Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

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Context Peroxisome proliferator–activated receptors (PPARs) are nuclear transcription factors that modulate gene expression. Therapeutic agents targeting 2 distinct families of PPARs (α and γ) have been introduced in the United States. The first dual-PPAR agonist, muraglitazar, was reviewed by a US Food and Drug Administration (FDA) advisory committee on September 9, 2005, resulting in a vote of 8:1 recommending approval for its use in controlling blood glucose levels in patients with type 2 diabetes.

Objective To evaluate the incidence of death, myocardial infarction (MI), stroke, congestive heart failure (CHF), and transient ischemic attack (TIA) in diabetic patients treated with muraglitazar compared with controls.

Design, Setting, and Participants The source material for this analysis consisted of documents about phase 2 and 3 clinical trials released under public disclosure laws for the FDA advisory committee meeting. All reviewed trials were prospective, randomized, double-blind, multicenter studies enrolling patients with type 2 diabetes and hemoglobin A_{1c} levels between 7% and 10%. Patients (N=3725) were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo as monotherapy or in combination with metformin or glyburide in trials ranging from 24 to 104 weeks.

Main Outcome Measures The primary outcome was the incidence of death, nonfatal MI, or nonfatal stroke. A more comprehensive composite outcome included these events plus the incidence of CHF and TIA.

Results In the muraglitazar-treated patients, death, MI, or stroke occurred in 35 of 2374 (1.47%) patients compared with 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone treatment groups (controls) (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; *P*=.03). For the more comprehensive outcome measure that included TIA and CHF, the incidence was 50 of 2374 (2.11%) for muraglitazar compared with 11 of 1351 (0.81%) for controls (RR, 2.62; 95% CI, 1.36-5.05; *P*=.004). Relative risks for each of the individual components of the composite end point exceeded 2.1 but were not statistically significant. Incidence of adjudicated CHF was 13 of 2374 (0.55%) muraglitazar-treated patients and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; *P*=.053).

Conclusions Compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death, major adverse cardiovascular events (MI, stroke, TIA), and CHF. This agent should not be approved to treat diabetes based on laboratory end points until safety is documented in a dedicated cardiovascular events trial.

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PEROXISOME PROLIFERATOR–activated receptors (PPARs) are ligand-activated nuclear transcription factors that modulate expression of a large number of genes.[1] In the United States, therapeutic agents that target 2 distinct families of PPARs (α and γ) have been introduced. Examples of PPAR-α agents include the fibric acid derivatives fenofibrate and gemfibrozil. These agents modulate lipid metabolism primarily by lowering serum triglyceride levels and modestly increasing levels of high-density lipoprotein (HDL) cholesterol.

In several clinical trials, these PPAR-α agents have reduced cardiovascular events or demonstrated slowing of atherosclerosis progression.[2-4] The PPAR-γ agonists increase insulin sensitivity and are widely used as antidiabetic agents.[5] Two drugs are currently available, pioglitazone and rosiglitazone. Because both abnormal lipid levels and insulin resistance are believed to promote atherosclerosis in diabetic patients, several pharmaceutical companies have sought to develop dual-PPAR agonists that target both the α and γ families.[6]

The first dual-PPAR to reach the US Food and Drug Administration (FDA) for consideration of approval is muraglitazar, a strong PPAR-γ agonist with moderate PPAR-α effects.[7] The development program for muraglitazar included a series of clinical trials exam-

See editorial comment.

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Table 1. Muraglitazar Clinical Trials in Diabetic Patients

Study, Duration, and Daily Doses	No. Randomized
CV 168006 (104 weeks)	
Muraglitazar	
0.5 mg	236
1.5 mg	259
5 mg	245
10 mg	249
20 mg	239
Pioglitazone 15 mg	251
CV 168018 (24 weeks)	
Muraglitazar	
2.5 mg	111
5 mg	114
Placebo	115
CV 168021 (24 weeks)	
Muraglitazar 2.5 mg + glyburide	191
Muraglitazar 5 mg + glyburide	193
Placebo + glyburide	199
CV 168022 (78 weeks)	
Muraglitazar 2.5 mg + metformin	233
Muraglitazar 5 mg + metformin	205
Placebo + metformin	214
CV 168025 (26 weeks)	
Muraglitazar 5 mg + metformin	587
Pioglitazone 30 mg + metformin	572
Totals	
All muraglitazar dosages	2862
Muraglitazar dosages ≤5 mg	2374
Pioglitazone or placebo	1351

ining the effects of this agent on lipid levels and glycemic control in diabetic patients. These trials also collected clinical outcomes data for major events including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, transient ischemic attack (TIA), and congestive heart failure (CHF).

