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

Christoph Stettler, MD,[a] Sabin Allemann,[a,b] Peter Jüni, MD,[a,c] Carole A. Cull, PhD,[d] Rury R. Holman, MD,[d] Matthias Egger, MD, MSc,[a,c] Stephan Krähenbühl, MD,[e] and Peter Diem, MD[b] ***Bern, Switzerland; and Oxford, UK***

Background Uncertainty persists concerning the effect of improved long-term glycemic control on macrovascular disease in diabetes mellitus (DM).

Methods We performed a systematic review and meta-analysis of randomized controlled trials comparing interventions to improve glycemic control with conventional treatment in type 1 and type 2 diabetes. Outcomes included the incidence rate ratios for any macrovascular event, cardiac events, stroke, and peripheral arterial disease, and the number needed to treat intensively during 10 years to prevent one macrovascular event.

Results The analysis was based on 8 randomized comparisons including 1800 patients with type 1 DM (134 macrovascular events, 40 cardiac events, 88 peripheral vascular events, 6 cerebrovascular events, 11 293 person-years of follow-up) and 6 comparisons including 4472 patients with type 2 DM (1587 macrovascular events, 1197 cardiac events, 87 peripheral vascular events, 303 cerebrovascular events, 43 607 person-years). Combined incidence rate ratios for any macrovascular event were 0.38 (95% CI 0.26-0.56) in type 1 and 0.81 (0.73-0.91) in type 2 DM. In type 1 DM, effect was mainly based on reduction of cardiac and peripheral vascular events and, in type 2 DM, due to reductions in stroke and peripheral vascular events. Effects appear to be particularly important in younger patients with shorter duration of diabetes.

Conclusions Our data suggest that attempts to improve glycemic control reduce the incidence of macrovascular events both in type 1 and type 2 DM. In absolute terms, benefits are comparable, although effects on specific manifestations of macrovascular disease differ. (Am Heart J 2006;152:27-38.)

There is uncertainty about the place of improved glycemic control in the prevention of macrovascular disease in patients with diabetes mellitus (DM).[1,2] The development of macrovascular complications, including cardiac, cerebrovascular, and peripheral vascular complications, is an important concern considering that a substantial proportion of premature deaths in patients with type 1 DM[3] and most deaths in type 2 DM are related to macrovascular disease.[4]

From the [a]Department of Social and Preventive Medicine, University of Bern, Switzerland, [b]Division of Endocrinology and Diabetes, University of Bern, Switzerland, [c]MRC Health Services Research Collaboration Department of Social Medicine, University of Bristol, UK, [d]Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK, and [e]Department of Internal Medicine, University of Basel, Switzerland.

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Reprint requests: Peter Diem, MD, Division of Endocrinology and Diabetes, University of Bern–Inselspital, 3010 Bern, Switzerland.

E-mail: peter.diem@insel.ch

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The beneficial effects of improved glycemic control on microvascular complications, including retinopathy, nephropathy, and neuropathy, have been documented in several randomized studies published during the last 20 years. In patients with type 1 DM, this was conclusively shown by DCCT[5] and, in patients with type 2 DM, by UKPDS.[6] Although these and other studies[5,7-13] prospectively recorded the occurrence of macrovascular complications, they did not conclusively answer the question whether improved glycemic control effectively reduces macrovascular complications. By pooling data from several studies, meta-analysis of the existing data could clarify this issue.[14] In collaboration with the original investigators who provided additional information on macrovascular outcomes, we did a comprehensive systematic review and meta-analysis of all randomized controlled trials in patients with type 1 and type 2 DM.

Methods

Literature search and eligibility criteria

We aimed to identify all randomized controlled comparisons of improved glycemic control that assessed macrovascular disease in types 1 and 2 DM. Using Cochrane methodology,[15]

we searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register for relevant studies. We considered studies in any language. Electronic searches were supplemented by hand-searching of reference lists, reviews, relevant book chapters, conference abstracts, and specialist journals. We evaluated each study for inclusion in the meta-analysis on the basis of 6 criteria: (1) study design (randomized controlled trial), (2) target population (general population of patients with either type 1 or type 2 DM), (3) comparison of regimens aiming to improve glycemic control (subcutaneous insulin injections, insulin pump, oral antidiabetic agents, or a combination of the previous) with conventional treatments, (4) documentation of glycemic control by measurement of glycated hemoglobin (HbA_{1c}), (5) follow-up of at least 2 years, and (6) prospective recording of macrovascular events. Two reviewers (CS, SA) independently assessed publications for eligibility, with discrepancies being resolved in consultation with a third reviewer (PD).

Data extraction and outcome measures

Data on the characteristics of studies, patient populations, and interventions were extracted independently by 2 investigators (CS and SA), with disagreements resolved by a third reviewer (PD). This included the extraction of data on the distribution of cardiac risk factors at study end (blood pressure, lipid factors, body mass index, and smoking). All relevant publications from a study were considered, including, for example, early publications describing the study design. Authors from all studies were sent a standardized data extraction form and were asked to check the information extracted from published articles and, where necessary, to provide additional clinical and biochemical data. We defined macrovascular end points as (1) cardiac events, including fatal and nonfatal myocardial infarction (defined as evidence of acute myocardial infarction confirmed by electrocardiogram [ECG] and/or serum enzymes, confirmed nonacute myocardial infarction based on serial reading of baseline and biennial ECG and/or serum enzymes), any type of bypass graft and percutaneous transluminal angioplasty, angina pectoris (defined as evidence of ischemic heart disease confirmed by a new ECG abnormality or an ECG that becomes abnormal on exercise), congestive heart failure (based on clinical criteria, eg, Kerley's B lines, rales, raised jugular venous pressure, or third heart sound), and death due to cardiac disease or sudden death; (2) stroke (fatal and nonfatal, thrombotic or hemorrhagic); and (3) peripheral vascular disease, including intermittent claudication (defined as pain in leg(s) occurring with exercise, no pain at rest, no tissue necrosis, clinical impression combined with objective evidence [measurement of ankle blood pressure, examination of pulse rates, Doppler, angiography]), diabetes-related amputation of lower extremity, any type of peripheral artery bypass or angioplasty, and death due to peripheral arterial disease. The incidence of fatal or nonfatal macrovascular events of any type was the primary end point. Secondary outcomes included fatal or nonfatal cardiac events, stroke, peripheral arterial disease, and macrovascular deaths.

