

Long-term Risk of Cardiovascular Events With Rosiglitazone

A Meta-analysis

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THE FIRST THIAZOLIDINEDIONE, troglitazone, was removed from the market because of toxic effects in the liver. Two other thiazolidinediones, rosiglitazone and pioglitazone, received regulatory approval in 1999 for glycemic control in the treatment of type 2 diabetes. Subsequently, these agents were reported to improve cardiovascular risk factors such as insulin resistance, blood pressure,¹ and microalbuminuria and surrogate markers of cardiovascular disease such as serum C-reactive protein² and carotid intimal thickness.³

No serious adverse events were recognized at the time of approval. However, since approval, there have been a number of serious adverse events reported with both thiazolidinediones. Rosiglitazone has been linked to a broad spectrum of potentially serious adverse events, such as heart failure,^{4,5} vision loss due to macular edema in spontaneous reports,⁶ fractures in women,⁷ and, more recently, myocardial infarction (MI).⁸

The current package insert for rosiglitazone is incomplete and outdated. It warns users that "rosiglitazone, alone or in combination with other anti-diabetic agents may cause fluid reten-

See also pp 1180 and 1216.

Context Recent reports of serious adverse events with rosiglitazone use have raised questions about whether the evidence of harm justifies its use for treatment of type 2 diabetes.

Objective To systematically review the long-term cardiovascular risks of rosiglitazone, including myocardial infarction, heart failure, and cardiovascular mortality.

Data Sources We searched MEDLINE, the GlaxoSmithKline clinical trials register, the US Food and Drug Administration Web site, and product information sheets for randomized controlled trials, systematic reviews, and meta-analyses published in English through May 2007.

Study Selection Studies were selected for inclusion if they were randomized controlled trials of rosiglitazone for prevention or treatment of type 2 diabetes, had at least 12 months of follow-up, and monitored cardiovascular adverse events and provided numerical data on all adverse events. Four studies were included after detailed screening of 140 trials for cardiovascular events.

Data Extraction Relative risks (RRs) of myocardial infarction, heart failure, and cardiovascular mortality were estimated using a fixed-effects meta-analysis of 4 randomized controlled trials (n=14 291, including 6421 receiving rosiglitazone and 7870 receiving control therapy, with a duration of follow-up of 1-4 years).

Results Rosiglitazone significantly increased the risk of myocardial infarction (n=94/6421 vs 83/7870; RR, 1.42; 95% confidence interval [CI], 1.06-1.91; P=.02) and heart failure (n=102/6421 vs 62/7870; RR, 2.09; 95% CI, 1.52-2.88; P<.001) without a significant increase in risk of cardiovascular mortality (n=59/6421 vs 72/7870; RR, 0.90; 95% CI, 0.63-1.26; P=.53). There was no evidence of substantial heterogeneity among the trials for these end points (I²=0% for myocardial infarction, 18% for heart failure, and 0% for cardiovascular mortality).

Conclusion Among patients with impaired glucose tolerance or type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of myocardial infarction and heart failure, without a significantly increased risk of cardiovascular mortality.

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tion leading to heart failure."⁹ It indicates that "rosiglitazone in combination with other agents, like other thiazolidinediones, may increase risk of cardiovascular adverse events."⁹ It also warns "that patients with New York Heart Association class I and II heart

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failure may have increased risk of cardiovascular adverse events.”⁹ It also issues precautions about “worsening macular edema which has been reported in post-marketing experience in some diabetics who were taking rosiglitazone or another thiazolidinedione.”⁹

There is no clinical trial evidence that rosiglitazone-induced glycemic control leads to a reduction in the macrovascular complications of type 2 diabetes. Limited information is currently available to clinicians on the magnitude of the adverse events attributed to rosiglitazone and on their public health impact.

Our objective was to systematically review the current evidence of the risks of MI, heart failure, and cardiovascular mortality with long-term rosiglitazone use.