An advisory committee for the FDA Endocrinology and Metabolic Drugs Division reviewed these studies at an open public hearing on September 9, 2005, and recommended approval of the drug as monotherapy for treatment of type 2 diabetes (by an 8:1 vote) and as combination therapy in patients with blood glucose not adequately controlled with metformin (by a 7:2 vote).[8] Public disclosure laws require the release of briefing documents for advisory committee meetings, which are made available to the public via the FDA Web site at the time of the public hearing. The current study represents an analysis of the muraglitazar trials performed in diabetic patients, publicly released by the sponsor and FDA for the advisory panel meeting.[9,10]

METHODS

Analyzed Studies

We reviewed the FDA briefing documents available via the FDA Web site for the September 9, 2005, public hearing. There were 2 major documents, an analysis of data in the muraglitazar clinical development program provided by FDA staff[9] and a separate document prepared by the developers of the drug (Bristol-Myers Squibb and Merck).[10] These documents provide data for 5 clinical trials that assessed safety and efficacy in diabetic patients. Efficacy assessments included primarily the effects of muraglitazar on various measures of glycemic control and lipids. Safety assessment included reporting of major adverse events including cardiovascular outcomes.

Four of the reviewed studies were phase 3 trials and 1 study was identified as phase 2. Two different comparators were studied in these 5 trials: placebo and the approved PPAR-γ agonist pioglitazone. A high rate of edema and CHF with high doses of muraglitazar was observed early in the development program and the sponsor ceased development of daily dosages higher than 5 mg, only requesting regulatory approval for dosages of 5 mg/d or less.[10] Accordingly, we restricted our analysis to treatment groups using muraglitazar doses of 5 mg/d or less. This analysis yielded 2374 patients exposed to muraglitazar and 1351 patients exposed to comparator agents, of which 823 received pioglitazone and 528 placebo. A literature search found a single publication reporting results from 1 of these trials,[11] and only 2 of the studies are listed on a clinical trials registration site (http://www.clinicaltrials.gov). Therefore nearly all information was derived from the FDA briefing documents.

Outcome Measures

Occurrence of all-cause mortality, cardiovascular death, nonfatal MI, nonfatal stroke, CHF, and TIA were assessed by examination of detailed listings of adverse patient events reported by the study sponsor in the FDA documents. The documents do not provide specific information on the process used to verify these events. The CHF events were described as centrally adjudicated, but there is no mention of an adjudication process for other types of events.

For composite end points, to avoid double counting of patients with more than 1 event, each patient was classified by the event with the greatest severity. Thus, a patient with MI who subsequently died as a consequence of this event was classified as experiencing cardiovascular death but not MI. For analytical purposes, the event rates for both comparators (placebo and pioglitazone) were pooled and compared with event rates for muraglitazar. From the crude event rates, relative risks (RRs), 95% confidence intervals (CIs), and *P* values were calculated for each individual type of event.

The primary outcome measure was a composite end point commonly used in cardiovascular trials: the combined incidence of death, MI, or stroke. A more specific outcome measure was generated by substituting cardiovascular death for all-cause mortality. A more comprehensive outcome measure was generated by adding CHF and TIA events to the composite. Statistical comparisons between muraglitazar-treated and control patients were calculated using the Wald χ^2 test and SAS version 8.0 software (SAS Institute Inc, Cary, NC). $P \leq .05$ was considered statistically significant.

RESULTS

The 5 clinical trials in patients with diabetes who were exposed to muraglitazar or a comparator are summarized in TABLE 1. These studies varied in duration from 24 to 104 weeks and included patients who received muraglitazar monotherapy or muraglitazar in combination with 2 other diabetes treatments, either metformin or glyburide. Several features were common to all 5 trials. Patients were aged 18 to

70 years, had a body mass index less than 41, triglycerides lower than 600 mg/dL (6.8 mmol/L), and hemoglobin A_{1c} levels between 7% and 10%.[9,10] Patients with class III or IV CHF were excluded. Also excluded were patients with a history of MI, unstable angina, stroke, TIA, angioplasty, or coronary artery bypass graft surgery within 6 months prior to enrollment. The following narratives briefly describe these studies.

