

The Record on Rosiglitazone and the Risk of Myocardial Infarction

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In this issue of the *Journal*,¹ Home and colleagues report interim results from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes, or RECORD, study (NCT00379769). The RECORD study is a 6-year, open-label, noninferiority trial in which patients with type 2 diabetes who had inadequate glucose control with metformin or sulfonylurea alone were randomly assigned to receive rosiglitazone (Avandia) or the combination of metformin and sulfonylurea. The primary outcome was a composite of hospitalization and death from cardiovascular causes. As of March 2007, data were available on the 4447 patients randomly assigned to receive one of these treatments and followed for a mean of 3.75 years. Rosiglitazone was associated with a small, nonsignificant increase in the risk of the primary outcome (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). For the fatal or nonfatal myocardial infarction outcome, the hazard ratio was 1.16 (95% CI, 0.75 to 1.81). According to the authors, “the findings are important in answering some of the safety concerns raised by the recent meta-analysis by Nissen and Wolski.”²

The RECORD trial has several strengths. Among the most important are interim sensitivity analyses that include events pending adjudication and a design that compares dual-agent combination therapies in a long-term trial among high-risk patients with diabetes.

The trial also has several weaknesses in design and conduct. Although outcomes were reviewed in a blinded fashion, the randomization was not concealed.³ The primary outcome, which was a composite of all hospitalizations and deaths from cardiovascular causes, is a weak choice for a noninferiority design.^{4,5} A preferred cardiovascular outcome would have been, for instance, myocardial infarction or death from coronary heart disease.⁶ Including all cardiovascular hospitalizations, some of which are not likely to be related to the randomized treatments, in a composite outcome will tend to drive the relative risk toward the null and enhance the chances of a finding of noninferiority. Finally, the use of a composite outcome to design the trial will generally yield few data

and low power for any composite-outcome elements that might be of special interest.

The primary weakness in the conduct of the trial is the exceptionally low event rate in a high-risk population of patients with diabetes. For the myocardial infarction outcome, for instance, the event rate in the RECORD control group was 4.5 per 1000 person-years. With a mean age near 60 years, the patients in the RECORD trial had had diabetes for an average of 7 years, about 25% had preexisting clinical cardiovascular disease, and almost 80% had hypertension. The myocardial infarction rate of 4.5 per 1000 person-years in the RECORD study is about 40% of the incidence rate in a population-based study of patients with diabetes 56 to 60 years of age⁷ and is close to rates seen in the general population 55 to 59 years of age.⁸ Incomplete ascertainment of events is perhaps the most likely explanation for this difference. Loss to follow-up was high (about 10%). Another explanation may be the large number of eastern European countries involved in the study. Medical care, including criteria for cardiovascular hospitalization, may differ between eastern and western Europe.

The “exceptional circumstances” cited by the authors in their decision to report interim findings from this long-term trial were the result of publication of the meta-analysis by Nissen and Wolski.² The primary finding of the meta-analysis was an increase in the risk of myocardial infarction associated with treatment with rosiglitazone (odds ratio, 1.43; 95% CI, 1.03 to 1.98). Although the limitations in design and conduct of the RECORD trial argue for a cautious interpretation of its findings, the results for risk of myocardial infarction (hazard ratio, 1.16; 95% CI, 0.75 to 1.81) are nonetheless compatible with those of the meta-analysis. The overlap between the 95% confidence intervals for the trial and the meta-analysis is substantial.

Combining the findings about the risk of myocardial infarction from the RECORD trial and the meta-analysis provides a cumulative summary of the clinical-trial evidence. A variance-weighted fixed-effects meta-analysis that includes the

RECORD trial, ADOPT (A Diabetes Outcome Prevention Trial, NCT00279045),⁹ the DREAM trial (Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication, NCT00095654),¹⁰ and the stratum of small trials in the meta-analysis by Nissen and Wolski still suggests that rosiglitazone is associated with an increased risk of myocardial infarction (odds ratio, 1.33; 95% CI, 1.02 to 1.72). Use of the updated myocardial event rates provided by Krall¹¹ yields an odds ratio of 1.36 (95% CI, 1.04 to 1.78). Thus, even with the findings from the RECORD trial included, the possibility of a benefit in terms of the risk of myocardial infarction remains remote, and there is still significant evidence of harm. The level of risk, a hazard ratio of 1.33, is substantial and approximately equivalent in magnitude, but in the opposite direction, to the health benefits of lipid-lowering statin drugs.