Assessment of methodological quality

Two of us (CS and SA) independently assessed the adequacy of the concealment of allocation of patients to treatment groups, blinding of care providers and research staff ascertaining macrovascular outcomes, and the proportion of randomized patients included in analyses.[16] Disagreements were resolved in discussion with a third reviewer (PJ).

Statistical analysis

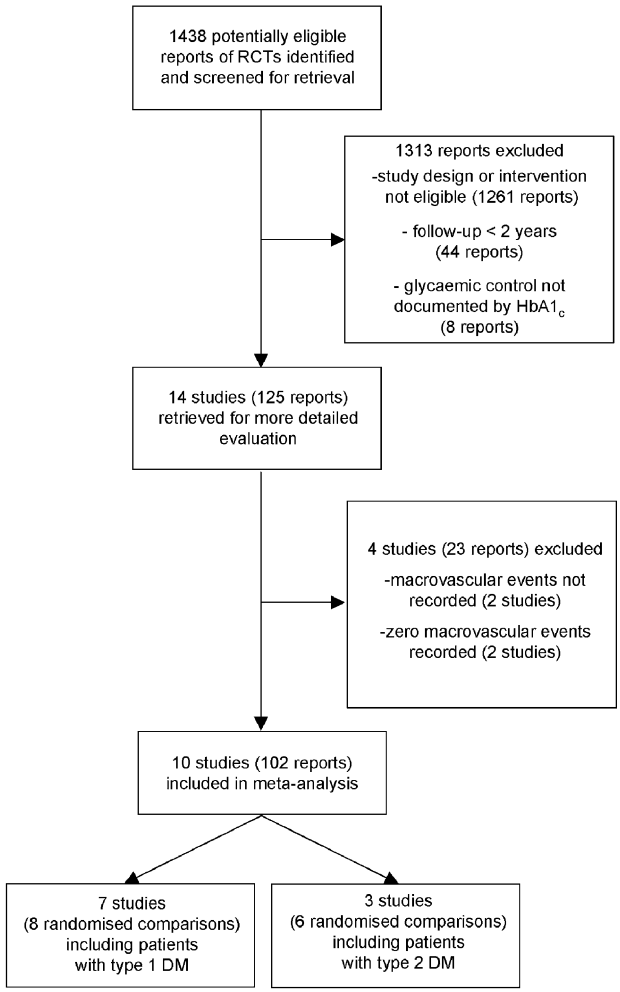
We calculated the incidence of macrovascular events separately for each treatment group by dividing the number of events by the number of person-years of follow-up. For each comparison and end point, the incidence rate ratio (IRR) was obtained by dividing the incidence in the intensified treatment group by the incidence in the control group. Comparisons with no outcome events in either group were excluded from the respective analysis. Comparisons with events only in one group were analyzed by adding one half to all cells. We combined IRRs in fixed-effects meta-analysis, assuming that the observed variation in treatment effects in the different studies is entirely due to sampling variation and that the underlying treatment effect is the same in all study populations. The weight for each study was calculated by using the inverse of the variance of the estimated log IRR in the corresponding study (inverse variance weighting). In addition, we calculated the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance: $I^2 = 100\% \times (Q - df)/Q$, where Q is the Cochran heterogeneity statistic and df is the degrees of freedom.[17] Mild heterogeneity will account for <30% of the variation, and pronounced heterogeneity will account for substantially >50%. The number of patients that need to be treated intensively to prevent one macrovascular event[18] was calculated by applying the combined IRRs to incidence rates typical for conventionally treated patients. In sensitivity analyses, we repeated calculations using random-effects models (attributing increased weight to smaller comparisons) and did tests of funnel plot asymmetry to assess for publication bias.[19,20] The extent to which the effect of improved glycemic control was modified by study-level variables was explored in univariable metaregression models.[21] The following variables were considered: reduction of HbA_{1c} achieved with intensified treatment, duration of DM, mean age at baseline, proportion women, year of study begin, year of study reporting, and study quality (concealment of allocation, blinding, and the proportion of randomized patients included in analyses). Finally, we repeated analyses excluding one study[22] where the prevalence of smoking was substantially higher in the intensive treatment group. Results are presented as IRRs with 95% CIs and numbers needed to treat (NNTs) to prevent one macrovascular event. All analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX).

Results

Identification of eligible studies and comparisons

We screened 1438 reports and excluded 1313. The remaining 125 reports, which reported on 14 different studies, were retrieved for detailed evaluation. Ten studies that included 14 randomized comparisons of intensified and conventional treatment were included (Figure 1). Eight comparisons had been performed in patients with type 1 DM[5,7,8,10-12] and 6 in patients with type 2 DM.[6,9,22,23] The DCCT in patients with

Figure 1



Identification of eligible randomized controlled trials. *RCTs*, Randomized controlled trials.

type 1 DM[5] and the Kumamoto study in patients with type 2 DM[9] included 2 parallel comparisons in patients with and without diabetic complications (secondary and primary prevention arms). The UKPDS contributed 3 comparisons: (1) comparison of an intensified regimen based on sulfonylurea or insulin with conventional treatment in nonoverweight patients ("UKPDS 1" in this article); (2) comparison of an intensified regimen based primarily on sulfonylurea or insulin with conventional treatment in overweight patients (>120% of ideal body weight, "UKPDS 2"); and (3) comparison of intensified metformin-based regimen with conventional treatment in overweight patients ("UKPDS 3"). There was overlap in groups receiving conventional treatment in UKPDS 2 and 3; this was taken into account in the meta-analysis by reducing the weight of the respective groups.

