Ph.D. thesis

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Evidence-based assessments of glucose-lowering interventions for patients with type 2 diabetes mellitus - systematic reviews with meta-analyses and trial sequential analyses of randomised clinical trials

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Preface

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Papers

This Ph.D. thesis is based on the following papers:

Paper I. Hemmingsen B, Lund SS, Wetterslev J, Vaag A. Oral hypoglycaemic agents, insulin resistance and cardiovascular disease in patients with type 2 diabetes. Eur J Endocrinol. 2009;161(1):1-9 **(Number 18 in the reference list)**

Paper II. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2 **(Number 43 in the reference list)**

Paper III. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898 **(Number 42 in the reference list)**

Paper IV. Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, Sonne DP, Lundstrøm LH, Almdal T. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Submitted to Cochrane Database of Systematic Reviews xxxx, Issue X **(Number 39 in the reference list)**

Paper V. Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, Sonne DP, Lundstrøm LH, Almdal T. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Submitted to BMJ **(Number 40 in the reference list)**

Paper VI. Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ 2012;344:e1771 **(Number 41 in the reference list)**

Summary

Background

Cochrane reviews with meta-analyses and trial sequential analyses of randomised clinical trials provide guidance for clinical practice and health-care decision making. High quality systematic reviews can facilitate implementation of evidence-based medical interventions into clinical practice. Patients with type 2 diabetes mellitus have a high number of complications and increased mortality. Therefore, interventions based on evidence are highly warranted. Furthermore, the prevalence of type 2 diabetes mellitus is increasing so effective interventions without undue harms are requested by the society to reduce the suffering and costs.

Objectives

To assess the benefits or harms of targeting intensive glycaemic control versus targeting conventional glycaemic control; of sulphonylurea monotherapy versus other antidiabetic monotherapy or placebo; and of metformin plus insulin versus insulin alone in patients with type 2 diabetes mellitus.

Methods

We performed three systematic reviews of all relevant randomised clinical trials. To quantify the estimated effect of various interventions, we performed meta-analyses using The Cochrane Collaboration risk of bias tools and trial sequential analysis to adjust the risk of random errors for sparse data and repetitive testing. All reviews were based on published protocols. Included trials were identified through The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature (LILACS), and Cumulative Index to Nursing & Allied Health Literature (CINAHL). In addition, we handsearched abstracts of major diabetes conferences as well as checked the reference lists of the included trials and identified (systematic) reviews, meta-analyses, and health technology assessment reports. We searched the US Food and Drug Administration website for unpublished trials. Two authors independently screened the retrieved titles and abstracts for inclusion. Authors of the included trials were asked if

they knew of any additional relevant trials. Data extraction and the assessment of risk of bias were conducted by two authors independently of each other.

Results

The three systematic reviews included a total of 116 trials with 51,385 participants. Only one of the trials could be considered low risk of bias regarding all bias domains. Only 17 of the trials were classified as lower risk of bias considering only generation of the allocation sequence, allocation concealment, and blinding. The reporting of patient-important outcomes was in general sparse.

We included 20 trials with 16,106 participants randomised to targeting intensive glycaemic control versus 13,880 participants randomised to targeting conventional glycaemic control. In a random-effects model, targeting intensive glycaemic control versus targeting conventional glycaemic control did not significantly affect all-cause mortality (relative risk (RR) 1.01, 95% confidence interval (CI) 0.90 to 1.13), cardiovascular mortality (RR 1.06, 95% CI 0.90 to 1.26), or non-fatal myocardial infarction (RR 0.86, 95% CI 0.76 to 1.00). In a random-effects model, targeting intensive glycaemic control reduced the risk of amputation (RR 0.64, 95% CI 0.43 to 0.95; P = 0.03), the composite outcome of microvascular disease (RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006), retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P = 0.002), retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; P = 0.03), and nephropathy (RR 0.78, 95% CI 0.61 to 0.99; P = 0.04). Targeting intensive glycaemic control increased the risk of severe hypoglycaemia (RR 2.05, 95% CI 1.39 to 3.02; P = 0.0003). Trial sequential analysis for all-cause mortality suggested that a 10% or greater relative risk reduction could be rejected at this point. Trial sequential analysis showed that only a part of the required information size to establish evidence for a 10% relative risk increase or reduction was accrued so far for the following outcomes: cardiovascular mortality, non-fatal myocardial infarction, amputation, retinopathy, and retinal photocoagulation. Trial sequential analyses disregarding the risk of bias showed that firm evidence for a 10% relative risk reduction in favour of intensive glycaemic control was established for the composite microvascular outcome. Trial sequential analysis disregarding the risk of bias showed conclusive evidence for a relative risk increase of 30% for severe hypoglycaemia in favour of conventional glycaemic control.

We included 72 randomised clinical trials with 9589 participants randomised to a sulphonylurea versus 12,805 randomised to the control group of any other antidiabetic monotherapy, placebo, or no intervention. First-generation sulphonylurea versus placebo showed statistical significance for cardiovascular mortality in favour of placebo (RR 2.63, 95% CI 1.32 to 5.22; P = 0.006). The remaining comparisons of sulphonylurea monotherapy versus other antidiabetic monotherapies or no intervention could either not be performed due to lack of data, or showed no significance for all-cause mortality, cardiovascular mortality, or non-fatal myocardial infarction. The risk of macrovascular complications was changed in favour of second-generation sulphonylurea compared with metformin (RR 0.67, 95% CI 0.48 to 0.93; P = 0.02). However, trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% relative risk reduction was accrued so far. The risk of severe hypoglycaemia was elevated with second-generation sulphonylurea compared with metformin (RR 5.64, 95% CI 1.22 to 26.00; P = 0.03) and the thiazolidinediones (RR 6.11, 95% CI 1.57 to 23.79; P = 0.009). However, trial sequential analysis showed that only a minor fraction of the required information sizes was accrued so far.

We included 26 randomised clinical trials with 2286 participants randomised to metformin plus insulin versus insulin alone, of which 23 trials with 2117 participants could provide data in this systematic review. Metformin plus insulin versus insulin alone did not significantly affect all-cause mortality (RR 1.30, 95% CI 0.57 to 2.99), cardiovascular mortality (RR 1.70, 95% CI 0.35 to 8.30), or severe hypoglycaemia (RR 2.43, 95% CI 0.54 to 10.85). The reporting of macrovascular and microvascular complications was infrequent, and all the outcomes assessed could either not be meta-analysed due to lack of data or showed non-significant effect estimates.

Conclusions

Firm evidence for a 10% relative risk reduction for the composite microvascular outcome with intensive glycaemic control was the only benefit of the investigated and most commonly used glucose-lowering interventions in patients with type 2 diabetes mellitus. Almost all of the trials had methodological limitations leading to systematic error (bias)

risks, small number of participants and outcomes leading to random error (play of chance) risks, and short trial duration. Many of the patient-important outcomes were poorly reported in most of the trials. There is an urgent need for randomised clinical trials with low risk of bias and low risk of random errors to justify the use of some of the most prescribed glucose-lowering interventions.

Epidemiology of type 2 diabetes mellitus (Paper I)

The number of people with type 2 diabetes mellitus (T2DM) is increasing due to population growth, aging, and sedentary life style. Worldwide, the number of patients with T2DM was estimated to be 177 millions in 2000 and is foreseen to rise to 366 millions in 2030.[1] Patients with T2DM may have moderately elevated levels of blood glucose for a long time without any symptoms, and therefore remain undiagnosed for years.[2] Immediate consequences of marked hyperglycaemia are thirst, weight loss, and polyuria.[3] Epidemiological studies have shown increased macrovascular complications, microvascular complications, and mortality in patients with T2DM.[4-7] In addition, epidemiological studies in patients with T2DM have indicated an association between the level of glycaemic control and the risk of mortality, macrovascular, and microvascular complications.[8-11]

The improvement in life expectancy and decrease in cardiovascular mortality in the non-diabetic population during the last few decades, is also seen among patients with T2DM.[12-14] The incidences of both macrovascular and microvascular complications in patients with T2DM are also declining.[15-17] Despite these optimistic trends, the risks of macrovascular and microvascular complications, as well as death are still highly elevated compared to the non-diabetic population.[12;13;15-17] The antidiabetic drugs applied to reduce blood glucose might influence the cardiovascular risks (Paper I).[18] There are no epidemiological studies implying that any antidiabetic drugs influence the risk of developing microvascular complications.

Recommendations for treatment of type 2 diabetes mellitus

A number of medical organisations have developed guidelines or recommendations for the treatment of patients with T2DM, e.g., the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE),[19] Texas Diabetes Council,[20] Canadian Diabetes Association (CDA),[21] International Diabetes Federation (IDF),[22] UK National Institute for Health and Clinical Excellence (NICE),[23] and American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD).[24]

The most widely used is the ADA/EASD position statement, which was published for the first time in 2006.[25] While being one of the series from ADA,[26] it was the first position issued under the EASD. The ADA/EASD position statements from 2006 and 2009 stated that specific glycaemic goals can substantially reduce morbidity and that the treatment of hyperglycaemia had top priority.[25;27] The ADA/EASD position statements have advocated for a glycosylated haemoglobin A1c (HbA1c) target around 7% since their first publication.[24;25;25;27] The newest ADA/EASD position statement 2012 states that the glycaemic management in T2DM has become very complex and controversial.[24] Therefore, individualisation of the glycaemic goal is emphasised.[24] Both the ADA/EASD position statement and the International Diabetes Federation and the Canadian Diabetes Association guidelines suggest lowering HbA1c to < 7% in most patients.[21;22;24] The most recent glycaemic goal set by the AACE/ACE is an HbA1c level of 6.5%.[19] The current guideline with the lowest glycaemic target is the Texas Diabetes Council, which suggest an HbA1c level around 6%.[20] All the current T2DM guidelines recommend individualised glycaemic targets depending on the characteristic of the patients.[19-24]

The ADA/EASD position statements recommend the initial interventions in T2DM to be lifestyle changes with or without metformin.[24;25;27] All the ADA/EASD position statements agree that if metformin cannot be used, another oral agent could be started as first-line, e.g., a sulphonylurea.[24;25;27] The newest ADA/EASD position statement recommends metformin as first-line glucose-lowering drug over sulphonylurea.[24] The arguments in favour of metformin being lower influence on body weight, lower costs, lesser risk of hypoglycaemia, and the possibility that cardiovascular events are reduced.[24] If glycaemic control cannot be achieved or maintained with metformin monotherapy another oral antidiabetic agent is recommended to be added, e.g., a sulphonylurea.[24;25;27]

Due to the progressive nature of T2DM most patients will eventually after years of disease duration be prescribed insulin.[28;29] The ADA/EASD position statements recommends metformin to be continued when insulin is initiated, due to less weight gain with combination therapy.[24;25;27] However, this recommendation is based on one randomised clinical trial with 43 participants followed for 24 weeks.[30] The newest International Diabetes

Federation guideline recommends the use of insulin in combination with metformin based on data from a Cochrane reivew.[22;31] However, this review did only include a small part of the available trials and no data on mortality, macrovascular, and microvascular outcomes were reported.[22;31]

Epidemiology of treatment of type 2 diabetes mellitus

The effect of glucose-lowering interventions in patients with T2DM is monitored through measurements of HbA1c, which is a measurement of long-term glycaemic control, i.e., how well the blood glucose levels have been controlled during the previous 2 to 3 months.[2] To determine whether glycaemic control was improving in patients with diabetes, three phases of the National Health and Nutrition Examination Survey (NHANES), conducted between 1999 and 2004 were reviewed for trends in HbA1c.[32] Data showed that mean HbA1c for the entire NHANES population cohort declined from 7.82% in 1999 to 7.18% in 2004. During the same time period the number of patients with HbA1c < 7% increased from 37% to 56%.[32] The proportion of patients with HbA1c > 9% was reduced from 21% to 12%.[32] However, it is possible that earlier detection of diabetes during the years could bias the results towards lower mean HbA1c.[32] Furthermore, no separate estimates for glycaemic control for type 1 or type 2 diabetes mellitus were made.[32]

Several epidemiological studies confirm that the prescription of metformin is increasing, and that metformin currently is the most prescribed agent for glycaemic control.[33-36] While the prescription of metformin as monotherapy has increased, the prescription of sulphonylurea monotherapy has declined.[29;33-36] Metformin surpassed sulphonylureas as the leading glucose-lowering drug in 2004.[29;35] From 2000 to 2009, the prescription of sulphonylurea as first-line antidiabetic intervention for patients with T2DM in Denmark has declined from 61% to 10%.[29] While the prescription of sulphonylurea monotherapy declines, the prescription of newer and more expensive antidiabetic interventions increases.[29;35-37] The sulphonylureas are often prescribed in combination with metformin, when monotherapy with metformin fails.[33-35] Insulin prescribed as monotherapy is declining in patients with T2DM.[33;34;38] On the other hand, there is an increase of the use of insulin combined with metformin.[33-35;38]

Based on guidelines it is obvious that confusion exists about intensification of glycaemic control as well as the evidence for applying widespread antidiabetic interventions. In order to try to clarify the current evidence for the antidiabetic interventions prescribed, we performed three systematic reviews. One addressing the issue of intensive glycaemic control, and two addressing the choice of antidiabetic drugs.[39-43]

Targeting intensive glycaemic control versus targeting conventional glycaemic control in patients with type 2 diabetes mellitus (Paper II and III)

In this systematic review, we included 20 trials with 16,106 participants randomised to targeting intensive glycaemic control versus 13,880 participants randomised to targeting conventional glycaemic control. The trials were included irrespective of the setting in which intensive glycaemic control was applied, the glycaemic target in the intensive glycaemic control arm, and the glucose-lowering drug(s) prescribed to reach the glycaemic target. The definition of intensive and conventional glycaemic control varied among the included trials. The definitions of the target of intensive glycaemic control were for most of the trials expressed as HbA1c from less than 6.0% to 7.5%. The definitions of conventional glycaemic control varied, but were mostly expressed as an HbA1c from 7% to 9%. The intervention could be applied in three different settings: usual care setting (n = 14 trials); intensive glycaemic control as a part of acute intervention (n = 3 trials); and intensive glycaemic control as a part of multimodal intervention (n = 3 trials). The outcomes were meta-analysed for all trials together and for each setting separately.

One trial was judged as low risk of bias on all bias domains. Eight of the trials were judged as lower risk of bias considering only sequence generation, allocation concealment, and blinding. Combination of data showed no significant effect of intensive versus conventional glycaemic control on all-cause mortality (relative risk (RR) 1.01, 95% confidence interval (CI) 0.90 to 1.13; 29,731 participants, 18 trials) or cardiovascular mortality (RR 0.90, 95% CI 0.90 to 1.26; 29,731 participants, 18 trials). Trial sequential analysis suggested that a relative risk reduction of 10% or greater could be rejected for all-cause mortality (Figure 1).

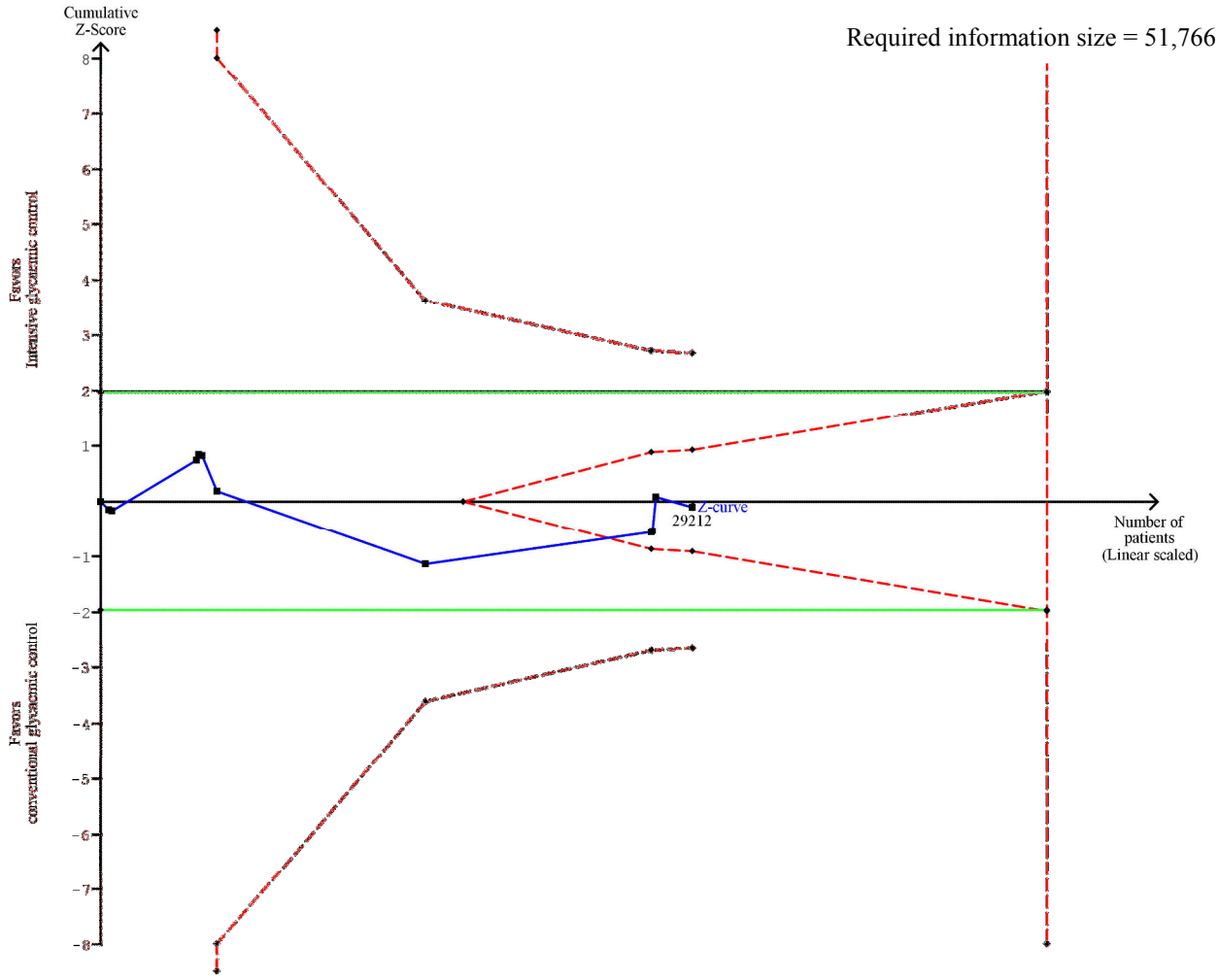

Figure 1 Trial sequential analysis of all-cause mortality (intensive glycaemic control applied in any setting). Heterogeneity-adjusted required information size of 51,766 participants calculated based on the proportion of mortality of 8.8% in the conventional glucose control group, relative risk reduction of 10%, α = 5%, β = 20%, and I^2 = 40%. The actual accrued number of participants was 29,212, only 56% of the required information size. Solid blue cumulative Z curve does not cross the dashed red trial sequential monitoring boundaries for benefit or harm, but boundaries for futility (red inner wedge boundaries) are crossed. Horizontal green lines illustrate traditional level of statistical significance (P = 0.05).

Targeting intensive glycaemic control did not reveal any significant differences in the effect estimates of the composite macrovascular outcome (RR 0.92, 95% CI 0.80 to 1.05; 28,509 participants, 10 trials), non-fatal stroke (RR 0.96, 95% CI 0.80 to 1.16; 28,760 participants, 11 trials), cardiac revascularization (RR 0.84, 95% CI 0.67 to 1.05; 2289 participants, 5 trials), and peripheral revascularization (RR 0.92, 95%CI 0.81 to 1.06; 13,477 participants,

7 trials). For all trials meta-analysed together, the risk of non-fatal myocardial infarction was not significantly reduced in the random-effects model (RR 0.86, 95% CI 0.76 to 1.00; 29,174 participants, 12 trials) but in the fixed-effect model (RR 0.86, 95% CI 0.78 to 0.96; P = 0.006; 29,714 participants, 12 trials). For the trials exclusively dealing with glycaemic control in usual care setting, the risk of non-fatal myocardial infarction was significantly reduced in both the fixed-effect and in the random-effects model (RR 0.85, 95% CI 0.76 to 0.95; P = 0.004; 28,111 participants, 8 trials). This finding was, however, not confirmed in the trial sequential analysis (Figure 2).

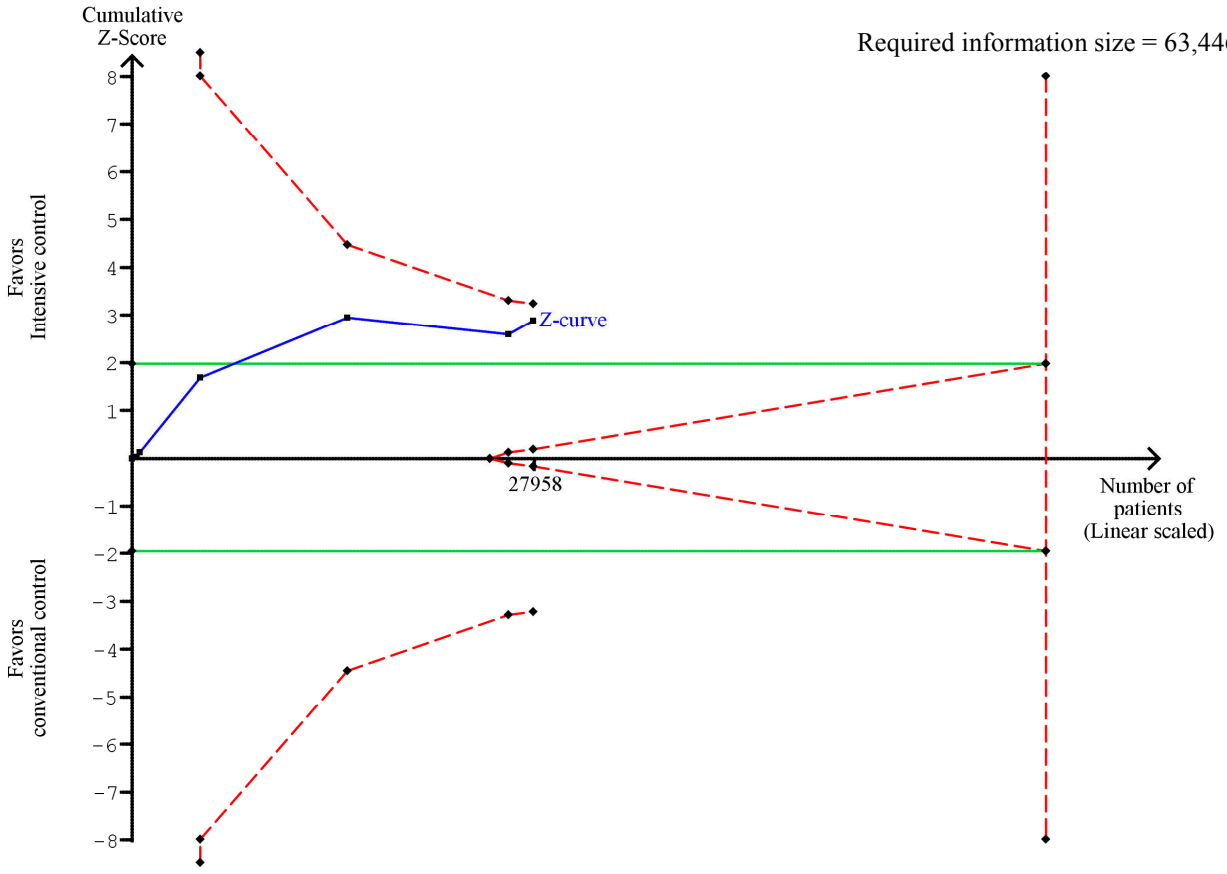

Figure 2 Trial sequential analysis for non-fatal myocardial infarction (trials exclusively dealing with glycaemic control in usual care setting). Heterogeneity-adjusted required information size of 63,446 participants calculated based on the proportion of non-fatal myocardial infarction of 4.5% in the conventional glucose control group, a relative risk reduction of 10%, α = 5%, β = 20%, and I^2 = 0%. The actual accrued number of participants was 27,958, only 44% of the required information size. The solid blue cumulative Z curve does not cross the dashed red trial sequential monitoring boundaries for benefit or harm.

Targeting intensive glycaemic control reduced the risk of amputation (RR 0.64, 95% CI 0.43 to 0.95; P = 0.03; 6960 participants, 8 trials), the composite microvascular outcome (RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006; 25,760 participants, 4 trials), retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P = 0.002; 10,230 participants, 8 trials), retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; P = 0.03; 11,142 participants, 7 trials), and nephropathy (RR 0.78, 95% CI 0.61 to 0.99; P = 0.04; 27,929 participants, 9 trials). However, in a fixed-effect model, nephropathy did not show statistical significance (RR 0.97, 95% CI 0.93 to 1.00). For the trials exclusively dealing with glycaemic control in usual care setting, statistical significance was not present for nephropathy (RR 0.83, 95% CI 0.64 to 1.06; 27,769 participants, 8 trials). Trial sequential analysis disregarding the risk of bias showed only firm evidence for a 10% relative risk reduction of the composite microvascular outcome from all trials in favour of targeting intensive glycaemic control. The remaining effect estimates showing significance in the cumulative meta-analyses were not confirmed in the trial sequential analyses.

The risks of both mild (RR 1.50, 95% CI 1.31 to 1.72; P < 0.00001; 18,923 participants, 11 trials) and severe hypoglycaemia (RR 2.05, 95% CI 1.39 to 3.02; P = 0.0003; 28,127 participants, 12 trials) were increased with targeting intensive glycaemic control but substantial heterogeneity was present. The definition of severe hypoglycaemia varied among the included trials. Trial sequential analysis disregarding the risk of bias showed that firm evidence was reached for a 30% relative risk increase in severe hypoglycaemia when targeting intensive glycaemic control (Figure 3).

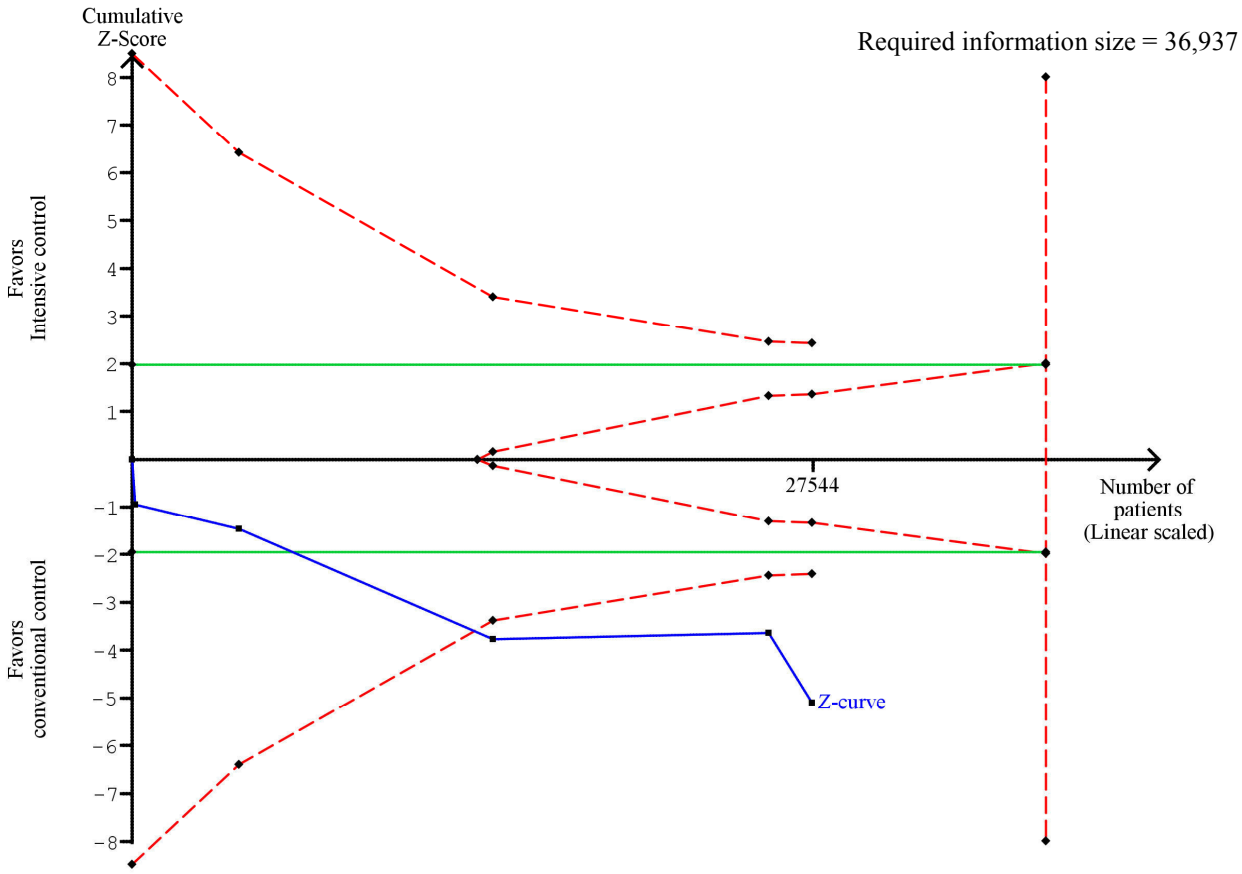

Figure 3 Trial sequential analysis for severe hypoglycaemia (trials exclusively dealing with glycaemic control in usual care setting). Heterogeneity-adjusted required information size of 36,937 participants calculated based on the proportion of severe hypoglycaemia of 2.9% in the conventional glucose control group, a relative risk reduction of 30%, α = 5%, β = 20%, and I^2 = 73%. The solid blue cumulative Z curve crosses the trial sequential boundary for harm, indicating that sufficient evidence has been reached for a 30% increase in relative risk with targeted intensive glycaemic control.

