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Association Between Extent of Thiazolidinedione Exposure and Risk of Acute Myocardial Infarction

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Abstract

Study Objectives—To determine if an association exists between thiazolidinedione (rosiglitazone or pioglitazone) exposure and acute myocardial infarction, and if the timing of drug initiation relative to the onset of myocardial infarction affected the frequency of the event.

Design—Nested, case-control study.

Data Source—Health care claims from California, Florida, New York, Ohio, and Illinois from the Medicaid Analytic Extract database for calendar years 2001–2002.

Patients—Of patients who received metformin plus a sulfonylurea during a defined eligibility period, we identified 2316 cases who had a primary discharge diagnosis of acute myocardial infarction and 9700 controls, who were defined by means of risk-set sampling.

Measurements and Main Results—We reviewed demographic and clinical characteristics of the cases and controls, and documented initiation of thiazolidinedione therapy. We noted the time of therapy initiation within 180 days of the index date (date of acute myocardial infarction for cases, same date for matched controls) and assessed any association between the start of thiazolidinedione therapy and acute myocardial infarction, relative to use of metformin plus a sulfonylurea. We performed secondary analyses using various time intervals between start of thiazolidinedione and onset of event (0–90 and 91–180 days before the index date). Applying conditional logistic regression, we obtained adjusted odds ratios (AORs) and 95% confidence intervals (CIs). After adjustment for confounding, starting rosiglitazone (AOR 1.00, 95% CI 0.72–1.39) or pioglitazone (AOR 1.04, 95% CI 0.74–1.45) therapy in the 180 days before the index date was not associated with acute myocardial infarction. Point estimates for rosiglitazone (AOR 1.29, 95% CI 0.85–1.94) and, less so, pioglitazone (AOR 1.15, 95% CI 0.73–1.81) in the 90 days before the index date suggested a small increase in the rate of acute myocardial infarction shortly after the start of these drugs; however, the CIs were wide.

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Conclusion—Starting thiazolidinedione therapy was not associated with acute myocardial infarction. However, our data did not exclude the possibility of elevated risk immediately after beginning therapy. Clinicians should be cautious when prescribing thiazolidinediones, especially rosiglitazone, for patients at high risk for having an acute myocardial infarction.

Keywords

pharmacoepidemiology; Medicaid Analytic Extract; thiazolidinedione; rosiglitazone; pioglitazone; myocardial infarction

The United States Food and Drug Administration recently expanded the black-box warning for rosiglitazone to include a potential for ischemic cardiac adverse effects.¹ Studies have revealed conflicting results about the cardiovascular safety of thiazolidinediones, a class of drugs that includes rosiglitazone and pioglitazone. Outcomes have ranged from estimates of no effect in two epidemiologic studies^{2,3} to an estimated 43% increase in the rate of acute myocardial infarction in a meta-analysis of randomized trials of rosiglitazone.⁴ Another meta-analysis showed that pioglitazone lowered the risk of acute myocardial infarction by 18%,⁵ which was similar to the estimate derived from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) trial.⁶ The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study, a randomized trial of rosiglitazone that focused on cardiovascular outcomes, uncovered no increased risk of cardiovascular events among users of rosiglitazone after a mean follow-up of 3.75 years.⁷

The mechanism by which thiazolidinediones could increase cardiovascular risk is uncertain. One hypothesis is that thiazolidinediones adversely affect serum lipid levels.⁸ The drugs cause an increase in intravascular volume and body mass, which may raise myocardial oxygen demand.^{4,8} Each potential causal mechanism is likely related to a specific time frame of increased risk. If thiazolidinediones cause acute myocardial infarction by expanding intravascular volume, the effect would appear quickly (e.g., within 60–90 days) because this physiologic effect occurs rapidly after the start of therapy.^{8,9} We hypothesized that the delayed consequences of weight gain and adverse effects on serum lipid levels would likely require more time than this (e.g., up to 180 days) to induce acute myocardial infarction. Previous studies showed slight weight gain at 12 weeks, which persisted to 1 year after the start of thiazolidinedione therapy.^{10,11}