Characteristics of trials, patients, and interventions

Nine comparisons were performed in Europe,[6-8,10-12,23] 3 in North America,[5,22] and 2 in Asia.[9] Mean follow-up ranged from 2.0 to 8.0 years in patients with type 1 DM and from 2.3 to 10.7 years in type 2 DM. Appropriate methods of allocation concealment were described for 8 comparisons.[5,8,11,12,24] For 7 comparisons, the degree of blinding of outcome assessors remained unclear.[7-10,12] Eleven comparisons had been analyzed according to the intention-to-treat principle.[5-7,9,12,22,23] In the remaining 3, the proportion of patients excluded from the analysis ranged from 5.4% to 13.6%.

The 14 randomized comparisons included a total of 6272 patients, 1800 patients with type 1 DM (11 293 person-years of follow-up) and 4472 patients with type 2 DM (43 607 person-years of follow-up). Study populations were heterogeneous, both in type 1 and type 2 DM, with a range of mean ages and durations of DM at baseline (Table I). In type 1 DM, intensified treatment typically consisted of multiple injection therapy or continuous subcutaneous insulin infusion using a pump, with intensive self-monitoring of blood glucose. Conventional treatment was based on 1 to 3 injections, with or without occasional blood glucose monitoring. In type 2 DM, attempts to improve glycemic control consisted of subcutaneous insulin injections or hypoglycemic agents combined with insulin injections, generally with blood glucose monitoring, whereas for conventional treatment, the number of insulin injections was either reduced or treatment was with hypoglycemic agents or diet alone, with less intensive blood glucose monitoring. Mean baseline HbA_{1c} ranged from 8.8% to 11.8% in patients with type 1 DM and from 7.0% to 9.5% in type 2 DM (Table II). At the conclusion of studies, differences in HbA_{1c} between intensified and conventional treatment groups ranged from −0.5% to −1.9% in type 1 and from −0.3% to −2.2% in type 2 DM. The prevalence of cardiac risk factors was similar between treatment groups (Table III), with one exception: in the Veterans Affairs study,[22] smoking was more prevalent in the intensive group, 23% versus 13% at baseline and 21% versus 8% at study end.

Macrovascular events and mortality

Additional outcome data were obtained for 12 comparisons.[5-10,12,22,23] A total of 134 macrovascular events of any type were recorded in type 1 DM and 1587 events in type 2 DM. The number of events and person−years of follow-up is shown in Table IV. The results from fixed-effects meta-analyses are shown in Figure 2 and Table V. Combined IRRs were 0.38

Table I. Baseline characteristics of randomized trials comparing intensified blood glucose control with conventional control in patients with type 1 and type 2 DM

Study (year of publication)	n (intensified/ conventional)	Female (%)	Mean age (y)	Mean duration of diabetes (y)	Mean follow-up (y)	Intervention in intensified group	Intervention in conventional group
Type 1 DM							
Holman et al (1983)[11]	36/38	36	42.4	18.7	2.0	2 daily injections, iSMBG	2 daily injections, SMBG
Verrillo et al (1988)[10]	22/22	45	37.5	20.0	5.0	3 daily injections, iSMBG	1-2 daily injections, SMBG
Lauritzen (1991)[7]	18/16	41	34.0	19.0	8.0	CSII, iSMBG	1-3 daily injections, SMBG
Feldt-Rasmussen et al(1992)[7]	18/17	43	30.5	15.0	5.0	CSII, iSMBG	2-3 daily injections, SMBG
DCCT Primary Prevention (1993)[5]	348/378	49	26.5	2.6	6.5	CSII, MIT, iSMBG	1-2 daily injections, SMBG
DCCT Secondary Intervention (1993)[5]	363/352	47	27.0	8.8	6.5	CSII, MIT, iSMBG	1-2 daily injections, SMBG
SDIS (1993)[8]	48/54	47	30.9	17.0	7.5	MIT, iSMBG	2-3 daily injections, SMBG
MCSG (1995)[12]	36/34	27	37.0	19.5	5.0*	CSII, MIT, iSMBG	2 daily injections, SMBG
Type 2 DM							
Veterans Affairs (1997)[22]	75/78	0	60.2	7.9	2.3	Stepwise regimen (insulin, SU). iSMBG	1-2 daily injections, SMBG
UKPDS 1 (1998)[6]	1433/589	26	53.7	0	10.3	Stepwise regimen beginning with SU or insulin (metformin, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
UKPDS 2 (1998)[6]	1296/549	53	52.7	0	9.7	Stepwise regimen beginning with SU or insulin (metformin, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
UKPDS 3 (1998)[23]	342/411	54	52.9	0	10.7	Stepwise regimen beginning with metformin (SU, MIT if needed), iSMBG	Stepwise regimen beginning with diet (SU, metformin, insulin if needed), SMBG
Kumamoto Primary Prevention (2000)[9]	28/27	49	48.0	6.6	8.0	MIT, iSMBG	1-2 daily injections, SMBG
Kumamoto Secondary Intervention (2000)[9]	27/28	53	51.0	10.6	8.0	MIT, iSMBG	1-2 daily injections, SMBG

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based. *iSMBG*, Intensive self-monitoring of blood glucose; *SMBG*, self-monitoring of blood glucose; *CSII*, continuous subcutaneous insulin infusion; *MIT*, multiple insulin injection therapy; *SU*, sulfonylurea.
*Median.

