A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors
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CRD summary
This review compared the efficacy of thiazolidinediones on cardiovascular risk factors and glycaemic control in patients with type 2 diabetes. The authors concluded that thiazolidinediones have similar effects on measures of glycaemic control and body weight, while pioglitazone has a more favourable lipid profile, but direct head-to-head comparisons are needed. These conclusions seem justified.

Authors' objectives
To compare the efficacy of thiazolidinediones on cardiovascular risk factors and glycaemic control in patients with type 2 diabetes.

Searching
MEDLINE, the Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, and the NHS Centre for Reviews and Dissemination's databases were searched from inception to January 2004 for articles published in English; the search terms were not reported. In addition, bibliographic references of all relevant articles, online industry submissions, and recent conference proceedings from the American Diabetes Association were checked.

Study selection
Study designs of evaluations included in the review
Blinded or open, randomised controlled trials (RCTs) were eligible for inclusion. At least 30 participants must have been enrolled in each trial.

Specific interventions included in the review
Studies that compared pioglitazone hydrochloride (30 or 45 mg/day) or rosiglitazone maleate (4 or 8 mg/day) with placebo were eligible for inclusion. Treatment could be provided as monotherapy or in combination with other antidiabetic medication (e.g. sulfonylureas, metformin, or insulin). A minimum treatment duration of 12 weeks was required; the medium duration of treatment was 16 and 26 weeks for the pioglitazone and rosiglitazone trials, respectively.

Participants included in the review
Adults with type 2 diabetes were eligible for inclusion. The participants enrolled in the pioglitazone and rosiglitazone trials were of similar age (56.6 versus 57.5 years) and body mass index (29.3 versus 29.7).

Outcomes assessed in the review
Studies were required to report blood glucose level (HbA1c) to be eligible for inclusion. Fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), total cholesterol, triglyceride, systolic and diastolic blood-pressure, and weight were also collected, but lipids and weight were not a requirement for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened and selected papers for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
The authors did not report what criteria were used to assess methodological quality. No studies were excluded on the basis of methodological quality. Two reviewers independently assessed the primary studies for methodological quality; any disagreements were resolved by consensus.
Data extraction
Two reviewers independently extracted the data from the primary studies; any disagreements were resolved by consensus. The mean change from baseline was reported for each outcome.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. Weighted mean differences and their 95% confidence intervals (CIs) for each outcome variable were pooled across individual trials using a fixed-effect model; where statistically significant heterogeneity was found, a random-effects model was to be used.

How were differences between studies investigated?
Heterogeneity was tested for using the chi-squared test. Sensitivity analyses were assessed using meta-regression models.

Results of the review
Twenty-three RCTs were included: 10 of pioglitazone (n=3,305) and 13 of rosiglitazone (n=5,245).

Blood glucose level.
Pioglitazone, when used as monotherapy, significantly reduced HbA1c levels by -0.99% (95% CI: -1.32, -0.66) at a dose of 30 mg/day and by -1.21% (95% CI: -1.79, -0.62) at 45 mg/day, compared with placebo. When used in combination with other antidiabetic agents, pioglitazone (30 and 45 mg/day) significantly reduced HbA1c levels by -1.16% (95% CI: -1.41, -0.90) and -1.56% (95% CI: -1.96, -1.16), respectively, in comparison with placebo.

Rosiglitazone, when used as monotherapy, significantly reduced HbA1c levels by -0.90% (95% CI: -1.42, -0.38) at a dose of 4 mg/day and by -1.50% (95% CI: -1.75, -1.24) at 8 mg/day. When used in combination with other antidiabetic agents, rosiglitazone (4 and 8 mg/day) significantly reduced HbA1c levels by -1.05% (95% CI: -1.19, -0.90) and -1.26% (95% CI: -1.48, -1.04), respectively, in comparison with placebo.

FBG.
Pioglitazone, when used as monotherapy, significantly reduced FBG concentrations at doses of 30 and 45 mg/day, compared with placebo. When used in combination with other antidiabetic agents, pioglitazone (30 and 45 mg/day) significantly reduced FBG concentrations in comparison with placebo.

Similarly, rosiglitazone, when used as monotherapy, significantly reduced FBG concentrations at a dose of 4 mg/day. When used in combination with other antidiabetic agents, rosiglitazone (4 and 8 mg/day) significantly reduced FBG concentrations in comparison with placebo.

Lipids.
Rosiglitazone, when used as monotherapy or in combination with other antihyperglycaemic agents, significantly increased LDL-C level (15 mg/dL, 0.39 mmol/L). No statistically significant difference was shown for the effect of pioglitazone on LDL-C level (-0.4 mg/dL, -0.01 mmol/L) compared with placebo.

Treatment with rosiglitazone had no statistically significant effect on the fasting plasma triglyceride concentration. Pioglitazone was shown to significantly decrease fasting plasma triglyceride level (-40 mg/dL, 0.45 mmol/L).

Both rosiglitazone and pioglitazone were found to significantly increase the HDL-C concentration, by 2.7 mg/dL (0.07 mmol/L) and 4.55 mg/dL (0.12 mmol/L), respectively.

A significant increase in total cholesterol was shown with rosiglitazone when compared with placebo (21.3 mg/dL, 0.55 mmol/L). Treatment with pioglitazone had no statistically significant effect on total cholesterol level (-0.1 mg/dL).
Blood-pressure.

No significant differences were shown between rosiglitazone and placebo in changes in systolic or diastolic blood-pressure.

Weight.

The average weight gain within 6 months of treatment initiation with thiazolidinediones was 2.7 kg (95% CI: 1.8, 3.7). Significant heterogeneity was found, but sensitivity analyses indicated that drug grouping did not explain this heterogeneity. An average weight gain of 0.73 kg (95% CI: 0.23, 1.23) without statistical heterogeneity was demonstrated in the Japanese trials, compared with an average weight gain of 3.3 kg (95% CI: 2.5, 4.2) with significant statistical heterogeneity in the non-Japanese trials.

Authors' conclusions
Pioglitazone and rosiglitazone had similar effects on measures of glycaemic control and body weight, while pioglitazone demonstrated a more favourable plasma lipid profile. However, head-to-head comparisons are required to determine whether there are differences in efficacy between these two agents.

CRD commentary
The review question was supported by clearly defined inclusion and exclusion criteria. Several electronic databases were searched; however, the restriction to studies reported in English might have resulted in incomplete retrieval of the available dataset, and publication bias was not assessed. Appropriate steps were taken to minimise the potential for bias or error in the study selection, quality assessment and data extraction processes. While the authors stated that methodological quality was assessed, no details of the criteria used or the results of this assessment were given. The statistical analyses were appropriate, and the authors explored some differences in the characteristics of the selected studies. The authors’ conclusions are suitably cautious and appear to follow from the results presented.

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

Research: The authors stated that direct head-to-head comparative trials of pioglitazone and rosiglitazone are needed, as well as longer-term assessments of cardiovascular outcomes.

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