The purpose of this nested case-control study was to determine if an association exists between thiazolidinedione (rosiglitazone or pioglitazone) use and the frequency of acute myocardial infarction. We evaluated patients in a Medicaid population starting rosiglitazone or pioglitazone versus those receiving metformin plus a sulfonylurea. We also assessed if the time interval between starting thiazolidinedione therapy and onset of the acute myocardial infarction had any effect on the frequency of the event. We evaluated the timing to further our understanding of the potential mechanism by which thiazolidinediones may exacerbate acute cardiovascular events.

Methods

Data Source

To identify our patient population for this nested case-control study, we used the Medicaid Analytic Extract (MAX) database, a centralized collection of state Medicaid claims. The database provides patient-specific information on dispensed outpatient drugs, outpatient services, hospital utilization, long-term care residence, and other services. Diagnoses and procedures are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and/or *Current Procedural Terminology, Fourth Edition*. Drugs are recorded according to national drug codes. We linked national drug codes to the Multum Lexicon (Cerner Multum, Denver, CO) to ascertain drug names, strengths, dosage forms, and routes of administration. We used MAX data from California, Florida, New York, Ohio, and Illinois from calendar years 2001–2002, the most recent data that were available. These states represented areas containing large Medicaid-covered populations with substantial racial and ethnic diversity.

Study Population

Our cohort consisted of individuals who had enrolled in fee-for-service Medicaid coverage for at least 180 days and who used both metformin plus a sulfonylurea during their Medicaid enrollment. The MAX data did not contain exact dates of eligibility; therefore, we defined eligibility as two or more claims for any Medicaid service. Cohort eligibility began on the date of the first claim and ended on the date of the last claim. Defining eligibility in this manner offered an additional advantage in that it increased the likelihood that we could fully assess study variables and compare participants with regard to factors that influenced Medicaid use. We used 180 days of enrollment as a criterion to ensure that all required data would be available.

Before identifying cases and controls from our cohort, we noted that certain patient characteristics (e.g., obesity) were not recorded completely in the Medicaid claims. We used proxy measures that correlated with these characteristics, and to increase comparability between cases and controls with respect to unmeasured characteristics, we excluded individuals who lacked at least one inpatient claim; that is, each person needed to have at least one hospitalization claim and at least one additional outpatient or inpatient claim.

We then identified those patients who had a primary discharge diagnosis of acute myocardial infarction (ICD-9-CM 410.xx). This code has an estimated positive predictive value of 94% in a Medicare population.¹² We excluded those patients without 180 days of eligibility before their first acute myocardial infarction and those who did not match to at least one control; the remaining patients were considered our case patients.

We randomly selected up to five age- and state of residence–matched controls from the cohort using risk-set sampling.¹³ Thus, potential controls were sampled from the pool of eligible persons at risk when the case occurred; this method allowed for controls to later become cases and for individuals to serve as controls for more than one case.¹⁴ We required controls to have 180 days of eligibility before the matched case's index date. The index date was defined as the date on which acute myocardial infarction occurred.

Drug Exposure

The MAX pharmacy file comprehensively recorded all Medicaid-reimbursed transactions at outpatient and long-term care pharmacies. We defined exposure to rosiglitazone or pioglitazone in multiple ways to determine how timing of therapy could affect the rate of acute myocardial infarction. For the primary analysis, we considered persons exposed if they started taking pioglitazone or rosiglitazone in the 180 days before the index date. This definition was used to assess whether thiazolidinediones increased the rate of acute myocardial infarction by any quick-acting mechanism, and it was consistent with the window of time that we considered necessary to fully examine study variables before the index date.

