Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials

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CRD summary
The review concluded that use of thiazolidinediones was associated with a higher risk of incident heart failure, severe heart failure and peripheral oedema in patients with or at risk of type 2 diabetes. Potential for language, publication and information biases might limit the reliability of the pooled results.

Authors' objectives
To quantify the risks of heart failure and peripheral oedema with the use of thiazolidinediones (TZDs) in patients with or at risk of developing type 2 diabetes mellitus and explore the differential effects of rosiglitazone and pioglitazone.

Searching
PubMed, EMBASE, Web of Science and Scopus were searched to December 2009 for articles published in English. Search terms were reported. Four relevant conference proceedings were searched for the six years prior to the study. Reference lists of relevant articles and reviews were searched.

Study selection
Placebo-controlled randomised controlled trials (RCTs) that evaluated the effects of TZD treatment on the primary outcome of heart failure in patients with or at high risk of type 2 diabetes were eligible for inclusion. The secondary outcome was peripheral oedema. Trials had to have a sample size greater than 100 patients and a follow-up of at least three months. Trials of active comparators were excluded.

The included trials studied rosiglitazone (2 to 8mg/day) and pioglitazone (7.5 to 45mg/day) in patients with type 2 diabetes, metabolic syndrome, impaired fasting glucose, impaired glucose tolerance and insulin resistance syndrome. Definitions of heart failure varied across trials. Trial duration ranged from 0.25 to 3.25 years. The proportion of male patients ranged from 26% to 89%. Mean age of patients varied from 52.5 to 68.5 years. Most patients were ethnically white.

Abstracts were reviewed independently prior to full text retrieval. The authors did not state how many reviewers carried out the final study selection.

Assessment of study quality
Two reviewers assessed trial quality using Jadad criteria of randomisation, blinding, and description of withdrawals/dropouts to give a score of up to a maximum 5. Trials with a score of 3 or more were considered high quality.

Data extraction
Data were extracted on heart failure and peripheral oedema.

Three reviewers performed data extraction. Disagreements were resolved by consensus.

Methods of synthesis
A Mantel-Haenszel fixed-effect meta-analysis was used to calculate pooled odds ratios (ORs), together with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using $X^2$ and I². Relative risks (RR) were estimated. Sensitivity analysis was assessed using two different models: the Peto fixed-effect model and the DerSimonian and Laird random-effect model.
Subgroup analysis was undertaken on the basis of type of patient and follow-up. Meta-regression was performed to explore the effects of trial characteristics (including type of TZD) on outcomes. The number needed to harm (NNH) was calculated. Publication bias was assessed via funnel plots and Egger's test.

Results of the review
Twenty-nine RCTs (20,254 patients) were included in the review: 18 trials of rosiglitazone (11,756 patients) and 11 trials of pioglitazone (8,498 patients). The quality of the included trials was generally good; only one trial scored less than 3 on the Jadad scale. Trial sample size ranged from 105 to 5,238 patients. Length of follow-up ranged from three to 39 months.

Compared with control, with TZDs there was a statistically significantly greater risk of heart failure (OR 1.59, 95% CI 1.34 to 1.89, I²=0%; 10 trials), severe heart failure (OR 1.47, 95% CI 1.16 to 1.87, I²=0%; 10 RCTs) and peripheral oedema (OR 2.04, 95% CI 1.85 to 2.26, I²=48%; 27 RCTs). There was a higher risk of heart failure with rosiglitazone (OR 2.73, 95% CI 1.46 to 5.10, I²=0%; eight trials) than with pioglitazone (OR 1.51, 95% CI 1.26 to 1.81, I²=0%; two trials). Results using risk ratios and for NNH were presented in the review.

Subgroup analysis indicated no significant differences on the basis of patient type or length of follow-up. Sensitivity analysis with different meta-analysis models showed similar results to the main model. Multivariable meta-regression indicated that baseline risk of heart failure was significantly associated with risk of heart failure (p=0.01). There was evidence of publication bias with the heart failure outcome (Egger's test p<0.0001) and oedema outcome (Egger's test p<0.0001).

Authors' conclusions
Use of TZDs was associated with a higher risk of incident heart failure, severe heart failure and peripheral oedema in patients with or at risk of type 2 diabetes.

CRD commentary
Inclusion criteria for the review were defined clearly. It appeared that a range of relevant data sources were accessed for published and unpublished material. There was potential for language bias, as only articles in English were included. Publication bias was assessed and was detected for both outcomes. Attempts were made to reduce reviewer error and bias throughout quality assessment and data extraction, but the extent to which this was applied to study selection was unclear. Quality assessment was undertaken using a standard checklist, which indicated that the included trials were generally of good quality.

Trials were combined using appropriate statistical methods. Statistical heterogeneity was assessed. The authors noted that heart failure and oedema were not the primary outcomes in the included trials and this may have introduced information bias into the review.

Potential for language, publication and information biases might limit the reliability of the pooled results.

Implications of the review for practice and research
Practice: The authors stated that growing evidence regarding use of TZDs suggested that these should not be used in patients with heart failure. In patients without heart failure, TZDs should be used with caution or be avoided in favour of other antidiabetic drugs with a better risk/benefit profile.

Research: The authors stated that some people could argue that longer-term trials were necessary to observe harmful effects. The authors also strongly suggested calculating NNHs for trials in the context of baseline risk, absolute risk increases and follow-up times.

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