

BMJ Open Targeting intensive versus conventional glycaemic control for type 1 diabetes mellitus: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials

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ABSTRACT

Objective: To assess the benefits and harms of targeting intensive versus conventional glycaemic control in patients with type 1 diabetes mellitus.

Design: A systematic review with meta-analyses and trial sequential analyses of randomised clinical trials.

Data sources: The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded and LILACS to January 2013.

Study selection: Randomised clinical trials that prespecified different targets of glycaemic control in participants at any age with type 1 diabetes mellitus were included.

Data extraction: Two authors independently assessed studies for inclusion and extracted data.

Results: 18 randomised clinical trials included 2254 participants with type 1 diabetes mellitus. All trials had high risk of bias. There was no statistically significant effect of targeting intensive glycaemic control on all-cause mortality (risk ratio 1.16, 95% CI 0.65 to 2.08) or cardiovascular mortality (0.49, 0.19 to 1.24). Targeting intensive glycaemic control reduced the relative risks for the composite macrovascular outcome (0.63, 0.41 to 0.96; $p=0.03$), and nephropathy (0.37, 0.27 to 0.50; $p<0.00001$). The effect estimates of retinopathy, ketoacidosis and retinal photocoagulation were not consistently statistically significant between random and fixed effects models. The risk of severe hypoglycaemia was significantly increased with intensive glycaemic targets (1.40, 1.01 to 1.94). Trial sequential analyses showed that the amount of data needed to demonstrate a relative risk reduction of 10% were, in general, inadequate.

Conclusions: There was no significant effect towards improved all-cause mortality when targeting intensive glycaemic control compared with conventional glycaemic control. However, there may be beneficial effects of targeting intensive glycaemic control on the composite macrovascular outcome and on nephropathy, and detrimental effects on severe hypoglycaemia. Notably, the data for retinopathy and ketoacidosis were inconsistent. There was a severe lack of reporting on patient relevant outcomes, and all trials had poor bias control.

Strengths and limitations of this study

- The systematic review is based on a published protocol.
- We included 18 randomised clinical trials from a comprehensive search with no language limitations or restrictions on outcomes reported in the trials.
- The available evidence was evaluated with trial sequential analysis and sensitivity analysis.
- All trials had a high risk of bias.
- The trials lacked reporting on patient relevant outcomes.

INTRODUCTION

Patients with type 1 diabetes mellitus are at increased risk of developing microvascular and macrovascular complications, as well as an increased risk of all-cause mortality compared with the background population.¹ Observational studies suggest that reduction of blood glucose levels in patients with type 1 diabetes mellitus is associated with lower risk of vascular complications.² A large randomised clinical trial, the Diabetes Control and Complications Trial (DCCT),^{3–46} suggested a beneficial effect of strict glycaemic control on the risk of primarily microvascular complications in patients with type 1 diabetes mellitus. Since the completion of the DCCT,^{3–46} the patients included have been followed in an observational study (Epidemiology of Diabetes Interventions and Complications (EDIC)). Based on this study it has been generally accepted that tight glycaemic control should be the preferred glycaemic approach for patients with type 1 diabetes mellitus, in order to reduce the risk of complications and death.^{47–48} Since the

publication of the results of the DCCT,^{3–46} no large scale trials have been conducted challenging this approach.

The treatment recommendations for patients with type 1 diabetes mellitus are to a large extent based on the DCCT.^{3–46} There is currently no up-to date comprehensive systematic review investigating the benefits and harms of targeting intensive glycaemic control compared with conventional glycaemic control in randomised clinical trials, regardless of the length of intervention and the age of participants. Intensive glycaemic control may cause increased risk of hypoglycaemia. In addition, achieving intensive glycaemic control in patients with type 1 diabetes mellitus typically requires markedly increased efforts of the individual patient as well as the use of increased resources from the healthcare system, due to additional doctor visits, glucose measurements and insulin injections.⁴⁹

The definition of intensive glycaemic control varies among trials and guidelines. The DCCT^{3–46} applied an intensive intervention target of glycosylated haemoglobin A1c (HbA_{1c}) <6.05%,^{3–46} whereas the intensive target was HbA_{1c} <7.5% in the Microalbuminuria Trial.^{50 51} The guidelines also lack consistency. The American Diabetes Association recommends a HbA_{1c} level for patients with type 1 diabetes mellitus of less than 7%⁴⁷ whereas the International Diabetes Federation recommends less than 6.5%.⁴⁸

This systematic review combines current evidence from randomised clinical trials on the effect of targeting intensive glycaemic control versus conventional glycaemic control on all-cause mortality, cardiovascular mortality, cardiovascular disease, microvascular disease, cancer, body mass index, weight, adverse events, mild and severe hypoglycaemia, costs of intervention, quality of life and ketoacidosis in patients with type 1 diabetes mellitus.

METHODS

This review follows the recommendations of The Cochrane Collaboration,⁵² and is based on a published protocol.⁵³ We included all randomised clinical trials with prespecified different targets of glycaemic control in participants at any age with type 1 diabetes mellitus.

Search strategy

We searched in *The Cochrane Library*, Medline, EMBASE, Science Citation Index Expanded, and LILACS in January 2013 for randomised clinical trials of targeting intensive glycaemic control versus conventional glycaemic control in patients with type 1 diabetes mellitus. Web appendix 1 describes the search strategies for each database. We also searched abstracts present at the American Diabetes Association and the European Association for the Study of Diabetes congresses. We searched reference lists of the included trials in (systematic) reviews and meta-analyses and health technology assessment reports. Clinicaltrials.gov was searched for trial protocols, unpublished data and ongoing trials. We

performed internet searches for all trials, as well as contacted authors for information about additional trials.

Study selection

Two authors (PK and BH or BG) independently screened titles and abstracts according to the inclusion criteria. We included a trial if it was a randomised clinical trial; compared targeting intensive glycaemic control versus conventional glycaemic control; and undertaken in patients with type 1 diabetes mellitus. Trials only including pregnant patients were excluded. We included trials irrespective of duration, language, publication status and predefined outcomes.

In the published protocol, we predefined inclusion of all trials comparing patients treated to a specific target for intensive glycaemic control with patients treated to a conventional target.⁵³ The intensive glycaemic targets varied among the trials, but all the included trials compared the results of aiming at a distinct lower target compared with the target of the control group. That is, trials investigated the effect of the use of more versus less intensive glucose targets in patients with type 1 diabetes mellitus, irrespective of differences among trials in predefined targets and achieved glycaemic control. Trials investigating the effect of different insulin regimens without a predefined difference in terms of glycaemic targets between groups were therefore excluded.

Data extraction and risk of bias assessment

Two authors (PK and BH or BG) independently extracted information from each included trial by using standard data extraction forms, and assessed the risk of bias as defined in *The Cochrane Handbook of Systematic Reviews of Interventions*.⁵² We assessed the following risk of bias domains: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, academic bias and sponsor bias.^{52 53} For each domain, bias control was classified as adequate, unclear or inadequate. Owing to the nature of the design of comparing intensive glycaemic targets versus conventional glycaemic targets, it is not possible to blind the healthcare providers and the patients. Blinding was considered adequate if the outcome assessors were blinded. As most trials were with a high risk of bias, we divided the trials into those with a lower risk of bias, and those with a high risk of bias based on assessment of sequence generation, concealment of allocation, and blinding (table 4).^{52 53} When we judged all three domains to be of low risk of bias, we designated the trial as having a lower risk of bias.

Discrepancies between the initial two authors' assessments were resolved by involvement of a third author (BH or BG). We extracted data at a trial level on several baseline characteristics of the participants (such as age, duration of disease and HbA_{1c}), and outcomes. The predefined primary outcomes reported in this review were:⁵³ *all-cause mortality*; *cardiovascular mortality*; and *severe adverse events*. Our secondary outcomes were⁵³:

macrovascular complications (reported as a composite outcome); *non-fatal myocardial infarction*; *non-fatal stroke*; *amputation of lower extremity*; *cardiac or peripheral revascularisation*; *mild and severe hypoglycaemia*; *microvascular complications* (reported as a composite outcome); *retinopathy*; *nephropathy*; *retinal photocoagulation*; *end-stage renal disease*; *cancer*; *congestive heart failure*; *ketoacidosis*; *weight/body mass index (BMI)*; *health-related quality of life*; and *cost of interventions*. We sought any relevant missing information from the original author(s) of the trial. When we identified more than one publication of an original trial, we assessed these together to maximise data collection. In case of substantial disagreement between older and newer publications, we contacted the authors. Data were extracted for both the end of the intervention period (the active treatment phase) and to the longest follow-up, if the trial had an observational follow-up period beginning after the active treatment phase.

Statistical analyses

We used Review Manager V.5.2⁵⁴ for statistical analyses. We summarised dichotomous data as relative risks with 95% CIs. We used a random effects model and a fixed effect model.^{55–56} In case of discrepancy between the two models, we reported both results; otherwise, we reported the random effects model. We examined heterogeneity with the I^2 statistic. The data were analysed according to the intention-to-treat analysis.

We planned the following subgroup analyses for the primary outcomes: trials with a high risk of bias compared to trials with a lower risk of bias; published trials compared to unpublished trials; the use of human insulin compared to the use of insulin analogues; trials including participants at all ages compared to trials including participants older than 18 years.

Data were cross checked with previous meta-analyses^{57–61} and additional data could be included from three meta-analyses.^{57–59}

We conducted trial sequential analyses.^{62–63} This is similar to interim analyses in a single trial, where monitoring boundaries are used to decide whether a trial could be terminated early when a p value is sufficiently small to show the anticipated effect. Because there is no reason why the standards for a meta-analysis should be less rigorous than those for a single trial, analogous trial sequential monitoring boundaries can be applied to meta-analysis.^{64–66} Trial sequential analysis depends on the quantification of the required information size (the required sample size of the meta-analysis). In this context, the smaller the required information size the more lenient the trial sequential monitoring boundaries are, and accordingly, the more lenient the criteria for statistical significance will be. On the basis of predetermined criteria⁵³ we calculated the diversity-adjusted required information size based on the diversity (D^2) among the included trials.⁶² We conducted the trial sequential analyses with an intention to maintain an overall 5% risk of a type I error, which is the standard in most meta-analyses

and systematic reviews. We calculated the required information size to detect or reject an intervention effect of a 10% relative risk reduction with a risk of a type II error of 20% (power of 80%). For the dichotomous outcomes, the event proportion in the control group was based on the data from the meta-analysis. For the continuous outcomes, we calculated the required information size to detect or reject the achieved differences from the meta-analyses. We used TSA V.0.9 β for these analyses.⁶⁷

RESULTS

Figure 1 summarises the result of the search. We excluded 58 references after further evaluation. The reason for exclusion was a lack of predefined differences in glycaemic targets (36 trials); participants were not patients with type 1 diabetes mellitus or we could not separate data on patients with type 1 diabetes mellitus (10 trials); the trial was not randomised (11 studies); or the trial included only pregnant participants (1 trial). Fourteen references were not identified in the original search, but were retrieved from additional sources, of whom only one was a randomised clinical trial.⁶⁸ Excluded studies are listed in web appendix 3.

We included 18 randomised trials, described in 136 publications. All trials were published in English. The trials included 2254 participants, of whom 1110 were randomised to target intensive glycaemic control versus 1144 to conventional glycaemic control. Table 1 shows key characteristics of the included trials and table 2 shows key characteristics of the trial participants.

The intervention target for glycaemic control varied among trials in both the intensive and conventional groups (table 3). Some trials predefined the intensive glycaemic target in terms of HbA_{1c} or preprandial or postprandial blood glucose concentration (table 3). Trials intending to lower the blood glucose in the intervention group to a larger extent than in the conventional group were included. In contrast, trials investigating whether glycaemia were lowered more by one treatment than another, for example, by different insulin regimens but without specifying differences in glucose targets or intentions with respect to differences in glucose levels, were excluded. Achieved treatment targets varied among trials, in general, the achieved HbA_{1c} seldom reached the planned target.

A trial by Linn *et al* 2003⁶⁹ was never published. Through correspondence, it was stated that no publication was made due to lack of statistical significance.

We used the author's definitions of type 1 diabetes mellitus. Seven trials reported the diagnostic criteria for type 1 diabetes mellitus. These trials included patients with C-peptide level <0.1–0.2 pmol/mL in the postabsorptive state and/or 6 min after intravenous injection of 1 mg glucagon.^{3–46 69–86} All trials excluded participants with severe concurrent illnesses, except for The Minnesota DCCT^{83–86} which had kidney transplantation as an inclusion criterion.

The DCCT^{3–46} contributed with most of the participants (63.9%). The trial intervention period had a mean of 6.5 years, and was stopped 1 year before originally planned due to the positive results (especially on microvascular complications) in the intensive intervention group. EDIC is the observational long-term follow-up study including 96% of the living patients from DCCT. In the EDIC, patients were no longer randomised to different glycaemic targets, but were still seen regularly at the clinics, and patients in the former conventional group were offered intensive glycaemic control (similar to the former intensive group). A trial design with an intervention period and an epidemiological follow-up period were seen in seven of the included trials.

Owing to the relatively short intervention time in the included trials (excluding the DCCT) and young participants, the event-rate was relatively low for most of the outcomes. We therefore performed a Peto OR and continuity adjustment ad modum Sweeting for zero events with a value of 0.01, to test whether it would change the statistical significance for the following outcomes: all-cause mortality, cardiovascular mortality, retinopathy, retinal photocoagulation, nephropathy, end-stage renal disease and hypoglycaemia. The sensitivity analyses did not change the results noticeably for any of the outcomes.

Bias risk assessment

The quality of the included trials was in general low, and all trials had a high risk of bias (table 4). Seven of the included trials had a low risk of bias according to generation of the sequence, and two trials had a low risk of

bias according to allocation concealment (table 4). Only the DCCT^{3–46} was judged as a trial with lower risk of bias according to our definition, but still had high risk of bias due to incomplete data on outcomes and academic bias.

Clinical outcomes

All-cause mortality

Nine trials provided information on all-cause mortality in a total of 1971 participants, reporting 42 deaths (figure 2A). Meta-analysis showed no statistically significant effect of targeting intensive glycaemic control compared with conventional glycaemic control (risk ratio (RR) 1.16, 95% CI 0.65 to 2.08; $p=0.61$). Heterogeneity was absent ($I^2=0\%$; $p=0.89$). Sensitivity analysis including only data from intervention periods did not change the lack of statistical significance of the effect estimate (RR 1.16, 95% CI 0.60 to 2.26; $p=0.66$; figure 2B). Data from DCCT^{3–46} were only available from the end of the intervention period (mean 6.5 years).

Worst–best case scenario showed statistical significance in favour of a conventional glycaemic target (RR 2.96, 95% CI 1.86 to 4.71; $p<0.0001$). Best–worst case scenario showed statistical significance in favour of an intensive glycaemic target (RR 0.45, 95% CI 0.28 to 0.71; $p=0.0007$).

The predefined subgroup analyses according to insulin types, risk of bias and publication status could not be performed due to lack of data. Subgroup analyses of the trials including participants at all ages versus trials only including participants over 18 years showed no statistically significant differences between subgroups, that is, no statistically significant interaction. Sensitivity

Figure 1 Flow diagram of identification of randomised clinical trials for inclusion.

