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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; $P=0.03$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; $P=0.06$).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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THIAZOLIDINEDIONE DRUGS ARE WIDELY used to lower blood glucose levels in patients with type 2 diabetes mellitus. In the United States, three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity, and two currently available agents, rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda). The thiazolidinediones are agonists for peroxisome-proliferator-activated receptor γ (PPAR- γ). PPAR- γ receptors are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues.^{1,2} Rosiglitazone was introduced in 1999 and is widely used as monotherapy or in fixed-dose combinations with either metformin (Avandamet, GlaxoSmithKline) or glimepiride (Avandaryl, GlaxoSmithKline).

The original approval of rosiglitazone was based on the ability of the drug to reduce blood glucose and glycated hemoglobin levels.³ Initial studies were not adequately powered to determine the effects of this agent on microvascular or macrovascular complications of diabetes, including cardiovascular morbidity and mortality.³ However, the effect of any antidiabetic therapy on cardiovascular outcomes is particularly important, because more than 65% of deaths in patients with diabetes are from cardiovascular causes.⁴ Therefore, we performed a meta-analysis of trials comparing rosiglitazone with placebo or active comparators to assess the effect of this agent on cardiovascular outcomes. The source material for this analysis consisted of publicly available data from the original registration package submitted to the Food and Drug Administration (FDA), another series of trials performed by the sponsor after approval, and two large, prospective, randomized trials designed to study additional indications for the drug.

METHODS

ANALYZED STUDIES

Table 1 lists the 42 trials included in this meta-analysis. We screened 116 phase 2, 3, and 4 trials for inclusion. Of these, 48 trials met the predefined inclusion criteria of having a randomized comparator group, a similar duration of treatment in all groups, and more than 24 weeks

of drug exposure. Six of the 48 trials did not report any myocardial infarctions or deaths from cardiovascular causes and therefore were not included in the analysis because the effect measure could not be calculated. Of the remaining 42 studies, 38 reported at least one myocardial infarction, and 22 reported at least one death from cardiovascular causes. In these trials, 15,560 patients were randomly assigned to regimens that included rosiglitazone, and 12,283 were assigned to comparator groups with regimens that did not include rosiglitazone.

Multiple groups of patients who received rosiglitazone within a single trial were pooled together, when applicable. The control group was defined as patients receiving any drug regimen other than rosiglitazone. The trials fall into three categories. One group includes five of the studies submitted to the FDA for the March 22, 1999, advisory board hearing that recommended approval of rosiglitazone. Group-level data from these five studies are available in publicly disclosed briefing documents archived on the FDA Web site.⁶ Data from these same trials are also reported in a summary fashion on a clinical-trial registry Web site maintained by the drug manufacturer, GlaxoSmithKline.⁵ Reports of four of these five trials were also published in peer-reviewed journals.⁷⁻⁹ In these five trials, 1967 patients were randomly assigned to receive rosiglitazone, and 793 patients were assigned to receive various comparator drugs (Table 1).

Other studies that we included in the meta-analysis were initially identified in the GlaxoSmithKline clinical-trial registry.⁵ As noted in Table 1, we included 35 studies in this category, 9 of which were published in peer-reviewed journals and 26 of which remain unpublished.¹⁰⁻¹⁸ Whenever possible, the results obtained on the GlaxoSmithKline Web site were cross-checked with the publication. In cases of disagreement between published and unpublished data, data derived from the manufacturer's Web site were used. In this group of 35 trials, 9502 patients were randomly assigned to receive rosiglitazone, and 5961 patients were assigned to receive various comparator drugs.

A third data source consisted of two large, recently published trials, the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM) trial²⁰ and the A Diabetes

Outcome Prevention Trial (ADOPT) (ClinicalTrials.gov number, NCT00279045).²¹ In the DREAM study, 2635 patients were randomly assigned to receive rosiglitazone and 2634 patients were assigned to receive placebo. The DREAM study was designed to determine whether rosiglitazone could prevent the development of type 2 diabetes in patients at high risk for this disorder. In the ADOPT trial, 1456 patients were randomly assigned to receive rosiglitazone and 2895 patients were assigned to receive either metformin or glyburide. The ADOPT study was designed to assess the durability of glycemic control with rosiglitazone therapy, as compared with therapy with metformin or glyburide.

