Systematic review: glucose control and cardiovascular disease in type 2 diabetes

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CRD summary
This review found that intensive glucose control reduced the risk for some cardiovascular disease outcomes in patients with type 2 diabetes (e.g. non-fatal myocardial infarction), but did not reduce the risk for cardiovascular death or all-cause mortality, and increased the risk for severe hypoglycaemia. As some participants were double-counted in the analyses, the authors’ conclusions should be viewed with caution.

Authors' objectives
To evaluate the benefits and harms of intensive versus conventional glucose control for adults with type 2 diabetes.

Searching
MEDLINE was searched without language restrictions (January 1950 to April 2009), with a randomised controlled trial (RCT) search filter. Search terms were reported. Reference lists were also searched and experts were contacted.

Study selection
RCTs of adults (19 years or older) with type 2 diabetes were eligible for inclusion, if they compared an intensive glucose control group with a conventional treatment group (with a priori specification of glycaemic goals for both groups). Clinical cardiovascular disease needed to be the primary end-point and the sample size had to be at least 500 patients.

The included patients had a mean age ranging from 53 to 66 years and were 47 to 97% male. The majority of patients in the included studies were white and had a mean duration of diabetes of 0 to 11.5 years. Aspirin was used by 2 to 55% of patients, where reported, and the median duration of intervention ranged from 3.4 to 10.7 years. Mean baseline body mass index ranged from 28 to 32kg/m². The intensive glucose treatments were: sulfonylurea or insulin; metformin; hypoglycaemic agents plus other drugs; gliclazide plus other drugs; and metformin plus rosiglitazone or insulin. The comparators were diet with or without pharmacological treatment, current therapy (if gliclazide was being taken this was substituted with another sulfonylurea), or glimepiride plus rosiglitazone or insulin.

Two reviewers independently selected studies and disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed for randomisation procedures, blinded assessment of outcomes, adjudication procedures for outcomes and follow-up. The number of reviewers that assessed validity was not reported.

Data extraction
The main outcomes were: number of clinical cardiovascular disease, coronary heart disease, stroke and chronic heart failure events; cardiovascular deaths; and all-cause mortality. Non-fatal myocardial infarction, fatal myocardial infarction, fatal stroke, non-fatal stroke, peripheral artery disease and severe hypoglycaemic events were also reported. Relative risks (RRs) and risk differences (RDs) and corresponding 95% confidence intervals (CIs) were calculated.

Data were extracted independently by two reviewers.

Methods of synthesis
RRs and RDs (per 1000 patients over five years of treatment) were pooled using fixed-effect and DerSimonian and Laird random-effects models. Due to between study heterogeneity, only the results of the random-effects model were presented. Statistical heterogeneity was assessed using the DerSimonian and Laird Q test and I² statistic. Subgroup analysis was used to examine the effect of intensive glucose control on all study outcomes. RRs for outcomes in early versus more recent trials were also compared.
Results of the review
Five RCTs were included in the review (27,802 patients). Study size ranged from 753 to 11,140 participants. All of them reported the blinded outcome assessment and independent adjudication for outcomes. All RCTs also reported intention-to-treat analysis and had a randomised open-label design. Follow-up rates varied from 85.5 to 99.8%.

**Disease**: Intensive glucose control was associated with reduced risk of cardiovascular disease (relative risk 0.90, 95% CI: 0.83 to 0.98; risk difference -15, 95% CI: -24 to -5; five RCTs) and chronic heart disease (relative risk 0.89, 95% CI: 0.81 to 0.96; risk difference -11, 95% CI: -7 to -5; five RCTs) compared with conventional treatment. Subgroup analyses of early versus more recent trials showed similar results. No significant statistical heterogeneity was found.

**Mortality**: Intensive glucose control had no significant effect on cardiovascular mortality or all-cause mortality compared with conventional treatment, but there was significant heterogeneity between results of the subgroup analyses; p values for heterogeneity between subgroups were 0.095 (cardiovascular) and 0.105 (all-cause). Early trials (two RCTs) showed non-statistically significant protective effects of intensive glucose control on cardiovascular and all-cause mortality, whereas later trials (three RCTs) indicated non-significant increased risks for these outcomes.

**Other outcomes**: Intensive glucose control had no significant effect on overall risk of stroke or chronic heart failure compared with conventional treatment (no significant statistical heterogeneity found). It was associated with a 16% reduced risk of non-fatal myocardial infarction (five RCTs) and absolute risk reductions of nine events per 1000 patients over five years of treatment in overall and subgroup analyses. No association was found between intensive glucose control and fatal myocardial infarction (five RCTs), non-fatal stroke (five RCTs), fatal stroke (five RCTs) or peripheral artery disease (four RCTs).

**Hypoglycaemia**: Intensive glucose control was associated with a two-fold increase in severe hypoglycaemia (an absolute increase of 39 events per 1000 patients). Evidence of statistical heterogeneity was found (p<0.001, I²=85.4%). In subgroup analyses there was no association between intensive glucose control and severe hypoglycaemia in the early trials (two RCTs) and a 2.5-fold increase in the more recent trials (absolute increase of 54 events per 1000 patients over five years; three RCTs).

Sensitivity analyses reported similar results and did not substantially alter the main findings.

Authors' conclusions
Intensive glucose control reduced the risk for some cardiovascular disease outcomes (such as non-fatal myocardial infarction), did not reduce the risk for cardiovascular death or all-cause mortality, and increased the risk for severe hypoglycaemia.

CRD commentary
The review question was supported by clear inclusion criteria for participants, intervention, outcomes and study design. The search was limited to only one database. No language restrictions were applied, reducing the possibility of language bias in this database. Limited efforts to retrieve unpublished data were reported, which may have reduced the possibility of publication bias. Study selection and data extraction were performed in duplicate, reducing the risk of error and bias. It was not clear how many reviewers were involved in validity assessment.

Data were pooled in meta-analyses which seemed to be appropriate as statistical and clinical heterogeneity were assessed and taken into consideration. Statistical heterogeneity remained present for some outcomes, suggesting other sources of variation. Reporting of intensive and comparator treatments were unclear for one study. Though language and publication bias cannot be ruled out this appeared to be a reasonably well-conducted review.

A correction has been published, which stated that one trial was a substudy of another included trial and 411 patients were double-counted. Caution should be used when interpreting the authors' conclusions.

Implications of the review for practice and research
**Practice**: The authors stated that health care providers should focus their efforts on combining elements of lifestyle modification, glucose control that minimises hypoglycaemia, blood pressure reduction, and lipid lowering, to optimally
curtail the risk of cardiovascular disease in patients with type 2 diabetes.

**Research:** The authors stated that more research was needed to distinguish between the effects of insulin-sensitisation agents, such as thiazolidinediones and metformin.

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