Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials


CRD summary
This well-conducted systematic review determined the efficacy of improved long-term glycaemic control on macrovascular disease in diabetes mellitus (DM). The authors' conclusion, that attempts to improve glycaemic control reduced the incidence of macrovascular complications in types 1 and 2 DM, is likely to be reliable, although applicability to other populations (i.e. elderly patients and patients with longer duration of DM) is questionable, as the authors acknowledged.

Authors' objectives
To determine the efficacy of improved long-term glycaemic control on macrovascular disease in patients with types 1 and 2 diabetes mellitus (DM).

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched for relevant papers unrestricted by language; the search dates and terms were not provided. Additional studies were located through searches of reference lists, reviews, relevant book chapters, conference abstracts (unspecified) and specialist journals (unspecified).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up period of at least 2 years were eligible for inclusion in the review.

Specific interventions included in the review
Studies of interventions to improve glycaemic control compared with conventional treatment were eligible for inclusion. Eligible interventions included one or more of the following: subcutaneous insulin injections, insulin pump and oral antidiabetic agents. Interventions reported in the review also included blood glucose self-monitoring (normal or intensified). Conventional treatment in the type 1 diabetes studies used one to three insulin injections with or without occasional blood glucose monitoring; conventional treatment in the type 2 diabetes studies used a reduced number of insulin injections or treatment with hypoglycaemic agents or diet alone, with less intensive blood glucose monitoring.

Participants included in the review
Studies of patients with types 1 and 2 DM were eligible for inclusion. The mean ages of the participants ranged from 26.5 to 60.2 years, and the mean duration of DM ranged from less than 1 year to 20 years. The proportion of female participants ranged from 0 to 54%, although most studies had between 40 and 54%.

Outcomes assessed in the review
Studies that prospectively recorded macrovascular events were eligible for inclusion. Macrovascular end points included cardiac events, stroke and peripheral vascular disease. Primary outcomes included the incidence of fatal or nonfatal macrovascular events of any type, whilst secondary outcomes included fatal or nonfatal cardiac events, stroke, peripheral arterial disease and macrovascular deaths. Further details and definitions of eligible end points were reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected papers for inclusion in the review; any disagreements were resolved by consultation with a third reviewer.
Assessment of study quality
The quality of the primary studies was assessed using the following criteria: adequacy of allocation concealment, blinding of the care providers and outcome assessors, and loss to follow-up. Two reviewers independently assessed the methodological quality of the primary studies; any disagreements were resolved by consultation with a third reviewer.

Data extraction
Two reviewers independently extracted the data from the primary studies; any disagreements were resolved by consultation with a third reviewer. The authors of the primary studies were sent a standardised form on which to check the data that had been extracted and, where necessary, they were asked to provide further information. In addition to the standard data extraction, information on the distribution of cardiac risk factors at study end was extracted, and the incident rate ratio (IRR) with 95% confidence intervals (CIs) was calculated for each comparison end point. Studies with zero events in both intervention and control groups were excluded from the meta-analysis; those studies with zero events in one group were analysed by adding 0.5 to all cells in the 2x2 tables.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a fixed-effect model for each outcome grouped by type 1 or type 2 DM. Summary estimates were presented as IRRs with 95% CIs. The number-needed-to-treat (NNT) to prevent one macrovascular event was calculated. Publication bias for all end points was assessed using funnel plots.

How were differences between studies investigated?
Statistical variation across the studies was assessed using the I-squared statistic. Analyses were repeated in sensitivity analyses using a random-effect model. Univariate regression models were used to investigate the following variables: effect of reduction in glycosylated haemoglobin (HbA1c); duration of DM; mean age at baseline; proportion of women; year study began; year study reported; and study quality.

Results of the review
Ten studies, reporting 14 comparisons, were included in the meta-analysis. Seven studies, including 8 comparisons (n=1,800), were in patients with type 1 DM; 3 studies, including 6 comparisons (n=4,472), were in patients with type 2 DM. Nine comparisons were performed in Europe, three in North America and two in Asia.

Quality.
Eight comparisons reported adequate allocation concealment. The degree of blinding in 7 comparisons was unclear. An intention-to-treat analysis was carried out in 11 comparisons.

