Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

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CRD summary
This review assessed the risk of developing congestive heart failure and cardiac deaths in people with prediabetes or type 2 diabetes who have used thiazolidinediones (TZDs). The authors concluded that the risk of heart failure, but not the rate of cardiovascular death, was higher with TZDs compared with control. The authors’ conclusions seem appropriate although longer term studies are required.

Authors' objectives
To assess the risk of development of heart failure and death from cardiovascular causes in people with prediabetes or type 2 diabetes who have used thiazolidinediones (TZDs).

Searching
MEDLINE, EMBASE, DARE and the Cochrane Library were searched from January 1998 to March 2007 for English language studies; the search terms were provided). In addition, the databases of the European Society of Cardiology, American Heart Association, American College of Cardiology and American Diabetes Association were searched for papers that had not yet been indexed. The bibliographies of retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
Randomised double-blind controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Trials of TZDs were eligible for inclusion. The TZDs used in the included studies were rosiglitazone (4 to 8 mg daily) and pioglitazone (15 to 45 mg daily). The comparators were placebo, glimepiride, metformin with sulfonylurea, glibenclamide and metformin.

Participants included in the review
Trials that included men with prediabetes or type 2 diabetes were eligible for inclusion. All participants in the included studies had prediabetes or type 2 diabetes. The mean age range was 54.7 to 64 years. Eighty-three per cent of the participants were white and 64.8% were male. With the exception of one study where all the participants had stable NYHA class I-II heart failure at baseline, very few participants in the included studies had heart failure at baseline (range: 0 to 2.5%).

Outcomes assessed in the review
Trials reporting risk or frequency data for congestive heart failure (CHF) and cardiovascular death were eligible for inclusion. The definition of CHF varied between the included studies, though most used investigator-reported or adjudicated events requiring admission to hospital. Data on heart failure events not requiring admission to hospital were excluded. The mean length of follow-up in the included studies was 29.7 months (range: 12 to 48).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that quality was assessed on the basis of risk of selection bias (incorporation of age, gender and cardiac disease history in risk estimates), attrition bias (loss-event ratio of less than 10%) and detection bias. Two
investigators independently extracted the data and, presumably, the quality assessment was conducted likewise. Any discrepancies were resolved through discussion.

Data extraction
Two researchers independently extracted the data and any discrepancies were resolved through discussion. The number of events of interest in the intervention and comparison groups was extracted and the relative risk (RR) and 95% confidence interval (CI) calculated. In the trial using two control groups (metformin and glibenclamide) these were collapsed into one control group.

Methods of synthesis
How were the studies combined?
The trials were pooled using a fixed-effect meta-analysis; if statistical heterogeneity was detected they were then pooled using a random-effects model. Egger's and Begg's tests were used to investigate potential publication bias.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the I-squared test. In addition to pooling all trials, rosiglitazone and pioglitazone were also pooled separately. Meta-regression analysis was used to investigate the influence of type of control used, and several sensitivity analyses were conducted.

Results of the review
Seven double-blind RCTs (n=20,191) were included.

There were 360 CHF events. There was an increased risk of CHF with TZD compared with control (RR 1.72, 95% CI: 1.21, 2.42, p=0.002). Statistical heterogeneity was very low (I-squared 23%). There was an increased risk of heart failure compared with control for both rosiglitazone (RR 2.18, 95% CI: 1.44, 3.32, p=0.0003; 5 studies) and pioglitazone (RR 1.32, 95% CI: 1.04, 1.68, p=0.02; 2 studies). The risk of cardiovascular death was not significantly increased for TZD compared with control, nor for rosiglitazone and pioglitazone compared with control. The findings were not altered by sensitivity analyses that excluded trials with specific characteristics.

Authors' conclusions
In patients with prediabetes or type 2 diabetes, the risk of CHF was higher in patients given TZDs than controls, though these patients did not have a higher rate of cardiovascular death. CHF in patients given TZDs might not carry the risk that is usually associated with CHF caused by progressive systolic or diastolic dysfunction of the left ventricle.

CRD commentary
There was a clearly stated review question and several appropriate sources were searched for trials. However, there is a risk that relevant studies were missed as only English language studies were included and unpublished studies were not specifically sought. Funnel plots suggested that there may be publication bias, though given the small number of studies these were difficult to interpret. Study quality was assessed but not reported, apart from the fact that the studies were double-blind. Appropriate methods were used to reduce error and bias in the data extraction, though it was unclear whether similar processes were used at the study selection stage.

The analyses seemed appropriate and both statistical and clinical heterogeneity were investigated. Stratified analyses were presented for two TZDs; however, as the authors pointed out, there were insufficient data to assess whether the risk of heart failure differed between the two drugs. The authors' conclusions seem reasonable given the evidence presented, though the interpretation that CHF associated with TZDs might not carry the same risks as heart failure caused by progressive left ventricle dysfunction requires further investigation.

Implications of the review for practice and research
Practice: TZDs should not be used for glycaemic control in patients with heart failure and should be used cautiously in patients with cardiovascular disease who do not have heart failure. Where patients have type 2 diabetes without cardiovascular disease and a low absolute risk of CHF, the use of TZDs should be weighed against the risks and benefits of alternative medications for diabetes.

Research: Trials that have longer follow-up, and that investigate the effect of TZDs on overall cardiovascular outcome and whether congestive heart failure should be regarded as an adverse effect of TZDs or a cardiovascular end point, are required.

Bibliographic details

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Other publications of related interest

This additional published commentary may also be of interest. Eurich DT, Majumdar SR. Review: thiazolidinediones increase congestive heart failure but not cardiovascular deaths in prediabetes or type 2 diabetes. ACP J Club 2008;148:39.

Indexing Status
Subject indexing assigned by NLM

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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.