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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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KEYWORDS
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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

rates observed in control groups and of the known epidemiologic relationship between HbA1c and cardiovascular risk [2]. Considering that the mean difference in HbA1c between groups was 0.9%, expected reduction in the incidence of events with intensive therapy was assumed as 16%, 12%, and 15%, for cardiovascular disease, myocardial infarction, and stroke, respectively. Furthermore, a power calculation was performed in order to assess the statistical power to detect (at $p < 0.05$) a significant reduction of cardiovascular events, as predictable by epidemiological studies [2].

Heterogeneity was assessed by using I^2 statistics. If no heterogeneity was detected, we applied both a random-effects and a fixed-effects model. We report the results of the random-effects models [10] because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication bias caused by the tendency of published studies to be positive, we used funnel plots, the Begg adjusted rank correlation test [11], and the Egger regression approach [12]. However, because these tests have low statistical power when the number of trials is small [13], undetected bias may still be present.

Weighted mean differences in body mass index at endpoint, and Mantel–Henzel Odds Ratio (MH-OR) with 95% confidence interval for all categorical endpoints, were calculated using a random effect model. A meta-regression was performed to assess the effect of putative moderators on variations of cardiovascular morbidity and mortality induced by intensified glucose control. Moderators considered included mean age, duration of diabetes, BMI, and HbA1c, and proportion of subjects with known cardiovascular disease, at enrolment; proportion of patients treated with different hypoglycemic drugs at endpoint; severe hypoglycemia during the trial (absolute difference in annual rate of first episode of severe hypoglycemia between intensive and control group, calculated on the basis of the number of subjects with at least one episode, assuming the incidence of severe hypoglycemia as constant throughout the study). All those analyses were performed using Comprehensive Meta-Analysis version 2.2.046 (NJ, USA).

Results

The Begg adjusted rank correlation test (Kendall tau, 0.20; $p = 0.31$) and the Egger regression approach (intercept, 0.406 [CI, −3.689 to 4.501]) suggested no major publication bias.

The process of retrieval of clinical trials is summarized in Appendix. Some large-scale trials were excluded, as they did not meet all inclusion criteria: HbA1c values were not reported in The University Group Diabetes Program (UGDP) [14], and between-group difference in mean HbA1c during follow-up did not reach the pre-defined 0.5% threshold in ADOPT (A Diabetes Outcome Progression Trial) [15], Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) [16] and Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI)-2 [17]; the Kumamoto study [18], which was centered on microvascular events, did not have a cardiovascular endpoint, while in the DIGAMI trial [19], although the duration of follow-up was longer than three years, the actual period of intensive treatment defined by the study protocol lasted for only 12 months. Therefore, only five trials were included in the meta-analysis (Table 1). For the UKPDS, data from the main analysis [7] were combined with those separately described for metformin [20], as part of the same randomization; some of the results were retrieved from other publications [21]. Some of the results of PROACTIVE, which were not described in the original publication [8], were retrieved from a subsequent paper on the same trial [22]. The study quality, as represented by randomization procedures, allocation, appropriate description of drop-outs, and intention-to-treat analysis, was satisfactory for all those studies; three out of four trials were open-label [5–7], while another one was designed as a double-blind study [8].

Retrieved studies included 17,267 and 15,362 patients (92,955 and 71,595 patient × years) in the intensive and conventional therapy groups, respectively, with a weighted mean age of 60.9 years. Weighted mean HbA1c, duration of diabetes, and BMI at enrolment were 7.5%, 6.4 years, and 29.3 kg/m^2, respectively. The weighted mean difference in HbA1c between intensive and conventional therapy during the trial was −0.9% whereas mean HbA1c at endpoint in the intensive therapy groups was 7.0%. Therapeutic strategies used to improve metabolic control in intensified treatment groups varied across trials; in the UKPDS, different monotherapies (sulphonylureas, metformin and insulin) were compared with a nonpharmacological treatment, but

Table 1 Principal characteristics of the studies included in the meta-analysis.

