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Rosiglitazone Revisited

An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

Steven E. Nissen, MD; Kathy Wolski, MPH

Context: Controversy regarding the effects of rosiglitazone therapy on myocardial infarction (MI) and cardiovascular (CV) mortality persists 3 years after a meta-analysis initially raised concerns about the use of this drug.

Objective: To systematically review the effects of rosiglitazone therapy on MI and mortality (CV and all-cause).

Data Sources: We searched MEDLINE, the Web site of the Food and Drug Administration, and the GlaxoSmithKline clinical trials registry for trials published through February 2010.

Study Selection: The study included all randomized controlled trials of rosiglitazone at least 24 weeks in duration that reported CV adverse events.

Data Extraction: Odds ratios (ORs) for MI and mortality were estimated using a fixed-effects meta-analysis of 56 trials, which included 35 531 patients: 19 509 who received rosiglitazone and 16 022 who received control therapy.

Results: Rosiglitazone therapy significantly increased the risk of MI (OR, 1.28; 95% confidence interval [CI], 1.02-1.63; *P*=.04) but not CV mortality (OR, 1.03; 95% CI, 0.78-1.36; *P*=.86). Exclusion of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial yielded similar results but with more elevated estimates of the OR for MI (OR, 1.39; 95% CI, 1.02-1.89; *P*=.04) and CV mortality (OR, 1.46; 95% CI, 0.92-2.33; *P*=.11). An alternative analysis pooling trials according to allocation ratios allowed inclusion of studies with no events, yielding similar results for MI (OR, 1.28; 95% CI, 1.01-1.62; *P*=.04) and CV mortality (OR 0.99; 95% CI, 0.75-1.32; *P*=.96).

Conclusions: Eleven years after the introduction of rosiglitazone, the totality of randomized clinical trials continue to demonstrate increased risk for MI although not for CV or all-cause mortality. The current findings suggest an unfavorable benefit to risk ratio for rosiglitazone.

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Author Affiliations:
Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

CONTROVERSY REGARDING the cardiovascular safety of the diabetes drug rosiglitazone arose in 2007 after the publication of a meta-analysis that demonstrated a significantly elevated risk for myocardial infarction (MI) and a borderline significant increased risk for cardiovascular (CV) mortality.[1] The debate over the CV safety of rosiglitazone therapy has continued during the past 3 years, recently receiving renewed attention after the release of a report from the US Senate Committee on Finance that provided additional details about internal analyses conducted by the maker of rosiglitazone, GlaxoSmithKline (GSK), and the US Food and Drug Administration (FDA).[2,3] No large, definitive CV outcomes trials have been conducted with rosiglitazone, although an open-label, noninferiority trial reported results in 2009 (RECORD [Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes]).[4] That study was limited by low event rates, which resulted in insufficient statistical power to confirm or refute evidence of an increased risk for ischemic myocardial events.[4-8]

Rosiglitazone was initially approved in 1999 to treat hyperglycemia in patients with type 2 diabetes mellitus. The standards for approval of diabetes drugs during that era required only demonstration of the reduction of hemoglobin A_{1c} levels in trials of moderate duration (typically 24-52 weeks) in the absence of any apparent safety concerns. Controversy emerged soon after the drug's introduction, when reports first suggested that the use of rosiglitazone and a related drug, pioglitazone, could precipitate congestive heart failure in susceptible individuals.[9] Then, in 2003, the Uppsala Drug Monitoring Group of World Health Organization alerted GSK about an unusually large number of spontaneous re-

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ports associating rosiglitazone use with congestive heart failure and ischemic myocardial events.[2] GlaxoSmithKline subsequently conducted 2 internal patient-level meta-analyses of CV risk (the first completed in 2005 and the second in 2006), which were eventually published in 2008.[10] Both analyses showed a significantly elevated risk for ischemic myocardial events. These analyses were supplied to the FDA and posted on the company's clinical trial registry, but neither GSK nor the FDA made any public statement about the findings.

As a consequence of a court settlement in 2004 with the State of New York, GSK was required to post clinical trial results on a public Web site.[11] Using this data source, we performed a study-level meta-analysis that demonstrated a statistically significant 43% increase in the risk for MI and a borderline significant 64% increase in the risk for CV mortality.[1] Subsequently, meta-analyses by other authors were published, some of which confirmed these findings, while others reported inconclusive results.[12,13] The most comprehensive patient-level analysis was conducted by the FDA and confirmed an odds ratio (OR) of 1.38 for myocardial ischemic events (95% confidence interval [CI], 1.1-1.8; $P = .02$).[14]

An FDA Advisory Committee in 2007 concluded that the use of rosiglitazone increased the risk of MI but did not recommend removing the drug from the market.[15] Subsequently, a consensus algorithm published by the American Diabetes Association and the European Association for the Study of Diabetes unanimously recommended against the use of rosiglitazone, but the drug continues to be marketed, with annual sales exceeding $1 billion in 2009.[16] In the absence of definitive trials, a comprehensive meta-analysis remains the most appropriate means to evaluate the overall CV safety of rosiglitazone. Our objective was to update the 2007 meta-analysis that initiated the concerns about rosiglitazone therapy, using similar methods to the original study but also using alternative analyses to enable inclusion of trials with no CV events.

METHODS

ANALYZED STUDIES

The studies included in the meta-analysis are listed in **Table 1**. The prespecified criteria for inclusion of trials required that studies have a randomized comparator group, a similar duration of treatment in all study groups, and more than 24 weeks of drug exposure. To identify potential studies for inclusion in the meta-analysis, we initially screened the clinical trials registry established by the manufacturer of rosiglitazone, GSK.[20] Because this registry was mandated by a legal settlement,[11] we assumed this registry to be complete but further searched for missing trials via MEDLINE and the FDA Web site. We screened 202 clinical trials for inclusion in the meta-analysis, excluding 146 for reasons summarized in **Figure 1**. The remaining 56 trials met all of the prespecified criteria for inclusion. Fifteen of the 56 trials did not report any MIs, and 30 of the trials did not report any CV mortality. The trials without events were not included in the primary prespecified analysis but were included in an alternative analysis.

The 56 trials included in the meta-analysis randomized 35 531 patients: 19 509 assigned to receive rosiglitazone and 16 022 assigned to comparator groups. Three groups of trials were identified. In 1999, GSK submitted 1 group of 5 studies to the FDA for presentation to the Advisory Committee, which recommended approval of rosiglitazone use.[18] In these 5 trials, 1967 patients were randomly assigned to receive rosiglitazone and 793 patients received comparator drugs or placebo. A second group of 48 trials were primarily identified from the GSK clinical trials registry. In these 48 trials, 11 231 patients were randomly assigned to receive rosiglitazone and 7473 received comparator drugs or placebo. The third group of trials included 3 larger prospective randomized trials that were published in major medical journals.[4,18,19] In these 3 trials, 6311 patients were randomly assigned to receive rosiglitazone and 7756 patients received comparator drugs. Four of the 5 registration trials and all 3 large trials were published, but most (35 of 48) trials identified via the GSK registry remain unpublished.

