (which can lead to or exacerbate heart failure) is a known side effect of TZDs, and a black box warning is included in the US product labeling for both drugs.5,3 Neither drug has been studied in an individual randomized, double-blind, clinical trial sufficiently populated or designed to definitively evaluate the effect of treatment on CV morbidity and mortality.

In 2007, a Food and Drug Administration (FDA) Advisory Committee discussed the risk of myocardial infarction (MI) in patients treated with TZDs, with emphasis on rosiglitazone. The committee reviewed results of long-term randomized, controlled outcomes studies,8–11 meta-analyses, data from GlaxoSmithKline, and results from large observational studies provided by WellPoint and Tricare.12 The committee agreed that rosiglitazone was associated with greater risk of MI when compared with placebo, metformin, or sulfonylureas; however, the final assessment was that overall risk-benefit did not justify removal from the market.13,14

Subsequent to the FDA advisory committee meeting, a retrospective study by Gerritus et al15 directly compared...
pioglitazone and rosiglitazone on CV events in T2DM patients using the Ingenix Research Database. This study found 28% increased relative risk in MI with rosiglitazone compared with pioglitazone. More recently, studies examining the relationship between TZDs and AMI, acute heart failure (AHF), and all-cause mortality in the elderly were published and found an increased risk of AHF and all-cause mortality in rosiglitazone-treated versus pioglitazone-treated patients.16,17 With inconsistent findings from prior research, the regulatory and health care community continues to lack definitive information about the CV safety of TZDs.

The current study directly compares risk of AMI, AHF, or all-cause death among pioglitazone- and rosiglitazone-treated patients using the HealthCore Integrated Research Database (HIRD). The study population is similar to that of the Gerritus study but improves on the existing observational research by using a propensity score–matched population of new rosiglitazone and pioglitazone users and examines the aforementioned composite end point. This study represents an enhanced version of the WellPoint data that was previously presented to the FDA in 2007.

WHAT IS KNOWN

• Long-term head-to-head trials comparing rosiglitazone and pioglitazone with respect to cardiovascular safety outcomes do not exist; however, meta-analyses have identified increased cardiovascular risk with rosiglitazone compared with pioglitazone.
• Some observational studies have similarly suggested an increased risk of cardiovascular events with rosiglitazone.

WHAT THE STUDY ADDS

• This study directly compared the risk of acute myocardial infarction, acute heart failure hospitalization, and all-cause mortality among rosiglitazone- and pioglitazone-treated patients using a propensity score–matched population of nearly 40 000 new users enrolled in a commercial health plan.
• This study found no significant differences in risk of acute myocardial infarction, acute heart failure hospitalization, and all-cause mortality among rosiglitazone-treated patients.
• These findings contrast with observational data in similarly aged patient populations in suggesting that at least within the power of the study, rosiglitazone does not increase cardiovascular risk.

Methods

Study Design and Setting

This was a retrospective cohort study that used available administrative medical/pharmacy data and national mortality data from January 1, 2000, to December 31, 2005. The HIRD consists of claims data collected from WellPoint members. The database includes dates of eligibility, benefit design, medical/pharmacy claims, and diagnostic laboratory results. Data for this study were collected from US health plans located in California, Georgia, Virginia, and Missouri.

Study Participants/Cohort Identification

Patients ≥18 years of age with a new rosiglitazone or pioglitazone claim between January 1, 2001, and December 31, 2005, were included. The first rosiglitazone or pioglitazone claim during the study period was defined as the index date regardless of other antidiabetic medication claims in the patients’ history. Patients were excluded if they did not have continuous health plan eligibility for ≥365 days before their index date (preindex period) or had a prediabetes pharmacy claim for insulin. Previous CV events were not criteria for exclusion.