Study (Ref.)	Trial Duration (ys)	# Patients, int./conv.	Age (ys)	Duration of DM (ys)	Patients with IHD (%)	BMI baseline (kg/m^2)	BMI endpoint (kg/m^2) int./conv.	Weight differences[a] (kg) int./conv.	HbA1c baseline %	HbA1c endpoint (%) int./conv.
ACCORD [6]	3.5	5128/5123	62	10.0	34.8	32.2	33.4/32.3	3.5/0.5	8.3	6.4/7.5
ADVANCE [5]	5.0	5571/5569	66	8.0	32.3	28.0	28.0/28.0	−0.1/−1.0	7.5	6.5/7.3
PROACTIVE [8]	2.9	2605/2633	62	8.0	100.0	30.8	NR	3.6/−0.4	7.8	7.0/7.6
UKPDS 33 + 34 [7,20]	11.1	3071/1138	54	0.0	0.0	27.5	30.0/27.7	8.0/4.0	6.2	8.1/8.8
VADT [31]	6.3	892/899	60	11.5	40.0	31.3	33.8/32.3	5.2/2.5	9.4	6.9/8.4

Ys: years; Int.: intensified hypoglycemic treatment group; Conv.: conventional group; DM: diabetes mellitus; IHD: ischemic heart disease (previously known); NR: not reported.

[a] Difference between endpoint and baseline.

a large majority of patients received combinations of more than one drug during the trial, either in the intensified and in control groups. In the PROACTIVE trial, pioglitazone or placebo was added to pre-existing hypoglycaemic therapy (usually with more than one drug). In ACCORD, ADVANCE, and VADT, different therapeutic algorithms were used, all leading to combined treatment with two or more drugs in most cases, with a relevant proportion of subjects in intensified therapy groups receiving insulin therapy.

The number of events observed in the studies included in the meta-analysis is reported in Table 2. The calculated power to detect a significant ($p < 0.05$) reduction of incidence of cardiovascular events, in comparison with the rates actually observed in control groups, was 0.81, 0.62, 0.23, 0.74, and 0.97, for ACCORD, ADVANCE, PROACTIVE, UKPDS, and VADT, respectively.

Intensive therapy was associated with a significant reduction of the incidence of cardiovascular events and myocardial infarction, while no significant effect of improved metabolic control was detected on the incidence of stroke or heart failure, and in all-cause and cardiovascular mortality (Fig. 1).

Intensified treatment for type 2 diabetes was associated with a significant weight gain and increased hypoglycemic risk. In the four trials which reported BMI at endpoint [5–8,20], intensive therapy produced an increase of BMI by 1.2 [0.3–2.2] kg/m^2 ($p = 0.015$). The number of patients experiencing at least one episode of hypoglycemia was reported in three trials [5,6,15]. In the UKPDS, only the annual rate of severe hypoglycemia was reported [7,20]; the total number of subjects experiencing severe hypoglycemia was estimated on the basis of the recurrency rates in different groups of treatment reported for the first six years of the trial in another publication [23], i.e. 24% for insulin, 2% for sulphonylureas, none for other treatments. The PROACTIVE trial reported only the number of subjects requiring medical assistance for hypoglycemia [8]. The proportion of severe hypoglycemia requiring medical assistance in the ACCORD trial, which reported the incidence of both overall severe hypoglycemia and severe hypoglycemia requiring medical assistance was applied to provide an estimation of the cumulative incidence of severe hypoglycemia in the PROACTIVE trial. Combining the results of all the five trials, the risk of severe hypoglycemia in intensified treatment arm was significantly increased (MH-OR 3.01 [1.47–4.60]; $p < 0.001$). Similar results were obtained when excluding either PROACTIVE, UKPDS, or both (data not shown).