Participants were considered new users of a thiazolidinedione if they met the eligibility criteria and had not taken thiazolidinediones within the 180 days before initiation of the drug. Users of pioglitazone or rosiglitazone who did not meet this definition were evaluated by using separate variables that represented them as prevalent users of the drugs.

For our secondary analyses (for each comparison of rosiglitazone and pioglitazone), we defined variables representing a start of thiazolidinedione therapy within 0–90 or 91–180 days before the index date. We used these exposure definitions to refine our understanding of the timing of the potential effect under study, as we hypothesized that timing was related to the potential causal mechanism.

We considered all dosages and durations in the 180 days before the index date. Data from patients who used both pioglitazone or rosiglitazone during this period were excluded from the primary estimates. We created a separate variable to evaluate these participants.

Potential Confounders

We considered as potential confounders various demographic characteristics, previous diagnoses, drug use, and factors related to use of health care that may have affected the risk for acute myocardial infarction. These confounders included age, sex, and race-ethnicity, as well as a previous diagnosis of obesity, angina pectoris, unstable angina, previous myocardial infarction, previous coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention), other coronary disease (e.g., chronic coronary insufficiency, arteriosclerosis), chronic heart failure, cardiomyopathy, cerebrovascular disease, hypertension, hyperlipidemia, smoking, chronic pulmonary disease, depression, bipolar disorder, and dementia.^{15–17}

From the MAX personal summary files, we collected age, sex, and race-ethnicity data as reported by the states' Medicaid programs. Participants had a potentially confounding diagnosis if any field on their claims in their inpatient, long-term care, or other therapies file listed at least one appropriate ICD-9-CM diagnostic code during the defined eligibility period before the index date.

We also assessed as potential confounders the effect of the Charlson comorbidity index,^{18,19} of at least one previous nursing home visit, and of multiple previous hospitalizations. Using data from each person's eligibility period, we calculated the Charlson comorbidity index and

categorized it to reflect a low (score of 0–1), medium (2–3), or high (4) burden of comorbidity.

Another potential confounder was systemic (excluding ophthalmic and otic drugs) use of certain drugs during eligibility but before the index date. These drugs were first-generation sulfonylureas (for sensitivity analyses), nonsulfonylurea secretagog, α -glucosidase inhibitors, cholesterol-lowering drugs, diuretics, β -blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, α -blockers, antiplatelet agents, digoxin, antiarrhythmics, benzodiazepines, non-benzodiazepine hypnotics, anticonvulsants, opiates, atypical antipsychotics, antidepressants, antibiotics, corticosteroids, selective estrogen receptor modulators, and hormone replacements.^{20–26}

We classified patients as using a drug if the MAX pharmacy file indicated that the agent of interest was dispensed at least once before the index date.

Statistical Analysis

We set parameters for our exposure variables in several ways. In our cases and controls, use of both metformin and a sulfonylurea was required during the 180 days before the index date (date on which matched case had acute myocardial infarction). To minimize potential confounding, however, controls could have started these drugs before the 180 days. We included, as controls, all patients with claims showing evidence of any use of metformin plus a sulfonylurea. Although the duration of prevalent use of these drugs was unknown, our control group was expected to have had a longer history of diabetes mellitus (since they had been taking antidiabetic drugs for a longer time) versus a group of patients who had just started metformin plus a sulfonylurea. Moreover, patients generally use metformin plus a sulfonylurea before starting a thiazolidinedione.²⁷ Therefore, the chosen exposure comparison group was most comparable to a group starting thiazolidinedione with respect to characteristics of diabetes, including the extent to which diabetes raises their risk of acute myocardial infarction. We applied no further restrictions on the use of the two drugs.

We used separate models to make three comparisons: first, any start of a thiazolidinedione relative to prevalent use of metformin plus a sulfonylurea in the 180 days before the index date; second, any start of a thiazolidinedione in the 0–90 or 91–180 days before the index date relative to prevalent use of metformin plus a sulfonylurea in the 180 days before the index date; and third, start of a thiazolidinedione with or without metformin plus a sulfonylurea versus prevalent use of metformin plus a sulfonylurea in the 180 days before the index date.