(95% CI 0.26-0.56) in type 1 and 0.81 (0.73-0.91) in type 2 DM, indicating a substantial risk reduction in type 1 DM and a smaller risk reduction in type 2 DM ($P < .001$ for difference between the 2 diabetes types). Thirteen comparisons contributed to the analysis of cardiac events. Forty events were recorded in type 1 and 1197 in type 2 DM. The combined IRRs were 0.41 (0.19-0.87) and 0.91 (0.80-1.03) ($P = .040$ for difference). The analysis of peripheral vascular events was based on 10 comparisons. Eighty-eight events were recorded in type 1 and 87 events in type 2 DM. The combined IRRs in type 1 DM were 0.39 (0.25-0.62)

Table II. Glycated hemoglobin levels at baseline and differences between intensified and conventional treatment groups at study end

Study (year of publication)	HbA_{1c} at baseline(%)		HbA_{1c} at study end(%)		
	Intensified	Control	Intensified	Control	Difference
Type 1 DM					
Holman et al (1983)[11]	11.7	11.8	9.5	10.2	−0.7
Verrillo et al (1988)[10]	10.8	11.1	7.9	8.7	−0.8
Lauritzen (1991)[7]	9.6	8.8	7.6	8.1	−0.5
Feldt-Rasmussen et al (1992)[7]	9.5	9.3	7.3	9.2	−1.9
DCCT Primary Prevention (1993)[5]	8.8	8.8	7.1	9.0	−1.9
DCCT Secondary Intervention (1993)[5]	9.0	8.9	7.1	9.0	−1.9
SDIS (1993)[8]	9.5	9.4	7.1	8.5	−1.4
MCSG (1995)[12]	10.3	9.8	8.9	9.8	−0.9
Type 2 DM					
Veterans Affairs (1997)[22]	9.3	9.5	7.1	9.2	−2.1
UKPDS 1 (1998)[6]	7.1	7.0	7.5	8.3	−0.8
UKPDS 2 (1998)[6]	7.1	7.2	8.0	8.3	−0.3
UKPDS 3 (1998)[23]	7.2	7.0	8.0	8.3	−0.3
Kumamoto Primary Prevention (2000)[9]	9.5	8.8	7.2	9.4	−2.2
Kumamoto Secondary Intervention (2000)[9]	9.3	9.0	7.2	9.4	−2.2

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based.

and 0.58 (0.38-0.89) in type 2 DM (P = .22 for difference). Six strokes were observed in type 1 and 303 in type 2 DM. Combined IRRs were 0.34 (0.05-2.57) and 0.58 (0.46-0.74), respectively (P = .54 for difference). Figure 3 summarizes effect estimates for any macrovascular event and for cardiac, peripheral vascular, and stroke events by type of DM. In 3 studies[7,10,11] (all in patients with type 1 DM), no macrovascular deaths occurred. Nine deaths occurred in type 1 DM and 441 in type 2 DM. Combined IRRs were comparable: 0.89 (0.27 to 2.98) and 0.88 (0.72 to 1.08) for type 1 and 2 DM, respectively.

Numbers needed to treat to prevent one macrovascular event

The incidence of macrovascular events in conventionally treated patients with type 1 DM ranged from 0.6 per 100 person-years in the MCSG trial[12] to 4.7 in the study of Feldt-Rasmussen et al.[7] For calculation of NNTs, we assumed a typical incidence of 1 per 100 person-years. In conventionally treated patients with type 2 DM, incidences were more heterogeneous and ranged from 1.3 per 100 person-years in the Kumamoto secondary intervention arm[9] to 13.7 in the Veterans Affairs study.[22] We calculated NNTs assuming typical incidences of 4 per 100 person-years (lower risk) and 8 per 100 person-years (higher risk). Using the IRRs from our meta-analysis (0.38 for type 1 DM and 0.81 for type 2 DM), the numbers of patients that need to receive intensified treatment for 10 years to prevent one macrovascular event were 16 for type 1 DM, 14 for low-risk type 2 DM, and 7 for high-risk type 2 DM.

Sensitivity and metaregression analyses

Combined IRRs from random-effects models were similar to those from the fixed-effects models. There was little evidence of funnel plot asymmetry in both types of DM (P > .3 for all end points). In type 1 DM, the reduction in the risk for macrovascular events associated with improved glycemic control was greater in studies that achieved larger reductions in HbA_{1c} levels (P = .050). No such interaction was evident for type 2 DM. In type 2 DM, the beneficial effect of improved glycemic control decreased with longer diabetes duration (P = .040). Similarly, older age of study populations was associated with smaller effect (P = .024). A comparable trend was found for type 1 DM, although it did not reach statistical significance. There was little evidence for associations with the proportion of women or dimensions of study quality and the inclusion of the year of study begin or reporting did not significantly influence the results. Finally, when excluding the Veterans Affairs study,[22] the IRR for macrovascular event of any type was 0.79 (95% CI 0.71-0.88).

Discussion

In this systematic review and meta-analysis, we found that improved glycemic control translated into substantial reductions in macrovascular risk in type 1 DM while producing a smaller reduction in patients with type 2 DM. In type 1 DM, important beneficial effects were evident for cardiac and peripheral vascular events. In type 2 DM, substantial effects were observed for peripheral vascular disease and stroke, whereas cardiac events were not

Table III. Other cardiac risk factors at study end

	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)		Total cholesterol (mmol/L)		HDL cholesterol (mmol/L)	
Study	**Int**	**Conv**	**Int**	**Conv**	**Int**	**Conv**	**Int**	**Conv**
Type 1 DM								
Holman et al (1983)[11]	129	133	79	85	4.8	5.1	1.4	1.4
Verrillo et al (1988)[10]	142	140	96	94	na	na	na	na
Lauritzen (1991)[7]	131	131	85	85	na	na	na	na
Feldt-Rasmussen et al (1992)[7]	131	133	82	90	na	na	na	na
DCCT Primary Prevention (1993)[13]	111	114	71	72	4.6	5.0	1.3	1.3
DCCT Secondary Intervention (1993)[13]	111	114	71	72	4.6	4.7	1.2	1.2
SDIS (1993)[8]	126	133	77	78	na	na	na	na
MCSG (1995)[12]	130	127	79	73	na	na	na	na
Type 2 DM								
Veterans Affairs (1997)[22]	137	139	80	83	5.2	5.2	1.0	1.0
UKPDS 1 (1998)[6]	137	137	76	76	5.0	5.0	1.1	1.1
UKPDS 2 (1998)[6]	141	139	79	77	5.2	5.2	1.1	1.0
UKPDS 3 (1998)[23]	141	140	78	77	5.3	5.2	1.1	1.1
Kumamoto Primary Prevention (2000)[9]	126	120	69	68	5.3	5.3	1.3	1.3
Kumamoto Secondary Intervention (2000)[9]	132	139	72	75	5.3	5.3	1.3	1.3

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein; *BMI*, body mass index; *Int*, intensified treatment group; *Conv*, conventional treatment group; *na*, not applicable.

