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Prevention of cardiovascular disease through glycemic control in type 2 diabetes: A meta-analysis of randomized clinical trials

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Abstract *Background and aims:* Randomized clinical trials (RCTs) aimed at the assessment of the efficacy of lowering blood glucose in the prevention of diabetic complications have always failed to detect a significant effect on cardiovascular events. Aim of this meta-analysis is the assessment of the effects of improvement of glycemic control on the incidence of cardiovascular diseases in patients with type 2 diabetes.
Methods: The RCTs were included in this meta-analysis if: a) the between-group difference in mean HbA1c during the trial was at least 0.5%, b) they had a planned duration of treatment of at least 3 years, c) if they had a cardiovascular endpoint. Data for analysis were extracted independently by two observers and potential contrasts were resolved by a senior investigator.
Results: Five studies (17,267 and 15,362 patients in the intensive and conventional therapy groups, respectively) were included. Intensive treatment, which reduced mean HbA1c by 0.9% on average, was associated with a significant reduction of incident cardiovascular events and myocardial infarction (OR 0.89 [0.83—0.95] and 0.86 [0.78—0.93], respectively), but not of stroke or cardiovascular mortality (OR 0.93 [0.81—1.07] and 0.98 [0.77—1.23], respectively). In meta-regression analysis, a higher BMI duration of diabetes, and incidence of severe hypoglycaemia were associated with greater risk for cardiovascular death in intensive treatment groups.
Conclusion: Intensified hypoglycaemic treatment in type 2 diabetic patients leads to a significant reduction of the incidence of myocardial infarction, while it does not affect the incidence of stroke and cardiovascular mortality. Hypoglycemia induced by intensified treatment could be associated with increased cardiovascular mortality.

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Introduction

Type 1 and type 2 diabetes are associated with increased cardiovascular risk [1]. Furthermore, among diabetic patients, those with higher blood glucose and glycated hemoglobin (HbA1c) show a greater incidence of major cardiovascular events [2]. In type 1 diabetes, follow-up data from a large randomized clinical trial suggest that the improvement of metabolic control, obtained through intensive insulin treatment, can prevent cardiovascular disease in the long term [3]; similar results have been obtained in the long-term follow-up of the UK Prospective Diabetes Study (UKPDS), performed in type 2 diabetic patients [4]. Conversely, in type 2 diabetes, trials aimed at the assessment of the efficacy of lowering blood glucose in the prevention of micro- and macrovascular complications have always failed to detect a significant effect on cardiovascular events [5—7]; the only partial exception is represented by the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) [8], which showed a significant reduction of the incidence of some cardiovascular diseases, although it failed to reach the principal composite endpoint (death or major nonfatal cardiovascular events) for which it had been designed.

The negative results of those trials could have been determined by an insufficient sample size. In fact, the extent of risk reduction induced by lowering of HbA1c, as estimated by epidemiological studies [2], appears to be rather small; therefore, even large-scale trials could have had an insufficient statistical power to detect the effects of treatments. It should be considered that two of the largest trials [5,7] were designed for a composite endpoint which included microvascular complications, and were therefore undersized for cardiovascular diseases as a separate endpoint; furthermore, another large trial [6], which was specifically designed for cardiovascular outcomes, had to be prematurely terminated because of an unexpected, significant difference in mortality between groups. The combination of the results of those trials could yield some relevant further information, which cannot be obtained by individual trials due to their insufficient statistical power.

Aim of this meta-analysis is the assessment of the effects of improvement of glycemic control on the incidence of cardiovascular diseases in patients with type 2 diabetes.

Methods

The study was performed according to the recommendations of the QUOROM statement [9].

Data sources

An extensive search of Medline, EMBASE, and the Cochrane Library (any date up to December 1st, 2008, restricted to randomized clinical trials, published in English) was performed for all trials containing in any field the words ''diabetes'' and ''stroke'' or ''myocardial infarction'' or ''heart failure''.

Study selection

The meta-analysis was performed on randomized clinical trials assessing the effects of improved metabolic control on cardiovascular outcomes in type 2 diabetic patients. Trials were included in the analysis if they satisfied the following criteria:

(1) Randomized clinical trials enrolling patients with type 2 diabetes; if other populations were enrolled in the same study, the trial was included only if separate outcome results for patients with type 2 diabetes were reported;
(2) Data on HbA1c available for all treatment groups;
(3) Between-group difference in mean HbA1c during the trial of at least 0.5%;
(4) Planned duration of treatment of at least 3 years;
(5) Similar therapy for concurrent cardiovascular risk factors (hypertension, hyperlipidemia, etc.) in all treatment groups;
(6) Cardiovascular events as the principal trial endpoint, or included in a principal composite endpoint.

Data extraction

Data were retrieved from the paper reporting the main results of each trial; missing information was searched for in other publications on the same trial, or, when unavailable, on abstracts of communications at Congresses or dedicated websites.

Data for analysis were extracted independently by two observers (E.M., M.M.) and potential contrasts were resolved by a senior investigator (N.M.).

The following events were taken into consideration:

(1) death from any cause;
(2) cardiovascular death (determined by any cardiac cause, cerebrovascular disease, or peripheral artery disease);
(3) fatal or nonfatal acute myocardial infarction (MI);
(4) fatal or nonfatal stroke;
(5) cardiovascular events (defined as either fatal or nonfatal MI, stroke, or peripheral artery disease);
(6) fatal and nonfatal chronic heart failure (CHF).

Furthermore, body mass index (BMI) at the end of the study was retrieved, together with the proportion of patients experiencing at least one severe hypoglycemic episode (i.e., requiring hospitalization or assistance from a third person), and the proportion of patients treated with insulin, thiazolidinediones, and insulin secretagogues, at the end of the study. Baseline HbA1c and BMI, as well as age, duration of diabetes, and proportion of patients with known cardiovascular disease at enrolment were considered as putative moderators of the effect of intensified glucose control on incidence of cardiovascular events.

Data synthesis and analysis

For each trial, the number of events expected in the intervention group was calculated on the basis of the observed