In summary, when targeting intensive glycaemic control combined for all settings of patients with T2DM, the risk of composite microvascular complications is significantly reduced, but the risk of severe hypoglycemia is significantly increased. For the remaining outcomes the effect estimates were non-significant, or the significance could not be confirmed in the trial sequential analysis (i.e., trial sequential analysis could not rule out a type I error). For the trials exclusively dealing with glycaemic control in the usual care setting, the only outcome showing significance that could be confirmed in the trial sequential analysis was severe hypoglycaemia. For the remaining outcomes meta-analysed in the usual care setting, there was either no significance of the effect estimate,

or the significance could not be confirmed in the trial sequential analysis. Furthermore, only one of the trials had low risk of bias. Accordingly, systematic errors (bias) and random errors (play of chance) cannot be excluded as an explanation for the positive findings.

Sulphonylurea monotherapy for patients with type 2 diabetes mellitus (Paper IV and V)

In this systematic review we included 72 randomised clinical trials with 9589 participants randomised to a sulphonylurea versus 12,805 randomised to the control group of any other antidiabetic monotherapy, placebo, or no intervention. Each generation (first, second or third) of sulphonylurea was included in the analyses. First-generation sulphonylureas were prescribed in 10 trials, second-generation sulphonylureas in 55 trials, and third-generation sulphonylureas in 9 trials. The duration of the intervention varied from 24 weeks to 10.7 years. None of the included trials were judged as low risk of bias on all bias domains. Seven trials were judged as lower risk of bias only considering sequence generation, allocation concealment, and blinding. The reporting of patient-important outcomes was sparse.

First-generation sulphonylureas versus placebo or insulin did not show statistical significance for all-cause mortality (versus placebo: relative risk (RR) 1.46, 95% confidence interval (CI) 0.87 to 2.45; 553 participants, 2 trials; versus insulin: RR 1.18, 95% CI 0.88 to 1.59; 1944 participants, 2 trials). First-generation sulphonylurea versus placebo showed statistical significance for cardiovascular mortality in favour of placebo (RR 2.63, 95% CI 1.32 to 5.22; P = 0.006; 553 participants, 2 trials). First-generation sulphonylureas versus insulin did not show statistical significance for cardiovascular mortality (RR 1.36, 95% CI 0.68 to 2.71; 1944 participants, 2 trials). We could not meta-analyse comparisons of first-generation sulphonylureas with any comparator regarding macrovascular and microvascular disease or hypoglycaemia due to lack of data.

Second-generation sulphonylureas versus metformin (RR 0.98, 95% CI 0.61 to 1.58; 3528 participants, 6 trials), thiazolidinediones (RR 0.92, 95% CI 0.60 to 1.41; 4955 participants, 7 trials), insulin (RR 0.96, 95% CI 0.79 to 1.18; 1642 participants, 4 trials), meglitinide (RR 1.44, 95% CI 0.47 to 4.42; 2038 participants, 7 trials), or incretin-based interventions (RR

1.39, 95% CI 0.52 to 3.68; 1503 participants, 2 trials) showed no statistical significant effects regarding all-cause mortality.

Second-generation sulphonylureas versus metformin (RR 1.47, 95% CI 0.54 to 4.01; 3528 participants, 6 trials), thiazolidinediones (RR 1.30, 95% CI 0.55 to 3.07; 4955 participants, 7 trials), insulin (RR 0.96, 95% CI 0.73 to 1.28; 1642 participants, 4 trials), or meglitinide (RR 0.86, 95% CI 0.24 to 3.04; 2038 participants, 4 trials) showed no statistical significant effects regarding cardiovascular mortality. Second-generation sulphonylureas versus metformin and thiazolidinediones showed statistically significance in favour of the comparators for severe hypoglycaemia (versus metformin: RR 5.64, 95% CI 1.22 to 26.00; P = 0.03; 3637 participants, 4 trials; versus thiazolidinediones: RR 6.11, 95% CI 1.57 to 23.79, P = 0.009; 5851 participants, 7 trials). Second-generation sulphonylureas versus meglitinides showed no statistical significance for the risk of severe hypoglycaemia (RR 2.87, 95% CI 0.91 to 8.99).

Third-generation sulphonylureas could not be included in any meta-analyses of all-cause mortality, cardiovascular mortality, macro- or microvascular complications, or severe hypoglycaemia due to lack of data.

Metformin and insulin versus insulin alone for type 2 diabetes mellitus (Paper VI)

We included 26 randomised clinical trials with 2286 participants, of which 23 trials with 2117 participants could provide data in this systematic review. The total daily dose of metformin in the intervention groups varied between 1000 mg and 2550 mg. Insulin regimens differed among the trials, and also varied among the intervention groups within some trials. None of the trials were judged as low risk of bias on all bias domains. Only two trials had lower risk of bias considering only sequence generation, allocation concealment, and blinding. Very few trials provided data on patient-important outcomes.

Metformin and insulin versus insulin alone did not significantly affect all-cause mortality (relative risk (RR) 1.30, 95% confidence interval (CI) 0.57 to 2.99; 1627 participants, 16 trials) or cardiovascular mortality (RR 1.70, 95% CI 0.35 to 8.30; 1498 participants, 15

trials). In a fixed-effect model, but not in a random-effects model, severe hypoglycaemia was significantly more frequent with metformin and insulin than with insulin alone (RR 2.83, 95% CI 1.17 to 6.86; P = 0.02; 1303 participants, 11 trials). This leaves the interpretation of the intervention effect open.

Discussion

Summary of main results

Our systematic reviews investigated the benefits and harms of recommended and widespread used glucose-lowering interventions in patients with T2DM.[39-43] We included data from 116 trials with a total of 51,385 participants. Our systematic reviews are more comprehensive than previous meta-analyses addressing the same interventions.[31;31;44-47] Besides including macrovascular outcomes, we have included microvascular outcomes, which also are of major importance for patients with T2DM.[39-43] Our key findings, in each of the systematic reviews, are that there is lack of statistical significant difference between the interventions we investigated versus control interventions regarding all-cause mortality or cardiovascular mortality. However, the trials and meta-analyses of the investigated interventions are under-powered to draw firm conclusions on patient-important outcomes. The application of trial sequential analyses in our systematic reviews showed that several large new trials are required before firm evidence for a benefit or harm of any of the interventions on the primary outcomes may be established.[39-43] Other important findings are that targeting intensive glycaemic control may reduce the risk of non-fatal myocardial infarction, amputation of a lower extremity, as well as microvascular complications. However, a firm conclusion will have to await further trials for some of these outcomes. It is important to notice that conventional glycaemic control is not synonymous with no glycaemic control, but just less strict control. Due to lack of reporting, we were only able to meta-analyse a few macrovascular as well as microvascular outcomes in our other reviews.[39-41] Besides non-fatal macrovascular complications for the comparison second-generation sulphonylureas versus metformin, there was no significance of the comparisons for macrovascular outcomes for the review of sulphonylurea monotherapy versus other glucose-lowering interventions or no intervention, and the review of insulin combined with metformin versus insulin alone.[39-41] Risk of severe hypoglycaemia was

increased with intensive glycaemic control.[42;43] For the review comparing sulphonylurea monotherapy with other antidiabetic monotherapies, the risk of severe hypoglycaemia was significantly increased in favour of metformin and the thiazolidinediones compared with second-generation sulphonylurea.[39;40] For the comparison of insulin plus metformin versus insulin alone on severe hypoglycaemia, significance was not present in the random-effects model, but only in the fixed-effect model.[41]

Overall completeness and applicability of the evidence

We conducted an extensive search for trials, included publications in all languages, and had no restriction on the outcomes reported in the trials.[39-43] We have included trials with large ranges for duration of T2DM, duration of the interventions, age, and different risks of cardiovascular disease. Even the interventions were applied in different ways within the same comparison. The participants of the included trials represented a very diverse sampling of the population with T2DM. The results of our review should therefore be interpreted with caution. Nevertheless, the heterogeneity in this review might indeed reflect the well-known heterogeneity in clinical practice. Recently, a Cochrane systematic review has observed that clinical outcomes in patients that participate in randomised trials are comparable to similar patients outside trials.[48]

The diagnosis of T2DM varied among trials, and some trials used a definition of T2DM, which may have included participants with impaired glucose tolerance.[3;49;50] Some of the trials only included participants with newly diagnosed T2DM, whereas others included patients with a longer duration of T2DM. Moreover, the cardiovascular risk profile differed because of differences in inclusion criteria, for example inclusion of participants with acute cardiovascular events, microvascular disease, or at high risk of cardiovascular disease. However, it should be kept in mind that participants with existing co-morbidities, especially renal or hepatic disease, were excluded from many of the included trials. Detailed information about the participants was presented in most trials. Many of the trials were conducted in Europe or Northern America.

Based on the included systematic reviews, it unfortunately has to be concluded that it is not possible to estimate the ‘optimal’ glycaemic intervention strategy, estimate the ‘optimal’

monotherapy, and finally it remains uncertain if insulin should be prescribed with metformin or not.[39-43]

Quality of the evidence

The risk of bias was high in most of the trials in our systematic reviews.[39-43;51-53] Among the 116 trials included in our reviews, only one trial was classified as having low risk of bias according to all bias domains (generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias). We were therefore unable to make subgroup analyses comparing the trials with low risk of bias compared to trials with high risk of bias. Instead, we performed the subgroup analyses comparing trials with lower risk of bias (considering only adequate sequence generation, allocation concealment, and blinding) to trials with high risk of bias (see below). Therefore, we have been comparing trials that all had high risk of bias according to all bias domains. This could explain the lack of statistical difference for these subgroup analyses. Without a group of trials with low risk of bias it is hard to come close to the 'truth'.

Among the 116 trials, only 17 (14.7%) were classified as having lower risk of bias according to randomisation, allocation concealment, and blinding. Especially, the reporting of generation of the randomisation sequence and the allocation concealment were lacking. Generation of the randomisation sequence and allocation concealment were classified unclear in 66% and 69% of the trials, respectively. Because of the design of the trials, comparing intensive glycaemic control with conventional glycaemic control, it was not feasible to require blinding of investigators and participants. We therefore defined blinding of outcome assessors as adequate blinding. The two trials included in two systematic reviews, The United Kingdom Prospective Diabetes Study (UKPDS) and The University Group Diabetes Programme (UGDP), were therefore classified as lower risk of bias trials in the review of glycaemic control and unclear risk of bias trials in the review of sulphonylurea monotherapy.[39;40;42;43]

A relatively large proportion of the trials received funding from the pharmaceutical industry. A Cochrane review has found that trials sponsored by the pharmaceutical industry lead to more favourable conclusions.[54]

The inability to use individual patient data to assess whether certain characteristics (e.g., history of cardiovascular events, duration of disease at baseline) affect the degree of cardiovascular risk might reduce the clinical translation of the results. We explored heterogeneity by sensitivity analyses, subgroup analyses, and in one review with meta-regression.

Our results are based on trials with few data. Many of the included trials were not designed or powered to detect our predefined outcomes, which might have resulted in insufficient data from these trials. Besides, if certain primary outcomes had been prespecified in the individual trials, the outcome might be more systematically and uniformly collected in the trials. In addition, it might be that some of the included outcomes were included from trials with too short duration to influence the outcomes, e.g., macrovascular and microvascular complications. We were able to assess some of the predefined outcomes in all but six of the included trials.

We tried in all cases to ask for supplementary information from the authors. However, outcome reporting bias could influence the results of our meta-analyses.

Potential biases in the review process

Selective publication of the findings of trials with positive results and time-lag bias may lead to overestimation of intervention effects and false-positive conclusions about intervention effects.[54-56] Despite an extensive search of major diabetes conference abstracts, the US Food and Drug Administration homepage, and correspondence with authors of the included trials and relevant pharmaceutical companies, we only retrieved two unpublished trials.[39] However, several authors kindly provided additional data, so unpublished information were obtained on 30 trials (26%). Even though we made a big effort, we might not have succeeded in retrieving all existing unpublished data on the

topics. Such unpublished, unretrieved data are more likely to draw intervention effects towards the neutral.

Lack of reporting of the trial methods of the included trials in our systematic reviews were common.[39-43] The methodological quality of the randomised clinical trials included in a systematic review can have a substantial influence on the effect estimate of the intervention, which may alter the validity of the conclusions of a systematic review.[53] Randomised clinical trials with inadequate bias control tend to exaggerate beneficial intervention effects.[51;52;54;57] We have tried to clarify the systematic errors in all the included trials. All authors were contacted for clarification if one of the bias domains was not adequately reported. Despite this, more than half of the trials were judged as unclear risk of bias for generation of the randomisation sequence and allocation concealment.

Most of our trials had surrogate variables as primary outcomes, especially the changes in HbA1c and fasting blood glucose levels from baseline. However, as these are non-validated surrogate variables, they might fail to serve as valid predictor of intervention effects on important health outcomes.[58] Clinical trials evaluating a surrogate variable require fewer participants to adequately power the trial and a much shorter duration.[59-62] Most of the included trials had a glycaemic variable as the primary outcome, which make the power to assess patient-important outcomes from the same population low.[62] Besides, our primary outcomes, all-cause mortality and cardiovascular mortality, are relatively infrequent, this means that a relatively large sample size might be needed to detect any relevant intervention effects.[62;63] Clinical researchers should realise that intervention effects on a non-validated surrogate outcomes is not sufficient to predict an effect on the clinical outcome. To validate a surrogate outcome necessitates an intervention effect on both the surrogate outcome and the patient-important outcome – and that the effect on the surrogate predicts the effect on the patient-important outcome.

In order to limit the risk of random errors due to sparse data and repetitive testing in cumulative meta-analysis, we performed trial sequential analyses to estimate the required information size (meta-analytic ‘sample size’) to detect an a priori anticipated 10% relative risk reduction or increase for our primary outcomes.[39-43] For the meta-analysis of all-cause

mortality comparing targeting intensive with conventional glycaemic control for the trials in usual care setting, 60% of the heterogeneity-adjusted required information size was accrued. The proportion of participants achieved before firm evidence could be established for the primary outcomes were even lower for the remaining meta-analyses.[39-43] Besides, we performed trial sequential analyses for the meta-analyses of binary and continuous outcomes showing significance in the random-effects and fixed-effect models.[39-43] However, the lack of confirmation of the prespecified relative risk reductions in the trial sequential analyses do not necessary reflect that no clinical significant differences are present. We just seem to need more data to prove this.

Agreements and disagreements with other studies and reviews

Cardiovascular disease is the major cause of death in T2DM and it is therefore of central importance to understand the effect of a glycaemic target as well as the glucose-lowering interventions on cardiovascular outcomes.[4-6;18] Three recent randomised clinical trials in patients with T2DM were not able to detect (or reject) the possibility of reduced mortality or cardiovascular disease with intensive compared with conventional glycaemic control.[60;64;65] The controversies have made management of hyperglycaemia in T2DM to one of the most debated fields in medicine. Most guidelines recommend HbA1c target between 6.5% and 7%, but also emphasise the need for individualised assessment.[19;22;24] The strategy used to search and collect the existing evidence for the ADA/EASD position statement is not described, and there is no grading of the evidence.[24] Our systematic review investigating the effect of intensive glycaemic control versus conventional glycaemic control could not be designed to investigate which glycaemic level that might be ideal due to lack of individual patient data.[42;43] However, we only included five relatively small trials involving 543 participants with the glycaemic target of HbA1c at 7% versus another less stringent glycaemic target.[66-70] However, only three of these trials[66;68;69] exclusively assessed the effects of glycaemic control and only one of these trials had a duration of more than one year.[69] Besides, most of the included trials had sparse data on the number of participants achieving the glycaemic target at the end of follow-up, and, when reported, the proportion of participants achieving the glycaemic target was relatively low.[42;43] The reason for the ADA/EASD position statement to recommend an HbA1c about 7% seems to be based on an ‘expert opinion’ rather than the existing evidence.[24] The argument for not making

evidence based approach to the ADA/EASD position statement is based on the number of available antidiabetic interventions and possible combinations being too large.[24;71]

Guidelines or similar treatment recommendations from international medical societies, especially the ADA/EASD position statement, are important because they not only influence the clinical practice, but also the design of clinical trials by suggesting/defining 'the gold standard'. If such standards are not optimal seen from the patients' perspectives, both clinicians and trialists may be misled.

Results from randomised clinical trials and epidemiological studies show a reduced risk of cardiovascular disease when hypertension is treated and cholesterol levels are lowered.[72-77] The beneficial effects of lowering blood pressure targets in patients with T2DM are best shown for stroke.[78] Despite this, the proportion of patients with T2DM who achieve HbA1c levels below 7% are higher than the proportion achieving the recommended targets for blood pressure and cholesterols.[79-81] As no evidence is established for the benefits of intensive glycaemic control, and harms seems imminent, concerns arise, if too much emphasis is placed on controlling hyperglycaemia in patients with T2DM.[42;43]

At the time of diagnosis or when lifestyle interventions fail to achieve a certain glycaemic target, antidiabetic drugs are initiated.[24] The use of sulphonylureas was implemented in the treatment of T2DM in the 1950s.[82] Treatment recommendations from medical societies do not recommend sulphonylurea as the first-line antidiabetic drug.[19;21-24] A relatively small trial of obese participants have made a huge influence on the recommendations, and limited the use of sulphonylurea as monotherapy.[29;35;36;49] The sulphonylureas are now largely prescribed as a part of a combination regime.[35] In our Cochrane review including all trials of sulphonylurea monotherapy versus any other comparator, no firm evidence was found for any benefit or harm of sulphonylurea prescribed as first-line therapy when compared with any other antidiabetic intervention or placebo.[39] Unfortunately, the UKPDS 34 publication did not report patient-important outcomes for the participants randomised to sulphonylurea.[39;40;49] Most of the patient-important outcomes for the comparison of sulphonylurea and metformin in the current review were therefore reported from the 'A Diabetes Outcome Progression Trial' (ADOPT) trial, which showed fewer macrovascular

complications with sulphonylurea monotherapy compared with metformin or rosiglitazone monotherapy.[39;40;83] On the other hand, the risk of severe hypoglycaemia might be reduced with metformin or thiazolidinedione monotherapy.[39;40] Our review of sulphonylurea monotherapy found astonishing lack of reporting of patient-important outcomes for all comparisons including the newer, and more expensive antidiabetic interventions.[29;35;39]

The current diabetes guidelines recommend combination of insulin and metformin rather than insulin alone.[22;24] The recommendations might be a major reason why more clinicians continue to use metformin when insulin is initiated.[33-35;38] However, our meta-analysis of metformin plus insulin versus insulin alone did only find significance in favour of metformin plus insulin for surrogate variables including weight, insulin dose, and HbA1c, but not for patient-important outcomes.[41;84]

Table 1. Summary of existing Cochrane reviews of glucose-lowering interventions for patients with type 2 diabetes mellitus.

Title	**No of trials (participants)**	**Effect on mortality**	**Effect on macrovascular complications**	**Effect on microvascular complications**
Dietary advice for treatment of type 2 diabetes mellitus in adults[85]	18 (1467)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Exercise for type 2 diabetes mellitus[86]	14 (377)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus[87]	22 (4659)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Metformin monotherapy for type 2 diabetes mellitus[44]	29 (5259)	Obese participants allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropamide, glibenclamide, or insulin for all-cause mortality (P = 0.03) and conventional treatment for diabetes-related death (P = 0.03) or all-cause mortality	Obese patients allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropamide, glibenclamide, or insulin for any diabetes-related outcomes (P = 0.009) or conventional treatment for any diabetes-related	Obese patients allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropamide, glibenclamide, or insulin for any diabetes-related outcomes (P = 0.009) and conventional treatment for any diabetes-related

		(P = 0.01). Based on data from one trial.	outcomes (P = 0.004), and myocardial infarction (P = 0.02).	outcomes (P = 0.004).
Alpha-glucosidase inhibitors for type 2 diabetes mellitus[88]	41 (8130)	No statistical significant difference. Few data.	No statistical significant difference. Few data.	No statistical significant difference. Few data.
Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus[89]	25 (12864)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Meglitinide analogues for type 2 diabetes mellitus[90]	15 (3781)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Pioglitazone for type 2 diabetes mellitus[91]	22 (6200 randomised to pioglitazone)	Not possible to assess. One trial provided data.	Not possible to assess. One trial provided data.	Not possible to assess.
Rosiglitazone for type 2 diabetes mellitus[92]	18 (3888 randomised to rosiglitazone)	Not possible to assess. One trial contributed with data.	Not possible to assess. One trial contributed with data, indicated increased cardiovascular risk.	Not possible to assess.
Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus[93]	8 (4193)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Insulin detemir versus insulin glargine for type 2 diabetes mellitus[94]	4 (2250)	Not possible to assess.	Not possible to assess.	Not possible to assess.
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus[31]	20 (1811)	Not possible to assess.	Not possible to assess.	Not possible to assess.

The lack of evidence in our systematic reviews and meta-analyses is the common standard for the glucose-lowering interventions applied for patients with T2DM. Summary of existing Cochrane reviews of antidiabetic interventions for patients with T2DM shows that the antidiabetic interventions have little if any supporting evidence (Table 1).[31;44;85-94]

Randomised clinical trials are essential to clarify the benefits and harms of medical interventions. To collect and combine results from randomised clinical trials, it is required that the reporting is adequate. From 2005 the International Committee of Medical Journal Editors required that clinical trials should be indexed in a clinical trial registry to be qualified for publication in a journal.[95] However, the quality of trial protocols varies, but hopefully new international Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations will heighten the standard of the trial protocols.[96] Besides lack of adequate trial protocols, adequate reporting of the randomised clinical trials is also a challenge. Preferably, trials should focus on patient-important outcomes or at least report them adequately. The CONSORT (CONsolidated Standards of Reporting Trials) Statement was first published in 1996, with the latest updated version in 2010.[97;98] Despite improvement in the reporting of several important aspects of trial methods since the introduction of the CONSORT statement, poor reporting is still a problem.[99;100]

Combining the data from randomised clinical trials may help clinicians in making guidelines.[101;102] This demands a transparent and reproducible procedure for collecting and combining existing evidence. Therefore, the reporting of systematic reviews should follow the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[103] When guidelines are developed based on systematic reviews and meta-analyses, it is important to keep in mind that the best available evidence might not be synonymous with sufficient evidence.

Conclusions

Overall, the evidence for making recommendations for any intervention in relation to lowering glucose in patients with T2DM is vague. Even the benefit and harm trade-off of the corner stone in antidiabetic intervention, the lowering of the blood glucose, is questionable. The same is the case for the antidiabetic interventions prescribed to reduce blood glucose. The scientific evidence behind the currently used T2DM glucose-lowering agents is sparse. More large scale randomised clinical trials with low risk of bias applying transparent and uniform reporting are urgently required.

Dansk resumé

Baggrund

Eftersom prævalensen af type 2 diabetes mellitus (T2DM) er stigende, er det af stor samfundsmæssig interesse at at reducere omkostningerne til behandling af diabetes og de hermed associerede sendiabetiske komplikationer. Aktuelle ph.d.-afhandling undersøgte evidensen for brugen af udbredte anti-diabetiske interventioner ved hjælp af Cochrane litteraturbedømmelser (engelsk: systematic reviews) med meta-analyser og forsøgssekventielle analyser (engelsk: trial sequential analysis).

Formål

At vurdere fordele og ulemper ved: 1) intensiv versus koventionel glykæmisk kontrol hos patienter med T2DM; 2) sulfonylurea monoterapi versus anden antidiabetisk monoterapi intervention eller placebo hos patienter med T2DM; 3) metformin plus insulin versus insulin alene hos patienter med T2DM.

Metode

Vi gennemførte meta-analyserne i henhold til Cochrane samarbejdets anbefalinger samt forsøgssekventiel analyse. Inkluderede studier blev fundet ved søgning i The Cochrane Llibrary, MEDLINE, EMBASE, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature (LILACS) og Cumulative Index to Nursing & Allied Health Literature (CINAHL). Derudover søgte vi konferencerapporter fra større diabetiske kongresser og tjekkede referencerne fra de inkluderede forsøg samt relevante systematiske litteraturoversigter, meta-analyser og publikationer fra medicinsk teknologivurdering. To forfattere screenede søgeresultaterne for om de indfriede inklusionskriterierne samt ekstraherede data.

Resultater

Tre systematiske oversigtsartikler inkluderede i alt 116 randomiserede kliniske forsøg med 51 385 patienter. Kun ét forsøg havde lav risiko for bias (systematisk risiko for overestimering af gavn). Kun 17 af forsøgene blev klassificeret som havende lavere bias

risiko vedrørende randomiseringssekvens, allokering og blinding end de øvrige forsøg. Rapporteringen af patient-vigtige effektmål var sparsom.

Målrettet intensiv glykæmisk kontrol sammenlignet med konventionel glykæmisk kontrol ændrede ikke signifikant på risikoen for død uanset årsag eller kardiovaskulær død. Risikoen for ikke-fatalt myokardieinfarkt var statistisk signifikant reduceret i fixed-effect modellen. Målrettet intensiv glykæmisk kontrol reducerede risikoen for amputation, mikrovaskulære komplikationer som samlet effektmål, retinopati, retinal fotokoagulation og nefropati. Forsøgssekventielle analyser viste tilstrækkelig evidens for en 10% relativ risikoreduktion var opnået for mikrovaskulære komplikationer som samlet effektmål. Målrettet intensiv glykæmisk kontrol øgede risikoen for alvorlig hypoglykæmi. Forsøgssekventiel analyse viste tilstrækkelig evidens for en relativ risikoforøgelse på 30% for alvorlig hypoglykæmi ved intensiv glykæmisk kontrol.

Første-generation sulfonylurea versus placebo viste statistisk signifikans for kardiovaskulær død i placebos favør. Ingen af de øvrige sammenligninger mellem sulfonylurea monoterapi og anden antidiabetisk monoterapi eller placebo påvirkede død uanset årsag, kardiovaskulær død eller ikke fatalt-myokardieinfarkt signifikant. Risikoen for makrovaskulære komplikationer var i anden-generation sulfonylureas favør sammenlignet med metformin. Risikoen for alvorlig hypoglykæmi var signifikant øget ved sammenligning af anden-generations sulfonylurea versus metformin og thiazolidinedioner. Forsøgssekventiel analyse viste at der ikke var opnået tilstrækkelig evidens for de patient-vigtige effektmål med statistisk signifikans i de traditionelle meta-analyser.

Metformin plus insulin versus insulin alene påvirkede ikke statistisk signifikant død uanset årsag eller kardiovaskulær død. Rapporteringen af makrovaskulære og mikrovaskulære komplikationer var sparsom, kun få kunne meta-analyseres, og ingen viste signifikante effektestimater. Risikoen for alvorlig hypoglykæmi var øget i fixed-effect modellen ved metformin og insulin kombineret versus insulin monoterapi.

Konklusioner

Baseret på tilgængelige data fandt vi ikke sikker evidens for klinisk anvendelse af de undersøgte interventioner til behandling af patienter med T2DM. En stor del af forsøgene var af lav metodologisk kvalitet, inkluderede få patienter og havde kort forsøgsvarighed. De patient-vigtige effektmål var sparsomt rapporteret i de fleste forsøg. Der er et presserende behov for flere store randomiserede forsøg af høj metodologisk kvalitet for at evaluere anvendelsen af de undersøgte interventioner.

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REVIEW

Oral hypoglycaemic agents, insulin resistance and cardiovascular disease in patients with type 2 diabetes

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Abstract

This article is a narrative review of the current evidence of the effects on cardiovascular disease (CVD) of oral hypoglycaemic agents that increase insulin sensitivity in patients with type 2 diabetes (T2D). In overweight T2D patients, metformin has been demonstrated to reduce CVD risk, and this beneficial effect may be conserved with the combination of metformin and insulin treatment. However, the effect of glitazones on CVD is uncertain. There is conflicting evidence from large randomized trials to support a protective effect against CVD of lowering blood glucose *per se* but a systematic review with meta-analysis is lacking. It may be reasonable to aim for an intervention targeting multiple CVD risk factors such as dyslipidaemia, hypertension and albuminuria in T2D patients.