DATA EXTRACTION

For the 5 studies included in the original submission for FDA approval, study-level data were extracted from publicly available briefing documents that were downloaded from the FDA Web site.[21] Data from these same trials were also reported in a summary fashion on the Clinical Trial Registry Web site maintained by GSK.[20] For the 4 registration trials that were published in peer-reviewed medical journals, we obtained adverse event data from data tables in the manuscripts.[22-25] These 3 sources (FDA documents, GSK Web site, and publications) were cross-checked for consistency. In cases of disagreement between published and unpublished data, data derived from the manufacturer's Web site were used. For the 3 larger outcome trials, study-level data were extracted from data tables contained in the published manuscripts.[4,18,19] For the remaining group of 48 trials that were available primarily on the GSK clinical trials registry, data on reported adverse outcomes were extracted from the study summaries included in the posted individual trial reports.

In cases in which several treatment groups received rosiglitazone within a single trial, the rosiglitazone-exposed groups were pooled together for analysis. For each study, the control group was defined as patients receiving any drug regimen other than rosiglitazone, including placebo. With the exception of the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication)[18] and RECORD trials, the included studies did not centrally adjudicate either MI or mortality. We reviewed data summaries provided in the FDA review documents, the GSK clinical-trial registry Web site, and published trial results and then abstracted data from the adverse event tabulations for MI and mortality (CV and all-cause). Because we did not have access to individual patient data, time-to-event analyses for adverse events could not be performed, which precluded the calculation of hazard ratios (HRs). Because only summary data tables were available, it was not possible to determine whether the same patient had both an MI and CV mortality, which precluded calculation of outcomes based on the composite of MI or CV death. Accordingly, the 3 outcomes (MI, CV death, and all-cause mortality) are reported separately.

STATISTICAL ANALYSES

Because most of the included trials had few events, we prespecified the use of the Peto method to calculate ORs and 95% CIs.[26-28] This approach excludes trials with no adverse events, since an OR cannot be calculated for such studies. To account for trials with no events, we also determined ORs and 95% CI's using an

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Table 1. Rosiglitazone Clinical Trials Included in the Meta-analysis

Clinical Trial No.	Phase	No. of Weeks	Rosiglitazone Therapy		Control Therapy	
			Agent	No.	Agent	No.
Trials Included in Original Registration Package						
49653/011	3	24	Rosiglitazone	357	Placebo	176
49653/020	3	52	Rosiglitazone	391	Glyburide	207
49653/024	3	26	Rosiglitazone	774	Placebo	185
49653/093	3	26	Rosiglitazone ± metformin	213	Metformin	109
49653/094	3	26	Rosiglitazone and metformin	232	Metformin	116
Subtotal				**1967**		**793**
Additional Phase 2, 3, and 4 Efficacy Trials						
100684	4	52	Rosiglitazone and glyburide	43	Glyburide	47
49653/143	4	24	Rosiglitazone and glyburide	121	Glyburide	124
49653/211	4	52	Rosiglitazone and usual care	110	Usual care	114
49653/284	4	24	Rosiglitazone and metformin	382	Metformin	384
712753/008	4	48	Rosiglitazone and metformin	284	Metformin	135
AVM100264	4	52	Rosiglitazone and metformin	294	Metformin and sulfonylurea	302
BRL 49653C/185	4	32	Rosiglitazone ± metformin	563	Usual care ± metformin	142
BRL 49653/334	4	52	Rosiglitazone	278	Placebo	279
BRL 49653/347	4	24	Rosiglitazone and insulin	418	Insulin	212
49653/015	3	24	Rosiglitazone and sulfonylurea	395	Sulfonylurea	198
49653/079	3	26	Rosiglitazone ± glyburide	203	Glyburide	106
49653/080	3	156	Rosiglitazone	104	Glyburide	99
49653/082	3	26	Rosiglitazone and insulin	212	Insulin	107
49653/085	3	26	Rosiglitazone and insulin	138	Insulin	139
49653/095	3	26	Rosiglitazone and insulin	196	Insulin	96
49653/097	3	156	Rosiglitazone	122	Glyburide	120
49653/125	3	26	Rosiglitazone and sulfonylurea	175	Sulfonylurea	173
49653/127	3	26	Rosiglitazone and glyburide	56	Glyburide	58
49653/128	3	28	Rosiglitazone	39	Placebo	38
49653/134	3	28	Rosiglitazone	561	Placebo	276
49653/135	3	104	Rosiglitazone and glypizide	116	Glypizide	111
49653/136	3	26	Rosiglitazone	148	Placebo	143
49653/145	3	26	Rosiglitazone and gliclazide	231	Gliclazide	242
49653/147	3	26	Rosiglitazone and sufonylurea	89	Sulfonylurea	88
49653/162	3	26	Rosiglitazone and glyburide	168	Glyburide	172
49653/234	3	26	Rosiglitazone and glimepiride	116	Glimepiride	61
49653/330	3	52	Rosiglitazone	1172	Placebo	377
49653/331	3	52	Rosiglitazone	706	Placebo	325
49653/137	3	32	Rosiglitazone and metformin	204	Glyburide and metformin	185
SB-712753/002	3	24	Rosiglitazone and metformin	288	Metformin	280
SB-712753/003	3	32	Rosiglitazone and metformin	254	Metformin	272
SB-712753/007	3	32	Rosiglitazone ± metformin	314	Metformin	154
SB-712753/009	3	24	Rosiglitazone, metformin, and insulin	162	Insulin	160
49653/132	2	24	Rosiglitazone and sulfonylurea	442	Sulfonylurea	112
AVA100193	2	24	Rosiglitazone	394	Placebo	124
AVD100521 (APPROACH trial[17])	3	78	Rosiglitazone	331	Glipizide	337
AVD102209	3	26	Rosiglitazone and insulin	132	Insulin	131
AVD104742	3	28	Rosiglitazone	160	Pioglitazone or placebo	213
ARA102198	2	26	Rosiglitazone	49	Placebo	49
AVA105640	3	24	Rosiglitazone	331	Placebo or donepezil	250
49653/044	3	26	Rosiglitazone and metformin	101	Metformin	51
49653/096	3	26	Rosiglitazone and glyburide	232	Glyburide	115
49653/109	3	26	Rosiglitazone	52	Glipizide	25
49653/282	4	24	Rosiglitazone and metformin	70	Glyburide and metformin	75
49653/325	3	24	Rosiglitazone and glimepiride	196	Glimepiride	195
49653/351	3	52	Rosiglitazone	28	Placebo	29
49653/369	4	26	Rosiglitazone	25	Glibenclamide	24
49653/452	2	24	Rosiglitazone	26	Placebo	25
Subtotal				**11 231**		**7473**
Published Large Prospective Randomized Trials						
DREAM trial[18]	3	156	Rosiglitazone	2635	Placebo	2634
ADOPT[19]	3	208	Rosiglitazone	1456	Metformin or glyburide	2895
RECORD trial[4]	3	260	Rosiglitazone	2220	Metformin plus sulfonylurea	2227
Total				**19 509**		**16 022**

Abbreviations: ADOPT, A Diabetes Outcome Progression Trial; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients With Cardiovascular History; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.