From conditional logistic regression models for variable-matched data, we derived crude and adjusted odds ratios (AORs) and 95% confidence intervals (CIs). Because we used risk-set sampling, we interpreted the ORs as incidence rate ratios.²⁸ To adjust for confounding, we used nonparsimonious modeling and included variables that we considered a priori to be potentially related to the occurrence of acute myocardial infarction. We did this to account for potential confounding due to joint distribution of multiple variables. We evaluated and ruled out multi-collinearity by monitoring for large (10-fold) increases in the standard error of any variable when a new factor was added to the model.

Results

Patient Characteristics

From the MAX database, a cohort of 307,121 individuals were identified who met our original study criteria. We then excluded 211,789 persons who did not have at least one inpatient claim, thus making our source population 95,332 individuals. From these patients, we selected 3825 cases but then excluded 1489 who did not have 180 days of eligibility before their first acute myocardial infarction and 20 who did not match to at least one control. This left 2316 cases for whom up to five age- and state of residence-matched controls were identified. A total of 9700 controls was used (1174 cases matched to five controls, 640 matched to four, 318 matched to three, 132 matched to two, and 52 matched to one).

Table 1 shows the distribution of principal demographic characteristics, previous diagnoses, and factors related to the use of health care. More than 40% of participants were aged 70 years or older. Cases and controls were well matched for age. Cases were more likely than controls to be non-Hispanic White (46% vs 39%) and less likely than controls to be non-Hispanic Black (14% vs 18%). A greater proportion of cases had higher overall Charlson comorbidity index scores than the control group. With regard to specific diagnoses, cases were more likely than controls to have had a myocardial infarction (50% vs 10%), unstable angina (16% vs 12%), and angina pectoris (18% vs 13%). Fewer than 20% of cases and controls had at least one claim for long-term care, and cases were more likely than controls to have had at least two inpatient hospitalization claims before the index date. Distributions of potential confounders were similar when compared among exposure categories.

Drug Use

Table 2 shows the distribution of drug use during the defined eligibility period before the index date. Both cases and controls commonly used cardiovascular drugs, with higher use of 13-blockers (46% vs 36%), cholesterol-lowering drugs (57% vs 51%), and nitrates (42% vs 29%) among the cases. Use of concomitant antidiabetic drugs was comparable between cases and controls, as was use of psychotropic and other drugs.

Table 3 summarizes the prevalent or incident use of antidiabetic drugs of interest in the 180 days before the index date. Eighty cases and 300 controls began taking rosiglitazone in the 180 days before the index date, whereas 70 and 269, respectively, started pioglitazone in the same period. The overall mode daily dose and dose range for rosiglitazone were the same between the groups. The overall mode daily dose of pioglitazone was higher among cases than controls (45 vs 30 mg). Doses of other drugs were comparable, with the exception of glipizide whose mode dose was higher in the case group than in the control group.

Risk of Acute Myocardial Infarction

Table 4 shows crude and adjusted ORs and 95% CIs for the start of rosiglitazone or pioglitazone at different times relative to prevalent use of metformin plus a sulfonylurea. Start of rosiglitazone (AOR 1.00, 95% CI 0.72–1.39) or pioglitazone (AOR 1.04, 95% CI 0.74–1.45) in the 180 days before the index date was not associated with the rate of acute

myocardial infarction. Adjusted ORs for beginning rosiglitazone or pioglitazone within 90 days of the index date suggested an increase in the rate of acute myocardial infarction, but the CIs were wide. Estimates comparing a start of rosiglitazone (AOR 1.04, 95% CI 0.72–1.51) or pioglitazone (AOR 1.16, 95% CI 0.80–1.68) within the 180 days before the index date with concurrent use of metformin plus a sulfonyleurea yielded no discernible increase in the rate of acute myocardial infarction.