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Introduction

The prevalence of type 2 diabetes (T2D) is increasing worldwide (1). Insulin resistance in peripheral tissues and inadequate compensatory insulin secretion are essential elements in the pathogenesis of T2D. Impaired insulin secretion is caused by decreased β-cell mass and the dysfunction of existing β-cells. Genetic abnormalities and intrauterine influences may also contribute to the disease process. Aspects of body composition (e.g. obesity) and lifestyle (e.g. high calorie intake and/or reduced physical activity) seem to be important for the degree of insulin resistance and thus probably for the development and progression of T2D. Insulin resistance in combination with relatively impaired insulin secretion leads to hyperglycaemia and compensatory hyperinsulinaemia (2, 3).

As T2D is a progressive disease, the glucose-lowering intervention strategy must be adjusted over time to achieve and maintain good glycaemic control (4). Patients with T2D should be recommended lifestyle interventions. This might be supplemented by oral hypoglycaemic agents, mainly metformin (which increases insulin sensitivity) and/or insulin secretagogues (sulphonylureas, SUs or glitinides, which stimulate insulin secretion). Glitazones (which increase insulin sensitivity) and acarbose (which reduces gut glucose uptake) are less frequently recommended. If the combination of lifestyle interventions and oral hypoglycaemic agents do not achieve the glycaemic targets, insulin injections may be added, for example according to a consensus algorithm for the initiation and adjustment of therapy (4). Promising new glucose-lowering interventions indirectly stimulate insulin secretion by inhibiting the breakdown of the incretin hormone GLP1 or by increasing the incretin hormone levels by s.c. injection of a GLP1 analogue (5). The most appropriate use of incretin-based therapy in the treatment of T2D has not yet been identified (4).

The ultimate goal of T2D treatment is to reduce mortality and the risk of microvascular and macrovascular complications. The latter (mainly atherosclerosis) are the most frequent cause of increased mortality among T2D patients (6). Several studies suggest a causal association between insulin resistance and atherosclerosis (7–9). This is of clinical interest, since many patients with T2D take oral hypoglycaemic agents that affect insulin sensitivity.

The purpose of the present paper is to give a brief overview of studies focusing on the association between cardiovascular disease (CVD) and oral glucose-lowering interventions with insulin sensitizing agents.

Method

A literature search of the MEDLINE/PubMed database (from 2000 until December 2008) was conducted using the following terms: type 2 diabetes mellitus; atherosclerosis; endothelium; metformin; thiazolidinediones; peroxisome proliferator-activated receptor (PPARγ); cardiovascular disease; and mortality.

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The importance of insulin resistance and/or hyperinsulinaemia in the development of atherosclerosis

Atheroslerosis is characterized by the presence of atherosclerotic plaques in the arterial wall. These contain cholesterol-filled macrophages and smooth muscle cells and might be complicated by rupture or thrombosis, resulting in clinical symptoms (10). Endothelial dysfunction (e.g. increased expression of endothelial adhesion molecules, inhibition of activity of nitrogen oxide (NO) and affected vasopermeability or vasomotility), transport of cholesterol into the arterial wall, oxidation of cholesterol, proliferation of smooth muscle cells and inflammation are all essential elements in the atherosclerotic process (10).

Studies have indicated a connection between hyperinsulinaemia and activation of both atherogenic and anti-atherogenic pathways (7–9). Insulin resistance in the arterial wall might lead to inhibition of phosphatidylinositol 3-kinase activity, which has anti-atherogenic effects (Fig. 1). At the same time, a compensatory increase in insulin levels might stimulate possible atherogenic signalling pathways, including the MAP kinase pathway (Fig. 1).

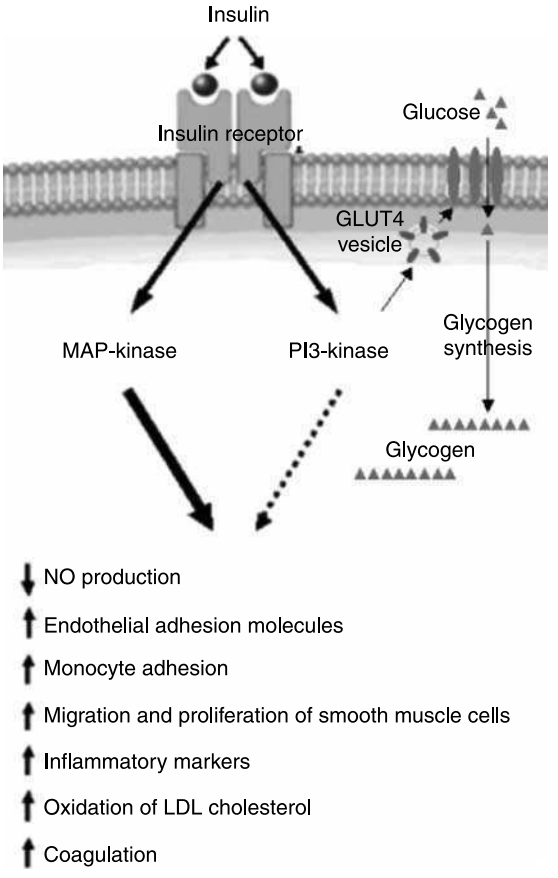

Figure 1 The effect of insulin on the vascular cells in type 2 diabetes.

Studies conducted on cell cultures and rodents have shown that insulin resistance and hyperinsulinaemia reduce NO activity and stimulate the migration and proliferation of smooth muscle cells, the expression of cellular adhesion molecules, inflammatory markers, oxidation of low-density lipoprotein (LDL) cholesterol and coagulation (7–9, 11). In addition, insulin *per se* seems to have the capacity to both increase and decrease vascular tonus (12).

Metformin

Metformin reduces blood glucose levels by inhibiting hepatic glucose production and reducing insulin resistance. The plasma insulin levels are unchanged or reduced (13). Several trials indicate that metformin has anti-atherogenic effects (e.g. reduced levels of blood cholesterol, inflammatory markers, vascular adhesion molecules and coagulation parameters as well as reduced endothelial dysfunction; 13–16; Table 1).

In a substudy of the United Kingdom Prospective Diabetes Study (UKPDS), 753 overweight patients with T2D were randomized to conventional (diet) treatment or intensive glycaemic control with metformin or SU/insulin for an average of 10 years (13). Metformin resulted in lower insulin levels and improved glycaemic control compared with conventional (diet) treatment. Compared with the conventional treated group, patients allocated to metformin treatment had a significant 32% risk reduction for any diabetes-related outcome measure, as well as significant risk reductions of 39, 42 and 36% for myocardial infarction, diabetes-related death and all-cause mortality respectively. Metformin significantly reduced the incidence of CVD compared with treatment with SU/insulin independent of the achieved level of HbA1c (13). A recent 10-year follow-up study of patients who participated in the UKPDS reported continued benefit of metformin therapy (17). Metformin treatment did not reduce the number of patients with microvascular outcome meaures. There are no reported data comparing CVD risk in the metformin and SU groups alone (17, 18). The benefits of metformin are supported by a systematic review with a meta-analysis (19).

In the 'A Diabetes Outcome Progression Trial' (ADOPT), 4360 newly diagnosed T2D patients were allocated to interventions for 4 years with rosiglitazone (a glitazone), glyburide (SU) or metformin. Although ADOPT was not statistically powerful enough to detect substantive differences in CVD risk, surprisingly, there were fewer CVD events in the glyburide group than in the rosiglitazone and metformin groups. There was no significant difference in the CVD risk between the metformin and rosiglitazone groups. In the glyburide group, however, more participants dropped out and the follow-up period was shorter (3.3 years) than in the other two groups (both 4 years) (20).

Table 1 Hypoglycaemic agents effect on biomarkers

Hypoglycaemic agent	Biomarkers reflecting cardiovascular risk
Metformin	Reduce endothelial dysfunction Reduce blood cholesterol Reduce inflammatory markers Reduce vascular adhesion molecules Reduce coagulation parameters
Glitazones	Reduce endothelial dysfunction Reduce inflammatory markers Reduce coagulation parameters Increase HDL cholesterol Increase LDL cholesterol Increase LDL cholesterol particle size Reduce smooth muscle cell proliferation

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

In the DIGAMI-2 trial, 1181 patients with T2D were followed for 2 years after a myocardial infarction. There were no differences in CVD mortality between the intervention groups with insulin, SU or metformin. The risk of a new myocardial infarction increased significantly with insulin therapy, whereas metformin therapy had a protective effect (21).

In the UKPDS, non-obese patients with T2D were treated with insulin or SU, but the UKPDS (and other prospective studies) did not report data for CVD risk separately in this group of patients. Hence, in non-obese patients with T2D, there is a lack of evidence that metformin or other oral hypoglycaemic agents affect CVD risk. Recent short-term trials have demonstrated a similar effect of metformin and the insulin secretagogue, repaglinide, on HbA1c in non-obese patients with T2D. Metformin treatment reduced surrogate biomarkers reflecting CVD risk (i.e. reductions in body weight, insulin and cholesterol levels, markers of inflammation and endothelial dysfunction; 22–24; Table 1).

In a mixed population of obese and non-obese patients with T2D, the UKPDS surprisingly reported a significant 96% increase in mortality with the combined intervention of metformin and SU compared with intervention with SU alone (13). The authors explained these differences by the observation that patients allocated to the combined intervention group were on average about 5 years older, had higher blood glucose levels and a shorter duration of follow-up than the UKPDS population overall.

Observational studies have yielded conflicting results of combined intervention with metformin and insulin secretagogues with respect to the risk of CVD (25, 26). A recently published meta-analysis indicates an increased frequency of CVD by combined intervention with metformin and insulin secretagogues compared with diet or monotherapy (27).

The recently published 'Hyperinsulinemia: the Outcome of its Metabolic Effects' (HOME) trial, randomly allocated 390 patients with T2D to either placebo or metformin in addition to ongoing insulin therapy. The participants were included regardless of body mass index (BMI). The patients randomized to metformin in combination with insulin were slightly older, had more CVD and were less often smokers than the patients randomized to placebo; other baseline characteristics were comparable (28). The primary outcome was an aggregate of microvascular disease, CVD and mortality. Secondary outcomes were CVD (fatal and non-fatal) and microvascular disease separately. The follow-up period was 4.3 years. At the end of the trial there was no significant decrease for the risk of the primary outcome. However, metformin treatment significantly reduced the risk of secondary CVD outcomes (e.g. myocardial infarction, stroke, peripheral arterial reconstruction) by 39% ($P=0.02$). The reduction observed in the secondary microvascular outcome was non-significant ($P=0.43$). The combination of insulin and metformin reduced insulin requirements and improved glycaemic control compared with combination of insulin and placebo. The changes in body weight partly explained the difference in CVD, whereas the changes in glycaemic control and insulin levels did not. The occurence of hypoglycaemic events was comparable between both groups (29).

Glitazones

Glitazones work by binding to the PPARγ, which increases insulin sensitivity (4). Several studies have shown that glitazones improve CVD risk biomarkers (i.e. lowering of blood pressure, triglycerides, inflammatory markers and coagulation parameters; increase in HDL cholesterol; improved endothelial function and inhibition of smooth muscle cell proliferation) (30–33). A potential pro-atherogenic effect by treatment with glitazones is an increase in LDL cholesterol (31) (Table 1). However, glitazones also increase the size of LDL particles, which theoretically makes the LDL particles less atherogenic. This effect is more pronounced in pioglitazone than rosiglitazone (34). Although both glitazones activate the same receptor, the observed differences with respect to their effects on the lipid profile may be due to the activation/inhibition of different genes (35).

A randomized trial in patients with T2D reported a reduced progression of carotid artery intimal thickness measured by ultrasound for treatment with pioglitazone compared with an insulin secretagogue (36).

The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PRO-active) trial randomized 5238 patients with T2D and known CVD to add-on placebo or pioglitazone (31). The primary outcome measure (a composite of CVD events) was insignificantly reduced with pioglitazone intervention, whereas the secondary CVD outcome measure (death, non-fatal myocardial infarction and stroke) was significantly reduced (31). Pre-specified subgroup analyses from PROactive

reported a potential cardiovascular protective effect of pioglitazone in patients with T2D and previous stroke or myocardial infarction. *Post hoc* subgroup analyses reported similar results in patients with T2D but without known peripheral arterial disease (37).

Meta-analyses have revealed a significant increase in CVD risk with rosiglitazone treatment, whereas pioglitazone has possible cardiovascular protective effects (38, 39). This safety-jeopardizing signal of rosiglitazone has prompted the publishing of preliminary data from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial. This trial examines the effect of rosiglitazone in combination with either metformin or insulin secretagogues in ~4500 patients with T2D free of known CVD. Preliminary data after 3.75 years follow-up indicate that rosiglitazone treatment results in a non-significant increase in CVD risk. However, the few CVD events mean that these analyses have low statistical power. The complete data are due to become available in 2009 (40).

In addition, both pioglitazone and rosiglitazone treatment have been associated with an increased risk of congestive heart failure (31, 37, 38, 40, 41).

Anti-diabetic treatment in general and CVD risk

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included 10 251 T2D patients with HbA1c $\geq$ 7.5% and known CVD or risk factors for CVD. The trial tested the hypothesis that intensive control of glycaemic levels, blood pressure and the lipid profile reduce the incidence of CVD and death compared with the standard treatment (42). At baseline, approximately one-third of the participants used insulin and a similar proportion had known CVD. The participants were randomly allocated to intensive glycaemic control, targeting a HbA1c level of $<$6.0%, or standard glycaemic control, targeting a HbA1c level of 7.0–7.9%. Combinations of all available types of anti-diabetic drugs were used to achieve the glycaemic targets. The median HbA1c level at baseline was 8.1%. After a median follow-up of 3.5 years the HbA1c level in the group allocated to intensive glycaemic control was 6.4% compared with 7.5% in the conventionally treated group. During the trial, 92% and 58% of the patients received glitazones in the intensive and in the conventional treatment groups respectively (both groups used almost exclusively rosiglitazone). About 90% of patients in both groups received metformin. Between the intensively versus the conventionally treated groups, the difference in the composite primary outcome measure of non-fatal CVD and CVD death did not reach statistical significance. However, a significantly lower frequency of non-fatal myocardial infarction was observed in the intensively treated group. Data on microvascular outcome measures have not yet been published. The glycaemic intervention arm of the trial was stopped in February 2008 because of a higher mortality rate (total and/or CVD death) in the group allocated to intensive glycaemic control compared with conventional control (257 vs 203 deaths in the intensive and conventional groups respectively). Preliminary analyses have not identified any specific cause for the higher mortality. In particular, no conclusive evidence has been found to suggest that certain oral hypoglycaemic agents or combinations thereof were responsible for the increased risk of death. Pre-specified subgroup analyses showed significant heterogeneity in the primary outcome according to known CVD or baseline HbA1c. Thus, a reduced incidence of the primary outcome was observed among participants allocated to the intensive glycaemic control with a level of HbA1c $\leq$ 8.0% or no known CVD before randomization. By contrast, in the groups with known CVD or baseline HbA1c of $>$8.0%, the effect between interventions on the primary outcome was neutral. For total mortality, no significant heterogeneity was observed between the intervention groups with respect to known CVD or baseline HbA1c (42).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomly allocated 11 140 patients with T2D and known CVD or high CVD risk to intensive or conventional glycaemic control groups (43). Unlike the ACCORD and the Veterans Affairs Diabetes trial (VADT – see below), at inclusion, the ADVANCE trial did not specify a requirement for the level of HbA1c and patients were almost exclusively insulin-naive (1–2% used insulin at baseline). Similar to the ACCORD trial, approximately one-third of the patients had known CVD. Patients in the intensive intervention group were all treated with gliclazide (SU), in addition to any marketed anti-diabetic agent, to achieve a target level of HbA1c of 6.5% or less. In the conventionally treated group, the HbA1c target was defined by local treatment guidelines. From a median baseline HbA1c of 7.2%, after a median follow-up of 5 years, the intensive group achieved a median HbA1c of 6.4% compared with 7.0% in the conventional group. During the ADVANCE trial, only about 10–15% and 70% of the patients received intervention with glitazones and metformin respectively; the proportion of patients treated with glitazones taking rosiglitazone was not reported. This was in contrast to the ACCORD trial in which a much higher proportion of patients in the intensive glycaemic group received the glitazone intervention. The ADVANCE trial reported, in contrast to the ACCORD trial, with intensive compared with conventional glycaemic control, a significant reduction in the composite primary outcome measure of microvascular and macrovascular (non-fatal CVD and CVD death) events. Also, in contrast to the ACCORD trial, the ADVANCE trial reported no differences in CVD

or mortality with intensive compared with conventional glycaemic control. The significant difference in the primary outcome measure in the ADVANCE trial was primarily caused by a reduction of microvascular events (nephropathy).

The VADT trial randomly allocated 1791 patients with T2D to intensive intervention versus conventional intervention (44). At inclusion, patients were required to have a level of HbA1c of $\geq$7.5% and, at baseline, about half of the patients used insulin and 40% had known CVD. The median baseline level of HbA1c was 9.4%. In the intensive intervention group, the target level of HbA1c was $\leq$6.0% (similar to the ACCORD trial) and, in the conventionally treated group, a separation of 1.5% in HbA1c compared with the intensive intervention group was aimed for. About 60–70% of the patients in the two groups received rosiglitazone; the number of metformin-treated patients was not reported (44). After a median follow-up of 5.6 years, the intensive intervention group achieved a level of HbA1c of 6.9% compared with 8.5% in the conventional group. There was no significant difference in the primary outcome measure (a composite of CVD events) between the intensive and conventional glycaemic control groups. Also, there was no evidence of increased mortality in the intensive intervention group and preliminary data indicate that intervention with rosiglitazone was not associated with higher mortality (44). However, somewhat similar to the ADVANCE trial, with intensive versus conventional glycaemic control, VADT reported significantly reduced progression of albuminuria (i.e. microvascular disease). The ADVANCE trial showed an apparently lower risk of severe hypoglycaemia than did the ACCORD and VADT trials (about 3% and 15–20% of patients had $\geq$1 severe hypoglycaemic episode respectively, in the ADVANCE trial and the ACCORD and VADT trials; 45).

Discussion

Studies conducted on cell cultures and animals indicate a possible relationship between insulin resistance, compensatory hyperinsulinaemia and the development of atherosclerosis (Fig. 1). It is unclear whether a similar mechanism exists in humans. Several studies report possible anti-atherogenic effects of oral hypoglycaemic agents that increase peripheral insulin sensitivity and thereby reduce the insulin requirement (7–9, 11–17, 22–24, 30, 32, 33; Table 1). If these effects are of clinical significance, intervention with oral hypoglycaemic agents that increase insulin sensitivity might be an attractive choice. A review of all oral hypoglycaemic agents indicates that those agents that increase insulin sensitivity are also associated with reduced CVD (metformin and glitazones; 41) – in contrast to other oral anti-diabetic agents (46).

Metformin has become the treatment of first choice, as it reduced CVD risk among overweight patients with T2D in the UKPDS (13; Table 2). Data from this study have also strongly indicated that insulin secretagogues and insulin treatment do not lead to increased CVD risk. A potential inhibition of potassium channels in the heart during SU treatment, in addition to the suspicion of a relatively pro-atherogenic effect of hyperinsulinaemia, previously gave rise to concern about increased CVD risk of treatment with insulin or insulin secretagogues (47). However, the possibility that the higher glycaemic level in the conventional (diet) treatment group increased CVD risk cannot be excluded. In turn, this might have been equalized (but not eliminated) as a result of higher (supra-physiological) plasma insulin levels and/or inhibition of potassium channels by treatment with insulin and/or insulin secretagogues. Thus, it is theoretically possible that the 'protective' effects of metformin against CVD as primarily observed in the UKPDS were caused by the lowering of blood glucose without a concomitant increase in plasma insulin levels.

In passing, it must be emphasized that there is no evidence to support the hypothesis that insulin and/or insulin secretagogues themselves increase the risk of CVD. Moreover, these treatments have a significant role in reducing the risk of microvascular complications in patients with T2D. The recently published 10-year follow-up from the UKPDS trial suggests that treatment with SU/insulin reduces the CVD risk and, also the risk of microvascular complications. Hence, metformin and SU/insulin may be equally effective as the treatment of first choice in patients with T2D (17, 18). Finally, the potassium channels in the heart are less affected by the newer insulin secretagogues than by those of earlier generations.

Table 2 Summary of oral hypoglycaemic agents

Oral hypoglycaemic agents
Metformin
May be the intervention of first choice in both normal and overweight patients with type 2 diabetes
Probably has a protective action against macrovascular disease
Glitazones
Is used in addition to other anti-diabetics when monotherapy or combination therapy fails
The effect on macrovascular disease is not clear and the interventions are suspected of inducing heart failure and osteoporotic fractures
Metformin/sulfonylurea combination therapy
Is used when monotherapy fails
The effect on macrovascular disease is not clarified
Metformin/insulin combination therapy
May be used to reduce insulin dose, weight gain and probably to protect against macrovascular disease
Recent data support a protective effect against macrovascular disease, but more data are needed

The positive reports from the UKPDS of the effect of metformin in lowering CVD risk were supported by a meta-analysis, and in a follow-up analysis from the DIGAMI-2 trial as well as by the recent HOME trial (19, 21, 29). The reporting of lower CVD risk by glyburide intervention in the ADOPT trial was surprising, but is partly supported by the 10-year follow-up from the UKPDS. However, the data related to CVD risk in the ADOPT trial should be interpreted cautiously because of their lack of statistical power to demonstrate CVD differences and disparities in drop-out and duration of follow-up between the groups (20).

Whether a potential beneficial effect of metformin is present in all patients with T2D regardless of BMI cannot be concluded from the UKPDS. Several previous treatment guidelines have recommended insulin secretagogues as a first-line intervention in non-obese T2D patients, similarly to the UKPDS design (48). Despite the lack of trials with cardiovascular clinical outcome measures in non-obese patients with T2D, metformin is recommended by two international diabetes associations as a drug of first choice for most patients with T2D regardless of their BMI (4). In non-obese patients with T2D, trials of shorter duration have indicated that metformin and insulin secretagogues have equal glucose-lowering potentials, although metformin showed potential beneficial effects on a number of CVD risk biomarkers (22–24). Nevertheless, there is still a need for trials and systematic reviews using clinically relevant outcomes before a well-documented first-line oral hypoglycaemic agent for non-obese patients with T2D can be established. Metformin and insulin secretagogues may, with appropriate caution, be equal first-choice candidates for interventions in these patients.

It cannot be concluded from the literature whether combination therapy with metformin and SU has harmful effects, as indicated by the UKPDS (13, 25–27). At present, the international guidelines recommend combination therapy when monotherapy fails (4).

The HOME trial suggested that the potential beneficial effect of metformin on CVD was maintained when used in combination with insulin in patients with T2D (29). The HOME trial indicated that this effect of metformin therapy might at least partly have resulted from the effect of metformin to lower body weight. Although the HOME study did not clearly indicate so, the insulin sparing effect of metformin therapy might also have influenced the occurrence of CVD in that study. However, the primary composite micro- and macrovascular end point of the HOME trial was not influenced by adjunct metformin therapy (29).

There is a need for better documentation of the potential protective effect of metformin on CVD in patients with T2D, and the results from the rather small UKPDS and HOME trials need to be confirmed in new trials. There is also still a need for larger trials to clarify whether the potential protective effects of metformin on CVD are maintained in combination with insulin. Moreover, the effect of metformin therapy on microvascular disease remains uncertain.

It is still debated whether glitazones have atherogenic or anti-atherogenic effects. Trials have indicated a possible anti-atherogenic effect of pioglitazone (31, 38). The meta-analysis by Nissen *et al*. raised concerns about whether rosiglitazone had pro-atherogenic properties (39), but has since been criticized. Several methodological weaknesses have been highlighted, in particular the failure to state a hypothesis, exclusion of trials with zero events, analysing the number of events instead of time to events, the statistical model (using a fixed-effects model instead of the more plausible random-effects model, which would have shown that rosiglitazone had a non-significant effect on CVD). The US Food and Drug Administration concluded that the results were of concern, but did not consider the evidence sufficient to justify withdrawal of rosiglitazone from the market (46, 49). Preliminary data from the RECORD trial could neither confirm nor discount an increased risk of CVD during glitazone treatment (40). However, glitazones are relatively expensive, increase body weight, cholesterol levels and the frequency of osteoporotic fractures. This calls for caution in the use of glitazones until their effects are clarified, with respect not only to the lowering of blood glucose levels, but also to the reduction of macrovascular disease and/or mortality (4).

A major problem in relation to the choice of antidiabetic intervention is that it remains unclear whether there is a direct causal relationship between lowering blood glucose and the risk of developing CVD – as highlighted by the ACCORD, ADVANCE and VADT trials (42–44). In patients with type 1 diabetes, the Epidemiology of Diabetes Interventions and Complications (EDIC) study reported a reduced CVD risk as a result of lowering blood glucose (50). The *post hoc* analysis of the UKPDS trial also suggested such a relationship in patients with T2D (51). As emphasized by the authors of the ACCORD trial, it is not possible to separate the impact of individual events occurring after randomization (including achieved blood glucose levels, the reduction in blood glucose, administration of hypoglycaemic agents, etc.) on clinical outcomes (the same applies to ADVANCE and VADT; 42–44). Accordingly, the cause of the higher mortality rate in the intensive group of the ACCORD trial cannot be clarified and exploratory analyses have not been able to identify any specific oral hypoglycaemic agents as being potentially more harmful than others. Details of these exploratory analyses still await publication (42). In relation to the main concern of the present paper, however, it is remarkable that almost all the patients (92%) in the intensively treated group of the ACCORD trial, compared with only somewhat more than half (58%) in the conventionally treated group, received intervention with glitazones. Hence, the unequal

(by comparison with the conventional group) and small proportion of patients who did not receive intervention with glitazones in the group allocated intensive glycaemic control probably meant that there was insufficient statistical power to enable any potential harmful effect of the glitazone intervention to be demonstrated. By contrast, the proportion of patients taking metformin during the trial was similar in the two groups (~90%), which strongly suggests that the use of metformin did not explain the higher mortality in the intensive intervention group.

As outlined, the observed differences in mortality in the ACCORD compared with the ADVANCE and VADT studies cannot readily be explained. As a consequence of the ACCORD trial, targeting a level of HbA1c of 6.0% or less by using anti-diabetic polypharmacia may not be recommendable in patients with a high risk of CVD and poor glycaemic control. On the other hand, in high-risk CVD patients, the ADVANCE trial indicates a reduction in microvascular complications without an increase in CVD risk with the treatment goal being a HbA1c level of 6.5% or lower. Also, the ADVANCE trial, using the target of HbA1c of 6.5% or less in the intensively treated group, showed an apparently lower risk of severe hypoglycaemia compared with the ACCORD or VADT trials, both of which set a target of HbA1c of 6.0 or less in the intensive intervention groups.

Results from clinical trials using cholesterol-lowering therapy with simvastatin indicate an improved prognosis in patients with T2D (52, 53). Anti-hypertensive treatment has also been shown to be of major importance in the prevention of cardiovascular events in patients with T2D (54). The Steno-2 trial reported reduced mortality when using aggressive interventions targeting multiple CVD risk factors in patients with T2D with high-risk of CVD (55).

In conclusion, despite much research, it has still not been clarified which anti-diabetic interventions prevent CVD to the greatest extent in patients with T2D. Oral hypoglycaemic agents, which increase insulin sensitivity (metformin and glitazones), may have a beneficial effect on CVD risk in patients with T2D, but conclusive documentation is still unavailable, and updated systematic reviews with meta-analyses are warranted. There is uncertainty regarding the relationship between glitazones, CVD and also osteoporosis. Primarily based on the results from the UKPDS, metformin is recommended as the initial treatment in overweight and obese patients with T2D. In non-obese patients with T2D both metformin and insulin secretagogues may be the intervention of first choice. Anti-diabetic treatment should be intensified using combination therapy and insulin with the aim of achieving the HbA1c targets, but systematic reviews with meta-analyses may yield valuable knowledge about the preferred HbA1c level and drug combinations that will be of value in designing future intervention strategies. Elevated blood pressure and lipid levels should be aggressively treated independently of the anti-diabetic treatment.

Declaration of interest

Søren Søgaard Lund and Allan Vaag have reported equity in Novo Nordisk A/S. Allan Vaag has received funds from Novo Nordisk A/S for research. Søren Søgaard Lund and Allan Vaag have received fees from Novo Nordisk A/S for speaking and Allan Vaag has received fees from Novo Nordisk A/S for organising education. Søren Søgaard Lund and Allan Vaag are employees at the Steno Diabetes Center, Gentofte, Denmark. The Steno Diabetes Center is an independent academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation. Allan Vaag is a member of the editorial board for European Journal of Endocrinology. Jørn Wetterslev and Bianca Hemmingsen declare no conflict of interest.