OUTCOME MEASURES

We reviewed data summaries provided in the FDA review documents, the GlaxoSmithKline clinical-trial registry Web site, and published trial results and then abstracted from the adverse-event tabulations information on myocardial infarction and death from cardiovascular causes. With the exception of the DREAM study, the included trials did not describe adjudication of myocardial infarction or death from cardiovascular causes. Time-to-event data for cardiovascular events were not available in any of these trials, which precluded the calculation of hazard ratios. Because only summary data were available, it was not possible to discern whether the same patient had both events. Therefore, an outcome measure based on the composite of death or myocardial infarction could not be constructed. Accordingly, these two outcomes are reported separately.

STATISTICAL ANALYSIS

Many trials had few cardiovascular events, so the odds ratios and 95% confidence intervals were calculated with the use of the Peto method.²²⁻²⁴ Because all trials had similar durations of follow-up for all treatment groups, the use of odds ratios represents a valid approach to assessing the risk associated with the use of rosiglitazone. Trials in which patients had no adverse cardiovascular events in either group were excluded from analyses. All reported P values are two-sided. Statistical heterogeneity across the various trials was tested with the use of Cochran's Q statistic. A P value of more than the nominal level of 0.10

for the Q statistic indicated a lack of heterogeneity across trials, allowing for the use of a fixed-effects model. For additional analyses, the active comparator control groups were subgrouped into the following four classes for comparison with rosiglitazone: metformin, sulfonylurea, insulin, and placebo. Odds ratios and 95% confidence intervals were calculated for each subgroup with the use of methods similar to those used in the pooled analyses. Data were analyzed with the use of Comprehensive Meta-Analysis software, version 2.2 (Biostat).

RESULTS

BASELINE CHARACTERISTICS

Table 2 reports the doses of rosiglitazone and comparator drugs, baseline demographic characteristics, study periods, and glycated hemoglobin levels or fasting blood glucose levels for patients enrolled in the trials. The patients were relatively young, averaging less than 57 years of age for both the rosiglitazone group and the control group. Overall, there was a moderate predominance of men. Diabetes control was relatively poor, with a mean baseline glycated hemoglobin level of approximately 8.2% for both study groups.

MYOCARDIAL INFARCTION AND DEATH

Table 3 reports the myocardial infarction events and deaths from cardiovascular causes that were reported in the 42 clinical trials we reviewed. There were 86 myocardial infarctions in the rosiglitazone group and 72 in the control group. There were 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in the control group. Table 4 lists the odds ratios, 95% confidence intervals, and P values for myocardial infarction and death from cardiovascular causes for the rosiglitazone group and the control group. The summary odds ratio for myocardial infarction was 1.43 in the rosiglitazone group (95% confidence interval [CI], 1.03 to 1.98; P=0.03). The odds ratio for death from cardiovascular causes in the rosiglitazone group, as compared with the control group, was 1.64 (95% CI, 0.98 to 2.74; P=0.06). Table 4 also lists odds ratios and 95% confidence intervals for the pooled group of trials that were smaller and of shorter duration; results for the DREAM and ADOPT studies are shown separately.

Table 1. Clinical Trials of Rosiglitazone in the Meta-Analysis.*

Study and Reference	Registry Number	Phase	Duration wk	Drug	Rosiglitazone Group	No. of Patients	Drug	Control Group	No. of Patients
Trials included in original registration package									
49653/011 ^{5,7}		3	24	Rosiglitazone		357	Placebo		176
49653/020 ^{5,6}		3	52	Rosiglitazone		391	Glyburide		207
49653/024 ^{5,6,8}		3	26	Rosiglitazone		774	Placebo		185
49653/093 ^{5,6,9}		3	26	Rosiglitazone with or without metformin		213	Metformin		109
49653/094 ^{5,6,9,10}		3	26	Rosiglitazone and metformin		232	Metformin		116
Subtotal						1,967			793
Additional phase 2, 3, and 4 efficacy trials									
100684 ⁵		4	52	Rosiglitazone and glyburide		43	Glyburide		47
49653/143 ⁵		4	24	Rosiglitazone and glyburide		121	Glyburide		124
49653/211 ⁵		4	52	Rosiglitazone and usual care		110	Usual care		114
49653/284 ^{5,11}		4	24	Rosiglitazone and metformin		382	Metformin		384
712753/008 ⁵		4	48	Rosiglitazone and metformin		284	Metformin		135
AVM100264 ⁵	NCT00359112	4	52	Rosiglitazone and metformin		294	Metformin and sulfonylurea†		302
BRL 49653C/185 ⁵		4	32	Rosiglitazone with or without metformin		563	Usual care with or without metformin		142
BRL 49653/334 ⁵		4	52	Rosiglitazone		278	Placebo		279
BRL 49653/347 ⁵	NCT00054782	4	24	Rosiglitazone and insulin		418	Insulin		212
49653/015 ^{5,12}		3	24	Rosiglitazone and sulfonylurea‡		395	Sulfonylurea‡		198
49653/079 ⁵		3	26	Rosiglitazone with or without glyburide		203	Glyburide		106
49653/080 ^{5,13}		3	156	Rosiglitazone		104	Glyburide		99
49653/082 ^{5,14}		3	26	Rosiglitazone and insulin		212	Insulin		107
49653/085 ⁵		3	26	Rosiglitazone and insulin		138	Insulin		139
49653/095 ⁵		3	26	Rosiglitazone and insulin		196	Insulin		96
49653/097 ⁵		3	156	Rosiglitazone		122	Glyburide		120

