Rosiglitazone and Outcomes for Patients With Diabetes Mellitus and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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Background—Rosiglitazone improves glycemic control for patients with type 2 diabetes mellitus, but there remains controversy regarding an observed association with cardiovascular hazard. The cardiovascular effects of rosiglitazone for patients with coronary artery disease remain unknown.

Methods and Results—To examine any association between rosiglitazone use and cardiovascular events among patients with diabetes mellitus and coronary artery disease, we analyzed events among 2368 patients with type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Total mortality, composite death, myocardial infarction, and stroke, and the individual incidence of death, myocardial infarction, stroke, congestive heart failure, and fractures, were compared during 4.5 years of follow-up among patients treated with rosiglitazone versus patients not receiving a thiazolidinedione by use of Cox proportional hazards and Kaplan–Meier analyses that included propensity matching. After multivariable adjustment, among patients treated with rosiglitazone, mortality was similar (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.58–1.18), whereas there was a lower incidence of composite death, myocardial infarction, and stroke (HR, 0.72; 95% CI, 0.55–0.93) and stroke (HR, 0.36; 95% CI, 0.16–0.86) and a higher incidence of fractures (HR, 1.62; 95% CI, 1.05–2.51); the incidence of myocardial infarction (HR, 0.77; 95% CI, 0.54–1.10) and congestive heart failure (HR, 1.22; 95% CI, 0.84–1.82) did not differ significantly. Among propensity-matched patients, rates of major ischemic cardiovascular events and congestive heart failure were not significantly different.

Conclusions—Among patients with type 2 diabetes mellitus and coronary artery disease in the BARI 2D trial, neither on-treatment nor propensity-matched analysis supported an association of rosiglitazone treatment with an increase in major ischemic cardiovascular events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00006305.

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Key Words: coronary disease ■ diabetes mellitus ■ myocardial infarction ■ pharmaceutical preparations ■ rosiglitazone ■ thiazolidinediones

Rosiglitazone is a member of the thiazolidinedione class of peroxisome proliferator–activated receptor-γ agonists, which have favorable effects on glycemic control by reducing insulin resistance,[1] a critical factor that contributes to hyperglycemia in patients with type 2 diabetes mellitus. In early studies, thiazolidinediones including rosiglitazone demonstrated effects associated with cardiovascular benefit, including improvement of endothelial dysfunction,[2–4] reduction of inflammatory markers,[5,6] and inhibition of atherosclerosis progression.[7,8]

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More recent meta-analyses of randomized trials and retrospective case-control studies comparing rosiglitazone with placebo or other therapies for type 2 diabetes mellitus suggested increased risk of myocardial infarction (MI) or death with rosiglitazone use.[9–14] These meta-analyses included predominantly small, short-term, nonadjudicated treatment trials in lower-risk populations, each with very few events, which prompted controversy regarding their interpretation.[15] The only completed prospective trial to evaluate safety among patients treated with rosiglitazone, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study,[16,17] showed no increase in the rate of cardiovascular or all-cause death attributable to rosiglitazone. In 2010, the European Medicines Agency suspended rosiglitazone from the market,[18] the US Food and Drug Administration issued a safety alert restricting prescription of rosiglitazone,[19] and an ongoing major randomized trial to test the cardiovascular safety of rosiglitazone among patients with or at risk for cardiovascular disease was terminated prematurely.[20,21]

None of the trial data included in the reports that suggested hazard with rosiglitazone focused on patients with diabetes mellitus and established coronary artery disease (CAD), a high-risk group for serious complications of both inadequate glycemic control and any potential adverse cardiovascular effects of rosiglitazone or other antihyperglycemic therapy. The effect of rosiglitazone on cardiovascular outcomes particularly in patients with established CAD, therefore, remains unknown.

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 2368 patients with both type 2 diabetes mellitus and angiographically documented CAD were randomly assigned to prompt revascularization or initial medical therapy and to insulin-sensitizing drugs or insulin-providing drugs and followed up for clinical outcomes for an average of ≥4.5 years. The primary outcomes of BARI 2D have been reported.[22] Although thiazolidinedione treatment was not determined by random assignment, during the trial a large number of patients were treated with a thiazolidinedione, the majority of whom received rosiglitazone within the randomly assigned insulin-sensitization arm. To examine outcomes associated with rosiglitazone use in this patient population, we present a post hoc comparison of major cardiovascular events, including death, MI, stroke, and congestive heart failure (CHF), as well as the incidence of fractures, among participants in BARI 2D who did and did not receive rosiglitazone.

Methods

Study Population and Design

The design of BARI 2D has been described previously.[23] Briefly, from January 1, 2001, to March 31, 2005, 2368 participants were enrolled at 49 international clinical sites. Treatment continued until the 6-year visit or until the last visit before December 1, 2008. Eligibility criteria included a diagnosis of both type 2 diabetes mellitus and angiographically documented CAD of sufficient severity to warrant consideration of revascularization. All patients had to be candidates for elective percutaneous coronary intervention or coronary artery bypass graft surgery. Patients were excluded if they required immediate revascularization or had >50% obstruction in the left main artery, a creatinine level >2.0 mg/dL (177 μmol/L), a glycohemoglobin level >13.0%, NYHA class III or IV heart failure, hepatic dysfunction, or if they had undergone percutaneous coronary intervention or coronary artery bypass graft surgery within the previous 12 months.

