Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis

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CRD summary
This review concluded that intensive glycaemic control did not reduce the occurrence of heart failure-related events in patients with type 2 diabetes mellitus; intensive glycaemic control therapy with thiazolidinediones increased the risk of heart failure. Limitations in the search strategy (possible missed trials) and variation between the included trials mean that these conclusions should be interpreted cautiously.

Authors' objectives
To assess the effect of more intensive glycaemic control on the risk of heart failure in patients with type 2 diabetes mellitus.

Searching
PubMed, the Cochrane Register of Controlled Trials (CENTRAL), metaRegister of Controlled Trials, and CINAHL were searched from January 1970 to October 2010 for studies published in English; search terms were reported. Bibliographies of original articles, reviews, textbook chapters, and practice guidelines were screened for additional studies. Experts in the field and pharmaceutical firms were contacted to identify uncompleted, unpublished, or missed studies.

Study selection
Randomised controlled trials (RCTs) that compared an intensive glucose control strategy with conventional treatment in adult patients (19 years or over) with type 2 diabetes mellitus were eligible for inclusion. Trials where other populations were enrolled were included if separate outcome data could be extracted for patients with type 2 diabetes mellitus. Trials were required to report glycated haemoglobin (HbA1c) data for all treatments groups, follow up participants for at least two years, report heart failure-related outcomes, and use intention-to-treat analyses. Trials were excluded if they had an equivocal treatment allocation process, loss to clinical follow-up of 20% or over in any trial arms, a short-term setting, or enrolment of clinically unstable patients.

Included trials were published from 1997 to 2009. Most participants were male (61%) and Caucasian. The overall mean age of participants was 62 years; most were overweight (mean body mass index was 30kg/m²). With the exception of one trial (UKPDS) of patients with newly diagnosed type 2 diabetes mellitus, the weighted mean diabetes duration was eight years. Almost half (46%) of participants reported previous cardiovascular events. One trial (PROactive) included only participants with evidence of extensive macrovascular disease. All trials excluded patients with severe symptoms of heart failure. Intensive therapy groups varied and were usually treated with multiple interventions. Standard therapy groups were treated with insulin once daily, standard diet, metformin, sulphonylureas, placebo, or the same drugs as the intensive therapy groups but with different doses or treatment goals.

Two reviewers screened studies for inclusion; disagreements were resolved by consensus amongst the authors.

Assessment of study quality
Methodological characteristics of each trial (such as study design, random allocation procedures, and end point assessment) were critically appraised.

Two reviewers independently assessed study quality; disagreements were resolved by consultation with a third reviewer.

Data extraction
Data were extracted on the definition of a heart failure event used by each trial, the number of heart failure-related events (both fatal and nonfatal) in each treatment group.

Approximate absolute event rates were calculated by dividing the number of events in each group by the number of
person-years. Odds ratios (ORs) for heart failure-related events, with 95% confidence intervals (CIs), were calculated for each trial. Changes in glycated haemoglobin concentration and body weight between the intensive and standard therapy groups were also extracted. Two trials, which shared a common standard therapy group, were analysed as one to avoid double counting.

Data were independently extracted by two reviewers using a standardised form. Disagreements were resolved by consultation with a third reviewer.

**Methods of synthesis**

Pooled odds ratios, with 95% confidence intervals, were calculated for heart failure-related events using a DerSimonian and Laird random-effects model, weighted by sample size. Between-trial heterogeneity was assessed using $\chi^2$, $I^2$ and L'Abbe plots.

A subgroup analysis was performed to investigate the effect of high versus low use of thiazolidinediones for achievement of strict glycaemic control on the risk of heart failure-related events. A sensitivity analysis was conducted which included only studies specifically designed to compare intensive and standard treatments.

Publication bias was assessed using Funnel plots and Egger's test.

**Results of the review**

Seven RCTs (reported in eight articles) with 37,229 participants (range 153 to 11,140) were included in the review; 19,562 participants were randomised to intensive therapy and 17,667 were randomised to standard therapy. One trial was double blind and six were open label. The mean length of follow-up ranged from 2.3 to 10.1 years.

There were 1,469 episodes of heart failure (107 fatal) across all the included trials. Event rates per 1,000 person years of follow-up ranged from 2.9 to 27.7 in the intensive therapy groups and from 2.4 to 20.0 in standard therapy groups.

Meta-analysis showed no significant difference in the occurrence of heart failure between the intensive and standard therapy groups (OR 1.20, 95% CI 0.96 to 1.48; $I^2=69\%$).

The sensitivity analysis of trials specifically designed to compare intensive and standard therapy gave similar results.

Subgroup analyses showed no effect on heart failure where the glucose lowering regime involved low thiazolidinedione use, but high thiazolidinedione use was associated with slightly increased heart failure (OR 1.33, 95% CI 1.02 to 1.72; $I^2=69\%$; four RCTs) compared with standard glycaemic control.

Data on the mean difference in glycated haemoglobin concentration and body weight between intensive and standard therapy groups were also reported.

There was no evidence of publication bias.

**Authors' conclusions**

The use of intensive glycaemic control therapy did not reduce the occurrence of heart failure-related events in patients with type 2 diabetes mellitus. Intensive glycaemic control therapy using thiazolidinediones increased the risk of heart failure.

**CRD commentary**

The review addressed a clearly stated research question, which was defined by appropriate inclusion criteria. A number of sources were searched for relevant studies, but the restriction to English language trials raised the possibility of language bias. Although the authors reported no evidence of publication bias, the assessment (including less than 10 trials) meant that its reliability was questionable, so relevant studies may have been omitted. Measures to minimise error and bias were applied throughout the review process.

Some details of study design were extracted and reported, but this did not comprise a formal quality assessment. These details were not incorporated into the reporting of results, so it was not possible to assess the potential effects of primary trial quality on the findings of the review. The calculation of pooled estimates of treatment effect was of
questionable value, given the high levels of between trial heterogeneity observed (such as differences between treatment and control groups, and the comorbidities present).

The authors’ conclusions reflect the data presented, but should be interpreted cautiously given the limitations outlined.

Implications of the review for practice and research
The authors did not specify any recommendations for clinical practice or research.

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