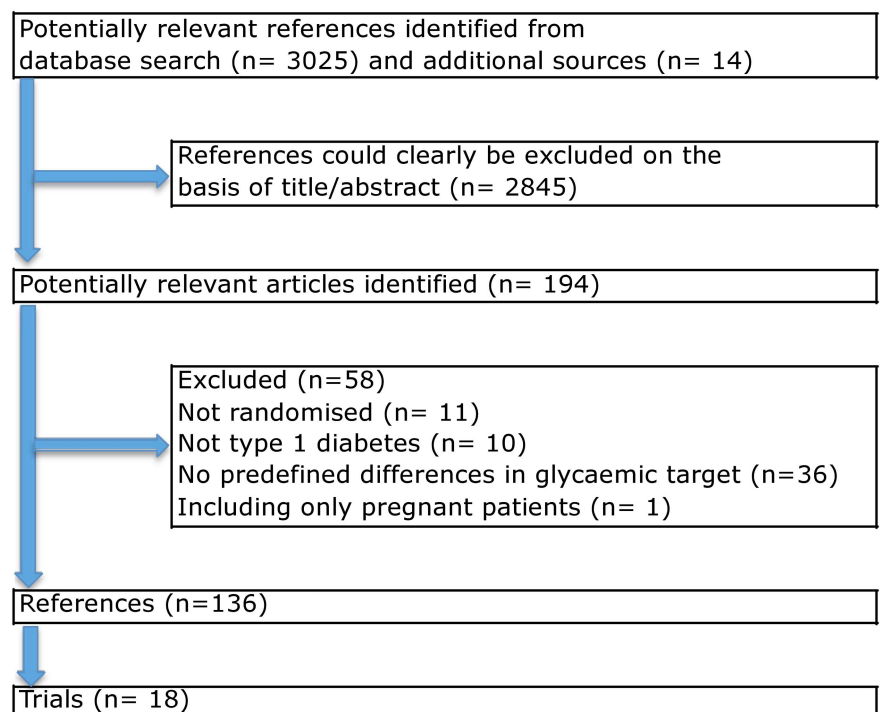


Table 1 Key characteristics of the included randomised clinical trials

Trial	Location	Duration of intervention	Length of follow up
DCCT/EDIC 1983 ^{3–46}	29 centres; USA and Canada	6.5 years	25 years
Franklin <i>et al</i> ¹⁰⁴	Scotland	1 year	1 year
Hvidovre 1982 ⁶⁸	1 centre; Denmark	10 days	180 days
Kroc 1984 ^{112–117}	6 centres; North America and England	2 years*	2 years
Linn <i>et al</i> ¹¹⁰	Germany	5 years	5 years
Linn <i>et al</i> [†] ⁶⁹	4 centres; Germany	3 years	3 years at least†
Microalbuminuria ^{50 51}	9 centres; England and Wales	5 years	5 years
Minnesota DCCT 1983 ^{83–86}	2 centres; USA	5 years	5 years
Oslo 1986 ^{73–80}	Norway	4 years	8 years
Oxford 1983 ¹¹¹	England	2 years	2 years
Perlman <i>et al</i> ¹⁰⁵	1 centre; Canada	1 year	1 year
Service <i>et al</i> ⁸¹	USA	2.5 years	2.5 years
Shah <i>et al</i> ¹⁰¹	USA	I: 14 days C: 1 year	1 year
Steno 1a 1982 ^{72 119 120 121}	1 centre; Denmark	2 years	8 years
Steno 1b 1986 ^{70–72}	1 centre; Denmark	2 years	5 years
Stockholm 1985 ^{87–98}	Sweden	5 years	14 years
Verrillo <i>et al</i> ⁸²	Italy	5 years	5 years
Hershey <i>et al</i> ¹⁰² and White ¹⁰³	2 centres; USA	1.5 years	1.5 years

*The study was planned to last for 8 months, but after the 8 months 23 participants (out of 34) in the intervention group and 24 participants (out of 34) in the control group agreed to continue their intervention for additional 16 months, and all participants were re-evaluated after 2 years.

†We only have the study protocol. No results were published and the author was not able to pass any data to us.

DCCT/EDIC, Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications; Minnesota DCCT, Minnesota Diabetes Control and Complication Trial.

analysis excluding the trial with the longest duration (DCCT/EDIC^{3–46}) did not change the lack of statistical significance of the effect estimate (RR 1.03, 95% CI 0.53 to 1.98; $p=0.93$). The Minnesota DCCT^{83–86} included participants with renal transplantation; sensitivity analyses excluding this trial did not change the lack of statistical significance (RR 1.48, 95% CI 0.71 to 3.10; $p=0.30$).

Trial sequential analysis showed that only 1.18% of the required information size to detect or reject a 10% relative risk reduction was accrued, and the trial sequential monitoring boundaries were not crossed (figure 2C).

Cardiovascular mortality

Seven trials provided information on cardiovascular mortality in a total of 1802 participants (figure 3A). Meta-analysis showed no statistical significance of targeting intensive glycaemic control compared with conventional glycaemic control (RR 0.49, 95% CI 0.19 to 1.24; $p=0.13$). Heterogeneity was absent ($I^2=0\%$; $p=0.84$). Worst–best case scenario showed no statistical significance (RR 1.31, 95% CI 0.66 to 2.57). Best–worst case scenario showed statistical significance in favour of targeting intensive glycaemic control (RR 0.27, 95% CI 0.12 to 0.62; $p=0.002$). Sensitivity analysis including only data from intervention periods did not change the lack of statistical significance of the effect estimate (RR 0.81, 95% CI 0.16 to 4.19; $p=0.81$; figure 3B).

The predefined subgroups comparing insulin types, risk of bias and unpublished trials could not be performed, due to a lack of data. Subgroup analyses of the

trials according to the age of participants showed no statistically significant differences between subgroups (ie, no significant interaction). Sensitivity analysis excluding the trial with the longest duration (DCCT/EDIC^{3–46}) did not change the statistical significance of the effect estimate (RR 0.70, 95% CI 0.19 to 2.66; $p=0.60$).

Trial sequential analysis showed that only 0.84% of the required information size to detect or reject a 10% relative risk reduction was accrued, and the trial sequential monitoring boundaries were not crossed (see web appendix 3, figure 9).

Macrovascular complications

Three trials provided information on macrovascular complications in a total of 1577 participants (figure 4A). We used the authors' definitions of macrovascular complications, which varied among the included trials, see web appendix 4. A total of 87 participants with a macrovascular complication were reported of whom 83 participants were from DCCT/EDIC.^{3–46} Meta-analysis showed a statistically significant effect of targeting intensive glycaemic control compared with conventional glycaemic control (RR 0.63, 95% CI 0.41 to 0.96; $p=0.03$). Heterogeneity was absent ($I^2=0\%$; $p=0.65$). It was not possible to perform a sensitivity analysis including only data from intervention periods due to a lack of data.

Sensitivity analysis excluding the trial with the longest duration (DCCT/EDIC^{3–46}) changed the statistical significance of the effect estimate to no statistically significant effect (RR 0.99, 95% CI 0.15 to 6.57; $p=0.99$).

Table 2 Key characteristics of the trial participants

Trial	Number of participants Intensive/ conventional (total)	Age (years)* Intensive (SD)/ conventional (SD)	Duration of disease at baseline (years)* Intensive (SD)/conventional (SD)	Weight at baseline (kg)* Intensive (SD)/ conventional (SD)	BMI at baseline (kg/m ²)* Intensive (SD)/ conventional (SD)
DCCT/EDIC 1983 ³⁻⁴⁶ Franklin <i>et al</i> ¹⁰⁴	711/730 (1441) 31 / C ₁ : 28 C ₂ : 33 (92)	27.1 (7.1)/26.5 (7.1) 12.6 (11.2–15.4)†/ C ₁ : 12.7 (10.5–14.8) † C ₂ : 14.1 (11.7–15.6) †	6.0 (4.2)/5.7 (4.1) 5.4 (2.9–7.7)†/ C ₁ : 3.2 (1.7–6.7)† C ₂ : 4.8 (2.6–8.6)†	NR NR	23.4 (2.7)/23.5 (2.9) 0.44 (0.04–1.04)† / C ₁ : 0.38 (–0.44–0.83)† C ₂ : 0.13 (–0.55–1.0)† **
Hvidovre 1982 ⁶⁸	7/9 (16)	27 (21–37)†/28 (17–35)†	Newly diagnosed	93% (80–104) †/87.5% (75–104)† ‡	NR
Kroc 1984 ^{112–117} Linn <i>et al</i> ¹¹⁰ Linn <i>et al</i> § ⁶⁹	35 /35 (70) 23/19 (42) NR	31.9 (10.1)/34.0 (9.5) 27 (8)/29 (8) NR	16.5 (6.5)/18.2 (7.1) 7.2 (5.2) days/7.6 (5.6) days NR	NR 66 (11.8) /68 (11.8) 5.7 (5.2)/5.5 (5.0)¶	NR NR NR
Microalbuminuria ^{50 5} Minnesota DCCT 1983 ^{83–86}	36/34 (70) 52/47 (99)	37 (19–59)†/37 (17–58)† 35 (6)/36 (8)	21 (6–35)/18 (7–34) 23 (6) /21 (5)	NR NR	26 (18–40)†/26 (19–34)† 28.2 (8.2)/26 (4.3)
Oslo 1986 ^{73–80}	I ₁ : 15 I ₂ : 15 /15 (45)	I ₁ : 26 (19–42)† I ₂ : 26 (18–38)† / 26 (18–36)†	I ₁ : 12.8 (6.8–20.8)† I ₂ : 12.8 (6.4–23.3)† /12.7 (6.8–12.0)†	I ₁ : 71.7 (10) I ₂ : 68.6 (9.3) / 71.7 (10.5)	NR
Oxford 1983 ¹¹¹ Perlman <i>et al</i> ¹⁰⁵ Service <i>et al</i> ⁸¹ Shah <i>et al</i> ¹⁰¹	36/38 (74) 7/7 (14) 7/8 (15) 12/14 (26)	41.6 (11.5)/43.2 (12.6) 13.9 (2.3)/11.6 (1.6) 33/31 13.2 (2.4)/13.8 (5.2)	18.1 (5.1)/19.2 (7.1) Newly diagnosed 1.1/1.3 Newly diagnosed	NR 43 (12)/41 (12) 100%/101% ‡ NR	NR NR NR NR
Steno 1a 1982 ^{72 119 120 121}	18/16 (34)	35 (21–50)†/32 (24–46)†	19 (11–33)†/19 (9–27)†	105% (84–123)†/100% (79–123)† ‡	NR
Steno 1b 1986 ^{70–72} Stockholm 1985 ^{87–98}	18/18 (36) 48/54 (102)	32 (18–48)†/29 (18–47)† 30.0 (7.5)/31.7 (7.3)	15 (10–26)†/15 (5–26)† 17.9 (6.4)/16.3 (4.9)	NR NR	NR 22.6 (1.9)/22.8 (2.5)
Verrillo <i>et al</i> ⁸² Hershey <i>et al</i> ¹⁰² and White ¹⁰³	22/22 (44) 17/17 (34)	37 (9.8)/38 (9.0) 13.9 (2.8)/14.3 (2.7)	19 (5)/2 (6) Newly diagnosed	NR NR	25.8 (3.5)/26.2 (3.7) NR

*Mean or median.

†Range.

‡Bodyweight % of ideal.

§We only have the study protocol. No results were published and the author was not able to pass any data to us.

¶Weight loss (kg).

**BMI SD score.

BMI, body mass index; C₁, conventional group 1; C₂, conventional group 2; DCCT/EDIC, Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications; Minnesota DCCT, Minnesota Diabetes Control and Complication Trial; NR, not reported; I₁, intensive group 1; I₂, intensive group 2.

Table 3 Glycaemic control

Trial	HbA _{1c} at baseline (%)* Intensive (SD)/ conventional (SD)	Fasting blood glucose at baseline (mmol/L)* † Intensive (SD)/ conventional (SD)	Treatment target: intensive glycaemic control	Treatment target: conventional glycaemic control	Achieved HbA _{1c} (%)* Intensive (SD)/ conventional (SD)
DCCT/EDIC 1983 ^{3–46}	9.1 (1.6)/9.1 (1.6)	12.99 (4.6)/12.79 (4.4)	HbA _{1c} between 4.05–6.05%. FBG between 3.88–6.05 mmol/L and 9.99 mmol/L 90–120 minutes post-prandial and 3.60 mmol/L or above after 3 am	HbA _{1c} <13.11% and absence of symptoms of glycosuria, hyperglycaemia and ketonuria	7.9 (1.1)/8.0 (1.0)
Franklin <i>et al</i> ¹⁰⁴	10.2 (2.0) / C ₁ : 10.2 (1.6) C ₂ : 9.8 (1.8)	NR	Expected lower HbA _{1c} compared to the conventional treated group, due to Intensive pump treatment†	Conventional treatment	9.2 (2.2)/ C ₁ : 10.3 (1.7) C ₂ : 10.1 (1.7)
Hvidovre 1982 ⁶⁸	NR	23.3 (12.6–39.5) §/18.1 (14.0–25.8) §	Near normo-glycaemia	Conventional treatment	6.4 mmol/L/9.0 mmol/L
Kroc 1984 ^{112–117}	10.3 (2.4)/10.1 (1.8)	10.98 (3.3)/10.39 (3.0)	BG between 3.1 and 6.4 mmol/L before meal, and <8.9 mmol/L 90 minutes after meal	To avoid extreme hyperglycaemia, ketosis and symptomatic hypoglycaemia	8.1 (1.2)/10.0 (2.3)
Linn <i>et al</i> ¹¹⁰	12.4 (5.5)/13.1 (6.2)	9.4 (5.6)/9.1 (2.7)¶	HbA _{1c} <6.5%, with a preprandial BG <6.8 mmol/L and postprandial BG <10 mmol/L	Conventional treatment with absence of symptoms attributable to glycosuria, or frequent hypoglycaemia	6.6 (1.6)/8.0 (2.8)
Linn <i>et al</i> ⁶⁹ Microalbuminuria ^{50 51}	NR 10.3 (1.99)/9.8 (1.64)	NR NR	Optimal glycaemic control HbA _{1c} ≤7.5%. FBG between 4–7 mmol/L and a 2 hs postprandial BG ≤10 mmol/L	Conventional glycaemic control Conventional treatment	NR 8.9 (1.5)/9.8
Minnesota DCCT 1983 ^{83–86}	NR	13.65 (3.1)/13.37 (2.7)	HbA _{1c} <7%, home capillary BG between 3.33–8.32 mmol/L before meals and at bedtime, and postprandial ≤9.98 mmol/L	To avoid hyperglycaemic symptoms with 60% of home capillary BG >11.10 mmol/L and 20% >16.65 mmol/L. Since 1983 target changed to HbA _{1c} A1 <12%	9.6 (1.6)/11.7 (0.13)
Oslo 1986 ^{73–80}	I ₁ : 9.4 (1.5) I ₂ : 10.1 (1.9) /9.5 (1.9)	I ₁ : 8.1 (1.0) I ₂ : 9.1 (0.9) / 8.2 (1.0)	Near normo-glycaemia	Conventional treatment	I ₁ : 9.4 (1.5) I ₂ : 10.1 (1.9) /9.5 (1.9)
Oxford 1983 ¹¹¹	11.7 (1.6)/11.8 (2.1)	NR	Preprandial BG between 4–7 mmol/l	Conventional treatment	9.5 (1.6)/10.33 (2.31)
Perlman <i>et al</i> ¹⁰⁵	14.6 (2.4)/15.8 (4.8)	28.4 (14.4)/25.8 (8.9)††	Fasting euglycaemia and normal glucose excursions	Preprandial BG between 4.4– 10.0 mmol/L and no glycosuria	11.2 (4.5)/12.9 (2.9)
Service <i>et al</i> ⁸¹	10.4/9.6	8.9/9.2	HbA _{1c} within normal range and mean plasma glucose <11.1 mmol/L	Conventional treatment to eliminate symptoms with a mean plasma glucose <11.1 mmol/L	9.8/9.6
Shah <i>et al</i> ¹⁰¹	18.2 (6.2)/15.9 (5.6)	NR	BG between 3.3–4.4 mmol/L preprandial and 1 h postprandial	BG <7.8 mmol/L preprandial and 11.1 mmol/L after 1 h postprandial	7.2 (2.4)/10.8 (4.5)