The protocol was approved by the institutional review board at the University of Pittsburgh and at each participating site. All patients provided written informed consent. All data were analyzed at the University of Pittsburgh. An independent data and safety monitoring board approved the study protocol and monitored the safety of patients.

Treatments and Rosiglitazone Exposure

Patients were randomly assigned to 2 treatment strategies in a 2-by-2 factorial design: (1) Prompt coronary revascularization and intensive medical therapy or intensive medical therapy and delayed revascularization, if needed, and (2) insulin-sensitizing therapy or insulin-providing therapy. Patients assigned to an insulin-sensitizing strategy were treated with thiazolidinediones or metformin or both, if needed. Patients assigned to an insulin-provision strategy were treated with insulin or sulfonylurea or a meglitinide. Patients in the insulin-sensitization group could receive insulin-providing drugs and patients in the insulin-provision group could receive insulin-sensitizing drugs if the glycohemoglobin level could not be maintained below 8.0% with only the protocol-assigned drugs.

At entry into BARI 2D, most patients were already receiving antidiabetic therapy, including 240 patients who were taking rosiglitazone and 204 who were taking pioglitazone. Patients entering the trial who were already receiving rosiglitazone but in whom it was discontinued were not considered among the rosiglitazone-treated group unless rosiglitazone was reinitiated at a later date. After random assignment to the insulin-sensitization versus insulin-provision groups, medical therapy was adjusted by the site diabetologists per study protocol with a goal of achieving a target glycohemoglobin level of <7.0%. At least 1 drug from each of the major antidiabetic drug classes was available during the study at no cost to the patients, including rosiglitazone for patients prescribed a thiazolidinedione. Exposure to rosiglitazone after trial entry or its discontinuation was recorded at each follow-up visit for the determination of on-treatment intervals and coincident events. For the propensity-matched analysis (see Statistical Analysis section below), patients who were initiated on rosiglitazone within the first 6 months after trial entry were considered exposed (detailed methods are provided in the online-only Data Supplement). Pioglitazone was not available free of charge but could be and was prescribed, albeit in a small minority of patients. The number of patient-years on pioglitazone was considered insufficient for specific analysis. With a focus on treatment strategy and glycohemoglobin goals rather than individual agents, many patients had adjustments in medical therapy, including initiation or discontinuation of rosiglitazone, over the course of the trial.

Patients were treated according to current guidelines, with target levels of low-density lipoprotein cholesterol of <100 mg/dL (2.6 mmol/L) and blood pressure of ≤130/80 mm Hg. Patients were seen monthly for the first 6 months and every 3 months thereafter.

Outcomes

The primary end point of BARI 2D was death of any cause, and the principal secondary end point was a composite of death, MI, or stroke. The definition of MI has been described previously.[22,24] MI was classified by a core electrocardiography laboratory, and stroke and cause of death were adjudicated by an independent clinical events committee unaware of study group assignments. CHF, defined by the occurrence of 1 or more of dyspnea on exertion, bilateral pedal edema, fatigue, orthopnea, and paroxysmal nocturnal dyspnea, was ascertained by each site quarterly starting in the second half of 2002. Information on occurrence of bone fracture was collected retrospectively from patients in June 2007 and prospectively annually thereafter; both were elicited on the case report forms and site reported.

Statistical Analysis

Analyses included a post hoc comparison of adverse event rates accrued among patients while undergoing treatment with rosiglitazone versus event rates accrued among patients not receiving a thiazolidinedione, which included tracking changes in treatment over time. Unadjusted endpoint frequencies were expressed as number of events per 100 patient-years. For outcome comparisons, the adjusted and unadjusted hazard ratio (HR) was calculated from Cox proportional hazards regression

models that analyzed drug use as a time-dependent variable. For this analysis, each patient was followed up until 6 months after his or her last known prescription for diabetes mellitus. Beyond that point, diabetes mellitus therapy was treated as unknown. Only events that occurred while diabetes mellitus therapy was known were included. Separate analyses were also performed to examine a potential legacy effect of rosiglitazone treatment by attributing events during exposure and additional events that occurred within 3 or 6 months of discontinuing rosiglitazone to the drug.

An additional analytic method used propensity matching to approximate an intention-to-treat approach for the comparison of events among rosiglitazone-treated participants versus matched participants not treated with a thiazolidinedione. For this analysis, patients assigned to insulin-sensitization therapy who were prescribed rosiglitazone any time in their first 6 monthly visits were matched with a propensity score with similar patients assigned to insulin provision who were not prescribed thiazolidinedione during the same 6-month period. The propensity score represented a sum of patient characteristics associated with the likelihood of being prescribed rosiglitazone during the first 6 months of the trial (see the online-only Data Supplement for details). Among the 2207 participants who survived at least 6 months and had a clinic visit documented at 4 to 6 months after randomization, 748 were categorized as having received rosiglitazone treatment, 96 patients were prescribed pioglitazone during the first 6 months after study entry and were excluded, and 1363 patients constituted the group not prescribed a thiazolidinedione. The propensity for being treated with rosiglitazone was empirically determined by logistic regression models that accounted for use of rosiglitazone before study entry and whether the patient had been randomly assigned to the insulin-sensitization or insulin-provision arm. The full propensity model is shown in Tables IA through ID in the online-only Data Supplement. The number of matched patients in each analysis varied slightly among the outcomes of death, MI, and stroke because of the exclusion of the few patients who had the outcome occur during the first 6 months. For CHF, the number of patients available for analysis was less because the collection of quarterly data on its occurrence was started later, in the second half of 2002.

