The Rosiglitazone Meta-Analysis

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The recently published meta-analysis on the "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes" by Nissen and Wolski[1] has created significant concern among health care practitioners and patients. About 7 million people throughout the world take rosiglitazone, and the drug accounts for more than $3 billion in annual sales for GlaxoSmithKline (Middlesex, United Kingdom).[2] The implications of this analysis, which suggest an association between a drug commonly used to treat diabetes and an increase in cardiovascular event rates, deserve both our attention and our scrutiny.

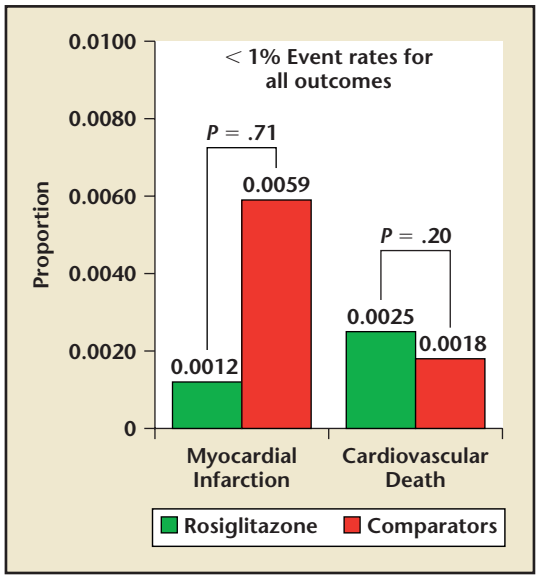
Rosiglitazone belongs to the class of agents known as thiazolidinediones (TZDs), which are agonists of the peroxisome proliferator-activated receptor (PPAR) gamma, a member of the nuclear receptor superfamily of ligand-activated transcription factors. In addition to their insulin-sensitizing effects, the TZDs have been found to ameliorate the pro-atherogenic components of the insulin-resistance syndrome, including dyslipidemia, the procoagulant state, and endothelial dysfunction. However, it is important to not underestimate the effects of PPAR agonists, because the resulting activation of and suppression of a large number of genes may have very complex biologic effects that are difficult to anticipate. In addition, it is important to appreciate the differing metabolic effects of the 2 commercially available TZDs, rosiglitazone and pioglitazone, each of which may produce distinct biologic effects and, consequently, may be associated with different cardiovascular event rates.

The Meta-Analysis

Nissen and Wolski[1] reviewed 42 trials that met their inclusion criteria of study duration longer than 24 weeks, use of a randomized control group not receiving rosiglitazone, and availability of outcome data for myocardial infarction and death from cardiovascular causes. They concluded that rosiglitazone as compared with the "control" group had an odds ratio (OR) for myocardial infarction of 1.43 (95% confidence interval [CI], 1.03-1.98; $P = .03$) and an OR for death from cardiovascular causes of 1.64 (95% CI, 0.98-2.74; $P = .66$).

The overall rates of myocardial infarction and cardiovascular death were small (less than 1% for each) and similar when compared in absolute terms, as shown in Figure 1.

Figure 1. *Absolute rates of myocardial infarction and cardiovascular death reported in 42 trials of patients who received rosiglitazone or comparator(s).[1] As shown, absolute event rates are less than 1% for all outcomes and not statistically different.*



The analysis by Nissen and Wolski is limited in several respects, which places significant limitations on the ability to draw definitive conclusions from the study, despite what has been reported in both the lay media and the medical press. The analysis excluded trials in which no cardiovascular events occurred. Eliminating these trials worked to raise the proportions of myocardial infarction and death in both the rosiglitazone group and the "control" group to a level below 1% over 25 to 56 weeks duration. The use of meta-analytic techniques is optimized when zero-event trials are excluded to eliminate the need for imputed values, but from a safety point of view, these studies give important information—which is consequently ignored in the analysis by Nissen and Wolski.