Exposure Assessment

New users of TZDs were identified from members’ pharmacy records. Two exposure groups were formed, based on the prescribed TZD on index date. Patients were considered to be on continuous therapy if the period between prescription refills was <1.5 times the days supply of the preceding TZD claim. The end of continuous therapy with TZD was the number of days after the last TZD refill, as indicated in the days supply field. Patients were also excluded if they were exposed to both rosiglitazone and pioglitazone during follow-up because there is no clear evidence showing how long the pharmacological effect would remain when patients discontinue their first therapy. Furthermore, if patients switched medication within 60 days after discontinuing the first drug, they were censored after the first period of continuous therapy.

A primary analysis and 2 sensitivity analyses were conducted to explore the impact of TZD exposure on composite CV event risk (see Outcome Definition Section). In the primary analysis, TZD exposure was measured from index date until the earliest of: end of study period (December 31, 2005), termination from health plan, occurrence of AMI or AHF, or death. In the 2 sensitivity analyses, the period of risk was varied. In the first sensitivity analysis, patients were followed from index date until end of continuous therapy plus 60 days, occurrence of an AMI/AHF/death, or end of health plan enrollment, whichever occurred first. In the second sensitivity analysis, patients were followed from index date until end of continuous therapy (most stringent criteria), occurrence of an AMI, AHF or death, or end of health plan enrollment, whichever occurred first. In addition, an analysis was also conducted to explore the impact of TZD exposure on a subgroup of patients ≥65 years of age. Impact of TZD exposure on individual outcomes of AMI, AHF, and death was also assessed.

Outcome Definition

The primary outcome measure was time to diagnosis of AMI, AHF, or all-cause death among newly treated pioglitazone or rosiglitazone patients regardless of history of AMI or AHF. Inpatient and emergency room medical claims were searched for diagnosis codes that indicated occurrence of AMI or AHF; no length of stay requirement was imposed. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code 410.xx for AMI19,20 and 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 for AHF were used to identify events. The National Death Index (NDI) Plus database was linked to obtain information about death date for patients who died during the study period. Depending on the type of identifiers used and methods for matching patients (social security numbers, name/sex/date of birth matching, etc) accuracy of the NDI ranges from 83% to 98%.22,23 Patients with any cause of death recorded were included.

A Waiver of Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorization was obtained from an institutional review board to allow researchers to access identifying information about patients who had died. Approval was obtained by the National Center for Health Statistics for access to the NDI. All study materials were handled in compliance with HIPAA.

Statistical Analysis

Descriptive Statistics

Demographic and baseline characteristics of each cohort were compared. χ² tests were used to compare categorical variables.
Student t test tests were used to compare continuous variables. Point estimates of event rates and differences were computed with 95% confidence intervals.