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Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus (Review)

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[Intervention Review]

Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

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ABSTRACT

Background

Patients with type 2 diabetes mellitus (T2D) exhibit an increased risk of cardiovascular disease and mortality compared to the background population. Observational studies report a relationship between reduced blood glucose and reduced risk of both micro- and macrovascular complications in patients with T2D.

Objectives

To assess the effects of targeting intensive versus conventional glycaemic control in T2D patients.

Search methods

Trials were obtained from searches of CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, and CINAHL (until December 2010).

Selection criteria

We included randomised clinical trials that prespecified different targets of glycaemic control in adults with T2D.

Data collection and analysis

Two authors independently assessed the risk of bias and extracted data. Dichotomous outcomes were assessed by risk ratios (RR) and 95% confidence intervals (CI).

Main results

Twenty trials randomised 16,106 T2D participants to intensive control and 13,880 T2D participants to conventional glycaemic control. The mean age of the participants was 62.1 years. The duration of the intervention ranged from three days to 12.5 years. The number of participants in the included trials ranged from 20 to 11,140. There was no significant difference between targeting intensive and

conventional glycaemic control for all-cause mortality (RR 1.01, 95% CI 0.90 to 1.13; 29,731 participants, 18 trials) or cardiovascular mortality (RR 1.06, 95% CI 0.90 to 1.26; 29,731 participants, 18 trials). Trial sequential analysis (TSA) showed that a 10% RR reduction could be refuted for all-cause mortality. Targeting intensive glycaemic control did not show a significant effect on the risk of non-fatal myocardial infarction in the random-effects model but decreased the risk in the fixed-effect model (RR 0.86, 95% CI 0.78 to 0.96; P = 0.006; 29,174 participants, 12 trials). Targeting intensive glycaemic control reduced the risk of amputation (RR 0.64, 95% CI 0.43 to 0.95; P = 0.03; 6960 participants, 8 trials), the composite risk of microvascular disease (RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006; 25,760 participants, 4 trials), retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P = 0.002; 10,230 participants, 8 trials), retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; P = 0.03; 11,142 participants, 7 trials), and nephropathy (RR 0.78, 95% CI 0.61 to 0.99; P = 0.04; 27,929 participants, 9 trials). The risks of both mild and severe hypoglycaemia were increased with targeting intensive glycaemic control but substantial heterogeneity was present. The definition of severe hypoglycaemia varied among the included trials; severe hypoglycaemia was reported in 12 trials that included 28,127 participants. TSA showed that firm evidence was reached for a 30% RR increase in severe hypoglycaemic when targeting intensive glycaemic control. Subgroup analysis of trials exclusively dealing with glycaemic control in usual care settings showed a significant effect in favour of targeting intensive glycaemic control for non-fatal myocardial infarction. However, TSA showed more trials are needed before firm evidence is established.

Authors' conclusions

The included trials did not show significant differences for all-cause mortality and cardiovascular mortality when targeting intensive glycaemic control compared with conventional glycaemic control. Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings.

PLAIN LANGUAGE SUMMARY

Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Patients with type 2 diabetes mellitus (T2D) have an elevated mortality and morbidity compared to the general population. T2D is characterised by several metabolic defects that include impaired insulin secretion and action causing chronic hyperglycaemia (high glucose levels in the blood). Chronic hyperglycaemia is strongly associated with increased risk of kidney, eye, and nerve complications (microvascular complications) as well as increased risk of stroke, heart disease, and amputations (macrovascular complications). Although epidemiological studies indicate that reducing blood glucose in patients with T2D reduces their risk of death and morbidity, it has not been possible to unequivocally confirm this finding in large-scale randomised controlled trials (RCT). It is still not clear whether targeting more intensive glycaemic control is better than targeting conventional glycaemic control for reducing mortality or heart disease.

We identified 20 RCTs. A total of 16,106 T2D patients randomised to intensive glycaemic control and 13,880 T2D patients randomised to conventional glycaemic control were included in the analyses. The trials were primarily conducted in Europe and Northern America. The mean duration of the intervention period varied from three days to 12.5 years. The mean age of the participants of the included trials was 62.1 years.

We could not find any significant reduction in either death from any cause or death from heart disease when targeting intensive glycaemic control compared with conventional control. Intensive glycaemic control, however, reduced the risk of amputation of a lower extremity and of microvascular complications while increasing the risk of hypoglycaemia. Targeting intensive glycaemic control did not appear to change the risk of macrovascular complications as a composite outcome (an outcome consisting of several items with importance to macrovascular complications), non-fatal stroke, cardiac revascularization (a procedure to reconstruct damaged heart blood vessels), and peripheral revascularization. In trials exclusively dealing with glycaemic control in the usual care setting, a significant reduction in non-fatal myocardial infarction, in favour of targeting intensive glycaemic control, was shown. However, more trials are needed before

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Intensive glycaemic control compared to conventional glycaemic control for type 2 diabetes mellitus

Patient or population: patients with type 2 diabetes mellitus
Settings:
Intervention: Intensive glycaemic control
Comparison: conventional glycaemic control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk conventional glycaemic control	Corresponding risk Intensive glycaemic control				
All-cause mortality Follow-up: median 23.1 months	**88 per 1000**	**89 per 1000** (79 to 99)	**RR 1.01** (0.9 to 1.13)	29731 (18 studies)	⊕⊕⊕◯ **moderate**[1]	
Cardiovascular mortality Follow-up: median 23.1 months	**45 per 1000**	**48 per 1000** (40 to 57)	**RR 1.06** (0.9 to 1.26)	29731 (18 studies)	⊕⊕⊕◯ **moderate**[2]	
Non-fatal myocardial infarction Follow-up: median 51 months	**48 per 1000**	**42 per 1000** (36 to 48)	**RR 0.87** (0.76 to 1.00)	29174 (12 studies)	⊕⊕⊕◯ **moderate**[3]	
Non-fatal stroke Follow-up: median 3.5 years	**29 per 1000**	**28 per 1000** (23 to 34)	**RR 0.96** (0.8 to 1.16)	28760 (11 studies)	⊕⊕⊕◯ **moderate**[4]	

Amputation of lower extremity Follow-up: median 7.8 years	**20 per 1000**	**13 per 1000** (9 to 19)	**RR 0.64** (0.43 to 0.95)	6960 (8 studies)	⊕⊕◯◯ **low**[5]
End-stage renal disease Follow-up: median 10.0 years	**16 per 1000**	**14 per 1000** (11 to 17)	**RR 0.87** (0.71 to 1.06)	28075 (7 studies)	⊕⊕⊕◯ **moderate**[6]
Severe hypoglycaemia Follow-up: median 2.9 years	**30 per 1000**	**61 per 1000** (42 to 91)	**RR 2.05** (1.39 to 3.02)	28127 (12 studies)	⊕⊕⊕⊕ **high**[7]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Trial sequential analyses showed that more data are needed.
[2] Trial sequential analysis showed that more data are needed.
[3] Trial sequential analysis showed that more data are needed.
[4] A relatively few number of non-fatal strokes was provided.
[5] Only a few number of amputations are reported. Most of the events reported are from UKPDS.
[6] Only a few number of events reported.
[7] Heterogeneity was considerable. The definition of severe hypoglycaemia differed between trials. Besides, the reporting of severe hypoglycaemia is very prone to bias because of non-blinded participants. The potential bias is unlikely to change the result.

BACKGROUND

Description of the condition

The prevalence of type 2 diabetes mellitus (T2D) is increasing world-wide (King 1998). Insulin resistance in peripheral tissues and inadequate compensatory insulin secretion are essential elements in the pathogenesis of T2D. Reduced insulin secretion is caused by a decrease in the β-cell mass, dysfunction of existing β-cells, or both. A consequence of this is chronic hyperglycaemia (elevated levels of plasma glucose) with disturbances of carbohydrate, fat, and protein metabolism (LeRoith 2002).

Chronic hyperglycaemia is strongly associated with microvascular (for example nephropathy, retinopathy, and neuropathy) as well as macrovascular complications (for example ischaemic heart disease, stroke, and ischaemia of the lower extremities). The mortality rate is increased among patients with T2D compared to the non-diabetic population. The main cause of the increased mortality is macrovascular disease (Almdal 2004; de Marco 1999; Stamler 1993).

For a detailed overview of diabetes mellitus, please see 'additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups'). For an explanation of methodological terms see the main glossary in *The Cochrane Library*.

Description of the intervention

Since the discovery of insulin for the treatment of diabetes mellitus, the primary immediate goal in the treatment of diabetes mellitus has been to normalise or near normalise blood glucose (Bliss 2005). T2D is a progressive disease with β-cell function deteriorating over time (UKPDS-33 1998). Therefore, the glucose-lowering treatment must be intensified over that time in order to achieve near normal glycaemia. All T2D patients are initially advised to follow 'lifestyle' interventions including weight loss and increased physical activity (AACE/ACE Consensus Statement 2009; Nathan 2009). However, in order to maintain optimal glycaemic control over time the large majority of T2D patients will require additional glucose-lowering pharmacological therapy. The most commonly used first-line glucose-lowering medications are oral glucose-lowering drugs, primarily metformin (which increases insulin sensitivity). Insulin secretagogues (sulphonylureas, glinides, or incretin-based therapies) that stimulate insulin secretion are also recommended and used among first-line therapy options (AACE/ACE Consensus Statement 2009; Nathan 2009). In addition to lowering blood-glucose, sulphonylureas or glinides often increase the risk of hypoglycaemia and promote weight gain whereas metformin or incretin-based therapies appear to have either neutral or beneficial effects (for example weight loss) when given as monotherapy (AACE/ACE Consensus Statement 2009; Nathan 2009).

If lifestyle changes and maximum tolerated doses of oral glucose-lowering drugs that are given as monotherapy fail to achieve the glycaemic goal, other glucose-lowering drugs may be added. In the case of suboptimal glycaemic control using oral glucose-lowering drugs, insulin treatment can be initiated. In contrast to other glucose-lowering medications, there is theoretically no upper limit to the dose of insulin, above which further glucose-lowering will be absent. Hence insulin can be used at all stages of the disease.

At present, the evidence forming the basis for the recommendations set out in the current guidelines for treating T2D mostly consists of the documented ability of the various interventions to reduce blood glucose, as well as data on adverse effects such as weight gain or hypoglycaemia. Only a few clinical trials have reported patient-relevant clinical outcomes, and the effects of the anti-diabetic interventions are therefore not well established and to some extent even contradictory. For example, there has been great concern about the cardiovascular risk profile of rosiglitazone. The concerns resulted in a recent withdrawal of all rosiglitazone-containing anti-diabetic medicines by the European Medicines Agency (EMA 2010). The US Food and Drug Administration (FDA) also re-evaluated the use of rosiglitazone but decided to keep rosiglitazone on the market and place more restrictions on its manufacturer (Cohen 2010). Otherwise, there is no compelling evidence demonstrating clear beneficial or harmful effects on mortality or diabetic complications of other currently available glucose-lowering drugs (Nathan 2009).

The question of whether lowering or intending to lower blood glucose per se in patients with T2D is beneficial with respect to several patient-relevant outcomes, for example mortality and cardiovascular disease, remains unanswered. In patients with type 1 diabetes mellitus, a beneficial effect of intensive glycaemic control on cardiovascular disease and mortality has been suggested (DCCT/EDIC 2005). In persons with T2D, observational studies suggest that hyperglycaemia is associated with an increased risk of cardiovascular disease and mortality (UKPDS-35 2000), and a 10-year follow-up from the 'UK Prospective Diabetes Study' (UKPDS) suggested long-term beneficial effects of intensive glucose control on cardiovascular disease and mortality (UKPDS-80 2008). However, in patients with T2D, three recent randomised clinical trials have not been able to detect (or reject) reduced cardiovascular morbidity or mortality as a result of intensive glycaemic control when compared with conventional glycaemic control (ACCORD 2008; ADVANCE 2008; VADT 2009). In fact, the 'Action to Control Cardiovascular Risk in Diabetes' (ACCORD) trial showed increased mortality in the group allocated intensive glycaemic control compared with the conventional glycaemic control group. Such an adverse effect was not observed in the 'Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation' (ADVANCE) trial or the 'Veterans Affairs Diabetes Trial' (VADT) despite very similar achieved levels of glycaemic control, about 6.5% to 7.0%, in all three trials. The cause of the increased mortality in the AC-

CORD trial has not been clarified but factors such as baseline glycaemic level, neuropathy, and aspirin use were shown to significantly influence the effect on mortality when targeting intensive glycaemic control. In contrast, factors such as diabetes duration, age, hypoglycaemia, pre-existing cardiovascular disease, and drug interactions have been suggested but they have not been shown to be of importance (Calles-Escandon 2010).

The trials used different glycaemic targets and glucose-lowering strategies to achieve these targets. Hence, the definition of intensive and conventional glycaemic control varied between trials. The ACCORD trial and VADT used a target glycosylated haemoglobin A1c (HbA1c) for intensive glycaemic control of below 6.0%, compared to a target of below 6.5% in the ADVANCE trial. The definition of conventional glycaemic control was expressed as a target HbA1c of 7% to 8% in all except the ADVANCE trial, which refereed to local guidelines (Table 1). The results from these trials have created a debate about the optimal choice of glycaemic target. At present (February 2011), the American Diabetes Association (ADA) recommends an HbA1c level of less than 7.0% as the standard glycaemic treatment goal, whereas the International Diabetes Federation (IDF) recommends an HbA1c level of less than 6.5% (ADA 2010; IDF 2005; Nathan 2009).

In relation to prevention of microvascular complications in T2D patients, maintenance of tight blood glucose control was identified to exhibit a beneficial effect on diabetes-related microvascular complications in both randomised clinical trials and in observational studies (ADVANCE 2008; Ohkubo 1995; UKPDS-33 1998; UKPDS-35 2000). However, among the trials there are inconsistencies with respect to which type of microvascular complications that are prevented by intensive glycaemic control. For example, in the UKPDS trial the reduction in microvascular events was primarily due to the observed reduction in retinopathy, whereas in the ADVANCE trial it was due to a reduction in nephropathy and in the Kumamoto trial it was both.

Some trials investigate the effects of intensive glycaemic control combined with intensive control of other risk factors by using a so-called multimodal approach. These trials have, for example, investigated concomitant allocation to intensive treatments for blood pressure, lipids, and blood glucose in the same treatment arm. In such trials, therefore, it is not possible to estimate the effects of each treatment component (see for example, Steno-2 2008). Other trials applied a so-called factorial design by investigating the effect of targeting several cardiovascular risk factors within each treatment arm in the same trial. With the applied stratification in those studies the influence of each risk factor could be estimated (for example, ACCORD 2008). The investigators of the ACCORD trial recently published the results from the blood pressure-control arm and the lipid-control arm. The blood pressure trial randomly assigned participants from the ACCORD trial to targeted intensive blood pressure control (systolic pressure less than 120 mm Hg) versus conventional blood pressure control (systolic pressure less than 140 mm Hg). Intensive blood pressure control did not however reduce the risk of the composite macrovascular outcome (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) compared with conventional blood pressure control. The lipid arm of the ACCORD trial investigated the effect of simvastatin in combination with fenofibrate treatment compared with simvastatin monotherapy. The conclusion of this treatment arm was that the lipid treatment did not influence the risk of cardiovascular events (ACCORD 2008).

Hence, as primarily suggested by the ACCORD trial, uncertainty remains about the putative beneficial effect of reducing blood glucose compared with the potential risks in T2D patients. In particular, there have been major concerns regarding the extent to which intensive glycaemic control may increase the risk of cardiovascular disease and mortality, which has not yet been clarified. Although there is general agreement that intensive glycaemic control reduces the risk of microvascular disease, there are inconsistencies among trials with respect to which types of microvascular disease are reduced. Also, guidelines differ with respect to the recommended optimal glycaemic level for patients with T2D.

Adverse effects of the intervention

The incidence of adverse effects appears to increase when more aggressive metabolic targets for glycosylated haemoglobin A1c (HbA1c) are applied (especially with the addition of insulin) (ACCORD 2008; ADVANCE 2008; UKPDS-33 1998). Furthermore, experimental and observational studies have suggested that hyperinsulinaemia, for example caused by supraphysiologic doses of exogenous insulin, may lead to increased atherosclerosis (Muis 2005). However, a larger number of glucose-lowering drugs, or larger doses of these drugs, are usually required to achieve more intensive glucose targets. This makes the distinction between the beneficial and harmful effects of the anti-diabetic drugs and of lowering glucose difficult.

The most common adverse reaction to glucose-lowering treatment is hypoglycaemia. The symptoms of mild episodes of hypoglycaemia are often well tolerated by patients, such as hunger, palpitations, tremor, and sweating. Mild hypoglycaemia often precedes severe hypoglycaemia, which can result in more serious symptoms such as confusion, coma, or even death (ADA Workgroup on Hypoglycemia 2005). A recent publication of the ACCORD trial found a link between symptomatic severe hypoglycaemia and increased risk of death (Bonds 2010); the ADVANCE trial did not find any relationship between repeated episodes of severe hypoglycaemia and death (Zoungas 2010). In addition, a cohort study has suggested an association between a history of severe hypoglycaemia and the risk of dementia among older patients with T2D (Whitmer 2009). Moreover, the different classes of anti-diabetic interventions have specific adverse reactions, for example gastrointestinal disturbances with metformin (Saenz 2005); weight gain, oedema, bone fractures, and heart failure with glitazones (Richter 2006; Richter 2007). Weight gain and injection site reactions are among the common adverse effects of insulin (Horvath 2007).

There has also been some concern about a potential increased risk of cancer in patients treated with insulin glargine compared with treatment with other types of insulin. Two recent cohort studies showed an increased risk of cancer-related death and all-cause mortality, whereas two other cohort studies could not find such a relationship (Currie 2009; Hemkens 2009; Jonasson 2009; SDRN 2009). The hypothesis that intensive glycaemic control could increase the risk of cancer compared with conventional glycaemic control in patients with T2D was not supported in a recent meta-analysis (Johnson 2011). However, in order to analyse whether intensive glycaemic control affects the risk of cancer in an unbiased way, a review should not exclude patients with type 1 diabetes mellitus. That is why this outcome has been excluded from this review.

Why it is important to do this review

It is still unknown if intensive glycaemic control is superior to conventional glycaemic control for reducing mortality and cardiovascular disease in patients with T2D. The dramatic increase in the number of T2D patients places serious demands on healthcare services. Cardiovascular disease is the main cause of the higher mortality in T2D patients. It is therefore relevant to clarify whether intervention regimens that target reduced blood glucose actually improve important patient outcomes such as mortality and cardiovascular disease. A previous meta-analysis, in 2006, suggested that improvement of glycaemic control may reduce macrovascular disease in T2D patients primarily due to a reduction in stroke and peripheral vascular events (Stettler 2006). Since the latter review, large-scale trials have been conducted comparing intensive versus conventional glycaemic control (that is ACCORD, ADVANCE, and VADT). Two recent meta-analyses among others based on the three recent trials have found that intensive glycaemic control in T2D patients led to a significant reduction in the incidence of myocardial infarction, whereas the incidence of stroke and cardiovascular mortality were not affected (Mannucci 2009; Ray 2009). These meta-analyses exclusively included trials that were published in English, with cardiovascular events as the primary outcome and with glycaemic control measured as HbA1c (Mannucci 2009; Ray 2009). Mannucci et al performed a meta-analysis of data from non-fatal and fatal myocardial infarction together, whereas Ray et al reported non-fatal myocardial infarction separately. Importantly, these meta-analyses included trials based on the achieved (that is, follow-up) rather than the target (that is, randomly allocated) differences in glycaemic control. Thus, trials without predefined differences in the targets of glycaemic control were included. For example, head-to-head anti-diabetic drug comparisons with a similar target of HbA1c of below 6.5% in both intervention groups were included, such as the 'PROspective pioglitAzone Clinical Trial In macroVascular Events' (PROactive) trial of add-on pioglitazone versus placebo (PROactive 2005). This chosen strategy of selection is potentially problematic since, in a clinical trial, the target and the achieved glycaemic levels represent different variables. The achieved glycaemic levels and the clinical outcomes are net results (that is, outcomes) of effects operating at baseline and during follow-up but they do not necessarily impact on each other. In contrast, the different glycaemic targets, as part of the randomised treatment regimen, by potentially causing different changes to be made during the trial in the glucose-lowering treatments in each treatment arm impact on the outcomes whether as clinical outcomes or as achieved glycaemic levels. Thus, trial participants will always have an achieved glycaemic level but they will only have a target level if this has been predefined. This target level may either be similar or different between the treatment arms. In other words, in a clinical trial it is probably not possible to randomise participants to an achieved glycaemic level; for example, in daily life it is unlikely that all participants can be kept to a given blood glucose concentration. Hence, to some extent, achieved glycaemic levels represent observational data and preclude inferences about causality with respect to their influence on other outcomes. In contrast, target levels, as part of the randomised treatment strategy, can support inferences about causality. Therefore, to most optimally address the clinical effect of aiming for intensive glycaemic control, which probably is the relevant question to address for the treatment guidelines as well as for the clinician, it is necessary to meta-analyse trials primarily based upon predefined differences in glycaemic targets.

Two other recent meta-analyses, by Kelly et al (Kelly 2009) and Turnbull et al (Turnbull 2009), included only randomised clinical trials with predefined differences in glycaemic target and with cardiovascular disease as the primary outcome. Moreover, both meta-analyses set a lower limit for the number of included patients in the included randomised clinical trials and the meta-analysis by Turnbull and colleagues did not include the intensively treated group, with metformin therapy, from the UKPDS. Further, none of the reviews until now have explored the required information size (the cumulative meta-analysis sample size) to detect or reject specific, clinically relevant intervention effects (Higgins 2010; Wetterslev 2008; Wetterslev 2009).

In summary, there are still uncertainties concerning the optimal therapy for T2D, for example the HbA1c target level. The risk of reducing blood glucose in T2D patients may be influenced by different factors, for example diabetes duration, age, and previously cardiovascular disease. Therefore, the balance of benefits and harms of tight glycaemic control are still unknown and need to be explored. The present systematic review focuses on one of the most important and, as yet, unsolved issues among the clinical questions, that is the clinical effect of targeting intensive glycaemic control per se in T2D patients. In contrast, in this review the effect of achieved glycaemic levels or of specific glycaemic targets is of no interest.

OBJECTIVES

To assess the effects of targeted intensive glycaemic control compared with targeted conventional glycaemic control in patients with T2D.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials of any design comparing targeted intensive glycaemic control with targeted conventional glycaemic control in patients with T2D. Published and unpublished trials in all languages were included.

Types of participants

Adults aged 18 years and above with T2D were included. The diagnosis of T2D should have been established at randomisation into the trial using standard criteria (for example, ADA 1997; ADA 1999; ADA 2003; ADA 2008; NDDG 1979; WHO 1980; WHO 1985; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, the authors' definition of T2D was used.

Types of interventions

All included trials should have, prior to patient allocation, predefined in the protocol the different glycaemic targets for intensive and conventional glycaemic control. Intensive treatment regimens are usually directed towards an average glycaemic target with a glycosylated haemoglobin A1c (HbA1c) level of, for example, 7.0% (measured according to the 'Diabetes Control and Complications Trial' (DCCT) standard) or less compared with a conventional treatment regimen, irrespective of which glucose-lowering interventions are used to obtain the intervention targets. Trials using HbA1c equivalents (for example, total glycosylated haemoglobin) to compare predefined intensive versus conventional glycaemic treatment were included as well. Furthermore, if no HbA1c (or equivalent) target levels were predefined, trials targeting metabolic control as measured by fasting blood or plasma glucose (usually directed towards 8 mmol/L or less) or postprandial blood or plasma glucose (usually directed towards 11 mmol/L or less) also fulfilled the criteria for inclusion. Trials with a prespecified glycaemic target in the intensive group only were also included. However, as outlined, studies with different target levels in fasting or postprandial blood or plasma glucose but with similar HbA1c (or equivalent) target levels between interventions, or no specified target levels, did not fulfil the criterion for inclusion.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Cardiovascular mortality (death from myocardial infarction, stroke, and peripheral vascular disease)

Secondary outcomes

- Macrovascular complications (non-fatal myocardial infarction, non-fatal ischaemic stroke, non-fatal haemorraghic stroke, amputation of lower extremity, and cardiac or peripheral revascularization).
- Microvascular complications (manifestation and progression of nephropathy, end-stage renal disease, manifestation and progression of retinopathy, and retinal photocoagulation).
- Adverse events (number of patients with any untoward medical occurrence not necessarily having a causal relationship with the treatment). We reported adverse events that lead to treatment discontinuation separately. We defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines as any event that leads to death, that was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which may have had jeopardised the patient or required intervention to prevent it (ICH 1997). All other adverse events were considered to be non-serious.
- Congestive heart failure.
- Hypoglycaemia, definitions may be heterogeneous between trials. Hypoglycemia was defined as mild (controlled by patient), moderate (daily activities interrupted but self-managed), or severe (requiring assistance).
- Health-related quality of life measured with validated instruments.
- Cost(s) of treatment.

Macrovascular and microvascular outcomes were both assessed as a composite outcome and as each outcome separately.

Timing of outcome measurement

All outcome measures were assessed independently of the timing of the outcome measurements. The trials were divided according to their intervention periods into short (less than two years) and long (equal or greater than two years) duration.

Covariates, effect modifiers and confounders

Trials assessing multimodal treatment together with intensive glycaemic control were included in the analyses. It was planned that if the results of the interaction analyses between the interventions

with respect to the clinical outcomes were not available in the publications from these trials, the authors of the trials would be contacted to provide this information. These data would have been taken into account in the interpretation of the results of the meta-analyses. Furthermore, it was planned that the presence of any such significant interactions would be subjected to sensitivity analysis (see 'Sensitivity analysis'). None of the trials assessing multimodal treatment were designed to assess the interactions between the interventions used.

Search methods for identification of studies

Electronic searches

The following sources were searched to identify relevant trials:

- *The Cochrane Library* (Issue 4, 2010);
- MEDLINE (8 December 2010);
- EMBASE (8 December 2010);
- Science Citation Index Expanded (8 December 2010);
- Latin American Caribbean Health Sciences Literature (LILACS) (8 December 2010);
- Cumulative Index to Nursing & Allied Health Literature (CINAHL) (8 December 2010).

We intended to search 'The Chinese Biomedical Literature Database', but we did not get any response to our request from the Chinese Cochrane Centre.

The overall search strategy combined searches for T2D and for intensive versus conventional glycaemic control with searches for randomised controlled trials. The search strategies are listed in full in Appendix 1.

We searched for ongoing trials using the following databases:

- Current Controlled Trials (www.controlled-trials.com/) (assessed January 2011);
- ClinicalTrials.gov (www.clinicaltrials.gov/) (assessed January 2011);
- Centre Watch Clinical Trials Listing Service (www.centerwatch.com/) (assessed January 2011);
- International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch/) (assessed January 2011).

Searching other resources

In addition, we handsearched abstracts from major diabetes conferences (American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD)). We contacted relevant pharmaceutical companies and the US Food and Drug Administration (FDA) for unpublished clinical trial data relevant to the review. We tried to identify additional trials by searching the reference lists of included trials and (systematic) reviews, meta-analyses, and health technology assessment reports.

Data extractions of all relevant non-English articles were obtained.

Additional key words of relevance were not identified during any of the electronic or other searches. It was not necessary to add additional key words.

Data collection and analysis

Selection of studies

Publications were excluded and full-text articles not retrieved if two of the authors (BH and AV, CG, CH, SL, TA) could determine with certainty from the titles and abstracts identified in the initial search that the trial was: performed in patients with type 1 diabetes mellitus, was not a randomised clinical trial, or did not compare targeted intensive glycaemic control versus targeted conventional glycaemic control. If we could not exclude a publication with certainty on the basis of the title, abstract, or both, the full text of the article was obtained. In cases of differences in opinion, JW was consulted.

Full-text articles were also retrieved if the study clearly fulfilled the inclusion criteria: (i) compared targeted intensive glycaemic control with targeted conventional glycaemic control; (ii) included patients with T2D; and (iii) was a randomised clinical trial. Inter-rater agreement for study selection was measured using the kappa statistic (Cohen 1960).

In some cases it was not possible to resolve disagreements without additional information and the authors of the articles were contacted.

A flow diagram of the number of studies identified and excluded at each stage was prepared in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement (Liberati 2009).

Data extraction and management

Two authors (BH and CH or TA) independently extracted information on each trial using standard data extraction forms. The forms included data concerning trial design, participants, interventions, and outcomes as detailed in the selection criteria described above. For details see: 'Characteristics of included studies', 'Glycaemic control in trials' (Table 1), 'Overview of study populations' (Table 2), 'Interventions in trials' (Appendix 2), 'Cardiovascular risk factors and body mass index at the end of follow-up' (Appendix 3), 'Definition of mortality and cardiovascular outcomes in study or as reported' (Appendix 4), 'Definition of microvascular outcomes in study or as reported' (Appendix 5), and 'Definition of hypoglycaemia in study or as reported' (Appendix 6). Any relevant, missing information was sought from the original author(s) of the article. Differences between authors were resolved by discussion and involvement of a third author.