Table IV. Number of events and corresponding person-years

	Person-years		Any macrovascular event	
Study	**Intensified**	**Conventional**	**Intensified**	**Conventional**
Type 1 DM				
Holman et al (1983)[11]	72	76	0	1
Verrillo et al (1988)[10]	110	110	4	3
Lauritzen (1991)[7]	144	128	1	0
Feldt-Rasmussen et al (1992)[7]	90	85	0	4
DCCT Primary Prevention (1993)[13]	2262	2457	12	38
DCCT Secondary Intervention (1993)[13]	2360	2288	15	46
SDIS (1993)[8]	360	405	3	6
MCSG (1995)[12]	178	168	0	1
Total	5576	5717	35	99
Type 2 DM				
Veterans Affairs (1997)[22]	169	176	35	24
UKPDS 1 (1998)[6]	14760	6067	509	276
UKPDS 2 (1998)[6]	12571	3126	423	116
UKPDS 3 (1998)[23]	3659	2199	105	88
Kumamoto Primary Prevention (2000)[9]	224	216	0	4
Kumamoto Secondary Intervention (2000)[9]	216	224	4	3
Total	31599	12008	1076	511

UKPDS 1 and 2, in calculations, the number of events and the person-years in the placebo group were halved to prevent double counting. UKPDS 2 and 3, there was overlap in groups receiving conventional treatment and this was taken into account in the meta-analysis by reducing the weight of the respective groups to prevent double counting. UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and sulfonylurea based; UKPDS 3, overweight and metformin based.

found to be reduced significantly. Of note, the number of patients that need to be treated to prevent one macrovascular event (NNT) was lower for type 2 DM compared with type 1 DM. This reflects a higher incidence of macrovascular events in patients with type 2 DM and thereby a higher a priori risk. Interestingly, improved glycemic control was particularly beneficial in younger patients with shorter diabetes duration.

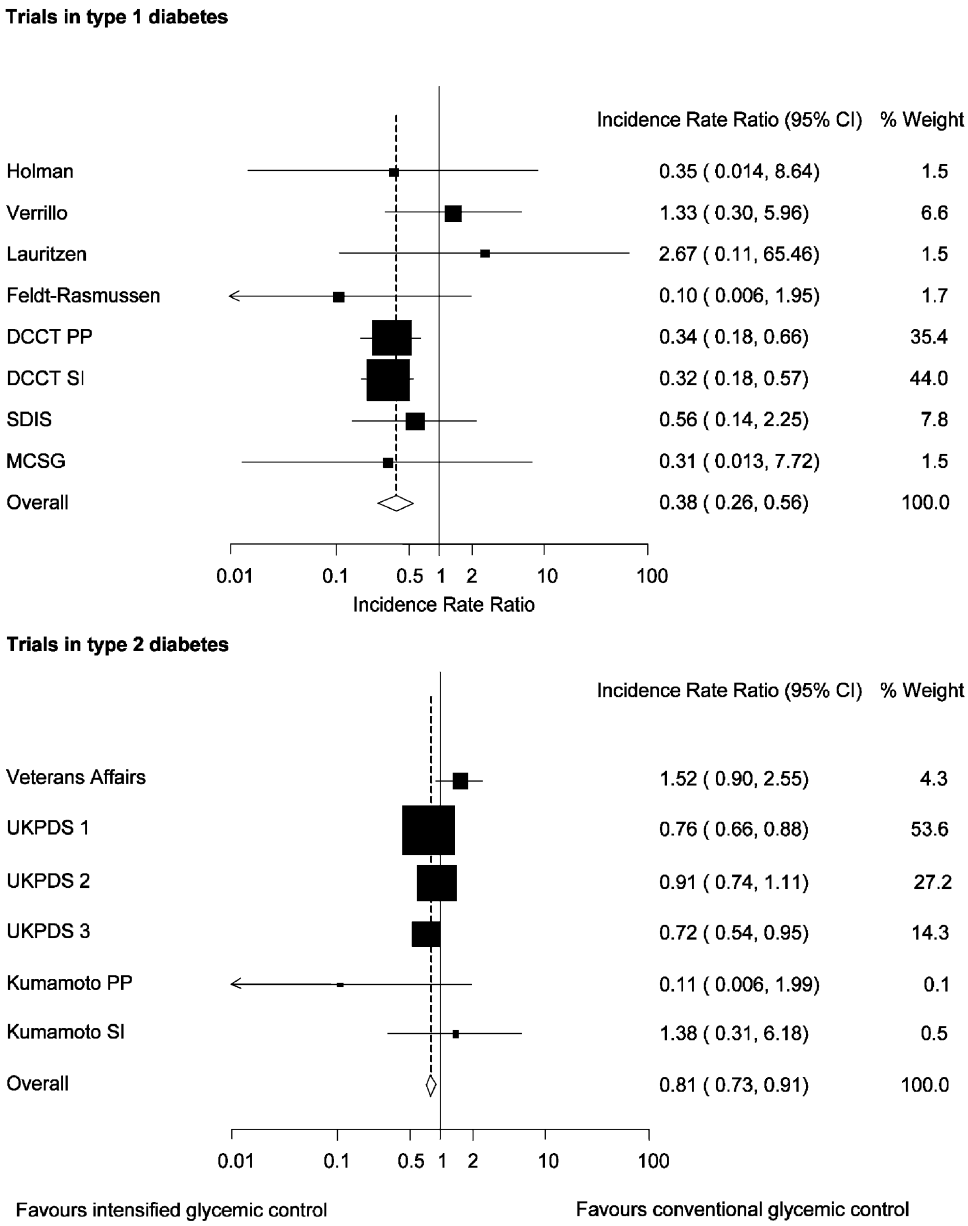
LDL cholesterol (mmol/L)		Triglycerides (mmol/L)		BMI (kg/m^2)		Percentage of smokers (%)	
Int	**Conv**	**Int**	**Conv**	**Int**	**Conv**	**Int**	**Conv**
2.7	2.9	1.6	1.8	24.9	24.8	na	na
na	na	na	na	na	na	na	na
na	na	na	na	na	na	na	na
na	na	na	na	na	na	na	na
2.8	3.1	1.1	1.2	26.2	25.1	28	23
2.9	3.0	1.1	1.1	27.2	25.3	27	21
na	na	na	na	23.9	23.3	na	na
na	na	na	na	na	na	na	na
3.4	3.3	2.0	2.0	31.9	32.7	21	8
3.2	3.2	1.6	1.5	26.0	25.4	29	36
3.4	3.4	2.0	2.0	33.0	32.4	30	25
3.4	3.4	2.2	2.0	31.7	32.2	27	27
na	na	1.1	1.2	21.5	21.3	na	na
na	na	1.1	1.2	21.5	21.3	na	na