Outcomes that occurred after the 6-month time point were compared between the 2 propensity-matched groups in time-to-event analyses with Kaplan–Meier and Cox proportional hazards models. Survival analysis consisted of a stratified Cox regression model with a robust sandwich covariance matrix to account for dependence among matched subjects. The adjusted HRs were based on a statistical adjustment for the following baseline variables: Diabetes mellitus therapy, diabetes mellitus duration, glycohemoglobin level, sex, age, country, obesity, smoking, family history of CAD, previous revascularization, history of transient ischemic attack/non-CAD, atrial fibrillation, abnormal left ventricular ejection fraction, history of MI, history of CHF, either having high low-density lipoprotein or taking statins, having low high-density lipoprotein (HDL), either having high triglycerides or taking fibrates, prior amputation, albuminuria, and serum creatinine. To estimate the power to detect putative harm or benefit of rosiglitazone in BARI 2D, we considered that the meta-analysis by Nissen and Wolski[9] reported rosiglitazone to be associated with an odds ratio of 1.43 for MI and an odds ratio of 1.64 for death of cardiovascular causes. On the basis of a fixed sample size of 667 per group, the more conservative BARI 2D propensity analysis had 80% power to detect an HR of 1.34 (similar to an odds ratio of 1.44) and 90% power to detect an HR of 1.40 (odds ratio of 1.54) of rosiglitazone for death/MI/stroke. Results were considered significant at $P<0.05$.

Role of the Funding Sources

The trial was sponsored by the National Institutes of Health, with additional support from multiple industry sponsors, including the manufacturer of rosiglitazone, GlaxoSmithKline, Inc. Industry sponsors had no role in the collection or analysis of the data, had no access to outcome data at any time during the trial, and did not participate in the design or drafting of this manuscript or its content.

Results

Patients Treated With Rosiglitazone

The baseline characteristics of patients treated with rosiglitazone versus those not treated with a thiazolidinedione during BARI 2D are shown in Table 1. BARI 2D participants showed a high prevalence of risk factors associated with ischemic cardiovascular events, including hypertension in almost 90%, a history of previous MI in nearly one third, a history of coronary revascularization in one fourth, and recent anginal symptoms in >60%. There were 992 patients (42%) who were treated with rosiglitazone at some point during the trial, including 885 patients randomly assigned to the insulin-sensitization group and 107 patients randomly assigned to the insulin-provision group, contributing up to 3025 patient-years of exposure to rosiglitazone for analysis (Table 2). Patients who were treated with rosiglitazone had a higher baseline level of hemoglobin A1c, a longer duration of diabetes mellitus, more albuminuria, and were marginally younger than patients not treated with a thiazolidinedione.

In terms of predominant exposure or freedom from exposure to thiazolidinedione drugs during an average of 4.5 years of follow-up in BARI 2D, 485 patients were exposed to rosiglitazone during at least 80% of their follow-up, 50 patients were exposed to pioglitazone during at least 80% of their follow-up, and 1404 patients were free of any thiazolidinedione during at least 80% of their follow-up. Exposure to pioglitazone did not reach 500 person-years during follow-up.

Cardiovascular Outcomes Associated With Use of Rosiglitazone

The cardiovascular outcomes associated with rosiglitazone use when comparing events accrued among patients in BARI 2D who were being treated with rosiglitazone with patients who were not receiving a thiazolidinedione are shown in Table 3. During follow-up, there were 240 deaths, 57 of which occurred during 3025 patient-years of direct exposure to rosiglitazone compared with 183 deaths during 7146 patient-years free of exposure to a thiazolidinedione. In unadjusted analysis, compared with patients not receiving a thiazolidinedione, patients treated with rosiglitazone experienced a similar rate of all-cause death (1.88 versus 2.56 per 100 patient-years; HR=0.77, P=0.08); a significantly lower composite incidence of death, MI, and stroke (3.79 versus 5.81 per 100 patient-years; HR=0.71, P=0.002), and a significantly lower incidence of stroke (0.28 versus 0.77 per 100 patient-years; HR=0.37, P=0.008). The rate of fatal or nonfatal MI (2.16 versus 3.16 per 100 patient-years; HR=0.76, P=0.06) was not significantly different. Although more frequent among patients taking rosiglitazone, in the present analysis, the incidence of CHF was not significantly different between patients who were receiving rosiglitazone and those who were not receiving va thiazolidinedione (3.31 versus 3.07 per 100 patient-years; HR=1.08, P=0.62).

After adjustment for differences in baseline characteristics and use of other antidiabetes medications (Figure 1), compared with no thiazolidinedione, treatment with rosiglitazone was associated with a similar incidence of all-cause death (HR=0.83; 95% confidence interval [CI], 0.58–1.18; P=0.29), and a significantly lower incidence of the composite of death, MI, and stroke (HR=0.72; 95% CI, 0.55–0.93; P=0.01) and of stroke alone (HR=0.36; 95% CI, 0.16–0.86; P=0.02). After adjustment, the incidence of MI (HR=0.77; 95% CI, 0.54–1.10; P=0.15) remained lower and the incidence of CHF higher (HR=1.22; 95% CI, 0.82–1.82; P=0.32) for patients undergoing treatment with rosiglitazone compared with patients not taking a thiazolidinedione, but the differences were not

Table 1. Baseline Characteristics According to Rosiglitazone Use Versus No Thiazolidinedione Treatment During Follow-Up in BARI 2D

