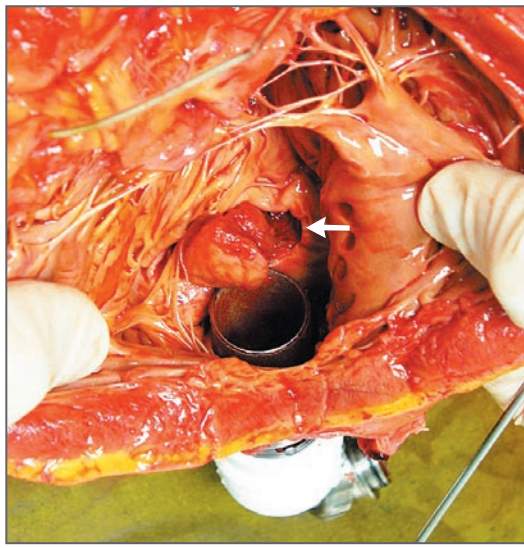


Figure 1. Intraventricular View of the Left Ventricle at Autopsy.

The opened left ventricle reveals a semicircular defect in the interventricular septum (arrow) directly adjacent to the inflow cannula of the left ventricular assist device. A piece of septal myocardium that is partially obstructing the inflow cannula can be seen below the defect. The size and shape of the defect match the dimensions of the inflow cannula exactly.



This is a potentially fatal complication of LVAD therapy.

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Rosiglitazone and Cardiovascular Risk

TO THE EDITOR: The study by Nissen and Wolski (June 14 issue)¹ shows increased rates of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment for type 2 diabetes. The authors' results are intriguing because a simple calculation of the pooled data shows a higher rate of myocardial infarction in the control group than in the rosiglitazone group (0.59% vs. 0.55%). In contrast, the Peto odds ratio for myocardial infarction of 1.43 (95% confidence interval [CI], 1.03 to 1.98) that is reported in the article shows a significantly increased risk in the rosiglitazone group.

Since it is unusual for a weighted analysis to be so different from that of simple pooled data, particularly when events are uncommon, I repeated the analyses with the use of more common statistical methods. The findings reported for the Peto odds ratio were replicated, but this statistic was the only one that was significant. Neither the relative risk nor the common odds ratio showed a significant increase in either myocardial infarction or death from cardiovascular causes. The addition of findings from the recently reported Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial² did not materially influence these results (Table 1).

The use of the Peto odds ratio is not recommended when there is substantial imbalance in the numbers of patients in many trials,⁴ as was

Table 1. Comparison of Statistical Analyses of 42 Trials Involving Rosiglitazone.*

Test Statistic	Value (95% CI)	
	Myocardial Infarction	Death from Cardiovascular Causes
Data from Nissen and Wolski¹		
Relative risk	1.27 (0.95–1.71)	1.33 (0.84–2.12)
Odds ratio	1.28 (0.95–1.72)	1.33 (0.83–2.13)
Peto odds ratio	1.43 (1.03–1.98)	1.64 (0.98–2.74)
Risk difference	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Data from Nissen and Wolski plus RECORD²		
Relative risk	1.24 (0.97–1.58)	1.07 (0.76–1.49)
Odds ratio	1.24 (0.97–1.59)	1.07 (0.76–1.50)
Peto odds ratio	1.33 (1.02–1.73)	1.15 (0.81–1.64)
Risk difference	0.00 (0.00–0.00)	0.00 (0.00–0.00)

* Data were calculated with the use of RevMan software, version 4.3.1, provided by the Cochrane Collaboration.³ Calculations of the relative risk, odds ratio, and risk difference were performed with the use of a zero-cell correction of 0.5 and Mantel–Haenszel weighting procedures; calculation of the Peto odds ratio was performed without the use of zero correction and with the hypergeometric variance in the event count in the intervention group. The weights for each trial represented the amount of information in that trial, and a fixed-effects model was assumed. All calculations are available on request.

the case in the study by Nissen and Wolski. When allocation ratios between the rosiglitazone group and the control group were 2:1 or higher, the Peto odds ratio was substantially higher than either the risk ratio or the common odds ratio. Every trial with an allocation ratio of 3:1 or 4:1 and a relative risk of more than 0.7 showed similarly extreme results for the Peto odds ratio. The risk difference showed little evidence of large effects, but this procedure is also not recommended for meta-analyses of rare events.⁴

Unfortunately, the Peto odds ratio was the only statistic reported by Nissen and Wolski. My additional analyses show that the estimated effect of rosiglitazone on myocardial infarction is sensitive to the choice of the treatment-effect estimator, especially at high allocation ratios and risk ratios above 1. These findings weaken the inference that rosiglitazone causes a significant increase in the risk of myocardial infarction and an increase in the risk of death from cardiovascular causes that has borderline significance.

