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## Rosiglitazone — Continued Uncertainty about Safety

Jeffrey M. Drazen, M.D., Stephen Morrissey, Ph.D., and Gregory D. Curfman, M.D.

On May 21, 2007, the *Journal* published a meta-analysis by Nissen and Wolski<sup>1</sup> that indicated an increased cardiovascular risk associated with rosiglitazone (Avandia), a thiazolidinedione used to treat type 2 diabetes. We published this analysis because it indicated an increase of about 40% in the risk of myocardial infarction among patients receiving rosiglitazone as compared with those receiving either an alternative oral diabetes therapy (metformin or a sulfonylurea) or placebo. Since rosiglitazone is widely used for the treatment of type 2 diabetes and since the analysis considered all publicly available data on the topic, we published the article to make health care professionals and their patients aware of these potential adverse effects. Although we ensured that the article<sup>1</sup> and accompanying editorial<sup>2</sup> spelled out both the strengths and the weaknesses of the analysis, we knew that a patient-level analysis performed by the manufacturer of rosiglitazone confirmed the findings.<sup>3</sup> The article raised substantial uncertainty about the cardiovascular safety of rosiglitazone. Even a small increase in cardiovascular risk in a fragile population of patients with type 2 diabetes is of considerable concern.

As a result of our publication of this article,

the steering committee of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes, or RECORD, trial (NCT00379769) undertook an unplanned interim analysis of some of the cardiovascular end points in that trial. The results of that interim analysis appear in this issue of the *Journal*.<sup>4</sup> The RECORD (NCT00379769) study is an open-label, randomized, controlled, noninferiority trial in which cardiovascular outcomes are evaluated in patients being treated with a variety of antidiabetic regimens that either contain or do not contain rosiglitazone. The trial is scheduled to end when there is a median of 6 years of follow-up; the mean follow-up reported in the article published in this issue is 3.75 years. In an analysis including all reported primary end points, the hazard ratio (rosiglitazone regimens vs. others) was 1.11 (95% confidence interval, 0.93 to 1.32). As is evident from the 95% confidence interval around the point estimate, the data are consistent with as much as a 7% decrease in cardiovascular risk and as much as a 32% increase in risk. Consequently, the data from the interim analysis are inconclusive owing to low statistical power. The low power is due in part to incomplete follow-up and unexpectedly low

event rates. Even when the study is completed, whether there will be adequate statistical power to reach a definite conclusion about cardiovascular safety is uncertain.

The RECORD trial was designed as a noninferiority trial with a noninferiority margin of 20% (i.e., an upper bound of the 95% confidence interval exceeding 1.20 fails to establish noninferiority). The upper bound of 1.32 found in the interim analysis indicates that the noninferiority of rosiglitazone, as compared with non-rosiglitazone regimens, has not been established. In short, this means that there is continued uncertainty about the cardiovascular safety of rosiglitazone. Furthermore, the upper bound of 1.81 for the myocardial infarction end point indicates that the RECORD data are not discordant with the results of the meta-analysis by Nissen and Wolski, given that the 95% confidence intervals in the two studies overlap extensively.

The clinical impact of these data needs to be clarified. To do so, we asked a diabetologist, a cardiovascular epidemiologist, and a drug-safety expert to give their interpretations, which can be found in the accompanying editorials.<sup>5,6</sup> Both editorials express uncertainty about the safety of rosiglitazone.

When a drug is approved for marketing, its full safety profile cannot be known, and the data from the two studies we have published<sup>1,4</sup> represent a

clear example of how difficult it can be to determine drug safety. In this age of freely available information, drugs cannot easily be parsed into “safe” and “unsafe” categories. Instead, there will be shades of safety that must be graded against shades of efficacy. As new data about the safety of an approved drug become available, they should not be suppressed. On the contrary, they should be reported to health care professionals, patients, and participants in ongoing clinical trials, even if that means creating uncertainty about the safety of a drug. Although there may be uncertainty about a drug’s safety, there should be no uncertainty about the need for open and honest disclosure.

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## Rosiglitazone and Cardiotoxicity — Weighing the Evidence

David M. Nathan, M.D.

The recently published meta-analysis by Nissen and Wolski,<sup>1</sup> which suggested a significant increase in the risk of myocardial infarction associated with treatment with rosiglitazone (Avandia) and an increase of similar magnitude, albeit nonsignificant, in the risk of death from cardiovascular causes, has created a furor in the press and a quandary for physicians and their patients. Given the vagaries of meta-analyses in general and of this meta-analysis in particular — owing to the absence of primary or time-to-event data, as acknowledged both in the article and in the accompanying editorial<sup>2</sup> — clinicians have been

left uncertain as to whether rosiglitazone should still be considered for the treatment of type 2 diabetes. Because millions of patients with diabetes are being treated with rosiglitazone worldwide, the answer to this question has major implications.

With the goal of providing the “current totality of evidence,” Home and colleagues report, in this issue of the *Journal*, an unscheduled interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes, or RECORD, study (NCT00379769) — a multicenter, drug-company-sponsored,