CV 168006 was a phase 2 monotherapy dose-ranging trial designed to explore the effects of a 40-fold range of daily doses (from 0.5 to 20 mg) in patients with type 2 diabetes. During the first 24 weeks, mean glucose concentrations were monitored and dosages were titrated subsequently to meet prespecified levels of glycemic control. There was a long-term extension phase of 104 weeks. A single control group was included that received 15 mg/d of pioglitazone, which could be titrated up to 45 mg/d to achieve glycemic control. Because 24.9% of patients receiving the 10-mg muraglitazar dose and 40.1% of those receiving 20 mg experienced edema, these 2 doses were not used in subsequent trials.[9,10]

CV 168018 was a phase 3 monotherapy study of the 2.5- and 5-mg muraglitazar doses compared with a matching placebo. Only patients never previously treated with an antidiabetic agent were eligible. This trial was recently published.[11]

CV 168021 was a phase 3 placebo-controlled study comparing 2.5 or 5 mg of muraglitazar with placebo in diabetic patients with hyperglycemia not adequately controlled with glyburide. There was a blinded 102-week long-term phase, but these results were not available at the time of the FDA advisory panel meeting.

CV 168022 was a randomized, double-blind, placebo-controlled study that compared muraglitazar 2.5 or 5 mg with placebo in patients with hyperglycemia not adequately controlled with metformin alone.

CV 168025 was a phase 3 study of the effect of addition of 5 mg of muraglitazar compared with 30 mg of pioglitazone in patients whose hyperglycemia was not adequately controlled with metformin alone.

Table 2. Baseline Demographic and Laboratory Characteristics*

	Monotherapy Studies (CV 168006, CV 168018)		Combination Therapy Studies (CV 168021, CV 168022, CV 168025)	
	Muraglitazar (n = 729)	Comparators (n = 366)	Muraglitazar (n = 1409)	Comparators (n = 985)
Age, mean (SD), y	53.5 (10)	52.5 (9.6)	55.1 (8.7)	54.6 (9.0)
Men, No. (%)	417 (57.2)	198 (54.1)	724 (51.4)	500 (50.8)
White race, No. (%)	595 (81.6)	290 (79.2)	1229 (87.2)	878 (89.1)
Body weight, mean (SD), kg	89.2 (17.9)	89.7 (18.5)	88.0 (18.3)	89.8 (17.9)
Body mass index, mean (SD)†	31.2 (4.9)	31.6 (4.9)	31.3 (4.8)	31.7 (4.9)
Hemoglobin A_{1c}, mean (SD), %	8.1 (1.1)	8.2 (1.1)	8.1 (1.0)	8.1 (1.0)
Fasting plasma glucose, mean (SD), mg/dL	178 (54)	184 (51)	172 (48)	174 (50)
Blood pressure, mean (SD), mm Hg				
Systolic	129 (14.8)	129.4 (15.3)	131 (15.0)	131.4 (15.7)
Diastolic	79.7 (8.7)	80.1 (8.30)	80.3 (8.9)	80.4 (8.8)
LDL cholesterol, mean (SD), mg/dL	123.7 (33.3)	128.4 (37.6)	113.1 (34.4)	112.3 (33.0)
HDL cholesterol, mean (SD), mg/dL	43.0 (9.9)	43.7 (10.6)	45.4 (10.5)	45.6 (10.7)
Statin use, No. (%)	148 (20.3)	64 (17.5)	343 (24.3)	238 (24.2)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversions: To convert glucose to mmol/L multiply values by 0.0555; to convert cholesterol to mmol/L multiply values by 0.0259.
*Values represent the number of patients for which data were submitted by the study sponsors.[10]
†Calculated as weight in kilograms divided by height in meters squared.

Demographics and Baseline Characteristics

TABLE 2 reports the baseline characteristics of the patients enrolled in these trials. The FDA documents include patients who received muraglitazar or a comparator, pooling the placebo and pioglitazone treatment groups. The patients were relatively young (mean <55 years) and obese (mean body mass index >30). Both sexes were approximately equally represented. Diabetes control was relatively poor, with mean hemoglobin A_{1c} levels higher than 8.0%.

