

Comparison of Cardiovascular Outcomes in Elderly Patients With Diabetes Who Initiated Rosiglitazone vs Pioglitazone Therapy

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Background: Recent meta-analyses have raised the possibility that rosiglitazone maleate may increase the risk of ischemic cardiovascular events, whereas pioglitazone hydrochloride could not be linked to such a risk. We compared cardiovascular outcomes and mortality between patients initiating pioglitazone vs rosiglitazone therapy.

Methods: We assembled an inception cohort of Medicare beneficiaries older than 65 years with state-sponsored prescription drug benefits who had diabetes mellitus and initiated treatment with rosiglitazone or pioglitazone between January 1, 2000, and December 31, 2005. The study outcomes included all-cause mortality, myocardial infarction, stroke, and hospitalization for congestive heart failure.

Results: Of 28 361 patients selected, 50.3% initiated treatment with pioglitazone and 49.7% with rosiglitazone. Most baseline characteristics were similar between the groups. As preferred in drug safety research, we censored patients at crossover or at 60 days after discontinuation of

therapy with their study drug; during 29 060 person-years of follow-up, 1869 patients died. After adjustment for a large number of patient characteristics, Cox regression models revealed 15% greater mortality among patients who initiated therapy with rosiglitazone compared with pioglitazone (95% confidence interval, 5%-26%). Use of rosiglitazone was also associated with a 13% greater risk of congestive heart failure (95% confidence interval, 1%-26%). No differences between the 2 drugs were found in their rates of myocardial infarction or stroke.

Conclusions: Our findings from a large population-based cohort of US seniors are compatible with an increased risk of all-cause mortality and congestive heart failure in patients initiating therapy with rosiglitazone compared with similar patients initiating therapy with pioglitazone. Limitations of this study include residual confounding due to its nonrandomized nature.

Arch Intern Med. 2008;168(21):2368-2375

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IN 1997, THE AVAILABLE OPTIONS for the treatment of diabetes mellitus were expanded by a new class of oral hypoglycemic medications, the thiazolidinediones (TZDs). The TZDs sensitize end organs to insulin through their effect on the peroxisome proliferation-activated receptor γ .¹ The peroxisome proliferation-activated receptor system consists of a group of nuclear receptors (α , γ , and δ) that serve as transcription factors for genes important in glucose, lipid, and bone metabolism.² The main clinical benefits from TZD treatment are decreased insulin resistance, better glycemic control, and, thus, delayed requirement for initiation of insulin treatment in patients whose diabetes would otherwise no longer be controlled with oral agents.³ Troglitazone, the first TZD to be introduced into clinical practice in 1997, was removed from the market after safety concerns about hepatotoxicity. In 1999,

rosiglitazone maleate and pioglitazone hydrochloride were approved and marketed. It soon became apparent that these 2 TZDs also had important adverse effects. Both were shown to lead to an increased risk of congestive heart failure (CHF),¹ and a recent black box warning was added for both drugs cautioning their use in patients with preexisting CHF.⁴ Furthermore, in 2 independently conducted meta-analyses of very similar trials, rosiglitazone was associated with increased risks of myocardial infarction (MI) and CHF when compared with control groups.^{5,6} A similar meta-analysis of randomized trials also found an increased risk of CHF for pioglitazone.⁷ In contrast to the meta-analysis of rosiglitazone, however, patients receiving pioglitazone had a lower risk of the composite end point of death, MI, or stroke compared with patients randomized to the control arms of the studies included in the meta-analysis.⁷

These discrepant findings between rosiglitazone and pioglitazone prompted discussion about the continued marketability of rosiglitazone⁸ and whether patients receiving rosiglitazone should switch to pioglitazone therapy. However, to date, only sparse information has become available from head-to-head comparisons between these 2 drugs. A single randomized trial of 802 patients with type 2 diabetes mellitus treated by diet alone or monotherapy with an oral hypoglycemic agent compared the effects of these 2 TZDs on lipid levels and glycemic control for 24 weeks.⁹ Although the drugs achieved similar glycemic control, the study revealed lipid effects that markedly favored pioglitazone over rosiglitazone. However, the study was clearly not designed or powered to detect differences in important long-term clinical outcomes. A recent case-control study from Canada described increased odds of hospitalization for CHF or MI and of death in patients receiving TZD monotherapy compared with other oral hypoglycemic treatment combinations.¹⁰ Although the effect estimates gave the impression that these findings might be attributable to rosiglitazone and not pioglitazone use, no direct comparison between the 2 TZDs was performed because of the relatively small number of cases receiving one of these agents.¹⁰

We specifically designed and conducted the present study to provide information on this open research question. In a large cohort of elderly patients with diabetes who initiated therapy with a TZD, we tested for subsequent differences in cardiovascular outcomes and all-cause mortality between users of rosiglitazone and pioglitazone.