Assessment of risk of bias in included studies

Methodological quality was defined as the confidence that the design and the report of the randomised clinical trial restricted bias in the comparison of the intervention (Moher 1998). According to empirical evidence, the methodological quality of the trials was based on sequence generation; allocation concealment; blinding (participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias (Gluud 2006; Higgins 2008; Kjaergard 2001; Moher 1998; Schulz 1995; Wood 2008).

Two authors (BH and CH or TA) independently assessed the risk of bias in each trial by means of the Cochrane Collaboration's risk of bias tool. Any differences in opinion were resolved through discussion with JW. The identified trials published in Russian and Chinese were judged for risk of bias by the data extractor, who also evaluated the trials.

Risk of bias components were classified as follows.

Sequence generation

- Low risk of bias, if the allocation sequence was generated by a computer, a random number table, or similar.
- Uncertain risk of bias, if the trial was described as randomised but the method used for the allocation sequence generation was not described.
- High risk of bias, if a system involving dates, names, or admittance number was used for the allocation of patients (quasi-randomised). Such trials were not found, but would have been excluded.

Allocation concealment

- Low risk of bias, if the allocation of participants involved a central independent unit; on-site locked computer; or consecutively numbered, sealed envelopes.
- Uncertain risk of bias, if the trial was described as randomised but the method used to conceal the allocation was not described.
- High risk of bias, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Such trials were not found but would have been excluded.

Blinding

It was not possible to blind the healthcare provider and the patients in the treatment groups. Blinding was therefore considered adequate if the outcome assessors were blinded, although we were aware of the fact that such trials may be subject to bias.

- Low risk of bias, if the outcome assessors were blinded and the method of blinding was described.
- Uncertain risk of bias, if the outcome assessors were blinded and the method of blinding was not described.
- High risk of bias, if the outcome assessors were not blinded.

Incomplete data outcomes

- Low risk of bias, if any post randomisation drop-outs or withdrawals, if they occurred, were clearly described and the reasons for these drop-outs were described.
- Uncertain risk of bias, if it was not clear whether there were any drop-outs or withdrawals or if the reasons for these drop-outs were not clear.
- High risk of bias, if the reasons for missing data were likely to be related to the outcomes: (1) 'as-treated' analysis were performed; (2) potentially inappropriate application of simple imputation; (3) potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Low risk of bias, if all the predefined (primary and secondary) outcomes mentioned in the trial´ s protocol or in the design article were reported and the reporting had been done in the prespecified way.
- Uncertain risk of bias, if there was insufficient information to assess whether a risk of selective outcome reporting was present.
- High risk of bias, if not all the prespecified outcomes were reported, if the primary outcomes were changed, or if some of the important outcomes were incompletely reported.

Sponsor bias

- Low risk of bias, if the trial was unfunded or was not funded by an instrument, equipment, or drug manufacturer.
- Uncertain risk of bias, if the source of funding was not clear.
- High risk of bias, if the trial was funded by an instrument, equipment, or drug manufacturer.

Academic bias

- Low risk of bias, if the author of the trial had not conducted previous trials addressing the same interventions.
- Uncertain risk of bias, if it was not clear if the author had conducted previous trials addressing the same interventions.
- High risk of bias, if the author of the trial had conducted previous trials addressing the same interventions.

Besides investigating each bias domain, we also evaluated the overall risk of bias. When sequence generation, allocation concealment, and blinding criteria were judged to be adequate, the trial was classified as a low risk of bias trial.

We planned to explore the influence of individual risk of bias criteria in subgroup analyses.

Measures of treatment effect

Dichotomous data

Data on dichotomous outcomes were statistically summarised as relative risks (RR) with 95% confidence intervals (CI). The risk difference (RD) and number needed to treat (NNT) were also calculated.

Continuous data

Continuous outcomes were summarised as difference in means (MD) with 95% CI, and an overall MD was calculated in the meta-analysis. For studies addressing the same outcome but using different outcome measures (for example different scales measuring quality of life) standardised mean differences (SMD) were used.

Time-to-event data

Most trials recruit their participants over a defined recruitment period and are followed up until a fixed date, beyond the end of recruitment. Therefore, the last recruited participants will be observed for a shorter period than those recruited first and will therefore be less likely to experience an event. Time-to-event outcomes (for example time until death) were planned to be expressed as hazard ratios (HR) with 95% CI. The natural logarithm (ln) of the HR and its standard error (SE) were calculated. We preferred the univariate HR, when available.

Dealing with missing data

Missing data were sought by contacting the trial authors. The impact of any missing data was discussed. Evaluations of randomised patients in intention-to-treat and available case analyses were performed.

When using meta-analysis for combining results from several studies with binary outcomes (that is, event or no event) adverse effects may be rare but serious and hence important (Sutton 2002). Most meta-analytic software does not include trials with zero events in both arms (intervention versus control) when calculating relative risk (RR). Exempting these trials from the calculation of RR and CI may lead to the overestimation of a treatment effect. In case of trials with zero events in both arms, we applied a sensitivity analysis by empirical continuity corrections to these trials as proposed by Sweeting et al (Keus 2009; Sweeting 2004).

Intention-to-treat analysis is recommended in order to minimise bias in the analysis of the efficacy of randomised clinical trials. It estimates pragmatically the benefit of a change in treatment policy rather than the potential benefit in patients who receive the treatment exactly as planned (Hollis 1999). Full application of intention to treat is possible when complete outcome data are available for all randomised participants. Despite the fact that about half of all published reports of randomised clinical trials state that intention-to-treat analysis is used, handling of deviations from randomised allocation varies widely and many trials have missing data on the primary outcome variable (Hollis 1999). The methods used to deal with deviations from randomised allocation are generally inadequate, potentially leading to bias (Hollis 1999). Performing an intention-to-treat analysis in a systematic review is not straightforward in practice since review authors must decide how to handle missing outcome data in the contributing trials (Gamble 2005). No consensus exists about how missing data should be handled in intention-to-treat analysis, and different approaches may be appropriate in different situations (Higgins 2008; Hollis 1999).

In the case of missing data, we planned to apply 'complete-case analysis' for primary and secondary outcomes, which simply excludes all participants with the missing outcome from the analysis, as well as 'worst-best' and 'best-worst' scenario analyses. We applied 'complete-case analysis', and 'worst-best' and 'best-worst' scenario analyses for the primary outcomes and for non-fatal myocardial infarction only.

Dealing with duplicate publications

When more than one publication of an original trial was identified, we assessed those articles together to maximise data collection. In the case of substantial disagreements between older and newer articles the authors were contacted.

Assessment of heterogeneity

A priori, the authors evaluated the clinical diversity of the included trials. Heterogeneity was identified by visual inspection of the forest plots and by using a standard Chi^2 test, with a significance level of α = 0.1. Heterogeneity was specifically examined with the I^2 statistic. Values of I^2 between 0% to 40% were graded as: heterogeneity might not be important. An I^2 statistic between 30% to 60% was graded as representing moderate heterogeneity, I^2 between 50% to 90% was graded as substantial heterogeneity, and I^2 between 75% to 100% was graded as considerable heterogeneity (Higgins 2008). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual trial characteristics and the subgroup characteristics for the main body of evidence.

Clinical heterogeneity was assessed by comparing the trials with regard to different clinical variables: patient characteristics, duration of disease, glycaemic target, other targeted metabolic variables, and outcome. When significant clinical, methodological, or statistical heterogeneity was found, we surveyed the individual trials to determine potential reasons for it.

We used both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In the case of discrepancy between the two models, we reported both results. We originally planned to report only the fixed-effect model however, due to

substantial heterogeneity between the included trials, we decided to report primarily the random-effects model.

Between-trial heterogeneity was explored by meta-regression, depending on the available data. Therefore meta-regression was performed to explore a possible association between the intervention effects estimated in the trials and the following covariates that were selected in the protocol: average fasting blood glucose at baseline, average HbA1c at baseline, average duration of diabetes at baseline, and duration of intervention. Meta-regression was performed using the software Comprehensive Meta Analysis. The statistical method for the meta-regressions was a random-effects meta-regression analysis based on unrestricted maximum likelihood. All log risk ratios were based on Mantel-Haenszel analyses.

Assessment of reporting biases

Funnel plots were drawn to provide visual assessment as to whether treatment effects were associated with trial size. There are a number of reasons for the asymmetry of a funnel plot (for example, methodological design of trials and publication bias) (Higgins 2008).

Data synthesis

The median reported in the included trials was assumed to approximate to the arithmetic mean. Data were summarised statistically if they were: available, of sufficient quality, and sufficiently similar (clinical heterogeneity). Statistical analyses were performed according to the statistical guidelines referenced in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Trial sequential analysis

Trial sequential analysis is a methodology that combines an information size calculation (cumulated sample size to detect or reject a certain relative intervention effect) for meta-analysis with the threshold of statistical significance. It is a tool for quantifying the statistical reliability of data in a cumulative meta-analysis, adjusting significant values and confidence intervals for repetitive and early testing on accumulating data. Trial sequential analysis was conducted on the primary and the secondary outcomes (Brok 2008; Brok 2009; Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008). Meta-analysis may result in type I errors due to systematic errors (bias) or random errors due to repeated or early significance testing when updating meta-analysis with new trials (Brok 2008; Brok 2009; Higgins 2010; Wetterslev 2008).

In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value, that is the cumulative Z-curve crosses the monitoring boundaries (Lan 1983). Sequential monitoring boundaries can be applied to meta-analysis as well, called trial sequential monitoring boundaries (Higgins 2010). In trial sequential analysis, the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed (Wetterslev 2008).

The idea in trial sequential analysis is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials are needed. If the Z-curve does not cross the boundary, then there is insufficient evidence to reach a conclusion. To construct the trial sequential monitoring boundaries, the required information size is needed and is calculated as the least number of participants needed in a well-powered single trial (Brok 2008; Brok 2009; Pogue 1997; Pogue 1998; Wetterslev 2008). We applied trial sequential analysis since it decreases the risk of type I error due to sparse data and potential multiple updating in a cumulative meta-analysis, and it provides us with important information in order to estimate the level of evidence of the experimental intervention. Additionally, trial sequential analysis provides us with important information regarding the need for additional trials and the required information size.

We applied trial sequential monitoring boundaries according to an information size suggested by the estimated intervention effect and an information size based on an a priori effect corresponding to a numbers needed to treat (NNT) or harm (NNH) of 50 to 100. This may include a 10% to 30% relative risk reduction (RRR) for benefit or harm using an overall type one error level of 5% (α = 0.05) and a type two error level of 20% (ß = 0.20 or power = 80%).

We conducted trial sequential analysis on the primary outcomes. Moreover, it was applied to all secondary outcomes that showed significant effect estimates in both the random-effects and fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned if one of the primary outcome measures demonstrated statistically significant differences between intervention groups. In any other case, subgroup analyses were planned as a hypothesis generating exercise. The following subgroup analyses were planned:

- anti-diabetic intervention used to achieve glycaemic target (drug classes compared to each other, the use of monotherapy compared to combination therapy);
- glycosylated haemoglobin A1c (HbA1c) level less than 7.0% compared to HbA1c equal or greater than 7.0%;
- defined target in terms of HbA1c compared to non-HbA1c target;
- cardiovascular disease at baseline;
- peripheral revascularization and retinal photocoagulation (because the interventions depend on the local clinical practice);

- age less than 65 years compared to age equal to or greater than 65 years.

All outcomes were analysed in the subgroups according to the type of intervention applied: trials exclusively dealing with glycaemic control in the usual care setting, glycaemic control as a part of an acute intervention, and multimodal intervention in a usual care setting. Trials exclusively dealing with glycaemic control in usual care were defined as those trials with random allocation to targeting intensive versus conventional glycaemic control without parallel (non-factorial) allocation to concomitant control of other risk factors than blood glucose, such as blood pressure or lipids. Factorial allocation to other regimens than glucose-lowering treatment, such as blood pressure or lipid-lowering treatment, was allowed in this group. Acute intervention should not be part of the treatment protocol. Multimodal intervention in usual care settings was defined as those trials with parallel (non-factorial) random allocation to concomitant control of other risk factors than blood glucose, such as blood pressure or lipids, where acute intervention should not be part of the protocol. Acute intervention was defined as those trials where intensive versus conventional glycaemic control was initiated as part of an acute intervention during hospital admission for other reasons than control of diabetes, for example in participants with acute myocardial infarction. There was no requirement for the duration of the intervention in the acute intervention group, that is longer-term trials with follow-up over several years could be included. These three subgroups, according to the type of intervention, were mutually exclusive.
The following subgroup analyses were performed for the primary outcomes and non-fatal myocardial infarction.

- Comparing trials with low risk of bias regarding sequence generation, allocation concealment, and blinding to trials with high risk of bias regarding sequence generation, allocation concealment, and blinding.
- Comparing trials with long study duration (> 2 years) to the trials with short study duration (≤ 2 years).
- Comparing the trials using the filters: diagnostic criteria, language of publication, source of funding (industry versus other).

Tests of interaction were planned to determine the effect of a subgroup on the intervention effect.

Heterogeneity examined by meta-regression

Meta-regression was conducted for the following covariates:

- average duration of diabetes at baseline;
- average fasting blood glucose at baseline;
- average HbA1c at baseline;
- average duration of the intervention.

Sensitivity analysis

We performed sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding the trials with longest duration or the largest trial to establish how much they influenced the results;

- repeating the analysis including trials with zero events in the treatment groups with the trial sequential analysis program, applying an empirical continuity correction of 0.01 for zero events (Sweeting 2004);

- repeating the analysis excluding only those trials assessing multimodal treatment with documented statistical interactions between the interventions on the clinical outcomes;

- repeating the analysis excluding trials assessing acute effects of glycaemic control (less than 48 hours);

- repeating the analysis excluding unpublished trials.

The sensitivity analysis "Repeating the analysis excluding only those trials assessing multimodal treatment with documented statistical interactions between the interventions on the clinical outcomes" was not possible as none of the trials assessing multimodal treatment were designed to assess the interactions of the interventions used.
The sensitivity analysis including trials with zero events in the treatment groups with the trial sequential analysis program applying an empirical continuity correction was performed (Sweeting 2004).
The robustness of the results was tested by repeating the analysis using different measures of effects size (relative risk, odds ratio, etc.) and different statistical models (fixed-model and random-effects models).

RESULTS

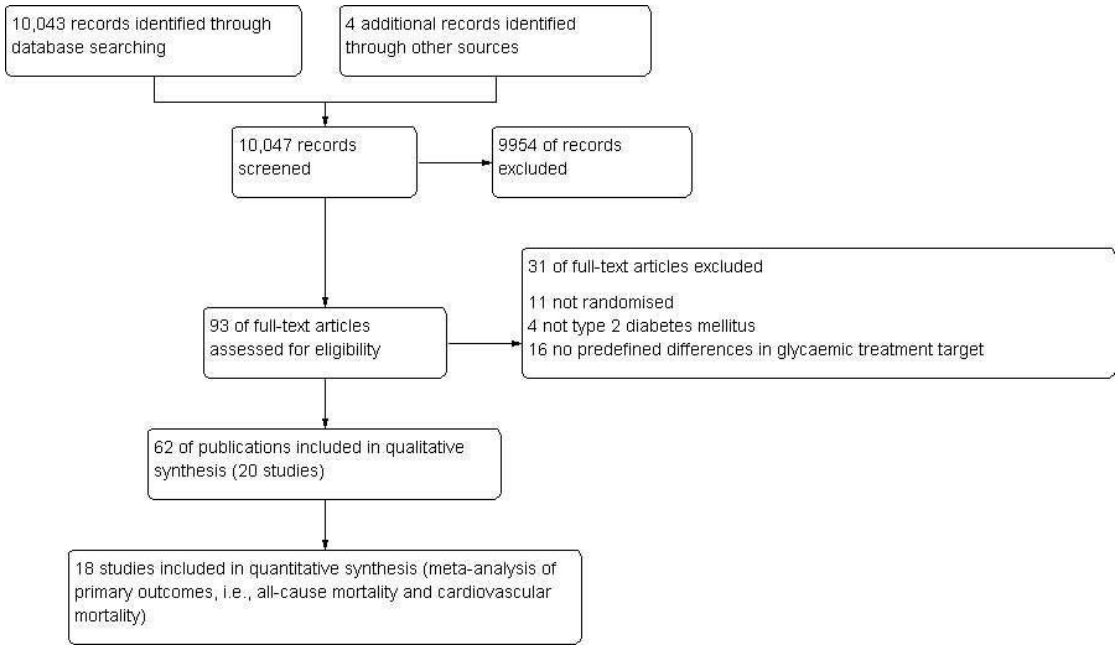
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The initial search of the databases identified 10,043 records, of which 89 full papers were examined further. The other studies were excluded on the basis of their titles and abstracts because they clearly did not meet the inclusion criteria (Figure 1). After screening the full text of the selected papers, 20 randomised trials described in 62 publications met the inclusion criteria. Eighteen trials were published in English, one in Russian (REMBO 2008), and one in Chinese (Yang 2007).

Figure 1. Study flow diagram.



Abstracts from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) conferences did not provide information on additional trials. The same was the case for making contact with relevant pharmaceutical companies and the US Food and Drug Administration (FDA). One relevant health-technology assessment report was found (AHRQ 2007). Eleven meta-analyses comparing intensive glycaemic control versus conventional glycaemic control in T2D patients were also retrieved (Kelly 2009; Ma 2009; Mannucci 2009; Marso 2010; Ray 2009; Selvin 2004; Stettler 2006; Turnbull 2009; Wang 2009; Wu 2010; Zhang 2010). Neither the health-technology assessment report nor the meta-analyses provided references to any additional trials. All authors of the included trials were sent a reference list and a request for information on additional trials, if possible. One publication was provided by an author (Genell Knatterud). Screening references of the University Group Diabetes Program (UGDP) provided the design article for this trial, which was not retrieved from the search (UGDP 1975). The ACCORD provided a comprehensive trial protocol, which they referred to in one of the included trials (ACCORD 2008). Through Internet searches for additional information on the included trials, the ADVANCE trial provided information on a web page, from which information about the sub studies were obtained.

Inter-rater agreement between the two trial selectors was 84%, using the kappa statistic.

Searching websites for ongoing trials showed 10 trials with potential relevance (ADDITION 2001; ADVANCE-ON; CABG USCDP; Chen 2009; DARE; GLUCOSURG1; HFDM; LIMBISCH; REMIT Pilot Trial; VADT-FS 2008). The trials will be included when updating the review.

Missing data

We contacted all corresponding authors of the included trials for further details. Extraction schemes were sent to all the authors so that they could provide additional data or comment on the retrieved data. Bagg, Bonds, Ryden, Hage, Kishawa, Stefanidis, Service, Gaede and Petersen, and Abraira provided us with further information (ACCORD 2008; Bagg 2001; DIGAMI 2 2005; IDA 2009; Kumamoto 2000; Melidonis 2000; Service 1983; Stefanidis 2003; Steno-2 2008; VA CSDM 1995; VADT 2009). Our request might not have reached all authors because of changes of contact information since the publication of the trial. Internet searches were made on these authors in order to find updated contact information. Additional information about the UKPDS (UKPDS 1998) was obtained from other meta-analyses (Kelly 2009; Ray 2009; Turnbull 2009).

Dealing with duplicate publications

Several of the included trials consisted of more than one publication. In one of the included trials a discrepancy between two publications describing the same participants was observed (Becker 2003). We were unfortunately not able to obtain contact information on the first authors of the duplicate articles. The article in

the Netherlands Journal of Medicine (2003) described the details of the study population reported on in Diabetes Care 1998. We corresponded with two of the other authors who unfortunately were not able to clarify the discrepancy between the publications (see 'Characteristics of included studies').

The UKPDS consists of several publications and we were in doubt about the overlap between the conventional treatment groups in UKPDS 33 and UKPDS 34 (UKPDS 1998). An author of both articles (Rury Holman) confirmed a complete overlap between the participants in the conventional treatment groups in UKPDS 33 and UKPDS 34. The intensively treated group receiving metformin in the UKPDS 34 was not a part of the intensively treated group in the UKPDS 33. Thus, where possible, all intensively treated patients from UKPDS were included whether allocated to insulin, sulphonylurea, or metformin; as were the conventional group from UKPDS 33. Data on the composite macrovascular outcome in UKPDS were obtained from the meta-analysis by Turnbull et al in which follow-up was truncated to five years and only data from UKPDS 33 were reported (Turnbull 2009). It was only possible to retrieve the reported number of retinopathies and nephropathies from UKPDS 33, and not from UKPDS 34. All other outcomes from UKPDS 33 and UKPDS 34 were reported after 10 years of follow-up.

Included studies

We included data from 20 trials. All were randomised clinical trials assessing the effect of intensive glycaemic control versus conventional glycaemic control in patients with T2D. A total of 29,986 participants were included, of which 16,106 were randomised to intensive glycaemic control and 13,880 were randomised to conventional glycaemic control (Table 2). For full details please see the table 'Characteristics of included studies'.

Trial designs

All 20 included trials were randomised clinical trials of which three had a factorial design (ACCORD 2008; ADVANCE 2008; UKPDS 1998). None of the included trials had a cross-over design. The ACCORD and UKPDS used a partly factorial design since only a proportion of the patients were also randomised to other treatment arms besides the glucose control arm: blood pressure control, ACCORD (46% of participants) and UKPDS (27% of participants); and lipid-lowering, ACCORD (54% of participants) (ACCORD 2008; UKPDS 1998). In contrast, the ADVANCE trial randomised all patients to a glucose control arm as well as a blood pressure control arm (ADVANCE 2008). The tests for interaction between the allocation in the glucose trial and that in the blood pressure or lipid trials on the primary outcome in the ACCORD trial did not reach statistical significance (P = 0.08 for blood pressure, and P = 0.36 for lipids) (ACCORD 2008). In the ADVANCE trial, again no significant interaction was observed on the primary outcomes with allocation to the glucose and the blood pressure trials (P > 0.50) (ADVANCE 2008). Interaction tests for allocation to glucose control and blood pressure control have not been reported from the UKPDS (UKPDS 1998). Thus, in the ACCORD and ADVANCE trials the effects on the primary outcome of either of the randomised interventions should be independent of each other. There are no statistical data to support this conclusion from UKPDS.

As part of the glucose control arms, the ADVANCE and UKPDS included concomitant randomisation to specific glucose-lowering drugs in the intensively treated groups. Besides the target of glycosylated haemoglobin A1c (HbA1c) below 6.5% in the ADVANCE trial and 7.0% in the REMBO (Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure) trial, all participants in the intensively treated group received modified release gliclazide (ADVANCE 2008; REMBO 2008). In the UKPDS, besides the target of fasting plasma glucose below 6.0 mmol/L, all intensively treated patients received dietary advice and they were randomly allocated to receive either insulin, sulphonylurea or metformin, whereas all conventionally treated patients, besides the target of fasting plasma glucose below 15 mmol/L and who were without symptoms of hyperglycaemia, only received dietary advice (UKPDS 1998). In three trials the participants were randomised into intensive multimodal treatment of various risk factors, including differences in glycaemic treatment target values (Guo 2008; Steno-2 2008; Yang 2007). Two trials had more than two intervention groups. We only extracted data from two intervention groups in these trials (DIGAMI 2 2005; UGDP 1975). In both trials we extracted the data from the most intensive treatment group and from the conventional treatment group. The 'Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction' (DIGAMI) 2 trial had three intervention groups. We have used the data for group 1 as targeting intensive glycaemic control and group 3 as targeting conventional glycaemic control. All other concomitant interventions were identical for the groups (DIGAMI 2 2005). The 'University Group Diabetes Program' (UGDP) randomised the participants to five different therapeutic regimens: insulin variable, insulin standard, tolbutamide, phenformin, or placebo. We chose to report the insulin variable (IVAR) group as the intensive group and insulin standard (ISTD) group as the conventional group (UGDP 1975).

The included trials were mainly conducted in Northern America and Europe. The number of study centres ranged from 1 to 215. Three trials were multinational (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005).

The mean duration of the intervention period varied from three days (Stefanidis 2003) to 12.5 years (UGDP 1975). Three of the included trials reported a longer follow-up period than the intervention period (ACCORD 2008; Steno-2 2008; UKPDS 1998). For the Steno-2 trial, we have reported the outcomes to the longest follow-up time because the follow-up was complete for all par-

ticipants (Steno-2 2008). We did not include the results of the longest follow-up for the UKPDS because a relatively small proportion of the randomised participants were included in the follow-up analyses (UKPDS-80 2008). The microvascular complications reported from the ACCORD trial were from the longest follow-up, that is 1.5 years after termination of the glucose arm of the trial (ACCORD 2008). The Kumamoto trial had planned an intervention duration of six years (Kumamoto 2000). Only two of the included 110 participants changed their glycaemic intervention regimen after the predefined intervention period and the trial continued through the initiative of the participants. Because only two participants changed therapy, we reported all data except for mild hypoglycaemia (data not available) after 10 years of follow-up (Kumamoto 2000).

Trial participants

Four trials did not describe how the T2D diagnosis was established (ADVANCE 2008; Jaber 1996; Lu 2010; REMBO 2008). In the UGDP trial, T2D diagnosis was based on the sum of four glucose values from a glucose tolerance test. As a result of this definition, participants with impaired glucose tolerance were included in the trial (UGDP 1975). According to the diagnostic criteria of T2D established in 1989 by ADA and the World Health Organization (WHO), three participants in each of the intervention groups included in our analysis would have been diagnosed as having normal glucose levels. Thirty-one participants in the conventional treatment and 28 participants in the intensive treatment group fulfilled the criteria for impaired glucose tolerance. The main criterion for diagnosis in the UKPDS was based on two fasting glucose values (UKPDS 1998). This definition of T2D was less stringent than the WHO criteria (WHO 1985). All participants in the UGDP and UKPDS had a dietary run-in period of four weeks and three months, respectively. In the UGDP, participants who developed symptomatic hyperglycaemic were excluded. In the UKPDS, the participants with fasting blood glucose of 6.1 to 15.0 mmol/L after three months on a diet were randomised to UKPDS 33 and UKPDS 34. In the VADT trial, 127 participants failed to reach the diagnostic C-peptide level (VADT 2009).

The mean age of the participants of the included trials was 62.1 years (varying from 49.1 years to 68.2 years) (DIGAMI 2 2005; Guo 2008).

The duration of T2D at entry into the trials ranged between newly diagnosed to a mean disease duration of 15 years (Stefanidis 2003). Established T2D diagnosis within one year before entry into the trial was an inclusion criterion in four trials (Guo 2008; UGDP 1975; UKPDS 1998; Yang 2007). The risk profile with respect to cardiovascular disease among the trial participants was very different at entry in the included trials. Five trials had as an inclusion criterion for ongoing cardiovascular disease (DIGAMI 2 2005; IDA 2009; Melidonis 2000; REMBO 2008; Stefanidis 2003). In the REMBO trial all participants had congestive heart failure (REMBO 2008). Three trials had as a part of the inclusion criteria high risk of cardiovascular disease (besides T2D) (ACCORD 2008; ADVANCE 2008; Steno-2 2008). The Steno-2 and Lu et al trials were the only included trials that had microalbuminuria as an inclusion criterion (Lu 2010; Steno-2 2008). The Kumamoto trial stratified the participants into two groups: a primary prevention population and a secondary intervention population. All participants in the primary prevention population had no microvascular disease at baseline whereas all in the secondary intervention population had either microalbuminuria or retinopathy (Kumamoto 2000).

Most exclusion criteria consisted of liver disease, kidney disease, or other severe concurrent illness.

Characteristics of interventions

The anti-diabetic interventions used in the trials often included add-on regimens consisting of several oral anti-diabetic interventions. If these regimens could not reach the glycaemic target, then insulin was initiated. The usual add-up regimen was identical in the intensive and conventional intervention groups of the trials, except in three trials where participants targeting intensive glucose control were given gliclazide (ADVANCE 2008; REMBO 2008) or a sulphonylurea (glibenclamide, chlorpropamide, or glipizide), metformin, or insulin (UKPDS 1998). Gliclazide was discontinued in the participants randomised to conventional glycaemic target in the ADVANCE trial (ADVANCE 2008). The combination of oral anti-diabetic interventions and insulin was allowed in most trials. Two trials only allowed insulin monotherapy in both the intensive intervention group and the conventional intervention group (Kumamoto 2000; UGDP 1975). One trial allowed combination therapy in the conventional group but only insulin in the intensive treatment group (Melidonis 2000). One trial allowed combination therapy in the intensive intervention group, but not in the conventional intervention group (VA CSDM 1995). One trial did not specify in detail what the next treatment step would be in the intensive treatment group if the maximum dose of sulphonylurea could not keep the glycaemic target (Jaber 1996). Trials which had acute cardiovascular disease as an inclusion criterion had a treatment algorithm for insulin infusion for the intensive intervention group, starting at hospital admission (DIGAMI 2 2005; Melidonis 2000; Stefanidis 2003).