The effect of moderators on between-group differences in incidence of cardiovascular disease and cardiovascular mortality is reported in Table 3. The proportion of patients receiving insulin or insulin secretagogues could not be retrieved for the UKPDS. A higher BMI and a longer duration of diabetes at enrolment were associated with a negative effect of intensified glucose control on cardiovascular mortality (Fig. 2). Furthermore, a significant correlation was found between the risk of severe hypoglycemia and that of cardiovascular death associated with intensive treatment of diabetes (Fig. 2). Conversely, none of the factors considered appeared to moderate the effect of intensified treatment on the overall incidence of cardiovascular events.

Discussion

This meta-analysis shows that the improvement of metabolic control, obtained through the intensification of hypoglycemic therapy, reduces the incidence of cardiovascular disease in patients with type 2 diabetes. This result does not appear to be moderated by endpoint HbA1c in intensified treatment group, suggesting that improvement of metabolic control could be beneficial across a wide range of HbA1c values. This result is consistent with epidemiological data, showing an association of HbA1c with cardiovascular risk in type 1 and type 2 diabetic patients [2], and with results of long-term follow-ups of randomized clinical trials in type 1 [3] and type 2 [4] diabetic patients. The reduction of cardiovascular risk obtained through the improvement of metabolic control is smaller than that expected on the basis of epidemiological studies [2]; in fact, some studies fail to detect a significant benefit despite a sufficient statistical power [6,15]. Apparently, the reduction of HbA1c produces the expected improvement on the risk of myocardial infarction, but not of stroke.

The lack of any protective effect of intensified hypoglycemic treatment with respect to heart failure, despite

Table 2 Principal outcomes and adverse effects of the studies included in the meta-analysis.

Study (Ref.)	# Patients, int./conv.	All-cause mortality, int./conv.	Cardiovascular mortality, int./conv.	Cardiovascular events, int./conv.	Myocardial infarction, int./conv.	Stroke, int./conv.	Chronic heart failure, int./conv.	Severe hypoglyc., int./conv.
ACCORD [6]	5128/5123	257/203	135/94	352/371	205/248	76/72	152/124	830/261
ADVANCE [5]	5571/5569	498/553	253/289	557/590	310/337	238/246	220/231	150/81
PROACTIVE [8]	2605/2633	177/186	127/136	257/313	206/245	92/119	209/153	29/16[a]
UKPDS 33 +34 [7,20]	3071/1138	547/213	291/131	621/261	426/188	160/55	91/36	301/13[b]
VADT [31]	892/899	95/102	38/29	235/264	64/78	28/36	76/82	187/90

Int.: intensified hypoglycemic treatment group; Conv.: conventional group; DM: diabetes mellitus; IHD: ischemic heart disease (previously known); Hypoglyc.: hypoglycemia.

[a] Estimate, based on reported cases needing medical assistance, assuming a ratio between overall severe hypoglycemia and severe hypoglycemia requiring medical assistance as that of ACCORD [6].

[b] Estimate, based on reported yearly incidence, assuming a recurrency rate of severe hypoglycemia as that reported for moderate/severe hypoglycemia in Ref. [23].