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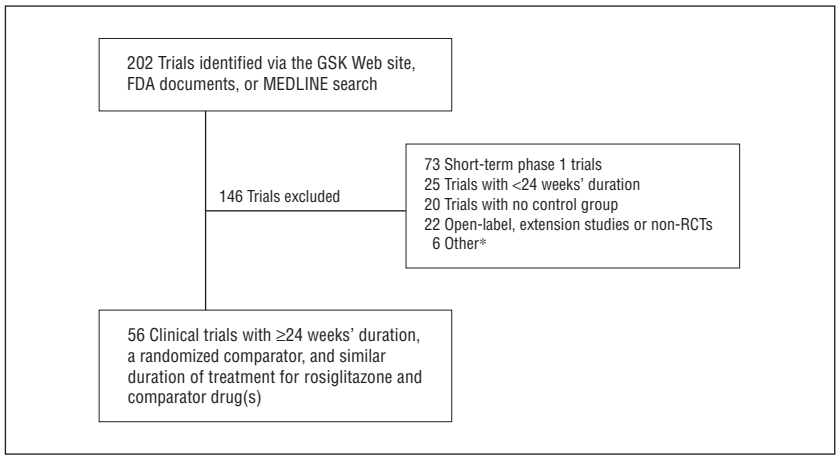

Figure 1. Flow diagram showing the numbers of studies included and excluded from the analysis and the reasons for exclusion. FDA indicates Food and Drug Administration; GSK, GlaxoSmithKline; and RCT, randomized controlled trial. *Includes pediatric studies, terminated early, or summary analysis.

alternative method in which smaller studies were grouped by randomization ratios and larger trials were considered individually. This alternative analysis used the Mantel-Haenszel method to calculate ORs and 95% CIs.[29] With this approach, all 56 trials meeting inclusion criteria were included in the alternative analysis. All reported *P* values are 2-sided. Statistical heterogeneity across the 56 trials was tested using the Cochran Q statistic. $P > .10$ was considered evidence of a lack of heterogeneity. This analysis revealed no heterogeneity, allowing use of a fixed-effects model. Additional analyses classified by trial duration (shorter or longer than 1 year) and type of comparator drug (insulin, metformin, sulfonylurea, or placebo) were assessed using the Peto method in a similar fashion to the overall analyses. The number needed to harm (NNH) was estimated based on the annualized rate of MI that was observed in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial,[5] normalizing this rate to the 5-year duration typically used in NNH calculations. Data were analyzed with Comprehensive Meta-analysis software (Version 2.2; Biostat, Englewood, New Jersey).

RESULTS

BASELINE CHARACTERISTICS

The dosages of study drugs, baseline demographic characteristics, study periods, and hemoglobin A_{1c} levels are listed in **Table 2**. The mean age of patients was approximately 57 years; 55% were male; and more than 80% were white. The mean hemoglobin A_{1c} level at baseline averaged 8.2%. Dosages of rosiglitazone varied from 2 to 8 mg/d, with most studies titrating patients to 8 mg/d during the course of the study. Although nearly all trials enrolled patients with type 2 diabetes mellitus, a few studies included patients treated for investigational indications, including psoriasis, Alzheimer disease, rheumatoid arthritis, or multiple sclerosis. A single study, the DREAM trial, was designed as a diabetes prevention study to assess whether rosiglitazone therapy could prevent the new onset of type 2 diabetes in high-risk individuals.

PRIMARY OUTCOMES

The individual trials contributing to the meta-analysis and the numbers of MIs and CV deaths are listed in **Table 3**. For MI, the Cochran Q statistic, including the RECORD trial, was 30.3 ($P = .87$; $I^2 = 0\%$). Excluding the RECORD trial, the Q statistic for MI was 29.7 ($P = .86$; $I^2 = 0\%$. For CV mortality, including the RECORD Trial, the Q statistic was 16.2 ($P = .91$; $I^2 = 0\%$). Excluding the RECORD Trial, the Q statistic was 12.8 ($P = .97$; $I^2 = 0\%$).

Table 4 shows the results of the primary prespecified analyses, and **Figure 2** lists the results in subgroups classified by trial duration or comparator drug. For the 41 trials with at least 1 MI, the Peto OR for rosiglitazone relative to comparator drugs was 1.28 (95% CI, 1.02-1.63; $P = .04$). Excluding the RECORD trial from the analysis yielded similar results, but with a higher OR (OR, 1.39; 95% CI, 1.02-1.89; $P = .04$). The results were similar in subgroups that were classified by trial duration. For trials of less than 12 months' duration, the OR for MI was 1.76 (95% CI, 0.93-3.33). For trials that were longer than 12 months, the OR for MI was 1.22 (95% CI, 0.95-1.57). All subgroups that were classified by comparator drug(s) show elevated estimates for the OR for MI, ranging from 1.26 to 3.49, but with wide confidence intervals (Figure 2).

For the 26 trials with at least 1 event, the Peto OR for CV mortality for rosiglitazone relative to comparator drugs was 1.03 (95% CI, 0.78-1.36; $P = .86$) (Table 4). However, excluding the RECORD trial had a large effect on the results. For the 25 trials with at least 1 CV death, excluding the RECORD trial, the OR was 1.46 (95% CI, 0.92-2.33; $P = .11$). For trials with a duration of less than 12 months, the estimated OR was 2.32 (95% CI, 0.93-5.78). For trials with a duration of longer than 12 months, the OR was 0.94 (95% CI, 0.70-1.27) (Figure 2). All subgroups that were classified by comparator drug(s) show elevated estimates for the OR for CV mortality, ranging from 1.13 to 2.02, but with wide confidence intervals (Figure 2).

ALTERNATIVE ANALYSES

To permit inclusion of studies with no CV events, an alternative analysis was performed in which smaller studies were pooled by randomization ratios. The pooling of smaller studies allows inclusion of all 56 trials meeting the prespecified inclusion criteria, regardless of the presence or absence of adverse events. **Figure 3** shows Mantel-Haenszel ORs for the pooled smaller studies classified by randomization ratio, with the 3 larger trials considered individually. The results of this alternative analysis are very similar to the primary results obtained using the Peto method. For MI, the OR was 1.28 (95% CI, 1.01-1.62), including the RECORD trial, and 1.38 (95% CI, 1.01-1.87), excluding the RECORD trial. For CV mortality, the OR, including the RECORD trial, was 0.99 (95% CI, 0.75-1.32), and the OR was 1.36 (95% CI, 0.84-2.21), excluding the RECORD trial.