METHODS

STUDY POPULATION AND FOLLOW-UP

For this study, we used medical claims data from the New Jersey Pharmaceutical Assistance for the Aged and Disabled program (January 1, 1999, through December 31, 2004) and the Pennsylvania Pharmaceutical Assistance Contract for the Elderly program (January 1, 1999, through December 31, 2005). These means-tested programs provide comprehensive prescription drug coverage for eligible elderly patients in New Jersey and Pennsylvania. Neither program had any restrictions or prior-authorization programs in place for either TZD. The claims data from each drug-benefit program were merged with Medicare Parts A and B claims for these patients.

From National Drug Code numbers of all filled prescriptions, we identified all patients who filled a prescription for any TZD (index prescription). We then used the earliest TZD claim and required that at least 1 claim for any prescription be present both in the 6 months prior to and in more than 6 months prior to that index claim to ensure that the index claim represented new TZD use. Thus, we ensured that the index claim truly reflected new TZD use. Patients were retained whether they previously had or had not used any other diabetes drugs. We excluded patients who used troglitazone and those who initiated therapy with rosiglitazone or pioglitazone using a fixed-dose combination with metformin hydrochloride. Patients 65 years or younger on the index date were also excluded.

MAIN EXPOSURES

From the index prescription, we categorized patients as incident rosiglitazone or pioglitazone users. To assign exposure sta-

tus, our main analyses considered patients to be exposed until 60 days after the date on which the supply from their most recently filled prescription expired or until a prescription for the other TZD indicated exposure crossover, at which point patients were censored (as treated-exposure models). In secondary analyses, patients were considered exposed to their baseline drug indefinitely (constant-exposure models).

OTHER PATIENT CHARACTERISTICS

From the enrollment files, we defined each patient's age on the index date, sex, and race (white, black, or other). From claims spanning the 6 months before the index prescription, we ascertained previous diagnoses of complications due to diabetes (nephropathy, dialysis dependency, gastroparesis, retinopathy, and neuropathy), prior use of other diabetes drugs (insulin, sulfonylureas, metformin, and other), and the number of diabetes-related physician visits and hospital admissions. We also defined the presence of prior cardiovascular diagnoses (atrial fibrillation, coronary artery disease, CHF, cerebrovascular disease, hypertension, MI, and peripheral artery disease) and procedures (ie, angiography, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, and stent insertion). Prior use of cardiovascular medications was also ascertained from prescription claims during the 6 months before the first TZD claim, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, statins, antiplatelet drugs (ticlopidine hydrochloride and clopidogrel bisulfate), and nitrates. We further captured other comorbidities (ie, chronic obstructive pulmonary disease, dementia, depression, other mental disease, any malignancy, and obesity), prior health care utilization (ie, number of hospital days, physician visits, prescriptions for different generic drugs filled, and any nursing home stay), and calendar year of the index prescription.

OUTCOMES

Four different study outcomes were selected for study, the primary one being all-cause mortality. The secondary end points of MI, stroke (ischemic or hemorrhagic), and hospitalization for CHF were each ascertained from Medicare claims using previously validated algorithms that had positive predictive values of 94%, 96%, and 94% for accurately identifying the respective outcome of interest.¹¹⁻¹³

STATISTICAL ANALYSES

Patient characteristics were compared between those receiving rosiglitazone and pioglitazone using 2-tailed *t* tests for continuous variables and χ^2 tests for categorical variables.