**Multivariate Analyses**

**Propensity Score Matching**

Propensity score matching was used to control for measured potential confounders. A logistic regression model was developed to estimate the probability of receiving rosiglitazone or pioglitazone on index date. Demographic/clinical variables were identified in the 12-month preindex period for inclusion as covariates in the propensity score model. The final list of variables included in the logistic regression model were based on previous research by Graham et al and included age, sex, health plan, preindex Deyo-Charlson comorbidity index score, index year, preindex CV disease conditions (ischemic heart disease, congestive heart failure, diabetes, transient ischemic attack/stroke, other cerebrovascular disease, arrhythmia, peripheral vascular disease), preindex CV-related medication (loop diuretics, calcium channel blockers, thiazide diuretics, nitrates, platelet aggregation inhibitors, warfarin, β-blockers, digoxin, antiarrhythmics, lipid-lowering agents, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers), preindex medications (biguanides, sulfonylurea, other antidiabetic drugs, preindex cyclooxygenase-2 inhibitors), preindex obesity, preindex smoking status, and preindex diabetes complications (nephropathy, retinopathy, neuropathy, unspecified diabetic complications). Once the propensity scores were obtained, patients in each cohort were matched with Parsons 1:1 greedy 4→1 digit matching algorithm. The quality of the match was determined by comparing baseline characteristics on the matched sample and standardized differences. Cox proportional hazards models were used to evaluate independent effects of exposure to rosiglitazone and pioglitazone on time to CV event and mortality. The matched cohort model was adjusted for exposure to rosiglitazone or pioglitazone. Exposure to rosiglitazone or pioglitazone was handled as a categorical (dummy) variable in the exposure to rosiglitazone or pioglitazone. Exposure to rosiglitazone compared with the rosiglitazone cohort (41.3% versus 38.6%, respectively) and slight differences in the index year that patients initiated therapy. In the subpopulation of patients ≥65 years of age, mean age was 72 years; no significant differences in baseline demographics were found between groups except for slight differences in the year patients initiated index therapy. There were 3475 patients excluded because of exposure to both rosiglitazone and pioglitazone during the study period. After matching by propensity score, 14,469 patients were included in each cohort; the C-statistic for logistic regression in the propensity score matching was 0.56 and probability value for Hosmer and Lemeshow goodness-of-fit test was 0.57. Table 2 describes the demographic/baseline characteristics of the cohorts after matching. Mean age was 54 years with 58% male in both groups. Demographics were not significantly different between groups. Mean duration of follow-up was 19.4 ± 15.4 months for rosiglitazone and 19.8 ± 15.6 months for pioglitazone. Therapy duration was 14.4 ± 14.4 months for rosiglitazone and 14.7 ± 14.8 months for pioglitazone.
Preindex comorbidities were similar after propensity score matching between groups (Table 2). Less than 1% of matched patients in each cohort had a preindex AMI (0.50% versus 0.62%, respectively) or congestive heart failure (0.79% versus 0.81%, respectively) diagnosis. In both groups, approximately 2.2% of patients had a preindex ischemic heart disease diagnosis. The most commonly prescribed types of preindex CV medication for the cohorts were lipid-altering medications (39.4% versus 39.6%, respectively) and angiotensin-converting enzyme inhibitors (29.2% versus 28.9%, respectively). No significant differences were observed between groups for preindex diabetes severity indicators.

For patients unable to be matched, a higher percent were male in the pioglitazone compared with rosiglitazone cohort (59.1% versus 55.1%, respectively), as shown in Table 2. In addition, a higher portion of pioglitazone compared with rosiglitazone patients used specific preindex CV and diabetes-related medications, particularly lipid-altering medications. Diabetic nephropathy and retinopathy were significantly lower in the rosiglitazone cohort compared with pioglitazone.
pioglitazone, whereas diabetic neuropathy and diabetic hospitalizations were higher in the rosiglitazone cohort.

In the postindex period, risk of AMI or AHF or death was similar between groups regardless of history of AMI or hospitalizations were higher in the rosiglitazone cohort (Table 3). The event rate for rosiglitazone was 26.38 per 1000 person-years (4.14%) in the matched pioglitazone group (Table 3). The rate of AMI, AHF, or death per 1000 person-years was 11.44 for rosiglitazone and pioglitazone in this population are at 65 years of age, there were still no significant difference was observed in the rate of composite event in the full sample after adjusting for relevant covariates in the primary analysis (HR, 1.00; 95% CI, 0.90 to 1.11; \( P=0.981 \)) and in both sensitivity analyses.

**Discussion**

The results of this cohort study suggest that patients exposed to rosiglitazone and pioglitazone in this population are at similar risk of AMI, AHF, or all-cause death. Our findings are in line with previous studies that have shown similar risk of AMI, AHF, or all-cause death in patients with diabetes.

