Evaluation of thiazolidinediones on cardiovascular outcomes in patients with type 2 diabetes mellitus: a systematic review

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CRD summary
This review concluded that rosiglitazone appeared safe in conjunction with close monitoring for treating diabetic patients without current or previous cardiovascular disease and that pioglitazone may have potentially beneficial effects on lipid profiles. Limitations in the methods and reporting of this review mean its conclusions cannot be considered reliable.

Authors' objectives
To evaluate the effects of rosiglitazone on cardiovascular outcomes in patients with type 2 diabetes mellitus. The secondary objective is to assess the effects of rosiglitazone and pioglitazone on lipid profiles and the effects of all thiazolidinediones on lipid parameters.

Searching
PubMed, The Cochrane Library and International Pharmaceutical Abstracts were searched between 1998 and December 2007 for articles in English. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of at least 24 weeks duration that compared rosiglitazone (2mg/day to 8mg/day) alone or in combination with other anti-diabetic drugs were eligible for inclusion. Studies with any other anti-diabetic medication in adults with haemoglobin A1c (HbA1c) over 7% or fasting blood plasma glucose (FPG) greater than 126mg/dL were eligible. Primary or secondary outcomes in the studies had to be cardiovascular and non-cardiovascular adverse effects or events.

The primary objective of the review was to evaluate effects of rosiglitazone on cardiovascular outcomes in patients with type 2 diabetes mellitus. The secondary objective was to assess effects of rosiglitazone and pioglitazone on lipid profiles. Only studies published between 2000 and 2007 were included for the primary objective. For the secondary objective, RCTs published between 1998 and 2007 that compared effects of either rosiglitazone with pioglitazone or thiazolidinedione monotherapy with placebo on lipid profiles were eligible.

For the primary objective, most studies compared rosiglitazone 8mg/day with another monotherapy (metformin, sulfonylurea or placebo); other studies assessed 4mg/day or 2mg/day. Half of the studies evaluated rosiglitazone in combination with other anti-diabetic agents. Study duration ranged from 24 weeks to four years. Baseline body mass index (BMI) ranged from 28kg/m² to 34.6kg/m². Patient age ranged from 52 to 64.3 years. HbA1c ranged from 7.35% to 9.5%. FPG ranged from 151mg/dL to 268mg/dL. Duration of diabetes was from 4.6 to 12.7 years. For the secondary objective, studies compared rosiglitazone (2mg/day to 8mg/day) with pioglitazone (15mg/day to 45mg/day) or placebo and pioglitazone with placebo. Study durations ranged from eight weeks to one year. Baseline body mass index ranged from 24.3kg/m² to 35.6kg/m². Patient age was from 53 to 63 years.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the 22 items from the CONSORT (Consolidated Standards of Reporting Trials) statement.

The authors did not report how many reviewers performed quality assessment.
Data extraction
Results for the proportions of patients with myocardial infarction, cardiovascular death, coronary heart failure and other cardiovascular events (stroke, ventricular tachycardia/fibrillation and ischaemic attack) and adverse events were extracted. For the secondary objective, mean change in lipid parameters (total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol) was extracted for each treatment group.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
Results were presented narratively.

Results of the review
Fifteen studies were included for the primary objective (n ranged from 203 to 4447) and 14 for the secondary objective (n for treatment groups ranged from 11 to 303). Between seven and 17 of the CONSORT items were met by all studies.

Primary objective: Six studies reported myocardial infarction for the rosiglitazone 8mg/day group. Proportions ranged from 0.9% to 1.9%. Five studies reported cardiovascular deaths for the rosiglitazone 8mg/day group with a maximum proportion of 1.3%. Two studies of 4mg/day and one study of 2mg/day reported that there were no cardiovascular deaths. Six studies reported coronary heart failure for the rosiglitazone 8mg/day group; proportions ranged from 0.95% to 1.7%. One study reported 1.9% of patients in the rosiglitazone 4mg/day group developed coronary heart failure. Other cardiac events were reported in six studies of rosiglitazone 8mg/day and more rosiglitazone treated patients reported adverse events. Higher doses of rosiglitazone were associated with greater reductions in HbA1c and FPG.

Secondary objective: Treatment with 0.1mg/day to 2mg/day of rosiglitazone resulted in no statistically significant changes in all lipid parameters compared with placebo. Higher doses of rosiglitazone showed no effect on changes in high-density lipoprotein or triglyceride levels. However, rosiglitazone doses of between 4mg/day and 8mg/day showed statistically significant changes in total and low-density lipoprotein cholesterol. Statistically significant changes in high-density lipoprotein cholesterol (from 4mg/dL to 6mg/dL) and triglyceride (from -36mg/dL to -54 mg/dL) were observed for most pioglitazone 30mg/day groups compared with placebo. Pioglitazone at other doses did not affect lipid parameters. Four studies that compared rosiglitazone (2mg/day, 4mg/day or 8mg/day) with pioglitazone (15mg/day, 30mg/day or 45mg/day) reported statistically significant differences between treatment groups for all lipid parameters.

Authors’ conclusions
Rosiglitazone appeared safe to be used alongside close monitoring in diabetic patients without current or previous cardiovascular disease. Pioglitazone may be a better treatment option based on current cardiovascular safety data and potentially beneficial effects on lipid profiles.

CRD commentary
This review covered two objectives and reported separate inclusion criteria for each. Only studies published in English were included, which increased risks of language and publication biases. No details of the review methods were reported, so it was unclear whether study selection, quality assessment and data extraction were performed in duplicate. Study quality was assessed using the CONSORT statement, but this is a reporting guide and not a validity assessment tool. No details of the individual studies or their quality were reported. Most results, apart from a few for the secondary objective, were reported at a group level by drug dose. Limitations in the methods and reporting of this review mean its conclusions about drug safety cannot be considered reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more clinical trials with improved design and analysis were needed to confirm the review conclusions.
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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.