For each end point, we calculated the number of patients in each group, their contributed person-years, the number of events experienced, and their event rates per 1000 person-years. Time-to-event analyses using Cox proportional hazards models were conducted for all outcome evaluations, and crude and fully adjusted incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs) were calculated using models that simultaneously blocked for state and calendar year. We searched for any violations of the proportionality assumption by testing for significance of interaction terms with time. The main analyses considered all patients who fulfilled the stated inclusion criteria; secondary analyses eliminated patients with any nursing home stays before the index date. Analyses of MI, stroke, and hospitalization for CHF were additionally stratified by the absence vs the presence of diagnosed cardiovascular disease, cerebrovascular disease, or CHF, respectively, be-

fore the index date. We also conducted subgroup analyses in strata defined by the presence or absence of prior insulin treatment and nitrate use, as well as formal tests for effect modification by these variables.

We used commercially available software (SAS for Windows, release 8.2; SAS Institute Inc, Cary, North Carolina) for all statistical analyses. This study was approved by the institutional review board of Brigham and Women's Hospital.

RESULTS

COHORT SELECTION AND CHARACTERIZATION

From the selection algorithm, we identified 28 361 study patients who were older than 65 years when they filled their first TZD prescription. Of those, 14 260 (50.3%) were incident pioglitazone users and 14 101 (49.7%) were incident rosiglitazone users. Baseline characteristics of pioglitazone and rosiglitazone users were very similar in demographics, with only minor differences in race, prior diabetes treatment, and complications from diabetes. Rosiglitazone users had more diagnosed coronary artery disease and CHF and less use of β -blockers and statins before the index date. These patients were also more likely to have resided in a nursing home and to have had more hospital days in the previous 6 months compared with pioglitazone users (**Table 1**).

STUDIES OF ALL-CAUSE MORTALITY

In our primary analyses (as-treated models) that censored patients who failed to refill their prescription within 60 days after their previous supply had ended, or who switched to the other TZD studied (only 0.5% switched TZDs), 1869 patients died during 29 060 person-years of follow-up (**Table 2**). Median (mean) time exposed to the study drug in as-treated models were 217 (380) and 215 (369) days for pioglitazone and rosiglitazone users, respectively. The corresponding crude event rates per 1000 person-years were 59.7 for pioglitazone and 69.2 for rosiglitazone initiators, which yielded an unadjusted IRR of 1.17 (95% CI, 1.06-1.28). Multivariate adjustment attenuated this estimate: rosiglitazone users had a 15% (95% CI, 5%-26%) increased mortality rate compared with pioglitazone users. Under constant-exposure assumptions of the initiated treatment, the relative mortality findings were less pronounced (**Table 3**). Unadjusted analyses revealed an IRR of 1.08 (95% CI, 1.02-1.14). After multivariate adjustment, rosiglitazone users had a 7% (95% CI, 1%-14%) increased mortality rate compared with pioglitazone users. These findings were essentially unchanged after eliminating all patients with a previous nursing home stay from analysis ($n=1867$; results not shown). The study findings were essentially unchanged in important subgroups, including those defined by prior insulin and nitrate use.

STUDIES OF CARDIOVASCULAR MORBIDITY

In as-treated models, 737 patients experienced an MI, with an event rate of 26.5 per 1000 person-years in rosiglitazone users and 24.7 in pioglitazone users (crude IRR, 1.10;

95% CI, 0.95-1.27) (Table 2). Multivariate adjustment revealed an IRR of 1.08 (95% CI, 0.93-1.25), which was more pronounced in patients who had not previously been diagnosed as having coronary artery disease (IRR, 1.17; 95% CI, 0.89-1.53) (Table 2). Similar findings were obtained for stroke, that is, no difference in stroke risk by glitazone used in continuous-exposure models, with on-drug exposure models suggesting a nonsignificant association toward greater stroke risk in rosiglitazone vs pioglitazone users who had been diagnosed as having cerebrovascular disease before the index prescription (IRR, 1.14; 95% CI, 0.92-1.41) (Table 2). In adjusted analyses, the time to first hospitalization for CHF was shorter in rosiglitazone compared with pioglitazone users, with a 13% (95% CI, 1%-26%) increased risk in on-drug exposure and an 11% (3%-19%) increased risk in constant-exposure models. This excess risk seemed to reside predominantly among patients who had not been diagnosed as having CHF before filling their first TZD prescription, with a 21% (95% CI, 3%-42%) increased risk in on-drug exposure models and a 19% (95% CI, 7%-31%) increased risk in constant-exposure models. The study findings were essentially unchanged in important subgroups, including those defined by prior insulin and nitrate use (data not shown).