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Table 2. Dosages, Baseline Demographic Characteristics, Study Periods, and Hemoglobin A_{1c} (HbA_{1c}) Levels

Clinical Trial No.	Study	Dosage	Population	Study Period	Age, y	% Male Sex	% Race[a]	Baseline HbA_{1c} Level
100684	Rsg/Gly	4-8 mg	Korean patients with type 2 DM	Dec 2003-Jul 2005	55.2	53.5	100 (A)	NA
	Gly	5-15 mg			54.5	45.6	100 (A)	
49653/143	Rsg/Gly	8 mg	Type 2 DM poorly controlled with Gly	Jul 2005-Jan 2003	52	45.3	44:56 (B:H)	9.2
	Gly	Per usual			53	48.3	38:62 (B:H)	9.4
49653/211	Rsg	4 mg	Type 2 DM with CHF	Jul 2001-Nov 2003	64.3	84.3	99	7.7
	Plc	NA			63.9	79.0	99	7.8
49653/284	Rsg/Met	4-8 mg/1 g	Type 2 DM	Jun 2001-Feb 2003	55.5	51.1	72	8.1
	Met	1-2 g			55.6	51.0	71	7.9
712753/008	Rsg/Met	8 mg/1 g	Type 2 DM poorly controlled with Met	Jun 2003-Dec 2005	54.6	63.2	70	Baseline not reported
	Rsg/Met	4 mg/2 g			56.0	65.2	78	
	Met	2 g			56.9	53.4	69	
AVM100264	Rsg/Met	4-8 mg/2 g	Overweight type 2 DM poorly controlled with Met	Jul 2004-Jan 2006	58.5	52.7	94	8.0
	Met/Su	2 g/titrated			59.3	52.5	95	8.0
BRL49653C/185	Rsg/Elm/Met	4 mg/1.5 g	Type 2 DM	May 2000-May 2002	58.0	65.2	76	7.5
	Rsg/Elm	4 mg			59.0	60.2	78	7.4
	Met/Elm	1.5 g			60.0	56.4	78	7.5
	Elm	NA			57.0	60.9	83	7.4
BRL 49653/334	Rsg	4-8 mg	Type 2 DM or Ins resistance syndrome	Mar 2002-Nov 2004	67.7	44.8	99	6.3
	Plc	NA			67.3	47.7	100	6.3
BRL 49653/347	Rsg/Ins	4 mg	Type 2 DM poorly controlled with Ins	Nov 2002-Apr 2004	52.6	48.1	57	9.0
	Rsg/Ins	2-4 mg			52.7	60.0	57	8.9
	Ins/Plc	Per usual			53.8	46.2	57	9.1
49653/011	Rsg	8 mg	Type 2 DM	Sep 1996-Sep 1997	60.7	66.9	73	8.8
	Rsg	4 mg			59.6	64.5	75	9.0
	Plc	NA			58.8	65.8	74	9.0
49653/015	Rsg/Su	4 mg	Type 2 DM	Aug 1996-Mar 1998	60.6	53.2	98	9.2
	Rsg/Su	2 mg			61.0	62.8	86	9.2
	Su	NA			61.9	57.3	97	9.2
49653/020	Rsg	8 mg	Type 2 DM	Oct 1996-May 1998	60.9	57.6	97	8.2
	Rsg	4 mg			60.4	68.2	99	8.1
	Gly	Titrated			60.1	70.4	99	8.2
49653/024	Rsg	4 mg/d	Type 2 DM	Jan 1997-Feb 1998	57.5	58.6	76	8.9
	Rsg	2 mg BD			56.8	59.1	78	8.9
	Rsg	8 mg/d			58.9	65.7	80	8.9
	Rsg	4 mg BD			56.5	59.9	71	9.0
	Plc	NA			57.7	68.8	79	8.9
49653/079	Rsg	4 mg	Type 2 DM poorly controlled with maximum dose of Gly	Apr 1997-Mar 1998	59.1	63.6	70	9.1
	Rsg/Gly	4 mg/20 mg			57.7	69.4	70	9.2
	Gly	20 mg			58.5	66.7	69	9.3
49653/080	Rsg	8 mg	Type 2 DM	Nov 1996-May 2000	55.1	75.0	73	8.9
	Gly	2.5-5 mg			56.1	70.1	76	9.4
49653/082	Rsg/Ins	8 mg	Type 2 DM poorly controlled with Ins	Jul 1997-Aug 1998	57.7	54.3	71	9.0
	Rsg/Ins	4 mg			57.1	56.6	72	9.1
	Ins	Per usual			55.6	55.8	68	8.9
49653/085	Rsg/Ins	4-8 mg	Type 2 DM	May 2000-Jun 2001	61.3	54.0	99	Baseline not reported
	Ins	Per usual			61.5	46.8	100	
49653/093	Rsg/Met	8 mg/2.5g	Type 2 DM poorly controlled with Met	Jun 1997-Apr 1998	57.8	60.0	58	8.7
	Rsg	8 mg			58.8	53.7	59	8.7
	Met	2.5 g			59.5	67.0	60	8.8
49653/094	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled with Met	Apr 1997-Mar 1998	58.3	68.2	77	8.9
	Rsg/Met	4 mg/2. 5g			57.5	62.1	80	8.9
	Met	2.5 g			58.8	74.3	81	8.6
49653/095	Rsg/Ins	8 mg	Type 2 DM poorly controlled with Ins	Aug 1997-Dec 1998	57.4	58.9	73	9.1
	Rsg/Ins	4 mg			57.8	63.9	68	8.8
	Ins	Per usual			58.9	45.3	73	9.1
49653/097	Rsg	8 mg	Type 2 DM	Aug 1997- Jan 2001	55.8	72.1	74	8.9
	Gly	Titrated			56.0	70.8	84	8.8
49653/125	Rsg/Su	4 mg	Type 2 DM	May 1999-Aug 2000	54.6	45.7	56 (A)	9.1
	Su	Per usual			57.3	42.4	59 (A)	8.9
49653/127	Rsg/Gly	8 mg/<20 mg	Type 2 DM poorly controlled with Gly	Jan 1999-Dec 1999	60.0	51.0	75	9.1
	Gly	<20 mg			59.4	66.0	75	8.9
49653/128	Rsg/Su	4 mg	Type 2 DM on concurrent SU	May 1999-Jun 2000	58.3	51.3	100 (A)	9.6
	Su	Per usual			57.7	42.1	100 (A)	9.9
49653/134	Rsg/Gly/Met	8 mg	Type 2 DM on Gly and Met	Mar 1999-Aug 2000	55.5	62.0	71	8.7
	Rsg/Gly/Met	4 mg			55.6	58.0	68	8.6
	Gly/Met	Per usual			55.8	61.0	71	8.7
49653/135	Rsg/Glip	4-8 mg/20-40 mg	Elderly type 2 DM	May 1999-Oct 2002	68.7	74.1	90	7.6
	Glip	20-40 mg			68.2	71.2	91	7.3
49653/136	Rsg/Su/Ins	4-8 mg	Type 2 DM with chronic renal failure on SU and/or Ins	Jul 1999-Jun 2001	64.9	60.7	97	8.2
	Su/Ins	Per usual			66.3	60.8	98	8.3
49653/145	Rsg/Su	8 mg	Type 2 DM	Oct 1999-Nov 2000	61.1	57.3	97	8.5
	Su	Per usual			61.9	62.7	98	8.6
49653/147	Rsg/Su	8 mg	Type 2 DM in Indo-Asian patients	Jul 1999-Aug 2000	54.3	20.2	100 (A)	9.2
	Su	Per usual			54.1	25.3	100 (A)	9.1
49653/162	Rsg/Gly	8 mg	Type 2 DM	Nov 2000- Apr 2002	60.0	55.1	97	7.9
	Gly	Maximum 15 mg			59.9	61.8	96	8.0

