EDITORIAL

Rosiglitazone and Cardiotoxicity — Weighing the Evidence

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The recently published meta-analysis by Nissen and Wolski,[1] 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[2] — 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, open-label, noninferiority trial.[3] Whereas the 42 trials included in the published meta-analysis were generally directed at studying glycemia and were not designed or powered to study potential adverse events such as cardiovascular disease, the RECORD trial was specifically designed to measure the effects on cardiovascular outcomes of treatment with rosiglitazone combined with metformin or sulfonylurea, as compared with those of treatment with metformin combined with sulfonylurea. The primary end point of the RECORD trial consists of an aggregate of time to first hospitalization for a cardiovascular event or death from cardiovascular causes.[4] According to the RECORD investigators who designed the study, including employees of the drug's manufacturer, GlaxoSmithKline, the RECORD trial was directed at determining whether the "promising" impact of thiazolidinediones on insulin sensitivity and cardiovascular risk factors would translate into an improvement in cardiovascular clinical outcomes.[4] In addition, the investigators wanted to "address concerns over cardiac failure; confirm that the better outcomes associated with improved glucose control, as reported by the UKPDS [the United Kingdom Prospective Diabetes Study], are applicable to this group of drugs; and allay concerns based on LDL [low-density lipoprotein] cholesterol concentrations rather than LDL particle atherogenicity." In my opinion, several of these goals seem to reflect a company-oriented posture regarding rosiglitazone, rather than a neutral scientific inquiry.

As noted, the RECORD trial was designed specifically to study the cardiovascular effects of treatment with rosiglitazone, and results from a well-designed, adequately powered clinical trial are usually more reliable than results from a meta-analysis. Unfortunately, this interim analysis, performed after a mean of 3.75 years (about 60% of the planned 6-year duration of the study), fails to provide exculpatory evidence. First, the unexpectedly low rate of events (only about 2.5% per year, as compared with the 11% per year that went into the sample-size calculation) and a higher-than-expected rate of loss to follow-up (almost 3% per year, as compared with a projected 2% per year) have left RECORD extremely underpowered for the primary outcome. Second, the choice of the active comparator, metformin plus sulfonylurea,

is problematic. In a substudy of the UKPDS, the addition of metformin to treatment with sulfonylurea was associated with a 96% increase in diabetes-related mortality (P=0.039) among patients randomly assigned to receive this treatment.[5] Although this result was described by the UKPDS investigators as a possible "play of chance," it has never been adequately explained or explored. The results of the RECORD trial should be interpreted with this UKPDS finding in mind. Specifically, any difference or lack of difference in outcomes between the treatment groups may be predicated on a potential adverse effect of metformin plus sulfonylurea.

With these caveats in mind, the results of this underpowered interim analysis suggest a possible adverse effect of treatment with rosiglitazone on the primary outcome, rather than the benefit that was hypothesized. Although the only outcome that was significantly more frequent with rosiglitazone was the risk of congestive heart failure, which more than doubled, Figure 2 in the article by Home et al.[3] reveals a separation between the treatment groups for the adjudicated and total primary outcomes that, with more time and more events, could become significant. Considering the low power of the study and the trend for more adverse cardiovascular outcomes in the rosiglitazone-treated group, it is highly unlikely that the study will ever establish a cardiovascular benefit for rosiglitazone.

The interim results of the RECORD trial do not provide any assurance of the safety of treatment with rosiglitazone. Neither the original meta-analysis, with an odds ratio for myocardial infarction of 1.43 (95% confidence interval [CI], 1.03 to 1.98),[1] nor the meta-analysis performed independently by GlaxoSmithKline (odds ratio, 1.31; 95% CI, 1.01 to 1.70),[6] nor the current finding, with a hazard ratio of 1.08 (95% CI, 0.89 to 1.31)[3] can be considered conclusive. In the aggregate, however, these analyses support a concern regarding the safety of rosiglitazone.

With the continuing uncertainty regarding the safety of treatment with rosiglitazone, what should physicians and patients do? It is important to remember that there are now nine classes of antidiabetic medications available, including several older medications that are relatively efficacious in lowering glycated hemoglobin levels and are less expensive than the thiazolidinediones.[7] Each class has a unique set of side effects and associated adverse events. Controlling glycemia by keeping glycated hemoglobin levels as close to the nondiabetic range as possible has been established as the primary goal of these medications, given the salutary results of intensive therapy as demonstrated in high-quality clinical trials.[5,8] The results of clinical trials of the effects of glycemic control on microvascular complications in type 1 and type 2 diabetes, combined with the results of studies in animal models, have supported the maintenance of lower glycated hemoglobin levels as advantageous, regardless of the means used to achieve that control. However, now that we are faced with evidence that specific medication regimens used to treat type 2 diabetes may have an adverse macrovascular effect independent of achieved levels of glycated hemoglobin, this premise may be challenged. Of note, a recently published analysis of the first 1122 participants in the RECORD trial studied for 18 months, using a noninferiority approach, showed that the glycemic control achieved did not differ significantly between the treatment groups.[9]

It is reasonable to ask whether physicians should feel comfortable using a drug that might have an 8% excess risk of severe cardiovascular disease or death from cardiovascular causes. Given the other choices of therapy available, including pioglitazone, which has limited clinical trial data suggesting a protective cardiovascular effect[10] (albeit in a study that has been criticized for its design and its analysis), the answer should be no. Unless further studies can provide convincing assurance that treatment with rosiglitazone does not increase the risk of cardiovascular disease, the largely circumstantial evidence of the meta-analyses and the nonsignificant trend in the current report from the RECORD trial must be taken seriously. Physicians may find it difficult to explain to patients why they are starting treatment with a potentially dangerous drug when other choices with longer and better safety records are available. And although changing from a drug that is apparently working well to another medication may represent a challenge, the same safety concerns pertain. Whether ongoing studies for specific indications — such as reduction of restenosis after angioplasty and stent implantation, for which there is preliminary evidence of a benefit with rosiglitazone[11] — should continue will need to be considered individually,

on the basis of potential risks and benefits. The jury may still be out with regard to the cardiotoxicity of rosiglitazone, but when it comes to patient safety, "first, do no harm" should outweigh any presumption of innocence.

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