COMMENT

In a large cohort of new users of rosiglitazone and pioglitazone, we found that—despite being very similar to new pioglitazone users—new rosiglitazone users experienced higher rates of all-cause mortality and a greater incidence of hospitalization for CHF. These findings were robust across different modeling and exposure assumptions. By contrast, our work did not demonstrate any difference in the risks of MI or stroke between the 2 drugs. To our knowledge, this is the first study specifically aimed at detecting any differences in relative cardiovascular safety between these 2 TZDs in typical elderly patients initiating such therapy.

These findings need to be considered in awareness of the limitations of this study. Patients were not randomized to receiving the 2 study drugs but were prescribed these at the discretion of their physicians. During the study years, there was no evidence of superiority of one drug over the other, suggesting that their use was random. From observed baseline characteristics, this assumption was supported. Very few differences in baseline characteristics existed, and their differences between the treatment groups, although statistically significant, were very small. Furthermore, multivariate adjustment should have removed the confounding from these observed imbalances. Clinical outcomes were not adjudicated, but their ascertainment from claims has been shown to be highly accurate in validation studies. We had no data on laboratory variables such as achieved glycemic control in our patients, but trials have demonstrated comparable achieved glycosylated hemoglobin A_{1c} concentrations between the 2 TZDs.⁹ Furthermore, hemoglobin A_{1c} is a relatively poor marker of subsequent cardiovascular outcomes in type 2 diabetes mellitus. Although superior to

Table 1. Baseline Characteristics of Study Patients by Drug Exposure Class

Characteristic	% of Patients	
	Pioglitazone Hydrochloride (n=14 260)	Rosiglitazone Maleate (n=14 101)
Mean age, y	76.3	76.3
Male	26.0	26.4
Race		
White	86.2	85.0
Black	10.1	10.9
Other	3.7	4.1
Diabetes medications		
Insulin	18.2	16.8
Metformin hydrochloride	33.1	33.3
Sulfonylurea	56.2	55.6
Other	5.6	5.3
Diabetes complications		
Nephropathy	4.3	4.4
Gastroparesis	0.4	0.4
Retinopathy	6.8	7.1
Neuropathy	12.3	11.7
Mean No. of diabetes-related physician visits	5.5	5.5
Any diabetes-related hospital admission	7.0	7.4
Prior cardiovascular diagnoses		
Atrial fibrillation	13.5	14.0
Coronary artery disease	39.2	41.1
CHF	21.1	22.4
Cerebrovascular disease	15.8	16.6
Hypertension	56.5	57.1
MI	1.8	2.2
Peripheral vascular disease	14.7	14.8
	Pioglitazone (n=14 672)	Rosiglitazone (n=16 047)
Prior cardiovascular procedures		
Angiography	3.9	3.7
Coronary artery bypass graft	0.9	0.9
PTCA	1.2	1.1
Stent	1.1	1.1
Prior cardiovascular medications		
ACEIs/ARBs	39.7	39.9
β-Blockers	33.7	32.8
Statins	39.1	37.4
Antiplatelet medications	9.5	9.4
Nitrates	19.9	19.6
Other comorbid conditions		
Chronic obstructive lung disease	17.7	17.9
Dementia	6.1	6.8
Depression	9.8	10.1
Dialysis	0.5	0.5
Liver disease	0.2	0.2
Malignancy	13.7	13.9
Obesity	4.9	4.4
Other mental conditions	5.2	5.4
Skin cancer	1.8	1.7
Health care utilization in preceding 180 days		
Nursing home	6.1	7.1
Mean No. of different drugs	8.3	8.1
Mean No. of hospital days	2.7	3.1
Mean No. of physician visits	5.2	5.2
Year of index prescription (relative share of prescriptions)		
2000	47.3	52.7
2001	48.0	52.0
2002	49.7	50.3
2003	51.1	48.9
2004	52.8	47.2
2005	57.2	42.8

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CHF, congestive heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Table 2. Associations of New Pioglitazone vs New Rosiglitazone Use and Subsequent Clinical Outcomes (On-Drug Exposure Models)