Discussion

Initiation of a thiazolidinedione at anytime within the 180 days before the index date was not associated with an increase in the rate of acute myocardial infarction. Adjustment for potential confounders did not materially affect our estimates. Although these data were inconclusive because of wide CIs, our point estimates suggested a somewhat elevated rate of acute myocardial infarction among persons who started rosiglitazone and, less so, pioglitazone, in the 90 days before the index date. This finding was coupled with an estimate suggesting that start of the drug 90–180 days before the index date was associated with a lower rate of acute myocardial infarction. Although our CIs were consistent with a wide range of potential estimates, we could not rule out elevations in risk on the order of 80–90%. If rosiglitazone did indeed cause acute myocardial infarction, these data suggested that the effect may have occurred quickly, followed by a survivor effect. This survivor effect may represent depletion of the population susceptible to acute myocardial infarction.²⁹

Were this potential association true, it would support the notion that rosiglitazone increases the risk of acute myocardial infarction by increasing intravascular volume and, thereby, raising myocardial oxygen demand.^{4,8} Persons starting a thiazolidinedione are unlikely to accumulate enough excess adipose tissue in 90 days to substantially elevate their risk of acute myocardial infarction. Likewise, adverse influences of the thiazolidinediones on serum lipid levels are unlikely to exert a clinical effect this quickly.^{8,9} However, if rosiglitazone were indeed causing acute myocardial infarction by this mechanism, one would expect to see a similar relation between pioglitazone use and acute myocardial infarction because pioglitazone is known to cause fluid retention and to exacerbate chronic heart failure.⁹ Our data did not refute this notion, but the relevant estimates were closer to the null value for pioglitazone than for rosiglitazone.

We found appreciable differences in the baseline prevalence of risk factors for acute myocardial infarction between cases and controls, but we noted only small differences between crude and adjusted estimates. The level of net confounding was low because some characteristics were rare in the study population, and others were not substantially associated with exposure status. For our comparison exposure, we chose prevalent metformin plus a sulfonyleurea assuming that this would capture patients most like those starting thiazolidinedione with respect to important risk factors for acute myocardial infarction; many patients are taking metformin plus a sulfonyleurea just before starting a thiazolidinedione.²⁷

Although potential confounding due to unmeasured or poorly measured variables might have limited our study results, risk factors for acute myocardial infarction are well documented.³⁰

In addition, they are often addressed in clinical practice, especially primary care.³¹ Because patient counseling would have been coded as an outpatient service, and pharmacotherapy would have been recorded in the MAX pharmacy file, we generally had direct or proxy measures that were valid for ascertaining the vast majority of potential confounders. Two exceptions were smoking and obesity. Since thiazolidinediones cause slightly more weight gain than the sulfonylureas, the propensity to use these agents is plausibly related to baseline body mass.³² This fact could have induced preferential prescribing of thiazolidinediones to persons at low risk for acute myocardial infarction and could have diluted estimates of the relation between thiazolidinediones and acute myocardial infarction. However, because obesity is common among persons with diabetes, one would expect most of our cohort to be overweight or obese regardless of therapy; this situation decreases the probability that this type of confounding is at play. Confounding by smoking was also unlikely; we are unaware of data suggesting that smoking is related to the selection of one antidiabetic agent over another.