49653/125 ^{5,15}	3	26	Rosiglitazone and sulfonylurea§	175	Sulfonylurea§	173
49653/127 ⁵	3	26	Rosiglitazone and glyburide	56	Glyburide	58
49653/128 ⁵	3	28	Rosiglitazone	39	Placebo	38
49653/134 ⁵	3	28	Rosiglitazone	561	Placebo	276
49653/135 ⁵	3	104	Rosiglitazone and glipizide	116	Glipizide	111
49653/136 ⁵	3	26	Rosiglitazone	148	Placebo	143
49653/145 ^{5,16}	3	26	Rosiglitazone and gliclazide	231	Gliclazide	242
49653/147 ^{5,17}	3	26	Rosiglitazone and sulfonylurea¶	89	Sulfonylurea¶	88
49653/162 ^{5,18}	3	26	Rosiglitazone and glyburide	168	Glyburide	172
49653/234 ⁵	3	26	Rosiglitazone and glimepiride	116	Glimepiride	61
49653/330 ⁵	3	52	Rosiglitazone	1,181	Placebo	382
49653/331 ⁵	3	52	Rosiglitazone	706	Placebo	325
49653/137 ⁵	3	32	Rosiglitazone and metformin	204	Glyburide and metformin	185
SB-712753/002 ⁵	3	24	Rosiglitazone and metformin	288	Metformin	280
SB-712753/003 ⁵	3	32	Rosiglitazone and metformin	254	Metformin	272
SB-712753/007 ⁵	3	32	Rosiglitazone with or without metformin	314	Metformin	154
SB-712753/009 ⁵	3	24	Rosiglitazone, metformin, and insulin	162	Insulin	160
49653/132 ^{5,19}	2	24	Rosiglitazone and sulfonylurea	442	Sulfonylurea	112
AVA100193 ⁵	2	24	Rosiglitazone	394	Placebo	124
Subtotal				9,502		5,961
Recently published large, prospective, randomized trials						
DREAM ²⁰	3	156	Rosiglitazone	2,635	Placebo	2,634
ADOPT ²¹	3	208	Rosiglitazone	1,456	Metformin or glyburide	2,895
Total				15,560		12,283

* Studies are listed according to the number designated by the sponsor, GlaxoSmithKline, and are available on the company's Web site.⁵ ClinicalTrials.gov numbers are listed for trials included in that registry. DREAM denotes Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication, and ADOPT A Diabetes Outcome Prevention Trial.

† The administered drug was either glyburide or gliclazide.

‡ The administered drug was glyburide, gliclazide, or glipizide.

§ The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, glimepiride, or tolbutamide.

¶ The type of sulfonylurea was unspecified.

|| The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, glimepiride, or tolbutamide.

Table 2. Doses, Baseline Demographic Characteristics, Study Periods, and Glycated Hemoglobin Levels.*