METHODS

We used stringent selection criteria based on recommendations of the *Cochrane Handbook of Systematic Reviews of Interventions* on assessing adverse effects.¹⁰ The value of trial data on adverse effects relies on 2 major factors, the rigor of monitoring for the adverse effect and the completeness of reporting.¹⁰

Selection of Trials With Cardiovascular Adverse Event Data

The included trials had to state their intention to monitor cardiovascular adverse events in the “Aims” or “Methods” section and to explicitly report data (including zero events) on MI, heart failure, and cardiovascular mortality. Other specific inclusion criteria for trials were (1) a study design consisting of randomized controlled trials (RCTs) of rosiglitazone of at least 12 months duration; (2) study participants with impaired glucose tolerance or type 2 diabetes mellitus; (3) rosiglitazone as the intervention drug vs a control, which could be placebo or other nonthiazolidinedione oral hypoglycemic drugs, with the only difference between the treatment groups being the use of rosiglitazone.

Search Strategy

We conducted a literature search in September 2006 for RCTs and observational studies reporting on heart failure with thiazolidinediones. The findings and full details of the search terms and sources used are reported elsewhere.⁴ In May 2007, we conducted an updated search in MEDLINE and of the manufacturers’ clinical trials register,¹¹ the US Food and Drug Administration (FDA) Web site, and product information sheets. We searched PubMed with the filters *randomized controlled trial* and *rosiglitazone* with no date restrictions (193 hits). We also searched for systematic reviews in PubMed with the filter *systematic [sb]* and *rosiglitazone* (24 hits). We also looked at trial reports of all phase 3 and 4 published or unpublished trials of the GlaxoSmithKline clinical trials register (n=112).¹¹ During the final preparation of the manuscript, we received electronic notifications regarding newly published results from rosiglitazone trials that were included.^{12,13}

Our search was limited to English-language articles and included preapproval and unpublished studies. We also evaluated systematic reviews that analyzed beneficial outcomes on glucose control or cardiovascular end points in patients with type 2 diabetes, and we checked for relevant trial-level data on adverse events within these systematic reviews.

Data Extraction

Trials were identified and subjected to inclusion and exclusion criteria. Two reviewers (S.S. and Y.K.L.) independently and in duplicate assessed the eligibility and quality of trials for adverse event reporting and extracted numerical adverse events on MI, heart failure, and cardiovascular mortality. We also extracted data on overall mortality from the included trials. Published reports were reconciled with trials in the GlaxoSmithKline clinical trials register when possible. If there were multiple reports available for a particular study, we chose to extract ad-

verse events data from the most up-to-date journal-published version. We also extracted information on whether any cardiovascular adverse events were subjected to adjudication to assess the strength of adverse drug reaction reporting.

Statistical Analysis

We used Review Manager (RevMan), version 4.28 (The Nordic Cochrane Centre, Copenhagen, Denmark) to calculate relative risks (RRs) using a fixed-effects model. All reported *P* values are 2-sided. Statistical heterogeneity was assessed using the *I*² statistic. *I*² Values of 50% or more indicate a substantial level of heterogeneity.¹⁴ If there was substantial heterogeneity, we planned to explore individual study characteristics and those of subgroups of the main body of evidence.

We performed sensitivity analyses to explore the influence on effect size of statistical models (fixed and random effects), trial duration, and adjudication of cardiovascular events.

The number needed to harm (NNH) (and 95% confidence interval [CI]) with rosiglitazone was calculated by applying the RR estimates to the control event rate in a large trial population using Visual Rx, version 2.0.^{15,16} Herein, the NNH is the number of patients who need to be treated with rosiglitazone rather than with placebo or comparators for 1 additional patient to be harmed by an adverse cardiovascular event. We calculated the NNH with rosiglitazone in patients with type 2 diabetes and different baseline risks of cardiovascular events, as the NNH varies when rosiglitazone is used in a general population outside highly selected trial participants.¹⁷

RESULTS

We found 4 RCTs^{5,7,12,18} and 3 systematic reviews^{8,19,20} relevant to our analysis (FIGURE 1). Trial characteristics are shown in TABLE 1. Data on cardiovascular events and mortality in the included trials are shown in TABLE 2. The RRs for our pooled analyses of RCTs evaluating the

effects of rosiglitazone for MI, heart failure, and cardiovascular mortality are shown in FIGURE 2.

MI and Heart Failure

Our pooled data from 4 long-term trials involving 14 291 patients^{5,7,12,18} showed that rosiglitazone significantly increased the risk of MI compared with control (n=94/6421 vs 83/7870; RR, 1.42; 95% CI, 1.06-1.91; P=.02) (Figure 2). There was no evidence of substantial heterogeneity among the included trials (I²=0%).