**Table 5. Cox Proportional Hazards Models for Risk of Composite Event of Interest (AMI or Acute Heart Failure or All-Cause Mortality)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched patients</td>
<td>1.03 (0.91–1.15)</td>
<td>0.666</td>
</tr>
<tr>
<td>Age 65 + y</td>
<td>0.97 (0.83–1.12)</td>
<td>0.643</td>
</tr>
<tr>
<td>All patients</td>
<td>1.00 (0.90–1.11)</td>
<td>0.981</td>
</tr>
<tr>
<td>Patients were excluded 60 days after the end of index therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched patients</td>
<td>0.97 (0.74–1.26)</td>
<td>0.823</td>
</tr>
<tr>
<td>Age 65 + y</td>
<td>0.86 (0.61–1.21)</td>
<td>0.390</td>
</tr>
<tr>
<td>All patients</td>
<td>0.87 (0.68–1.11)</td>
<td>0.264</td>
</tr>
<tr>
<td>Patients were excluded at the end of index therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched patients</td>
<td>0.88 (0.64–1.20)</td>
<td>0.413</td>
</tr>
<tr>
<td>Age 65 + y</td>
<td>0.69 (0.46–1.02)</td>
<td>0.072</td>
</tr>
<tr>
<td>All patients</td>
<td>0.75 (0.57–1.00)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Pioglitazone was the reference group.
similar to a recent retrospective study by Habib et al., which found no difference in AMI between TZDs; however, they contrast another retrospective analysis of a younger, healthier insured population receiving rosiglitazone or pioglitazone by Gerritus et al. In review of administrative claims from US health plans, Gerritus et al. found that pioglitazone was associated with 22% relative risk reduction of MI (HR, 0.78, 95% CI, 0.63 to 0.96) compared with rosiglitazone after adjusting for baseline covariates. In both the Gerritus study and current analysis, baseline demographics/comorbidities were similar between groups that included results on all patients (including <65 years of age), and both studies included relevant covariates in their multivariate analyses; however, the current study used propensity score matching to ensure similarity at baseline between groups. Furthermore, administrative claim databases do not identify mortality, but the current study matched patient records with mortality data from the NDI to improve the accuracy of the results by potentially capturing deaths that occurred outside the hospital and utilized a composite end point of AMI, AHF, and all-cause mortality. The Gerritus study did not supplement their data with NDI data, and AHF was not included as an end point. Furthermore, mean duration of follow-up was 1.2 years in the Gerritus study and 1.6 years in the current study. Because events were very low in both studies, we believe additional follow-up time was important. In addition, statin use was higher in the pioglitazone compared with the rosiglitazone group in the Gerritus study. Differing levels of LDL-C and other lipid fraction level achievement over time is important when considering CV outcomes. Neither study evaluated lipid levels; however, the current study had equal use of statin therapies across groups.

After the publication of the Gerritus study, Winkelmaier et al. found a 13% greater risk of AHF (incident rate ratio, 1.13; 95% CI, 1.01 to 1.26) and 15% greater risk (incident rate ratio, 1.15; 95% CI, 1.05 to 1.26) of mortality associated with rosiglitazone compared with pioglitazone for patients who initiated therapy between January 1, 2000, and December 31, 2005, in a large study of Medicare patients >65 years of age. No significant differences were found in rates of MI. The current study evaluated risk of AMI, AHF, and death in a subpopulation of patients ≥65 years of age and found no significant differences between rosiglitazone or pioglitazone use during the period January 1, 2000, to December 31, 2005. Although the Winkelmaier study evaluated incidence relative rates, our study population had very few preindex events of interest, making the populations somewhat comparable though overall sample in the Winkelmaier study was much larger. Mean age was similar between the 2 studies, though preindex CV and diabetes-related comorbidities were higher in the Winkelmaier study. Mean duration of index therapy was approximately 3 months longer in the current study. Both studies included relevant covariates in their multivariate analyses; however, the current study used propensity score matching in the full sample to ensure similarity at baseline between groups. Propensity score matching was not used in the subsample of patients ≥65 years of age because of the small sample size; however, no significant differences were observed in baseline characteristics between groups except index year.