Study	Drug	Daily Dose	Population	Study Period	Age yr	Male Sex	Race† percent	Baseline Glycated Hemoglobin Level
100684	Rsg/Gly	4 or 8 mg	Korean patients with type 2 DM	Dec. 2003–July 2005	55.2	53.5	100 A	NA
	Gly	5–15 mg			54.5	45.6	100 A	NA
49653/143	Rsg/Gly	8 mg	Type 2 DM poorly controlled on glyburide	July 2005–Jan. 2003	52	45.3	44:56 B:H	9.2
	Gly	Usual care			53	48.3	38:62 B:H	9.4
49653/211	Rsg	4 mg	Type 2 DM with CHF	July 2001–Nov. 2003	64.3	84.3	99	7.7
	Plc	—			63.9	79.0	99	7.8
49653/284	Rsg/Met	4 or 8 mg/1 g	Type 2 DM	June 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 on Met	June 2003–Dec. 2005	54.6	63.2	70	NA
	Rsg/Met	4 mg/2 g			56.0	65.2	78	NA
	Met	2g			56.9	53.4	69	NA
AVM100264	Rsg/Met	4 or 8 mg/2 g	Overweight patients with type 2 DM poorly controlled on Met	July 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	—			57.0	60.9	83	7.4
BRL 49653/334	Rsg	4 or 8 mg	Type 2 DM or insulin resistance syndrome	March 2002–Nov. 2004	67.7	44.8	99	6.3
	Plc	—			67.3	47.7	100	6.3
BRL 49653/347	Rsg/insulin	4 mg	Type 2 DM poorly controlled on insulin	Nov. 2002–April 2004	52.6	48.1	57	9.0
	Rsg/insulin	2 or 4 mg			52.7	60.0	57	8.9
	Insulin/Plc	Usual care			53.8	46.2	57	9.1
49653/011	Rsg	8 mg	Type 2 DM	Sept. 1996–Sept. 1997	60.7	66.9	73	8.8
	Rsg	4 mg			59.6	64.5	75	9.0
	Plc	—			58.8	65.8	74	9.0
49653/015	Rsg/Su	4 mg	Type 2 DM	Aug. 1996–March 1998	60.6	53.2	98	9.2
	Rsg/Su	2 mg			61.0	62.8	86	9.2
	Su				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 once daily	Type 2 DM	Jan. 1997–Feb. 1998	57.5	58.6	76	8.9
	Rsg	2 mg twice daily			56.8	59.1	78	8.9
	Rsg	8 mg once daily			58.9	65.7	80	8.9
	Rsg	4 mg twice daily			56.5	59.9	71	9.0
	Plc	—			57.7	68.8	79	8.9
49653/079	Rsg	4 mg	Type 2 DM poorly controlled on maximum dose of Gly	April 1997–March 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	2.5–5.0 mg			56.1	70.1	76	9.4
49653/082	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	July 1997–Aug. 1998	57.7	54.3	71	9.0
	Rsg/insulin	4 mg			57.1	56.6	72	9.1
	Insulin	Usual care			55.6	55.8	68	8.9
49653/085	Rsg/insulin	4 or 8 mg	Type 2 DM	May 2000–June 2001	61.3	54.0	99	NA
	Insulin	Usual care			61.5	46.8	100	NA
49653/093	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled on Met	June 1997–April 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 on Met	April 1997–March 1998	58.3	68.2	77	8.9
	Rsg/Met	4 mg/2.5 g			57.5	62.1	80	8.9
	Met	2.5 g			58.8	74.3	81	8.6
49653/095	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	Aug. 1997–Dec. 1998	57.4	58.9	73	9.1
	Rsg/insulin	4 mg			57.8	63.9	68	8.8
	Insulin	Usual care			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	Usual care			57.3	42.4	59 A	8.9
49653/127	Rsg/Gly	8 mg/<20 mg	Type 2 DM poorly controlled on Gly	Jan. 1999–Dec. 1999	60.0	51.0	75	9.1
	Gly	<20 mg			59.4	66.0	75	8.9

Table 2. (Continued.)