The use of the fixed effects model, which is not very robust to the homogeneity assumption or to the reality that not all of the studies of rosiglitazone were considered, worked to find statistical significance when in fact it was not there. Given the sparseness of events and the very small event differences between the groups (14 myocardial infarctions and 17 cardiovascular deaths), the fairest test to apply is a simple chi-square. This approach would basically assume there was variable follow-up and, probably, heterogeneity of populations, protocols, and study designs, and thus all that can be known is the reported events of each group taken at face value. This analysis would generate 86 cases of myocardial infarction out of 15,560 patients in the rosiglitazone group versus 72 cases of myocardial infarction out of 12,283 patients in the placebo group: Mantel Haenszel chi-square = 0.14, OR = 0.94 (Cornfield 95% CI, 0.68-1.31), and $P = .71$. For cardiovascular death, there were 39 cases out of 15,560 patients in the rosiglitazone group versus 22 cases out of 12,283 patients in the placebo group: Mantel Haenszel chi-square = 1.61, OR = 1.40 (Cornfield 95% CI, 0.81-2.44), and $P = .20$.[3] Because there were very few events separating the 2 groups, the meta-analytic techniques were subject to alpha error—that is, finding an effect due to random chance. Figure 2 plots the P values generated according to the event difference between the 2 groups and assumes that the event rate is unchanged in the group not treated with rosiglitazone. The test statistic is the chi-square. As demonstrated, we would need to observe a difference of approximately 40 events in both myocardial infarction and cardiovascular death before we could be reasonably certain that rosiglitazone is in truth associated with cardiovascular events. Thus, based on the proportions reported by Nissen and Wolski, rosiglitazone was not statistically related to myocardial infarction or cardiovascular death, and these authors' conclusions are not supported by the available data.

What is of more interest and concern to clinicians is not the leveraged use of statistics, but the realization that a drug that improves glycemic control may be neutral on cardiovascular benefit. This is probably the case, since most of the data with rosiglitazone were compared to other antidiabetic medications, and although the baseline glycated hemoglobin values were reported, the treated values were not. Thus, we would need to evaluate the pooled glycohemoglobin values achieved to infer whether there was a difference in glycemic control that could have accounted for the outcomes.

The largest issue with this class of drugs that is not addressed in the article is edema, weight gain, and the concern over the development or worsening of heart failure. In overweight individuals, the average weight gain is approximately 5 kg with treatment.[4] Obese patients typically gain even more weight. Not all of the weight gain resolves when the drug is stopped, which implies the deposition of fat, a potentially

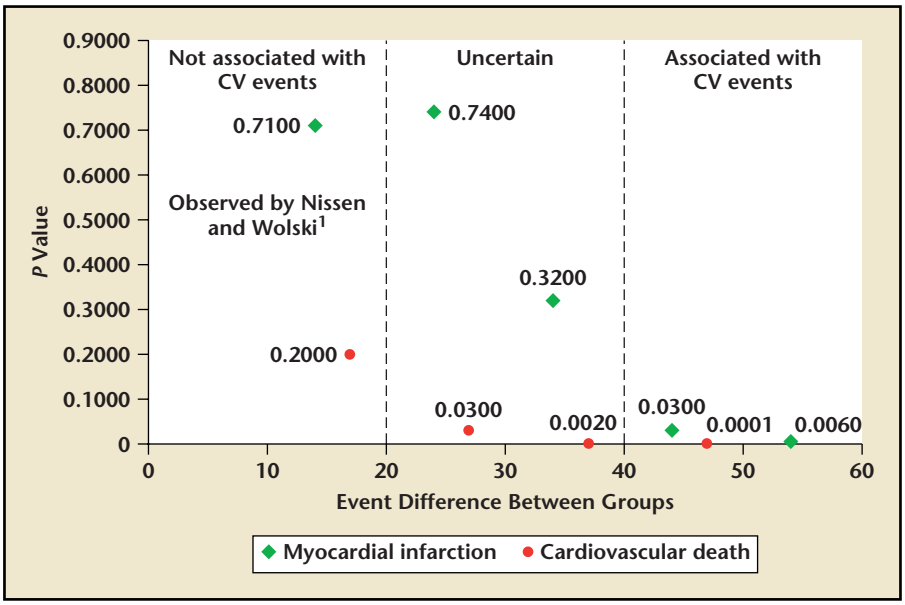


Figure 2. *Analysis of the pooled cardiovascular outcomes reported in 42 trials of patients who received rosiglitazone or comparator(s). The difference in absolute events (myocardial infarction, cardiovascular death) between the rosiglitazone and comparator groups are plotted on the x axis, with the first pair of differences reported by Nissen and Wolksi[1] plotted on the left. The* P *values generated by the Mantel Haenszel chi-square test statistic are plotted on the y axis. Theoretical event differences are sequentially plotted assuming progressively greater event differences with additional events accruing in the rosiglitazone group only. As shown, there would need to be an approximately 40-event difference between the groups to achieve statistical significance and clinical certainty that rosiglitazone was associated with CV events. CV, cardiovascular.*