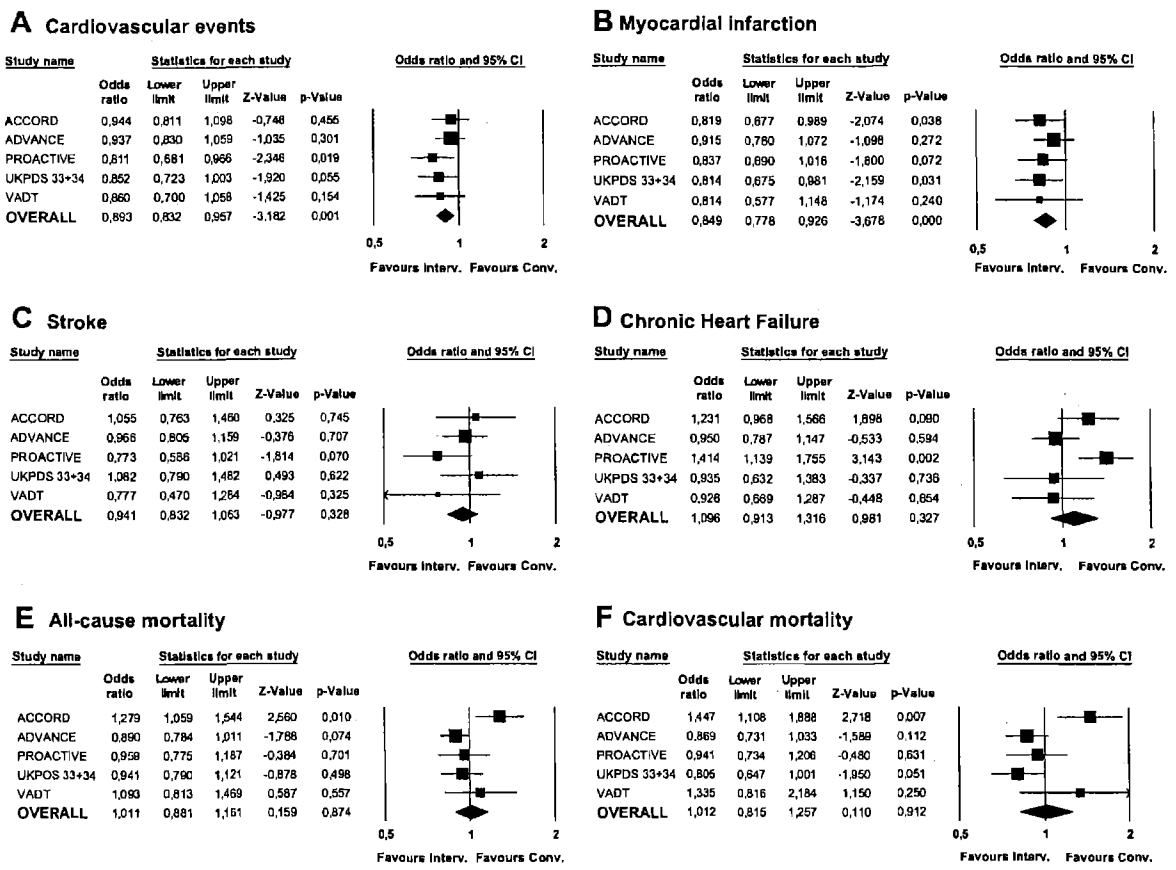

Figure 1 Effects of intensified hypoglycemic therapy on cardiovascular events (panel A), myocardial infarction (panel B), stroke (panel C), chronic heart failure (panel D), all-cause mortality (panel E) cardiovascular mortality (panel G). The size of the data markers represents the relative weight of the trial according to patient-years. Int.: intensified hypoglycemic treatment group; Conv.: conventional group.

the reduction in the incidence of myocardial infarction, which is a leading cause of ventricular dysfunction in diabetic patients, could appear surprising. However, it should be considered that some hypoglycemic treatments, such as thiazolidinediones [24] and, to a lesser extent, insulin [25], determine fluid retention and they can therefore aggravate the clinical expressions of heart failure in patients with left ventricular dysfunction. In fact, in one of the trials included, PROACTIVE [8], in which pioglitazone was used in the intensive treatment arm, a significant increase of the incidence of heart failure was observed, which is consistent with the results of other, shorter-term trials with thiazolidinediones [26,27]. In another trial, ACCORD [6], a nonsignificant trend toward increased risk for heart failure was observed in patients in the intensive therapy group, who received in most cases, together with other drugs, insulin and/or thiazolidinediones. Conversely, no detrimental effect of improvement of blood glucose on the incidence of heart failure was observed in other trials included in the meta-analysis [5,7].