The pooled data from 4 long-term trials involving 14 291 patients^{5,7,12,18} showed that the RR of heart failure with rosiglitazone significantly increased compared with placebo or active controls (102/6421 vs 62/7870; RR, 2.09; 95% CI, 1.52-2.88; P<.001) (Figure 2). There was no evidence of substantial statistical heterogeneity among the trials (I²=18%).

Cardiovascular Mortality

The pooled data from 4 trials showed that, compared with control therapy, rosiglitazone had no significant increase in risk of cardiovascular mortality (n=59/6421 vs 72/7870; RR, 0.90; 95% CI, 0.63-1.26; P=.53) (Figure 2)^{5,7,12,18}. There was no evidence of substantial statistical heterogeneity among the trials (I²=0%). Rosiglitazone had no effect on all-cause mortality (n=146/6421 vs 180/7870; RR, 0.99; 95% CI, 0.80-1.23; P=.92).^{5,7,12,18}

Sensitivity Analysis

The random-effects analysis of the cardiovascular events (MI and heart failure) from the 4 long-term trials^{5,7,12,18} yielded effect sizes that were similar in magnitude and direction to those obtained from fixed-effects analysis.

There was little or no heterogeneity in the meta-analysis of cardiovascular

events, suggesting a consistent treatment effect. After excluding the trial with the smallest number of participants and shortest follow-up,¹⁸ the

Figure 1. Study Selection

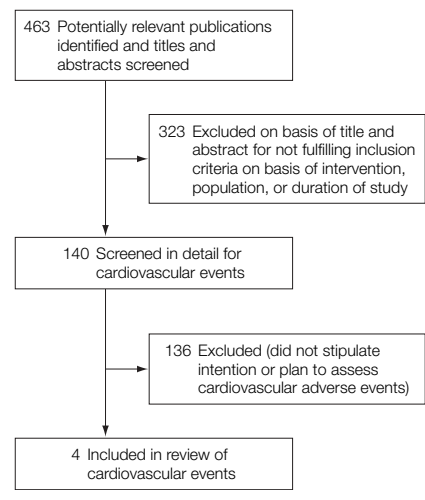


Table 1. Characteristics of Randomized Controlled Trials of Rosiglitazone Included in the Analysis of Cardiovascular Events

Source	Study Design	Duration of Treatment, Mean, y	Age, Mean, y	Male, %	Participants	Monitoring for Adverse Cardiovascular Outcomes	Adjudication/Review of Adverse Cardiovascular Outcomes
Gerstein et al, ⁵ 2006	Double-blind	3	54.6	41.7	Impaired glucose tolerance and/or fasting glucose Exclusions: cardiovascular disease and HF	Prespecified secondary outcomes were MI and HF	Adjudicated by blinded independent monitoring committee using prespecified diagnostic criteria
Kahn et al, ⁷ 2006	Double-blind	4	57	56	Type 2 DM, diagnosed within past 3 y and not taking any oral hypoglycemic drugs. Exclusions: unstable or severe angina, any degree of heart failure	"Adverse event categories of special interest" prespecified in analysis plan, including heart failure and myocardial ischemia	Blinded independent cardiologist checked listings of serious adverse events. Heart failure reports then reviewed by second blinded independent cardiologist, with third cardiologist arbitrating in case of disagreement; ongoing external review by FDA did not find evidence of significant miscoding of cardiovascular events; no misclassifications or omissions have so far been identified ²⁴
Home et al, ¹² 2007	Open-label	3.75	58.4	51.4	Type 2 DM Exclusions: recent hospitalization for cardiovascular event, planned cardiovascular procedure, HF	Primary outcome measure was hospitalization for cardiovascular events (including MI and HF)	Blinded end-point committee adjudicated using prespecified diagnostic criteria; about 85% of all reported events have been adjudicated
Dargie et al, ¹⁸ 2007	Double-blind	1	64.3	84	Type 2 DM with NYHA class I or II HF	Prespecified aim to compare cardiovascular morbidity and mortality; secondary outcomes included cardiovascular events	Cardiovascular end points reported to independent adjudication committee of 3 consultant cardiologists

