

# RAPID APPRAISAL

**Name of Trial:** Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes.

**Reference:** New Engl J Med. 2007; published online May 21. DOI:10.1056/NEJMoa072761

**Question:** Does rosiglitazone increase the risk of cardiovascular disease?

**Summary:** This systematic review suggests that rosiglitazone treatment is associated with a small (0.02%) but statistically significant increase in the risk of a myocardial infarction, but not for death from cardiovascular causes. However, this low quality review has a number of significant methodological weaknesses and the data presented are not sufficiently robust to recommend a change in current practice. Patients are advised not to cease treatment with rosiglitazone and to discuss concerns regarding their medication with their doctor at their next routine appointment. Warnings regarding the potential risk of cardiac ischaemic events were added to the prescribing information for rosiglitazone in 2006.

***Did the review ask a clearly focussed question?***

**Yes** – This systematic review evaluated the effect of rosiglitazone on the risk of myocardial infarction (MI) and death from cardiovascular causes compared to placebo or active comparator.<sup>1</sup>

***Did the authors look for the appropriate sort of papers?***

**Don't know** – Only limited details of the methodological criteria used to select studies for inclusion are reported. To be included in the review a study had to have a randomised comparator group, a similar duration of treatment in all groups, and more than 24 weeks of drug exposure. The outcome measures of interest were myocardial infarction or death from cardiovascular causes. A total of 116 phase two, three and four trials were screened for inclusion. Of these 48 met the initial eligibility criteria. Six of the 48 trials were excluded as they reported no myocardial infarctions or deaths from cardiovascular causes. Of the remaining 42 trials, 38 reported at least one myocardial infarction, and 22 reported at least one death from cardiovascular causes. Three main study groups were identified: five trials submitted to the Food and Drug Administration (FDA) for initial registration (four published in full); 35 studies identified from the GlaxoSmithKline (GSK) clinical trial registry (nine published in full); and two large recently published trials (DREAM<sup>2</sup> and ADOPT<sup>3</sup>).

The combined analyses included a total of 15,560 patients randomly assigned to regimens that included rosiglitazone, and 12,283 assigned to comparator groups defined as any drug regimen other than rosiglitazone. The dose of

rosiglitazone in included studies varied between 2mg to 8mg daily, alone or in combination with insulin, sulphonylureas, and/or metformin. The comparator arms were varied and included placebo alone or as add-on treatment to other antidiabetic agents, and other active antidiabetic regimens including; metformin, sulphonylurea and insulin. The majority of studies involved patients with type II diabetes, but the review also included two studies involving patients with chronic psoriasis and one in patients with Alzheimer's disease.

***Were the important relevant studies included?***

**Don't know** – The authors state that studies were identified through searches of the published literature, the FDA website, and the GSK clinical-trials registry. However, no specific details of the bibliographic databases used and the search strategies employed, are presented within the report and this raises significant doubts that all potentially relevant studies have been accessed. Therefore, the possibility of selection bias cannot be ruled out.

***Were the quality of the studies assessed?***

**No** – There was no reported evaluation of study quality, and although small trials were analysed separately, no other assessment relating to the precision and external validity of the included studies appears to have been undertaken.

***Was it reasonable to combine the results of the review?***

**Probably** – Heterogeneity was investigated for all outcome measures using the Chi-squared test (Q-test) and showed no significant statistical heterogeneity ( $p > 0.10$ ), suggesting it was

appropriate to use a fixed effects model which assumes that only within-study variation is taken to influence the uncertainty of results. However, there were some notable differences between the two study populations, particularly with regards to the predominance of males in the rosiglitazone group (60.7% vs. 53.3% for the comparator group). In addition, there is obvious clinical heterogeneity between the trials with respect to underlying risk factors for cardiovascular disease. Therefore the robustness of the results should also have been examined using the more 'conservative' random effects model which includes both within-study and between-study variation in the assessment of uncertainty

### **What is the overall result of the review?**

In the combined studies a total of 158 myocardial infarctions and 61 cardiovascular deaths were reported. In patients receiving rosiglitazone 86 myocardial infarctions (0.60%), and 39 deaths from cardiovascular causes (0.38%) were reported, compared to 72 (0.62%) and 22 (0.24%) in patients receiving an active comparator or placebo, respectively. The estimated risk, presented as a summary odds ratio, for a myocardial infarction in the rosiglitazone group was 1.43 (95% confidence interval [CI] 1.03 to 1.98,  $p=0.03$ ), corresponding to an absolute increased risk of 0.02%. The odds ratio for death from cardiovascular causes, was not statistically significant (OR 1.64; [95% CI, 0.98 to 2.74];  $p=0.06$ ).