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Dr. Bracken reports receiving fees from GlaxoSmithKline for consulting on an unrelated matter. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The meta-analysis by Nissen and Wolski includes two large trials with primary end points that did not include cardiovascular events. In the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM) trial,¹ the observation was stopped when diabetes developed in study patients. In the A Diabetes Outcome Prevention Trial (ADOPT),² observation was stopped when unsatisfactory glycemic levels occurred.

Since rosiglitazone provided better results than comparators in both trials, the mean follow-up in the rosiglitazone group was longer than that

in the control group. These differences were not accounted for in the meta-analysis. For example, in the ADOPT trial, the yearly incidences of myocardial infarction in the rosiglitazone group and the control group were 0.46% and 0.39%, respectively, with an estimated increase in risk in the rosiglitazone group of 18%, rather than 33%, as reported in the meta-analysis. Data on mean follow-up in the DREAM trial were not reported. However, the reported number of patients at all points of follow-up was higher in the rosiglitazone group than in the placebo group. Therefore, the effect of rosiglitazone on cardiovascular end points in longer-term trials could have been overestimated.

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TO THE EDITOR: Nissen and Wolski state that patients with diabetes who are treated with rosiglitazone face a “worrisome” risk of myocardial infarction ($P=0.03$) and death from cardiovascular causes ($P=0.06$). They base their conclusion on a meta-analysis of 42 trials showing an absolute difference in risk of only 0.2%, but they excluded 4 trials from the infarction analysis and 19 trials from the mortality analysis in which the rates were zero. Did these exclusions influence the results?

To find out, we performed a Bayesian meta-analysis^{1,2} of the entire data set with the use of a standard continuity correction that adjusts for values of zero.³ The resultant odds ratio for infarction dropped from 1.43 to 1.26 (95% CI, 0.93

to 1.72), and the odds ratio for death from cardiovascular causes dropped from 1.64 to 1.14 (95% CI, 0.74 to 1.74). Similarly corrected fixed-effects and random-effects analyses had similar results, and none of the resultant odds ratios remained significant. Although additional studies might be warranted, there is little here to justify what the authors (not to mention the media, the U.S. Congress, and worried patient groups) decry as an “urgent need for comprehensive evaluations.”

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TO THE EDITOR: In the editorial accompanying the article by Nissen and Wolski, Psaty and Furberg¹ disparage physicians who have prescribed rosiglitazone, saying that “physicians who chose to prescribe rosiglitazone perhaps focused on the single dimension of glycemic control,” and that many physicians “did not require proof of health benefits as a criterion for selecting rosiglitazone.” If physicians had required this higher standard, the authors write, “they would have been at a loss for evidence from large, long-term trials.”

Practicing physicians should not be faulted for prescribing rosiglitazone. Experts and clinical guidelines repeatedly emphasize that glycemic control is the important thing, no matter how you accomplish it. In a recent guideline, the American Diabetes Association states that “the goal of therapy is to achieve an A_{1c} [glycated hemoglobin level] as close to normal as possible,” without acknowledging that clinical outcomes may depend on both glycemic control and the therapies used to achieve it.² In addition, targets for glycated hemoglobin are increasingly used to judge the quality of care, without regard to specific therapies.³ It is unreasonable to expect that practicing physicians would be more knowledgeable about fine distinctions between outcomes and surrogate end points than are the experts who guide clinical practice.