(continued)

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Table 2. Dosages, Baseline Demographic Characteristics, Study Periods, and Hemoglobin A_{1c} (HbA_{1c}) Levels (continued)

Clinical Trial No.	Study	Dosage	Population	Study Period	Age, y	% Male Sex	% Race[a]	Baseline HbA_{1c} Level
49653/234	Rsg/Glim	8 mg	Type 2 DM	Jan 2001-Feb 2002	62.9	44.0	100	8.1
	Rsg/Glim	4 mg			60.5	57.0	100	8.2
	Glim	Titrated			65.0	60.0	100	7.9
49653/330	Rsg	8 mg	Chronic psoriasis	Jan 2003-Oct 2004	44.3	65.0	92	NA
	Rsg	4 mg			44.8	66.0	91	NA
	Rsg	2 mg			45.0	63.0	90	NA
	Plc	NA			44.5	63.0	93	NA
49653/331	Rsg	4 mg	Chronic psoriasis	Jan 2003-Oct 2004	44.9	64.1	88	NA
	Rsg	2 mg			45.2	62.0	90	NA
	Plc	NA			46.4	58.3	93	NA
49653/137	Rsg/Met	≥2 mg/≥1 g	Type 2 DM	Apr 2000-Mar 2004	60.0	63.4	78	Baseline not reported
	Gly/Met	≥5 mg/≥1 g			58.8	68.9	76	
SB-712753/002	Rsg/Met	4-8 mg/2-3 g	Type 2 DM poorly controlled	Jul 2003-Jun 2004	58.1	58.3	97	7.4
	Met	2-3 g			57.6	56.8	98	7.5
SB-712753/003	Rsg/Met	4-8 mg/1-3 g	Mild type 2 DM	Jun 2003-Dec 2004	58.9	54.7	98	7.2
	Met	1-3 g			59.0	55.5	99	7.2
SB-712753/007	Rsg/Met	2-8 mg/0.5-2 g	Drug-naïve type 2 DM	Oct 2003-Dec 2004	50.1	57.4	54	8.9
	Rsg	4-8 mg			51.5	56.5	58	8.8
	Met	0.5-2 g			50.6	58.5	59	8.8
SB-712753/009	Rsg/Met/Ins	8 mg/2 g	Type 2 DM on Ins	Oct 2003-Nov 2004	57.2	51.8	98	8.7
	Ins	Per usual			56.9	53.1	99	8.8
49653/132	Rsg/Su	4 mg/usual	Type 2 DM in China	Apr 1999-Feb 2000	58.9	47.6	100 (A)	9.9
	Rsg/Su	8 mg/usual			59.0	41.4	100 (A)	9.7
	Su	Per usual			58.8	45.7	100 (A)	9.6
AVA100193	Rsg	2 mg	Mild to moderate Alzheimer disease	Jan 2004-May 2005	71.0	44.1	100	Baseline not reported
	Rsg	4 mg			70.0	43.8	100	
	Rsg	8 mg			71.0	34.1	100	
	Plc	NA			72.0	36.9	100	
DREAM trial[18][b]	Rsg	4-8 mg	Impaired glucose tolerance or fasting glucose	Jul 2001-Aug 2003	54.6	41.7	66	104.5
	Plc	NA			54.8	39.9	66	104.5
ADOPT[19]	Rsg	4 mg	Recently diagnosed Type 2 DM	Apr 2000-Jun 2002	56.3	55.7	87	7.4
	Met	500 mg			57.9	59.4	89	7.4
	Gly	2.5 mg			56.4	58.0	89	7.4
AVD100521	Rsg	4 mg	Type 2 DM and CVD	Jan 2005- Aug 2008	61.8	70.4	69	7.1
	Glip	5 mg			60.2	65.6	64	7.2
AVD102209	Rsg/Ins	4 mg	Type 2 DM poorly controlled with Ins	Sep 2005-Nov 2006	56.8	61	100 (A)	9.6
	Ins/Plc	Per usual			55.9	66	100 (A)	9.6
AVD104742	Rsg	4-8mg	Type 2 DM poorly controlled with diet	Dec 2005-May 2007	55	100	100 (A)	8.9
	Pio	15-45mg			56	99	100 (A)	8.8
	Plc	NA			54	33	100 (A)	9.0
ARA102198	Rsg	8 mg	Rheumatoid arthritis	Nov 2004-Dec 2006	56.8	6	100	NA
	Plc	NA			56.2	4	100	NA
AVA105640	Rsg	2 mg	Mild to moderate Alzheimer disease	Feb 2007-Sep 2008	73.3	36	67	NA
	Rsg	8 mg			73.2	35	72	NA
	Donepezil	10 mg			72.9	37	75	NA
	Plc	NA			72.7	40	77	NA
49653/044	Rsg/Met	2 mg/2.5 g	Type 2 DM poorly controlled with Met	Mar 1998-Dec 1999	52.9	41.7	42	9.7
	Rsg/Met	4 mg/2.5 g			55.3	23.4	45	9.3
	Plc	NA			54.8	45.6	43	9.6
49653/096	Rsg/Gly	2 mg/≥10 mg	Type 2 DM poorly controlled with Gly	Apr 1997-Mar 1998	59.3	85	74	9.3
	Rsg/Gly	4 mg/≥10 mg			60.2	93	80	9.1
	Gly/Plc	≥10 mg			60.3	90	78	8.9
49653/109	Rsg	2 mg	Type 2 DM	Jan 1999-Apr 2002	52.7	51.8	82 (B)	7.9
	Rsg	4 mg			53.9	52	92 (B)	8.2
	Glip	2.5-10 mg			54.3	48	93 (B)	7.8
49653/282	Rsg	4-8 mg	Type 2 DM	Jun 2001-Nov 2003	60.7	56.5	80	7.6
	Gly	2.5-5 mg			59.6	63.8	79	7.6
49653/325	Glim/Rsg	2 mg/4 mg	Type 2 DM poorly controlled with non-TZD	Mar 2003-Jun 2004	53.9	54.7	68.5	8.2
	Glim	4 mg			53	58.6	65.2	8.0
49653/351	Rsg	4-8 mg	Type 2 DM with vascular disease or hypertension	Feb 2003-May 2005	62.2	75	63	NA
	Plc	NA			65.6	79	62	NA
49653/369	Rsg	4-8 mg	Type 2 DM	Jan 2003-Oct 2003	51.6	52	100	6.7
	Glib	2.5-10 mg			53.6	54.2	100	7.0
49653/452	Rsg	8 mg	Multiple sclerosis	Apr 2003-Nov 2004	41	12	76	NA
	Plc	NA			43	21	88	NA
RECORD trial[4]	Rsg/Met or Su	4-8 mg/per usual	Type 2 DM	Apr 2001-Dec 2008	58.4	51.4	99	7.8
	Met and Su	Per usual			58.5	51.7	99	8.0
			Weighted Adjusted Means					
			Rosiglitazone		56.7	55.2	85.4	8.2
			Control		57.4	54.4	74.0	8.3

