Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality

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CRD summary
This review, which included a very large number of patients, concluded that rosiglitazone treatment increased the risk of myocardial infarction, but not of cardiovascular or all-cause mortality, compared with placebo or alternative interventions. Despite a lack of validity assessment and poor reporting of some aspects of the review process, this conclusion is probably reliable.

Authors’ objectives
To assess the effect of rosiglitazone (diabetes drug) on myocardial infarction, cardiovascular mortality and all-cause mortality.

Searching
The clinical trials registry of GlaxoSmithKline (the manufacturer of rosiglitazone) was searched up to February 2010, together with MEDLINE database and the website of the US Food and Drug Administration (FDA).

Study selection
Randomised controlled trials (RCTs) of rosiglitazone, with similar durations of treatment in all trial groups and a minimum duration of 24 weeks treatment, were eligible for inclusion in the review.

The primary outcomes were myocardial infarction, cardiovascular mortality and all-cause mortality, although trials which reported no occurrences of cardiovascular events were specifically eligible for inclusion in the review.

The included trials predominantly enrolled patients with type 2 diabetes, although a small number enrolled patients with other indications; one trial was designed to assess prophylaxis against new-onset diabetes in high-risk individuals. Participants in included trials had a mean age of 57 years, 55% were male, and they were predominantly (over 80%) Caucasian. The mean baseline glycated haemoglobin (HbA₁c) was 8.2%. Doses of rosiglitazone ranged from 2mg/daily to 8mg/daily, with the majority of trials using upward titration of dose to 8mg/daily. A range of control interventions were used including placebo, glyburide, metformin, sulfonylurea, glimepiride, glipizide, insulin, usual care, and combinations of these. Trial duration ranged from 24 to 260 weeks.

The authors did not state how the papers were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted to permit the calculation of odds ratios (OR) with 95% confidence intervals (CI) for each of the assessed adverse outcomes. A decision was made not to calculate composite outcomes because lack of data precluded determination of whether individual patients experienced multiple outcomes. The data were extracted from all available sources for each trial and cross-checking was carried out.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Peto odds ratios with 95% confidence intervals were calculated. An alternative analysis using the Mantel-Haenszel method was used to allow the incorporation of trials reporting zero events. Numbers needed to harm (NNH) were also calculated. Heterogeneity was assessed using the Q statistic and I².

A sensitivity analysis excluding the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial was carried out. Subgroup analyses based on trial duration (less than 12 months versus more...
than 12 months) and comparator were also conducted.

**Results of the review**
Fifty-six RCTs, including a total of 35,531 patients, were included in the review: 19,509 patients received rosiglitazone, whilst 16,022 patients received control therapies.

Rosiglitazone significantly increased the risk of myocardial infarction (Peto OR 1.28, 95% CI 1.02 to 1.63). A similar result was obtained using a Mantel-Haenszel analysis.

The risk of cardiovascular mortality or all-cause mortality did not differ significantly between the rosiglitazone and control groups in either analysis.

There was no evidence of statistically significant heterogeneity in any of the analyses.

The results of sensitivity and subgroup analyses were also reported.

**Authors' conclusions**
Randomised clinical trial evidence continued to demonstrate an increased risk of myocardial infarction, although not of cardiovascular or all-cause mortality, for rosiglitazone. The current findings suggested an unfavourable benefit to risk ratio for rosiglitazone.

**CRD commentary**
The review question and inclusion criteria were clear. The authors searched several appropriate sources without reported restrictions. They did not report using methods designed to reduce reviewer bias and error in the selection of studies or the extraction of data, although cross-checking of data extracted from different sources was reported (for those included studies where this was possible).

No assessment of validity was reported, so the reliability of the evidence was difficult to determine. The use of meta-analysis was appropriate and included reasonable measures to explore the impact of including or excluding trials with particular characteristics. The authors' conclusions reflected the results of the review. Despite poor reporting of some aspects of the review process, and the lack of a validity assessment, the very large numbers of patients included in the review and appropriate statistical synthesis mean that the conclusions can probably be considered reliable.

One of the authors disclosed a number of financial relationships with various pharmaceutical companies.

In Sept 2010, following the availability of new evidence questioning the cardiovascular safety of rosiglitazone, the European Medicines Agency recommended the suspension of the marketing authorisation for rosiglitazone-containing anti-diabetes medicines.

**Implications of the review for practice and research**
**Practice:** The authors stated that the use of rosiglitazone solely to lower blood glucose levels is difficult to justify,

**Research:** The authors did not state any implications for further research.

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