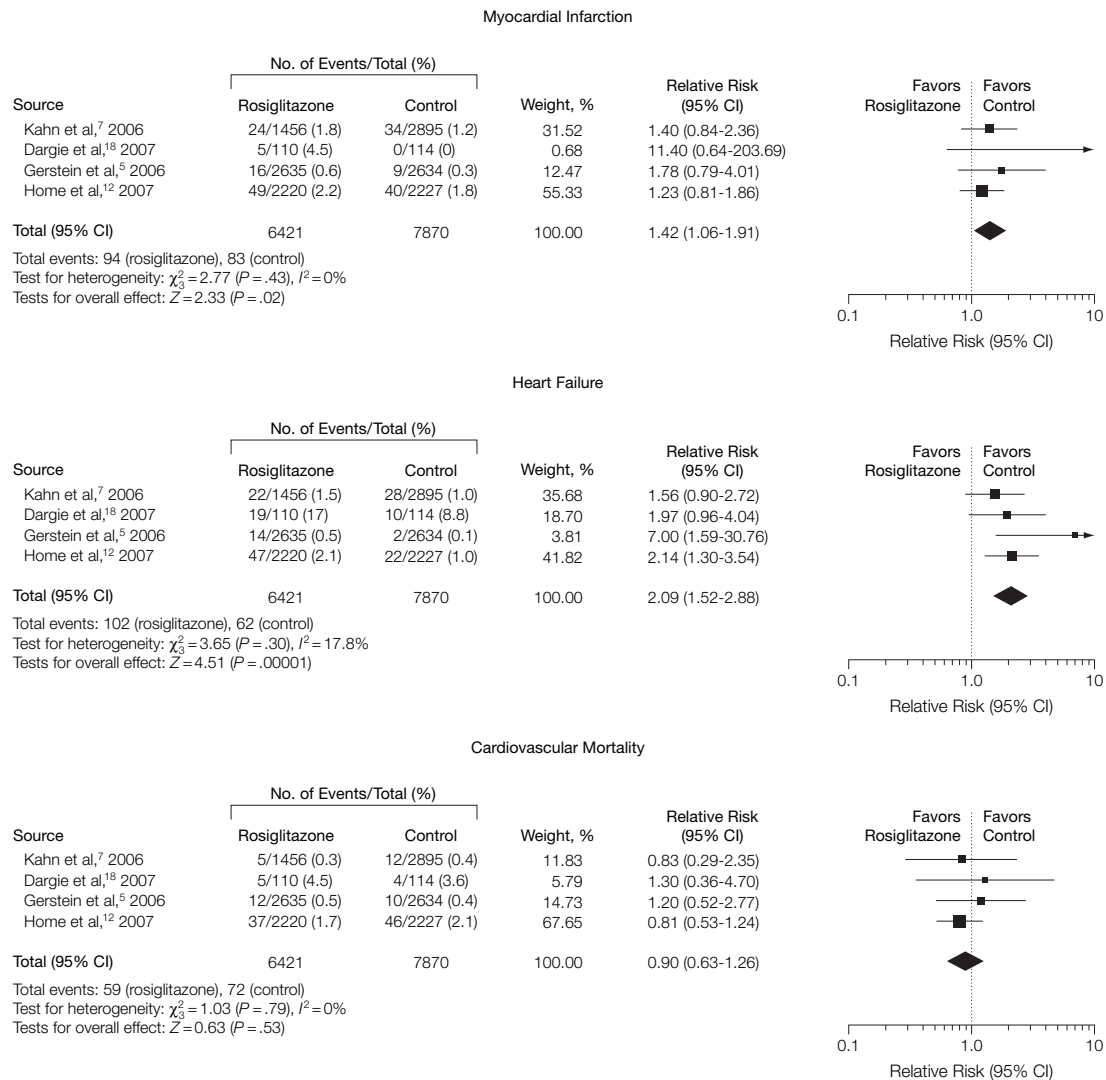
Abbreviations: DM, diabetes mellitus; FDA, US Food and Drug Administration; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association.

Table 2. Data on Cardiovascular Events and Mortality in Long-term Randomized Controlled Trials of Rosiglitazone