Continued

Table 3 Continued

Trial	HbA _{1c} at baseline (%) [*] Intensive (SD)/ conventional (SD)	Fasting blood glucose at baseline (mmol/L) [*] † Intensive (SD)/ conventional (SD)	Treatment target: intensive glycaemic control	Treatment target: conventional glycaemic control	Achieved HbA _{1c} (%) [*] Intensive (SD)/ conventional (SD)
Steno 1a 1982 ^{72 119–121}	9.6 (1.6)/8.8 (1.4)	9.6/8.8	Postprandial BG <9 mmol/L and no glucosuria	Postprandial BG <15 mmol/L and 24 h glucose excretion < 20 g. After 1 year restriction was added about no hypoglycaemia or ketonuria	7.6 (0.9)/8.1 (1.1)
Steno 1b 1986 ^{70–72}	9.5 (6.6–13.6)§/ 9.3 (7.0–11.7)§	10.0 (8.5)/11.3 (8.5)	Fasting blood glucose between 4–7 mmol/L and postprandial BG between 5–10 mmol/L and avoiding of blood glucose < 3 mmol/L	Postprandial morning BG <15 mmol/L and 24 h glucose excretion <20 g	7.9 (1.1)/9.1 (1.2)
Stockholm 1985 ^{87–98}	9.5 (0.2)/9.4 (0.2)	NR	Intensified treatment with individual goals for each patient	Conventional treatment by reduced BG without giving rise to serious hypoglycaemia	7.26 (0.85) /8.13 (1.10)
Verrillo <i>et al</i> ⁸²	11.1 (1.1)/11.8 (1.9)	11.1 (1.1)/11.8 (1.9)	Normo-glycaemia with absence for hypoglycaemia and avoiding BG <3 mmol/L. Preprandial BG between 4–8 mmol/L and 120 minutes postprandial BG < 10 mmol/L	Preprandial morning BG <12 mmol/L and 24 h urinary glucose excretion under 20 g	8.7 (0.5)/10.5 (0.5)
Hershey <i>et al</i> ¹⁰² and White ¹⁰³	8.26/9.96	NR	Preprandial BG between 3.9–6.7 mmol/L, and avoidance of hyperglycaemia	Preprandial BG between 4.4–10.0 mmol/L, and avoidance of hyperglycaemia	NR

^{*}Mean or median.

†Converted from mg/dL to mmol/L by dividing by 18.

‡An aim for a lower glycaemic target in the intensive group compared to the conventional group was confirmed by the author.

§Range.

¶Mean glucose level.

**We only have the study protocol. No results were published and the author was not able to pass any data to us.

††Random plasma glucose.

DCCT/EDIC, Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications; HbA_{1c}, glycated haemoglobin A_{1c}; Minnesota DCCT, Minnesota Diabetes Control and Complication Trial; NR, not reported; I₁, intensive group 1; I₂, intensive group 2; C₁, conventional group 1; C₂, conventional group 2. FBG, fasting blood glucose; BG, blood glucose.

Trial sequential analysis showed that only 3.84% of the required information size to detect or reject a 10% relative risk reduction was accrued so far, and the trial sequential monitoring boundaries were not crossed (figure 4B).

Nephropathy and end-stage renal disease

Five trials provided information on nephropathy in a total of 1635 participants (figure 5A). The definition of nephropathy varied among the included trials from albumin excretions rate >300 mg/24 h to a non-specific 'clinical nephropathy', see web appendix 4. Meta-analysis showed a statistically significant effect of targeting intensive glycaemic control compared with conventional glycaemic control (RR 0.37, 95% CI 0.27 to 0.50; $p < 0.00001$). Heterogeneity was low ($I^2 = 5\%$; $p = 0.38$). Sensitivity analysis including only data from intervention periods also found a statistical significance of the effect estimate (RR 0.35, 95% CI 0.12 to 1.00; $p = 0.05$; figure 5B).

Trial sequential analysis showed that only 10.4% of the required information size to detect or reject a 10% relative risk reduction was accrued, and the trial sequential monitoring boundaries were not crossed (figure 5C).

The effect of intensive glycaemic targets on end-stage renal disease was not statistically significant (RR 0.96, 95% CI 0.13 to 7.05, 3 trials, 124 participants). Sensitivity analysis including only data from intervention periods did not change the lack of statistical significance

of the effect estimate (RR 1.02, 95% CI 0.37 to 3.34). The Minnesota DCCT^{83–86} included participants with renal transplantation, and contributed with most data to the meta-analysis of this outcome. Sensitivity analyses excluding this trial did not change the lack of statistical significance (RR 0.59, 95% CI 0.23 to 1.52).

Severe adverse events

Two trials provided information on severe adverse events in a total of 1515 participants (figure 6). A total of 56 participants with a severe adverse event were reported (all data were from intervention period) whereas 54 participants were from DCCT/EDIC.^{3–46} Meta-analysis showed no statistically significant effect of targeting intensive glycaemic control compared with conventional glycaemic control (RR 1.03, 95% CI 0.61 to 1.72; $p = 0.92$). Heterogeneity was absent ($I^2 = 0\%$; $p = 0.98$). Worst–best case scenario showed no statistical significance in favour of intensive glycaemic targets (RR 1.25, 95% CI 0.76 to 2.04), and neither did best–worst case scenario (RR 0.73, 95% CI 0.45 to 1.18). Subgroup analyses of the trials according to risk of bias, insulin type and the age of the participants could not be performed due to a lack of data.

Trial sequential analysis showed that only 1.89% of the required information size to detect or reject a 10% relative risk reduction was accrued, and the trial sequential monitoring boundaries were not crossed (see web appendix 3, figure 10).

Table 4 Risk of bias of the included trials

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Academic bias	Sponsor bias
DCCT/EDIC 1983 ^{3–46}	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate	Adequate
Franklin <i>et al</i> ¹⁰⁴	Adequate	Adequate	Inadequate	Adequate	Unclear	Adequate	Adequate
Hvidovre 1982 ⁶⁸	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Unclear
Kroc 1984 ^{112–117}	Unclear	Unclear	Adequate	Adequate	Unclear	Adequate	Adequate
Linn <i>et al</i> ¹¹⁰	Adequate	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear
Linn <i>et al</i> ⁶⁹	Unclear	Unclear	Unclear	Unclear	Adequate	Inadequate	Unclear
Microalbuminuria ^{50 51}	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate
Minnesota DCCT 1983 ^{83–86}	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate
Oslo 1986 ^{73–80}	Adequate	Unclear	Adequate	Unclear	Unclear	Adequate	Inadequate
Oxford 1983 ¹¹¹	Unclear	Unclear	Adequate	Adequate	Unclear	Adequate	Adequate
Perlman <i>et al</i> ¹⁰⁵	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate
Service <i>et al</i> ⁸¹	Adequate	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear
Shah <i>et al</i> ¹⁰¹	Adequate	Unclear	Adequate	Adequate	Unclear	Adequate	Unclear
Steno 1a 1982 ^{72 119–121}	Unclear	Unclear	Adequate	Unclear	Unclear	Adequate	Inadequate
Steno 1b 1986 ^{70–72}	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate
Stockholm 1985 ^{87–98}	Adequate	Unclear	Adequate	Unclear	Unclear	Adequate	Inadequate
Verrillo <i>et al</i> ⁸²	Unclear	Unclear	Adequate	Unclear	Unclear	Adequate	Unclear
Hershey <i>et al</i> ¹⁰² and White ¹⁰³	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate

DCCT/EDIC, Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications; Minnesota DCCT, Minnesota Diabetes Control and Complication Trial.

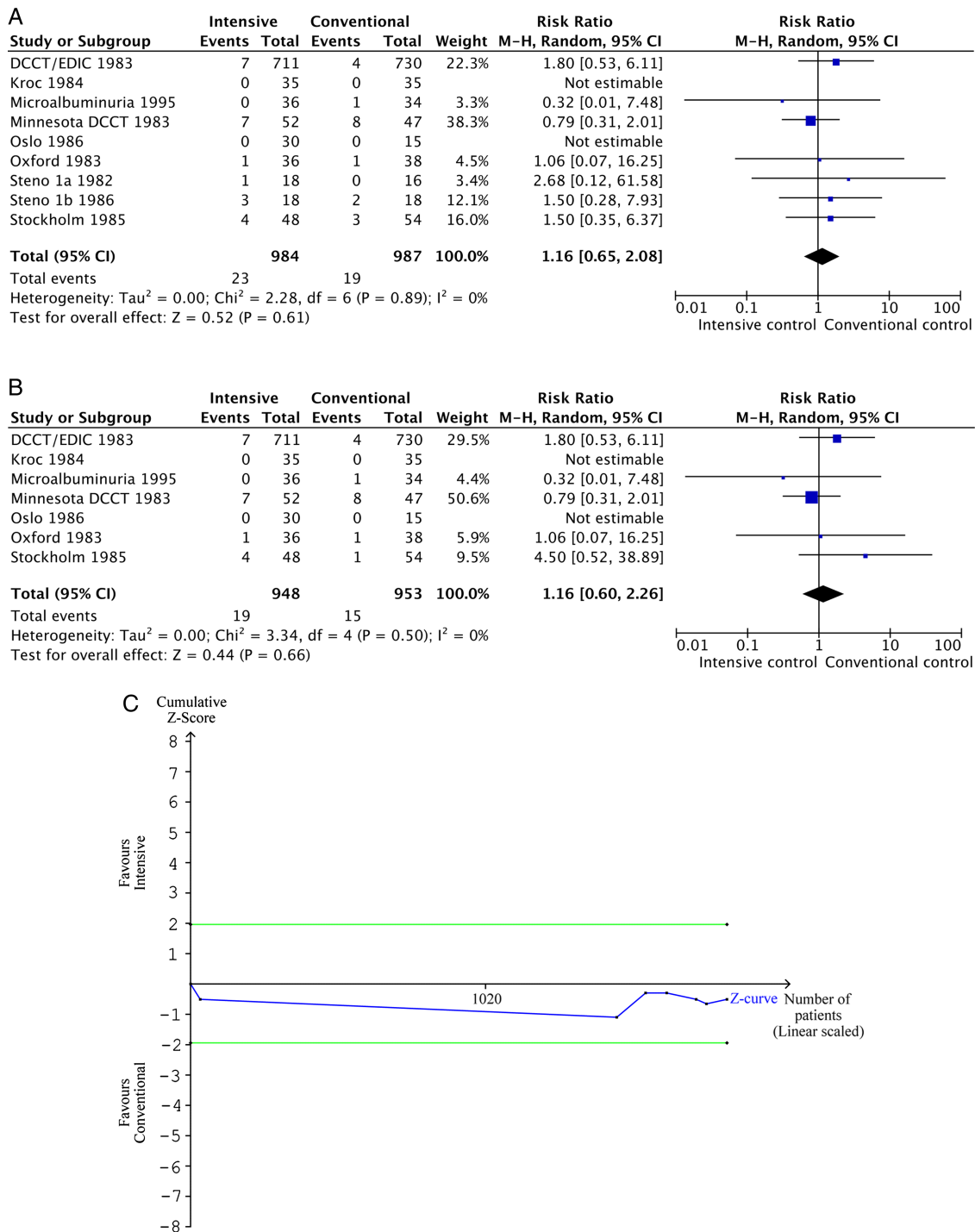


Figure 2 (A) Forest plot for all-cause mortality, meta-analysis of data to the longest follow-up. (B) Forest plot for all-cause mortality, meta-analysis of data to the end of the intervention period. (C) Trial sequential analysis of all-cause mortality. Trial sequence analysis revealed that only 1.18% (n=1971) of the diversity adjusted required information size of 167 034 participants was accrued so far. The number was calculated based on a proportion of mortality of 1.9% in conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it does not cross the horizontal solid green lines, illustrating the conventional level of statistical significance ($p=0.05$). The cumulative z-score does not cross the trial sequential monitoring boundaries, which cannot be seen on the figure due to lack of data.

Severe hypoglycaemia

The definition of severe hypoglycaemia varied among trials from requiring third party assistance to requiring hospitalisation of the participants (see web appendix 4).

Eleven trials including 1983 participants provided information on severe hypoglycaemia (figure 7A). Meta-analysis showed a beneficial effect, that is, fewer events in favour of a conventional glycaemic target (RR 1.40, 95% CI 1.01 to

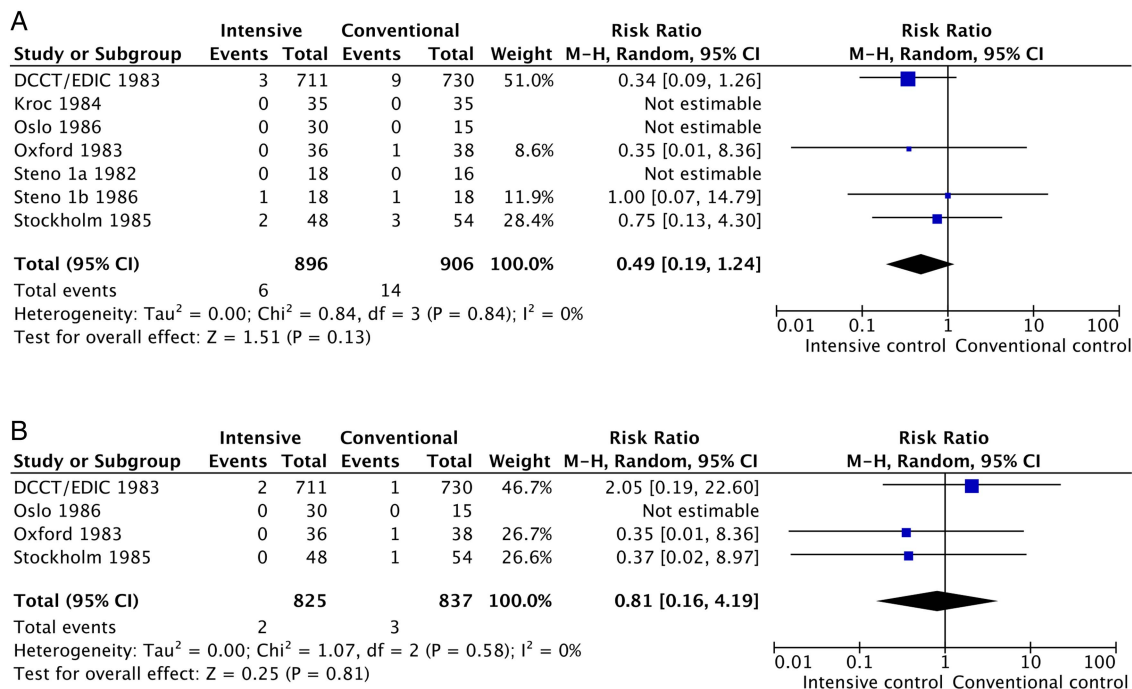


Figure 3 (A) Forest plot for cardiovascular mortality, meta-analysis of data to the longest follow-up. (B) Forest plot for cardiovascular mortality, meta-analysis of data to the end of the intervention period.