Abbreviations: A, Asian; ADOPT, A Diabetes Outcome Progression Trial; B, Black; BD, twice daily; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; Elm, enhanced lifestyle management; Glib, glibencamide; Glim, glimepride; Glip, glipizide; Gly, glyburide; H, Hispanic; Ins, insulin; Met, metformin; NA, not applicable; Pio, pioglitazone; Plc, placebo; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes; Rsg, rosiglitazone; Su, sulfonylurea; TZD, thiazolidinedione.

[a] All values other than A, B, and H refer to the percentage of whites in the study population.

[b] Hemoglobin A_{1c} NA; fasting blood glucose shown.

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Table 3. Myocardial Infarction (MI) and Cardiovascular (CV) Death in Rosiglitazone Trials

	Rosiglitazone			Comparators		
GSK Trial No.	No. of Patients	MI	CV Death	No. of Patients	MI	CV Death
Trials Included in Original Registration Package						
49653/011	357	2	1	176	0	0
49653/020	391	2	0	207	1	0
49653/024	774	1	0	185	1	0
49653/093	213	0	0	109	1	0
49653/094	232	1	1	116	0	0
Additional Phase 2, 3, and 4 Efficacy Trials						
100684	43	0	0	47	1	0
49653/143	121	1	0	124	0	0
49653/211	110	5	5	114	2	4
49653/284	382	1	0	384	0	0
712753/008	284	1	0	135	0	0
AVM100264	294	0	2	302	1	1
BRL 49653C/185	563	2	0	142	0	0
BRL 49653/334	278	2	0	279	1	1
BRL 49653/347	418	2	0	212	0	0
49653/015	395	2	2	198	1	0
49653/079	203	1	1	106	1	1
49653/080	104	1	0	99	2	0
49653/082	212	2	1	107	0	0
49653/085	138	3	1	139	1	0
49653/095	196	0	1	96	0	0
49653/097	122	0	0	120	1	0
49653/125	175	0	0	173	1	0
49653/127	56	1	0	58	0	0
49653/128	39	1	0	38	0	0
49653/134	561	0	1	276	2	0
49653/135	116	2	2	111	3	1
49653/136	148	1	2	143	0	0
49653/145	231	1	1	242	0	0
49653/147	89	1	0	88	0	0
49653/162	168	1	1	172	0	0
49653/234	116	0	0	61	0	0
49653/330	1172	1	1	377	0	0
49653/331	706	0	1	325	0	0
49653/137	204	1	0	185	2	1
SB-712753/002	288	1	1	280	0	0
SB-712753/003	254	1	0	272	0	0
SB-712753/007	314	1	0	154	0	0
SB-712753/009	162	0	0	160	0	0
49653/132	442	1	1	112	0	0
AVA100193	394	1	1	124	0	0
AVD102209	132	0	0	131	0	1
AVD104742	160	0	0	213	0	0
AVD100521 (APPROACH trial[17])	331	8	4	337	7	3
AVA105640	331	1	0	250	1	1
ARA102198	49	0	0	49	0	0
49653/044	101	0	0	51	0	0
49653/096	232	0	0	115	0	0
49653/109	52	0	0	25	0	0
49653/325	196	0	0	195	0	0
49653/282	70	0	0	75	0	0
49653/351	28	0	0	29	0	0
49653/369	25	0	0	24	0	0
49653/452	26	0	0	24	0	0
Published Large Prospective Randomized Trials						
DREAM trial[18]	2635	15	12	2634	9	10
ADOPT[19]	1456	27	2	2895	41	5
RECORD trial[4]	2220	64	60	2227	56	71

Abbreviations: ADOPT, A Diabetes Outcome Progression Trial; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients With Cardiovascular History; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.

EXPLORATORY ANALYSES

Substituting all-cause mortality for CV death in the primary analysis (Peto method) yielded similar results: the OR was 0.98 (95% CI, 0.82-1.17), including the RECORD trial, and 1.16 (95% CI 0.89-1.52), excluding the RECORD trial. For NNH calculations, the background rate for MI based on the ACCORD trial was 1.38% per year, or 6.9%

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Table 4. Primary Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

Method	No. of Studies	Rosiglitazone Group	Control Group	Peto OR (95% CI)	*P* Value
Risk for Myocardial Infarction[a]					
Including RECORD trial[4]	41	159/17 258	136/14 449	1.28 (1.02-1.63)	.04
Excluding RECORD trial	40	95/15 038	80/12 222	1.39 (1.02-1.89)	.04
Risk for Cardiovascular Mortality[b]					
Including RECORD trial	26	105/13 672	100/12 175	1.03 (0.78-1.36)	.86
Excluding RECORD trial	25	45/11 452	29/9949	1.46 (0.92-2.33)	.11

Abbreviations: CI, confidence interval; OR, odds ratio; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.

[a] Including RECORD trial: *Q* statistic, 30.3; *P*=.87; I^2=0%, Excluding RECORD trial: *Q* statistic, 29.7; *P*=.86; I^2=0%.

[b] Including RECORD trial: *Q* statistic, 16.2; *P*=.91; I^2=0%. Excluding RECORD trial: *Q* statistic, 12.8; *P*=.97; I^2=0%.