Cardiac events		Peripheral vascular events		Cerebrovascular events	
Intensified	**Conventional**	**Intensified**	**Conventional**	**Intensified**	**Conventional**
0	1	0	0	0	0
2	0	1	2	1	1
1	0	0	0	0	0
0	0	0	0	0	4
1	11	11	27	0	0
3	12	12	34	0	0
3	5	0	0	0	0
0	1	0	0	0	0
10	30	24	64	1	5
26	18	4	4	5	2
401	184	17	12	91	80
327	87.5	20	10	76	18.5
84	64.5	8	9	13	14.5
0	1	0	1	0	2
3	1	1	1	0	1
841	356	50	37	185	118

Strengths and limitations

This is the first systematic review and meta-analysis including all randomized controlled trials done in patients with type 1 and type 2 DM. The effects of improved glycemic control could thus be compared between the 2 types of DM within the same review framework, using identical definitions and methodology. Previous reviews were restricted to one type of DM and

Figure 2



Effect of intensified glycemic control on the risk for any type of macrovascular event in patients with type 1 and type 2 DM. Meta-analysis of randomized controlled trials.

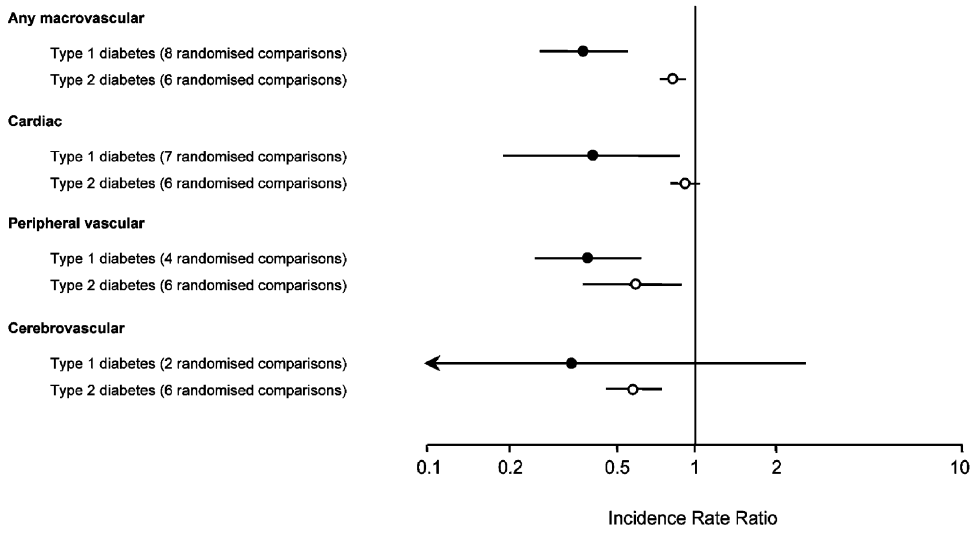
not directly comparable.[25,26] Our study was based on a comprehensive literature search. Original investigators checked the extracted data and contributed additional information. We acknowledge that the inclusion of large studies as DCCT in type 1 DM and UKPDS in type 2 DM could potentially have led to distortion of the results. As a consequence, whenever a study included several randomized comparisons, we included them separately to minimize individual weight and to maximize the power to identify factors that may modify the effect of improved glycemic control. For example, the separate inclusion of the primary and secondary prevention cohorts from the DCCT[5] and Kumamoto[9] studies meant that the power to detect a possible interaction between

Table V. Incidence rate ratios (95% CI) for any macrovascular event and cardiac, peripheral vascular, and cerebrovascular events

