Rosiglitazone Appears to Be Associated With an Increased Risk of Cardiovascular Events

Reviewed by Michael Pignone, MD, MPH

STUDY

Nissen S, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007, erratum *N Engl J Med* 357:100, 2007

SUMMARY

Design. Systematic review and meta-analysis of randomized trials of rosiglitazone compared with placebo or other active therapy that were at least 24 weeks in duration and that measured cardiovascular events.

Methods. The authors performed a literature search, including databases maintained by the U.S. Food and Drug Administration (FDA) and the manufacturer of rosiglitazone. Available studies were abstracted to identify incident myocardial infarctions and cardiovascular deaths. Data from included trials were combined using a fixed-effects model to estimate summary odds ratios for incidence of myocardial infarction and cardiovascular death.

Results. The authors identified 42 trials that met their inclusion criteria. These trials studied > 27,000 patients and ranged in duration from 24 to 208 weeks. Most trials enrolled middle-aged patients with moderately elevated hemoglobin A_{1c} (A1C) levels. There were 86 total myocardial infarctions in the rosiglitazone arms of the included studies and 72 in the control-group arms; 39 deaths from cardiovascular causes occurred in the rosiglitazone-assigned patients versus 22 in the control groups. The risk of myocardial infarction (odds ratio 1.43, 95% confidence interval [CI] 1.03–1.98) and cardiovascular deaths (odds ratio 1.64, 95% CI 0.98–2.74) were increased for rosiglitazone-assigned patients. Exploratory analyses suggest that the effect was similar for both large and small trials and that the adverse effect appeared larger when rosiglitazone was compared with placebo or insulin than when it was compared with a sulfonylurea or metformin.

Conclusions. Based on available data, rosiglitazone may be associated with an increased risk of myocardial infarction and death from cardiovascular causes.

COMMENTARY

This meta-analysis by Nissen and Wolski suggests that the use of rosiglitazone may be associated with an increased risk of myocardial infarction and cardiovascular death, based on available published and unpublished data. A similar analysis performed by the FDA (http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazoneHCP.htm) has apparently reached a similar conclusion.

Despite the large number of trials included in the meta-analysis and large number of total patients studied, relatively few total cardiovascular events occurred, making precise estimate of effects and any subgroup analyses difficult. Lack of access to individual patient-level data also limits the assessment of the role of important covariates, such as age, sex, and A1C; data were available only at the trial level. In addition, the analysis could not examine the relationship between the length of exposure to rosiglitazone and cardiovascular events.

How should we interpret the results of this study? We have limited data about the quality of some of the individual trials included in the meta-analysis, but in most cases, they appear to be of fair or good quality. Some of the studies did not use masking or blinding and thus have the risk of bias in the ascertainment of outcomes. Most did not have formal methods for adjudicating whether events that were reported as myocardial infarction or cardiovascular deaths actually met accepted criteria for these causes.

Another limitation of this meta-analysis is that it used a fixed-effects model for combining studies. A fixed-effect model assumes that all of the trials included drew their participants from the same underlying patient pool, an assumption that is difficult to support. It would have been more appropriate to use a random-effects model, which accounts for both within- and between-study variability. Fixed-effects models usually produce narrower confidence intervals for their summary estimates, which leads to overestimation of the precision of the data.

It is possible that data from studies not included in this meta-analysis would affect the observed risk of adverse cardiovascular events. It is unclear whether the review strategy identified all the relevant trials or whether data from any trials that were not included would change the findings with respect to cardiovascular disease risk. One important trial, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), is examining the effect of rosiglitazone

when added as a second agent to metformin or sulfonylurea (compared with the combination of metformin and sulfonylurea) and was designed to provide information on cardiovascular disease effects. The trial enrolled > 4,400 patients through 2003 and plans to follow patients for 5 years. A recent interim report from the trial[1] found that those assigned to rosiglitazone had a modest, nonstatistically significant risk of cardiovascular events (hazard ratio 1.08; 95% CI 0.89–1.31). It did, however, confirm the previously observed increased risk of heart failure seen with thiazolidinediones (hazard ratio 2.15; 95% CI 1.30–3.57).

Despite their limitations, the findings from the Nissen and Wolski meta-analysis and RECORD, combined with previous work documenting increased incidence of weight gain, edema, and heart failure with thiazolidinediones, raises several important questions about the role of rosiglitazone in the treatment of diabetes. To date, the principal documented benefit of rosiglitazone for patients with type 2 diabetes is the ability to reduce A1C, with an expected mean reduction of ~1.0–1.5 percentage points.[2] When used as an adjunct to other oral agents or in addition to insulin as a means of reducing A1C, its clinical benefits are presumed to be a decreased risk of microvascular events. This assumption is based on trials such as the Diabetes Control and Complications Trial and the U.K. Prospective Diabetes Study, which found reduced microvascular events associated with reductions in A1C achieved with other medications. No trials have directly examined whether the improvement in glycemic control with rosiglitazone has a similar, greater, or lesser effect on microvascular outcomes.

Because it is possible to achieve glycemic control with other agents, the amount of additional risk for adverse events with rosiglitazone—particularly serious ones, such as myocardial infarction, heart failure, or cardiovascular death—that can be tolerated is not large. The increased risk for heart failure and possible increased risk of myocardial infarction or cardiovascular death are particularly concerning because patients with diabetes are already at increased risk for these types of adverse events as a consequence of the disease itself.

REFERENCES

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