1.94; $p=0.05$). Heterogeneity was moderate ($I^2=46\%$; $p=0.05$). Sensitivity analysis including only data from intervention periods was not significantly affected in the random effects model (RR 1.35, 95% CI 0.97 to 1.87; $p=0.07$) but showed statistical significance in the fixed effect model favouring conventional glycaemic targets (RR 1.74, 95% CI 1.57 to 1.93; $p<0.00001$; [figure 7B](#)).

Trial sequential analysis showed that only 2.85% of the required information size to detect or reject a 10% relative risk reduction was accrued, and the trial sequential monitoring boundaries were not crossed ([figure 7B](#)).

Body mass index

Two trials provided information on body mass index in a total of 1276 participants ([figure 8A](#)). Meta-analysis of body mass index showed a statistically significant reduction to conventional glycaemic targets compared with intensive glycaemic targets (mean difference 1.13 kg/m², 95% CI 0.18 to 2.07; $p=0.02$). Heterogeneity was absent ($I^2=0\%$; $p=0.79$). Only one trial (DCCT³⁻⁴⁶) reported BMI after the intervention period, and a sensitivity analysis including only data from intervention periods could not be performed.

Trial sequential analysis showed that 34.8% of the required information size to confirm the observed difference between the interventions was accrued, and the trial sequential monitoring boundaries were not crossed ([figure 8B](#)).

Other assessed outcomes

We found no statistically significant effect of targeting intensive glycaemic control on the incidence of cancer (RR 3.12, 95% CI 0.33 to 29.65, 2 trials, 1515

participants) or non-fatal myocardial infarction (RR 0.58, 95% CI 0.26 to 1.32, 3 trials, 1577 participants).

Ketoacidosis was not significantly affected in the random effects model (RR 1.44, 95% CI 0.72 to 2.89, 7 trials, 1798 participants), but showed statistical significance in the fixed effect model favouring conventional glycaemic targets (RR 1.37, 95% CI 1.01 to 1.86; $p=0.04$). Sensitivity analysis including only data from intervention periods showed the same trend (see web appendix 3, [figure 11a-c](#)).

The definition of retinopathy varied among trials (see web appendix 4). Retinopathy was not significantly affected in the random effects model (RR 0.74, 95% CI 0.50 to 1.10, 9 trials, 1605 participants; web appendix 3, [figure 12a,b](#)), but showed statistical significance in the fixed effect model in favour of targeting intensive glycaemic control (RR 0.62, 95% CI 0.55 to 0.70; $p<0.00001$). Heterogeneity was substantial ($I^2=62\%$; $p=0.007$). Sensitivity analysis including only data from intervention periods showed the same trend (see web appendix 3, [figure 12c](#)).

Retinal photocoagulation was not significantly influenced in the random effects model (RR 0.41, 95% CI 0.16 to 1.04, 2 trials, 1238 participants; web appendix 3, [figure 13a,b](#)), but showed statistical significance in the fixed effect model favouring intensive glycaemic targets (RR 0.33, 95% CI 0.23 to 0.48; $p<0.00001$). Heterogeneity was moderate ($I^2=48\%$; $p=0.16$). Only one trial (DCCT³⁻⁴⁶) reported retinal photocoagulation after the end of the intervention period, and a sensitivity analysis including only data from intervention periods could not be performed.

Sensitivity analyses excluding the trial with the longest duration (DCCT/EDIC³⁻⁴⁶) changed the effect estimate

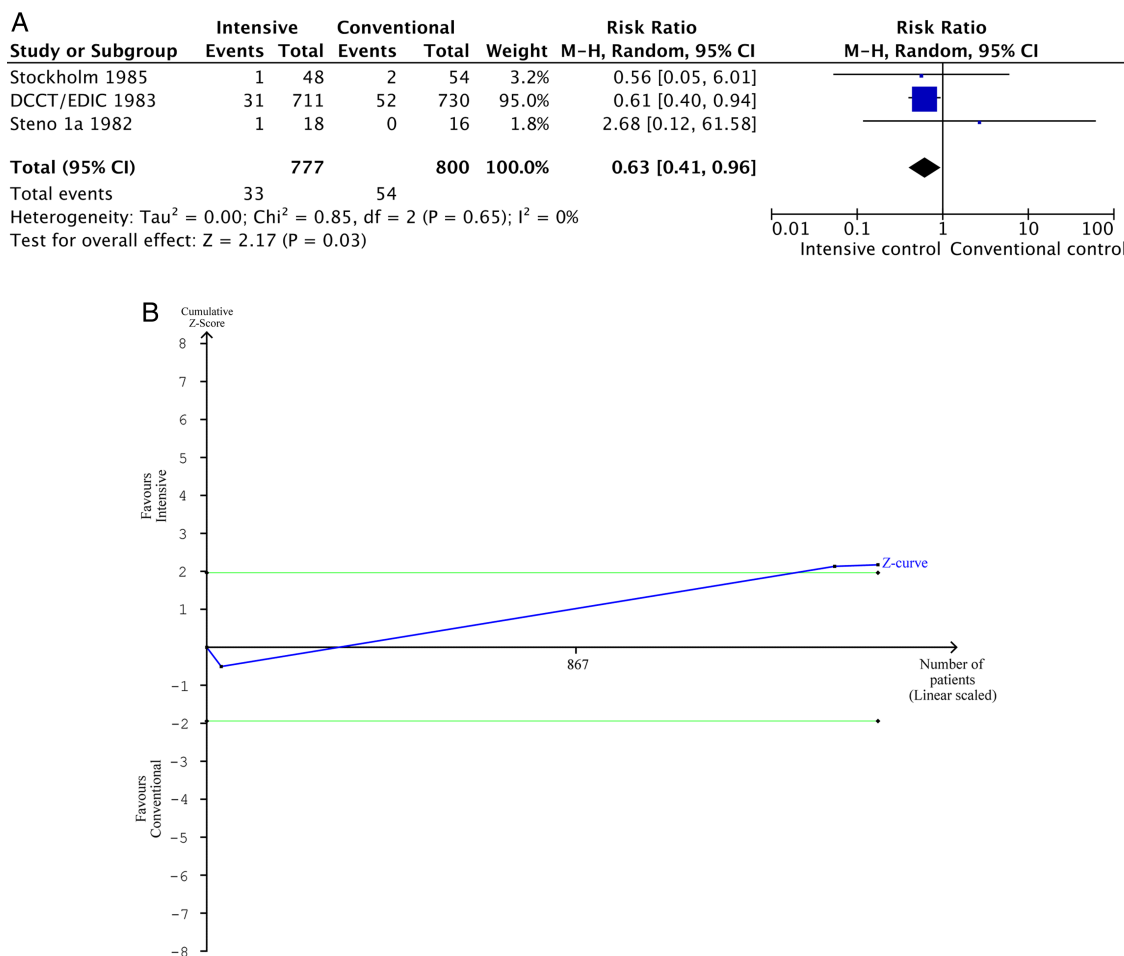


Figure 4 (A) Forest plot for macrovascular complications, meta-analysis of data to the longest follow-up. (B) Trial sequential analysis of macrovascular complications. Trial sequential analysis revealed that only 3.84% (n=1577) of the diversity adjusted required information size of 41 068 participants was accrued so far. The number was calculated based on a proportion of macrovascular complications of 6.8% in conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green line, illustrating the conventional level of statistical significance ($p=0.05$), favouring intensive glycaemic control. The cumulative z-score does not cross the trial sequential monitoring boundaries, which cannot be seen on the figure due to lack of data.

to a lack of statistical significance on the following outcomes: macrovascular complications, BMI, retinopathy and hypoglycaemia. Nephropathy was the only outcome that showed statistical significance before and after the sensitivity analysis excluding the trial with the longest duration (DCCT/EDIC³⁻⁴⁶).

Outcomes that could not be meta-analysed

Congestive heart failure was only reported in DCCT³⁻⁴⁶ from the intervention period, and only one participant in each group developed heart failure. Non-fatal stroke was also only reported in DCCT³⁻⁴⁶ with zero events during the intervention period, but in the follow-up period one patient developed a non-fatal stroke in the intensive group and five patients in the conventionally treated group.

Amputation of lower extremity was only reported in DCCT/EDIC³⁻⁴⁶ with seven patients in the intensive group and eight in the conventional group becoming amputated.

Revascularisation was only reported in DCCT/EDIC.³⁻⁴⁶ Peripheral revascularisation was reported with none patients in the intensive group and two in the conventional group. Coronary revascularisation was reported with 11 patients in the intensive group and 20 in the conventional group.

Health-related quality of life was assessed in two studies (Stockholm⁸⁷⁻⁹⁸ and DCCT³⁻⁴⁶), but only DCCT³⁻⁴⁶ published the results. Quality of life was measured with self-administered multiple choice 46-items specifically for the DCCT,³⁻⁴⁶ but showed no statistically significant difference between the intensive and conventional groups.

Costs of intervention was only reported in DCCT,³⁻⁴⁶ in which it was concluded that the intensive treatment (US\$4000/year) was three times as expensive as the conventional treatment (US\$1700/year), but may give cost savings as a result of the averted complications.

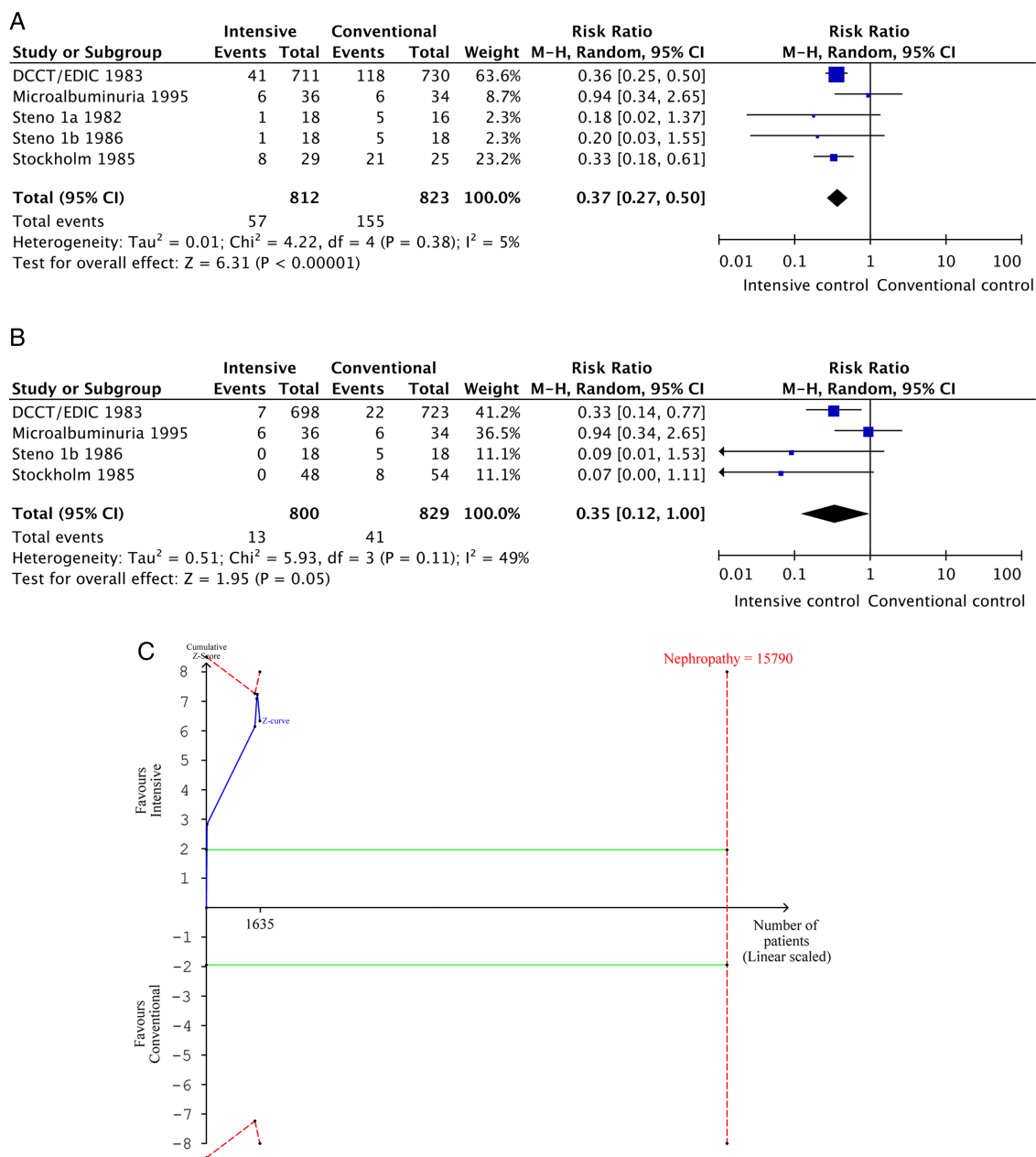


Figure 5 (A) Forest plot for nephropathy, meta-analysis of data to the longest follow-up. (B) Forest plot for nephropathy, meta-analysis of data to the end of the intervention period. (C) Trial sequential analysis of nephropathy. Trial sequential analysis revealed that only 10.4% (n=1635) of the diversity adjusted required information size of 15 721 participants was accrued so far. The number was calculated based on a proportion of nephropathy of 18.8% in conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=17\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green line, illustrating conventional level of statistical significance ($p=0.05$), favouring intensive glycaemic control. The cumulative z-score does touch the dotted red trial sequential monitoring boundaries after the second trial but returns to a level below the monitoring boundary hereafter.

Microvascular complications (as a composite outcome, using the authors' definition) were not reported for the included trials. Weight, adverse events, and mild hypoglycaemia were reported in a format that could not be included in a meta-analysis.