The main limitations of the meta-analysis are the quantity and quality of the available data.¹² The responsibility for the limited availability of high-quality data resides primarily with the manufacturer (GlaxoSmithKline) and also perhaps with the Food and Drug Administration (FDA). Insofar as the findings of the meta-analysis represent a valid estimate of the risk of myocardial infarction, the “exceptional circumstances” seem to us to be the history of missed opportunities in the scientific and regulatory evaluation of rosiglitazone, which was first approved in 1999.

As we indicated recently,¹² rosiglitazone was approved on the basis of its ability to improve glycemic control, a surrogate end point. Because high glucose levels increase the risk of vascular disease, a glucose-lowering drug is presumed to reduce the risk of major adverse health outcomes such as myocardial infarction. Rosiglitazone, however, appears to be associated with an increase rather than a decrease in the risk of myocardial infarction.

The manufacturer did not make a serious effort to verify the presumed health benefits of rosiglitazone in a timely fashion. In ADOPT,⁹ which compared rosiglitazone with metformin and glyburide in terms of the duration of glycemic control, cardiovascular events were not identified or recorded in a systematic fashion, and heart failure was the only outcome that was reviewed and adjudicated at the end of the trial.⁹ Nonetheless, even though misclassification and incomplete ascertainment of events effectively reduce the ability of a study to detect a difference in event rates,

rosiglitazone in ADOPT was associated with a higher risk of cardiovascular events, including heart failure, than glyburide.⁹

The DREAM trial,¹⁰ which included an adjudication of cardiovascular events, recruited a low-risk population of prediabetic patients to evaluate whether rosiglitazone, as compared with placebo, could prevent the chemical onset of diabetes. In the DREAM trial, rosiglitazone was associated with a lower risk of diabetes (hazard ratio, 0.38; 95% CI, 0.33 to 0.44) and with a higher though nonsignificant risk of myocardial infarction (hazard ratio, 1.66; 95% CI, 0.73 to 3.80). In the absence of evidence of actual health benefits, the public health rationale for the use of a drug to treat a precondition and thereby to prevent the onset of a related condition that would, normally and simply, mark the beginning of drug treatment is not clear. The DREAM study represents an effort to medicalize a predisease state.¹³

The DREAM trial and ADOPT focused largely on marketing questions and failed to address questions of myocardial infarction-related risk or benefit directly. These industry-sponsored trials do not represent compelling science.¹⁴

When drugs that have been approved on the basis of surrogate end points will be used by millions of people for many years, it is essential to document their health risks and benefits.¹⁵ Laboratory measures such as glycemic control must be converted into clinically meaningful outcomes.¹⁶ If manufacturers do not voluntarily initiate large, long-term trials that are of public health importance, then the FDA needs the authority to insist that they do so in a timely fashion.^{17,18}

In August 2006, the manufacturer of rosiglitazone provided the FDA and the European Medicines Agency with the results of several studies, including a meta-analysis¹⁹ similar to that by Nissen and Wolski.² In the manufacturer's meta-analysis, rosiglitazone was associated with an increased risk of myocardial ischemic events (hazard ratio, 1.31; 95% CI, 1.01 to 1.70). By October 2006, the product labels in Europe were revised to include this information.²⁰ The U.S. product label still does not identify ischemic cardiovascular disease as an adverse reaction in the general population of patients with diabetes. Why did the FDA not make this information public in a timely fashion?

The natural history of new drugs in the post-marketing setting includes major black-box warn-

ings for about 7.5% and withdrawal for about 2.7%.²¹ The primary measure of regulatory success is the timeliness of information, warnings, and withdrawals. With rosiglitazone, the FDA failed to warn or inform in a timely fashion.

The history of rosiglitazone highlights the importance of several recommendations made by the Institute of Medicine Committee on the Assessment of the US Drug Safety System.^{17,18} The FDA needs the leadership and the authority to require manufacturers to conduct high-quality postmarketing trials of selected drugs in a timely fashion. The House of Representatives, which is about to take up drug-safety legislation, has a unique opportunity to reinvigorate an essential regulatory agency that has many outstanding and dedicated scientists.

Patients and physicians will need to weigh the benefits and risks of treatment with rosiglitazone. Glycemic control and durability appear to be the major benefits.^{9,10} Rosiglitazone is also associated with significant weight gain, an adverse effect on low-density lipoprotein cholesterol, an increased risk of heart failure, an increased risk of fractures in women, and an apparent increase in the risk of myocardial infarction.^{1,2,9,10} Patients should not stop treatment on their own, but if they have concerns, they should consult their physicians. Together, patients and physicians can decide whether they wish to suspend the use of rosiglitazone.

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