Study	Treatment Groups	No. (%) of Participants			
		Heart Failure	Myocardial Infarction	Cardiovascular Mortality	All-Cause Mortality
Gerstein et al, ⁵ 2006	Rosiglitazone (n = 2635)	14 (0.5)	16 (0.6)	12 (0.5)	30 (1.1)
	Control (n = 2634)	2 (0.1)	9 (0.3)	10 (0.4)	33 (1.2)
Kahn et al, ⁷ 2006	Rosiglitazone (n = 1456)	22 (1.5)	24 (1.8)	5 (0.3)	34 (2.3)
	Metformin or glyburide (n = 2895)	28 (1.0)	34 (1.2)	12 (0.4)	62 (2.1)
Home et al, ¹² 2007	Rosiglitazone (n = 2220)	47 (2.1)	49 (2.2)	37 (1.7)	74 (3.3)
	Metformin or glyburide (n = 2227)	22 (1.0)	40 (1.8)	46 (2.1)	80 (3.6)
Dargie et al, ¹⁸ 2007	Rosiglitazone (n = 110)	19 (17) ^a	5 (4.5)	5 (4.5)	8 (7.2)
	Placebo (n = 114)	10 (8.8) ^a	0	4 (3.6)	5 (4.3)

^aAdverse event rates for heart failure (without independent adjudication) were extracted from the non-peer-reviewed GlaxoSmithKline clinical trials register because data were not provided in the published article.

Figure 2. Meta-analysis of Randomized Controlled Trials of Rosiglitazone vs Control for Myocardial Infarction, Heart Failure, and Cardiovascular Mortality



CI indicates confidence interval.

Table 3. Variation in Number Needed to Harm With Rosiglitazone in Populations With Different Baseline Risks of Cardiovascular Events

Event	Population	Baseline Risk of Event per Year, %	Relative Risk (95% CI) With Rosiglitazone From Meta-analysis	Number Needed to Harm (95% CI) per Year With Rosiglitazone
Myocardial infarction	Trial participants with recently diagnosed type 2 DM; mean age, 57 y with no history of unstable or severe angina ⁷	0.29		822 (379-5748)
	Cohort of US community-based patients with type 2 DM; aged 45-64 y with no prior history of MI (ARIC) ²¹	1.08	1.42 (1.06-1.91)	221 (102-1544)
	Cohort of US community-based patients with type 2 DM; aged 45-64 y with prior history of MI (ARIC) ²¹	3.22		74 (35-518)
Heart failure	Trial participants with recently diagnosed type 2 DM; mean age, 57 y with no history of congestive HF ⁷	0.24		383 (222-802)
	Cohort of US community-based patients with type 2 DM; mean age, 63 y with no history of HF ²²	3.09	2.09 (1.52-2.88)	30 (18-63)

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CI, confidence interval; DM, diabetes mellitus; HF, heart failure; MI, myocardial infarction.

pooled analysis of MI (RR, 1.35; 95% CI, 1.00-1.83; $P = .048$) and heart failure (RR, 2.12; 95% CI, 1.48-3.02; $P < .001$) with rosiglitazone from the 3 large trials of similar duration^{5,7,12} was similar in magnitude and direction.

The sensitivity analysis using data on adjudicated cardiovascular events only found that the RR for MI from all 4 trials^{5,7,12,18} (RR, 1.40; 95% CI, 1.03-1.89; $P = .03$) and the RR for heart failure from the 3 large trials^{5,7,12} in which heart failure was adjudicated (RR, 2.16; 95% CI, 1.48-3.15; $P < .001$) were similar in magnitude and direction to the RR estimates obtained for total cardiovascular events (adjudicated and non-adjudicated).

Estimated NNH With Rosiglitazone for MI and Heart Failure

Assuming an event rate for MI (0.29% per year) and heart failure (0.24% per year) similar to the control event rate in the low-risk population in ADOPT (A Diabetes Outcome Progression Trial),⁷ the annualized NNH for rosiglitazone for MI was estimated to be 822 (95% CI, 379-5748) and for heart failure was estimated to be 383 (95% CI, 222-802) (TABLE 3).

Several population-based observational studies of adult patients with type 2 diabetes in the United States have shown that the event rates of MI²¹ and heart failure²² are higher than seen in the aforementioned RCT.⁷

Assuming a baseline MI event rate of 10.8/1000 person-years in adult patients with type 2 diabetes with no history of MI from the Atherosclerosis at Risk in Communities Study,²¹ the NNH for MI with rosiglitazone is estimated to be approximately 220 per year (95% CI, 102-1544). Similarly, assuming a baseline event rate of 30.8/1000 person-years for heart failure from a large observational study among patients with type 2 diabetes without a history of heart failure,²² the NNH for heart failure with rosiglitazone is estimated to be 30 per year (95% CI, 18-63). The use of rosiglitazone in patients with a previous cardiac history of MI or heart failure will result in even more unfavorable NNHs (Table 3).

