Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis

CRD summary
This review compared the effects of intensive glucose control over conventional glucose control on cardiovascular outcomes of patients with type 2 diabetes, and found it could reduce the risk of major cardiovascular events, but increased the risk of severe hypoglycaemia. Overall, the conclusions appeared to reflect the results presented, but limitations with the review suggest caution is warranted.

Authors' objectives
To focus on the effects of intensive glucose control versus conventional glucose control on cardiovascular events in patients with type 2 diabetes.

Searching
MEDLINE, EMBASE and the Cochrane Register of Controlled Trials (CENTRAL) were searched for relevant studies. Language restrictions, date range and search terms were not reported. Reference lists of identified studies, previous reviews, and other original studies identified by electronic searching were scanned for further relevant articles.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the effects of intensive glucose control versus conventional glucose control on cardiovascular events in patients with type 2 diabetes.

The primary outcome was a composite endpoint of major cardiovascular events (including cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Secondary endpoints included the individual components of the composite endpoint, as well as all-cause mortality and heart failure.

In included trials, average age of patients ranged from 53 to 66 years; the duration of diabetes ranged from 0 to 10 years. Glycated haemoglobin (HbA1c) targets were below 6%, below 6.5%, or below 6.0mmol/L in the intensive glucose control groups.

It was unclear how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they performed a quality assessment.

Data extraction
Data required to calculate the relative risks (RRs), with 95% confidence intervals (CIs), for the primary endpoint (a composite endpoint combining cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) and secondary endpoints were extracted.

It was unclear how many reviewers performed data extraction.

Methods of synthesis
Relative risks, with 95% confidence intervals, were pooled using either a fixed-effect or random-effects model depending on the results of an I² test to assess statistical heterogeneity (fixed-effect was used if I² was less than 50%).

Publication bias was assessed using funnel plots and the Begg's and Egger's tests.

Results of the review
Seven trials were included in the review (n=34,144 patients, range 153 to 11,140). Five trials were described as double-blinded; two trials were open-label. Follow-up length ranged from 2.25 to 10.7 years.

Pooled results (based on seven trials) indicated that intensive glucose control was associated with statistically significant decreases in the risk of major cardiovascular events (RR 0.90, 95% CI 0.85 to 0.96; $I^2=34\%$) and non-fatal myocardial infarction (RR 0.84, 95% CI 0.76 to 0.93; $I^2=0\%$) compared with the conventional therapy group, but not for the risk of cardiovascular mortality, non-fatal stroke, all-cause mortality, and heart failure. However, pooled results also indicated that intensive glucose control was associated with a statistically significant and substantial increase in the risk of severe hypoglycaemia (RR 2.30, 95% CI 1.74 to 3.03; six trials; $I^2=59\%$) compared with the conventional therapy group.

Statistically significant heterogeneity was identified for the severe hypoglycaemia outcome, so a random-effects model was used to pool this result; there was no evidence of statistically significant heterogeneity for the other outcomes.

Funnel plots and the Begg's and Egger's tests for asymmetry were not statistically significant.

**Authors' conclusions**

Intensive glucose control strategies could effectively reduce the risk of major cardiovascular events, but significantly increased the risk of severe hypoglycaemia in patients with type 2 diabetes.

**CRD commentary**

The review question and study selection criteria were somewhat unclear. Although the search appeared to be fairly comprehensive, language restrictions and the date range were not reported. The number of reviewers who performed the study selection and data extraction was not clear, reducing review transparency and increasing the risk of reviewer error and bias at these stages.

No study quality assessment was reported, although some trial quality details were reported; most of the trials included were described as double-blinded. Sufficient primary study details were provided. The results were clearly reported. The synthesis appeared appropriate. The authors concluded that the intensive glucose control intervention reduced the risk of major cardiovascular events, although the main contribution to this was the reduction in non-fatal myocardial infarction, so considering only the composite endpoint may be misleading.

The conclusions appeared to reflect the results presented, but lack of quality assessment and poor reporting of the review processes mean some caution is warranted in interpreting the results.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors recommended that further large randomised controlled trials are warranted to identify the subgroups of patients who would benefit most from glucose control in terms of reducing cardiovascular risks with fewer adverse events, to define the best glycated haemoglobin target for various groups, and to test the efficacy of multifactorial intervention strategies for diabetic patients with various co-morbid conditions.

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**Bibliographic details**

Record Status
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.