	Exposure ^a	No. of Patients	Person-Years	No. of Events	Event Rates per 1000 Person-Years	IRR (95% CI)	
						Crude	Adjusted
All-cause mortality	Pioglitazone	14 260	14 830	885	59.7		
	Rosiglitazone	14 101	14 230	984	69.2	1.17 (1.06-1.28)	1.15 (1.05-1.26)
MI	Pioglitazone	14 260	14 686	363	24.7		
	Rosiglitazone	14 101	14 122	374	26.5	1.10 (0.95-1.27)	1.08 (0.93-1.25)
Prior CAD	Pioglitazone	5595	5262	255	48.5		
	Rosiglitazone	5788	5224	265	50.7	1.08 (0.91-1.28)	1.06 (0.89-1.26)
No prior CAD	Pioglitazone	8665	9424	108	11.5		
	Rosiglitazone	8313	8898	109	12.2	1.11 (0.85-1.45)	1.17 (0.89-1.53)
Stroke	Pioglitazone	14 260	14 651	388	26.5		
	Rosiglitazone	14 101	14 066	398	28.3	1.09 (0.95-1.25)	1.07 (0.93-1.23)
Prior CVD	Pioglitazone	2257	1947	170	87.3		
	Rosiglitazone	2335	1929	193	100.1	1.16 (0.94-1.43)	1.14 (0.92-1.41)
No prior CVD	Pioglitazone	12 003	12 704	218	17.2		
	Rosiglitazone	11 766	12 137	205	16.9	1.00 (0.82-1.21)	1.00 (0.82-1.21)
Hospitalization for CHF	Pioglitazone	14 260	14 616	614	42.0		
	Rosiglitazone	14 101	14 022	645	46.0	1.12 (1.00-1.25)	1.13 (1.01-1.26)
Prior CHF	Pioglitazone	3009	2486	317	127.5		
	Rosiglitazone	3163	2472	320	129.4	1.01 (0.87-1.18)	1.04 (0.89-1.22)
No prior CHF	Pioglitazone	11 251	12 130	297	24.5		
	Rosiglitazone	10 938	11 549	325	28.1	1.19 (1.02-1.40)	1.21 (1.03-1.42)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CVD, cerebrovascular disease; IRR, incidence rate ratio; MI, myocardial infarction.

^aPioglitazone is pioglitazone hydrochloride and rosiglitazone is rosiglitazone maleate.

Table 3. Associations of New Pioglitazone vs New Rosiglitazone Use and Subsequent Clinical Outcomes (Constant-Exposure Models)

	Exposure ^a	No. of Patients	Person-Years	No. of Events	Event Rates per 1000 Person-Years	IRR (95% CI)	
						Crude	Adjusted
All-cause mortality	Pioglitazone	14 260	25 619	2200	85.9		
	Rosiglitazone	14 101	25 597	2325	90.8	1.08 (1.02-1.14)	1.07 (1.01-1.14)
MI	Pioglitazone	14 260	25 160	846	33.6		
	Rosiglitazone	14 101	25 187	856	34.0	1.04 (0.95-1.15)	1.01 (0.92-1.12)
Prior CAD	Pioglitazone	5597	9407	568	60.4		
	Rosiglitazone	5788	9725	590	60.7	1.04 (0.93-1.17)	1.01 (0.90-1.14)
No prior CAD	Pioglitazone	8665	15 752	278	17.6		
	Rosiglitazone	8313	15 463	266	17.2	1.01 (0.85-1.19)	1.04 (0.88-1.23)
Stroke	Pioglitazone	14 260	25 077	928	37.0		
	Rosiglitazone	14 101	25 059	941	37.6	1.03 (0.94-1.13)	1.03 (0.94-1.12)
Prior CVD	Pioglitazone	2257	3611	400	110.1		
	Rosiglitazone	2335	3609	413	114.4	1.05 (0.91-1.20)	1.03 (0.89-1.18)
No prior CVD	Pioglitazone	12 003	21 466	528	24.6		
	Rosiglitazone	11 766	21 450	528	24.6	1.01 (0.81-1.14)	1.00 (0.88-1.13)
Hospitalization for CHF	Pioglitazone	14 260	24 936	1408	56.5		
	Rosiglitazone	14 101	24 846	1509	60.7	1.11 (1.03-1.19)	1.11 (1.03-1.19)
Prior CHF	Pioglitazone	3009	4573	718	157.0		
	Rosiglitazone	3163	4746	734	154.7	1.00 (0.91-1.11)	1.01 (0.91-1.12)
No prior CHF	Pioglitazone	11 251	20 362	690	33.9		
	Rosiglitazone	10 938	20 101	775	38.3	1.18 (1.07-1.31)	1.19 (1.07-1.31)

Abbreviations: See Table 2.