Baseline Characteristic	Total (n=2191)	No Thiazolidinedione (n=1199)	Treated With Rosiglitazone (n=992)	*P* Value
Female, %	29	28	30	0.37
Age, y, mean±SD	62.4±8.9	62.7±8.8	62.0±9.0	0.07
Race, %				0.46
Non-Hispanic, white	67	68	65	
Non-Hispanic, black	17	16	18	
Hispanic	12	12	12	
Asian plus other	5	4	5	
Education, %				0.14
Less than high school	37	38	35	
High school graduate	22	22	21	
Some post-high school	24	24	25	
Bachelor degree or higher	17	15	19	
Geography, %				0.005
United States	61	58	65	
Canada	16	17	14	
Mexico	4	4	4	
Brazil	16	17	15	
Czech Republic/Austria	3	4	3	
BMI, %				0.85
Normal (<25 kg/m^2)	9	10	9	
Overweight (25 to <30 kg/m^2)	35	35	34	
Class 1 obesity (30 to <35 kg/m^2)	32	31	32	
Class 2 obesity (35 to <40 kg/m^2)	16	15	16	
Class 3/4 obesity (≥40 kg/m^2)	9	9	9	
Cigarette smoking, %				0.03
Never smoked	33	31	35	
Former smoker	55	57	52	
Current smoker	12	12	13	
Family history of CAD/sudden cardiac death	43	41	45	0.12
Prior PCI, %	20	19	20	0.40
Prior CABG, %	6	6	7	0.21
History of angina within the last 6 wk, %	61	62	60	0.40
History of MI, %	32	32	32	0.85
History of stroke or TIA, %	10	10	10	0.95
History of carotid artery disease, %	8	8	7	0.33
Atrial fibrillation, %	1	1	1	0.88
Left ventricular dysfunction, %	17	16	18	0.31
History of CHF, %	6	7	6	0.95
History of hypertension, %	88	88	88	0.97
Taking statins, %	75	73	77	0.07
Total cholesterol ≥200 mg/dL, %	19	19	20	0.53
High total cholesterol or taking statin, %	83	82	85	0.05
LDL-C ≥130 mg/dL, %	14	14	13	0.45
High LDL-C or taking statin, %	82	80	83	0.12
HDL-C <40 mg/dL in men or <50 mg/dL in women, %	72	72	73	0.41
Taking fibrate, %	8	8	9	0.18

(*Continued*)

Table 1. Continued

Baseline Characteristic	Total (n=2191)	No Thiazolidinedione (n=1199)	Treated With Rosiglitazone (n=992)	*P* Value
Triglycerides ≥150 mg/dL, %	50	49	51	0.25
High triglycerides or taking fibrate, %	52	51	54	0.16
Taking gemfibrozil, %	4	3	4	0.33
Duration of diabetes mellitus, mean±SD	10.4±8.7	10.0±9.1	10.8±8.1	0.05
Glycohemoglobin, mean±SD	7.65±1.6	7.50±1.6	7.82±1.6	<0.0001
Prior amputation, %	1	1	1	0.38
Albuminuria, %				0.02
No albuminuria	68	71	65	
Microalbuminuria	22	20	25	
Macroalbuminuria	10	9	10	
Serum creatinine, mean±SD	1.04±0.28	1.04±0.27	1.04±0.28	0.54

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

statistically significant. Additional analyses were performed to examine a potential legacy effect of rosiglitazone treatment, in which events during exposure and additional events that occurred within 3 months or 6 months of discontinuing rosiglitazone were included and attributed to the drug. The adjusted HRs of the composite of death, MI, and stroke among patients treated with rosiglitazone versus those not taking a thiazolidinedione when the 3- and 6-month legacy effects were included were 0.80 (*P*=0.08) and 0.85 (*P*=0.20), respectively.

Propensity-Matched Analysis

When participants prescribed rosiglitazone during the first 6 months of the trial were propensity-matched with participants who were not prescribed a thiazolidinedione, the baseline characteristics were comparable (Table IE in the online-only Data Supplement). The 5-year cumulative risks of the specified cardiovascular events for the propensity-matched rosiglitazone and nonthiazolidinedione groups are shown in Table 4 and Figure 2A through 2E. In these analyses, there were no significant differences observed in the rates of death (HR=1.07); the composite of death, MI, and stroke (HR=0.94); MI (HR=0.88); and stroke (HR=0.75), or in the rate of CHF (HR=1.21) between patients prescribed rosiglitazone versus those not prescribed a thiazolidinedione.

Fracture Risk Associated With Use of Rosiglitazone

The rate of bone fractures was significantly higher among patients who received rosiglitazone than among patients who were not receiving a thiazolidinedione (adjusted HR=1.62; 95% CI, 1.05–2.51; *P*=0.03; Table 5). When the occurrence of bone fractures was stratified by sex, the magnitude of increase in relative risk appeared greater for women than for men (1.82 versus 1.47), although the interaction between sex and the increased risk of fracture attributable to rosiglitazone was not significant when formally tested (*P*=0.55). When fracture rate was compared with the propensity-matched analysis of participants prescribed rosiglitazone compared with participants who were not prescribed a thiazolidinedione within the first 6 months of study entry, there was a trend toward higher adjusted fracture rate observed among women prescribed rosiglitazone (Table II in the online-only Data Supplement). Kaplan–Meier time-to-event analysis (Figure 2F) suggested that the risk of bone fracture began to increase relatively late after exposure to rosiglitazone.