DISCUSSION

We identified 18 randomised clinical trials comparing the effects of targeting intensive glycaemic control versus

conventional glycaemic control. Of these trials, only 12 (n=2091 participants) provided sufficient information to be included in one or more meta-analyses. None of the trials had low risk of bias on all bias domains, and only one trial³⁻⁴⁶ was considered to have lower risk of bias according to our adapted definition of lower risk of bias. Our key finding is that the risk of all-cause mortality and cardiovascular mortality was not statistically significantly different by targeting intensive versus conventional glycaemic control

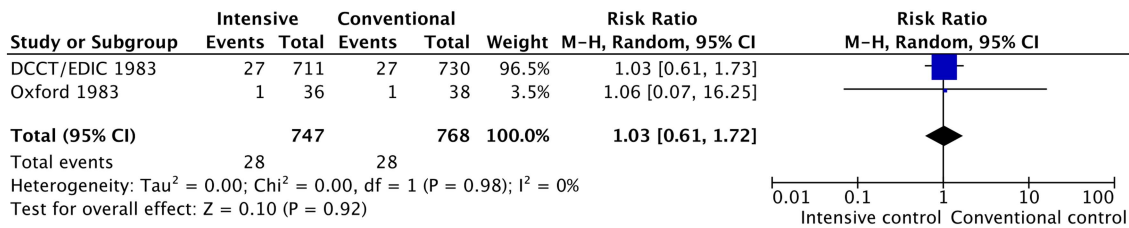


Figure 6 Forest plot for severe adverse events, meta-analysis of data to the longest follow-up.

in patients with type 1 diabetes mellitus. However, targeting intensive glycaemic control might reduce the risk of macrovascular complications (assessed as a composite outcome), and nephropathy. However, analyses of only the intervention period could not be done for the composite macrovascular outcome, and data for nephropathy was based on surrogate markers. Consistent statistical significance could not be established for retinopathy, retinal

photocoagulation or ketoacidosis. Importantly, meta-analyses of patient relevant outcomes were based on very sparse data, and the high risks of bias should be taken into account. No significant effects of targeting intensive glycaemic control were identified on the risks of severe adverse events, incidence of cancer, end-stage renal disease, non-fatal myocardial infarction or non-fatal stroke. The disadvantages of intensive glycaemic targets might be

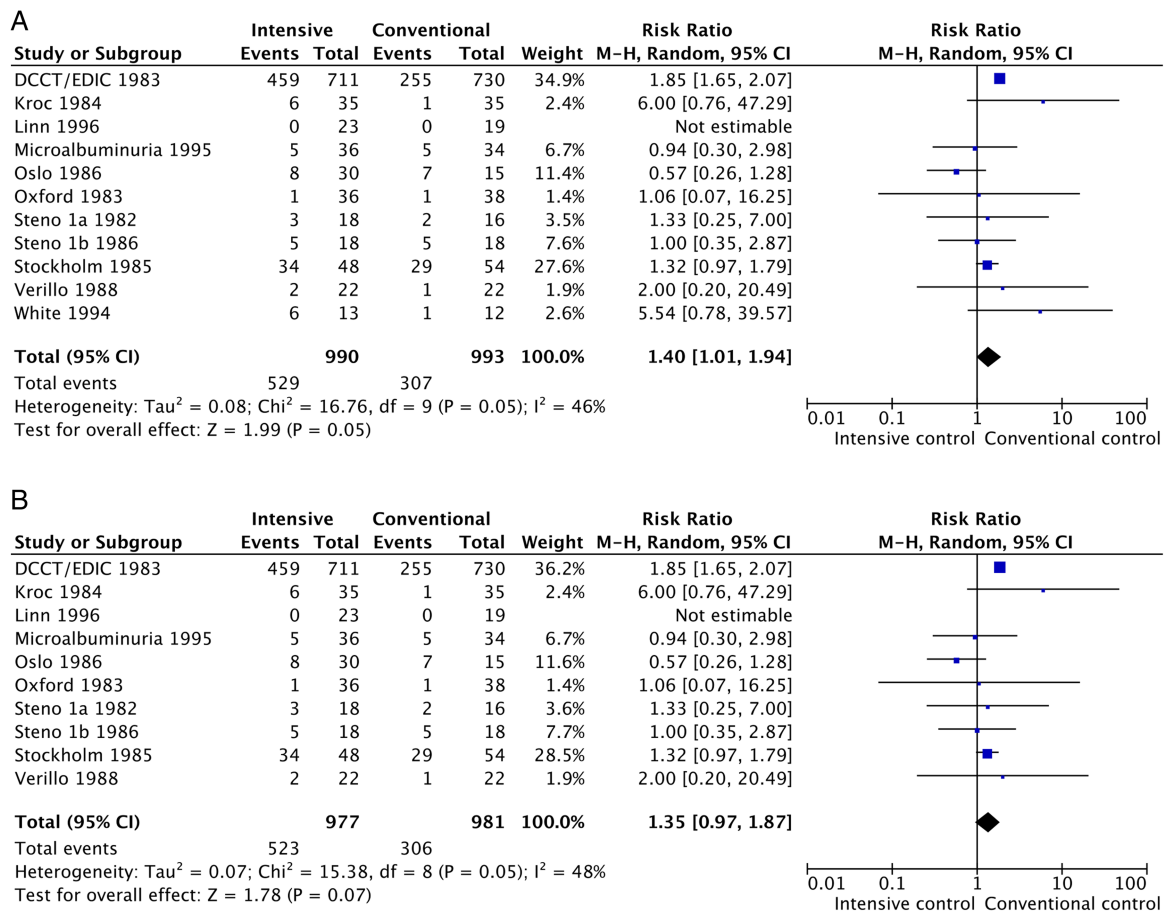


Figure 7 (A) Forest plot for severe hypoglycaemia, meta-analysis of data to the longest follow-up. (B) Forest plot for severe hypoglycaemia, meta-analysis of data to the end of the intervention period. (C) Trial sequential analysis of severe hypoglycaemia. Trial sequential analysis revealed that only 2.85% (n=1983) of the diversity adjusted required information size of 69 579 participants was accrued so far. The number was calculated based on a proportion of severe hypoglycaemia of 30.9% in conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=5\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green lines, illustrating the conventional level of statistical significance ($p=0.05$), favouring conventional glycaemic control. The cumulative z-score touch the traditional line of statistical significance but does not cross the trial sequential monitoring boundaries, which cannot be seen on the figure due to lack of data.

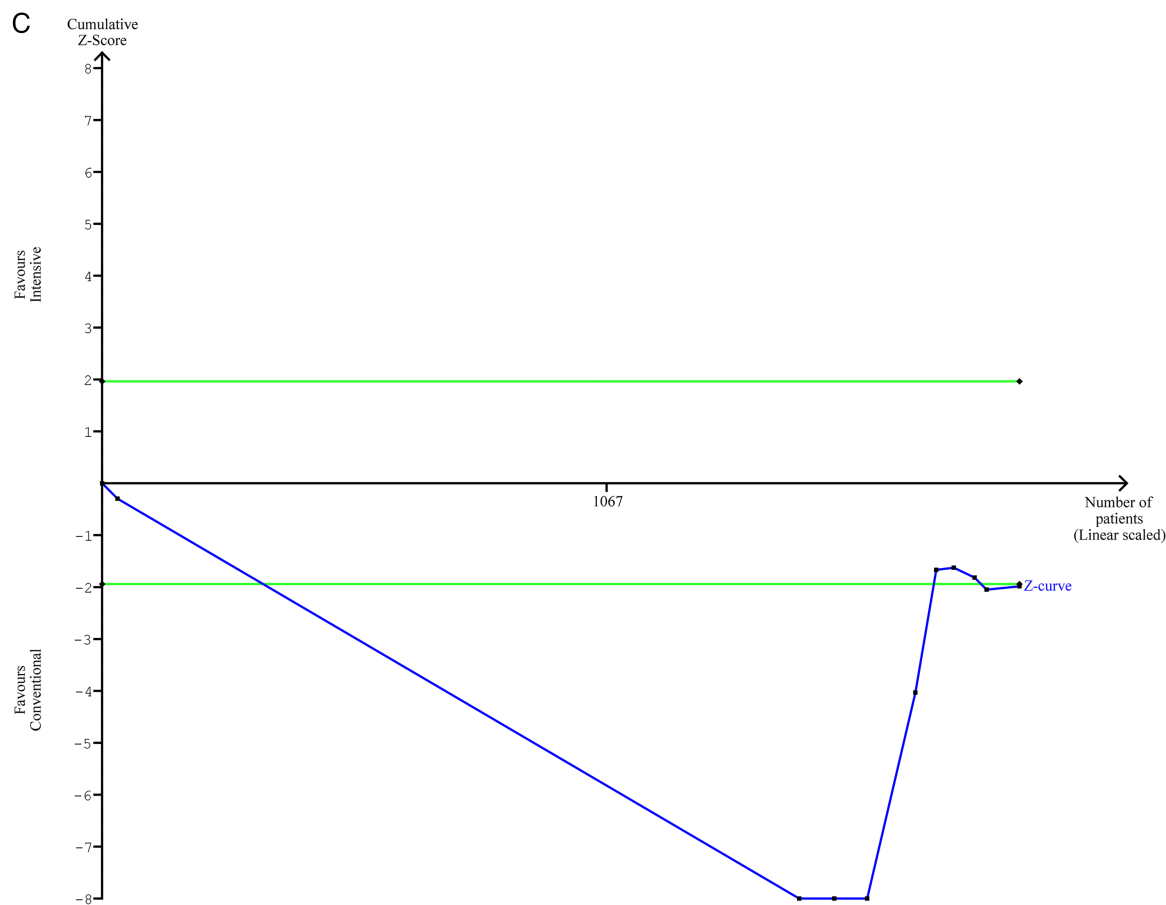


Figure 7 Continued

severe hypoglycaemia, ketoacidosis, and increase in body mass index, but data were sparse. Where available, analyses were made on data from the intervention period, and compared with data extracted to the longest follow-up; in general, these analyses showed no major differences.

After ended intervention, in the observational follow-up period, the patients were not required to continue the treatment into which they were randomised, but they were still included in the follow-up of their former group. This can lead to bias, but as long as the patients have had the intervention, they can provide data regarding the effect of the intervention. However, intensive glucose control is not applied as a temporary treatment, but as a lifelong intervention. The effects reported from observational periods of a trial following a temporary intervention may not be applicable to daily clinical practice and provide conclusive evidence of the consequences of continued use of the interventions beyond the initial intervention period.

The increased risk of ketoacidosis with intensive glycaemic targets may be due to different insulin administration in the two intervention groups. Many of the patients in intensive therapy were treated with insulin pumps, where the patients in the conventional group were treated with insulin injections. The insulin pumps from the 1980s and 1990s (where most of the trials were

performed) are known to increase the risk of ketoacidosis, due to malfunction of the pump. The association between an intensive glycaemic target and increased risk of ketoacidosis may therefore be confounded by the mode of insulin administration.

Strengths and limitations

Our systematic review has several strengths. We based it on a published protocol⁵³ with rigid inclusion criteria for randomised clinical trials. We applied a comprehensive search with no language limitations or restrictions on outcomes reported in the trials. Two authors independently extracted data. We contacted corresponding authors of all trials for additional data and to clarify methodological details, but only a few authors responded. We tried to evaluate the strength of the available evidence with trial sequential analysis on all our primary and statistically significant secondary outcomes.

We have included trials with large differences in the patients' average duration of type 1 diabetes mellitus, length of the interventions, patients' age, and assessment of glycaemic control, as well as prespecified targets of glycaemic control. We included trials irrespective of the language of publication and outcomes reported.

The weaknesses of our analyses and conclusions mirror the weaknesses in the individual included trials,

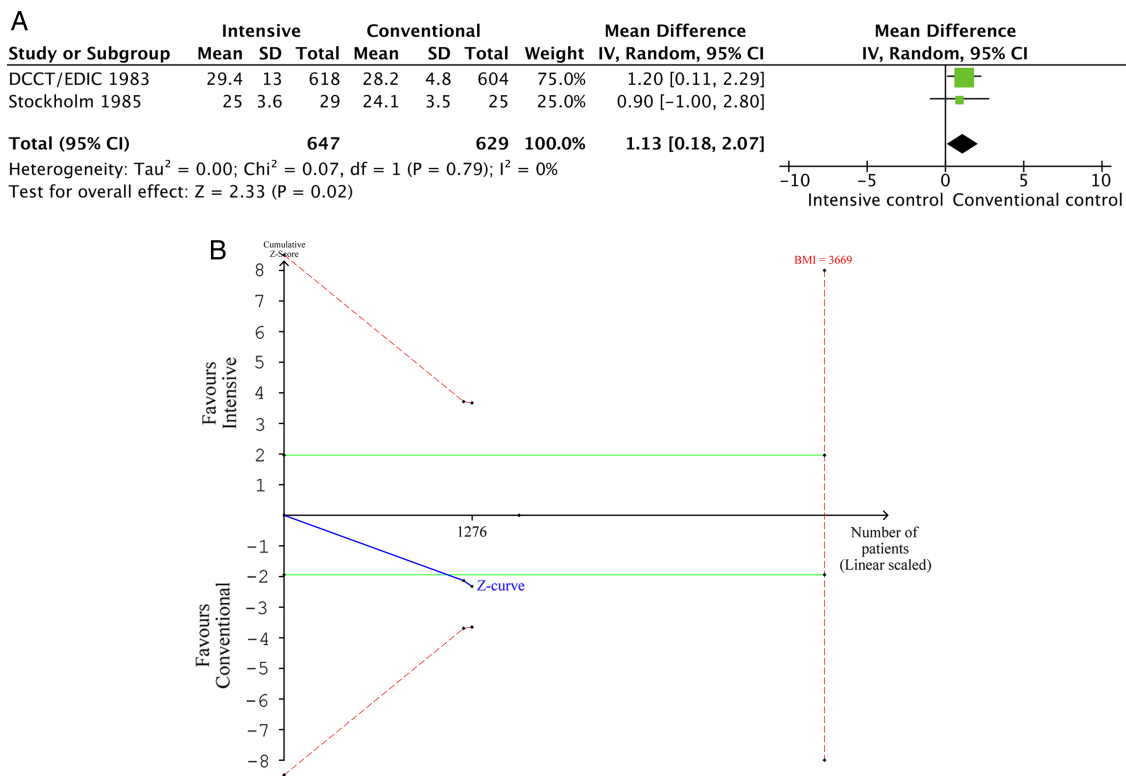


Figure 8 (A) Forest plot for body mass index, meta-analysis of data to the longest follow-up. (B) Trial sequential analysis of body mass index. Trial sequential analysis revealed that 34.8% ($n=1276$) of the diversity adjusted required information size of 3667 participants was accrued so far. The number was calculated based on a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, a mean difference of 1.13 kg/m^2 as achieved in the meta-analyses, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green line, illustrating the conventional level of statistical significance ($p=0.05$), favouring conventional glycaemic control. The cumulative z-score does not cross the dotted red trial sequential monitoring boundaries.

especially the high risk of bias, and the low number of patients included in the trials, highlighting the substantial lack of evidence on this topic. Only 1 of the 18 included trials was classified as lower risk of bias (DCCT³⁻⁴⁶) according to our definition of adequate sequence generation, allocation concealment and blinded outcome assessment. Such a definition does not rule out high risk of bias from other domains.⁵²

We included a large range and thus a diverse group of patients with type 1 diabetes mellitus. However, due to a potential selection bias of for instance more healthy and motivated patients in clinical trials, it is difficult to evaluate exactly how typical the participants in each of the clinical trials may have been compared with the general population of patients with type 1 diabetes mellitus. Nevertheless, the heterogeneity in this review might indeed reflect the well-known heterogeneity in clinical practice. It is also important to remember that the patient-care applied in the intensive compared with the conventional groups is likely to be different from the everyday clinical practice, due to more frequent visits for the intensive groups and possible differences between the two settings in the awareness with respect to the blood glucose control.