The results of our primary analysis comparing thiazolidinedione therapy initiation with use of metformin plus a sulfonylurea showed no increase in the rate of acute myocardial infarction. This outcome was consistent with those of two studies based on administrative data.^{2,3} In one study, as-treated Poisson regression analysis was performed to estimate the rate of acute myocardial infarction among users of thiazolidinediones.³ The other involved Kaplan-Meier plots of outcome-free survival time.² Neither analysis showed a relation between the timing of therapy initiation and the onset of a coronary outcome. In a claims-based epidemiologic study, use of rosiglitazone was associated with an early increase in the rate of acute myocardial infarction.³³

Although our estimates were imprecise, they did suggest an elevated rate of acute myocardial infarction shortly after rosiglitazone was started. The difference between our analysis and previous studies may have been due to multiple factors. First, our study population consisted of individuals who were older and generally sicker than previously studied groups. Our participants may have had a heightened baseline risk of acute myocardial infarction, which could have made them susceptible to the potential cardiac effects of increasing intravascular volume. Second, we evaluated the potential for time-varying effects by stratifying the patients relative to thiazolidinedione initiation. Analytic techniques in other studies may have inadvertently masked the potential for time-varying effects, especially Poisson regression, which has been used to evaluate current (incident and prevalent) use of the drugs.^{3,34}

Administrative data have certain advantages and disadvantages in etiologic research. Medicaid data provide information about a large and diverse population, many members of which have a high burden of comorbidity.³⁵ They allow for longitudinal assessments of the effects of drug use in a real-world setting. However, drug use is inferred from dispensings of the drugs of interest. A pharmacist's filling a prescription does not mean that the patient actually takes it. However, previous work has shown that these data are adequate for ascertaining drug exposure,³⁶ and researchers have used them for this purpose for years.³⁷ There is greater variability in the validity of using Medicaid data to ascertain disease

outcomes and potential confounders. However, a number of outcomes have been evaluated, including the ones we used,¹² and they have been shown adequate for etiologic research.

Despite our starting with more than 6 million patients, our study lacked power to rule out small elevations in risk in the subanalyses of interest, including evaluations of the influence of time of thiazolidinedione initiation relative to onset of myocardial infarction. However, our primary analysis for rosiglitazone had 90% power to detect an OR of 1.5 given an α of 0.05. Our subanalysis to compare use of rosiglitazone in the 0–90 and 91–180 days after the start had power greater than 90% to detect an OR of 2.0 ($\alpha = 0.05$). Because people qualify for Medicaid by being categorically or medically needy, they differ from the general population.³⁵ As a consequence, our results may not be generalizable to the population at large.

Conclusion

This study provides additional data regarding the potential association between thiazolidinedione use and the occurrence of acute myocardial infarction. Although our primary analysis revealed no increase in the rate of acute myocardial infarction among persons who started taking rosiglitazone or pioglitazone in the 180 days before the index date, point estimates from two secondary analyses suggested that rosiglitazone use may be associated with an increased rate of acute myocardial infarction immediately after its start. Analyses similar to ours must be conducted by using other data, especially evaluations with greater statistical power than ours to evaluate the effect of thiazolidinedione therapy at various time points after its initiation. Meanwhile, clinicians must be cautious when prescribing thiazolidinediones, especially rosiglitazone, for patients at high risk for having an acute myocardial infarction.

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Table 1

Demographic and Clinical Characteristics

Characteristic	No. (%) of Patients	
	Acute MI Cases (n=2316)	Controls (n=9700)
Age (yrs)^a		
< 50	197 (8.5)	869 (9.0)
50–59	468 (20.2)	1926 (19.9)
60–69	666 (28.8)	2800 (28.9)
70–79	664 (28.7)	2722 (28.1)
80	321 (13.9)	1383 (14.3)
Female sex	1436 (62.0)	6720 (69.3)
Race-ethnicity		
Non-Hispanic White	1067 (46.1)	3789 (39.1)
Non-Hispanic Black	318 (13.7)	1788 (18.4)
Asian	76 (3.3)	279 (2.9)
Hispanic or Latino	243 (10.5)	1153 (11.9)
Hawaiian or Pacific Islander	194 (8.4)	782 (8.1)
Other or unknown	418 (18.1)	1909 (19.7)
Charlson comorbidity index score		
0–1	800 (34.5)	5505 (56.8)
2–3	1027 (44.3)	3311 (34.1)
4	489 (21.1)	884 (9.1)
Medical history		
Obesity	132 (5.7)	884 (9.1)
Angina pectoris	396 (17.1)	1276 (13.2)
Unstable angina	360 (15.5)	1148 (11.8)
Previous MI	1152 (49.7)	917 (9.5)
Coronary revascularization	99 (4.3)	338 (3.5)
Other coronary artery disease ^b	975 (42.1)	3296 (34.0)
Chronic heart failure	772 (33.3)	2819 (29.1)
Cardiomyopathy	141 (6.1)	459 (4.7)
Cerebrovascular disease	464 (20.0)	2010 (20.7)
Hypertension	1526 (65.9)	6798 (70.1)
Hyperlipidemia	1416 (61.1)	5375 (55.4)
Smoking	103 (4.5)	551 (5.7)
Chronic pulmonary disease	669 (28.9)	3073 (31.7)
Depression	740 (32.0)	3411 (35.2)
Bipolar disorder	28 (1.2)	290 (3.0)