Interaction of Rosiglitazone With Other Medications

Coadministration of multiple antidiabetic and cardiovascular medications was common in BARI 2D. We examined whether there was an interaction between rosiglitazone and other coadministered medications on the long-term rates of adverse events associated with rosiglitazone using the on-treatment time-dependent analysis (Tables III and IV in the online-only Data Supplement). After adjustment for baseline characteristics and use of other diabetes mellitus–related medications, no significant interaction was observed on the composite rate of death, MI, and stroke (Table III in the online-only Data Supplement) or on individual rates of death, MI, stroke, or fractures (data not shown) when rosiglitazone was coadministered with insulin, metformin, gemfibrozil, other fibrates, sulfonylureas, nitrates,

Table 2. Thiazolidinedione Exposure During Follow-Up in BARI 2D

	Patient-Years of Exposure Among Participants in the Insulin-Sensitization Arm	Patient-Years of Exposure Among Participants in the Insulin-Provision Arm	Total Patient-Years
Rosiglitazone	2895 (54%)	130 (2%)	3025
Pioglitazone	434 (8%)	48 (1%)	482
No thiazolidinedione	1988 (38%)	5158 (97%)	7146

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes.

Table 3. Unadjusted Association of Cardiovascular Outcomes of Patients While Undergoing Treatment With Rosiglitazone Compared With No Thiazolidinedione During Follow-Up in BARI 2D

	Rosiglitazone		No Thiazolidinedione			
Outcome	No. of Events/ Patient-Years of Exposure	Rate per 100 Patient-Years	No. of Events/ Patient-Years of Exposure	Rate per 100 Patient-Years	HR (95% CI)	*P* Value
Death	57/3025	1.88	183/7146	2.56	0.77 (0.57–1.03)	0.08
Death/MI/stroke	105/2769	3.79	350/6024	5.81	0.71 (0.57–0.88)	0.002
MI	60/2783	2.16	193/6102	3.16	0.76 (0.57–1.02)	0.06
Stroke	8/2883	0.28	50/6494	0.77	0.37 (0.17–0.77)	0.008
CHF	64/1936	3.31	124/4045	3.07	1.08 (0.80–1.46)	0.62

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; and MI, myocardial infarction.

or angiotensin-converting enzyme inhibitors. A significant interaction was observed between rosiglitazone and concurrent metformin on the risk of CHF associated with rosiglitazone (Table IV in the online-only Data Supplement). The relative risk of CHF associated with use of rosiglitazone was significantly greater among patients who were not taking metformin (HR=1.89; 95% CI, 1.10–3.24; *P*=0.02) than among patients who were also being treated with metformin (HR=0.85; 95% CI, 0.52–1.38; *P*=0.50; interaction *P*=0.03).

Discussion

The analyses of long-term outcomes from the BARI 2D trial included in the present report provide no evidence that use of rosiglitazone is associated with increased rates of major adverse ischemic cardiovascular events among patients with type 2 diabetes mellitus and established CAD. In an analysis of events that occurred among all eligible patients during active treatment with rosiglitazone, the incidence of stroke and the composite incidence of death, MI, and stroke were significantly lower and there were nonsignificantly lower rates of nonfatal MI and death among patients receiving rosiglitazone than patients not treated with a thiazolidinedione. In an analysis of events accrued among propensity-matched patients who were prescribed versus not prescribed rosiglitazone starting during the first 6 months after study entry, the rates of death, MI, and stroke were not significantly different between the 2 groups of patients.

Because there has been intense focus on the cardiovascular safety of rosiglitazone, we used 2 complementary analytic methods of the BARI 2D data set to rigorously explore possible adverse events attributable to drug exposure. The first used Cox regression models to analyze drug use as a time-dependent variable, whereby any events occurring among patients while actually receiving rosiglitazone were attributed to the drug. A second analytic method used propensity matching, in which patients were grouped according to whether they were or were not prescribed rosiglitazone starting within the first 6 months of trial entry after randomization. Patients not prescribed a thiazolidinedione were then propensity matched with patients in the rosiglitazone group, and all events that occurred after 6 months until the end of follow-up were then attributed to patients according to their group assignment, whether rosiglitazone had been continued or discontinued later during the trial, to approximate an intention-to-treat approach. From our examination of >450 adjudicated ischemic cardiovascular events that occurred during 4.5 years of follow-up in BARI 2D, and with at least 2500 patient-years of exposure to rosiglitazone for each end point, it is notable that neither analysis suggested that rosiglitazone use was associated with a significant increase in adverse cardiovascular ischemic events, including death or MI.

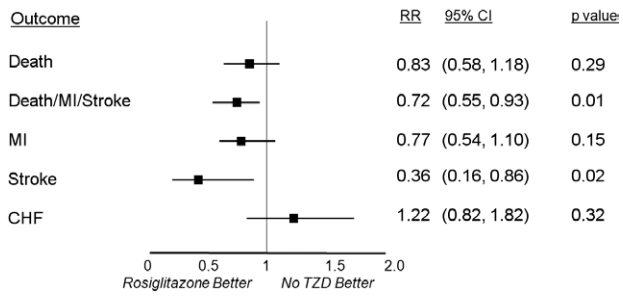

Figure 1. Relative risk (RR) of adverse cardiovascular outcomes for patients undergoing treatment with rosiglitazone compared with patients not treated with a thiazolidinedione, after adjustment for baseline characteristics and other diabetes mellitus–related medications. CHF indicates congestive heart failure; CI, confidence interval; MI, myocardial infarction; and TZD, thiazolidinedione.