permanent side effect. Sustained weight reduction is the only hope for remission of type 2 diabetes mellitus, and therefore treatment with TZDs, while aiding in glycemic control, may push patients farther from their ultimate goal. Fluid retention can worsen heart failure symptoms and potentially cause decompensation. This effect can be seen with TZDs, corticosteroids, and exogenous sodium. Thus, weight gain and edema should be the real limiting factors in the use of these drugs for treating diabetes, a condition for which there are many therapeutic choices.

Randomized Trials

The 2 largest randomized trials evaluating rosiglitazone are the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial and A Diabetes Outcome Progression Trial (ADOPT).[5,6] The goal of the DREAM trial was to evaluate treatment with rosiglitazone as compared with placebo among 5269 patients without cardiovascular disease or a history of diabetes but with impaired glucose tolerance. The rates of myocardial infarction were 0.6% in the rosiglitazone group versus 0.3% in the control group, and the rates of myocardial infarction/stroke and cardiovascular composite events were 1.2% in the rosiglitazone group versus 0.9% in the control group; none of the differences achieved statistical significance. There was no difference in mortality (1.1% in the rosiglitazone group vs 1.3% in the control group; $P = .70$). Chronic heart failure occurred significantly more frequently with rosiglitazone than placebo (0.5% vs 0.1%; $P = .01$).

In the ADOPT study, rosiglitazone, metformin, and glyburide were compared as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomized, controlled clinical trial involving 4360 patients. The patients were treated for a median of 4 years. The primary outcome was the time to monotherapy failure, which was defined as a confirmed level of fasting plasma glucose of more than 180 mg/dL, for rosiglitazone as compared with metformin or glyburide. At the 4-year evaluation, a hemoglobin A_{1c} of less than 7% was found in 40% of patients on rosiglitazone, as compared with 36% of patients on metformin ($P = .03$) and 26% of patients on glyburide ($P < .001$). Glyburide was associated with a lower risk of cardiovascular events (mostly congestive heart failure) than was rosiglitazone ($P < .05$); the risk associated with metformin was similar to that with rosiglitazone. Rosiglitazone was again associated with more weight gain and edema than either metformin or glyburide, but it had fewer gastrointestinal events than metformin and less hypoglycemia than glyburide ($P < .001$ for all comparisons).

The ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study will evaluate the long-term impact of de novo heart failure and decompensation of existing heart failure on cardiovascular outcomes, as well as on long-term glycemic control, in people with type 2 diabetes. This study will be a 6-year, randomized, open-label trial in patients with type 2 diabetes who have inadequate blood glucose control on metformin or sulphonylurea alone. The primary endpoint is the time to first cardiovascular hospitalization or death, blindly adjudicated by a central endpoints committee. In a recently published interim analysis of the RECORD trial, there was no significant difference in the adjudicated primary endpoint of hospitalization or death from cardiovascular causes (hazard ratio 1.08; 95% CI, 0.89-1.31) (Figure 3).[7] There was a statistically

