Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis

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CRD summary
This review of randomised trials concluded that rosiglitazone use for at least 12 months is associated with a significantly increased risk of myocardial infarction and heart failure, but not cardiovascular mortality, in patients with impaired glucose tolerance or type 2 diabetes. These conclusions appear appropriate given the evidence presented.

Authors' objectives
To systematically review the long-term cardiovascular risks of rosiglitazone.

Searching
PubMed and the manufacturer's website were searched for relevant rosiglitazone studies in September 2006, with updates in May 2007. Systematic reviews were also examined for relevant publications. The U.S. Food and Drug Administration's website and GlaxoSmithKline clinical trials register were also searched. Only English language publications were eligible for inclusion. The search terms were reported in a separate paper.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 12 months' duration were eligible for inclusion in the review.

Specific interventions included in the review
Studies evaluating rosiglitazone against placebo or other non-thiazolidinedione oral hypoglycaemic drugs were eligible for inclusion in the review. The control treatments included placebo, metformin and glyburide.

Participants included in the review
Studies including participants with impaired glucose tolerance or type 2 diabetes mellitus were eligible for inclusion in the review. The participants' mean age ranged from 54.6 to 64.3 years.

Outcomes assessed in the review
Studies stating their intention to monitor cardiovascular adverse events and explicitly reporting data on myocardial infarction (MI), heart failure and cardiovascular mortality were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
The authors mentioned that two reviewers independently assessed the quality of the trials. No formal assessment of internal validity was presented in the review, but the quality of adverse event reporting was given for each trial.

Data extraction
Two reviewers independently extracted the data for the review. Data on MI, heart failure, cardiovascular mortality and overall mortality were extracted, and relative risks (RRs) were calculated.

Methods of synthesis
How were the studies combined?
Pooled RRs were calculated using a fixed-effect model. The numbers-needed-to-harm and 95% confidence intervals (CIs) were also calculated.
How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic, with values greater than 50% considered to represent a substantial level of heterogeneity. Sensitivity analyses were conducted to explore the impact of statistical model (fixed-effect or random-effects), trial duration and adjudication of adverse events.

Results of the review
Four RCTs (n=14,291) were included in the review.

Rosiglitazone significantly increased the risk of MI compared with control (RR 1.42, 95% CI: 1.06, 1.91, p=0.02), with no evidence of substantial heterogeneity (I-squared 0%).

Rosiglitazone significantly increased the risk of heart failure compared with control (RR 2.09, 95% CI: 1.52, 2.88, p<0.01), with no evidence of substantial heterogeneity (I-squared 18%).

Rosiglitazone was not associated with an increased risk of cardiovascular mortality (RR 0.90, 95% CI: 0.63, 1.26, p=0.53); there was no evidence of substantial heterogeneity (I-squared 0%).

Rosiglitazone was not associated with an increased risk of overall mortality (RR 0.99, 95% CI: 0.80, 1.23, p=0.92). The degree of statistical heterogeneity was not stated.

Sensitivity analyses yielded similar findings to these main results.

Authors' conclusions
In patients with impaired glucose tolerance or type 2 diabetes, 12 months or greater use of rosiglitazone is associated with a significantly increased risk of MI and heart failure, without a significantly increased risk of cardiovascular mortality.

CRD commentary
This was a generally well-conducted review that was based on a question clearly defined in terms of the interventions, participants, study designs and outcomes. PubMed/MEDLINE and other appropriate sources were searched for relevant primary studies, though inclusion was limited to English language publications; therefore the potential for language bias cannot be entirely ruled out. To minimise the potential for error and bias, two reviewers were independently involved at key stages of the review process. The studies were synthesised using appropriate methods, although details of the validity assessment criteria were lacking, and attempts were made to assess statistical heterogeneity and the robustness of the review findings. The authors' conclusions appear appropriate given the evidence presented in the review.

Implications of the review for practice and research
Practice: The authors stated that health plans and physicians should avoid using rosiglitazone in patients with diabetes who are at risk of cardiovascular events, especially since safer treatment alternatives are available.

Research: The authors stated that trials with a larger population and longer follow-up would be required to draw definitive conclusions on cardiovascular mortality.

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