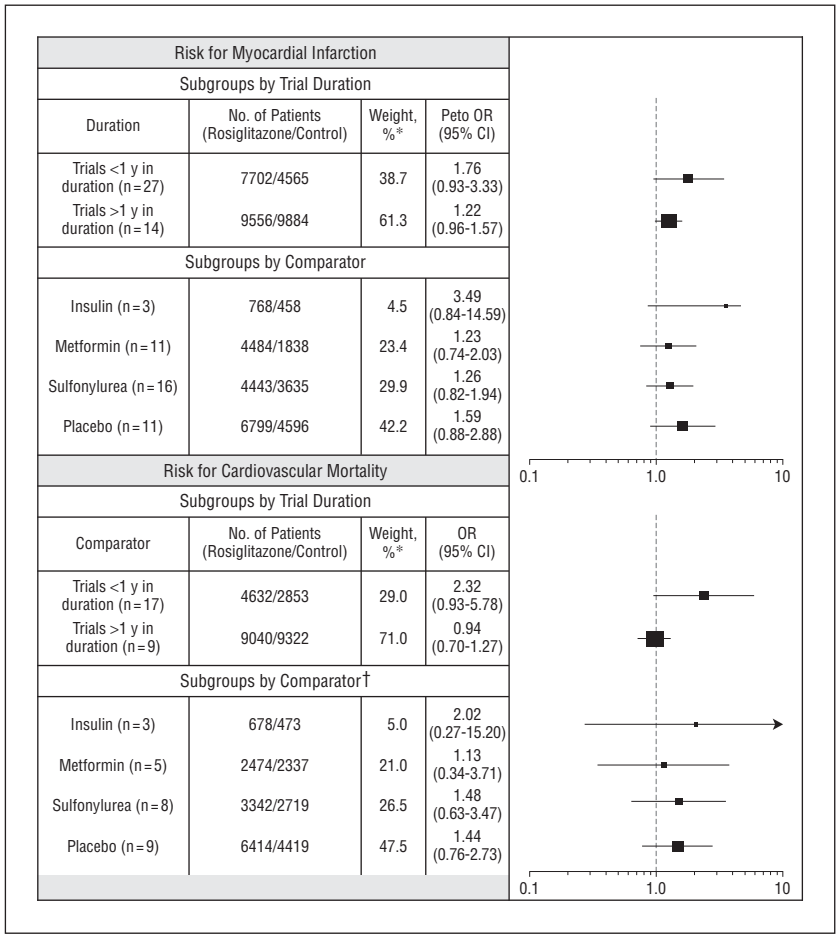

Figure 2. Risk for myocardial infarction and cardiovascular mortality in trials classified by study duration and comparator drug. CI indicates confidence interval; and OR, odds ratio. *Calculated by proportion of the total sample included in the meta-analysis. †The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial[4] was not included in the analysis of the comparator subgroup because of the combination treatment assignment, and ADOPT (A Diabetes Outcome Progression Trial)[19] was included separately for both the metformin (n=1454) and the sulfonylurea (n=1441) subgroups, according to randomized assignment.

over the 5-year period typically used in NNH estimates. Applying the odds of increased risk for MI with rosiglitazone from the current study, the NNH is estimated to be 1 additional MI per 52 patients (assuming OR=1.28 after inclusion of the RECORD trial) or 1 additional MI per 37 patients, (assuming OR=1.39 after exclusion of the RECORD trial) treated with rosiglitazone for 5 years.

COMMENT

The CV safety of rosiglitazone therapy has remained controversial after the publication of initial reports that suggested that the use of rosiglitazone increases the risk for MI and other ischemic myocardial events.[1,14,20] Despite 11 years on the market, rosiglitazone has not been studied in any definitive randomized controlled CV outcomes trials. Accordingly, a meta-analysis of existing clinical trials represents the most robust available approach to determining the CV safety of this drug. The current study analyzed MI and CV mortality for 56 randomized trials involving 35 531 patients. Using a study-level meta-analysis, the OR for MI was significantly increased but without evidence of an increase in CV or all-cause mortality. An alternative analysis that included trials with no CV events found a similar hazard (Figure 3). Subgroups classified by study duration and comparator drug also showed elevated OR estimates (Figure 2). These findings are consistent with prior meta-analyses conducted by GSK, the FDA, and most independent investigators demonstrating an increased risk of MI in patients treated with rosiglitazone.[1,10,14,20] The FDA has announced that it will conduct an advisory committee meeting in July 2010 to consider whether to remove rosiglitazone from the market.

The public health implications of these results are considerable. There are more than 23 million persons with diabetes in the United States alone and nearly 300 million worldwide.[30,31] Cardiovascular disease is the leading cause of death in patients with type 2 diabetes, representing approximately 68% of all causes of mortality.[30] The estimated 28% to 39% increase in the risk for MI observed for rosiglitazone use in the current analysis and the NNH of 52 or 37 (with and without the RECORD trial) represent a significant potential health burden. The magnitude of the ob-

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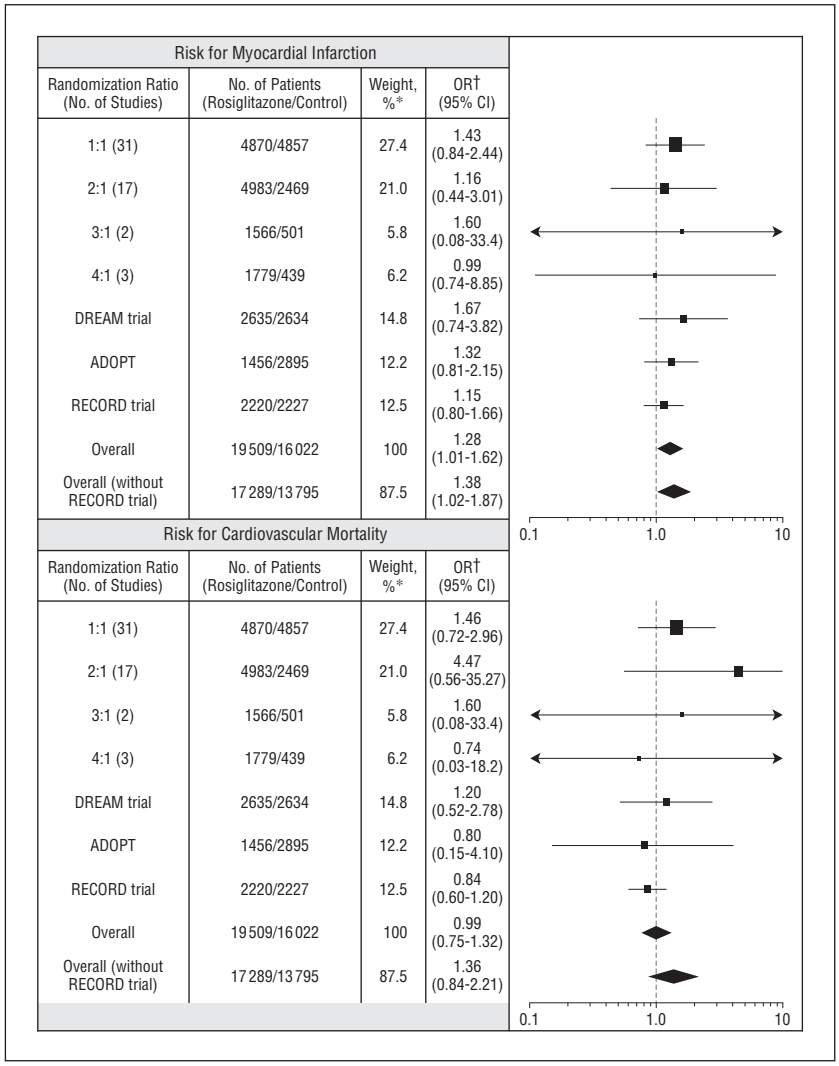