Based on the results of observational studies [2], the reduction of HbA1c by 0.9%, as obtained on average in the five trials included in the analysis, should be expected to reduce cardiovascular mortality by approximately 12%. However, no such improvement was observed. This disappointing result is largely due to the effect of the ACCORD trial [6], which reported an unexpected increase of mortality in the intensive therapy group. The reasons for the discrepancy between ACCORD [6] and the other available trials are difficult to ascertain. HbA1c levels reached by intensively treated patients in ACCORD [6] are considerably lower than those of UKPDS [7] and PROACTIVE [8], but they are similar to those of ADVANCE [5], which was not associated with any increase in all-cause or cause-specific mortality. Other possible determinants of excess mortality in ACCORD [6] could include the relatively higher BMI of patients enrolled, in comparison with the other studies, and the very aggressive therapeutic approach in the intensified treatment group, leading to a remarkable risk of hypoglycemia and a relevant weight gain [6].

The present meta-analysis confirms that intensification of glucose-lowering treatment in type 2 diabetic patients is associated with weight gain and increased hypoglycemic risk, as already observed in individual trials [5–8,15,20]. The absolute risk of hypoglycemia in intensive treatment group is very different across trials, being highest in

Table 3 Moderators for the effect of intensified treatment on cardiovascular morbidity and mortality.

Moderator	Q	Intercept	Slope	p
Cardiovascular events				
Age (years)	0.95	−0.632 [−1.673; +0.409]	+0.008 [−0.008; +0.025]	0.33
Duration of diabetes (years)	0.28	−0.153 [−0.310; +0.003]	+0.005 [−0.014; +0.024]	0.60
Patients with IHD (%)	2.68	+1.389 [−0.412;+3.191]	−0.225 [−0.494; +0.044]	0.10
HbA1c at baseline (%)	1.20	+0.742 [−0.800; +2.283]	−0.112 [−0.314; +0.089]	0.28
BMI at baseline (kg/m^2)	0.06	−0.071 [−1.159; +1.017]	−0.001 [−0.038; +0.035]	0.94
Weight variations (Kg)	1.05	−0.071 [−0.179; 0.036]	−0.012 [−0.037; 0.011]	0.31
Endpoint HbA1c intensive group (%)	2.73	+1.350 [−0.451;+3.151]	−0.218 [−0.487; +0.050]	0.11
Severe hypoglycemia[a]	0.33	−0.136 [−0.233; −0.038]	+1.769 [−4.238; +7.776]	0.56
Insulin-treated (%)[b]	1.99	−0.164 [−0.277; −0.052]	+0.005 [−0.002; +0.011]	0.16
Insulin secretagogue (%)[b]	1.26	−0.172 [−0.313; −0.032]	+0.003 [−0.003; +0.010]	0.26
Thiazolidinedione-treated (%)[b]	0.62	−0.092 [−0.183; −0.002]	−0.001 [−0.003; +0.001]	0.43
Cardiovascular mortality				
Age (years)	0.44	−0.535 [−1.963; +0.894]	+0.008 [−0.015; +0.031]	0.51
Duration of diabetes (years)	5.52	−0.274 [−0.488; −0.059]	+0.034 [−0.006; +0.063]	0.02
Patients with IHD (%)	0.66	−0.103 [−0.266; +0.061]	+0.001 [−0.002; +0.005]	0.42
HbA1c at baseline (%)	0.03	+0.229 [−2.792; +5.068]	-0.037 [−0.437; +0.362]	0.09
BMI at baseline (kg/m^2)	10.80	−2.940 [−4.666; −1.241]	−0.099 [−0.040; +0.158]	0.001
Weight variations (Kg)	0.027	−0.033 [−0.188; 0.121]	−0.002 [−0.037; 0.031]	0.87
Endpoint HbA1c intensive group (%)	2.53	+2.160 [−0.557; 4.878]	−0.328 [−0.733; +0.076]	0.11
Severe hypoglycemia[a]	10.73	−0.199 [−0.339; −0.061]	+16.955 [+6.811; +27.099]	0.56
Insulin-treated (%)[b]	1.10	−0.057 [−0.220; +0.107]	+0.005 [−0.005; +0.015]	0.29
Insulin secretagogue (%)[b]	2.20	+0.139 [−0.081; −0.359]	−0.007 [−0.016; +0.002]	0.14
Thiazolidinedione-treated (%)[b]	1.42	−0.101 [−0.237; +0.034]	−0.002 [−0.001; +0.006]	0.23

