Cardiac safety profile of rosiglitazone: a comprehensive meta-analysis of randomized clinical trials

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CRD summary
This review assessed the cardiovascular risk of rosiglitazone and found it to be associated with increased risk of heart failure, but not increased risk of myocardial infarction or cardiovascular mortality. Issues with potential publication bias and study quality mean that the authors' conclusion should be interpreted with some caution.

Authors' objectives
To assess the cardiovascular risk of rosiglitazone using a comprehensive dataset.

Searching
The reviewers searched MEDLINE (until 2007), GlaxoSmithKline website (http://ctr.gsk.co.uk/welcome.asp) and ClinicalTrials.gov for relevant articles. The MEDLINE search was restricted to studies published in English. Search terms were not reported.

Study selection
Eligible studies were randomised controlled trials that compared rosiglitazone with any other treatment over a duration of at least four weeks. Eligible outcomes included death from any cause, cardiovascular death, nonfatal coronary events, nonfatal acute myocardial infarction and nonfatal serious chronic heart failure.

In an online appendix, the reviewers provided some details of patient age, duration of diabetes, whether rosiglitazone was used as a monotherapy or combination therapy and comorbidities. The weighted mean age within trials was 55.2 years. Most trials included patients with type 2 diabetes (mean diabetes duration of 6.2 years). A small number of trials included a mixed population of people with and without diabetes. Rosiglitazone was administered either as monotherapy or combined with insulin, metformin and sulfonylureas. The main comparators included placebo, no treatment and metformin.

The number of reviewers who performed study selection was not reported.

Assessment of study quality
Two reviewers independently assessed studies in terms of adequacy of randomisation method, blinding procedures and reporting of withdrawals and drop-outs. Disagreements were resolved through adjudication with a third reviewer.

Data extraction
Data to enable calculation of odds ratios (ORs) and risk ratios (RRs) with 95% confidence intervals (CIs) were extracted by two reviewers who independently used a standardised form. Disagreements were resolved through adjudication with a third reviewer. Patient-year events were extracted for many outcomes. Study authors were contacted where necessary for data from studies not sponsored by GlaxoSmithKline.

Methods of synthesis
For the main analysis odds ratios with 95% CIs were pooled using DerSimonian and Laird random-effects models. Data were stratified in a series of subgroups based on whether or not participants had diabetes, comparator used, type of regimen (monotherapy or combination therapy), duration and whether or not the trial was included on the GlaxoSmithKline database.

Results of the review
The review included 164 studies (n=45,875 participants). Most studies were described as double-blind, but the method of blinding was not adequately reported in most of these studies. Most studies had adequate reporting of withdrawals. Methods of randomisation were not clearly stated in many publications.
The review estimated no statistically significant difference between rosiglitazone and no-rosiglitazone groups in terms of all-cause mortality (OR 0.90, 95% CI 0.73 to 1.12), cardiovascular mortality (OR 0.94, 95% CI 0.69 to 1.29), coronary events (0.09, 95% CI 0.90 to 1.31) and acute myocardial infarction (OR 1.14, 95% CI 0.90 to 1.45). Rosiglitazone was associated with a substantive and statistically significant increase in risk of chronic heart failure (OR 1.69, 95% CI 1.20 to 2.36).

Subgroup analyses appeared broadly consistent with the overall analysis (based on the authors' descriptive comparison), although they suggest some subgroup trends for individual outcomes.

**Authors' conclusions**
Rosiglitazone was associated with increased risk of heart failure. There was no evidence of increased risk of myocardial infarction or cardiovascular mortality.

**CRD commentary**
This review addressed a clear review question. A number of relevant sources were searched for published and unpublished studies. Data could not be retrieved for 17 unpublished studies, which increased the risk of publication bias. Study selection criteria were clear, which improved review transparency and repeatability. Despite the large number of included trials, sufficient primary study details were provided for each study within the online appendices. The study quality assessment and data extraction stages of the review seemed appropriate in method and were conducted in duplicate, which reduced risks of reviewer error and bias. Details in the appendices suggested that many trials did not have adequate randomisation, blinding and description of withdrawals and drop-outs. The method of synthesis seemed appropriate, but did not assess statistical heterogeneity. The results were clearly reported.

Issues with potential publication bias and study quality mean the authors' conclusion should be interpreted with some caution.

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 authorisations for rosiglitazone-containing anti-diabetes medicines.

**Implications of the review for practice and research**
The reviewers did not state any implications for practice and research.

**Funding**
Regione Roscana, TRESOR Project.

**Bibliographic details**

**PubMedID**
19328563

**DOI**
10.1016/j.ijcard.2009.01.064

**Original Paper URL**
http://dx.doi.org/10.1016/j.ijcard.2009.01.064

**Additional Data URL**
http://dx.doi.org/10.1016/j.ijcard.2009.01.064
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Diabetes Mellitus, Type 2 /drug therapy /mortality; Humans; Hypoglycemic Agents /adverse effects; Myocardial Infarction /mortality; Randomized Controlled Trials as Topic /statistics & numerical data; Risk Factors; Thiazolidinediones /adverse effects

AccessionNumber
12010006601

Date bibliographic record published
08/12/2010

Date abstract record published
27/07/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.