Mortality and Cardiovascular Events

TABLE 3 illustrates the adverse events occurring in the 5 reviewed clinical trials conducted in diabetic patients with muraglitazar dosages of 5 mg/d or less. TABLE 4 illustrates the event rates, RRs, and *P* values for muraglitazar compared with pioglitazone or placebo. The primary outcome measure (all-cause mortality, nonfatal MI, or nonfatal stroke) occurred in 35 of 2374 muraglitazar-treated patients (1.47%) vs 9 of 1351 control patients (0.67%) (RR, 2.23; 95% CI, 1.07- 4.66; *P*=.03). A more specific outcome measure, substituting cardiovascular death for all-cause mortality, occurred in 27 of 2374 muraglitazar-treated patients (1.14%) vs 7 of 1351 control patients (0.52%) (RR, 2.21; 95% CI, 0.96-5.08; *P*=.06). A more comprehensive outcome measure adding CHF and TIA events to the composite yielded an incidence of 50 of 2374 for muraglitazar-treated patients (2.11%) vs 11 of 1351 control patients (0.81%) (RR, 2.62; 95% CI, 1.36-5.05; *P*=.004).

Table 4 also shows the incidence rates and RRs for the individual components of the primary outcome measure and several other composite end points typically used in cardiovascular outcome trials. Individual components of the primary end point showed consistently greater incidence in the muraglitazar-treated group compared with controls (RRs ranging from 2.14 to 7.43). However, the number of events was small and differences for individual components of the primary out-

Table 3. Adverse Cardiovascular Events in the Muraglitazar Program

Study and Therapy	No. of Patients Exposed	Noncardiovascular Death	Cardiovascular Death	MI	Stroke	CHF	TIA
CV 168006							
Muraglitazar 0.5 mg	236	0	0	0	0	0	0
Muraglitazar 1.5 mg	259	2	0	0	0	0	1
Muraglitazar 5 mg	245	1	0	0	1	0	1
Pioglitazone 15 mg	251	1	0	1	1	0	0
CV 168018							
Muraglitazar 2.5 mg	111	0	0	0	1	1	0
Muraglitazar 5 mg	114	0	0	0	0	0	0
Placebo	115	0	0	1	0	0	0
CV 168021							
Muraglitazar 2.5 mg + glyburide	191	0	0	3	2	1	1
Muraglitazar 5 mg + glyburide	193	1	1	4	2	3	1
Placebo + glyburide	199	0	1	1	0	0	0
CV 168022							
Muraglitazar 2.5 mg + metformin	233	1	1	4	1	0	0
Muraglitazar 5 mg + metformin	205	3	1	3	0	1	0
Placebo + metformin	214	0	0	0	0	0	1
CV 168025							
Muraglitazar 5 mg + metformin	587	0	5	1	2	7	1
Pioglitazone 30 mg + metformin	572	1	0	1	1	1	0
Totals							
Muraglitazar ≤5 mg	2374	8	8	15	9	13	5
Pioglitazone or placebo	1351	2	1	4	2	1	1

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.

Table 4. Event Rates and Relative Risks

	No. (%)			
	Muraglitazar (n = 2374)	Control (n = 1351)	Relative Risk (95% CI)	*P* Value
Composite End Points				
All-cause mortality plus nonfatal MI or stroke	35 (1.47)	9 (0.67)	2.23 (1.07-4.66)	.03
All-cause mortality plus nonfatal MI, stroke, CHF, or TIA	50 (2.11)	11 (0.81)	2.62 (1.36-5.05)	.004
Cardiovascular death plus nonfatal MI or stroke	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death plus nonfatal MI, stroke, CHF, or TIA	42 (1.77)	9 (0.67)	2.69 (1.30-5.53)	.007
All-cause mortality or nonfatal MI	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death or nonfatal MI	19 (0.80)	5 (0.37)	2.17 (0.81-5.83)	.12
Individual End Points				
All-cause mortality	16 (0.67)	3 (0.22)	3.05 (0.89-10.5)	.08
Cardiovascular death	8 (0.34)	1 (0.07)	4.57 (0.57-36.5)	.15
Fatal or nonfatal MI	15 (0.63)	4 (0.30)	2.14 (0.71-6.46)	.18
Fatal or nonfatal stroke	9 (0.38)	2 (0.15)	2.57 (0.55-11.9)	.23
Fatal or nonfatal TIA	5 (0.21)	1 (0.07)	2.85 (0.33-24.4)	.34
Adjudicated CHF	13 (0.55)	1 (0.07)	7.43 (0.97-56.8)	.053

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

come measure were not statistically significant, with *P* values ranging from .053 to .34. The difference in the occurrence rate for adjudicated CHF was nearly significant, occurring in 13 of 2374 muraglitazar-treated patients (0.55%) and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; *P* = .053).