Study	Drug	Dose	Population	Study Period	Age yr	Male Sex	Race† percent	Baseline Glycated Hemoglobin Level
49653/128	Rsg/Su Su	4 mg Usual care	Type 2 DM on concurrent Su	May 1999–June 2000	58.3 57.7	51.3 42.1	100 A 100 A	9.6 9.9
49653/134	Rsg/Gly/Met Rsg/Gly/Met	8 mg 4 mg	Type 2 DM on Gly and Met	March 1999–Aug. 2000	55.5 55.6	62.0 58.0	71 68	8.7 8.6
49653/135	Gly/Met Rsg/Glip	Usual care 4 or 8 mg/ 20–40 mg	Elderly patients with type 2 DM	May 1999–Oct. 2002	55.8 68.7	61.0 74.1	71 90	8.7 7.6
49653/136	Glip Rsg/Su/insulin	20–40 mg 4 or 8 mg	Type 2 DM with chronic renal failure on Su, insulin, or both	July 1999–June 2001	68.2 64.9	71.2 60.7	91 97	7.3 8.2
49653/145	Su/insulin Rsg/Su	Usual care 8 mg	Type 2 DM	Oct. 1999–Nov. 2000	66.3 61.1	60.8 57.3	98 97	8.3 8.5
49653/147	Su Rsg/Su	Usual care 8 mg	Indo-Asian patients with type 2 DM	July 1999–Aug. 2000	61.9 54.3	62.7 20.2	98 100 A	8.6 9.2
49653/162	Su Rsg/Gly	Usual care 8 mg	Type 2 DM	Nov. 2000–April 2002	54.1 60.0	25.3 55.1	100 A 97	9.1 7.9
49653/234	Gly Rsg/Glim	Maximum, 15 mg 8 mg	Type 2 DM	Jan. 2001–Feb. 2002	59.9 62.9	61.8 44.0	96 100	8.0 8.1
49653/330	Rsg/Glim Glim	4 mg Up-titrated	Type 2 DM	Jan. 2001–Feb. 2002	60.5 65.0	57.0 60.0	100 100	8.2 7.9
SB-712753/003	Rsg Rsg Rsg Plc Rsg/Met Met	8 mg 4 mg 2 mg — 4 or 8 mg/1–3 g 1–3 g	Chronic psoriasis Mild type 2 DM	Jan. 2003–Oct. 2004 June 2003–Dec. 2004	44.3 44.8 45.0 44.5 58.9 59.0	65.0 66.0 63.0 63.0 54.7 55.5	92 91 90 93 98 99	NA NA NA NA 7.2 7.2

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	—			46.4	58.3	93	NA
49653/137	Rsg/Met	≥2 mg/≥1 g	Type 2 DM	April 2000–March 2004	60.0	63.4	78	NA
	Gly/Met	≥5 mg/≥1 g			58.8	68.9	76	
SB-712753/002	Rsg/Met	4 or 8 mg/ 2–3 g	Type 2 DM poorly controlled	July 2003–June 2004	58.1	58.3	97	7.4
	Met	2–3 g			57.6	56.8	98	7.5
SB-712753/007	Rsg/Met	2 or 8 mg/0.5–2.0 g	Type 2 DM without previous drug therapy	Oct. 2003–Dec. 2004	50.1	57.4	54	8.9
	Rsg	4 or 8 mg			51.5	56.5	58	8.8
	Met	0.5–2.0 g			50.6	58.5	59	8.8
SB-712753/009	Rsg/Met/insulin	8 mg/2 g	Type 2 DM with insulin	Oct. 2003–Nov. 2004	57.2	51.8	98	8.7
	Insulin	Usual care			56.9	53.1	99	8.8
49653/132	Rsg/Su	4 mg/usual care	Patients in China with type 2 DM	April 1999–Feb. 2000	58.9	47.6	100 A	9.9
	Rsg/Su	8 mg/usual care			59.0	41.4	100 A	9.7
	Su	Usual care			58.8	45.7	100 A	9.6
AVA100193	Rsg	2 mg	Mild-to-moderate Alzheimer's disease	Jan. 2004–May 2005	71.0	44.1	100	NA
	Rsg	4 mg			70.0	43.8	100	NA
	Rsg	8 mg			71.0	34.1	100	NA
	Plc	—			72.0	36.9	100	NA
DREAM	Rsg	4 or 8 mg	Impaired glucose tolerance or fasting glucose	July 2001–Aug. 2003	54.6	41.7	66	104.5†‡
	Plc	—			54.8	39.9	66	104.5†‡
ADOPT	Rsg	4 mg	Recently diagnosed type 2 DM	April 2000–June 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
Weighted adjusted means¶	Rsg				56.1	60.7	84.4	8.2
	Control				56.9	53.3	77.5	8.2

* Rsg denotes rosiglitazone, DM diabetes mellitus, Gly glyburide, Plc placebo, CHF congestive heart failure, Met metformin, ELM enhanced lifestyle management, Su sulfonylurea, Glip glipizide, Glim glimepiride, and NA not available.

† Percentages are the proportion of white patients, unless otherwise specified as black (B), Hispanic (H), or Asian (A).

‡ The fasting plasma glucose level (in milligrams per deciliter) is listed.

§ Weight-adjusted means were calculated for the rosiglitazone and control groups by multiplying individual means by sample sizes, adding them together, and dividing the sum by the total sample size for each treatment group.

Table 3. Myocardial Infarctions and Cardiovascular Deaths in Rosiglitazone Trials.

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		<i>number</i>			<i>number</i>	
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
100684	43	0	0	47	1	0
49653/143	121	1	0	124	0	0
49653/211	110	5	3	114	2	2
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

Table 3. (Continued.)