Study	Any macrovascular	Cardiac	Peripheral vascular	Cerebrovascular
Type 1 DM				
Holman et al (1983)[11]	0.35 (0.014-8.64)	0.35 (0.014-8.64)	0 events	0 events
Verrillo et al (1988)[10]	1.33 (0.30-5.96)	5.00 (0.24-104.15)	0.50 (0.05-5.51)	1.00 (0.06-15.99)
Lauritzen (1991)[7]	2.67 (0.11-65.46)	2.67 (0.11-65.64)	0 events	0 events
Feldt-Rasmussen et al (1992)[7]	0.10 (0.006-1.95)	0 events	0 events	0.10 (0.006-1.95)
DCCT Primary Prevention (1993)[13]	0.34 (0.18-0.66)	0.10 (0.013-0.76)	0.44 (0.22-0.89)	0 events
DCCT Secondary Intervention (1993)[13]	0.32 (0.18-0.57)	0.24 (0.07-0.86)	0.34 (0.18-0.66)	0 events
SDIS (1993)[8]	0.56 (0.14-2.25)	0.68 (0.16-2.82)	0.38 (0.02-9.21)	0 events
MCSG (1995)[12]	0.31 (0.013-7.72)	0.31 (0.013-7.72)	0 events	0 events
Combined IRR (fixed effect)	0.38 (0.26-0.56)	0.41 (0.19-0.87)	0.39 (0.25-0.62)	0.34 (0.05-2.57)
Heterogeneity (I^2, test of heterogeneity)	0.0%, $P = .579$	13.6%, $P = .326$	0.0%, $P = .957$	16.9%, $P = .273$
Type 2 DM				
Veterans Affairs (1997)[22]	1.52 (0.90-2.55)	1.50 (0.82-2.74)	1.04 (0.26-4.16)	2.60 (0.50-13.40)
UKPDS 1 (1998)[6]	0.76 (0.66-0.88)	0.90 (0.75-1.07)	0.58 (0.28-1.22)	0.47 (0.35-0.63)
UKPDS 2 (1998)[6]	0.91 (0.74-1.11)	0.93 (0.73-1.18)	0.50 (0.23-1.06)	1.02 (0.61-1.70)
UKPDS 3 (1998)[23]	0.72 (0.54-0.95)	0.78 (0.57-1.08)	0.60 (0.21-1.38)	0.54 (0.25-1.14)
Kumamoto Primary Prevention (2000)[9]	0.11 (0.006-1.99)	0.32 (0.013-7.89)	0.32 (0.013-7.89)	0.19 (0.009-4.02)
Kumamoto Secondary Intervention (2000)[9]	1.38 (0.31-6.18)	3.11 (0.32-29.91)	1.04 (0.06-16.58)	0.35 (0.014-8.49)
Combined IRR (fixed effect)	0.81 (0.73-0.91)	0.91 (0.80-1.03)	0.58 (0.38-0.89)	0.58 (0.46-0.74)
Heterogeneity (I^2, test of heterogeneity)	52.8%, $P = .060$	2.0%, $P = .404$	0.0%, $P = .948$	52.8%, $P = .060$

UKPDS 1, nonoverweight and sulfonylurea based; UKPDS 2, overweight and (SU) based; UKPDS 3, overweight and metformin based.

Figure 3



Effect of intensified glycemic control on the risk for any type of macrovascular event and of cardiac, peripheral vascular, and cerebrovascular events in patients with type 1 and type 2 DM. Combined estimates from meta-analyses of randomized controlled trials.

diabetes duration and the effect of improved glycemic control was enhanced. Random-effects model, attributing increased weight to smaller comparisons, revealed very comparable IRRs.

Although our study represents the largest body of evidence from randomized trials ever assembled to address this issue, the patients included in these trials may not be representative of patients with DM at large. Trials in type 1 DM enrolled young patients, most of them in their twenties and thirties, who were at low risk for macrovascular events. Trial participants with type 2 DM were also quite young, typically in their fifties.

Women were enrolled in all but one trial, but they generally were in the minority. The exclusion of women and older persons from trials has been documented previously, for example, in trials of statins.[27] It is difficult to judge whether the risk reductions observed in this meta-analysis are applicable to older patients and patients with longer duration of DM. We found that reductions in macrovascular risk tended to decrease with increasing age and duration of DM, particularly in type 2 DM, but in absolute terms, benefits may be as great or greater because of the increased macrovascular risk in the elderly. Finally, the duration of follow-up was generally <10 years, which may be insufficient if several years of treatment are required for effects to materialize fully.

Relation to other studies

Epidemiological studies have shown that the degree of blood glucose control achieved in patients with DM is associated with cardiac risk. Indeed, a recent meta-analysis of observational studies showed an increase in cardiac risk with increasing levels of HbA_{1c} both in patients with type 1 and type 2 DM.[28] Epidemiological analyses of the UKPDS showed a close relationship between HbA_{1c} and macrovascular risk.[29] In type 1 DM, the present analysis confirms an association of HbA_{1c} with macrovascular complications. Compared with a previous meta-analysis in patients with type 1 DM,[26] the present analysis included a larger number of studies and macrovascular events. In contrast to the aforementioned reports, metaregression analysis did not reveal a significant dependency of macrovascular risk on HbA_{1c} in type 2 DM. On one hand, this discrepancy could be due to statistical reasons in the present analysis and to the limitations of metaregression technique (analysis in type 2 DM only based on 6 comparisons, differences of HbA_{1c} lying in a close range). On the other hand, average changes in HbA_{1c} on study level might not entirely reflect efforts to improve glycemic control. The corresponding treatment strategies could nevertheless have beneficial effects on vascular end points not detected solely by measurement of HbA_{1c} (eg, reduction of postprandial hyperglycemia as a significant vascular risk factor as discussed hereinafter). In contrast to a broad analysis of interventions to prevent cardiac events in patients with type 2 DM,[25] we excluded the DIGAMI trial,[30] which showed that insulin-glucose infusion followed by a multidose insulin regimen improved prognosis in diabetic patients with acute myocardial infarction. The second DIGAMI trial[31] did not confirm a positive effect of intensified glycemic control in the setting of acute myocardial infarction. Recently, a U-shaped relationship of glycemic control with outcomes in acute coronary syndrome and myocardial infarction has been shown.[32] In contrast to these studies focusing on glycemic control in the setting of acute myocardial infarction, the present meta-analysis investigated the effect of improved long-term glycemic control in a general diabetic population.