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THE AUTHORS REPLY: Dr. Bracken expresses concern that the analysis of relative risk with the simple pooled trial data does not show an increased risk for rosiglitazone. Because the 48 analyzed studies included trials with sizes and randomization ratios that varied widely, performing a simple pooled analysis is not a statistically meaningful approach to integrating the trial results. We used the Peto odds ratio because this method is widely viewed as the optimal approach when there are relatively few events in individual trials.¹ In two of the trials in our study, 49653/234 and SB-712753/009, there were no myocardial infarctions or deaths from cardiovascular causes, but these trials were included in Table 3 of our article because they contributed to the analysis of death from any cause.

Dr. Bracken also expresses concern regarding potential amplification of odds ratios by the inclusion of trials with unbalanced allocation ratios. Combining all trials with the same allocation ratios (including those with zero events in both groups), we find no evidence of such an effect (Table 1). In fact, the exclusion of trials with a 3:1 or 4:1 allocation ratio gives a result nearly identical to that we reported, regardless of the method used (Peto odds ratio, 1.43 [95% CI, 1.02 to 1.98]; Mantel–Haenszel odds ratio, 1.42 [95% CI, 1.02 to 1.98]).

Mannucci et al. express concern about the potential for differential exposure for comparators in the DREAM and ADOPT trials. We find no evidence of such an effect. The “number at risk” values in the Kaplan–Meier plots for these trials refer to patients who did not reach a primary glycemic end point. Safety data are reported for the entire population with the use of an intention-to-treat approach. For the safety analysis, randomization ensures that exposure is balanced.

Drs. Diamond and Kaul suggest the use of a Bayesian approach to analyze the data from our study. However, this method remains controversial and is sensitive to the previous probability

Table 1. Results from Trials Grouped According to Allocation Ratio.*

Allocation Ratio	No. of Trials	No. of Myocardial Infarctions in Rosiglitazone Group versus Comparator Group	Mantel–Haenszel Odds Ratio (95% CI)	Peto Odds Ratio (95% CI)
1:1	21	24 vs. 15	1.61 (0.84–3.07)	1.59 (0.85–2.99)
2:1	14	14 vs. 6	1.15 (0.44–3.01)	1.15 (0.45–2.93)
3:1	2	2 vs. 0	1.60 (0.08–33.4)	3.75 (0.15–95.13)
4:1	3	4 vs. 1	0.99 (0.11–8.85)	0.99 (0.11–8.93)
DREAM (1:1)	1	15 vs. 9	1.67 (0.73–3.82)	1.65 (0.74–3.68)
ADOPT (0.5:1)	1	27 vs. 41	1.32 (0.81–2.15)	1.33 (0.80–2.21)

* The allocation ratio refers to the ratio of patients in the rosiglitazone group to those in the control group.

distribution selected by the investigators.² For Bayesian meta-analyses, confidence intervals are almost always wider than those calculated by other methods.

In selecting statistical methods for a meta-analysis, we believe it is important to approach the problem with the same rigor as that used in a randomized trial.² Accordingly, investigators should prespecify the approach and not apply a series of alternative methods in a post hoc manner.

In considering all of these alternative methods, it should be noted that the maker of rosiglitazone, GlaxoSmithKline, conducted its own analysis of “14,237 subjects in 42 controlled double-blind studies,” using logistic regression with adjustment for covariates and exposure.³ This analysis showed a significant increase of 31% in the risk of “myocardial ischemic events.” Presumably, the company did not deliberately select statistical methods that were likely to maximize the estimated hazard.

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THE EDITORIALISTS REPLY: Before the Food and Drug Administration approved rosiglitazone in

1999, the agency, which was concerned about the drug's effects on body weight and lipids, recommended that a post-marketing study of cardiovascular events be conducted to document the presumed health benefits of rosiglitazone-associated glucose lowering.¹ Despite the absence of such an events trial, the rapid expansion of the use of rosiglitazone depended on prescriptions written by physicians, who had a choice among available agents. Although the American Diabetes Association recommends the lowering of glycated hemoglobin levels, the recommendations identify the possibility of the prevention of macrovascular disease as grade B, or supported by epidemiologic studies rather than by randomized clinical trials.² The guidelines also feature metformin as the preferred first-line agent in the treatment of type 2 diabetes.

Treatment decisions based on surrogate end points should be made with caution. Insofar as the prescribing patterns of physicians coincide with high-quality evidence provided by large, long-term trials, they may also serve as an incentive for industry to conduct trials of sufficient range and scope to provide high-quality care to patients.

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