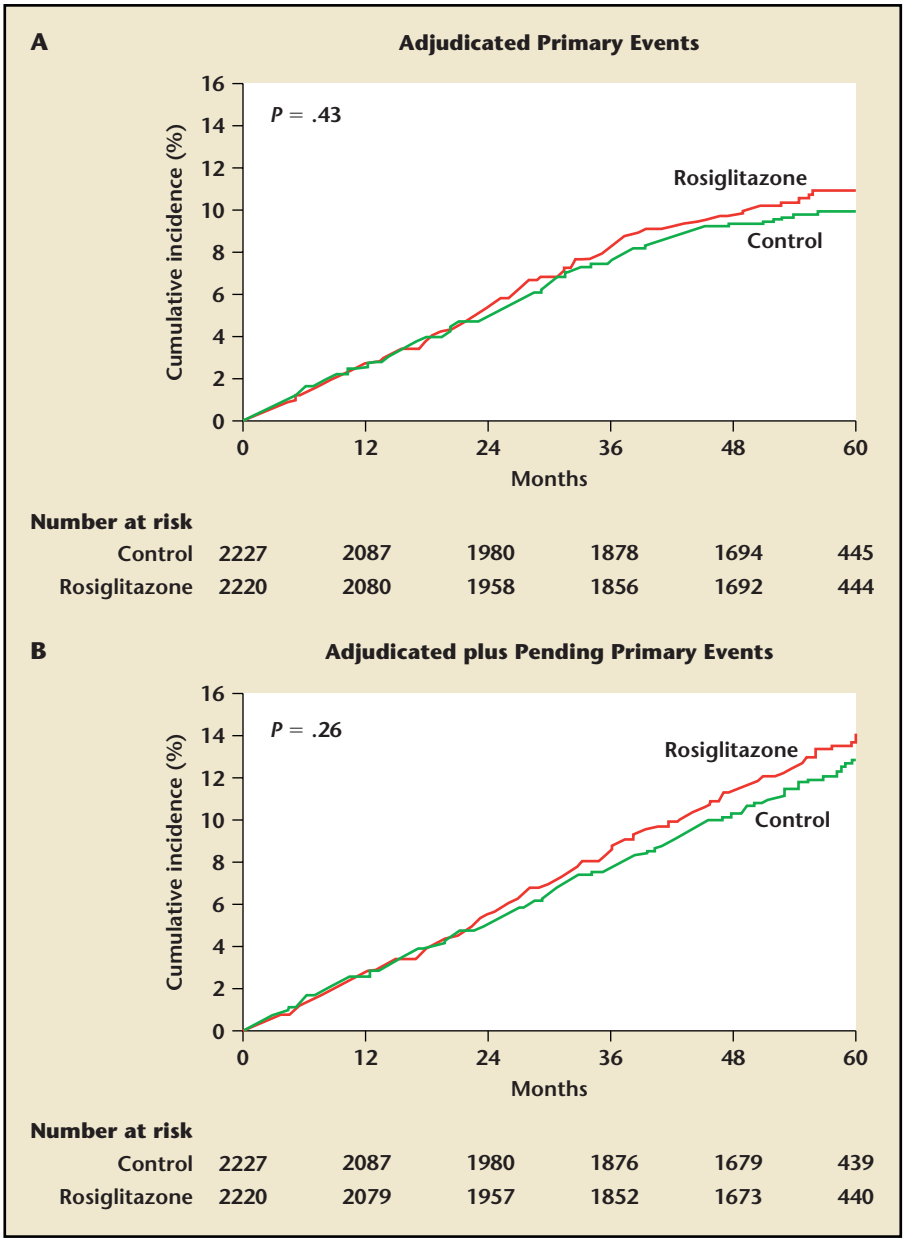


Figure 3. *In a recently published interim analysis of the RECORD trial, there was no significant difference in the adjudicated primary endpoint of hospitalization or death from cardiovascular causes (A). Data for adjudicated plus pending primary events were also nonsignificant (B). Adapted with permission from Home PD et al.[7] Copyright © 2007 Massachusetts Medical Society. All rights reserved. RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes.*

significant increase in the risk of heart failure in the rosiglitazone group as compared with the control group (hazard ratio 2.15; 95% CI, 1.30-3.57). Although we await the completion of the trial as it was originally designed, these results are consistent with our own analysis that the risk of rosiglitazone seems to be the development or exacerbation of fluid retention in those patients who are predisposed to congestive heart failure, rather than an increase in risk of myocardial infarction or death. Certainly it will be comforting if the final results of the RECORD trial show that rosiglitazone is actually protective against the development of cardiovascular events in diabetic patients rather than neutral or even negative in its cardioprotective abilities.

Conclusion

Future cardiovascular trials using this class of agents must adjudicate all cardiovascular events and account for de novo heart failure and decompensation of existing heart failure. In addition, future meta-analyses should at least report absolute event rates, meet some simple statistical tests of significance, and employ conservative techniques (random effects models) to find additional effects, if indeed they exist, among heterogenous trials with differing populations, protocols, and durations of follow-up.

Although the analysis by Nissen and Wolski has flaws, it has been useful in raising methodological and safety issues. It is hoped that the analysis will spur more investigation and higher quality methods in this area. We owe our patients nothing less. ■

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