Linear regression models. IHD: ischemic heart disease.

[a] Absolute increase of yearly rate of first episode in intensified treatment group (cases/patient × years).

[b] At endpoint, with the exclusion of UKPDS.

ACCORD [6]. In fact, a direct correlation can be observed between the increase incidence of severe hypoglycemia and that of cardiovascular mortality. It can be speculated that adrenergic activation induced by low glucose has a negative impact of the prognosis of pre-existing ischemic heart disease. Furthermore, intensified treatment is associated with a more negative impact on cardiovascular mortality in trials enrolling patients with a higher degree of obesity and a longer duration of diabetes. These results suggest that severe hypoglycemia resulting from intensified treatment could have a detrimental effect on the prognosis of major cardiovascular events, eventually producing an increase of cardiovascular mortality despite a reduction of morbidity, as observed in ACCORD [6]. This result is consistent with the negative prognostic effect of hypoglycemia in patients with myocardial ischemia, reported by epidemiological studies [28]. The negative impact of intensified treatment could be more evident in obese patients and in those with long-standing diabetes, suggesting that frailty of patients should be a criterion to consider when establishing therapeutic targets for glucose control. It should also be considered that renal failure, which is a known risk factor for hypoglycemia [29], is also associated with increased cardiovascular morbidity and mortality [30], possibly affecting the results of the present meta-regression. Unfortunately, the summary data used for meta-analysis do not allow a statistical adjustment of the effects of hypoglycemic risk on cardiovascular mortality for concurrent renal failure.

Another possible reason for heterogeneity of results on cardiovascular mortality could be represented by differences in cardiovascular risk profile in patients enrolled in individual studies. In particular, a more aggressive therapeutic approach produced a substantial reduction of blood pressure and cholesterol levels in the most recent trials [5,6,31] in comparison with older studies [7,20]. The possibility that other risk factors moderate the effect of tight glucose control on cardiovascular mortality should be considered, and explored through further studies, or through sub-group analysis of patient-level data of available trials.

It should be also recognized that individual drugs could have different, and even divergent, effects on cardiovascular risk. In particular, due to the results obtained on a small sample of overweight patients [20], metformin has been associated with reduced cardiovascular morbidity and mortality independently from its hypoglycemic action, while some doubts have been raised on the cardiac safety of insulin [17], thiazolidinediones [32,33], and some insulin secretagogues [34,35]; some evidences also suggest that