^aPioglitazone is pioglitazone hydrochloride and rosiglitazone is rosiglitazone maleate.

drug exposure ascertainment using other methods, claims data assume that patients actually take the medications they receive at the pharmacy.

These limitations are balanced by the strengths of this study. From a large database of lower–middle class senior citizens from 2 eastern states, we generated a large

cohort of new TZD users. We used an inception cohort design that is superior to prevalent user designs in that selection biases can be controlled better.^{14,15} By focusing on the specific comparison between 2 similar drugs that were perceived as equal at the time, we were able to avoid dealing with unobserved confounding that is arguably

present in studies comparing TZDs with other diabetes regimens. Both study drugs were freely available for prescription in both states, without any requirement for prior authorization or other restrictions and were available to patients for an equally small copayment. We subjected our analyses to several sensitivity analyses regarding the drug exposure definition, period covered, and patient characteristics. The results as reported remained robust throughout these tests.

Although both rosiglitazone and pioglitazone had been associated with increasing the risk of CHF, subsequently leading to a black box warning, the question of the cardiovascular safety of TZDs was brought to center stage only recently. In 2007, meta-analyses of rosiglitazone trials showed an increased risk of MI and a nonsignificant trend toward increased cardiovascular mortality in the rosiglitazone treatment groups compared with patients in the comparison arms of these trials.^{5,6} A similar meta-analysis of pioglitazone trials, by contrast, showed reduced event rates of a composite end point consisting of MI, stroke, and cardiovascular mortality.⁷ The results of this meta-analysis were predominantly driven by data from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (the PROactive Study).¹⁶ Although caution needs to be applied in drawing any direct inference on the differences in cardiovascular safety between the 2 TZDs from these separate meta-analyses, an impression is left that rosiglitazone therapy may generate undue harm without any additional clinical benefit. Weighing the evidence from these meta-analyses, however, an advisory panel of the US Food and Drug Administration voted against a ban of rosiglitazone and requested further research on the safety of this drug.⁸

Indeed, studies comparing rosiglitazone and pioglitazone are scarce. A single randomized controlled trial comparing the 2 drugs was conducted in 802 patients with type 2 diabetes mellitus for 24 weeks of follow-up.⁹ The trial aimed to describe metabolic differences in users of the 2 drugs. Compared with rosiglitazone, pioglitazone was found to yield favorable patterns of lipid markers such as lower concentrations of triglycerides and total and low-density lipoprotein cholesterol and higher concentrations of high-density lipoprotein cholesterol. Glycemic control was similar, demonstrated by comparable hemoglobin A_{1c} concentrations between the treatment arms.⁹ Although a favorable influence on lipid patterns raises the possibility that pioglitazone users may face a lower cardiovascular risk compared with rosiglitazone users, this question has not been studied with rigor. In the absence of randomized trial evidence, carefully conducted observational studies can guide clinical practice.

Few studies using administrative data sets have investigated the safety of TZDs. Typically, outcomes associated with their use were compared with those of other oral hypoglycemic regimens. Several such studies have found increased risks for TZD users, but they usually combined rosiglitazone and pioglitazone users. Kahler and colleagues¹⁷ found no difference in adjusted all-cause mortality between TZD users and patients receiving sulfonylurea monotherapy in a large Veterans Affairs cohort (hazard ratio, 1.04; 95% CI, 0.75-1.46). This analysis did