COMMENT

Two general families of PPAR agonists are currently approved for treatment of dyslipidemia and diabetes in the United States. The PPAR-α agents include the fibric acid derivatives gemfibrozil and fenofibrate, which have been available for several decades, although all of their modes of action have only recently been elucidated.[12] This class of agents is primarily used to treat dyslipidemia by reducing triglyceride levels while moderately elevating levels of HDL cholesterol.[13]

Two major outcome studies have demonstrated reductions in adverse cardiovascular events following administration of these agents for secondary cardiovascular prevention.[2,3] PPAR-γ agents are approved for glycemic control in patients with type 2 diabetes. Three drugs have been introduced in this class: rosiglitazone, pioglitazone, and troglitazone. The latter agent was withdrawn from the market due to hepatotoxicity. A recent outcomes study showed a trend toward reduction in vascular events for pioglitazone but increased incidence of CHF.[14]

Because of the favorable effects of PPAR-α and γ agonists, development of dual-PPAR agents has been considered a highly promising strategy for simultaneous treatment of both hyperglycemia and dyslipidemia in diabetic patients.[6] The first of these agents to be considered for FDA approval is muraglitazar, which can be characterized as a strong PPAR-γ agonist with moderate α effects.

With any new class of pharmaceutical agents, unexpected toxicity may emerge during the development program. However, in some cases, pharmaceutical sponsors defer or withhold publication of phase 2 and 3 clinical trial data until after drug approval. Accordingly,

documents submitted to the FDA for consideration of approval may constitute the only publicly available source of objective information for newly approved pharmaceutical agents. This has been the case for muraglitazar for which the public disclosure of phase 2 and 3 data occurred via the FDA Web site shortly before the advisory panel convened to consider the drug for approval on September 9, 2005.

From these public disclosure documents, we observed a numerical excess of adverse cardiovascular events for patients treated with muraglitazar compared with controls (patients treated with either placebo or pioglitazone). Therefore, to determine the incidence of death and major adverse cardiovascular events, we carefully reviewed the clinical trial data available within these documents and included all trials performed in diabetic patients submitted to the FDA. We excluded from analysis patients treated with the higher 10- and 20-mg doses of muraglitazar because further development of these dosages was terminated after a phase 2 trial demonstrated a high incidence of peripheral edema. We also did not include a small, short-term phase 2 trial that administered the drug to persons without diabetes to examine its effects on lipid levels. The remaining patients consisted of 2374 participants exposed to 5 mg/d or less of muraglitazar and 1351 exposed to placebo or pioglitazone.

The results of this analysis are concerning. For the most widely accepted composite end point of death, MI, and stroke, the RR for muraglitazar was 2.23. Other end points using narrower definitions (including only cardiovascular death) or broader composites (including CHF and TIA events) showed similar risks. The most inclusive composite end point that included all-cause mortality, nonfatal MI, stroke, TIA, and CHF showed a highly significant increase in RR for muraglitazar-treated patients (2.62; $P = .004$).

Furthermore, there was a highly consistent pattern of excess morbidity for all of the components of the major outcome measure with all RRs exceeding 2.1. The consistency in magnitude and direction of the adverse effects across multiple cardiovascular end points reduce the likelihood that these findings result from chance alone. These results are particularly concerning because the significant excess of adverse events was observed after only limited drug exposure ranging from 24 to 104 weeks. Moreover, patients who are enrolled in clinical trials often constitute the lowest-risk strata of patients, and the real world exposure would likely substantially amplify the risk. Taken as a whole, these data demonstrate that it is likely that muraglitazar, if approved by the FDA, would constitute an unacceptable patient hazard.