Characteristic	No. (%) of Patients	
	Acute MI Cases (n=2316)	Controls (n=9700)
Dementia	167 (7.2)	961 (9.9)
Health service utilization		
1 claim for long-term care before index date	367 (15.9)	1761 (18.2)
2 hospital stays during index year	748 (32.3)	2487 (25.6)

MI = myocardial infarction.

^aStudy participants were matched for age.

^bIncludes a diagnosis of coronary obstruction or embolism without or not resulting in MI, arteriosclerosis, coronary insufficiency, and certain sequelae of MI not classified elsewhere.

Table 2**Drug Therapy**

Drug	No. (%) of Patients	
	Acute MI Cases (n=2316)	Controls (n=9700)
Concomitant antidiabetic drugs		
First-generation sulfonylurea	11 (0.5)	28 (0.3)
Nonsulfonylurea secretagog	138 (6.0)	560 (5.8)
α -Glucosidase inhibitor	65 (2.8)	223 (2.3)
Cardiovascular drugs		
Cholesterol-lowering drug	1329 (57.4)	4902 (50.5)
Diuretic	1301 (56.2)	5183 (53.4)
β -Blocker	1060 (45.8)	3519 (36.3)
ACE inhibitor or ARB	1717 (74.1)	6771 (69.8)
Calcium channel blocker	1029 (44.4)	3950 (40.7)
Nitrate	979 (42.3)	2850 (29.4)
α -Blocker	131 (5.7)	567 (5.9)
Antiplatelet drug	1202 (51.9)	4393 (45.3)
Digoxin	395 (17.1)	1400 (14.4)
Antiarrhythmic	20 (0.9)	130 (1.3)
Psychotropic drugs		
Benzodiazepine	493 (21.3)	2251 (23.2)
Nonbenzodiazepine hypnotic	340 (14.7)	1510 (15.6)
Anticonvulsant	376 (16.2)	1919 (19.8)
Opiate	1028 (44.4)	4610 (47.5)
Atypical antipsychotic	216 (9.3)	1368 (14.1)
Antidepressant	866 (37.4)	4045 (41.7)
Other drugs		
Antibiotic	1629 (70.3)	7022 (72.4)
Corticosteroid	290 (12.5)	1450 (15.0)
Selective estrogen receptor modulator ^a	48 (2.1)	250 (2.6)
Hormone replacement ^a	184 (7.9)	1007 (10.4)

MI = myocardial infarction; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

^aEstimated among men and women.