not differentiate between the 2 TZDs, and the statistical power was rather limited as indicated by the wide CI. A study of younger patients that used claims data from United Healthcare, a large US insurer, found no difference in coronary heart disease events between TZD users and patients starting combination therapy consisting of metformin and sulfonylurea (adjusted hazard ratio, 1.02; 95% CI, 0.87-1.30).¹⁸ That study also did not differentiate between rosiglitazone and pioglitazone users. Another study from the same group and using the same database compared rosiglitazone users with metformin and sulfonylurea users and found no difference in the rate of MI or coronary revascularization, although there was a trend toward a lower risk with sulfonylurea use compared with rosiglitazone therapy (hazard ratio, 0.82; 95% CI, 0.67-1.02).¹⁹ Both studies were sponsored by the manufacturer of rosiglitazone. Yet another study using that insurance database was conducted by employees of the manufacturer of pioglitazone. They directly compared the outcomes between users of the 2 TZDs and found that pioglitazone users had a 22% (95% CI, 3%-37%) lower rate of hospitalized MI and a 15% (95% CI, 2%-25%) reduced rate of a combination of hospitalized MI and coronary revascularization.²⁰ That study differed from ours in several important aspects. First, the study patients were substantially younger than ours, with more than 80% of patients being younger than 65 years, substantially reducing the MI event rate compared with our study (approximately 10 vs 33 per 1000 person-years). Second, it seems that patients were excluded on the basis of their future patterns of TZD use (ie, if they filled ≤ 2 prescriptions for the index TZD during the 6 months after the index prescription), which may introduce bias. Third, death data were unavailable for study, and hospitalized stroke and CHF were not investigated.

The latest study, a matched case-control study based on claims data from Ontario, Canada, found increased rates of CHF (risk ratio, 1.65; 95% CI, 1.21-2.10), MI (1.40; 1.05-1.86), and death (1.29; 1.02-1.62) for TZD monotherapy users compared with users of other oral hypoglycemic combination therapies.¹⁰ Although not powered to compare rosiglitazone and pioglitazone users directly, most effect estimates suggested worse outcomes in patients receiving rosiglitazone compared with pioglitazone therapy.

The current study leaves us with an unexpected dilemma. If rosiglitazone use increases all-cause mortality compared with pioglitazone but no differences in diagnosed MI and stroke are observed between these drugs, what is the mechanism for this harmful mortality effect? Because cardiovascular disease represents more than 75% of mortality in patients with diabetes, there must almost certainly be a link. We hypothesize that many of the deaths were due to MI or stroke. These presumably cardiovascular deaths in our cohort of elderly patients may have occurred suddenly or before the diagnosis was established. Thus, our findings suggest a higher cardiovascular case fatality rate for rosiglitazone. Unfortunately, because of the lack of information on cause of death in our cohort, we cannot formally examine this possibility.

Our main analyses used an as-treated exposure definition, with the baseline exposure carried forward as a

sensitivity analysis. The latter corresponds to the intent-to-treat approach in randomized trials. Although the latter is clearly preferable in efficacy trials, as-treated analyses are preferable for drug safety research. This way, adverse events can be attributed to a specific exposure with greater certainty, and the bias induced by treatment crossover or nonpersistence can be avoided. Our findings from as-treated and constant-exposure models were quantitatively but not qualitatively different (more pronounced in as-treated than in constant-exposure models), which supports the point made.

The rates of all study events were lower in the as-treated analyses compared with the constant-exposure models (Tables 2 and 3). For example, the all-cause mortality rate was 64.3 per 1000 person-years during the person-time considered as receiving treatment, but it was 119.9 per 1000 person-years thereafter. There are several reasons for this interesting observation. First, patients with an inherently poor prognosis may discontinue use of these drug regimens (eg, patients at the end of their lives). Furthermore, it has consistently been shown that patients with poor adherence to therapy have worse prognoses in general than do patients who adhere to their medication regimens, even if that medication was a placebo.^{21,22} It is also important in a study like ours to evaluate whether censoring for treatment crossover or nonpersistence was differential between the comparison arms. We tested this possibility quantitatively and found that rosiglitazone-treated patients experienced slightly higher rates of discontinuation of use compared with pioglitazone users (54.3% vs 52.6%; $P = .003$). In multivariate Cox models of the composite outcome of discontinuation or switching, rosiglitazone-treated patients had a 5% greater rate of discontinuing their baseline drug (IRR, 1.05; 95% CI, 1.01-1.08). The bias introduced by such informative censoring is likely conservative. Patients using rosiglitazone were less likely to tolerate the drug, potentially from its increased risk of diagnosed CHF, which may have resulted in discontinuation of rosiglitazone therapy. Because such discontinuation is likely associated with worse outcomes, the observed IRRs are probably conservative in that they underestimate the true risk associated with rosiglitazone vs pioglitazone use.