Figure 3. Alternative analysis of risk for myocardial infarction and cardiovascular mortality, including studies with no events. ADOPT indicates A Diabetes Outcome Progression Trial[19]; CI, confidence interval; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication[18]; OR, odds ratio; and RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.[4] *Calculated by proportion of the total sample included in the meta-analysis. †Mantel-Haenszel method.

served effect is larger than might be anticipated in a safety analysis using intent-to-treat (ITT) methods. In ITT efficacy studies, discontinuation of therapy or crossovers between treatment groups bias the study toward the null hypothesis, thereby favoring the control treatment. However, in safety studies, similar flaws in study conduct bias the investigation toward a relative risk of 1.0, providing the potential for a false declaration of safety. Accordingly, using standardized ITT methods, it is statistically much more difficult to conclude that a therapy is unsafe than to demonstrate efficacy. Because we did not have access to patient-level data, we were unable to perform a useful alternative analysis that is commonly used in drug-safety studies, a "per protocol" approach that includes events that occurred "on-treatment" or within 30 days after discontinuation of treatment.

We elected to present analyses with and without the RECORD trial. Several of the concerns about the RECORD trial have been reported elsewhere.[5-8] The study was an open-label, randomized noninferiority trial that compared rosiglitazone with metformin or sulfonlyurea. The primary efficacy parameter was unconventional, CV hospitalization or death. The study postulated an annual event rate of 11% but observed an event rate of only 2.6%, a large mismatch that substantially reduced statistical power. The MI rate for the control group in the RECORD trial was 0.52% per year compared with 1.38% for a similar population in the ACCORD trial, raising the concern that MIs may have been incompletely ascertained. By the end of the trial, 40% of patients randomized to rosiglitazone therapy were no longer taking the drug. Nonadherence to randomized therapy represents an important issue in a safety trial because, as noted above, dropouts and crossovers bias the result toward the null hypothesis. Finally, the company compromised data integrity by publishing an unplanned interim analysis[32] and appears to have had access to ongoing study data at a time when the trial should have remained blinded.[2,6,7]

The limitations of our meta-analysis are notable. We had access to study-level data that were disclosed as a result of a court settlement and subsequently posted on a company Web site. The unavailability of patient-level data precluded a more statistically powerful analysis using time-to-event methods. However, it should be noted that the original 2007 meta-analysis was subsequently replicated by the FDA using time-to-event data, resulting a nearly identical relative risk. There are important strengths to the study. The number of patients and studies included in the analysis is substantially larger than was available for our original meta-analysis, which was completed in 2007. Furthermore, because disclosure of all clinical trials by the maker of rosiglitazone was mandated by a court order, the common problem of publication bias did not confound our analyses. The original 2007 analysis was criticized by some authors because it did not include clinical trials in which there were no events.[13] Therefore, in the current effort, we provided an alternative approach that includes all 56 trials, regardless of whether there were adverse events. With both methods, the OR was nearly identical.

A related issue involves the question of whether use of the other marketed thiazolidinedione, pioglitazone, carries similar risks. A large CV outcomes trial with pioglitazone, the PROACTIVE (Prospec-

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tive Pioglitazone Clinical Trial in Macrovascular Events) trial, which was published in 2005, did not show statistically significant benefits.[33] It showed a trend toward reduction in the primary efficacy parameter, a broad composite of CV events (HR, 0.90; 95% CI, 0.80-1.02; $P=.10$). However, a prespecified secondary end point of death, MI, and stroke showed a benefit (HR, 0.84; 95% CI, 0.72-0.98; $P=.03$). A patient-level meta-analysis of CV outcomes with pioglitazone analyzed 19 trials, with a total enrollment of 16 390 patients, and showed a statistically significant benefit on the composite of death, MI, and stroke (OR, 0.82; 95% CI, 0.72-0.94; $P=.005$). These findings effectively rule out a CV hazard for pioglitazone use and suggest the possibility of a CV benefit. However, it must be noted that the use of both rosiglitazone and pioglitazone has been associated with an increased risk of congestive heart failure.

The potential mechanism(s) for CV harm from rosiglitazone use (and the differences from pioglitazone use) remains to be elucidated, but there are several reasonable hypotheses. Rosiglitazone therapy increased low-density lipoprotein cholesterol (LDL-C) levels as much as 23% in trials, leading to approval.[21] Current FDA guidelines consider a drug that lowers LDL-C levels by at least 15% "approvable" for presumed CV benefits. Although the FDA has not established a level of increase in LDL-C that is presumed to cause harm, a drug that increases LDL-C levels would reasonably be expected to increase CV adverse events. Interestingly, the lipid effects of the 2 marketed thiazolidinediones, pioglitazone and rosiglitazone, are markedly different.[34] In a comparative efficacy trial, rosiglitazone therapy produced greater increases in LDL-C levels and raised triglyceride levels, while pioglitazone therapy reduced triglyceride levels. Pioglitazone therapy also produced significantly greater increases in high-density lipoprotein cholesterol compared with rosiglitazone therapy. Thiazolidinediones are nuclear receptor agonists that modulate expression of a large number of genes. There are major differences in the pattern of gene modulation for pioglitazone vs rosiglitazone.[35] Rosiglitazone activates a gene associated with production of matrix metalloproteinase 3, an enzyme linked to plaque rupture.[36]

There are also implications of these findings on the traditional approach used by regulatory authorities to approve drugs that are used to treat diabetes. Historically, evidence of a glucose-lowering effect, with no evidence for obvious safety issues, was sufficient for approval. In the wake of the rosiglitazone controversy, the FDA has mandated that sponsors of all new diabetes drugs perform CV outcomes studies sufficient to rule out an HR with an upper 95% CI of 1.8 before approval and 1.3 after approval.[37] Had such requirements been in place at the time rosiglitazone was developed, it seems likely that the drug would never have been approved.

The results of the current meta-analysis suggest an unfavorable benefit to risk ratio for rosiglitazone use. The implications of this finding warrant further discussion. Even a modest increase in the risk of MI in a diabetic population would have serious consequences. Reviewers within the FDA Office of Surveillance and Epidemiology calculated the number of major CV events potentially attributable to rosiglitazone therapy from 1999 to 2006, reporting a range from 41 000 to 205 000.[2] More recently, using lower estimates of the rate of drug use after the 2007 controversy, FDA reviewers have calculated the number of excess MIs (6000 annually) potentially attributable to rosiglitazone use relative to treatment with the alternative thiazolidinedione, pioglitazone.[3] Although hyperglycemia has been associated with an increased risk of microvascular adverse events, there are now 12 classes of drugs that are approved to lower blood glucose levels, including insulin. Because no unique benefits of rosiglitazone use have been identified, administration of this agent solely to lower blood glucose levels is difficult to justify.

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Correspondence: Steven E. Nissen, MD, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).
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