COMMENT

Decisions to approve or prescribe a drug should depend on the balance between the beneficial and harmful effects of that drug. The sum of favorable effects should be weighed against the sum of the unfavorable effects. In this review of rosiglitazone, we have summarized its reported adverse effects—an approximate doubling in risk of heart failure and a 42% increase in the risk of MI without any effect on cardiovascular mortality. On the positive side are the potential health benefits related to a modest mean 1% reduction of hemoglobin A_{1c}.²³

Two previous meta-analyses showed that the risk of MI was significantly increased by rosiglitazone.^{8,19} An unpublished meta-analysis (ZM 2005/00181/01) conducted in 2005 involving 14 237 participants from 42 double-blind RCTs determined the incidence of MI in the rosiglitazone group to be 1.99% vs 1.51% in controls (hazard ratio, 1.31; 95% CI, 1.01-1.70).¹⁹ A recently published pooled analysis of 42 RCTs among 28 443 patients reported an increase in the risk of MI with rosiglitazone compared with controls (odds ratio [OR], 1.43; 95% CI, 1.03-1.98; $P = .03$).⁸ This meta-analysis included small studies of short duration (<52 weeks), with heterogeneous populations (eg, nondiabetic psoriasis, Alzheimer disease), and differing duration of follow-up and did not systematically collect information on cardiovascular events.

In contrast, we included only long-term trials in diabetic/prediabetic populations that had specified an intention to evaluate cardiovascular adverse events. Our RR estimate of 1.42 for MI from only 4 long-term trials is similar to the OR estimate of 1.43 obtained by Nissen and Wolski⁸ from 42 RCTs. The majority of cardiovascular events in our analysis were subjected to adjudication; sensitivity analysis using adjudicated cardiovascular events only did not change the direction or magnitude of the effect.

A third meta-analysis²⁴ conducted by FDA staff was presented at an FDA hearing on rosiglitazone on July 30, 2007. The OR for all 42 trials combined was 1.4 (95% CI, 1.1-1.8; $P=.02$). The 35 placebo-controlled trials (monotherapy or added to active treatment) showed a statistically significant increase in serious ischemic events in the rosiglitazone groups (OR, 1.68; 95% CI, 1.03-2.07; $P=.04$) and, thus, documented the drug's harmful effect. When rosiglitazone was compared with other antidiabetic medications in the underpowered active-controlled trials, there was no statistically significant difference noted for the outcome of any cardiac ischemic event (OR, 1.06; 95% CI, 0.53-2.14). As illustrated by the wide CI, this lack of a difference should not be interpreted as a lack of cardiac risk with rosiglitazone compared with the other medications. Subgroup analyses presented at the hearing suggested that the risk of ischemic events with rosiglitazone may be potentiated with concurrent use of insulin or nitrates.²⁴

On August 14, 2007, the FDA added a boxed warning to the rosiglitazone label that states "Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients."⁹ It goes on to state that "Avandia is not recommended in patients with symptomatic heart failure. Initiation of Avandia in patients with established NYHA Class III or IV heart failure is contraindicated."⁹

Our study has several limitations. The risk ratios are imprecise because of the limited data from the RCTs of rosiglitazone. As a result of small numbers, the confidence intervals are wide. Information on the time-to-event data for MI and heart failure was unavailable, which precluded the calculation of hazard ratios. Thus, it is not possible to determine whether the harmful effects are immediate or if there is a lag time to harm. The earlier meta-analysis suggested a nonsignificantly increased risk of cardiovascular mortality,⁸ but we found no clear effect on cardiovascular mortality. Because the cardiovascular mortality rates in the 3 largest trials were less

than 1% per year, a larger population with longer follow-up would have to be analyzed to draw definitive conclusions on cardiovascular mortality.

The public health impact of potential harm associated with rosiglitazone is substantial. In 2003, an estimated 9.5 million patients in the United States used oral hypoglycemic agents.²⁵ In 2006, nearly 37% of the market share of oral hypoglycemic medications was held by rosiglitazone.²⁶ We estimate that there may be more than 3.5 million current users of rosiglitazone in the United States alone. Assuming these users to be at the lowest risk of cardiovascular events, similar to the trial population of ADOPT⁷ (Table 3), application of the conservative annualized NNHs of rosiglitazone for MI (NNH=822) and heart failure (NNH=383) would result in an estimated more than 4000 excess MIs and 9000 excess heart failure events. However, caution must be used in estimating event rates in the general population based on findings from meta-analyses.