The median dose of insulin used in the intensive intervention group was 0.6 (range 0.4 to 1.0) units of insulin/day/kg body weight (ADVANCE 2008; Bagg 2001; Kumamoto 2000; Steno-2 2008; VA CSDM 1995; VADT 2009). The median dose of insulin in the conventional intervention group was 0.5 (range 0.4 to 0.8) units of insulin/day/kg body weight (see 'Interventions in trials', Appendix 2).

The treatment targets for glycaemic control varied between trials in both the intensive treatment groups and the conventional treatment group. The ACCORD and VADT had the lowest HbA1c

target level in the intensive intervention groups (both less than 6%) (ACCORD 2008; VADT 2009). Some of the trials did not predefine the glycaemic target in values of HbA1c but employed fasting glucose concentration as the treatment target (Becker 2003; DIGAMI 2 2005; Guo 2008; Jaber 1996; Lu 2010; UGDP 1975; UKPDS 1998). Two trials only defined targets for blood glucose, without further specification of when the blood glucose was taken (Melidonis 2000; Stefanidis 2003). One trial reported glycaemic control by glycosylated haemoglobin (Jaber 1996). Many trials did not specify the target value for conventional glycaemic control. The Steno-2 trial intensified the glycaemic target in the conventional intervention group for the last two years of the intervention period. This change made the glycaemic target the same for the intensive and the conventional treatment group (Steno-2 2008).

Outcome measures of included trials

For details see Summary of findings for the main comparison, Table 1, Appendix 2; Appendix 3, Appendix 4, Appendix 5, Appendix 6 and Appendix 7.

All-cause mortality or cardiovascular mortality were a predefined outcome or a part of the predefined composite outcome in eight trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Steno-2 2008; UGDP 1975; UKPDS 1998; VA CSDM 1995; VADT 2009). The Kumamoto trial did not predefine mortality as an outcome in the planned intervention period of six years but assessed mortality as an outcome after 10 years (Kumamoto 2000).

Complications related to T2D, either microvascular or macrovascular, were a predefined outcome in nine trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Kumamoto 2000; Steno-2 2008; UGDP 1975; UKPDS 1998; VA CSDM 1995; VADT 2009).

Moderate hypoglycaemia was mostly reported together with mild hypoglycaemia, but two trials reported moderate hypoglycaemia separately (Melidonis 2000; Stefanidis 2003).

Patient satisfaction, general well-being or quality of life were assessed in six trials (Becker 2003; Jaber 1996; REMBO 2008; Steno-2 2008; UKPDS 1998; VA CSDM 1995). Other trials had quality of life defined as an outcome but the results are not yet available (ACCORD 2008; ADVANCE 2008; VADT 2009).

Some of the included trials (n = 11) did not predefine any of the outcomes we predefined as primary or secondary outcomes but assessed non-validated surrogate outcomes. It was possible to extract data on some of our predefined outcomes in most of these trials (Bagg 2001; Becker 2003; Guo 2008; IDA 2009; Jaber 1996; Lu 2010; Melidonis 2000; REMBO 2008; Service 1983; Stefanidis 2003; Yang 2007).

Excluded studies

Reasons for exclusion of studies are given in 'Characteristics of excluded studies'. Thirty-one studies were excluded after further evaluation. In two cases, we contacted the authors of the articles to identify whether there were predefined differences in glycaemic target (Chan 2009; Olivarius 2001). Main reasons for exclusion were: the trial was not randomised (n = 11), participants were not patients with T2D or we could not separate data on those patients with T2D (n = 4), or no predefined differences in the glycaemic treatment target existed (n = 16).

Risk of bias in included studies

The risk of bias assessment of the included trials was performed using previously described criteria (please see section, 'Assessment of risk of bias in included studies'). For details of the judgements made for the individual trials, please see 'Risk of bias in included studies', Figure 2, and Figure 3. When a risk of bias domain could not be judged as low risk of bias, the authors were asked for additional information.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

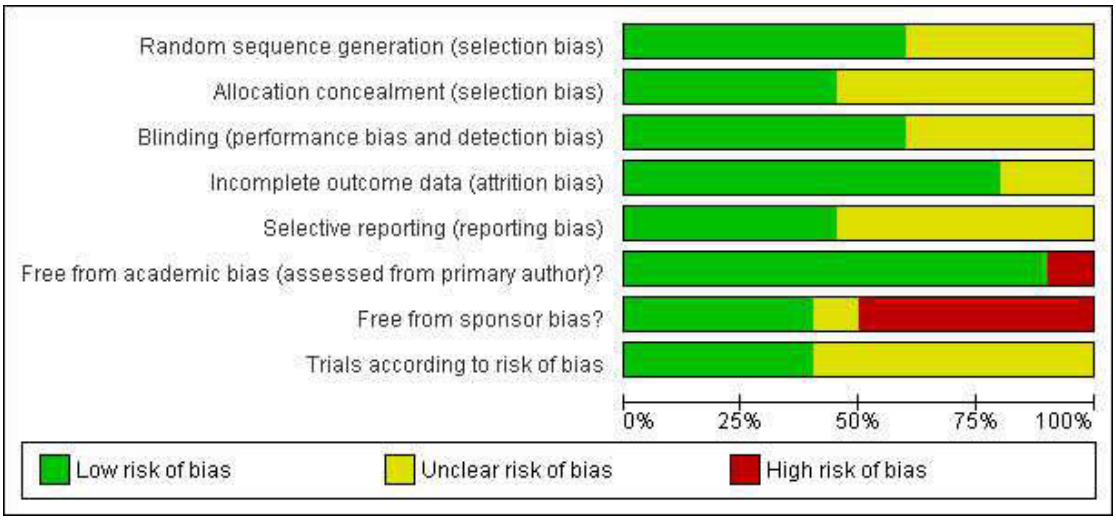
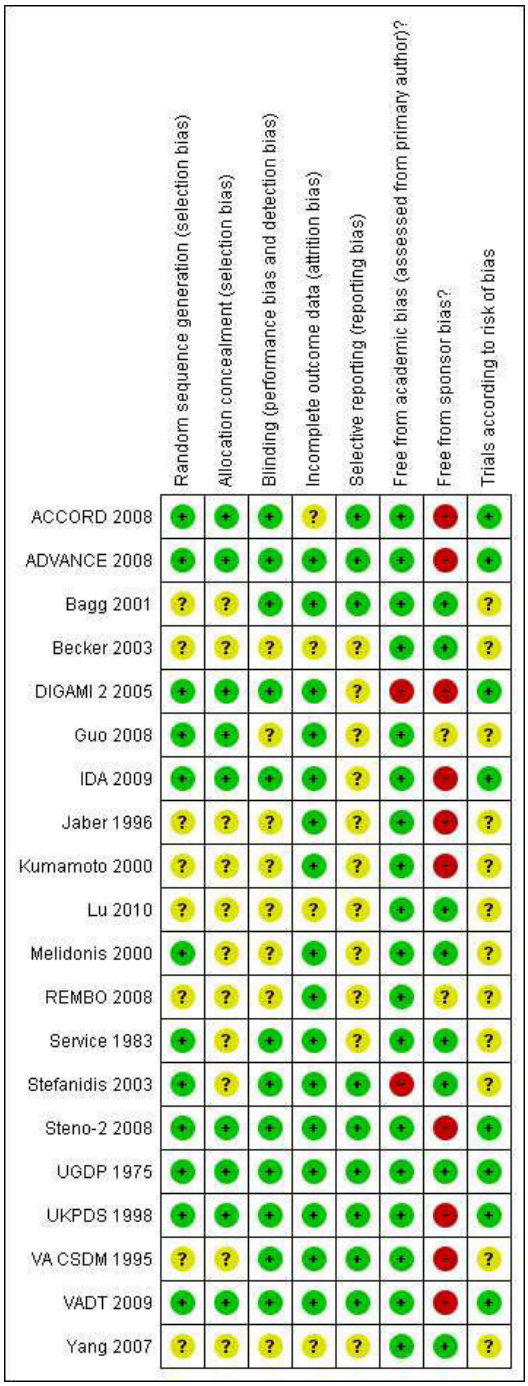


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Sequence generation

The generation of the allocation sequence was adequately described in 12 trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Guo 2008; IDA 2009; Melidonis 2000; Service 1983; Stefanidis 2003; Steno-2 2008; UGDP 1975; UKPDS 1998; VADT 2009). The remaining trials were described as randomised but the method for sequence generation was not described (Bagg 2001; Becker 2003; Jaber 1996; Kumamoto 2000; Lu 2010; REMBO 2008; VA CSDM 1995; Yang 2007).

Allocation

The method used to conceal allocation was adequately described in nine trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Guo 2008; IDA 2009; Steno-2 2008; UGDP 1975; UKPDS 1998; VADT 2009). The method for allocation concealment was judged as unclear in 11 trials (Bagg 2001; Becker 2003; Jaber 1996; Kumamoto 2000; Lu 2010; Melidonis 2000; REMBO 2008; Service 1983; Stefanidis 2003; VA CSDM 1995; Yang 2007).

Blinding

The method of blinding was adequately described in 13 trials (ACCORD 2008; ADVANCE 2008; Bagg 2001; DIGAMI 2 2005; IDA 2009; Melidonis 2000; Service 1983; Stefanidis 2003; Steno-2 2008; UGDP 1975; UKPDS 1998; VA CSDM 1995; VADT 2009). The method of blinding was unclear in seven trials (Becker 2003; Guo 2008; Jaber 1996; Kumamoto 2000; Lu 2010; REMBO 2008; Yang 2007).

Incomplete outcome data

Incomplete data were addressed adequately in the included trials except for four trials (ACCORD 2008; Becker 2003; Lu 2010; Yang 2007).

Selective reporting

The Kumamoto trial was continued through the initiative of the participants and more outcomes were therefore assessed than predefined in the primary article (Kumamoto 2000). For eleven of the included trials the risk of selective outcome reporting bias was judged as unclear (Becker 2003; DIGAMI 2 2005; Guo 2008; IDA 2009; Jaber 1996; Kumamoto 2000; Lu 2010; Melidonis 2000; REMBO 2008; Service 1983; Yang 2007). For the other trials the risk of selective outcome reporting bias was judged as low.

Other potential sources of bias

Most trials received funding from a private health insurance company or the medical industry to conduct the trial.

We divided the trials into those with a low risk of bias and a high risk of bias based on the assessment of sequence generation, allocation concealment, and blinding. The three bias domains were all assessed as low risk of bias in eight trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; IDA 2009; Steno-2 2008; UGDP 1975; UKPDS 1998; VADT 2009).

Effects of interventions

See: **Summary of findings for the main comparison** Intensive glycaemic control compared to conventional glycaemic control for type 2 diabetes mellitus

Primary outcomes

All-cause mortality

Several trials predefined death from any cause as the primary or secondary outcome (see section 'Description of studies'). Eighteen trials provided information on all-cause mortality and could be included in the analyses. The included trials reported 2809 deaths in 29,731 participants (Analysis 1.1). Meta-analyses with both the fixed-effect model and random-effects model showed no significant effect of intensive glycaemic control (random RR 1.01, 95% CI 0.90 to 1.13; 29,731 participants, 18 trials) (Analysis 1.1). Heterogeneity was moderate (I^2 = 40%, P = 0.08). One trial reported three deaths after the randomisation (Becker 2003), however the report did not describe to which intervention group the participants were randomised to or the cause of death. It was therefore not possible to use data on death from this trial.

Inspection of the funnel plot did not indicate bias (Analysis 1.1).

Repeating the analyses with the trials having an HbA1c target of 7% in the intensive intervention group did not change the results to significant values (random RR 0.69, 95% CI 0.27 to 1.74; I^2 = 0%) (Bagg 2001; Guo 2008; Kumamoto 2000; REMBO 2008; Yang 2007). Three of these trials were conducted in Asia and contributed only 17 events in 543 participants.

Because there was no statistically significant difference in the effect estimates between the intervention groups, and modest heterogeneity, the predefined subgroup analyses were not performed (see section 'Subgroup analysis and investigation of heterogeneity').

The subgroup analyses stratifying the trials according to risk of bias, study duration, diagnostic criteria, or funding source did not reveal any significant differences in effect estimates in the risk of all-cause mortality (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis

1.5). A test of interaction showed no significance between the subgroups. Because of lack of data, we were not able to conduct subgroup analyses on the trials published in languages other than English.

In stratifying for diagnostic criteria we chose to stratify according to whether the diagnostic criteria for T2D were described or not (Analysis 1.4).

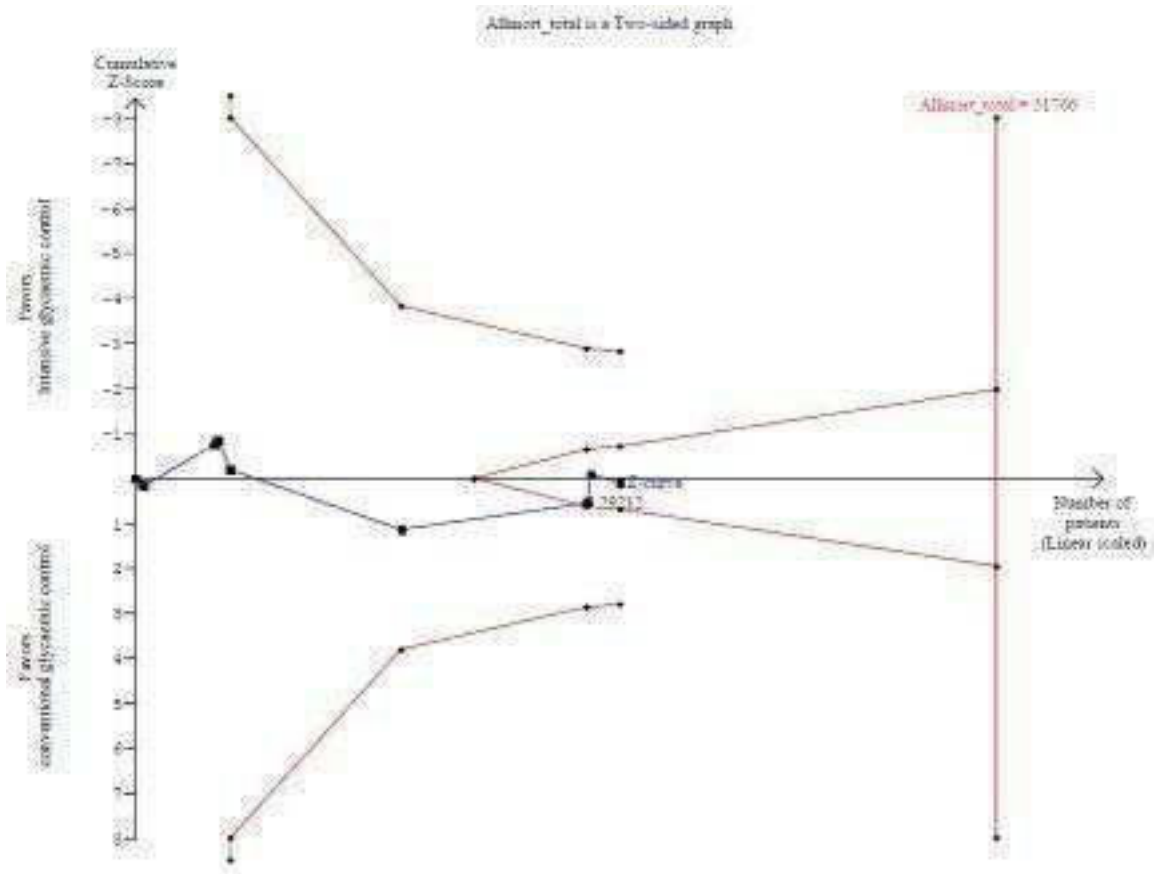
Subgroup analyses stratifying the included trials according to the intervention (trials exclusively dealing with glycaemic control in usual care setting, glycaemic control as a part of acute intervention, or multimodal intervention in usual care setting) were performed. The trials exclusively dealing with glycaemic control in the usual care setting showed no significant effect of the intervention (random RR 1.02, 95% CI 0.91 to 1.13; 28,359 participants, 12 trials) (Analysis 1.6). Heterogeneity was moderate (I^2 = 30%, P = 0.18). Trials applying intensive glycaemic control as an acute intervention showed a non-significant tendency to favour conventional glycaemic control (random RR 1.21, 95% CI 0.92 to 1.60; 903 participants, 3 trials) (Analysis 1.6). Heterogeneity was absent (I^2 = 0%, P = 0.99). One hundred and seventy of the 174 reported deaths were from the DIGAMI 2 trial. A test of interaction between the subgroups did not show any significance. Separate analyses of multimodal intervention in the usual care setting could not be performed as only the Steno 2 trial provided data.

We also performed a meta-analysis of trials with available hazard ratios (HR) for all-cause mortality. Neither the fixed-effect model nor the random-effects model showed significant differences between the interventions (random HR 0.96, 95% CI 0.74 to 1.23; 5 trials) (Analysis 1.7). However, there was considerable inter-trial heterogeneity (I^2= 82%, P = 0.0002). All trials included in the analyses, except the ACCORD trial, provided an unadjusted HR (ACCORD 2008). The HR available from the ACCORD trial was adjusted for the following variables: assignment to the blood pressure trial or the lipid trial, assignment to the intensive blood pressure intervention in the blood pressure trial, assignment to receive fibrate in the lipid trial, the seven clinical centre networks, and a previous cardiovascular event. Excluding the ACCORD trial did not influence the heterogeneity and did not change the effect estimate to give significant values. When excluding the Steno-2 trial, which assessed a multimodal intervention in the usual care setting, heterogeneity decreased (I^2 = 50%, P = 0.0002). The effect estimate remained non-significant (random RR 1.07, 95% CI 0.90 to 1.26).

Available case analysis did not result in any significant changes of effect estimates (random RR 1.01, 95% CI 0.90 to 1.14; 29,382 participants, 18 trials) (Analysis 1.8). Analysing the missing data as the best-case scenario (assuming that participants with unknown vital status receiving intensive glycaemic control were alive and that all participants receiving the conventional intervention with unknown vital status were dead) or worst-case scenario (assuming that participants with unknown vital status receiving intensive glycaemic control were dead and all participants with unknown vital status receiving conventional intervention were alive) did not reveal any statistical significance in effect estimates applying the random-effects model (best-case scenario: random RR 0.90, 95% CI 0.81 to 1.00; 29,731, 18 trials (Analysis 1.9); worst-case scenario: random RR 1.15, 95% CI 0.93 to 1.42; 29,731, 18 trials (Analysis 1.10)). The fixed-effect model for a best-case scenario showed a significant effect estimate favouring targeting intensive glycaemic control (fixed RR 0.90, 95% CI 0.84 to 0.96; P = 0.003; 29,731 participants, 18 trials) (Analysis 1.9). The worst-case scenario showed a significant effect in favour of conventional glycaemic control when applying the fixed-effect model (fixed RR 1.14, 95% CI 1.06 to 1.22; P = 0.0002; 29,731, 18 trials) (Analysis 1.10).

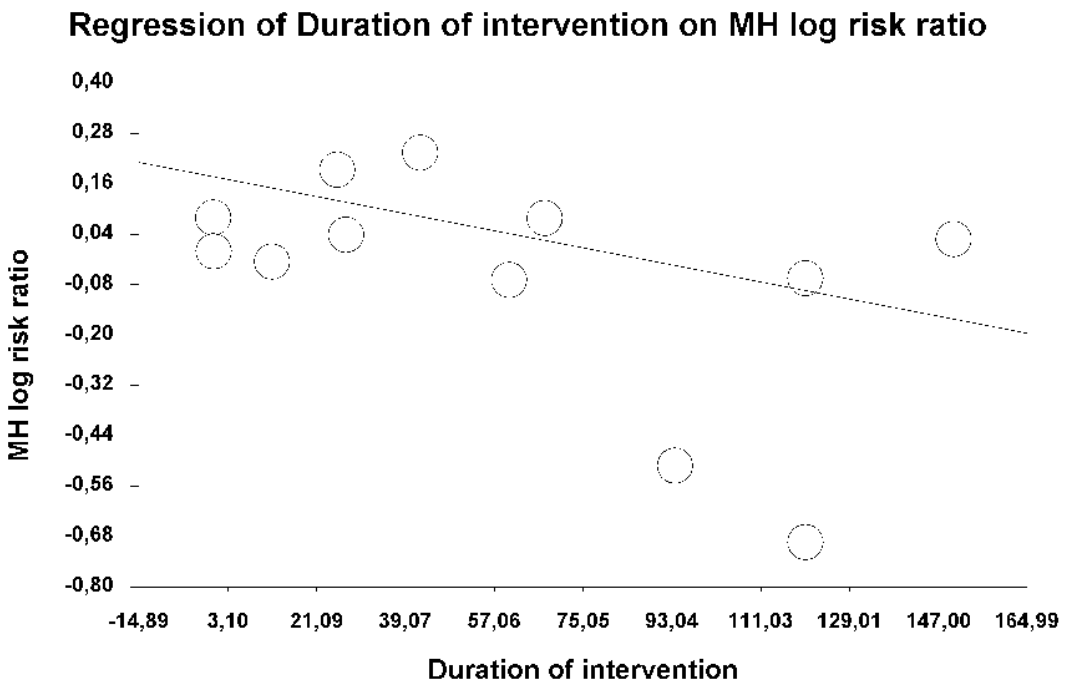
Trial sequential analysis with data from all included trials showed that only 29,212 patients of the required heterogeneity-adjusted information size of 51,766 were accrued and no firm evidence for benefit or harm was reached (Figure 4). The cumulative Z-curve crossed the futility boundaries suggesting that a 10% or greater relative risk reduction could be rejected at this point. Continuity correction of zero-event trials did not change the result. Applying trial sequential analysis on all-cause mortality from trials exclusively dealing with glycaemic control in usual care settings showed that no evidence of benefit or harm could be established on all-cause mortality as only 28,149 participants (60%) of the 46,677 required were accrued so far.

Figure 4. Trial sequential analysis of the random-effects meta-analysis of the effect of intensive glycaemic control versus conventional glycaemic control on all-cause mortality. The trial sequential analysis is performed with a type 1 error risk of 5% (two-sided), a power of 80%, an assumed control proportion of death of 8.8%, and an anticipated relative risk reduction (RRR) of 10%. The heterogeneity-adjusted required information size to detect or reject a RRR of 10% with a between trial heterogeneity of 40% is estimated to 51,766 participants. The actually accrued number of participants is 29,212, which is only 56% of the required information size. The blue cumulative z-curve does not cross the red trial sequential monitoring boundaries for benefit or harm. However, the boundaries for futility (the red inner wedge boundaries) are crossed. Accordingly, the red conventional boundaries (horizontal line at z=1.96 and z=-1.96) for harm or benefit are not crossed. Therefore, there is no evidence to support that intensive glycaemic control influences mortality and it is likely that a 10% RRR of mortality can be rejected with the chosen error risks.



Meta-regression for all the trials did not detect a statistically significant association between disease duration, fasting blood glucose at baseline, HbA1c at baseline and mortality. However, the duration of intervention may have some impact as the univariate meta-regression showed a trend towards a negative association between duration of the intervention and the risk ratio of all-cause mortality (P = 0.09) (Figure 5). This suggests that the RR may decrease (beneficial intervention effect increase or harmful effect decrease) when the duration of the intervention is increased. Meta-regression for the trials exclusively dealing with glycaemic control in usual care settings showed a positive correlation between fasting blood glucose as well as HbA1c at baseline and the risk ratio for all-cause mortality, suggesting that RR may increase when the fasting blood glucose as well as HbA1c at baseline increase.

Figure 5. Meta-regression: Y-axis: Risk ratio for all-cause mortality; X-axis: Duration of intervention (months). The meta-regression shows a tendency to a negative correlation for the risk ratio for all-cause mortality and duration of the intervention. Slope: -0.00226; P = 0.08737.



Cardiovascular mortality

Several trials predefined cardiovascular mortality as the primary or secondary outcome (see section 'Description of studies' and Appendix 4). A total of 18 trials provided information on cardiovascular mortality and were included in the analyses. A total of 1482 cardiovascular deaths in 29,731 participants were included in the meta-analysis (Analysis 1.11).

Neither the random-effects model nor the fixed-effect model showed a significant difference in effect estimates between intensive glycaemic control and conventional glycaemic control (random RR 1.06, 95% CI 0.90 to 1.26; I^2 = 37%, P = 0.09; 29,731 participants, 18 trials) (Analysis 1.11).
The funnel plot showed slight asymmetry (Analysis 1.11).

By excluding the ACCORD and VADT trials, heterogeneity fell to 10% (P = 0.35). The ACCORD and VADT trials were the two trials with the lowest HbA1c target values in the intensive intervention groups. The effect estimate did not change to significant values (random RR 0.98, 95% CI 0.85 to 1.13).
When excluding the largest trial, the ADVANCE trial contributing 11,140 participants, there was a significant benefit of targeting conventional glycaemic control (random RR 1.18, 95% CI 1.03 to 1.34; P = 0.01; I^2 = 0%).
Subgroup analyses stratifying the trials according to risk of bias, study duration, and funding source did not reveal any significant differences in effect estimates for cardiovascular mortality (Analysis 1.12; Analysis 1.13; Analysis 1.15). Trials describing the diagnostic criteria for T2D changed the effect estimate to significant values in favour of conventional control (random RR 1.17, 95% CI 1.02 to 1.35; P = 0.02) (Analysis 1.14). The test of interaction between the subgroups stratifying the trials according to diagnostic criteria showed significance (P = 0.03). No significance was shown with the test of interaction for the remaining subgroups.
Because of lack of data, we were not able to conduct subgroup analyses on the trials not published in English.
A meta-analysis of the 12 trials investigating the effect of intensive glycaemic control in trials exclusively dealing with glycaemic control in usual care settings showed no significant difference in effect estimates (random RR 1.11, 95% CI 0.92 to 1.35; 28,359 participants, 12 trials) (Analysis 1.16). Heterogeneity was moderate (I^2 = 46%, P = 0.08). Analysing trials assessing glycaemic control as a part of an acute intervention showed no significance in the effect estimate (random RR 1.06, 95% CI 0.78 to 1.44; 903 participants, 3 trials) (Analysis 1.16). One hundred and forty of the 144 deaths were reported in the DIGAMI 2 trial (DIGAMI 2 2005). The test of interaction showed no significance between the trials exclusively dealing with glycaemic control in usual care settings and the trials assessing glycaemic control as part of an acute intervention. In trials assessing multimodal intervention in usual care settings only the Steno-2 trial provided data, so meta-analysis could not be performed.
The random-effects model showed no significant difference in benefit targeting intensive glycaemic control using hazard ratios (HR) (random RR 0.88, 95% CI 0.56 to 1.38; 4 trials) (Analysis 1.17). Inter-trial heterogeneity was substantial (I^2 = 86%, P = 0.0001). Meta-analysis of the data using a fixed-effect estimate showed significant benefit of intensive glycaemic control (fixed RR 0.87, 95% CI 0.76 to 0.99; P = 0.03). All trials included in the analyses, except the ACCORD, provided an unadjusted HR (ACCORD 2008). Excluding the Steno-2 trial from the analysis reduced heterogeneity to 64% and neither the random-effects model nor the fixed-effect model effect model showed significant effect estimates (random RR 1.09, 95% CI 0.78 to 1.53).
Available case analyses did not result in any significant differences between the effect estimates (Analysis 1.18). When analysing the missing data as a best-case scenario (random RR 0.87, 95% CI 0.74 to 1.01; 29,731 participants, 18 trials) (Analysis 1.19) or worst-case scenario (random RR 1.15, 95% CI 0.93 to 1.42; 29,731 participants, 18 trials) (Analysis 1.20) in the random-effects model, no significant effect estimates were shown. When applying the fixed-effect model to the best-case analysis, significant benefit of intensive glycaemic control was shown (fixed RR 0.86, 95% CI 0.78 to 0.95; 29,731 participants, 18 trials) (Analysis 1.19). The worst-case scenario showed a significant effect estimate favouring conventional glycaemic control (fixed RR 1.32, 95% CI 1.20 to 1.45; 29,731 participants, 18 trials) (Analysis 1.20).
Trial sequential analysis for all included trials showed a lack of firm evidence for a benefit of targeting intensive glycaemic control for the reduction of cardiovascular mortality. Merely 29,212 of 100,707 required patients are randomised at this point. That is, only 29% of the required heterogeneity-adjusted information size to detect or reject a 10% relative risk increase (RRI) were actually accrued in randomised trials so far. For trials reporting cardiovascular mortality and exclusively dealing with glycaemic control in usual care settings barely 22% of required information size is accrued so far.
Meta-regressions for all trials and for the subgroup of trials exclusively dealing with glycaemic control in usual care settings could not detect any statistical significant association between duration of disease at baseline, fasting blood glucose at baseline, HbA1c at baseline, or duration of the intervention and cardiovascular mortality.