Each of the 2 analytic strategies, the on-treatment analysis and the propensity-matched analysis, has strengths and limitations. The on-treatment analysis includes cardiovascular outcomes from all of the BARI 2D patients receiving rosiglitazone and those receiving no thiazolidinedione and adjusts for differences in the baseline risk profile among these patients. An on-treatment analysis can produce biased treatment effect estimates when the initiation of drug treatment is influenced by severity of illness or other clinical indications or when the termination of the drug is influenced by adverse events or by markers of poor outcomes. In the context of the BARI 2D trial, half of the patients were assigned to a glycemic strategy of insulin sensitization and half were assigned to a strategy of insulin provision, and initiation of rosiglitazone treatment was generally determined by treatment assignment rather than individual patient indications. In addition, the incorporation of 3- and 6-month legacy effects attributes subsequent clinical events to rosiglitazone even if the drug was stopped because of complications such as fluid retention. Thus, the biases often seen with on-treatment analyses are minimized by the BARI 2D trial design and the inclusion of the legacy effect. In fact, given the large imbalance of rosiglitazone use concentrated in the insulin-sensitizing arm of BARI 2D, a lack of hazard with rosiglitazone is supported by the lack of difference in outcomes observed between the insulin-sensitization and

Table 4. Association of Cardiovascular Outcomes With Rosiglitazone Use in BARI 2D Among Propensity-Matched Participants Prescribed Versus Not Prescribed a Thiazolidinedione Within 6 Months of Study Entry

	Rosiglitazone		No Thiazolidinedione			
Outcome	Number of Events/ Patients	5-Year Cumulative Risk (%)*	Number of Events/ Patients	5-Year Cumulative Risk (%)*	HR (95% CI)	*P* Value
Death	74/686	10.4	72/686	9.3	1.07 (0.77–1.48)	0.70
Death/MI/stroke	113/667	18.2	123/667	18.3	0.94 (0.73–1.22)	0.66
MI	51/668	8.5	59/668	8.9	0.88 (0.61–1.28)	0.50
Stroke	14/686	2.0	19/686	3.0	0.75 (0.37–1.49)	0.41
CHF	61/512	13.6	50/512	11.6	1.26 (0.87–1.83)	0.23

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; and MI, myocardial infarction.

*Estimated from Kaplan–Meier analysis.

insulin-provision groups in the overall trial.[22] In distinction, the propensity-matching approach identifies patient pairs (1 insulin-sensitization patient who received rosiglitazone in the early phase of BARI 2D and 1 insulin-provision patient who did not receive a thiazolidinedione during the same period) that are similar with respect to the characteristics that are associated with the use of rosiglitazone. The number of patients included in the matched comparison is reduced compared with the full cohort, and as a result, these analyses have less power to detect differences attributable to treatment. However, the key advantage of the propensity-matched analysis is that it mimics a randomization process and an intention-to-treat analysis based on the observed risk factors. Neither the on-treatment nor the propensity analysis methods account for unobserved risk factors that may be related to treatment selection.

Along with cardiovascular ischemic events, additional adverse events previously associated with rosiglitazone use were examined. CHF was observed more frequently among patients receiving rosiglitazone than among patients not taking a thiazolidinedione, consistent with previous reports,[25,26] with a frequency that was significantly greater among patients receiving rosiglitazone who were not also receiving metformin (HR=1.89, *P*=0.02; Table IV in the online-only Data Supplement). Treatment with rosiglitazone was also associated with a higher incidence of bone fractures, consistent with previous observations reported from the A Diabetes Outcome Progression Trial (ADOPT)[27] and RECORD[17] trials. Similar to ADOPT and RECORD, whereas the rate of fracture was higher for both men and women, the relative increase in the risk of fractures associated with rosiglitazone use appeared greater among women than men, although the interaction term was not significant.

Previous analyses have suggested an increase in major ischemic cardiovascular events with rosiglitazone therapy. Nissen and Wolski[9] reported a meta-analysis of 42 trials in 2007 and an updated meta-analysis with 14 additional trials[10] in 2010 that included 35 531 subjects randomly assigned to rosiglitazone versus placebo or an alternative oral antidiabetes agent. Using a fixed-effects analytic model, their results suggested that patients treated with rosiglitazone experienced a significantly increased risk of MI. Additional meta-analyses[11,12] and retrospective case-control studies[13,28] also suggested an increased risk of adverse cardiovascular events among patients with type 2 diabetes mellitus treated with rosiglitazone. Although they raise important concerns regarding the cardiovascular safety of rosiglitazone, these reports represent meta-analyses of predominantly short-term treatment trials or case-control database analyses in lower-risk populations in which adverse events were not independently adjudicated, follow-up may have been imbalanced, and some trials with no events were excluded. Moreover, there was inconsistency across studies in the hazard reported and the estimation of risk,[9,11–13,28] while other studies did not suggest increased risk.[29,30] Nevertheless, given these reports, it has been argued that rosiglitazone should be avoided in patients with cardiovascular disease.[31]