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		number			number	
AVA100193	394	1	1	124	0	0
DREAM	2635	15	12	2634	9	10
ADOPT	1456	27	2	2895	41	5
Total		86	39		72	22

Table 5 lists odds ratios for myocardial infarction and death from cardiovascular causes associated with rosiglitazone for subgroups defined according to the comparator drug. Similar results were obtained when the analysis excluded trials with an active comparator group. The heterogeneity P values were 0.53 for myocardial infarction and 0.68 for death from cardiovascular causes across subgroups. As compared with placebo or other antidiabetic regimens, the estimated odds ratios in all cases were greater than 1.0, suggesting that observed adverse effects during rosiglitazone treatment were not unique to any specific comparator regimen.

In an analysis that was not prespecified, we also studied the effects of rosiglitazone on death from any cause. The odds ratio for death from any cause was 1.18 (95% CI, 0.89 to 1.55; P=0.24).

DISCUSSION

Our data show that, as compared with placebo or with other antidiabetic regimens, treatment with rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that was of borderline significance. The similar odds ratio for comparison with placebo suggests that the increased risk associated with rosiglitazone was not a function of the protective effects of active comparator drugs. However, these findings are based on limited access to trial results from publicly available sources, not on patient-level source data. Furthermore, results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events. Nonetheless, our findings are worrisome because of the high incidence of cardiovascular

events in patients with diabetes.⁴ Because exposure of such patients to rosiglitazone is widespread, the public health impact of an increase in cardiovascular risk could be substantial if our data are borne out by further analysis and the results of larger controlled trials.

Although we did not have access to the source data to construct a composite outcome that included myocardial infarction or death from cardiovascular causes, the increase in the odds ratios for both of these end points suggests that observed adverse effects associated with rosiglitazone were probably not due to chance alone. This meta-analysis included a group of trials that were of relatively short duration (24 to 52 weeks). The odds ratio for these shorter-term trials was similar to the overall results of the meta-analysis. Thus, in susceptible patients, rosiglitazone therapy may be capable of provoking myocardial infarction or death from cardiovascular causes after relatively short-term exposure. In contrast, long-term therapies that improve cardiovascular outcomes, such as statins and antihypertensive drugs, often take several years to provide benefits. Notably, the estimates for the odds ratios for myocardial infarction and death from cardiovascular causes appear elevated for rosiglitazone in comparison with placebo or other commonly prescribed antidiabetic therapies (Table 5).

The mechanism for the apparent increase in myocardial infarction and death from cardiovascular causes associated with rosiglitazone remains uncertain. One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo.²⁵ In observational stud-

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group <i>no. of events/total no. (%)</i>	Control Group <i>no. of events/total no. (%)</i>	Odds Ratio (95% CI)	P Value
Myocardial infarction				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,557 (0.38)	7/3700 (0.19)	2.40 (1.17–4.91)	0.02
DREAM	12/2,365 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2854 (0.18)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

ies and lipid-lowering trials, elevated levels of LDL cholesterol were associated with an increase in adverse cardiovascular outcomes. Thus, an increase in LDL cholesterol of the magnitude observed in the rosiglitazone group may have contributed to adverse cardiovascular outcomes, although the rapidity and magnitude of the apparent hazard was not consistent with an effect produced by lipid changes alone.

Several other properties of rosiglitazone may contribute to adverse cardiovascular outcomes. Rosiglitazone and other thiazolidinediones are known to precipitate congestive heart failure in susceptible patients.²⁶ Congestive heart failure is a physiological state that is associated with an increased intravascular volume. Volume overload increases stress on the left ventricular wall, a factor that determines myocardial oxygen demand. In susceptible patients, an increase in myocardial oxygen demand could theoretically provoke ischemic events. The administration of thiazolidinediones, including rosiglitazone, also produces a modest reduction in the hemoglobin level.²⁵ In susceptible patients, a reduced hemoglobin level may result in increased physiological stress, thereby provoking myocardial ischemia. A study of rosiglitazone that was conducted in rats reported an increase in the rate of death after experimentally induced myocardial infarction.²⁷

Rosiglitazone is not the first PPAR agonist that has been reported to increase adverse cardiovascular events. Muraglitazar, an investigational dual PPAR- α and PPAR- γ agonist, increased

adverse cardiovascular events, including myocardial infarction, during phase 2 and 3 testing.²⁸ After publication of an analysis of cardiovascular outcomes, muraglitazar was not approved by the FDA, and further development was subsequently halted by the manufacturer. Development programs for many other PPAR agonists have been terminated after evidence of toxicity emerged during preclinical studies or initial trials in humans. According to a former FDA official, more than 50 Investigational New Drug applications for novel PPARs have been filed, but no additional drugs have successfully reached the market in more than 6 years.²⁹ In some cases, these drugs have failed because of evidence of direct myocardial toxicity in studies in animals,²⁹ but few data on toxicity are available in the public domain because of the common industry practice of not publishing safety findings for failed products.