We believe it is always important to weigh efficacy and safety together in deciding the clinical utility of any drug. The efficacy for muraglitazar consisted of a lowering of blood glucose, reduction in triglycerides, and increase in HDL cholesterol.[9,10] These are laboratory end points and must be weighed in the context of the more important clinical outcomes. Drugs that lower blood glucose (sulfonylureas) or low-density lipoprotein cholesterol (ezetimibe) have been approved based on laboratory measures of efficacy. However, these approvals occurred after demonstration of excellent safety in fairly large patient populations. In contrast, muraglitazar does not lower low-density lipoprotein levels and the benefits of lowering blood glucose for other drugs have not always shown a reduction in serious vascular complications.[15] Thus, it is particularly important to weigh the efficacy results against the safety concerns.

It must be emphasized that atherosclerotic cardiovascular disease is particularly common in patients with type 2 diabetes, representing the cause of death in approximately 80% of diabetic patients. Thus, any drug used to treat diabetes requires careful scrutiny for its effects on atherosclerosis-related outcomes, such as MI and stroke. The apparent increase in adverse cardiovascular events in muraglitazar-treated patients is surprising because the drug showed favorable effects on triglycerides and HDL cholesterol in these same clinical trials. A related drug, gemfibrozil, a pure PPAR-α agent, has demonstrated impressive benefits in 2 major clinical outcome trials. However, other PPAR-α and γ agonists have shown a variety of potential cardiovascular toxicities in preclinical studies.[16-18]

The specific choice of composite end point requires additional comment. We emphasized a primary outcome measure that excluded CHF events because peripheral edema and CHF are known hazards of PPAR-γ agents and warnings are included in FDA-approved package inserts for pioglitazone and rosiglitazone.[19] Nonetheless, edema was very prominent in studies of muraglitazar, particularly at higher doses, occurring in 24.9% and 40.1% of patients exposed to the 10- and 20-mg doses, respectively.[9,10] Whether muraglitazar constitutes a greater or lesser risk for CHF in comparison to existing PPAR-γ drugs such as rosiglitazone and pioglitazone remains to be determined. The currently available data suggest that the incidence of CHF is at least as high with muraglitazar as with approved PPAR-γ agonists.[9,10] We also excluded TIA from the primary outcome measure because this is a more subjective end point than stroke or MI.

The precise mechanism underlying the increased cardiovascular toxicity observed with muraglitazar is uncertain. In different species, PPAR agonists exhibit a variety of biological effects that, if they occur in humans, might explain the results of this analysis.[16-18,20] It must be emphasized that each of the PPARs activate or suppress different genes with only partial overlap in activity. Accordingly, each agent must be considered separately from the efficacy and safety perspective.

The possibility of an interaction between muraglitazar and other antidiabetic therapies must also be considered. Most adverse cardiovascular events occurred in studies in which muraglitazar was combined with glyburide or metformin. However, the

number of events in any single study is too few to draw definitive conclusions about the RRs of muraglitazar with or without concomitant therapy with other agents. Other dual-PPARs in development may or may not exhibit similar hazards. Major differences in the effects of pure PPAR-γ agonists have been observed. Pioglitazone and rosiglitazone have differing effects on lipids[21] and neither exhibit the hepatotoxicity that resulted in market withdrawal of troglitazone.[22] Our findings emphasize the need for robust safety data for this class of drugs prior to regulatory approval.

There are important limitations to our analysis. The data used to determine incidence rates and RRs were derived from review of publicly disclosed regulatory documents. We did not have access to the original trial databases. The exact definitions for MI, stroke, and other events were not available. Other than CHF, adverse events were investigator- and sponsor-reported, not centrally adjudicated. The actual number of analyzed events was small, primarily because these trials enrolled only stable patients without a recent history of cardiovascular events and exposed patients to muraglitazar for a limited duration (24-104 weeks). Because we did not have access to trial databases, we used simple χ^2 analysis rather than the more powerful time-to-event methods. Accordingly, risk estimates, CIs, and *P* values could not be adjusted for other covariates, such as treatment center and duration of exposure to the drug. The number of events was too few to perform formal testing for heterogeneity.

Nonetheless, some important conclusions are warranted. Muraglitazar appears to increase the risk for morbidity and mortality in diabetic patients during relatively short-term treatment. The estimated magnitude of this risk is substantial with RRs indicating a doubling for irrevocable, major end points and composite outcomes. The consistency of these RRs suggests that this result is not due to chance. Accordingly, muraglitazar should not be used or approved to treat patients with diabetes until an appropriate dedicated trial to assess cardiovascular outcomes is performed.

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Acquisition of data: Nissen, Wolski.
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Drafting of the manuscript: Nissen, Topol.
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