Juurlink et al. evaluated time to composite of death, AMI, or AHF in patients >65 years of age who initiated rosiglitazone or pioglitazone between April 1, 2002, and March 31, 2008, and found 17% greater risk associated with rosiglitazone-treated patients (HR, 0.83; 95% CI, 0.76 to 0.90). When evaluating each outcome individually, rosiglitazone was associated with a 23% significantly greater risk for AHF and a 14% significantly greater risk of death. Similar to the Winkelmaier study, no significant differences were found in risk of AMI. Age, sex, and preindex comorbidities were similar between the Juurlink and current study, though higher use of metformin and sulfonylureas were noted in the Juurlink study. The Juurlink study censored patients at 3 years total observation or until end of the study, whichever occurred first. Mean therapy duration was approximately 6 months longer in the current study compared with the Juurlink study. Last, the Juurlink study evaluated patients with the use of an Ontario health insurance plan database, which may reflect differences in treatment between study populations. It is important to note that both the Winkelmaier and Juurlink studies included only elderly patients. The current study included younger patients enrolled in commercial health plans and could potentially reflect a healthier population; even elderly patients in the current study have full health coverage and may still be employed; thus they may be healthier than other older study populations. Furthermore, the number of elderly patients in the current study is small and unlikely to detect small differences between cohorts.

There are several possible explanations for the absence of an elevated risk for rosiglitazone in the present analysis. As discussed, one is the possibility that the commercially insured, relatively young population studied was less susceptible to an increased risk, and/or that there were too few events to document such risk, especially among the elderly. We did attempt to test the latter assumption by performing the same analyses in a subpopulation of older patients (ie, patients who were ≥65 years of age). Although event rate in this population dramatically increased, there was no significant difference in risk between groups. Last, another explanation for absence of elevated risk is that both rosiglitazone and pioglitazone confer an additional CV risk and that this would result in lack of difference between drugs when they were compared with one another.

**Study Limitations**

Administrative claim analyses are likely to be affected by channeling bias because patients may be more or less likely to receive a newer treatment if they had a poor response or an adverse event associated with an existing treatment. To address this potential bias, propensity score matching was used to help control channeling bias. Comparison of the data shows there were few differences between groups before matching. After matching, no statistically significant differences were observed in the variables of interest between patients in the preindex period.

A large database study provides greater number of patients and more statistical power to detect small differences; how-
ever, the study’s statistical power is limited by the rarity of events in the population and the ability to detect small differences in cohorts. In addition, because the current study database encompasses a commercially-insured population, elderly patients and those with substantial chronic illness who are at highest risk are underrepresented relative to the overall US population.

The majority of deaths in diabetic population are CV-related; thus, disease duration is a strong predictor of CVD. In this study, we could not assess length of time patients had diabetes because the preindex period was only 1 year; however, diabetes severity was accounted for in the multivariate model by identifying claims for diabetes-related complications. Furthermore, this study excluded patients who used insulin before TZD use because this may imply the disease has progressed to become a confounding factor related to AMI. However, because only a small subset of patients had electronic laboratory values available, no laboratory values (HbA1c, glucose) were evaluated to assess degree of diabetes control. Nonetheless, there was no reason to expect that glycemic control would differ between rosiglitazone and pioglitazone users.

In addition, claims for obesity and smoking status are likely to be undercoded, though it is assumed that it is nondifferential between cohorts. Last, the possibility remains that results were affected by unmeasured confounders (eg, body mass index, exercise, family history of CV disease, aspirin use) that have no surrogate in claims data. As a result, if these were differentially distributed across groups, comparisons between groups might miss the independent effect of treatment on CV event risk.

Despite these limitations, results of this study are particularly important to consider in light of the recent US Senate Finance Committee report regarding potential risks of rosiglitazone and the ongoing TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) CV safety trial comparing rosiglitazone to pioglitazone. Given that rosiglitazone is scheduled for review with the FDA later this year, it will be important for the FDA to have available all evidence for consideration at that time.

Conclusion
In the present retrospective study directly comparing rosiglitazone and pioglitazone with a propensity score–matched population, no significant differences were found in risk of AMI, AHF, or all-cause death. Previous meta-analysis, prospective studies, and observational studies have provided inconsistent results that make evaluating the safety and effectiveness of TZDs challenging. Further research to refine methodology, identify population segments potentially at elevated risk, and validate data/exposure using additional data elements such as medical charts and/or surveys is essential. Nevertheless, this study provides valuable results that contrast previously published observational data and adds to the body of evidence available for risk-benefit profile assessment of TZDs in the treatment of diabetes.

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