**Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone**

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**ABSTRACT**

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**Context** Studies have suggested that the use of rosiglitazonemay be associated with an increased risk of serious cardiovascularevents compared with other treatments for type 2 diabetes.

**Objective** To determine if the risk of serious cardiovascularharm is increased by rosiglitazone compared with pioglitazone,the other thiazolidinedione marketed in the United States.

**Design, Setting, and Patients** Nationwide, observational,retrospective, inception cohort of 227 571 Medicare beneficiariesaged 65 years or older (mean age, 74.4 years) who initiatedtreatment with rosiglitazone or pioglitazone through a MedicarePart D prescription drug plan from July 2006-June 2009 and whounderwent follow-up for up to 3 years after thiazolidinedioneinitiation.

**Main Outcome Measures** Individual end points of acute myocardialinfarction (AMI), stroke, heart failure, and all-cause mortality(death), and composite end point of AMI, stroke, heart failure,or death, assessed using incidence rates by thiazolidinedione,attributable risk, number needed to harm, Kaplan-Meier plotsof time to event, and Cox proportional hazard ratios for timeto event, adjusted for potential confounding factors, with pioglitazoneas reference.

**Results** A total of 8667 end points were observed duringthe study period. The adjusted hazard ratio for rosiglitazonecompared with pioglitazone was 1.06 (95% confidence interval[CI], 0.96-1.18) for AMI; 1.27 (95% CI, 1.12-1.45) for stroke;1.25 (95% CI, 1.16-1.34) for heart failure; 1.14 (95% CI, 1.05-1.24)for death; and 1.18 (95% CI, 1.12-1.23) for the composite ofAMI, stroke, heart failure, or death. The attributable riskfor this composite end point was 1.68 (95% CI, 1.27-2.08) excessevents per 100 person-years of treatment with rosiglitazonecompared with pioglitazone. The corresponding number neededto harm was 60 (95% CI, 48-79) treated for 1 year.

**Conclusion** Compared with prescription of pioglitazone,prescription of rosiglitazone was associated with an increasedrisk of stroke, heart failure, and all-cause mortality and anincreased risk of the composite of AMI, stroke, heart failure,or all-cause mortality in patients 65 years or older.

**INTRODUCTION**

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Rosiglitazone and pioglitazone are the only thiazolidinedionescurrently marketed in the United States. In mid-2007, a meta-analysisof 42 randomized controlled trials involving rosiglitazone reporteda 1.4-fold increase in risk of acute myocardial infarction (AMI)compared with non-thiazolidinedione therapies.[1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-1) Subsequently,a meta-analysis of 19 randomized controlled trials with pioglitazonefound a statistically significant reduction in the compositeoutcome of nonfatal AMI, stroke, and all-cause mortality anda nearly statistically significant reduction in nonfatal AMIalone,[2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-2) thereby suggesting a potential difference in cardiovascularrisk between the 2 thiazolidinediones.

The cardiovascular risks of rosiglitazone and pioglitazone havebeen compared with one another in several observational studies.[3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-3)-[11](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-11) Rosiglitazone increased AMI risk in 7 studies,[3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-3)-[6](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-6),[8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8)-[10](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-10)statistically significantly so in 3.[3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-3), [9](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-9)-[10](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-10) Stroke risk wasexamined in 2 studies, both of which reported a statisticallynonsignificant increase with rosiglitazone compared with pioglitazone.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [7](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-7) The risk of heart failure was statistically significantlyincreased with rosiglitazone compared with pioglitazone in 3studies,[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [7](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-7)-[8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8) with a nonsignificant increase in one other.[11](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-11) Lastly, the risk of all-cause mortality was statistically significantlyincreased with rosiglitazone compared with pioglitazone in 2studies.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8)

The availability of prescription drug data for Medicare beneficiaries,beginning with introduction of the Part D benefit in January2006, provided an opportunity to investigate whether rosiglitazoneincreases cardiovascular and mortality risks using a large,nationally representative population of elderly patients withtype 2 diabetes newly treated with a thiazolidinedione.

**METHODS**

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**Medicare Database**

Medicare is the largest health insurance program in the UnitedStates, providing coverage to persons 65 years or older, aswell as to persons younger than 65 years, who have end-stagerenal disease or are disabled.[12](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-12)-[13](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-13) Eligibility for MedicarePart A, which covers hospitalization expenses, begins automaticallyat age 65 years, whereas coverage for outpatient medical care(Part B) and prescription drugs (Part D) must be purchased.[13](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-13)-[14](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-14) Computerized data for Parts A and B are available from the1990s, while data for Part D are available since January 2006,when the Medicare prescription drug benefit took effect.