Secondary outcomes

Macrovascular complications

We predefined a composite outcome of macrovascular complications as a secondary outcome (non-fatal myocardial infarction, non-fatal ischaemic stroke, non-fatal haemorraghic stroke, amputation of lower extremity, and cardiac or peripheral revascularization). The definition of macrovascular disease as a composite outcome was clearly predefined in six trials (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Steno-2 2008; VA CSDM 1995; VADT 2009). The definition varied between trials (Appendix 4). The ACCORD and ADVANCE trials, which contributed most events, included non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes (ACCORD 2008; ADVANCE 2008). The UKPDS assessed diabetes-related complications as a composite outcome, which included both

macrovascular and microvascular complications (UKPDS 1998). The UKPDS only reported a composite outcome of macrovascular disease for the metformin group compared with the other groups; it did not report this outcome for the other intensive groups compared with the conventional group (UKPDS 1998). The composite macrovascular outcome (myocardial infarction, sudden death, angina, stroke, peripheral disease) reported in the UKPDS 34 showed a 30% risk reduction with metformin therapy compared with conventional therapy (P = 0.02). Unfortunately the number of participants was not reported. The number of participants with the composite macrovascular complications for UKPDS was therefore taken from the meta-analysis in Turnbull et al (Turnbull 2009). Three trials did not predefine assessment of a composite macrovascular outcome but it was possible to extract useable data (Bagg 2001; Becker 2003; Kumamoto 2000). The IDA 2009 trial reported a total of 17 participants who received a new percutaneous coronary intervention, coronary bypass surgery, or had symptoms of angina (IDA 2009). From the publication it could not be concluded which group the participants belonged to. The number of patients with cardiovascular disease from Becker et al was calculated as the number of patients with a history of cardiovascular disease at baseline minus the number of patients with cardiovascular disease at follow-up (Becker 2003). Many of the included trials reported a composite macrovascular outcome together with death due to cardiovascular disease or all-cause mortality (ACCORD 2008; ADVANCE 2008; DIGAMI 2 2005; Steno-2 2008).

Meta-analysis of data from 10 trials did not reveal any significant difference in the effect of intensive versus conventional intervention on the composite macrovascular outcome (random RR 0.92, 95% CI 0.80 to 1.05; 28,509 participants, 10 trials) (Analysis 1.21). Heterogeneity was substantial (I^2 = 61%, P = 0.006).

Subgroup analysis stratifying the trials according to the intervention could only be performed for trials exclusively dealing with glycaemic control in usual care settings. Neither the random-effects model nor the fixed-effect model revealed significant effect estimates (random RR 0.93, 95% CI 0.85 to 1.01; I^2 = 18%, P = 0.09; 27,569 participants, 8 trials) (Analysis 1.22). The analysis could not be performed for trials assessing glycaemic control as a part of an acute intervention and trials assessing multimodal intervention in usual care settings due to lack of data.

Non-fatal myocardial infarction

A total of 1384 non-fatal myocardial infarctions were recorded in 29,174 participants (Analysis 1.23). There was no significant effect of intensive glycaemic control in the random-effects model (random RR 0.86, 95% CI 0.76 to 1.00; 29,174 participants, 12 trials). However, the fixed-effect model showed a significant relative risk reduction when targeting intensive glycaemic control compared with conventional glycaemic control (fixed RR 0.86, 95% CI 0.78 to 0.96 (P = 0.006); RD -0.01, 95% CI -0.01 to 0.00; 29,174 participants, 12 trials) (Analysis 1.23). Heterogeneity might not be important (I^2 = 28%, P = 0.19).

The funnel plot did not raise any suspicion of bias (Analysis 1.23).

The details on how the diagnosis of myocardial infarction was established varied between trials. Eight trials provided detailed information on how they defined myocardial infarction (ACCORD 2008; DIGAMI 2 2005; Melidonis 2000; Steno-2 2008; UGDP 1975; UKPDS 1998; VA CSDM 1995; VADT 2009) (Appendix 4). Combining the data from these trials, the effect estimate was still only significant in favour of intensive glycaemic control in the fixed-effect model (random RR 0.84, 95% CI 0.71 to 1.00; fixed RR 0.83, 95% CI 0.74 to 0.94 (P= 0.002)). Heterogeneity was moderate but not statistically significant (I^2 = 36%, P = 0.14). Six trials had non-fatal myocardial infarction as part of the primary outcome (ACCORD 2008; ADVANCE 2008; Steno-2 2008; UGDP 1975; UKPDS 1998; VADT 2009). In a meta-analysis of the six trials both the random-effects model and the fixed-effect model revealed significant effect estimates (random RR 0.83, 95% CI 0.72 to 0.96 (P = 0.01); fixed RR 0.84, 95% CI 0.75 to 0.93 (P = 0.001)). Heterogeneity was moderate (I^2 = 31%, P = 0.20).

In the ACCORD trial almost all participants in the intensive group and more than half in the conventional group received rosiglitazone. Excluding the ACCORD trial from the analysis, neither the random-effects nor the fixed-effect model showed significant benefit of targeting intensive glycaemic control (random RR 0.89, 95% CI 0.75 to 1.06). In the ADVANCE trial more participants in the intensive intervention arm, compared with the conventional intervention arm, also received rosiglitazone. Sensitivity analysis excluding both the ACCORD and the ADVANCE trials showed no significant intervention effect (random RR 0.86, 95% CI 0.69 to 1.08).

Three trials had admission to hospital with acute myocardial infarction or unstable angina as an inclusion criterion (DIGAMI 2 2005; Melidonis 2000; Stefanidis 2003). Because all participants had an acute myocardial infarction, we used the number of re-infarctions when meta-analysing these trials. By excluding these trials from the analysis the benefit of targeting intensive glycaemic control was also present in the random-effects model (fixed RR 0.84, 95% CI 0.75 to 0.93 (P = 0.006); RD -0.01 95% CI -0.01 to 0.00). Heterogeneity fell (I^2 = 18%, P = 0.30). All the participants with hospital admission at entry and targeting intensive glycaemic control had their blood glucose initially lowered with insulin (DIGAMI 2 2005; Melidonis 2000; Stefanidis 2003).

Subgroup analyses stratifying the trials according to risk of bias, study duration, diagnostic criteria, or funding source did not reveal any significant differences in the effect estimates of non-fatal myocardial infarction applying random-effects model to the data (trials with long study duration: random RR 0.87, 95% CI 0.74 to 1.02 (Analysis 1.24); low-risk of bias trials: random RR 0.87, 95% CI 0.74 to 1.03 (Analysis 1.25); industry-funded: random RR 0.86, 95% CI 0.72 to 1.02 (Analysis 1.26)). The fixed-effect model showed significant effect estimates favouring intensive gly-

caemic control in trials with long study duration (fixed RR 0.86, 95% CI 0.78 to 0.96; P = 0.007; 29,008 participants, 9 trials) (Analysis 1.24); low risk of bias (fixed RR 0.87, 95% CI 0.78 to 0.96; P = 0.007; 28,745 participants, 7 trials) (Analysis 1.25); and industry-funding (fixed RR 0.86, 95% CI 0.77 to 0.96; P = 0.006, 28,594 participants, 8 trials) (Analysis 1.26). The trials describing how the diagnosis of T2D was performed showed a significant effect estimate favouring intensive glycaemic control (random RR 0.84, 95% CI 0.72 to 0.99; P = 0.002; 18,034 participants, 11 trials) (Analysis 1.27). The test of interaction showed no significance between the subgroup analyses.

Subgroup analyses stratifying the trials according to intervention were performed. The trials exclusively dealing with glycaemic control in usual care settings showed significant benefit of targeting intensive glycaemic control (random RR 0.85, 95% CI 0.76 to 0.95; P = 0.004; 28,111 participants, 8 trials) (Analysis 1.28). Heterogeneity was absent (I^2 = 0%, P = 0.70). When excluding the ACCORD trial from the analysis, the significance of the effect estimate disappeared (random RR 0.88, 95% CI 0.77 to 1.01; I^2 = 0%, P = 0.71). Three trials were analysed in the subgroup of glycaemic control as a part of acute intervention. The effect estimate did not reveal any significant effect estimate (random RR 1.26, 95% CI 0.88 to 1.80; 903 participants, 3 trials) (Analysis 1.28). Heterogeneity was absent (I^2 = 0%, P = 0.74). The test of interaction between the trials exclusively dealing with glycaemic control in usual care settings and the subgroup of trials assessing glycaemic control as part of an acute intervention showed significance (P = 0.04). The only trial providing data on non-fatal myocardial infarction with multimodal intervention in usual care settings was the Steno-2 trial so subgroup analysis was not performed.

Available case analyses showed significant benefit of intensive glycaemic control (fixed RR 0.86, 95% CI 0.78 to 0.96; P = 0.005; 27,332 participants, 12 trials) (Analysis 1.29) but the effect disappeared when applying the random-effects model (random RR 0.87, 95% CI 0.75 to 1.00). Analysing the missing data as a best-case scenario or worst-case scenario showed significance of the effect estimates (worst-case scenario: random RR 1.77, 95% CI 1.33 to 2.36; P < 0.0001; 29,174 participants, 12 trials (Analysis 1.30); best-case scenario: random RR 0.44, 95% CI 0.32 to 0.61; P < 0.00001 (Analysis 1.31)).

Trial sequential analysis showed a lack of firm evidence for benefit of targeting intensive glycaemic control for the reduction of non-fatal myocardial infarction. Only 29,021 patients (35%) have been accrued so far of the required heterogeneity-adjusted information size of 82,366 to detect a 10% relative risk reduction (RRR) of non-fatal myocardial infarction. Further, not even the futility boundaries were crossed, suggesting lack of evidence to reject a 10% RRR. Applying glycaemic control in trials exclusively dealing with glycaemic control in usual care settings were also not able to confirm a 10% RRR.

Neither the meta-regressions of all trials nor trials exclusively dealing with glycaemic control in usual care settings were able to detect a statistically significant association between duration of disease, fasting blood glucose at baseline, HbA1c at baseline, or duration of intervention and the risk of non-fatal myocardial infarction.

Non-fatal stroke

No significant difference was found for the risk of non-fatal stroke between the intervention groups (random RR 0.96, 95% CI 0.80 to 1.16; 28,760 participants, 11 trials) (Analysis 1.32). Heterogeneity might not be important (I^2 = 20%, P = 0.26). Of the 837 non-fatal strokes, 423 were reported from the ADVANCE trial (ADVANCE 2008). Originally we planned to report ischaemic and haemorrhagic stroke separately, but all trials except one (Kumamoto 2000) defined and reported both aetiologies for the non-fatal stroke composite. Five trials had non-fatal stroke as a part of their primary outcome (ACCORD 2008; ADVANCE 2008; Steno-2 2008; UKPDS 1998; VADT 2009). When meta-analysing these trials together, the effect estimate remained non-significant (random RR 0.93, 95% CI 0.74 to 1.17). For a description of stroke see Appendix 4.

In a separate meta-analysis of the trials exclusively dealing with glycaemic control in usual care settings the effect estimate remained non-significant (random RR 1.01, 95% CI 0.87 to 1.16; 27,697 participants, 7 trials) (Analysis 1.33). Heterogeneity was absent (I^2 = 0%, P = 0.73). It was not possible to meta-analyse data from trials assessing glycaemic control as a part of an acute intervention or a multimodal intervention in usual care settings due to lack of data.

Amputation of lower extremity

Meta-analysis showed a significantly reduced risk of amputation of a lower extremity when targeting intensive glycaemic control (random RR 0.64, 95% CI 0.44 to 0.95; P = 0.03; RD -0.01, 95% CI -0.01 to 0.00; 6960 participants, 8 trials) (Analysis 1.34). Heterogeneity was absent (I^2 = 0%, P = 0.59). However, the number of reported amputations was very low in both the intensive and conventional intervention groups (53 and 51, respectively). The UKPDS contributed almost half of the reported events (UKPDS 1998).

Four trials reported amputation of lower extremity without further description (Kumamoto 2000; Melidonis 2000; Stefanidis 2003; UGDP 1975). The Steno-2 and VA CSDM trials specified that the number for amputation was due to ischaemia, and the VADT specified amputation for ischaemic diabetic gangrene. UKPDS defined amputation as major limb complications requiring amputation of a digit or any limb for any reason. It is therefore not clear if the trials without further specification of amputation added minor amputation (for example a digit) to the reported number, as the UKPDS has done. Besides, the UKPDS included amputation for any reason, which was not the case for the VADT and Steno-2 trials. Accordingly, an amputation due to infection may not have

been reported as part of the outcome for the VADT and Steno-2, but would be for UKPDS. The different definitions of amputation of a lower extremity may explain the dominance of the UKPDS. It was unfortunately not possible to get reliable data from the two largest included trials (ACCORD 2008; ADVANCE 2008). Thus, it is very likely that amputation of a lower extremity is grossly under-reported.

Trial sequential analysis for all included trials showed that only 104 events, equalling 4.6% of the required sample size, have actually been accrued so far to establish firm evidence.

Stratifying the trials according to intervention could only be done for trials exclusively dealing with glycaemic control in usual care settings, which did not reveal a significant effect estimate (random RR 0.70, 95% CI 0.45 to 1.09; 6677 participants, 5 trials) (Analysis 1.35). Heterogeneity was absent (I^2 = 0%, P = 0.59).

Cardiac revascularization

The procedures used for cardiac revascularization were surgical revascularizations (for example artery by-pass grafting). The revascularization procedures in the DIGAMI 2 trial were primarily done as acute thrombolysis and it was not possible to extract the data regarding surgical revascularization (DIGAMI 2 2005). Stefanidis et al reported separately the number of participants with T2D and acute cardiovascular events undergoing invasive cardiovascular surgery (Stefanidis 2003). Melidonis et al, who also included participants with acute cardiovascular events and T2D, did not specify whether revascularization was surgical or medical; the number is therefore not included in the analyses (Melidonis 2000). The ADVANCE trial investigators reported coronary revascularization procedures as a part of the total coronary events. It was not possible to obtain the number of cardiac revascularizations as a separate number (ADVANCE 2008). Four trials reported cardial revascularization without further specifications (Kumamoto 2000; Stefanidis 2003; VA CSDM 1995; VADT 2009). The Steno-2 trial defined cardiac revascularization as coronary bypass-grafting (Steno-2 2008).

Of the 267 reported cardiac revascularization procedure, most were reported from the VADT trial (234 procedures) (VADT 2009). The effect estimate of the RR was not significant (random RR 0.84, 95% CI 0.67 to 1.05; 2289 participants, 5 trials) (Analysis 1.36). The I^2 was 0% (P = 0.74).

When stratifying the trials according to the intervention, it was only possible to investigate the subgroup consisting of trials exclusively dealing with glycaemic control in usual care settings. The effect estimate was not significant (random RR 0.85, 95% CI 0.67 to 1.07; 2054 participants, 3 trials) (Analysis 1.37). The I^2 was 0% (P = 0.67). There was a lack of data for trials with glycaemic control as part of an acute intervention and multimodal treatment.

Peripheral revascularization

A meta-analysis for peripheral revascularization did not reveal any significant differences in the effect of intensive versus conventional intervention (random RR 0.92, 95% CI 0.81 to 1.06; 13,477 participants, 7 trials) (Analysis 1.38). The ADVANCE contributed the majority of events (709 out of 768) (ADVANCE 2008). Unfortunately, the definition of peripheral revascularization was not described in the ADVANCE (ADVANCE 2008). We have therefore reported the peripheral vascular events without exactly knowing the definition used. It might be that amputation is reported as part of this outcome. The decision on when to intervene with peripheral revascularization might differ between both the trials and the study centres within each trial. The I^2 was 0% (P = 0.66).

When stratifying the trials according to the intervention, it was only possible to meta-analyse the subgroup consisting of trials exclusively dealing with glycaemic control in usual care settings. The effect estimate was not significant (random RR 0.93, 95% CI 0.81 to 1.07; 13,194 participants, 4 trials) (Analysis 1.39). Heterogeneity was absent (I^2 = 0%, P = 0.83). Meta-analysis of trials with glycaemic control as part of an acute intervention and multimodal intervention in usual care settings could not be conducted due to lack of data.

Microvascular complications

We predefined a composite outcome of microvascular complications as a secondary outcome (manifestation and progression of nephropathy, manifestation and progression of retinopathy, and retinal photocoagulation). It was possible to extract useable data from four trials that had predefined a composite microvascular outcome (ACCORD 2008; ADVANCE 2008; Steno-2 2008; UKPDS 1998). The Kumamoto trial did not report a composite microvascular outcome. On request, the authors gave us information on the total number of microvascular events after 10 years of follow-up (22 in the intensive group and 58 in the control group), but not the number of patients.

The definitions of the reported composite outcome varied between the included trials. In the Steno-2 trial microalbuminuria was an inclusion criterion. The reported composite outcome for microvascular disease was progression in any microvascular outcome during the follow-up period after 13.3 years (Steno-2 2008). This definition included both severe and less severe microvascular complications, for example onset of neuropathy and mild retinal changes. Neither the ADVANCE, ACCORD nor the UKPDS trials included neuropathy in their composite microvascular outcomes. The ADVANCE, ACCORD, and UKPDS trials included moderate to severe retinal events in their composite microvascular outcome (for example, development of proliferatives retinopathy, retinal photocoagulation). The nephropathy component of the composite microvascular outcome of the ADVANCE trial included development of macroalbuminuria, whereas the ACCORD and the UKPDS trials reported renal failure (Appendix 5) (ACCORD 2008).

We found benefit of targeting intensive glycaemic control compared with targeting conventional glycaemic control (random RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006; 25,760 participants, 4 trials) (Analysis 1.40). The I^2 was 17% (P = 0.31). The risk difference showed a non-significant result in the random-effects model. The magnitude of effect showed a 2% absolute risk reduction in the fixed-effect model (random RD -0.02, 95% CI -0.03 to -0.00; fixed RD -0.01, 95% CI -0.02 to -0.01; P = 0.001).

Analysing the trials exclusively dealing with glycaemic control in usual care settings showed significant effect estimates favouring intensive glycaemic control (random RR 0.88, 95% CI 0.79 to 0.97; P = 0.01; 25,600 participants, 3 trials) (Analysis 1.41). The I^2 was 45% (P = 0.16). The risk difference showed a 1% absolute risk reduction, however the CI included zero (random RD -0.01, 95% CI -0.02 to -0.00; P = 0.006). It was not possible to include in the meta-analysis glycaemic control as a part of acute intervention and multimodal intervention in usual care settings due to the lack of data.

Trial sequential analysis for all trials showed firm evidence for a 10% relative risk reduction of the composite outcome of microvascular complications in favour of targeting intensive glycaemic control. For the trials exclusively dealing with glycaemic control in the usual care settings showed no firm evidence for a 10% relative risk reduction.

Nephropathy

We predefined assessing the manifestation and progression of nephropathy. The definition of nephropathy varied among trials (see 'Definition of microvascular outcomes in study or as reported', Appendix 5). The ACCORD trial (ACCORD 2008) assessed nephropathy in different ways (development of microalbuminuria, development of macroalbuminuria, development of renal failure, doubling of serum creatinine or a decrease of glomerular filtration rate (GFR)). The outcome we have included in this analysis is the predefined composite renal outcome, which did not include development of microalbuminuria. The ADVANCE trial also reported a composite nephropathy outcome, which was defined similarly to the composite nephropathy outcome in the ACCORD trial but did not include decrease in GFR (ADVANCE 2008). The only trial including death due to renal disease under nephropathy was the ADVANCE trial. The UGDP assessed kidney function in three different ways: serum creatinine $\geq$ 1.5 mg/dL, urine protein $\geq$ 1gm/L, and urine protein 2+, which were all reported separately (UGDP 1975). We chose to report on the participants with urine protein > 1 gm/L. This definition might underestimate the number of participants with nephropathy compared to the other included trials, because of the high protein limit. The surrogate marker for nephropathy reported from the UKPDS trial was a two-fold plasma creatinine increase after nine years of follow-up (UKPDS 1998). The VA CSDM trial reported nephropathy as an elevated albumin-creatinine ratio (> 0.30), which was defined as overt nephropathy (VA CSDM 1995). The VADT divided nephropathy into three components that were reported separately. We chose to report on the number of participants with doubling of creatinine levels (VADT 2009). Bagg et al reported the number with nephropathy, defined as macroalbuminuria, based on a single urine assessment at the end of follow-up (Bagg 2001).

The participants of the Kumamoto trial were stratified at inclusion to a primary prevention population and a secondary prevention population (Kumamoto 2000). The primary prevention population only included participants without retinopathy and a urinary albumin excretion less than 30 mg/24 hour. The secondary prevention population had simple retinopathy and urinary albumin excretion less than 300 mg/24 hour. The primary prevention population who developed nephropathy and the secondary intervention population who progressed to nephropathy were reported together after 10 years of intervention. The number for nephropathy therefore included onset of microalbuminuria in the primary prevention population, which is not the case for the other trials reporting nephropathy. A large proportion of the participants in the Steno-2 trial progressed to nephropathy (defined as albumin excretion > 300 mg/24 hour) after 13.3 years of follow-up, but it is probable that all participants had microalbuminuria at inclusion (Steno-2 2008).

Targeting intensive glycaemic control showed significant reductions in nephropathy (random RR 0.78, 95% CI 0.61 to 0.99; P = 0.04; 27,929 participants, 9 trials) (Analysis 1.42). However, the result became non-significant when applying the fixed-effect model (fixed RR 0.97, 95% CI 0.93 to 1.00; 27,929, 9 trials) (Analysis 1.42). Heterogeneity was considerable (I^2 = 77%, P < 0.0001), which might be due to the different definitions and populations in the included trials.

Most events came from the ACCORD trial, which did not show any difference in the number of participants using the composite nephropathy outcome. The composite nephropathy outcome from the ACCORD trial was the only one which included GFR. When looking at each component of the composite nephropathy outcome separately, all were reduced by intensive glycaemic control but doubling of serum creatinine and decrease in GFR, which contributed the most events. Additional information obtained from a published letter by the authors reported that by far most of the events were due to decreased GFR (Ismail-Beigi 2010). Excluding the ACCORD trial from the analysis, the beneficial effect of intensive glycaemic control that had been non-significant in the random-effects model (random RR 0.71, 95% CI 0.51 to 1.00) changed to a significant effect when applying the fixed-effect model (fixed RR 0.79, 95% CI 0.69 to 0.90; P = 0.003). Both the UKPDS and the UGDP included participants with relatively mild metabolic disturbances and few cases of nephropathy compared to the other trials reporting on nephropathy. When excluding the UKPDS and the UGDP the effect estimate showed significant values with the random-effects model (random RR 0.77, 95% CI 0.61 to 0.99; P = 0.04) but not the fixed-effect model (fixed RR

0.97, 95% CI 0.94 to 1.00).

The trials exclusively dealing with glycaemic control in usual care settings showed no significant effect estimates (random RR 0.83, 95% CI 0.64 to 1.06; 27,769 participants, 8 trials) (Analysis 1.43). Heterogeneity was substantial (I^2 = 75%, P = 0.0002). It was not possible to analyse subgroups of trials with glycaemic control as part of an acute intervention or multimodal intervention in usual care settings due to lack of data.

End-stage renal disease

We pooled data on hard renal outcomes from six trials (ACCORD 2008; ADVANCE 2008; Kumamoto 2000; Steno-2 2008; UGDP 1975; UKPDS 1998; VADT 2009). The extractable data varied but all reported a measure of severe renal failure (for example, dialyses, death due to renal disease) (Appendix 5). As end-stage renal disease was not a predefined outcome in the protocol, the authors did not comment on the data. The results for the ADVANCE and ACCORD trials were a part of the reported outcome for nephropathy (except for three deaths due to renal failure in the ACCORD trial). Data extracted from Steno-2 and UGDP were the number of participants initiating renal dialyses. The measure from the VADT was exclusively the number of participants who died because of renal failure. Pooling data from all six trials did not show any significant effect estimate (random RR 0.87, 95% CI 0.71 to 1.06; I^2=0%, P = 0.45; 28,075 participants, 7 trials) (Analysis 1.44).

Stratifying the trials after intervention, it was only possible to carry out a meta-analysis of the trials exclusively dealing with glycaemic control in usual care settings. The effect estimate remained non-significant (random RR 0.88, 95% CI 0.72 to 1.07; I^2=0%; 27,915 participants, 6 trials) (Analysis 1.45).

Retinopathy

We collected data on the manifestation and progression of retinopathy of the included trials (see 'Definition of microvascular outcomes in study or as reported', Appendix 5). The ACCORD and ADVANCE trials conducted a substudy investigating the manifestation and progression of retinopathy from the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale (ACCORD 2008; ADVANCE 2008). Both the ACCORD and ADVANCE trials also reported severe retinopathy based on patient history. To make the comparisons more similar to those in the other included trials we reported retinopathy as defined in the sub studies, using the surrogate marker ETDRS scale. The ACCORD Eye reported data from 2856 participants followed up for four years (ACCORD 2008). The substudy of the ADVANCE trial assessing retinopathy randomised 1602 participants.

The trials using the ETDRS to classify retinopathy reported either a two-step or three-step increase as progression of retinopathy. The primary outcome of the ACCORD Eye consisted of at least three steps in the ETDRS, photocoagulation or vitrectomy. The article on the ACCORD Eye did not report each component of the composite primary outcome separately, only the composite outcome. In an answer to a letter, the authors of the ACCORD Eye reported each component separately and the number we report is the number of participants with a three-step increase in ETDRS (Rind 2010). The ADVANCE and Kumamoto trials reported progression of retinopathy by a two-step increase in the ETDRS (ADVANCE 2008; Kumamoto 2000). Besides reporting a two-step increase in the ETDRS, the ADVANCE trial also reported the number of participants with a three-step increase. Because a two-step increase was used in most trials to describe progression of retinopathy we used this number. The number reported for the primary prevention population in the Kumamoto trial was the number of participants who developed retinopathy (Kumamoto 2000). In the secondary intervention population, the number reported was the number of participants who progressed from simple retinopathy. For the UKPDS 1998, only data from the participants in the UKPDS 33 were available (UKPDS 1998). The UKPDS 34 reported a lower rate of progression of retinopathy with intensive glycaemic control using metformin after nine years (P = 0.044) compared with conventional control. However, the benefit of intensive glycaemic control with metformin disappeared after 12 years.

All but two trials reporting retinopathy used the ETDRS scale to report new retinopathy and progression of retinopathy (Steno-2 2008; UGDP 1975). The UGDP graded fundus photographs according to the Airlie House Classification but did not report the increase in retinopathy from the scale. Instead, the UGDP trial reported retinopathy as mild or severe retinal abnormalities. We chose to report the data for mild retinal abnormalities because these might be comparable to the ETDRS grading. The Steno-2 trial graded diabetic retinopathy according to another scale, the EURODIAB (European Community-funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes) six-grade scale (Steno-2 2008).

The risk of retinopathy was significantly reduced (random RR 0.79, 95% CI 0.68 to 0.92; P = 0.002; 10,230 participants, 8 trials) (Analysis 1.46). Heterogeneity was substantial (I^2 = 53%, P = 0.04). The absolute risk reduction was 4% applying the random-effects model (random RD -0.04, 95% CI -0.07 to -0.01; P = 0.01). Excluding the trials (Steno-2 and UGDP) not using the ETDRS to classify retinopathy still showed significant effect estimates (random RR 0.77, 95% CI 0.64 to 0.92; P = 0.05). Analysing data from trials using a two-step increase of the ETDRS as progression of retinopathy also showed significant effect estimates (random RR 0.80, 95% CI 0.65 to 0.98; P = 0.03). Heterogeneity was substantial (I^2 = 61%, P = 0.04). Both the UKPDS and UGDP included participants with mild glycaemic disturbances. Excluding these trials, the effect estimate still showed significant values (random RR 0.74, 95% CI 0.62 to 0.89; P = 0.002). Heterogeneity was substantial (I^2 = 56%, P = 0.05).

Subgroup analysis stratifying the trials according to the intervention was only possible for trials exclusively dealing with glycaemic control in usual care settings. The effect estimate was significant (random RR 0.80, 95% CI 0.67 to 0.94; P = 0.008; 10,070 participants, 7 trials) (Analysis 1.47). Heterogeneity was substantial (I^2 = 59%, P = 0.02). The absolute risk reduction was at 3%, however the CI included zero applying the random-effects model (random RD -0.03, 95% CI -0.07, to -0.00 (P = 0.03); fixed RD -0.03, 95% CI -0.04 to -0.02 (P < 0.0001)). Exclusion of UGDP and UKPDS indicated a more beneficial effect of intensive glycaemic control (random RR 0.73, 95% CI 0.58 to 0.93; P = 0.01).
Trial sequential analysis showed that more trials are needed before firm evidence is established based on the information from randomised clinical trials.

