Pioglitazone and cardiovascular risk: a comprehensive meta-analysis of randomized clinical trials

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CRD summary
This review found that pioglitazone was not associated with increased risk of cardiovascular events. Insufficient information presented and the conduct of the review made it difficult to draw any conclusions about the evidence presented and the reliability of the authors' conclusions.

Authors' objectives
To assess the effect of pioglitazone on the risk of non-fatal coronary events, cardiovascular mortality and all-cause mortality.

Searching
MEDLINE was searched from inception to 31 August 2007 for randomised controlled trials of human subjects published in English. Searches were also undertaken on the Food and Drug Administration, GlaxoSmithKline and ClinicalTrials.gov websites for unpublished studies. Authors and/or sponsors of the identified unpublished studies were contacted for further data.

Study selection
Randomised controlled trials (RCTs) with a duration of at least four weeks that investigated the use of pioglitazone compared to any other treatment were eligible for inclusion. Studies were excluded if they were incomplete or lasted less than four weeks or were without an adequate control or comparator group.

The patient populations were heterogeneous and included patients with Type 2 diabetes mellitus (72% of trials) and patients with other conditions. Most trials had non-cardiovascular endpoints. Comparators included placebo, insulin secretagogues, metformin, peroxisome proliferator-activated receptor (PPAR) agonists, insulin, α-glucosidase inhibitors and dipeptidyl peptidase-IV (DPP-IV) inhibitors. Follow up in the trials varied from eight to 156 weeks.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The methodological quality of the studies was assessed by an analysis of randomisation, blinding and reporting of withdrawals and dropouts.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were collected on the following outcomes: death from any cause; cardiovascular death; non-fatal coronary events (myocardial infarction, unstable angina and coronary revascularization) and non-fatal chronic heart failure. The reviewers were unable to calculate hazard ratios or composite endpoints because time-to-event data was not specified in the retrieved studies.

The data were extracted independently by two reviewers; discrepancies were resolved by a third reviewer.

Methods of synthesis
Odds ratios were calculated with corresponding 95% confidence intervals (CI) using a Mantel-Haenszel random-effects model. Trials with zero events were excluded from this analysis.

Analyses of trials that recorded zero events were also performed and pooled relative risks and 95% CIs calculated.

Separate subgroup analyses were performed, where possible, on the basis of cardiovascular endpoints, duration (greater or less than 24 weeks duration) and for comparisons of pioglitazone and metformin, sulphonylureas, rosiglitazone, dual...
PPARα/γ agonists (glitazars) and placebo. The results of PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROACTIVE), a particularly large trial, were described separately in the text and included in some of the analyses.

**Results of the review**

The total of 94 RCTs (n= 26,418) comprised 84 published trials and 10 unpublished trials. Data from 93 trials was included in the meta-analysis; data from the PROACTIVE trial (n=5 238) was not included in some of the meta-analysis, because the number of events was much larger than for the other studies.

Randomisation and blinding were described as adequate in 31 (33%) and 21 (22%) of the 94 trials. Withdrawals and dropouts were reported in 66 trials (70%).

**All-cause mortality:** There was no significant differences between pioglitazone and other treatments in the analysis of all trials, and for the PROACTIVE trial. In the meta-analysis where PROACTIVE was excluded and trials with at least one reported event were included, there was a significant reduction in mortality observed with pioglitazone treatment (odds ratio 0.30, 95% CI 0.14 to 0.63). Statistically significant reductions of all-cause mortality were observed for the analyses of Type 2 diabetic patients (relative risk 0.41, 95% CI 0.23 to 0.72; 68 trials) and long-term (≥24 weeks) compared with short-term studies (≤24 weeks). No significant reductions were observed when pioglitazone was compared with different treatments or placebo in analyses that included trials with zero events.

**Non-fatal coronary events:** In analyses of all trials, of trials with at least one event and of Type 2 diabetics, there were no statistically significant differences between pioglitazone and other treatments (relative risk 0.82, 95% CI: 0.55 to 1.23 for the last comparison; figures for the other comparisons were not provided). In the PROACTIVE trial, use of pioglitazone was associated with a significant reduction in non-fatal coronary events.

**Non-fatal heart failure:** A statistically significant increase in risk of heart failure with the use of pioglitazone was observed in the PROACTIVE trial and in trials that reported non-fatal heart failure that required hospitalisation (relative risk 1.32, 95% CI: 0.88 to 1.98). A small observed increase in the incidence of non-fatal heart failure was observed for all trials, but was not statistically significant (odds ratio 0.38, 95% CI: 0.90 to 2.12).

**Authors' conclusions**

The available evidence from the included studies did not indicate that use of pioglitazone was associated with increased risk of adverse cardiovascular events and all-cause mortality.

**CRD commentary**

The review addressed a question that was broad in scope. The search was limited to one electronic database, but there was also a search for unpublished trials. Steps taken to minimise bias were reported for some parts of the review process. Standard statistical methods were used to pool the data and potential sources of heterogeneity were explored. There appeared to be substantial clinical heterogeneity between patients in the included trials, as patients were included with Type 2 diabetes and other conditions. There was no information given on dose regimens of the study interventions and comparators. Given the clinical heterogeneity and the lack of information about the interventions and comparators, pooling these data may not have been appropriate. The included studies appeared to be of middling quality, given the inadequacy of blinding and randomisation procedures. Some data was only presented graphically in the review, which limited the interpretation of some of the findings. Some reporting errors, the lack of information presented and the conduct of the review made it difficult to draw conclusions from the evidence presented, and the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The reviewers did not state any implications for practice.

**Research:** The available data indicated that pioglitazone was not associated with increased adverse cardiovascular events. The cardiovascular risk profile of rosiglitazone was not clearly proven and should be clarified through an RCT that compared pioglitazone and rosiglitazone.

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