Claims for Parts A, B, and D are evaluated for data qualityand entered into an analyzable database, where they are linkedwith the Medicare Enrollment Database. Together, these provideinformation about demographic and enrollment characteristics,diagnoses, procedures, prescription drugs, and medical equipmentuse for each beneficiary. Prescription claims include days ofsupply and quantities dispensed and are mapped against referencedatabases to identify drug name and strength using the NationalDrug Code number.

We restricted the Medicare population to persons enrolled inParts A and B fee-for-service and Part D, because claims fromthese sources provide the data needed for research purposes.We linked these claims across all settings of care for eachbeneficiary, using a unique identifier to create a longitudinalrecord of each patient's health care utilization and relateddiagnoses.

**Design**

This study used a new-user inception cohort design. Patientswith at least 6 months of continuous Part D enrollment and atleast 12 months of continuous Parts A and B enrollment priorto the date of their first thiazolidinedione prescription andwho were 65 years or older on that date were identified; thosenot resident in a hospital or long-term care facility or receivinghospice care formed the rosiglitazone and pioglitazone inceptioncohorts.

During the year prior to thiazolidinedione initiation, datawere collected for each cohort member on the presence of cardiovascularor cerebrovascular disease, diabetes-related complications,lipid disorders, and other chronic medical conditions. The Charlsoncomorbidity score was calculated using claims from inpatienthospitalizations.[15](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-15)-[16](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-16) Data on use of medications prescribedfor the treatment of cardiovascular disease, diabetes, and otherchronic medical conditions were collected for the 6-month periodpreceding cohort entry. For purposes of analysis, these baselinevariables were separated into 2 categories: core (variablesfrequently included in analyses of cardiovascular end points)([Table 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T1) and [Table 2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T2)) and additional (variables more indicativeof general health or that represent medical conditions alreadycaptured by prescription drug use included as core variables)([Table 3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T3)). Data on race/ethnicity were based on self-declarationat the time of Medicare enrollment and were included to providean additional measure of cohort comparability.

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**Study End Points**

Acute myocardial infarction was defined by *International Classificationof Diseases, Ninth Revision* (*ICD-9*) code 410 in the first orsecond position of the hospital discharge diagnosis. In recentstudies, code 410 had a positive predictive value (PPV) between89% and 97% in a variety of US and Canadian administrative claimsdatabases.[17](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-17)-[21](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-21) Of note, code 410 in the first or second positionhad a PPV of 94% in a recent study using Medicare Part A data.[20](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-20) Out-of-hospital death occurring within 1 day of an emergencydepartment visit for acute ischemic heart disease was also classifiedas fatal AMI.[22](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-22)

Stroke was identified by *ICD-9* hospital discharge diagnosiscodes 430, 431, 433.x1, 434.x1, and 436, located in the firstposition only. When listed as the first discharge diagnosis,these codes have a PPV of 92% to 100%.[23](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-23)-[25](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-25)

Heart failure was identified by *ICD-9* hospital discharge diagnosiscodes 402.x1, 404.x3, and 428 in the first position only. Thesecodes have a PPV of 85% to 96%.[26](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-26)-[28](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-28)

All-cause mortality (referred to as "death" herein) was ascertainedby linkage to the Social Security Master Beneficiary Recorddatabase, which provides the date, but not cause, of death andcaptures more than 95% of deaths for persons 65 years or olderin the United States.[29](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-29)

Because cardiovascular disease accounts for nearly 70% of deathsin patients with diabetes,[30](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-30) all-cause mortality may be an indicatorof cardiovascular mortality in this study. For this reason,in addition to evaluating the time to event for the individualend points of AMI, stroke, heart failure, and death, we alsoevaluated the time to event for the composite end point of AMI,stroke, heart failure, or death.

**Follow-up and Analysis**

New users of rosiglitazone and pioglitazone underwent follow-upfrom cohort entry until the earliest occurrence of a study endpoint, a gap in continuous thiazolidinedione treatment exceeding7 days, a prescription fill for a different thiazolidinedione,a non–end-point hospitalization, or end of the study period(June 30, 2009). To guard against bias arising from informativecensoring, most importantly by events leading to death, anyend point events occurring within 14 days following a gap incontinuous treatment or admission to a hospital were countedin the analysis. This 14-day period of extended follow-up wasnot applied to thiazolidinedione switching, because it wouldnot be possible to distinguish effects attributable to rosiglitazonefrom those attributable to pioglitazone, nor was it appliedto censoring at the end of the study window because no datawere collected after that date.