Limited prospective data have been available to address this controversy. The RECORD study[16,17] compared cardiovascular outcomes in patients randomly assigned to receive rosiglitazone combined with metformin or with a sulfonylurea to patients receiving metformin or sulfonylurea alone. Of note, in RECORD, only 16.5% of the 4447 participants had a history of ischemic heart disease. At an average of 5.5 years of follow-up, the trial reported no significant difference between the rosiglitazone group and the control group regarding the primary end point of cardiovascular death or hospitalization for cardiovascular causes, satisfying the prespecified criterion for noninferiority. There were likewise no significant differences in MI (HR=1.14; 95% CI, 0.80–1.63; *P*=0.47) or death of cardiovascular causes (HR=0.84; 95% CI, 0.59–1.18; *P*=0.32), but the report concluded that the data were inconclusive for determining whether rosiglitazone was associated with an increase in the risk of MI.[17,32]

The current results from BARI 2D contribute prospective longitudinal data regarding outcomes related to treatment with rosiglitazone among high-risk patients, all of whom had established CAD documented by coronary angiography. Long-term outcomes were defined prospectively and adjudicated by an independent committee blinded to treatment assignment. The present analyses represent the largest experience with rosiglitazone use among patients with type 2 diabetes mellitus and CAD in whom long-term outcomes are available.

The present analyses did not detect any significant hazard of increased ischemic cardiovascular risk with rosiglitazone treatment despite its use in this particularly vulnerable, higher-risk population. Rather, our analysis of adverse events among patients while receiving rosiglitazone showed a lower incidence of the composite of death, MI, and stroke and of stroke alone among patients treated with rosiglitazone than among those not receiving a thiazolidinedione, and lower but not statistically

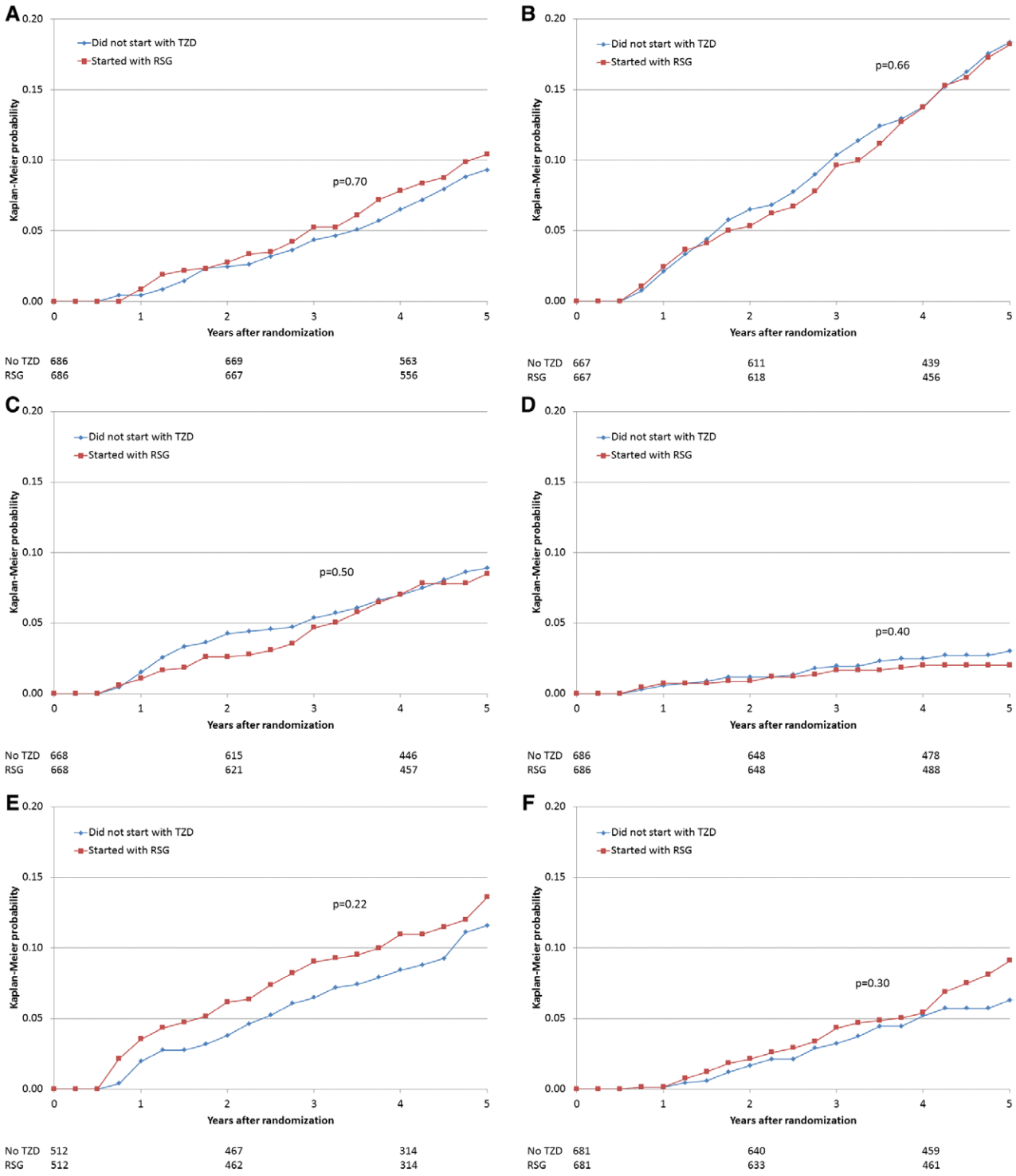

Figure 2. Kaplan–Meier curves during follow-up of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) comparing the incidence of events among propensity-matched patients in the insulin-provision arm who did not start the study with any thiazolidinedione (TZD) vs similar patients in the insulin-sensitization arm who started the study with rosiglitazone (RSG) of (**A**) all-cause death; (**B**) the composite of death, myocardial infarction, and stroke; (**C**) myocardial infarction (excluding procedure-related myocardial infarction); (**D**) stroke; (**E**) congestive heart failure; and (**F**) fractures. Numbers of patients at risk at baseline, 2 years, and 4 years are shown below each graph.