### **How precise are the results?**

This low quality review has a number of significant methodological weaknesses. The results were based on pooled data from short-term trials the majority of which were not designed to assess the risk of cardiovascular disease. In some of the included studies patients receiving rosiglitazone also received the comparator drug. The lack of patient-level data and independently adjudicated outcomes meant it was not possible to undertake time-to-event analyses, or to determine whether the same patient had both outcomes. Because the results are based on a relatively small number of overall events, the estimated odds ratios could be significantly affected by absent or misclassified outcomes.

The estimated risk of myocardial infarction was statistically significant ( $p=0.03$ ) by conventional standards, but the risk of cardiovascular death was not statistically significant ( $P=0.06$ ). However, the 95% confidence intervals for both outcomes are wide and approach or cross the line of no effect (1.03 to 1.98, and 0.98 to 2.74, respectively). No sensitivity analyses were undertaken to investigate dose-related risk or the differing response of patients with refractory and controlled diabetes or those with significant comorbidities.

In subgroup analyses no significant increase in the risk of a myocardial infarction was observed when rosiglitazone was compared separately to several active comparators, or when the pooled group of small trials with a shorter duration were analysed separately from those of larger trials. In their discussion the authors point out a number of limitations of the review and conclude that the current data are insufficient to assess the cardiovascular risks of rosiglitazone. No evidence is presented to show that rosiglitazone has a less favourable risk-benefit profile in comparison to other glitazones.

### **Can the results be applied to the local population?**

**Yes** - This review included 27,843 participants with a mean baseline glycated haemoglobin (HbA<sub>1c</sub>) level of 8.2%. The patient population was diverse and included overweight and insulin resistant patients, recently diagnosed type 2 diabetics, as well as those with significant comorbidities and underlying risk factors for cardiovascular disease. The mean age was about 57 years, the majority were of white race and there was a predominance of males. However, it should be noted that some of the patients included in this review were not treated in accordance with the licensed Indication for rosiglitazone.

### **Were all important outcomes considered?**

**No** – Trials in which patients had no adverse cardiovascular events in either group were excluded. This is likely to have significantly overstated the potential risk of cardiovascular events associated with rosiglitazone treatment, as inclusion of these participants will have altered the denominators for the outcomes. The data were not adequate to conduct dose-response analyses.

### **Does rosiglitazone increase the risk of cardiovascular disease?**

This systematic review suggests that rosiglitazone was associated with a small but statistically significant increase in the risk of a myocardial infarction, but not for death from cardiovascular causes. However, this low quality review has a number of significant methodological weaknesses. Consequently, the data presented in this review are not sufficiently robust to reliably assess the cardiovascular risk of rosiglitazone and further investigation of the drugs overall risk benefit profile are clearly warranted. The ongoing RECORD study is a large, randomised, open-label trial designed specifically to evaluate cardiovascular outcomes in patients treated with rosiglitazone as add-on therapy to either metformin or sulphonylurea.<sup>4</sup> Until the results of the RECORD study are reported the results of this review should be interpreted with due caution. The Medicines and Healthcare Regulations Authority (MHRA)<sup>5</sup> and

the European Medicines Agency (EMA)<sup>6</sup> have issued statements acknowledging the results of this study, but advise patients not to stop taking rosiglitazone and to discuss any concerns that they may have regarding their medication with their doctor at their next routine appointment. Prescribers should be aware that rosiglitazone is contraindicated in patients with a history of cardiac failure.<sup>7</sup> Since rosiglitazone was licensed in 2000 the Committee for Medicinal Products for

Human Use (CHMP) has kept rosiglitazone under close surveillance for cardiovascular effects, and the majority of the studies included in this review have already been assessed by the CHMP.<sup>6</sup> Warnings regarding a potential risk of cardiac ischaemic events were added to the prescribing information in 2006.<sup>7</sup>

## REFERENCES

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KEY: MA - meta-analysis, O – open-label study, RCT - randomised controlled trial, S - statement.

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