Baseline characteristics of the thiazolidinedione cohorts werecompared using standardized mean differences, calculated asthe difference in means or proportions of a variable dividedby a pooled estimate of the standard deviation of the variable.[31](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-31) This measure is not influenced by sample size and is usefulfor comparing cohorts in large observational studies. A valueof 0.1 SD or less indicates a negligible difference in meansbetween groups.[31](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-31) Kaplan-Meier cumulative incidence plots weregenerated showing time to event for all end points. Unadjustedincidence rates and rate differences (attributable risk) with95% confidence intervals (CIs) were calculated using cumulativecohort follow-up time. Hazard ratios (HRs) with 95% CIs werecalculated using Cox proportional hazards models, stratifiedby prior history of a cardiovascular end point and cancer, withadjustment for all remaining covariates ([Tables 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T1), [2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T2), and [3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T3)).The proportional hazards assumption was assessed using a testof weighted Schoenfeld residuals.[32](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-32) The number needed to harmwas estimated using the attributable risk.

Preplanned sensitivity analyses included repetition of the mainanalysis with zero days of follow-up after a gap in thiazolidinedionetherapy or hospitalization to identify evidence of informativecensoring and repetition of the main analysis restricted tostrata defined by baseline treatment with insulin, metformin,sulfonylureas, nitrates, or statins. Several unplanned, posthoc analyses were performed to evaluate the failure of someCox proportional hazards models to meet the proportional hazardsassumption. These unplanned analyses included those restrictedto patients who entered the study before or after publicationof a widely publicized meta-analysis of rosiglitazone randomizedtrials on May 21, 2007,[1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-1) and partitioning of follow-up timeinto intervals of 0 through 2 months, more than 2 through 4months, and more than 4 months.

This study was performed as part of the SafeRx Project, a jointinitiative of the Centers for Medicare & Medicaid Services,the US Food and Drug Administration, and the Office of the AssistantSecretary for Planning and Evaluation. It was approved by theResearch in Human Subjects Committee of the Food and Drug Administration'sCenter for Drug Evaluation and Research. Analyses were performedusing Stata version 11 (StataCorp, College Station, Texas).

**RESULTS**

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During the study period, 227 571 patients initiated thiazolidinedionetherapy and contributed 101 126 to 101 323 person-yearsof follow-up, depending on the end point analyzed. The meanage was 74.4 years in both cohorts, with a median follow-upof 105 days (range, 1-1093). The cohorts were similar with respectto background characteristics, with the exception of a slightimbalance in the proportion receiving a prescription co-paymentsubsidy ([Table 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T1)). They were also similar with respect to priormedical conditions and medication use ([Tables 2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T2) and [3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T3)).

During follow-up, there were 1746 AMIs (21.7% fatal), 1052 strokes(7.3% fatal), 3307 hospitalizations for heart failure (2.6%fatal), and 2562 deaths from all causes among cohort members([Table 4](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T4)). For the composite of AMI, stroke, heart failure,or death, the attributable risk was 1.68 (95% CI, 1.27-2.08)excess events per 100 person-years of rosiglitazone comparedwith pioglitazone treatment. The corresponding number neededto harm for this composite end point was 60 (95% CI, 48-79)persons treated for 1 year to generate 1 excess event.

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Kaplan-Meier cumulative incidence plots showed no differencesin risk for AMI between rosiglitazone and pioglitazone but didshow evidence of increased risk of stroke, heart failure, anddeath and for the composite of all events with rosiglitazonecompared with pioglitazone ([Figure 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083F1) and [Figure 2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083F2)).

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The adjusted HRs for stroke, heart failure, death, and the compositeof AMI, stroke, heart failure, or death were increased for rosiglitazonecompared with pioglitazone ([Table 4](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#JOC05083T4)). The adjusted HR for AMIwas not significantly increased. The proportional hazards assumptionwas met for AMI, stroke, and heart failure but not for deathor the composite of AMI, stroke, heart failure, or death.

To evaluate the nature and importance of this nonproportionality,we performed a series of unplanned, post hoc analyses. We restrictedthe cohorts to the 110 950 patients who entered the studyprior to the May 21, 2007, publication of the rosiglitazonemeta-analysis by Nissen and Wolski.[1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-1) Nearly identical resultswere obtained for the main analysis ([eTable 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920/DC1)), and the proportionalhazards assumption was now also met for death. An analysis restrictedto patients who entered the study after the May 2007 publicationdate produced results similar to those for the prepublicationperiod ([eTable 1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920/DC1)). Of note, there were only 15 009 patientsreceiving rosiglitazone during this latter period, who contributed5400 person-years of exposed observation time, compared with101 612 patients receiving pioglitazone who underwent follow-upfor 40 400 person-years.