different rates of death or MI. It may be relevant that one potential difference between BARI 2D and other studies reporting cardiovascular effects of rosiglitazone relates to the BARI 2D trial design, in which intensive medical therapy was provided for ischemic cardiovascular disease and its risk factors, and relief of angina symptoms and lowering of low-density lipoprotein cholesterol and blood pressure were obtained in most patients.[22] These results may imply that in the context of intensive treatment of cardiovascular risk factors, rosiglitazone may provide benefit with retained safety, alone or in combination

Table 5. Association of Fractures Among Patients While Undergoing Treatment With Rosiglitazone Compared With No Thiazolidinedione

	Rosiglitazone		No Thiazolidinedione					
	No. of Fractures/ Patient-Years of Exposure	Rate per 100 Patient-Years	No. of Fractures/ Patient-Years of Exposure	Rate per 100 Patient-Years	Unadjusted RR	*P* Value	Adjusted* HR (95% CI)	*P* Value
All patients	54/2744	1.97	86/6309	1.36	1.45	0.03	1.62 (1.05–2.51)	0.03
Men†	27/1997	1.35	45/4472	1.01	1.32	0.26	1.47 (0.84–2.55)	0.18
Women†	27/747	3.62	41/1838	2.23	1.70	0.03	1.82 (1.04–3.19)	0.04

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; and MI, myocardial infarction.

*Adjusted for baseline characteristics and other antidiabetes medications.

†*P* for interaction of rosiglitazone and sex=0.55.

with other hypoglycemic medications, for high-risk patients with type 2 diabetes mellitus and established CAD.

The present analyses of drug-drug interactions did not detect any significant interactions of rosiglitazone with nitrates, fibrates, angiotensin-converting enzyme inhibitors, metformin, or insulin to suggest these drugs significantly amplify any cardiovascular hazard from rosiglitazone, a concern previously raised by subgroup analyses performed by the US Food and Drug Administration.[11] Within the BARI 2D cohort, concurrent treatment with metformin appeared to mitigate the increased risk of CHF observed in metformin-naïve patients receiving rosiglitazone during the trial (relative risk=0.85, *P* for interaction=0.03), an interaction that has not been reported previously and that may merit further investigation.

Study Limitations

There are potentially important limitations to the present analyses and results. As acknowledged above, these were post hoc analyses, and the results were not derived from a randomized comparison. Despite careful multivariable adjustment, observed outcomes may be biased by unanticipated and unmeasured confounders and may be subject to the potential risks associated with multiple testing. Because of its design, using random assignment to antidiabetes treatment strategy rather than particular agent(s), antihyperglycemic medical therapy in BARI 2D was complex, with frequent medication additions and adjustments to reach the goal of glycohemoglobin <7%. The majority of patients were receiving >1 antidiabetes agent, and some patients were treated only transiently with rosiglitazone, whereas a small number were exposed, at different times, to both rosiglitazone and pioglitazone. It is therefore conceivable that the observed lack of ischemic cardiovascular hazards from rosiglitazone could be attributable to less use of rosiglitazone by investigators in patients they thought might be at increased risk of such events. Nevertheless, the lack of evidence of hazard remained after multivariable adjustment for baseline characteristics and other antidiabetic medications. In addition, rosiglitazone was provided at no cost by the manufacturer, and the effect that free availability of the drug may have had on the prescription of and patient adherence to rosiglitazone is unknown.

Conclusions

Among patients with type 2 diabetes mellitus and documented CAD in the BARI 2D trial, neither on-treatment nor propensity-matched outcome analysis supported an association of rosiglitazone treatment with an increase in major ischemic cardiovascular events.

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Disclosures

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CLINICAL PERSPECTIVE

Rosiglitazone is a thiazolidinedione that improves glycemic control for patients with type 2 diabetes mellitus, but there remains controversy regarding its association with increased cardiovascular hazard, and the cardiovascular effects of rosiglitazone for patients with established coronary artery disease remain unknown. The association between rosiglitazone use and cardiovascular events was examined among 2368 patients with type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial during 4.5 years of follow-up using both Cox proportional hazards models for on-treatment events and propensity-matched analyses. Among patients undergoing treatment with rosiglitazone, there was a significantly lower adjusted incidence of the composite outcome of death, myocardial infarction, and stroke, as well as of stroke, whereas the incidences of myocardial infarction, congestive heart failure, and death were not significantly different. Among propensity-matched patients, the risks of major ischemic cardiovascular events and congestive heart failure were not significantly different. There was a higher incidence of fractures observed among rosiglitazone-treated patients. An interaction was also observed between use of metformin and rosiglitazone that appeared to mitigate an increased risk of congestive heart failure with rosiglitazone. The results of these analyses from BARI 2D do not support an association of rosiglitazone treatment with an increase in major ischemic cardiovascular events among patients with type 2 diabetes mellitus and established coronary artery disease.