In conclusion, in a large cohort of elderly individuals with diabetes who initiated therapy with rosiglitazone or pioglitazone, we found increased risks of mortality due to any cause and of hospitalization for CHF in patients receiving rosiglitazone compared with similar patients who received pioglitazone. Increased risks of MI and stroke in rosiglitazone users were not observed within the predefined range of confidence. This study confirms the safety concerns that have been raised for rosiglitazone compared with pioglitazone, which, in turn, also cannot be considered a very safe drug given its well-documented effect on the risk of CHF. Although previous studies have indicated that the increased risk with rosiglitazone use resides predominantly in cardiovascular outcomes, the present study suggests that differences in all-cause mortality risk may be even more important to consider in elderly patients.

Accepted for Publication: June 2, 2008.

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Author Contributions: *Study concept and design:* Winkelmayr, Setoguchi, and Solomon. *Acquisition of data:* Winkelmayr and Solomon. *Analysis and interpretation of data:* Winkelmayr, Setoguchi, Levin, and Solomon. *Drafting of the manuscript:* Winkelmayr. *Critical revision of the manuscript for important intellectual content:* Winkelmayr, Setoguchi, and Solomon. *Statistical analysis:* Winkelmayr, Setoguchi, Levin, and Solomon. *Study supervision:* Winkelmayr.

Financial Disclosure: Dr Winkelmayr has participated, without receiving an honorarium, in the advisory boards of Amgen, Roche, Genzyme, and Fresenius. Dr Solomon has received salary support from Pfizer, Savient, Proctor & Gamble, and GlaxoSmithKline in the past 3 years; has served as an invited guest without honorarium to an advisory panel for Abbott; and has received consulting fees from D2 Hawkeye, a health information technology company.

Funding/Support: This study was supported by Scientist Development Grant 0535232N from the American Heart Association; a Norman S. Coplion Extramural Research Program Award from Satellite Healthcare, Inc; and investigator-initiated grants from Amgen, Fresenius Medical Care, and GlaxoSmithKline (Dr Winkelmayr).

REFERENCES

1. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med.* 2004;351(11):1106-1118.
2. Solomon DH, Winkelmayr WC. Cardiovascular risk and the thiazolidinediones: déjà vu all over again? *JAMA.* 2007;298(10):1216-1218.
3. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial [published correction appears in *Lancet.* 2006;368(9549):1770]. *Lancet.* 2006;368(9541):1096-1105.
4. US Food and Drug Administration. Center for Drug Evaluation and Research. <http://www.accessdata.fda.gov/scripts/cder/DrugsatFDA/>. Accessed February 22, 2008.
5. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med.* 2007;357(1):100]. *N Engl J Med.* 2007;356(24):2457-2471.
6. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 2007;298(10):1189-1195.
7. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA.* 2007;298(10):1180-1188.
8. Rosen CJ. The rosiglitazone story: lessons from an FDA Advisory Committee meeting. *N Engl J Med.* 2007;357(9):844-846.
9. Goldberg RB, Kendall DM, Deeg MA, et al; GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care.* 2005;28(7):1547-1554.
10. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA.* 2007;298(22):2634-2643.
11. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J.* 2004;148(1):99-104.
12. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF.

- Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005;43(5):480-485.
13. Lee DS, Donovan L, Austin PC, et al. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care*. 2005;43(2):182-188.
 14. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.
 15. Ray WA. Population-based studies of adverse drug effects. *N Engl J Med*. 2003;349(17):1592-1594.
 16. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279-1289.
 17. Kahler KH, Rajan M, Rhoads GG, et al. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. *Diabetes Care*. 2007;30(7):1689-1693.
 18. Johannes CB, Koro CE, Quinn SG, Cutone JA, Seeger JD. The risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy. *Pharmacoepidemiol Drug Saf*. 2007;16(5):504-512.
 19. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Saf*. 2007;16(7):711-725.
 20. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoepidemiol Drug Saf*. 2007;16(10):1065-1071.
 21. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol*. 2007;166(3):348-354.
 22. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006;333(7557):15.