We evaluated the strength of the available evidence by comprehensive analyses of the risk of sparse data and

repetitive testing with trial sequential analysis. Even though the conventional meta-analyses of composite macrovascular complications, nephropathy and severe hypoglycaemia indicated a statistically significant effect estimate, trial sequential analysis showed that sufficient evidence to detect or reject a 10% relative risk reduction or risk increase was not available for any of these outcomes. This was also the case with the achieved difference in body mass index.

This meta-analysis is limited by an inability to use individual patient data to assess whether certain characteristics (eg, a history of cardiovascular events, degree of HbA_{1c} reduction and duration of disease at baseline) affect the degree of cardiovascular risk. We explored heterogeneity by sensitivity analyses and subgroup analyses at trial level.

Diagnostic criteria and definitions of outcomes varied among the trials and were not always well defined. This can potentially lower the validity of the results, but since the definition of an outcome does not change within the trial, it is not likely to substantially affect the results in favour of any of the groups, and it may still be used to see a trend. That is, unless a significant and undetected between-trial heterogeneity exists for the intervention effect, for example, outcomes incorrectly termed

similarly, but representing different pathologies, in different trials.

In addition to the differences between the intensive glycaemic targets, the conventional target also varied among the trials. Furthermore, the measurement used to assess the levels of glycaemic control varied among the included trials. Some trials defined the glucose target by applying blood glucose, providing only a 'snapshot' of the overall glycaemic control. Most of the included trials expressed glycaemic targets as HbA_{1c}, reflecting an average of the blood glucose concentration over several weeks. The treatment in the intensive treated group and the conventional treated group differed in many ways besides different glycaemic targets, including the number of doctor visits, insulin type and administration. For example, the intensive treated group in the DCCT/EDIC^{3–46} could use insulin pumps or multiple daily injections (patients' and physicians' choice), whereas the conventional group had to use twice-daily insulin injections. No trial investigated the different glycaemic target keeping everything else the same. This is a major limitation, since it cannot be concluded that the effect we find between the groups is exclusively due to the use of different glycaemic targets.

The reporting of severe hypoglycaemia is problematic in several ways; first of all, the definitions of severe hypoglycaemia were diverse, some included incidents requiring a third party assistance and other hospitalisation. In addition, the design of the included trials made blinding of the participants difficult, which may lead to reporting bias.^{52 99 100} Many of the included trials were not designed or powered to assess our predefined outcomes, which explains the insufficient data from these trials. Furthermore, for some outcomes only a few trials could provide data. This increases the risk of outcome measure reporting bias.⁵²

Four trials included only patients below the age of 18 years (Shah *et al*¹⁰¹ included adolescents age not defined).^{101–105} These four trials did not report any macrovascular or microvascular outcomes, which might be due to the relatively short follow-up period. The effect of targeting intensive glycaemic control on patients younger than 18 years could therefore not be assessed.

Relation to other studies

Previous meta-analyses have been published.^{57–61 106} However, many of these claiming to assess the effect of targeting intensive glycaemic control versus conventional glycaemic control have included trials on the basis of achieved (ie, observed during follow-up) rather than targeted (ie, as randomly allocated) differences in glycaemic control.⁵⁸ For example, they included comparisons of insulin treatment regimens (continuous subcutaneous insulin infusions or multiple injections) with a similar target of HbA_{1c} below 6.5% in both intervention groups.¹⁰⁷ This type of strategy for selection is potentially problematic, as the levels of glycaemic control targeted and achieved in a clinical trial represent

different chosen variables. For example, unlike target levels, achieved levels of a variable cannot usually be guaranteed to have complete separation (at the patient level) between intervention groups. This precludes inferences with respect to causality between achieved levels of one outcome, for example, glucose control, and other outcomes, for example, vascular complications between groups. In contrast, target levels, if predefined to differ (ie, be completely separated) between groups, can better support inferences about causality. Therefore, to optimally assess the clinical effect of aiming for intensive glycaemic targets, which is probably a relevant question for the clinician as well as people trying to establish evidence-based guidelines, trials need to be meta-analysed on the basis of predefined differences in glycaemic targets.

Intensive glycaemic control is generally recommended in most countries due to the results of especially the DCCT/EDIC.^{3–46} Only a few observational studies have assessed the effects of glycaemic levels and the outcomes we predefined to assess in patients with type 1 diabetes mellitus. However, we retrieved one observational study showing that improved glycaemic control was associated with lower risk of heart failure.¹⁰⁸ However, such observational associations have well-known limitations as evidence.¹⁰⁹

The so far largest meta-analysis on this topic by Fullerton *et al* included 10 of the 18 trials included in the present analysis.^{3–46 50 51 70–80 82–86 102 103 110–114} They extracted the DCCT/EDIC^{3–46} as two separate trials: 'the primary prevention cohort' and 'the secondary intervention cohort' according to the presence of background retinopathy and microalbuminuria in the patients at baseline. They included one trial that did not meet standard criteria for randomisation. In contrast to Fullerton *et al*¹⁰⁶ we extracted DCCT as one trial (the primary and the secondary cohort together) and we included all trials that randomised patients to different targets, also if the target was not predefined but only an intention for better glycaemic control, and we did not have a time limit for the intervention period. In contrast to our results, Fullerton *et al* found an effect of intensive glycaemic control on retinopathy, but a sensitivity analysis showed that the effect was weaker regarding progression after manifestation. Consequently, the presence of retinopathy at treatment initiation could impact the relation between glucose-lowering and progression of retinopathy—a hypothesis that we did not specifically assess, but it should be considered in future trials and meta-analyses. A previous study from Stettler *et al*⁶⁷ also dealt exclusively with trials in which the patients were randomised to different glycaemic targets and included only 7 of 18 available trials.^{3–46 50 51 70–72 81 82 87–98 111}

Another large meta-analysis by Egger *et al*⁵⁸ included 9 of the 18 trials included in the present systematic review.^{3–46 49 50 70–82 87–98 111–117} They also included five trials with different achieved HbA_{1c}, but the patients were not randomised to different glycaemic targets. The differences in the setup and specification of the



intervention of the relevant trials make such an approach prone to additional bias and therefore difficult to assess the benefits and harms of the intervention.

A newly published Cochrane review by Callaghan *et al*¹¹⁸ investigated the effect of intensive glycaemic control on neuropathy in patients with type 1 and 2 diabetes mellitus, and we therefore chose not to include neuropathy as an outcome.

Our systematic review and meta-analyses is largely dominated by the data from DCCT/EDIC,^{3–46} however, the beneficial effects of targeting intensive glycaemic control were not as clear in our review as in the DCCT/EDIC.^{3–46} The definition of retinopathy varied among trials in our meta-analysis (web appendix 4), and duration of follow-up also (table 1). We found no consistent statistically significant effect on retinopathy (ie, the significance was present in the fixed effect, but not the random effect model) when meta-analysing all available randomised clinical trials of targeting intensive versus conventional glucose control in patients with type 1 diabetes mellitus. This is noteworthy, because retinopathy (sustained 3-step progression) was the primary outcome of DCCT. However, there was a baseline imbalance in favour of the intensive group for retinopathy in the secondary prevention cohort in DCCT—which was adjusted for in the analyses from the trial. Nonetheless, baseline imbalances can result from insufficient randomisation and can be problematic for the interpretation, in particular for the primary outcome—even if adjusted for.

Since the result of the DCCT/EDIC,^{3–46} only a few small trials have been investigating the effect of intensive glycaemic control. Our results suggest that more trials are needed before the results from the DCCT/EDIC can be confirmed. The difficulties in applying the results from DCCT/EDIC^{3–46} to a clinical context are many. The participants had a short duration of type 1 diabetes mellitus (mean 6 years), were without cardiovascular diseases, and were young (mean age 27 years). Besides, several of the trials, including DCCT/EDIC,^{3–46} had a very loose approach to the conventional treatment, that is, only to avoid symptoms of hyperglycaemia. Only one of the trials (n=99) randomised participants to a HbA_{1c} target of 7% in the intensive group—the target recommended by one of the major guidelines by The American Diabetes Association.⁴⁷ Trial investigators might conclude that trials randomising participants to a looser glycaemic control are unethical given the positive effect on the microvascular complications in the DCCT/EDIC.^{3–46} The positive effect on the microvascular outcomes in DCCT/EDIC was to a large extent delivered by surrogate markers, including the primary outcome, 3-step progression in retinopathy, and it should be kept in mind that, like in our meta-analysis, no statistically significant effect was shown for the hard clinical microvascular outcome, end-stage renal disease. Furthermore, in our meta-analysis, data on the most important outcomes such as all-cause mortality and cardiovascular mortality showed no effect of targeting an intensive glycaemic

control. It can therefore be questioned whether a new trial would be unethical. Owing to the lack of data in the relevant trials, it is hard to formulate guidelines. We advocate physicians to consider our results when weighing the benefits and harms of raising/lowering the glycaemic target in patients with type 1 diabetes mellitus.

CONCLUSIONS

We found no statistically significant effect of targeting an intensive glycaemic control compared with conventional glycaemic control on all-cause and cardiovascular mortality. However, we did find indications of a possible positive effect of targeting intensive glycaemic control on macrovascular complications as a composite outcome and on nephropathy. On the other hand, we found statistically significant more severe hypoglycaemia and increase in body mass index in the intensively treated patients. Notably, we found no consistent effect on retinopathy and ketoacidosis. The trial sequence analysis showed that the decision to choose a glycaemic intervention target is based on sparse data. In addition, most trials had poor bias control, and there was a severe lack of reporting on patient relevant outcomes. More randomised clinical trials with low bias risk are needed to conclude whether targeting an intensive glycaemic control is superior or not for improving patient relevant outcomes in patients with type 1 diabetes mellitus.

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Correction

Kähler P, Grevstad B, Almdal T, *et al.* Targeting intensive versus conventional glycaemic control for type 1 diabetes mellitus: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *BMJ Open* 2014;4:e004806. The list of authors should read:

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Contributors PK developed the protocol, was responsible for the searches, selected trials, extracted data, assessed risk of bias of trials, did the data analysis, and developed the final review. BH developed the protocol, was responsible for the searches, selected trials, extracted data, assessed risk of bias of trials, and developed the final review. BG developed the protocol, selected trials, extracted data, assessed risk of bias of trials, did the data analysis, and developed the final review. CG developed the protocol, selected trials, advised on statistical methods, and developed the final review. TA developed the initial idea for the review, developed the protocol, and developed the final review. AV developed the protocol, and developed the final review. JW developed the protocol, advised on statistical methods, and developed the final review. SSL contributed substantially to the interpretation of data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests PK, AV, SSL and TA have reported equity in Novo Nordisk A/S. SSL owns shares in dynamically traded investment funds, which may own stocks from pharmaceutical companies. AV have received fees from Novo Nordisk A/S for speaking. SSL is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; his contribution was his alone and does not necessarily reflect the official position of Boehringer Ingelheim.



CrossMark

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Web appendices

Web appendix 1. Search strategies

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (MEDLINE medical index term); exp = exploded MeSH; the dollar sign (\$) stands for any character(s); the question mark (?) substitutes one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent (i.e. number of words within range of search term)

The Cochrane Library:

#1 MeSH descriptor Diabetes mellitus, type 1 explode all trees

#2 (IDDM in All Text or T1DM in All Text or T1D in All Text)

#3 (("insulin* depend*" in All Text or "insuldepend*" in All Text) and not ("non insulin* depend*" in All Text or "non insulin- depend*" in All Text))

#4 ("typ? 1 diabet*" in All Text or "typ?1 diabet*" in All Text or "typ? l diabet*" in All Text or "typ?! diabet*" in All Text)

#5 (child* in All Text near/1 diabet* in All Text)

#6 (acidos* in All Text near/1 diabet* in All Text)

#7 (labil* in All Text near/1 diabet* in All Text)

#8 (britt* in All Text near/1 diabet* in All Text)

#9 (keto* in All Text near/1 diabet* in All Text)

#10 (juvenil* in All Text near/1 diabet* in All Text)

#11 (autoimmun* in All Text near/1 diabet* in All Text)

#12 (auto in All Text and (immun* in All Text near/1 diabet* in All Text))

#13 (sudden in All Text and (onset in All Text near/1 diabet* in All Text))

#14 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)

#15 (intensiv* in All Text near/3 control* in All Text)

#16 (conventional* in All Text near/3 control* in All Text)

#17 (regular in All Text near/3 control* in All Text)

#18 (tight* in All Text near/3 control* in All Text)

#19 (usual in All Text near/3 control* in All Text)

#20 (routin* in All Text near/3 control* in All Text)

#21 (standard* in All Text near/3 control* in All Text)

#22 (intensiv in All Text near/3 therap* in All Text)

#23 (conventional* in All Text near/3 therap* in All Text)

#24 (regular in All Text near/3 therap* in All Text)

#25 (tight* in All Text near/3 therap* in All Text)

#26 (usual in All Text near/3 therap* in All Text)

#27 (routin* in All Text near/3 therap* in All Text)

#28 (standard* in All Text near/3 therap* in All Text)

#29 (intensiv* in All Text near/3 treatment* in All Text)

#30 (conventional* in All Text near/3 treatment* in All Text)

#31 (regular in All Text near/3 treatment* in All Text)

#32 (tight* in All Text near/3 treatment* in All Text)

#33 (usual in All Text near/3 treatment* in All Text)

#34 (routin* in All Text near/3 treatment* in All Text)

#35 (standard* in All Text near/3 treatment* in All Text)

#36 (intensiv* in All Text near/3 intervention* in All Text)

#37 (conventional in All Text near/3 intervention* in All Text)

#38 (regular in All Text near/3 intervention* in All Text)

#39 (tight* in All Text near/3 intervention* in All Text)

#40 (usual in All Text near/3 intervention* in All Text)

#41 (routin* in All Text near/3 intervention* in All Text)

#42 (standard* in All Text near/3 intervention* in All Text)

#43 (intensiv* in All Text near/3 management* in All Text)
 #44 (conventional* in All Text near/3 management* in All Text)
 #45 (regular in All Text near/3 management* in All Text)
 #46 (tight* in All Text near/3 management* in All Text)
 #47 (usual in All Text near/3 management* in All Text)
 #48 (routin* in All Text near/3 management* in All Text)
 #49 (standard* in All Text near/3 management* in All Text)
 #50 (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
 #51 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49)
 #52 (#50 or #51)
 #53 (#14 and #52)

MEDLINE:

1 exp Diabetes Mellitus, Type 1/
 2 exp Diabetic Ketoacidosis/
 3 exp Diabetes Complications/
 4 (IDDM or T1DM or T1D).tw,ot.
 5 (("insulin* depend*" or "insulin?depend*") not ("non-insulin* depend*" or "non insulindepend*")).tw,ot.
 6 ("typ? 1 diabet*" or "typ? I diabet*" or "typ?1 diabet*" or "typ?I diabet*").tw,ot.
 7 ((acidosis* or juvenil* or child* or keto* or labil* or britt*) adj1 diabet*).tw,ot. 8 ((auto-immun* or autoimmun* or sudden onset) adj1 diabet*).tw,ot.
 9 (insulin* defic* adj1 absolut*).tw,ot.
 10 or/1-9
 11 exp Diabetes Insipidus/ 12 diabet* insipidus.tw,ot.
 13 11 or 12
 14 10 not 13
 15 ((intensiv* or conventional* or regular or tight* or usual or routin* or standard) adj3 (control* or therap* or treatment* or intervention* or management*)).tw,ot.
 16 14 and 15
 17 randomized controlled trial.pt.
 18 controlled clinical trial.pt. 19 randomi?ed.ab.
 20 placebo.ab.
 21 drug therapy.fs.
 22 randomly.ab. 23 trial.ab.
 24 groups.ab. 25 or/17-24
 26 Meta-analysis.pt.
 27 exp Technology Assessment, Biomedical/
 28 exp Meta-analysis/
 29 exp Meta-analysis as topic/
 30 hta.tw,ot.
 31 (health technology adj6 assessment\$).tw,ot.
 32 (meta analy\$ or metaanaly\$ or meta?analy\$).tw,ot.
 33 ((review\$ or search\$) adj10 (literature\$ or medical database\$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content\$ or systemat\$)).tw,ot.
 34 or/26-33
 35 25 or 34
 36 (comment or editorial or historical-article).pt.
 37 35 not 36
 38 16 and 37
 39 (animals not (animals and humans)).sh.
 40 38 not 39

EMBASE:

- 1 exp insulin dependent diabetes mellitus/
- 2 exp diabetic ketoacidosis/
- 3 (IDDM or T1DM or T1D).tw,ot.
- 4 (("insulin* depend*" or "insulin?depend*") not ("non insulin* depend*" or "non insulin?depend*")).tw,ot.
- 5 (("typ? 1" or "typ? l" or "typ?1" or "typ?l") adj1 diabet*).tw,ot.
- 6 ((acidos* or juvenil* or child* or keto* or labil* or britt*) adj1 diabet*).tw,ot.
- 7 ((auto-immun* or autoimmun* or sudden onset) adj1 diabet*).tw,ot.
- 8 (insulin* defic* adj1 absolut*).tw,ot.
- 9 or/1-8
- 10 exp diabetes insipidus/
- 11 diabet* insipidus.tw,ot.
- 12 10 or 11
- 13 9 not 12
- 14 ((intensiv* or conventional* or regular or tight* or usual or routin* or standard*) adj3 (control* or therap* or treatment* or intervention* or management*)).tw,ot.
- 15 13 and 14
- 16 exp Randomized Controlled Trial/
- 17 exp Controlled Clinical Trial/
- 18 exp Clinical Trial/
- 19 exp Comparative Study/
- 20 exp Drug comparison/
- 21 exp Randomization/
- 22 exp Crossover procedure/
- 23 exp Double blind procedure/
- 24 exp Single blind procedure/
- 25 exp Placebo/
- 26 exp Prospective Study/
- 27 ((clinical or control\$ or comparativ\$ or placebo\$ or prospectiv\$ or randomi?ed) adj3 (trial\$ or stud\$)).ab,ti.
- 28 (random\$ adj6 (allocat\$ or assign\$ or basis or order\$)).ab,ti.
- 29 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj6 (blind\$ or mask\$)).ab,ti.
- 30 (cross over or crossover).ab,ti.
- 31 or/16-30
- 32 exp meta analysis/
- 33 (metaanaly\$ or meta analy\$ or meta?analy\$).ab,ti,ot.
- 34 ((review\$ or search\$) adj10 (literature\$ or medical database\$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content\$ or systematic\$)).ab,ti,ot.
- 35 exp Literature/
- 36 exp Biomedical Technology Assessment/
- 37 hta.tw,ot.
- 38 (health technology adj6 assessment\$).tw,ot.
- 39 or/32-38
- 40 31 or 39
- 41 (comment or editorial or historical-article).pt.
- 42 40 not 41
- 43 15 and 42
- 44 limit 43 to human

LILACS

1. (Blood Glucose or Hyperglycemia or hemoglobin A, glycosylated or Diabetes mellitus) [Subject descriptor]
2. (control\$ or management) [Palavras]
3. (random\$ or placebo\$ or trial or group\$) [Palavras]

Science Citation Index Expanded

1. TS=(blood glucos* or glyce*emic* control or hyperglyc?emi* or h?emoglobin* A)
2. TS=(HbA1C or Hb A or HbA 1c or HbA or A1Cs)
3. TS=(glycosylated SAME h?emoglobin*)
4. TS=(glucos* SAME management*)
5. #4 OR #3 OR #2 OR #1
6. TS=(IDDM or T1DM)
7. TS=(insulin* depend*)
8. TS=(diabet* SAME (typ* 1 or typ* I))
9. #8 OR #7 OR #6
10. #9 NOT TS=(diabet* insipidus)
11. #10 OR #5
12. TS=((intensi* or tight or conventional* or regular or usual or routin* or standard) SAME (control* or therap* or treatment* or intervention* or management*))
13. #12 AND #11
14. TS=(random* OR blind* OR placebo* OR group*)
15. TS=(animal* NOT (animal* AND human*))
16. #14 NOT #15
17. #16 AND #13

Web appendix 2. Excluded trials and studies

Trial
Allen et al. 2012 ¹²¹
Aoki et al. 1995 ¹²²
Aoki et al. 1995 ¹²³
Arabi et al. ¹²⁴
Arslanoglu et al. 2000 ¹²⁵
Ashwell et al. 2005 ¹²⁶
Azar et al. 2002 ¹²⁷
Bangstad et al. 1992 ¹⁰⁵
Bangstad et al. 1994 ¹²⁸
Beck-Nielsen et al. 1985 ¹²⁹
Berghe et al. 2003 ¹³⁰
Bolli et al. 2009 ¹³¹
Bolli et al. 2009 ¹³²
Bougneres et al. 1993 ¹³³
Breton et al. 2012 ¹³⁴
Burkart et al. 1988 ¹³⁵
Christensen et al. 1987 ¹³⁶
Christiansen et al. 1987 ¹³⁷
Continuous Glucose Monitoring Study Group 2009 ¹³⁸
Cooper-DeHoff et al. 2010 ¹³⁹
DAFNE 2003 ¹⁴⁰
Dailey et al. 2000 ⁵

Della Manna et al. 2005 ¹⁴¹
Devries et al. 2002 ¹⁴²
DIGAMI 2000 ¹⁴³
DIGAMI2 2005 ¹⁴⁴
Echouffo-Tcheugui et al. 2008 ¹⁴⁵
Ernst et al. 2012 ¹⁴⁶
Fotinos et al. 2004 ¹⁴⁷
Friedrich et al 2006 ¹⁴⁸
Goicolea et al. 1989 ¹⁴⁹
Goicolea et al. 1987 ¹⁵⁰
Goicolea et al. 1986 ¹⁵¹
Gustafson et al. 2002 ¹⁵²
Guy et al. 2005 ¹⁵³
Hanaire-Broutin et al. 1996 ¹⁵⁴
Heber et al. 1977 ¹⁵⁵
Jermendy et al. 2007 ¹⁵⁶
Klonoff et al. 2009 ¹⁵⁷
Koci et al. 2007 ¹⁵⁸
Macleod et al. 1993 ¹⁵⁹
Marshall et al. 1987 ¹⁶⁰
Matanovic et al. 1012 ¹⁶¹
Mellbin et al. 2011 ¹⁶²
Mühlhauser, et al 1987 ¹⁶³
Mühlhauser et al. 2000 ¹⁶⁴
NOMAS 2008 ¹⁶⁵
Nosadini al. 1988 ¹⁶⁶
Olmos et al 1997 ¹⁶⁷
Pissarek et al. 1980 ¹⁶⁸
Retnakaran et al. 2004 ¹⁶⁹
Schnell et al. 1977 ¹⁷⁰
Selam et al. 1993 ¹⁷¹
Shishko et al. 1994 ¹⁷²
Sindaco et al. 1998 ¹⁷³
Stanton et al. 2004 ¹⁷⁴
Williams et al. 2010 ¹⁷⁵
Wiseman et al. 1985 ¹⁷⁶

DAFNE= Dose Adjustment For Normal Eating; DIGAMI= Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction; NOMAS= Northern Manhattan Study; DIGAMI2= Type 2 Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction.

Web appendix 3. Forest plots and Trial sequential analysis

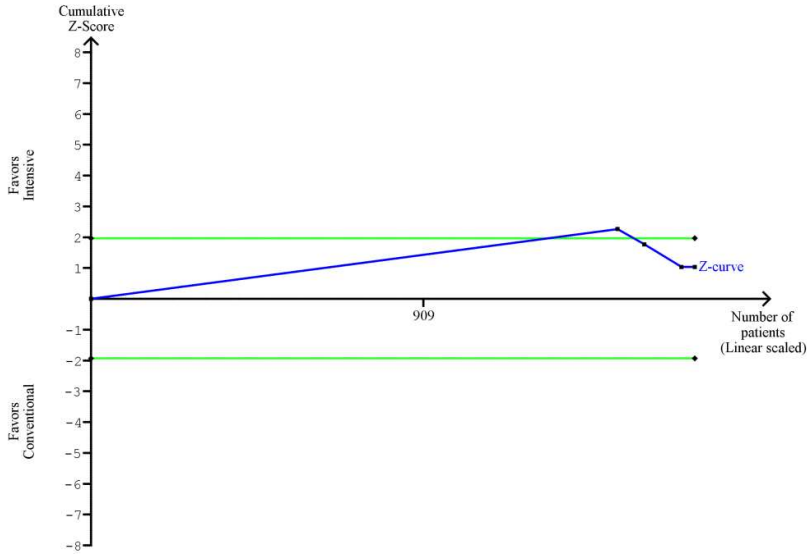


Figure 9 Trial sequential analysis of cardiovascular mortality (data extracted to the longest follow-up). Trial sequential analysis revealed that 0.84% (n=909) of the diversity adjusted required information size was accrued so far. The number was calculated based on a proportion of cardiovascular mortality of 1.5% in conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green lines, illustrating the conventional level of statistical significance ($P=0.05$), favoring intensive glycaemic control. The cumulative z-score does not cross the trial sequential alpha spending monitoring boundaries, which cannot be seen on the figure due to lack of data.

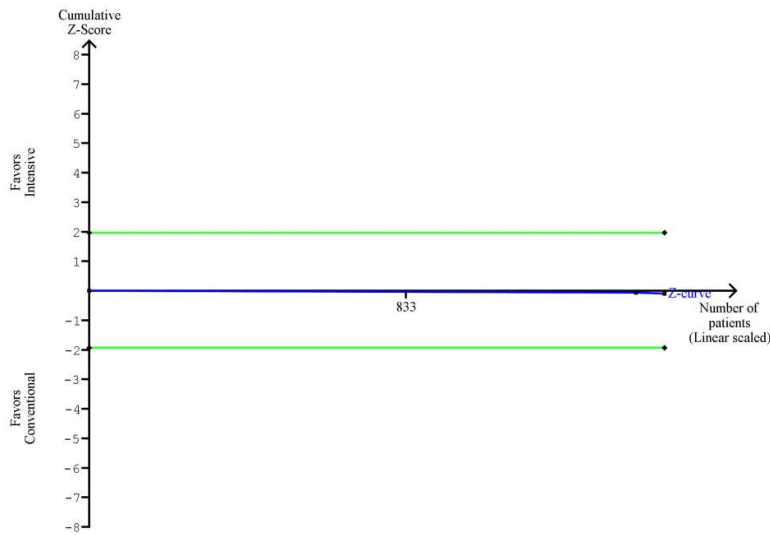


Figure 10 Trial sequential analysis of severe adverse events (data extracted to the longest follow-up). Trial sequential analysis revealed that 1.89% (n=833) of the diversity adjusted required information size was accrued so far. The number was calculated based on a proportion of severe adverse events of 3.6% in the conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it does not cross the horizontal solid green lines, illustrating the conventional level of statistical significance ($P=0.05$). The cumulative z-score does not cross the trial sequential alpha spending monitoring boundaries, which cannot be seen on the figure due to lack of data.

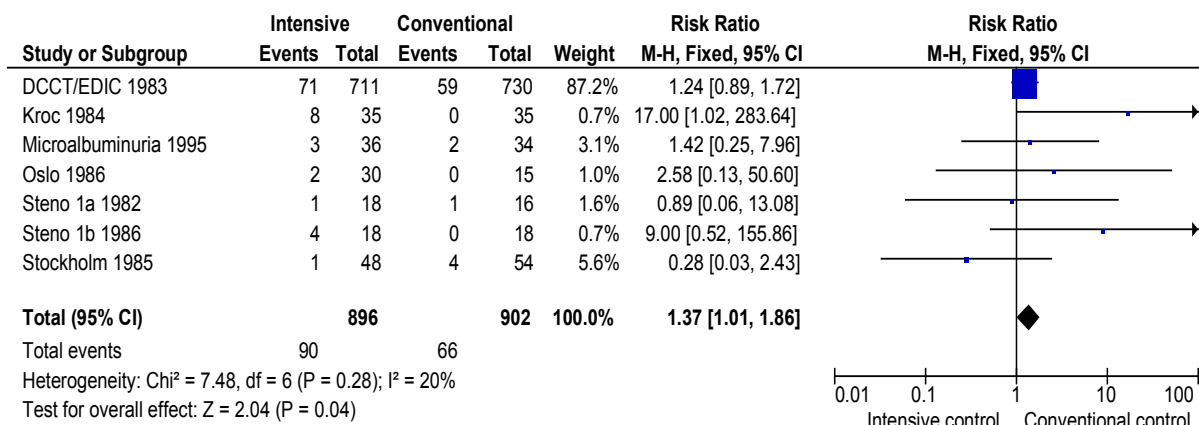


Figure 11a Forest plots for ketoacidosis, meta-analysis of data to the longest follow-up.

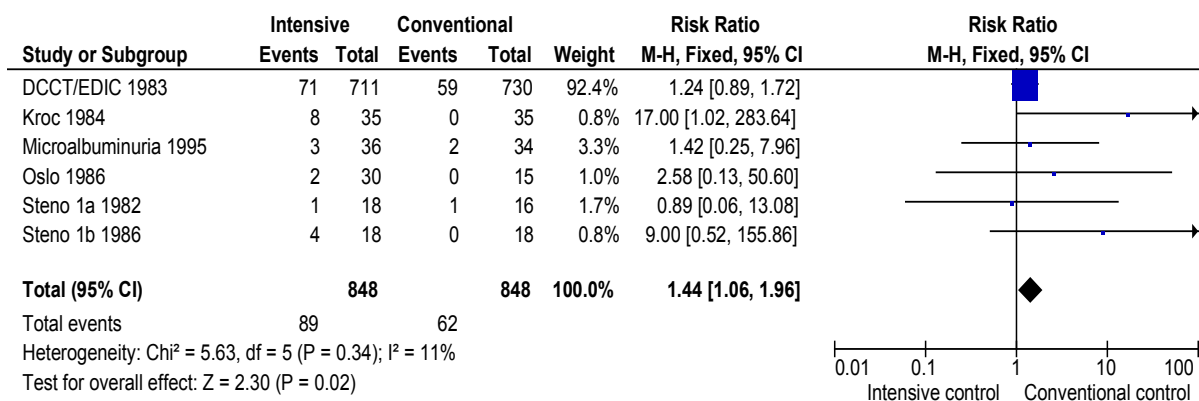


Figure 11b Forest plots for ketoacidosis, meta-analysis of data to the end of the intervention period.