We also partitioned follow-up time into 3 periods and repeatedthe main analysis for death-related end points using the entire(prepublication and postpublication) study population ([eTable 2](http://jama.ama-assn.org/cgi/content/full/jama.2010.920/DC1)). The HRs for death and for the composite of AMI, stroke,heart failure, or death were increased with rosiglitazone comparedwith pioglitazone during the first interval (0 through 2 months),somewhat lower but still increased during the second interval(>2 through 4 months), and were increased to a greater degreeduring the third interval (>4 months) than during the first.The proportional hazards assumption was met during each follow-upinterval for both death-related end points, and the HRs forrosiglitazone compared with pioglitazone were statisticallysignificantly increased during the third and final interval(HR for death, 1.21 [95% CI, 1.05-1.39]; HR for the compositeof AMI, stroke, heart failure, or death, 1.23 [95% CI, 1.14-1.34]).

Several preplanned sensitivity analyses were performed. We repeatedthe main analyses on the entire study population without allowingfor the 14-day follow-up after hospital admission or a breakin thiazolidinedione use. In this analysis, patients dying afterhospital admission or experiencing any study end point shortlyafter stopping thiazolidinedione were not counted. The riskof stroke and heart failure with rosiglitazone compared withpioglitazone remained statistically significantly increased,as did risk for the composite end point of AMI, stroke, heartfailure, or death ([eTable 3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920/DC1)). With no extended follow-up, theHR for all-cause mortality was no longer increased (1.07 [95%CI, 0.95-1.22]).

We also examined the effect of rosiglitazone compared with pioglitazoneon risk of study end points within separate subpopulations definedby baseline use or nonuse of insulin, metformin, sulfonylureas,nitrates, and statins. The HRs for each end point were similarin patients with and without baseline use of these agents ([eTable 4](http://jama.ama-assn.org/cgi/content/full/jama.2010.920/DC1)).

**COMMENT**

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Use of rosiglitazone was associated with an increased risk ofstroke, heart failure, and death and the composite of AMI, stroke,heart failure, or death compared with pioglitazone among Medicarebeneficiaries 65 years or older. Both thiazolidinediones havebeen shown to increase the risk of heart failure compared withtreatment with placebo or other antidiabetes medications.[33](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-33)-[34](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-34) Our study found that rosiglitazone was associated with a1.25-fold (95% CI, 1.16-1.34) increase in risk of heart failurecompared with pioglitazone, similar to the risk increase reportedin 2 other studies conducted among elderly persons.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8) Of note,a differentially increased risk of heart failure with rosiglitazonewas also suggested by a meta-analysis of randomized trials forboth drugs.[35](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-35) Heart failure is associated with increased 1-yearand 4-year mortality, and this mortality effect is greater inpatients with diabetes,[36](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-36) an effect that would not be capturedby our study because follow-up did not continue beyond the acuteepisode.

We were unable to determine whether one or both thiazolidinedionesincrease or decrease the absolute risk of any outcome, becausewe did not have a reference group treated with non-thiazolidinedionemedications only. However, these data suggest that rosiglitazonewas associated with a 1.27-fold (95% CI, 1.12-1.45) increasedrisk of stroke and a 1.14-fold (95% CI, 1.05-1.24) increasedrisk of death compared with pioglitazone. Increased mortalityin elderly patients treated with rosiglitazone compared withpioglitazone, of a magnitude similar to that described here,has also been reported in other studies.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8)

The risk of AMI was not different between the 2 thiazolidinedionesin this study of elderly Medicare patients. Two other studiesconducted in elderly persons (mean age, 72-76 years) also foundno difference in AMI risk between the 2 thiazolidinediones.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-5), [8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8) In contrast, most studies that have reported an increasedrisk of AMI with rosiglitazone were conducted in younger populations(mean age, 54-65 years), and most required that patients surviveto hospitalization to be counted.[1](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-1), [3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-3)-[4](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-4),[9](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-9)-[10](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-10) There may be nodifference in AMI risk between the 2 drugs in elderly persons.However, it is also possible that the pattern of cardiovascularoutcomes for rosiglitazone compared with pioglitazone changeswith advancing age. The incidence of sudden cardiac death increasesnearly 6-fold between the sixth and eighth decades of life,[37](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-37) perhaps contributing to a shift toward fatal AMI that does notreach hospital to be counted. In an older population of patientswith diabetes, in which nearly 70% of deaths have an underlyingcardiovascular cause,[30](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-30) the effect of an increase in suddencardiac death might be even greater. While the reason for theincreased risk of death with rosiglitazone compared with pioglitazoneseen in the elderly patients in our study and others is notknown,[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-5), [8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920#REF-JOC05083-8) it is plausibly attributable to an increase in aspecific cause rather than to a diffuse increase in all causesof death. We believe that this specific cause is most likelycardiovascular.