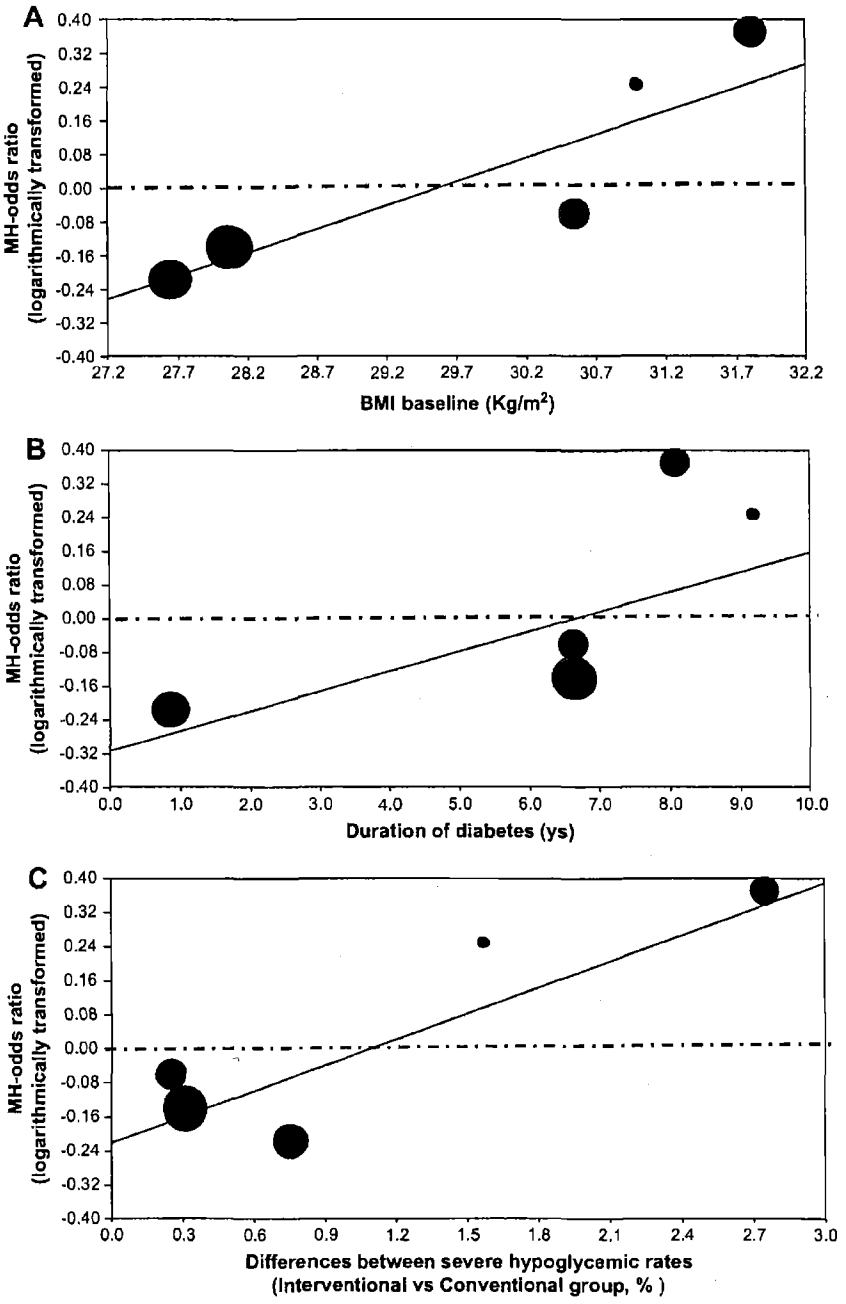

Figure 2 Correlation of baseline body mass index (A), duration of diabetes (B), and increased incidence of severe hypoglycemia (C), with the effect of intensified glucose control on cardiovascular mortality.

specific combinations of drugs, such as that of sulphonylureas and metformin, could affect negatively cardiovascular risk [20,36]. It is also possible that pioglitazone has beneficial effects on some cardiovascular outcomes independent of its effects on blood glucose [27], while there is no evidence of detrimental effects on cardiovascular disease for DPP-4 inhibitors and GLP-1 receptor agonists, even if the duration of trials performed on these new agents is insufficient to draw any definitive conclusion on their long-term cardiovascular safety [37,38]. The results of meta-regression analysis do not support the hypothesis of specific (and glucose-independent) effects of insulin, insulin secretagogues, or thiazolidinediones, on cardiovascular morbidity or mortality.