Table 3Use of Antidiabetic Drugs in the 180 Days Before the Index Date^a

Drug	Acute MI Cases (n=2316)	Controls (n=9700)
No. (%) of Patients		
Rosiglitazone	320 (13.8)	1316 (13.6)
Pioglitazone	268 (11.6)	1052 (10.9)
Insulin	494 (21.3)	1915 (19.7)
Metformin	1743 (75.3)	6837 (70.5)
Glimeperide	216 (9.3)	905 (9.3)
Glyburide	1020 (44.0)	3462 (35.7)
Glyburide, micronized	23 (1.0)	117 (1.2)
Glipizide	772 (33.3)	3310 (34.1)
Mode Dose (range) (mg/day)		
Rosiglitazone	8 (2–16)	8 (2–16)
Pioglitazone	45 (15–60)	30 (15–45)
Insulin	100 U (7.5–333 U)	100 U (7.5–375 U)
Metformin	1000 (500–2550)	1000 (500–2550)
Glimeperide	4 (1–16)	4 (1–16)
Glyburide	10 (1.25–30)	10 (1.25–25)
Glyburide, micronized	12 (3–12)	12 (1.5–24)
Glipizide	20 (1–40)	10 (2.5–40)

^aExcludes data for 23 cases and 57 controls who used both pioglitazone and rosiglitazone and data from 615 cases and 3113 controls who did not use one of the listed drugs during this period.

Table 4

Estimated Effect of Rosiglitazone or Pioglitazone on the Rate of Acute Myocardial Infarction Relative to Combined Use of Metformin and a Sulfonylurea^a

Time of Drug Use	No. (%) of Patients		OR (95% CI)	
	Acute MI Cases (n=2316)	Controls (n=9700)	Crude	Adjusted ^b
Start of rosiglitazone				
Within 180 days before index date	80 (3.5)	300 (3.1)	0.99 (0.76–1.28)	1.00 (0.72–1.39)
Within 90 days before index date	54 (2.3)	150 (1.6)	1.32 (0.96–1.83)	1.29 (0.85–1.94)
Within 91–180 days before index date	26 (1.1)	150 (1.6)	0.65 (0.42–1.01)	0.68 (0.40–1.16)
With metformin + a sulfonylurea within 180 days before index date	62 (2.7)	209 (2.2)	1.08 (0.81–1.46)	1.04 (0.72–1.51)
Prevalent use of rosiglitazone	240 (10.4)	1016 (10.5)	0.89 (0.76–1.04)	0.87 (0.71–1.06)
Start of pioglitazone				
Within 180 days before index date	70 (3.0)	269 (2.8)	1.00 (0.76–1.32)	1.04 (0.74–1.45)
Within 90 days before index date	37 (1.6)	130 (1.3)	1.10 (0.76–1.59)	1.15 (0.73–1.81)
Within 91–180 days before index date	33 (1.4)	139 (1.4)	0.91 (0.61–1.34)	0.93 (0.57–1.50)
With metformin + a sulfonylurea within 180 days before index date	57 (2.5)	196 (2.0)	1.11 (0.82–1.51)	1.16 (0.80–1.68)
Prevalent use of pioglitazone	198 (8.6)	783 (8.1)	0.96 (0.81–1.14)	0.99 (0.80–1.23)
Prevalent use of metformin + a sulfonylurea	1529 (66.0)	5809 (59.9)	1.00	1.00

OR = odds ratio; CI = confidence interval.

^aExcludes data for 23 case subjects and 57 control subjects who used both pioglitazone and rosiglitazone.

^bAdjusted for sex, race-ethnicity, residence in long-term care, number of inpatient hospitalizations, Charlson comorbidity index, angina pectoris, previous myocardial infarction, cerebrovascular disease, unstable angina, other cardiovascular disease, hyperlipidemia, hypertension, previous coronary revascularization, chronic pulmonary disease, and use of the following drugs: first-generation sulfonylureas, α -glucosidase inhibitors, cholesterol-lowering drugs, diuretics, β -blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, α -blockers, antiplatelet agents, digoxin, antiarrhythmics, benzodiazepines, nonbenzodiazepine hypnotics, anticonvulsants, opiates, atypical antipsychotics, antidepressants, antibiotics, corticosteroids, selective estrogen receptor modulators, and hormone replacements.