Another serious adverse event has also been attributed to the thiazolidinediones. A large number of cases of macular edema leading to blindness have been reported. During a recent 12-month period, the FDA received 66 reports of macular edema: 40 with rosiglitazone and 26 with pioglitazone. Health Canada has received 16 reports of macular edema attributed to rosiglitazone and none for pioglitazone. However, we found only 1 report of macular edema in the long-term clinical trials, and this was in the control group.

The lack of information on adverse effects is even more pronounced with pioglitazone, the other marketed thiazolidinedione. Pioglitazone is also known to increase risk of heart failure,²⁷ although it appears that rosiglitazone and pioglitazone may differ in the magnitude of the risk of MI. While rosiglitazone increases the risk of MI (from 31% to 43%), pioglitazone does not adversely increase this risk. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, which

involved patients with type 2 diabetes and a history of cardiovascular events (MI or stroke) but without heart failure, there was no increase in macrovascular events and death (HR, 0.90; 95% CI, 0.80-1.02; $P=.10$).²⁷ The risk of any heart failure event with pioglitazone in the PROactive study (RR, 1.43; 95% CI, 1.20-1.70; $P<.001$) appears to be lower than our estimates for heart failure with rosiglitazone (RR, 2.09; 95% CI, 1.52-2.88; $P<.001$) (Figure 2). Firm conclusions about the risk differences between the 2 agents cannot be made because of the absence of head-to-head comparisons.

Adequate cardiovascular risk factor control, including use of cardioprotective drugs, may help to reduce the likelihood of harm from rosiglitazone. The cardiovascular differences between rosiglitazone and pioglitazone may be partly explained by a difference in effects on lipids and lipoprotein particles and subclass.^{28,29} If the excess of MIs is mediated through the unfavorable effects of rosiglitazone on low-density lipoprotein cholesterol and triglycerides, it is possible that adequate lipid control with statins would reduce the MI risk. The reported statin use ranged from 15% (DREAM [Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication Trial]),⁵ to approximately 50% (ADOPT).⁷ Data on medication use are unavailable from RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Dysglycaemia).¹² Similarly, aspirin use could also reduce this risk in patients with diabetes and coronary disease. Patients with hypertension and diabetes who are treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be at a lower risk of heart failure. There is a possibility that the unfavorable cardiovascular effects of rosiglitazone could be blunted through the use of known cardioprotective drugs. As additional clinical trial data become available, stratified analyses ought to be conducted based on the use of these agents.

A Cochrane review of 18 RCTs involving 3888 patients with type 2 dia-

betes reported that rosiglitazone increased the risk of edema (OR, 2.27; 95% CI, 1.83-2.81) and caused significant weight gain (5.1 kg) without any benefit on measures of glycemic control or improvement in morbidity, mortality, costs, and health-related quality of life compared with other antidiabetic agents.²⁰ Another recent systematic review reported that older-generation agents (metformin and sulfonylureas) have superior effects on glycemic control, lipids, and other intermediate end points compared with the thiazolidinediones, without these detrimental adverse effects.³⁰

Our findings have potential regulatory and clinical implications. These data suggest a reversal of the benefit-to-harm balance for rosiglitazone present at the time of approval. Thus, currently there appear to be much safer treatment alternatives. Regulatory agencies ought to reevaluate whether rosiglitazone should be allowed to remain on the market. Health plans and physicians should not wait for regulatory actions. They should avoid using rosiglitazone in patients with diabetes who are at risk of cardiovascular events, especially since safer treatment alternatives are available.

Author Contributions: Dr Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Singh, Loke.

Acquisition of data: Singh, Loke.

Analysis and interpretation of data: Singh, Loke, Furberg.

Drafting of the manuscript: Singh, Loke.

Critical revision of the manuscript for important intellectual content: Singh, Loke, Furberg.

Statistical analysis: Singh, Loke.

Study supervision: Furberg.

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ratory and the CHS coordinating center. Funding was channeled through Wake Forest University and Dr Furberg was the CHS principal investigator, but he received no salary support and the funding period ended June 30, 2006. Dr Furberg did not benefit personally from the grant and has no funding from any other manufacturers of antidiabetic medications. No other financial disclosures were reported.

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