Intensive glycemic control and macrovascular events in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

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CRD summary
The review concluded that intensive glycaemic control significantly reduced major macrovascular events in type 2 diabetes versus conventional glucose control, but did not significantly reduce mortality from all causes or cardiovascular death. The evidence presented was strong, but potential limitations in the review process make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To compare the efficacy of intensive glycaemic control versus conventional glucose control in reducing macrovascular events in type 2 diabetes.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library and SciELO were searched to January 2009; search terms were not reported. Bibliographies of retrieved articles and abstracts of major relevant conferences were handsearched.

Study selection
Randomised controlled trials (RCTs) of patients with type 2 diabetes mellitus that measured glucose control level by measuring glycated haemoglobin A, C (HbA\textsubscript{1C}) were eligible for inclusion. The intervention needed to be an intensive glucose control strategy that targeted a HbA\textsubscript{1C} level of less than 7% and where controls did not require HbA\textsubscript{1C} to be strictly lower than 7%. The medication used for glucose control in intervention and control groups could be oral agents, insulin and multiple cardiovascular interventions. Primary outcomes were incidence of major macrovascular events, death from any cause and incidence of cardiovascular death.

There were three very large studies, one of which was based in 215 collaborating centres in 20 countries. Intensive treatment interventions included stepwise hypoglycaemic agents and multiple injection therapy combined with intensive glucose monitoring. Control groups used fewer insulin injections, half-maximal doses of hypoglycaemic agents or diet. One large study provided separate data for a sulphonyl-urea insulin group of patients and a metformin group; both were compared to conventional treatment. Mean duration of diabetes in patients, where reported, ranged from 7.9 to 11.5 years. Mean age was heterogeneous (no details reported). Mean baseline HbA\textsubscript{1C} ranged from 3.5% to 9.3% in the intervention group and 7.5% to 9.5% in the control group.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using a method similar to the standard Jadad scale. Disagreements were resolved by discussion. Criteria used included randomisation, allocation concealment and blinding. Trials were considered to have high risk of bias where one or more criteria were inadequate or unclear.

Data extraction
Numbers of events for each outcome were extracted to enable calculation of relative risk (RR) and 95% confidence intervals (CI).

The authors reported that two independent reviewers performed data extraction using a specially developed form.

Methods of synthesis
Relative risks were initially pooled using a random-effects model as heterogeneity was expected; a fixed-effect model
was used where no significant heterogeneity was found. Between-study heterogeneity was determined using $\chi^2$ and $I^2$.

Publication bias was assessed visually using funnel plots. Sensitivity analyses were performed on the effect of omitting smaller studies from the analysis.

**Results of the review**

Six RCTs were identified (n=28,065 participants, range 110 to 11,140). There were three very large studies with more than 4,500 participants. The four largest studies were of high quality (adequate randomisation, allocation and blinding). The smallest study did not meet any of the three quality criteria and the next smallest study did not meet the criterion for allocation. Mean follow-up ranged from 7.5 to 17.7 years. One large study provided two different sets of data. At the end of treatment, mean HbA1C ranged from 6.5% to 7.2% in the intervention group and 7.3% to 9.4% in the control group.

There was a significantly lower incidence of macrovascular events in the intensive glucose control group compared to controls (RR 0.92, 95% CI 0.87 to 0.98, $I^2=0\%$, fixed-effect model; seven study groups). The effect did not change when the two smallest studies were removed from the analysis.

Intensive glucose control was not associated with a significant decrease in mortality (RR 0.95, 95% CI 0.80 to 1.12, $I^2=66.7\%$, random-effects model; seven study groups) and had no significant effect on incidence of cardiovascular death (RR 1.10, 95% CI 0.79 to 1.53, $I^2=65.2\%$, random-effects model; five studies).

A funnel plot for macrovascular events showed no evidence of publication bias.

**Authors’ conclusions**

Control of glycaemia to normal (or near normal) levels in type 2 diabetes appeared to be effective in reducing the incidence of major macrovascular events. There were no significant differences in mortality from any cause and from cardiovascular death between the two glycaemia-control strategies.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched and efforts were made to identify unpublished studies. It was not clear whether language restrictions were applied and some studies may have been missed. Funnel plot analysis found no evidence of publication bias, but few studies were identified. Study quality was assessed using suitable criteria. Efforts were made to reduce error and bias in validity assessment and data extraction; the authors did not report whether this process also applied to study selection.

There were some differences between data in the tables and text (for example, final mean HbA1C levels). Baseline mean HbA1C levels reported in Table 1 were within the normal range or lower for the intervention group in three studies. The apparent differences in mean baseline HbA1C level between intervention and control groups were not highlighted and/or explained and were a source of concern. Some relevant study details were reported. No details of patient age or loss to follow-up were reported and there was little data relevant to the interventions used. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis seemed appropriate. A sensitivity analysis was performed.

Although the evidence presented was strong, potential limitations in the review process make the reliability of the authors’ conclusions unclear.

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

**Practice:** The authors highlighted the risk of hypoglycaemia with an intensive treatment control strategy, such as an ACCORD strategy (see Other Publications of Related Interest). They concluded that glycaemia-lowering strategies should be carefully considered including choice of glycaemic agents and mode of reducing HbA1C related to baseline patient characteristics.

**Research:** The authors recommended further studies of the effects of specific medications on HbA1C in type 2 diabetes and highlighted one ongoing study.
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