Some limitations of the present paper should be acknowledged. The range of endpoint HbA1c across trials is very wide. It is possible that the relationship between HbA1c and incidence of cardiovascular disease is not

linear, although epidemiological studies do not support such hypothesis [2]. It has been suggested that meta-regression analysis should be performed only when the number of available trials is greater than 10. This threshold is conventional, and it does not take into account the size of the trials included in the meta-regression. The results of the meta-regression should be considered with great caution, and interpreted as hypotheses for further research, rather than as definitive evidence to be applied in clinical practice. However, we feel that the possibility of a detrimental effect of severe hypoglycemia on cardiovascular mortality, which is biologically plausible [28], should be taken into account; in our opinion, this point deserves further research. The analysis on the effect of severe hypoglycaemia was based on the assumption that the proportion of severe events among all hypoglycaemic episodes in PROACTIVE was similar to that observed in ACCORD, which cannot be demonstrated; ACCORD was chosen as a comparator because it had the highest proportion of thiazolidinediones-treated patients, although the proportion of patients receiving sulphonylureas or insulin was somewhat higher in ACCORD.

In patients with type 2 diabetes, a hypoglycemic treatment aimed at reducing HbA1c levels is effective in preventing the onset and progression of microvascular complications, such as retinopathy [7] and nephropathy [5,7]. Available results from randomized clinical trials show that the intensification of hypoglycemic treatment, although accompanied by weight gain and by an increased risk of hypoglycemia, is also capable of reducing the incidence of myocardial infarction, while it does not seem to modify the risk of stroke and cardiovascular mortality; this benefit should always be considered in cost-effectiveness analyses of treatments for type 2 diabetes. At the same time, the increased incidence of severe hypoglycemia associated with intensified glucose-lowering treatment could eventually lead to an increase of cardiovascular mortality, particularly in obese patients and in those with longer duration of diabetes.

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Appendix A
Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.numecd.2009.03.021.

References

[1] Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care 2008;31:714–9.

[2] Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–31.

[3] Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53.

[4] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.

[5] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.

[6] Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.

[7] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.

[8] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.

[9] Clarke M. The QUORUM statement. Lancet 2000;355:756–7.

[10] Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533–7.

[11] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[12] Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[13] Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–29.

[14] The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of pheniformin therapy. Diabetes 1975;24(Suppl. 1):65–184.

[15] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.

[16] Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, et al. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. N Engl J Med 2007;357:28–38.

[17] Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650–61.

[18] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–17.

[19] Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation 1999;99:2626–32.

[20] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.

[21] Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006;20:395–401.
[22] Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007;38:865–73.
[23] Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002;25:330–6.
[24] Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care 2004;27:256–63.
[25] Koivisto VA. Insulin therapy in type II diabetes. Diabetes Care 1993;16(Suppl. 3):29–39.
[26] Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370:1129–36.
[27] Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab 2008;10:1221–38.
[28] Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation 2008;117:1018–27.
[29] Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. Diabet Med 2003;20:642–5.
[30] Ekundayo OJ, Muchimba M, Aban IB, Ritchie C, Campbell RC, Ahmed A. Multimorbidity due to diabetes mellitus and chronic kidney disease and outcomes in chronic heart failure. Am J Cardiol 2009;103:88–92.
[31] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.
[32] Vaccaro O, Riccardi G. Thiazolidinediones and cardiovascular risk: will the evidence so far available modify treatment strategies for type 2 diabetes? Nutr Metab Cardiovasc Dis 2008;18:85–7.
[33] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
[34] Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev 2006;22:477–82.
[35] Johnsen SP, Monster TB, Olsen ML, Thisted H, McLaughlin JK, Sorensen HT, et al. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther 2006;13:134–40.
[36] Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. Diabetes Care 2008;31:1672–8.
[37] Mannucci E, Rotella CM. Future perspectives on glucagon-like peptide-1, diabetes and cardiovascular risk. Nutr Metab Cardiovasc Dis 2008;18:639–45.
[38] Monami M, Iacomelli I, Marchionni N, Mannucci E. Dipeptydil peptidase 4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis, in press.