PPAR agonists such as rosiglitazone have very complex biologic effects, resulting from the activation or suppression of dozens of genes.³⁰ The patterns of gene activation or suppression differ substantially among various PPAR agonists, even within closely related compounds. The biologic effects of the protein targets for most of the genes influenced by PPAR agonists remain largely unknown. Accordingly, many different and seemingly unrelated toxic effects have emerged during development of other PPAR agents.²⁹ Some drugs have provoked multispecies, multi-organ system cancers; others have resulted in rhabdomyolysis or nephrotoxicity.²⁹ Troglitazone

was withdrawn from the market for rare, but sometimes fatal, liver toxicity. Accordingly, it must be assumed that a variety of unexpected toxic effects are possible when PPAR agonists are administered to patients.

The question as to whether the observed risks of rosiglitazone represent a “class effect” of thiazolidinediones must also be considered. Pioglitazone is a related agent also widely used to treat type 2 diabetes mellitus. However, unlike rosiglitazone, pioglitazone has been studied in a prospective, randomized trial of cardiovascular outcomes, called Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE).³¹ The primary end point, a broad composite that included coronary and peripheral vascular events, showed a trend toward benefit from pioglitazone (hazard ratio, 0.90; P=0.095). A secondary end point consisting of myocardial infarction, stroke, and death from any cause showed a significant effect favoring pioglitazone (hazard ratio, 0.84; P=0.027). Notably, pioglitazone appears to have more favorable effects on lipids, particularly triglycerides, than does rosiglitazone.³²

These emerging findings raise an important question about the appropriateness of the current regulatory pathways for the development of drugs to treat diabetes. The FDA considers demonstration of a sustained reduction in blood glucose levels with an acceptable safety profile adequate for approval of antidiabetic agents. However, the ultimate value of antidiabetic therapy is the reduction of the complications of diabetes, not improvement in a laboratory measure of glycemic control. Although reductions in blood glucose levels have been shown to reliably reduce microvascular complications of diabetes, the effect on macrovascular complications has proved to be unpredictable.³³ After the failure of muraglitazar and the apparent increase in adverse cardiovascular outcomes with rosiglitazone, the use of blood glucose measurements as a surrogate end point in regulatory approval must be carefully reexamined.

Our study has important limitations. We pooled the results of a group of trials that were not originally intended to explore cardiovascular outcomes. Most trials did not centrally adjudicate cardiovascular outcomes, and the definitions of myocardial infarction were not available. Many

Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06

of these trials were small and short-term, resulting in few adverse cardiovascular events or deaths. Accordingly, the confidence intervals for the odds ratios for myocardial infarction and death from cardiovascular causes are wide, resulting in considerable uncertainty about the magnitude of the observed hazard. Furthermore, we did not have access to original source data for any of these trials. Thus, we based the analysis on available data from publicly disclosed summaries of events. The lack of availability of source data did not allow the use of more statistically powerful time-to-event analysis. A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest. Although such a dedicated trial has not been completed for rosiglitazone, the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial may provide useful insights.³⁴

Despite these limitations, our data point to the urgent need for comprehensive evaluations to clarify the cardiovascular risks of rosiglitazone. The manufacturer’s public disclosure of summary results for rosiglitazone clinical trials is not sufficient to enable a robust assessment of cardiovascular risks. The manufacturer has all the source data for completed clinical trials and should make these data available to an external academic coordinating center for systematic anal-

ysis. The FDA also has access to study reports and other clinical-trial data not within the public domain. Further analyses of data available to the FDA and the manufacturer would enable a more robust assessment of the risks of this drug. Our data suggest a cardiovascular risk associated with the use of rosiglitazone. Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider

the potential risks of rosiglitazone in the treatment of type 2 diabetes.