Possible mechanisms

What factors could explain the finding that, in type 2 DM, improved glycemic control leads to a more modest reduction of macrovascular events and does not appear to have a significant impact on cardiac events? First, the metabolic abnormalities typical for type 2 DM not only lead to insulin resistance and hyperglycemia but also to dyslipidemia, arterial hypertension, endothelial dysfunction, and increased platelet activity and coagulability.[33] Improving blood glucose control without also addressing the other abnormalities, most importantly hypertension, dyslipidemia, and platelet hyperactivity, may therefore produce only limited benefit. Indeed, recent randomized trials of multifactorial interventions, including the tight blood pressure control arm of the UKPDS, showed substantial reductions in cardiac events.[29,34] Of note, in our analysis, the distribution of cardiac risk factors was similar both after randomization and at the conclusion of studies. One exception was the Veterans Affairs study[22] where smoking was more prevalent in the intensive treatment group. This imbalance, combined with the long duration of diabetes in this study population, may explain the anomalous results of this trial. Interventions that reduce insulin resistance have been shown to have antiatherogenic effects,[35-38] and this may have produced the somewhat larger benefits seen in overweight UKPDS patients randomized to metformin. In patients with type 1 DM, particularly younger patients, other macrovascular risk factors are less common and the nonenzymatic glycation of proteins and lipids, and the resulting formation of advanced glycation end products may thus be the predominant mechanism in the development of macrovascular and microvascular disease.[39,40]

Second, in trials in type 1 DM, the intensified regimen generally included basal and prandial insulin (multiple insulin injections or continuous subcutaneous insulin injection), which will have reduced postprandial as well as basal hyperglycemia. Postchallenge hyperglycemia is strongly associated with macrovascular complications. For example, in the DECODE study,[41] it was the postload blood glucose concentration that was independently associated with mortality. Furthermore, a post hoc analysis of the STOP-NIDDM trial[42] showed that decreasing postprandial hyperglycemia with the α-glucosidase inhibitor acarbose reduced cardiac risk in patients with impaired glucose tolerance. Intensified treatment regimens in type 2 DM focused mainly on normalizing basal blood glucose. The better control of postprandial hyperglycemia in type 1 DM may thus have contributed to the differences observed between the 2 types of DM.

Implications and conclusions

Our results suggest that, in type 1 DM, glycemic control is the essential treatment strategy leading not only to the well-documented reduction of microvascular complications but also to a substantial reduction of macrovascular disease. In patients with type 2 DM, improved glycemic control is associated with a more modest reduction in macrovascular complications. In these patients, the prevention of cardiac events must be effected by means of a broader treatment strategy, including antihypertensive, lipid-lowering, and platelet-inhibiting measures. The improvement of glycemic control itself appears to be particularly effective in younger patients with shorter duration of the disease. Ongoing studies will help to better define the benefits and risks of improved blood glucose control in type 2 DM, including the large ACCORD trial.[43]

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References

1. Haffner SJ, Cassells H. Hyperglycemia as a cardiovascular risk factor. Am J Med 2003;115(Suppl 8A):6S-11S.
2. Libby P, Plutzky J. Diabetic macrovascular disease: the glucose paradox? Circulation 2002;106:2760-3.
3. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. Diabetologia 1978;14:363-70.
4. Morrish NJ, Stevens LK, Head J, et al. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics) I: causes and death rates. Diabetologia 1990;33:538-41.
5. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.
6. 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.
7. Feldt-Rasmussen B, Mathiesen ER, Jensen T, et al. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. Diabetologia 1991;34:164-70.
8. Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. Diabetes 1994;43:313-7.
9. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23(Suppl 2):B21-9.
10. Verrillo A, de Teresa A, Martino C, et al. Long-term correction of hyperglycemia and progression of retinopathy in insulin dependent diabetes. A five-year randomized prospective study. Diabetes Res 1988;8:71-6.
11. Holman RR, Dornan TL, Mayon-White V, et al. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet 1983;1:204-8.
12. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. Microalbuminuria Collaborative Study Group, United Kingdom. BMJ 1995;311:973-7.
13. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75:894-903.
14. Egger M, Davey Smith G. Meta-analysis: potentials and promise. BMJ 1997;315:1371-4.
15. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 2002;31:150-3.
16. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001;323:42-6.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
18. Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309-12.
19. Egger M, Davey Smith G, Minder C. Bias in meta-analysis detected by a simple, graphical test—authors reply. BMJ 1998;316:470-1.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
21. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693-708.
22. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Arch Intern Med 1997;157:181-8.
23. 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.
24. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia 1991;34:877-90.
25. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001;111:633-42.
26. Lawson ML, Gerstein HC, Tsui E, et al. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis. Diabetes Care 1999;22(Suppl 2):B35-9.
27. Bartlett C, Davey P, Dieppe P, et al. Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001. Heart 2003;89:327-8.
28. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421-31.

29. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13.
30. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57-65.
31. Malmberg K, Ryden L, Wedel H, 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.
32. Svensson AM, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005;26:1255-61.
33. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287:2570-81.
34. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
35. Tan MH, Johns D, Strand J, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and l ipid profiles in patients with type 2 diabetes. Diabet Med 2004;21: 859-66.
36. Nesto R. C-reactive protein, its role in inflammation, type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. Diabet Med 2004;21:810-7.
37. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non–insulin-dependent diabetes mellitus. Drugs 1995;49:721-49.
38. Giugliano D, De Rosa N, Di Maro G, et al. Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive, obese women. Diabetes Care 1993;16:1387-90.
39. Brownlee M. Glycation products and the pathogenesis of diabetic complications. Diabetes Care 1992;15:1835-43.
40. Baynes JW. Role of oxidative stress in development of complications in diabetes. Diabetes 1991;40:405-12.
41. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: collaborative analysis Of Diagnostic criteria in Europe. Lancet 1999;354:617-21.
42. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486-94.
43. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, (http://www.accordtrial.org/public/index.cfm), accessed August 22, 2005.

Appendix A. Contributors

Christoph Stettler, Peter Diem, and Matthias Egger wrote the review protocol. Christoph Stettler and Sabin Allemann undertook the literature search, contacted trialists, performed data extraction, and assessed the methodological quality of trials. Rury R. Holman and Carole A. Cull performed data extraction on the UKPDS data. Matthias Egger, Peter Jüni, Sabin Allemann, and Christoph Stettler performed the statistical analyses. All authors contributed to the writing of the final draft of the manuscript.