The incidence rates of AMI, stroke, heart failure, and deathobserved for the pioglitazone cohort in our study were similarto those that can be calculated for the pioglitazone group ofthe PROactive trial, a large cardiovascular end point trialthat compared pioglitazone with other diabetes therapies (calculatedincidence rates from PROactive, per 100 person-years, were 1.6for AMI; 1.2 for stroke; 2.8 for heart failure; and 2.4 fordeath).[38](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-38) Although the mean age of patients in PROactive wasyounger than in our cohort (61.1 years vs 74.4 years), the PROactivecohort was rich in patients with established macrovascular disease,thereby making it more similar to an older population with longer-standingdiabetes. This similarity in rates suggests that event capturein our study was relatively complete. The event rates in ourstudy were also similar to those obtained by Juurlink et al[8](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-8) in a study of elderly patients with diabetes from Ontario, Canada.

Based on commercially available drug usage data purchased bythe US Food and Drug Administration (SDI, Vector One [VONA].US national prescription use of rosiglitazone and pioglitazone,1999-2009. Provided to the Food and Drug Administration undercontract), there were an estimated 2.84 million person-yearsof rosiglitazone use in patients 65 years or older in the UnitedStates from 1999-2009. With a number needed to harm of 60 personstreated for 1 year to produce 1 excess event of the compositeof AMI, stroke, heart failure, or death attributable to useof rosiglitazone rather than pioglitazone, the negative populationeffect of rosiglitazone may have been great.

Our study had a number of limitations. This was an observationalstudy, not a randomized trial, and so could be subject to biasesarising from confounding. To guard against this, we collecteddata on a wide array of variables known or suspected to be associatedwith the outcomes under study, as well as many variables relatedto general health. The 2 cohorts were virtually indistinguishablewith respect to these numerous baseline characteristics. Inthis regard, other observational studies that directly comparedrosiglitazone with pioglitazone also noted a marked similaritybetween drug groups with respect to baseline characteristicsand risk factors,[3](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-3)-[9](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-9) suggesting that the thiazolidinedionesare probably prescribed to comparable types of patients. Misclassificationof exposure or outcome is another potential limitation of observationalstudies but usually acts to reduce the strength of associations.We did not independently validate the diagnoses of AMI, stroke,or heart failure. There is currently no mechanism in place underthe SafeRx Project to obtain medical record data. However, the*ICD-9* diagnosis–coded case definitions that we adheredto in this study have been consistently well-validated in previousstudies using the same or similar hospitalization claims data.[17](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-17)-[28](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-28) Lastly, because prescription drug data from Medicare PartD have not been used extensively for purposes of comparativesafety, issues related to data quality must be considered. TheMedicare Part D data are collected and processed by the Centersfor Medicare & Medicaid Services in exactly the same manneras prescription data from Medicaid, which have been shown tobe complete and of high quality.[39](http://jama.ama-assn.org/cgi/content/full/jama.2010.920" \l "REF-JOC05083-39)

In conclusion, in a population of more than 227 000 patients65 years or older who initiated treatment with a thiazolidinedione,we found that, compared with pioglitazone, rosiglitazone wasassociated with an increased risk of stroke, heart failure,and death and an increased risk of the composite of AMI, stroke,heart failure, or death.

**AUTHOR INFORMATION**

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**Author Contributions:** Dr MaCurdy had full access to all of thedata in the study and takes responsibility for the integrityof the data and the accuracy of the data analysis.

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*Acquisition of data*: Worrall.

*Analysis and interpretation of data*: Graham, Ouellet-Hellstrom,MaCurdy, Ali, Sholley, Kelman.

*Drafting of the manuscript*: Graham, Ouellet-Hellstrom.

*Critical revision of the manuscript for important intellectualcontent*: Graham, Ouellet-Hellstrom, MaCurdy, Ali, Sholley, Worrall,Kelman.

*Statistical analysis*: Graham, Ouellet-Hellstrom, MaCurdy, Ali,Sholley.

*Obtained funding*: Graham, Worrall, Kelman.

*Administrative, technical, or material support*: Ouellet-Hellstrom,Worrall, Kelman.

*Study supervision*: Graham, MaCurdy.

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