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REFERENCES

- Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. *Lancet* 1999;354:141-8.
- Campbell IW. The clinical significance of PPAR gamma agonism. *Curr Mol Med* 2005;5:349-63.
- Center for Drug Evaluation and Research. Approval package: Avandia (rosiglitazone maleate) tablets. Company: SmithKline Beecham Pharmaceuticals. Application no. 21-071. Approval date: 5/25/1999. (Accessed May 15, 2007, at http://www.fda.gov/cder/foi/nda/99/21071_Avandia.htm.)
- American Diabetes Association. Complications of diabetes in the United States. (Accessed May 15, 2007, at <http://www.diabetes.org/diabetes-statistics/complications.jsp>.)
- GlaxoSmithKline. Rosiglitazone studies. (Accessed May 15, 2007, at <http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp>.)
- Center for Drug Evaluation and Research. Medical review(s). Application number: 021071. (Accessed May 15, 2007, at http://www.fda.gov/cder/foi/nda/99/21071_Avandia_medr.pdf.)
- Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:280-8. [Errata, *J Clin Endocrinol Metab* 2001;86:1659, 2002;2:iv.]
- Phillips LS, Grunberger G, Miller E, et al. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care* 2001;24:308-15. [Erratum, *Diabetes Care* 2001;24:973.]
- Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diabetes Obes Metab* 2003;5:163-70.
- Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000;283:1695-702. [Erratum, *JAMA* 2000;284:1384.]
- Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. *Curr Med Res Opin* 2005;21:2029-35.
- Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients. *Diabet Med* 2000;17:40-7.
- St John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care* 2002;25:2058-64.
- Raskin P, Rendell M, Riddle MC, et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 2001;24:1226-32.
- Vongthavaravat V, Wajchenberg BL, Waitman JN, et al. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. *Curr Med Res Opin* 2002;18:456-61.
- Baksi A, James RE, Zhou B, Nolan JJ. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. *Acta Diabetol* 2004;41:63-9.
- Barnett AH, Grant PJ, Hitman GA, et al. Rosiglitazone in Type 2 diabetes mellitus: an evaluation in British Indo-Asian patients. *Diabet Med* 2003;20:387-93.
- Kerenyi Z, Samer H, James R, Yan Y, Stewart M. Combination therapy with rosiglitazone and glibenclamide compared with upward titration of glibenclamide alone in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2004;63:213-23.
- Zhu XX, Pan CY, Li GW, et al. Addition of rosiglitazone to existing sulphonylurea treatment in Chinese patients with type 2 diabetes and exposure to hepatitis B or C. *Diabetes Technol Ther* 2003;5:33-42.
- The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-105. [Erratum, *Lancet* 2006;368:1770.]
- Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427-43. [Erratum, *N Engl J Med* 2007;356:1387-8.]
- Bradburn MJ, Deeks JJ, Berlin JA, Localio AR. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77.
- Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351-75. [Erratum, *Stat Med* 2006;25:2700.]
- Sutton A, Cooper N, Lambert P, Jones D, Abrams K, Sweeting M. Meta-analysis of rare and adverse event data. *Pharmacoeconomics Outcomes Res* 2002;2:367.
- Avandia (rosiglitazone maleate) tablets: prescribing information. Research Triangle Park, NC: GlaxoSmithKline, 2007 (package insert). (Accessed May 15, 2007, at <http://www.fda.gov/cder/foi/label/2007/021071s023lbl.pdf>.)
- Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association: October 7, 2003. *Circulation* 2003;108:2941-8.
- Lygate CA, Hulbert K, Monfared M, Cole MA, Clarke K, Neubauer S. The PPARgamma-activator rosiglitazone does not alter remodeling but increases mortality in rats post-myocardial infarction. *Cardiovasc Res* 2003;58:632-7.
- Nissen SE, Wolski K, Topol EJ. Effect

- of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; 294:2581-6.
29. El-Hage J. Peroxisome proliferator-activated receptor (PPAR) agonists: pre-clinical and clinical cardiac safety considerations. Rockville, MD: Center for Drug Evaluation and Research, 2006. (Accessed May 15, 2007, at http://www.fda.gov/cder/present/DIA2006/El-Hage_CardiacSafety.ppt.)
30. Lemay DG, Hwang DH. Genome-wide identification of peroxisome proliferator response elements using integrated computational genomics. *J Lipid Res* 2006; 47:1583-7.
31. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89.
32. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;28:1547-54.
33. Riveline JP, Danchin N, Ledru F, Varroud-Vial M, Charpentier G. Sulfonylureas and cardiovascular effects: from experimental data to clinical use: available data in humans and clinical applications. *Diabetes Metab* 2003;29:207-22.
34. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. *Diabetologia* 2005;48:1726-35.

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