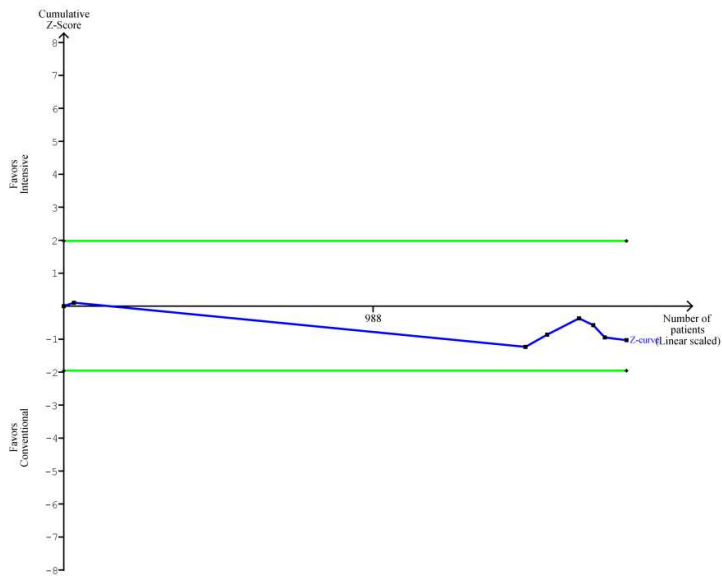


Figure 11c Trial sequential analysis of ketoacidosis (data extracted to the longest follow-up). Trial sequential analysis revealed that 1.04% ($n=988$) of the diversity adjusted required information size was accrued so far. The number was calculated based on a proportion of ketoacidosis events of 7.3% in the conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=0\%$. Solid blue line is the cumulative z-score, and it does not cross the horizontal solid green lines, illustrating the conventional level of statistical significance ($P=0.05$). The cumulative z-score does not cross the trial sequential alpha spending monitoring boundaries, which cannot be seen on the figure due to lack of data.

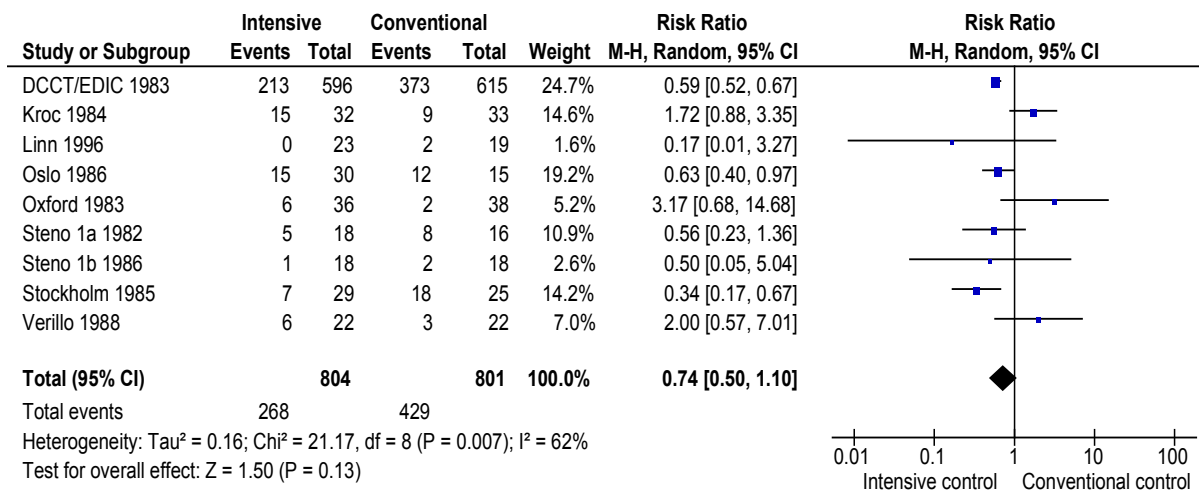


Figure 12a Forest plots for retinopathy, meta-analysis of data to the longest follow-up.

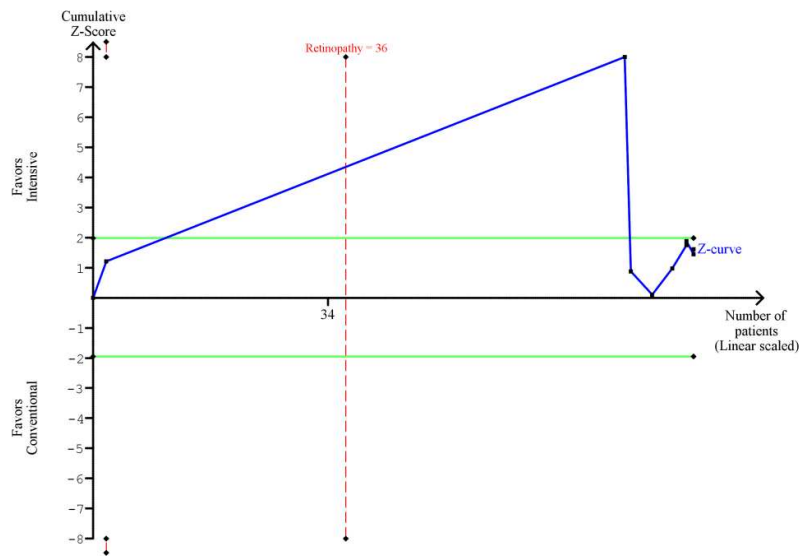


Figure 12b Trial sequential analysis of retinopathy (data extracted to the longest follow-up). Trial sequential analysis revealed that <1.00% (n=34) of the diversity adjusted required information size was accrued so far. The number was calculated based on a proportion of retinopathy of 53.6% in the conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=91\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green lines, illustrating the conventional level of statistical significance ($P=0.05$), favoring intensive glycaemic control, but returns to a non-significant value. The cumulative z-score does not cross the trial sequential alpha spending monitoring boundaries, which cannot be seen on the figure due to lack of data.

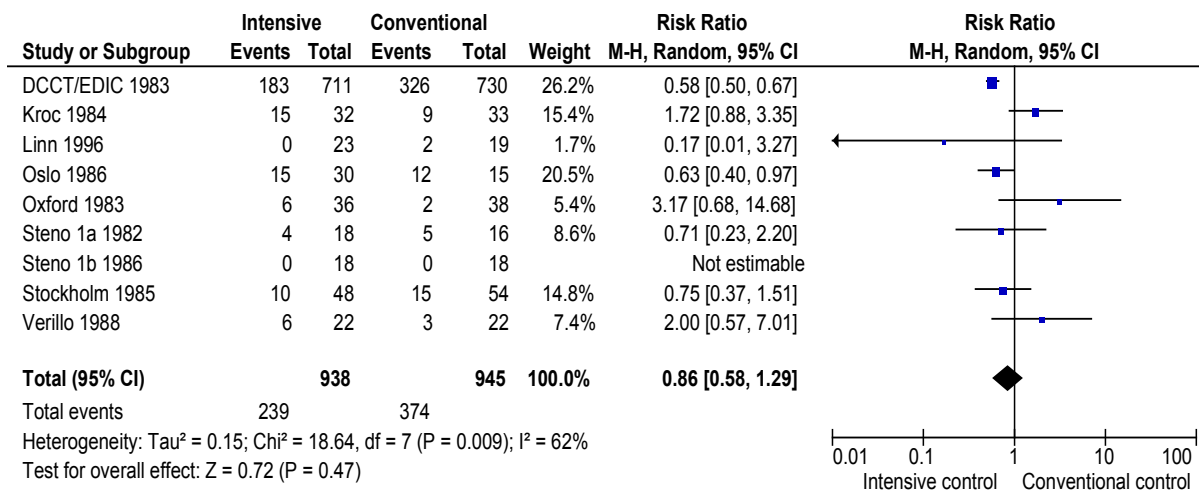


Figure 12c Forest plots for retinopathy, meta-analysis of data to the end of the intervention period.

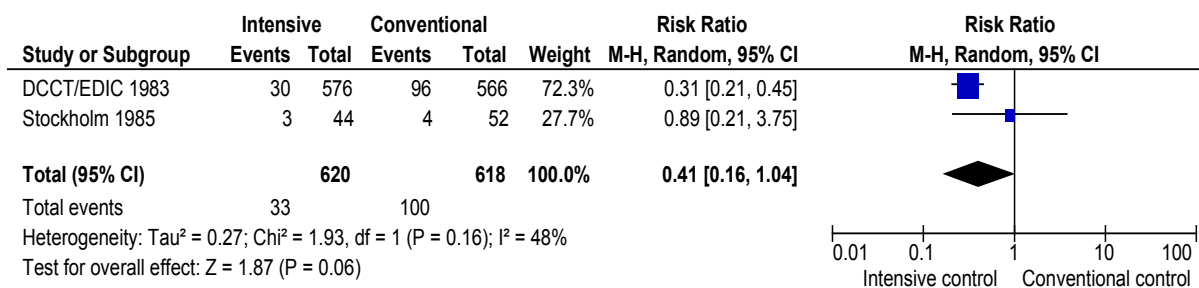


Figure 13a Forest plots for retinal photocoagulation, meta-analysis of data to the longest follow-up.

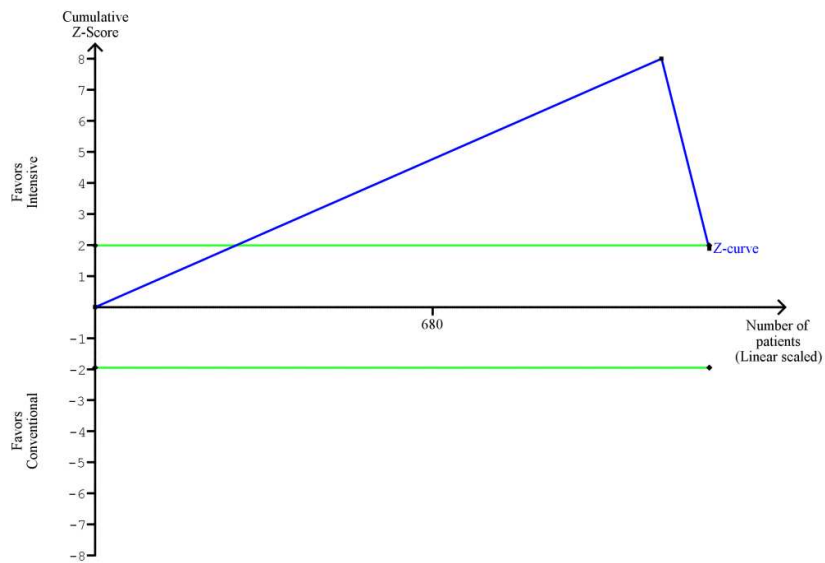


Figure 13b Trial sequential analysis of retinal photocoagulation (data extracted to the longest follow-up). Trial sequential analysis revealed that 1.32% (n=680) of the diversity adjusted required information size was accrued so far. The number was calculated based on a proportion of severe adverse events of 16.2% in the conventional glucose control group, a relative risk reduction of 10% in the intensive glycaemic group, $\alpha=5\%$, $\beta=20\%$, and $D^2=83\%$. Solid blue line is the cumulative z-score, and it crosses the horizontal solid green lines, illustrating the conventional level of statistical significance ($P=0.05$), favoring intensive glycaemic control, but returns to a non-significant value. The cumulative z-score does not cross the trial sequential alpha spending monitoring boundaries, which cannot be seen on the figure due to lack of data.

Web appendix 4. Outcome definitions or as reported

Trial	Nephropathy	Retinopathy	Macrovascular complications	Severe hypoglycaemia	End-stage renal disease
DCCT/EDIC 1983 ³⁻⁴⁶	Albumin excretion rate > 300 mg/24 hours. The follow-up data also includes patients with renal insufficiency (serum creatinin level ≥ 2 mg/dL or dialysis or renal transplantation)	A 3-step or more progression in retinopathy on the Early Treatment Diabetic Retinopathy Study scale	Nonfatal myocardial infarction or stroke; death judged to be due to cardiovascular disease; subclinical myocardial infarction; angina, confirmed by ischemic changes on exercise tolerance testing or by clinically significant obstruction on coronary angiography; or the need for revascularization with angioplasty or coronary-artery bypass. Subclinical ("silent") myocardial infarctions were identified on the annual electrocardiograms	An episode of hypoglycaemia in which the patient required assistance with treatment from another person to recover; in addition, the blood glucose level had to be documented as <50 mg/dL and/or the clinical manifestations had to be reversed by oral carbohydrate, subcutaneous glucagon, or intravenous glucose. Patients were asked to report severe hypoglycaemia immediately and were asked about the occurrence of any hypoglycaemia at each quarterly visit	Defined as the need for kidney transplant or the initiation of maintenance dialysis.
Franklin et al. 2008 ¹⁰²	-	-	-	-	-
Hvidovre 1982 ⁶⁷	-	-	-	-	-
Kroc 1984 ¹⁰⁹⁻¹¹⁴	-	Deterioration (by mean retinopathy level) assessed with Early Treatment Diabetic Retinopathy Study scale	-	Requiring i.v. glucose or intramuscular glucagon	-
Linn et al. 1996 ¹¹⁵	-	-	-	Unawareness in the patient	-
Linn et al. 2003 ⁶⁸	-	-	-	-	-
Microalbuminuria 1995 ⁴⁹ 50	Progression to clinical albuminuria (albumin excretion rate ≥ 200 µg/min)	-	-	Requiring the assistance of another person	'Renal failure' without specifying the criteria
Minnesota DCCT 1983 ⁸²⁻⁸⁵	-	-	-	-	Kidney transplantation
Oslo 1986 ⁷²⁻⁷⁹	-	Worsened changes in retinopathy assessed from fluorescein angiograms	-	Hypoglycaemic coma	-
Oxford 1983 ¹⁰⁸	-	Formation of new vessels	-	Requiring hospital admission	-
Perlman et al. 1984 ¹⁰⁴	-	-	-	-	-
Service et al. 1983 ⁸⁰	-	-	-	-	-
Shah et al. 1989 ¹⁰³	-	-	-	-	-
Steno 1a 1982 ^{71 116-118}	'Clinical nephropathy' without specifying the criteria	'Proliferative retinopathy' without specifying the criteria	Nonfatal cardiovascular events	Requiring hospital admission	-
Steno 1b 1986 ⁶⁹⁻⁷¹	Albumin excretions rate >300 mg/24 hours in 2 out of 3 24 hours urine specimens	'Proliferative retinopathy' without specifying the criteria	-	Patients requiring medical intervention	-
Stockholm 1985 ⁸⁶⁻⁹⁷	'Albuminuria' without specifying the criteria	'Proliferative retinopathy' after intervention period and 'Serious retinopathy' after follow-up period, without specifying the criteria	'Macrovascular complications' without specifying the criteria	Requiring help from someone else or resulting in coma	-
Verrillo et al 1988 ⁸¹	-	'Proliferative retinopathy' without specifying the criteria	-	Requiring hospital admission	-
White et al. 1994 ^{100 101}	-	-	-	Severe neurological dysfunction requiring intervention with glucagon or i.v. dextrose	-

DCCT/EDIC= Diabetes Control and Complication Trial / Epidemiology of Diabetes Interventions and Complications; Minnesota DCCT= Minnesota Diabetes Control and Complication Trial; i.v.=intravenous

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