Macrovascular events and mortality.
A total of 134 events (of any type) was recorded in type 1 DM, whilst a total of 1,587 events (of any type) was recorded in type 2 DM. Intensive glycaemic control was associated with a risk reduction in macrovascular events in both type 1 DM (IRR 0.38, 95% CI: 0.26, 0.56; based on 8 comparisons) and type 2 DM (IRR 0.81, 95% CI 0.73, 0.91; based on 6 comparisons) compared with conventional treatment. A substantial amount of variance across studies was found for type 2 DM. The NNT for 10 years to prevent one macrovascular event was 16 for type 1 DM, 14 for type 2 DM low risk and 7 for type 2 DM high risk.

Cardiac events. A total of 40 cardiac events was recorded in type 1 DM, whilst a total of 1,197 cardiac events was recorded in type 2 DM. A risk reduction was found in both type 1 DM (IRR 0.41, 95% CI: 0.19, 0.87; based on 7 comparisons) and type 2 DM (IRR 0.91, 95% CI: 0.80, 1.03; based on 6 comparisons) compared with conventional treatment, although this was not statistically significant in the latter.

Peripheral vascular events.
Totals of 88 and 87 events were recorded in types 1 and 2 DM, respectively. A risk reduction was found in both type 1
DM (IRR 0.39, 95% CI: 0.25, 0.62; based on 4 comparisons) and type 2 DM (IRR 0.58, 95% CI: 0.38, 0.89; based on 6 comparisons) compared with conventional treatment.

Strokes.

A total of 6 strokes was recorded in type 1 DM, whilst a total of 303 strokes was recorded in type 2 DM. A risk reduction was found in both type 1 DM (IRR 0.34, 95% CI: 0.05, 2.57; based on 2 comparisons) and type 2 DM (IRR 0.58, 95% CI: 0.46, 0.74; based on 6 comparisons) compared with conventional treatment, although this was not statistically significant in the former. A substantial amount of variance across studies was found for type 2 DM.

Studies that achieved a greater reduction in HbA1c demonstrated a greater reduction in risk for macrovascular events in type 1 DM; no interaction was found in type 2 DM. The beneficial effect of improved glycaemic control reduced with longer diabetes duration in type 2 DM. A reduction in the beneficial effect of improved glycaemic control in older age was shown in both type 1 DM and type 2 DM, although this was not statistically significant in the former. No statistically significant interaction of gender, year study began, year study was published, or study quality was found. There was no evidence of publication bias.

Authors' conclusions
Attempts to improve glycaemic control reduced the incidence of macrovascular complications in types 1 and 2 DM, although in patients with type 2 DM this was associated with a more modest reduction in cardiac events.

CRD commentary
The review question was supported by clear inclusion criteria. The search strategy was not restricted by language and publications bias was assessed. Attempts were made to prevent bias and error during the study selection, quality assessment and data extraction processes. The studies appear to have been combined appropriately, heterogeneity was assessed, and attempts were made to evaluate differences between the studies. Overall, this was a well-conducted systematic review and the authors' conclusions are likely to be reliable. The authors acknowledged that generalisability to other populations (i.e. elderly patients and patients with longer durations of DM) is questionable.

Implications of the review for practice and research
Practice: The authors stated that glycaemic control is an essential strategy leading to reductions in microvascular and macrovascular complications in type 1 DM, but that a broader treatment strategy is needed for the prevention of cardiac events in type 2 DM.

Research: The authors stated that ongoing studies, including a large ACCORD trial, would help to define the benefits and risks of improved glycaemic control in type 2 DM.

Funding
Novo Nordisk; Roche Diagnostics; Glaxo Smith Kline.

Bibliographic details

PubMedID
16824829

DOI
10.1016/j.ahj.2005.09.015
**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Blood Glucose /analysis; Comorbidity; Coronary Disease /epidemiology; Diabetes Mellitus, Type 1 /blood /drug therapy; Diabetes Mellitus, Type 2 /blood /drug therapy; Diabetic Angiopathies /blood /epidemiology /prevention & control; Female; Hemoglobin A, Glycosylated /analysis; Humans; Incidence; Male; Peripheral Vascular Diseases /blood /epidemiology; Postprandial Period; Randomized Controlled Trials as Topic; Risk Factors; Stroke /blood /epidemiology; Treatment Outcome

**AccessionNumber**
12006003698

**Date bibliographic record published**
30/06/2007

**Date abstract record published**
30/06/2007

**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.