Retinal photocoagulation

In the Kumamoto trial, all participants requiring photocoagulation were from the secondary intervention group (Kumamoto 2000). The VADT reported separate data for new retinal photocoagulation and any retinal photocoagulation (VADT 2009). We chose to group the measures together. The data from the ADVANCE trial are taken from the substudy (ADVANCE 2008). The ACCORD trial reported the number for photocoagulation and vitrectomy together in one publication; and the number of participants with retinopathy graded on ETDRS, vitrectomy and retinal photocoagulation in the report of the ACCORD Eye substudy (ACCORD 2008). However, the authors provided separate data on retinal photocoagulation from the participants in the ACCORD Eye substudy in an answer to a letter (Rind 2010). The UKPDS trial contributed most of the reported events (346 out of 751 events).
Targeting intensive glycaemic control showed significant reductions in retinal photocoagulation (random RR 0.77, 95% CI 0.61 to 0.97; P = 0.03; 11,142 participants, 7 trials) (Analysis 1.48). Heterogeneity was moderate (I^2 = 43%, P = 0.10). The risk difference in the random-effects model included zero (random RD -0.01, 95% CI -0.03 to 0.00; P = 0.15) but not in the fixed-effect model (fixed RD -0.02, 95% CI -0.03 to -0.01; P = 0.003).
Stratifying the trials after the intervention showed no significant effect estimate when applying the random-effects model but a significant effect applying the fixed-effect model to trials exclusively dealing with glycaemic control in usual care settings (random RR 0.82, 95% CI 0.65 to 1.03; fixed RR 0.82, 95% CI 0.71 to 0.95; P = 0.008; 10,982 participants, 6 trials) (Analysis 1.49). Heterogeneity was present (I^2 = 38%, P = 0.15).
Trial sequential analysis showed that more trials are needed before firm evidence is established for a 10% or more relative risk reduction based on the information from all randomised clinical trials together, as well as the trials exclusively dealing with glycaemic control in usual care settings.

Adverse events

We divided the reporting of adverse events into the following types: serious adverse events, non-serious adverse events, drop-outs due to adverse events (Analysis 1.50), and hypoglycaemia (Analysis 1.55). The reporting of serious adverse events was very heterogeneous. The funnel plot showed asymmetry for serious adverse events (Analysis 1.50).
One trial reported non-serious adverse events as adverse effects of angiotensin-converting enzyme (ACE)-inhibitor and simvastatin treatment (Steno-2 2008). The low reporting of non-serious adverse events is probably because the intervention in the included trials consisted of commonly used anti-diabetic drugs (see 'Adverse events', Appendix 8). Originally, we planned to perform a meta-analysis for non-serious adverse events but this had to be abandoned because we were only able to include one trial.
Some trials reported cardiovascular complications to T2D as serious adverse events whereas other trials had complications to T2D as an outcome and did not report them as serious adverse events. The reported measure of serious adverse events for the ADVANCE was hospitalisation in more than 24 hours for any cause (ADVANCE 2008). The data for serious adverse events for the UGDP were hospitalisations for cardiovascular disease (UGDP 1975). Four trials had as an inclusion criterion admission to hospital for coronary heart disease, and all participants were hospitalised as part of the inclusion criteria (DIGAMI 2 2005; IDA 2009; Melidonis 2000; Stefanidis 2003). For these trials we reported serious adverse events other than the 'mandatory' hospitalisation.
The reported number of serious adverse events in 'Data and analyses' included hospitalisation (Analysis 1.50). In the 'Adverse events' appendix (Appendix 8) hospitalisation was reported separately. The risk of serious adverse events was significantly higher when targeting conventional glycaemic control applying the fixed-effect model (fixed RR 1.06, 95% CI 1.02 to 1.11; P = 0.003; RD 0.01, 95% CI 0.00 to 0.02; 24,069 participants, 10 trials) (Analysis 1.50). When applying the random-effects model the effect disappeared (random RR 1.05, 95% CI 0.98 to 1.13). The heterogeneity between trials was moderate (I^2 = 44%, P = 0.06). The number of serious adverse events was primarily driven by the reported number from the ADVANCE trial (4882 out of 5503).
Serious adverse events were stratified according to intervention. The random-effects model showed no significant effect estimate in trials exclusively dealing with glycaemic control in usual care settings, but a significant effect when applying the fixed-effect model (random RR 1.05, 95% CI 0.97 to 1.14; fixed RR 1.06, 95% CI 1.02 to 1.11; P = 0.003; 23,786 participants, 7 trials) (Analysis 1.51). Heterogeneity was substantial (I^2 = 61%, P= 0.02). Two trials assessing glycaemic control as part of an acute intervention in patients with T2D contributed data (Melidonis 2000; Stefanidis 2003). Both trials were relatively small and only reported a few events. There was no significant effect estimate (random RR 0.95, 95% CI 0.41 to 2.18; 123 participants, 2 trials) (Analysis 1.51).
The test of interaction between trials exclusively dealing with gly-

caemic control in usual care settings and trials assessing glycaemic control as part of an acute intervention showed no significance. It was not possible to analyse data on multimodal intervention in usual care settings separately.

No significant difference in effect estimates was evident for drop-outs due to adverse events (random RR 1.67, 95% CI 0.86 to 3.26; 12,676 participants, 9 trials) (Analysis 1.50). Drop-outs due to adverse events showed no significant difference targeting intensive glycaemic control versus targeting conventional glycaemic control in trials exclusively dealing with glycaemic control in usual care settings (random RR 1.67, 95% CI 0.86 to 3.26; I^2 = 0%; 12,393 participants, 6 trials) (Analysis 1.52).

Congestive heart failure

Congestive heart failure has been associated with some anti-diabetic drugs (glitazones or high-dose insulin treatment). In the REMBO trial all participants had heart failure at inclusion, and the reported measure was therefore progression to non-compensated heart failure (REMBO 2008). There was no significant difference between the interventions (random RR 0.99, 95% CI 0.88 to 1.12; 27,792 participants, 9 trials) (Analysis 1.53).

Trials dealing exclusively with glycaemic control in usual care settings did not show any significant difference in the effect estimate for congestive heart failure (random RR 1.01, 95% CI 0.87 to 1.17; 27,587 participants, 6 trials) (Analysis 1.54). Two trials assessing intensive glycaemic control in glycaemic control as part of an acute intervention provided useable data, however the reported number was low (random RR 0.74, 95% CI 0.26 to 2.13; 123 participants, 2 trials) (Analysis 1.54). The test of interaction showed no significance between the subgroups. Because of lack of data we could not analyse congestive heart failure in the trials assessing multimodal intervention in usual care settings.

Hypoglycaemia

We predefined reporting hypoglycaemia as mild (controlled by patient), moderate (daily activities interrupted but self-managed), or severe (requiring assistance).

The definition of mild hypoglycaemia varied between trials (Appendix 6). The ACCORD trial did not systematically collect the number of mild hypoglycaemic episodes but the intensive treatment group participants did have more mild episodes of hypoglycaemia compared with the conventional treatment group (correspondence, Bonds, ACCORD 2008). The participants in the ACCORD trial reported the number of blood sugar levels < 3.9 mmol/L based on a finger stick measure before each visit. The trialists did not report on whether these episodes of hypoglycaemia were mild or severe. The DIGAMI 2 trial reported hypoglycaemia with or without symptoms. We have reported the data on hypoglycaemia with symptoms. The number was only reported for the initial 24 hours. The DIGAMI 2 trial did not report nor define severity of observed hypoglycaemia (DIGAMI 2 2005). The definition of a hypoglycaemic blood glucose level was < 3 mmol/L. The number of mild hypoglycaemic episodes reported for the UGDP was estimated from participants who changed their prescription one or more times during the follow-up because of reported (suspect or definite) hypoglycaemic episodes. Hypoglycaemia was not graded in the UGDP (UGDP 1975). The number of hypoglycaemic episodes in Stefanidis et el was only reported for the participants who completed the trial (Stefanidis 2003).

The risk of mild hypoglycaemia was significantly higher for participants randomised to targeted intensive glycaemic control (random RR 1.50, 95% CI 1.31 to 1.72; P < 0.00001; 18,923 participants, 11 trials) (Analysis 1.55). Heterogeneity was considerable (I^2 = 87%, P < 0.00001).

Analysing the trials exclusively dealing with glycaemic control in usual care settings for mild hypoglycaemia a significant effect estimate was shown in favour of conventional glycaemic control (random RR 1.57, 95% CI 1.35 to 1.82; P < 0.00001; 17,860 participants, 7 trials) (Analysis 1.56). Heterogeneity was considerable (I^2 = 91%, P < 0.00001). Trials with intensive glycaemic control as part of an acute interventions showed no significant effect estimate with the random-effects model but a significant effect estimate favouring intensive glycaemic control in the fixed-effect model (random RR 2.13, 95% CI 0.83 to 5.50; fixed RR 1.81, 95% CI 1.03 to 3.17; P = 0.04; 903 participants, 3 trials) (Analysis 1.56). Heterogeneity was substantial (I^2 = 54%, P = 0.11). The test of interaction showed no significance. Due to lack of data, we could not perform separate analysis of trials assessing multimodal intervention in usual care settings.

Only two trials provided separate data on moderate hypoglycaemia (Melidonis 2000; Stefanidis 2003). The number of reported moderate hypoglycaemic episodes was only five in total, all from one trial (Melidonis 2000). Due to a lack of data, we included the moderate hypoglycaemic events in the reporting of mild hypoglycaemic events as this was how the rest of the included trials reported on this outcome.

Severe hypoglycaemia was significantly more frequent when targeting intensive glycaemic control both applying the fixed-effect and random-effects models (random RR 2.05, 95% CI 1.39 to 3.02 (P = 0.0003); fixed RR 2.74, 95% CI 2.46 to 3.07 (P < 0.00001); random RD 0.02, 95% CI -0.01 to 0.06; fixed RD 0.05, 95% CI 0.05 to 0.06; P < 0.00001; 28,127 participants, 12 trials) (Analysis 1.55). Heterogeneity was considerable (I^2 = 79%, P < 0.00001). The ACCORD trial reported the number of hypoglycaemic events in two ways: requiring any assistance, and requiring medical assistance. We have reported the number requiring any assistance as this definition agreed best with the definition used in the other included trials (ACCORD 2008). Six trials, besides the ACCORD trial, described the assistance of a third person in their definition of serious hypoglycaemia (ADVANCE 2008; Bagg 2001; Kumamoto 2000; Steno-2 2008; UKPDS 1998; VA CSDM 1995). The VADT trial reported severe hypoglycaemia as a serious

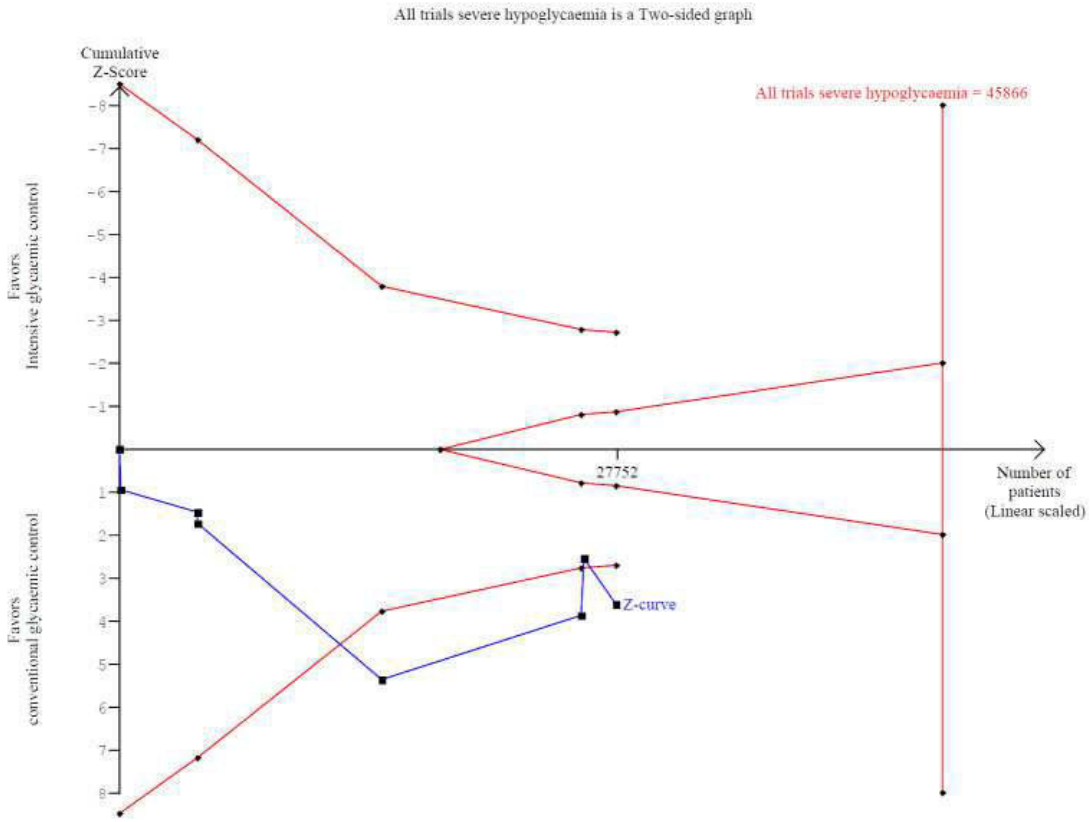
adverse event hypoglycaemia, that is life threatening, hospitalisation, disability, death or medical assistance (VADT 2009). Four trials reported severe hypoglycaemia but did not specify it further (IDA 2009; Jaber 1996; Melidonis 2000; Stefanidis 2003). Separate analysis of the trials providing a specific definition of severe hypoglycaemia did not alter the significance of the effect estimate (random RR 2.00, 95% CI 1.34 to 2.98; P = 0.006). Heterogeneity was still considerable (I^2 = 82%, P < 0.0001).

Inspection of the funnel plot for severe hypoglycaemia showed asymmetry, suggesting presence of bias not favouring the effect of intensive glycaemic control (Analysis 1.55).

Meta-regression with data from all included trials showed a positive correlation between the relative risk ratio for severe hypoglycaemia and the duration of disease at baseline, suggesting a higher RR (higher relative risk increase) for a higher average duration of disease. The risk of severe hypoglycaemia was not dependent on fasting blood glucose at baseline or HbA1c at baseline. A negative correlation between the relative risk ratio for severe hypoglycaemia and duration of the intervention was found suggesting a lower RR (less relative risk increase) with longer duration intervention. Meta-regression for the trials exclusively dealing with glycaemic control in usual care settings could only include information from five trials. The meta-regression showed significant correlation for all the covariates explored. A significant positive correlation was found between disease duration at baseline, HBA1c at baseline, and fasting blood glucose at baseline; whereas a negative correlation was shown for duration of intervention.

When applying trial sequential analysis to severe hypoglycaemia for all trials and for the trials exclusively dealing with glycaemic control in usual care settings a relative risk increase of 30% (number needed to harm = 50) was assumed to construct the trial sequential monitoring boundary. The cumulative Z-curve crossed the trial sequential monitoring boundary, indicating that there is firm evidence for a 30% increase in severe hypoglycaemia with intensive glycaemic control (Figure 6).

Figure 6. Trial sequential analysis for severe hypoglycaemia for all included trials. Boundary is crossed showing firm evidence is reached for a 30% relative risk increase when targeting intensive glycaemic control.



The subgroup analysis of severe hypoglycaemia for the trials exclusively dealing with glycaemic control in usual care settings showed a significant effect estimate (random RR 1.71, 95% CI 1.71 to 3.34; P < 0.00001; 27,844 participants, 9 trials) (Analysis 1.57). Heterogeneity was substantial (I^2 = 73%, P < 0.00001). Separate analysis of the trials providing a specific definition of severe hypoglycaemia did not change the effect estimate (random RR 1.71, 95% CI 1.71 to 3.34; P < 0.00001). It was not possible to conduct subgroup analyses for the trials with glycaemic control as part of an acute intervention and multimodal intervention in usual care settings.

Health-related quality of life and assessment of well-being

Six trials reported health-related quality of life or well-being (Becker 2003; Jaber 1996; REMBO 2008; Steno-2 2008; UKPDS 1998; VA CSDM 1995) (Appendix 7). The UKPDS assessed health-related quality of life using a specific questionnaire consisting of the following domains: mood disturbances, cognitive mistakes, symptoms, and work satisfaction; besides using an EQ-5D questionnaire. The anti-diabetic intervention did not significantly affect quality of life but the presence of complications related to T2D reduced quality of life (UKPDS 1998). The Steno-2 trial reported health-related quality of life as quality-adjusted life expectancy (Steno-2 2008). The VA CSDM trial assessed health-related quality of life by using a 20-item questionnaire (VA CSDM 1995).

The publication from van der Does et al assessed well-being by a composite questionnaire based on three validated questionnaires besides assessing well-being on Likert scales (Becker 2003). The results were not reported for intensive versus conventional glycaemic control but according to the decrease in HbA1c. Jaber et al assessed health-related quality of life using a form derived from Short Form-36 (Jaber 1996). The results were not reported for each intervention group, but the conclusion was that improved glycaemic control did not improve quality of life. The REMBO trial assessed quality of life from the Minnesota heart failure questionnaire. Health-related quality of life was unchanged for the two intervention groups after 12 months of follow-up (REMBO 2008).

It was unfortunately not possible to perform a meta-analysis on the data from the different scales using standardised mean differences (SMDs).

The ACCORD, ADVANCE, and VADT all had health-related quality of life as a predefined outcome (ACCORD 2008; ADVANCE 2008; VADT 2009). The results of these analyses are not yet available.

Costs of interventions

Costs of interventions were assessed in only three trials (Kumamoto 2000; Steno-2 2008; UKPDS 1998). All of the trials analysed the cost, as cost-effectiveness analyses with 3% annual discounting rate, except for the UKPDS which had a 3.5% discount rate. The Kumamoto trial provided data on the costs of 10 years of intervention and treatment of complications per participant. The UKPDS reported the data for the UKPDS 33 and UKPDS 34 separately; as for all other outcomes we combined the data for the intensive intervention groups in UKPDS 33 and UKPDS 34. The costs for the UKPDS were expressed as cost per participant during the trial period of 10 years. There was an incremental cost of intensive blood glucose control with insulin and sulphonylurea compared with conventional glycaemic control. The costs of intensive blood glucose control with metformin were lower compared with conventional blood glucose control. The Kumamoto trial classified the costs into two classes: costs of treatment, and costs of the complications. Costs of treatment were significant higher for patients in the intensive intervention group compared to the conventional treatment group. The costs of complications were higher in the conventional group. When combining the costs of treatment and complications the costs were reduced in the intensive treatment group during a 10-year intervention period. When discounting the costs at 3% the difference was still present but statistically insignificant (Kumamoto 2000). The Steno-2 trial found that lifetime direct medical costs were higher for the intensive treatment group compared to the conventional treatment group because of increased pharmacy and consultations when targeting intensive control. When including the lifetime expenses for treating the complications in the two intervention groups, intensive treatment was less expensive than conventional treatment even though the patients lived longer in the intensive treatment group (Steno-2 2008). It was not possible to add suitable data from the Steno-2 trial to the meta-analysis as the data were expressed as lifetime costs and quality-adjusted life years. In a meta-analysis of the results from the Kumamoto trial and UKPDS, there was no significant difference (MD 543.85, 95% CI -985.46 to 2073.16; 4319 participants, 2 trials) (Analysis 1.58).

The UKPDS and Steno-2 trials also expressed the costs as quality-adjusted life years, a measure of both increases in life expectancy and quality of life. The Steno-2 trial showed lower costs per quality adjusted life year when targeting intensive control compared with conventional control. UKPDS also found a reduced cost per quality adjusted life year for the participants randomised to intensive glycaemic control with metformin compared with conventional glycaemic treatment. However, there was an incremental cost per quality adjusted life-year gained for intensive blood glucose control with insulin and sulphonylurea compared with conventional glycaemic control.

The ACCORD, ADVANCE, and VADT trials all included cost-analysis as a predefined outcome (ACCORD 2008; ADVANCE 2008; VADT 2009). The results are not published yet.

DISCUSSION

Summary of main results

This Cochrane review is the first systematic review that includes all randomised trials assessing targeted intensive glycaemic control versus conventional glycaemic control in patients with type 2 diabetes mellitus (T2D). We included data from 20 trials with a total of 29,986 participants. Thereby our systematic review becomes far more comprehensive than previous meta-analyses addressing the same interventions, which included 27,049 participants and restricted the analyses to mortality and macrovascular events (Turnbull 2009). We also included microvascular complications, which like other diabetic complications can be disabling for patients.

Our key findings are that there is no significant difference between the interventions regarding all-cause mortality or cardiovascular mortality (see Summary of findings for the main comparison). Other important findings are that targeting intensive glycaemic control may reduce the risk of non-fatal myocardial infarction, amputation of a lower extremity, microvascular complications as a composite outcome, nephropathy, retinopathy, and retinal photocoagulation. However, a firm conclusion will have to await further trials for some of these outcomes. Targeting intensive glycaemic control increased the risk of serious adverse events as well as mild and severe hypoglycaemia.

Subgroup analyses stratifying the trials according to how the intervention was applied showed no difference for all-cause mortality or cardiovascular mortality, for trials exclusively dealing with glycaemic control in usual care settings and for glycaemic control as part of an acute intervention. Targeting intensive glycaemic control in trials exclusively dealing with glycaemic control in usual care settings may reduce the risk of non-fatal myocardial infarction, whereas this was not shown for intensive glycaemic control as part of an acute intervention in patients with T2D. The risk of the composite microvascular complications, retinopathy, as well as retinal photocoagulation might also be reduced when targeting intensive glycaemic control in trials exclusively dealing with glycaemic control in usual care settings but with increased risk of serious adverse events, mild and severe hypoglycaemia.

Our primary outcomes were all-cause mortality and cardiovascular mortality. Neither a random-effects nor fixed-effect model showed any significant effect on all-cause mortality or cardiovascular mortality when analysing all trials together or when analysing the trials exclusively dealing with glycaemic control in usual care settings and as part of an acute intervention. Separate analysis of intensive glycaemic control as a part of a multimodal treatment regime could not be performed due to lack of data. Stratifying the trials according to risk of bias, study duration, diagnostic criteria, or funding source did not give rise to significant effect estimates for all-cause mortality. A test of interaction between any of the subgroups did not reveal any significance. The same was the case for cardiovascular mortality, however stratifying the trials after diagnostic criteria showed a significant effect estimate for cardiovascular mortality in favour of conventional glycaemic control. A test of interaction between the subgroups when stratifying the trials according to the diagnostic criteria for T2D showed significance (P = 0.03). However, it should be noted that stratifying trials according to diagnostic criteria excluded the ADVANCE trial since this trial did not specify its criteria for the diagnosis of T2D. The ADVANCE trial was the largest trial included in the present meta-analysis (11,140 participants) with about one third of the total information size and did not find any evidence of increased cardiovascular mortality when targeting intensive versus conventional control (ADVANCE 2008). Thus, excluding the ADVANCE trial might substantially increase the weight of other studies in the analysis. For example, the ACCORD trial had about the same sample size as the ADVANCE trial, but, unlike the ADVANCE trial, its findings suggested an increased risk of cardiovascular death with targeted intensive versus conventional glycaemic control (ACCORD 2008). Meta-analysis of all available hazard ratio data for the primary outcomes did not show any significant effect estimates. Available case analysis showed no significant effect estimates for all-cause mortality or cardiovascular mortality. Worst-case scenarios showed a significant effect favouring conventional glycaemic control when applying a fixed-effect model for all-cause and cardiovascular mortality. However, significant effect estimates favouring intensive glycaemic control were also shown for the best-case scenarios for all-cause mortality and cardiovascular mortality. This implies that missing outcome data in trials could influence the effect estimates for targeting intensive versus conventional glycaemic control on all-cause and cardiovascular mortality, although the assumption reveals unrealistic effect estimates. However, the direction of such influence is uncertain.

Trial sequential analysis suggested a 10% relative risk reduction could be rejected for all-cause mortality. For cardiovascular mortality trial sequential analysis suggested that more trials are needed before firm evidence is established. Meta-regression for all trials was not able to show any statistically significant association between duration of disease, fasting blood glucose, or glycosylated haemoglobin A1c (HbA1c) at baseline and all-cause mortality. Meta-regression of all trials showed a trend toward a negative association between the duration of the intervention and the risk ratio for all-cause mortality, which indicates that increased duration of the intervention is associated with a tendency to increase the relative risk reduction of death with targeting intensive versus conventional glycaemic control. Meta-regressions for the subgroup of trials exclusively dealing with glycaemic control in usual care settings showed a positive correlation between fasting blood glucose and HbA1c at baseline and the risk ratio for all-cause mortality. Thus, for trials exclusively dealing with glycaemic control in usual care settings, patients with poorer glycaemic control at baseline (higher fasting blood glucose or HbA1c) might benefit less from targeting intensive versus conventional glycaemic control in terms of all-cause mortality than do patients with better glycaemic con-

trol at baseline. Neither meta-regression of all trials nor the subgroup analysis of trials exclusively dealing with glycaemic control in usual care settings showed any significant influence on cardiovascular mortality for the explored variables.

We found no significant influence of the intervention on macrovascular disease assessed as a composite outcome. Separate analysis of trials exclusively dealing with glycaemic control in usual care settings did not show significant effect estimate. Subgroup analyses for trials assessing the effect of targeting intensive glycaemic control as part of an acute intervention or multimodal intervention in usual care settings could not be performed. The reporting of a composite macrovascular outcome varied between trials.

Non-fatal myocardial infarction was reported in 12 trials, of which eight gave a detailed description of how the diagnosis was established. Meta-analysis of all 12 trials only revealed significant effect estimates using the fixed-effect model. When analysing non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings, significant effect estimates were present in both the random-effects and fixed-effect model. The trials assessing the effect of targeting intensive glycaemic control as part of an acute intervention all reported non-fatal myocardial infarction as re-infarction. There was no significant effect estimate for the trials assessing targeted intensive glycaemic control as part of an acute intervention. The test of interaction between the trials assessing the effect of targeting intensive glycaemic control as a part of acute intervention and the trials assessing the effect of targeting intensive glycaemic control as a part of acute intervention showed significance (P = 0.04). Due to lack of data, subgroup analysis of trials with multimodal intervention in usual care settings could not be performed. Meta-analysis of the trials with non-fatal myocardial infarction as a primary outcome showed a significant effect in both the random-effects and fixed-effect model. Subgroup analysis showed significant effect estimates favouring intensive glycaemic control when applying the fixed-effect model for trials with long study duration, low risk of bias, and industry funding. A test of interaction of the subgroups showed no significance. Available case analysis showed a significant effect estimate favouring intensive glycaemic control when applying the fixed-effect model. A best-case scenario showed significant effect estimates applying both the random-effects and fixed-effect models that favoured intensive glycaemic control. A worst-case scenario favoured conventional glycaemic control. Trial sequential analysis, however, showed that more trials are needed before there is firm evidence for a benefit of intensive glycaemic control, or lack of effect. Meta-regressions for all trials and the trials exclusively dealing with glycaemic control in usual care settings showed no significant association between the risk ratio of non-fatal myocardial infarction and the explored variables.

Originally we planned to report stroke according to the aetiology, but unfortunately this was not possible because of the reporting in the included trials. Stratifying the trials according to the intervention was only possible for the trials exclusively dealing with glycaemic control in usual care settings, which did not show any significance of the effect estimate. The reported non-fatal strokes were primarily from the ADVANCE trial. The result remained non-significant when analysing only the trials with predefined non-fatal stroke as a primary outcome.

A significant effect estimate in favour of targeting intensive glycaemic control was evident for amputation of a lower extremity. Stratifying the trials according to the intervention could only be done for those trials exclusively dealing with glycaemic control in usual care settings, which did not show a significant effect estimate. The meta-analysis of amputation of a lower extremity is extremely prone to bias. Besides differences in the definitions used for this outcome, the indication for amputation might vary within the different sites of a single trial. The data on amputation were primarily reported by UKPDS. Trial sequential analysis showed that only a minor proportion of the required sample size has been accrued so far.

Cardiac revascularization was not influenced by the intense of conventional intervention. Subgroup analyses could only be done for trials exclusively dealing with glycaemic control in usual care settings and did not show any significant effect of the intervention; most of the reported data were from the VADT trial.

Targeting intensive glycaemic control did not reveal any significant influence on need for peripheral revascularization. Subgroup analyses of the trials according to how intensive glycaemic control was applied was only possible for the trials exclusively dealing with glycaemic control in usual care settings, which did not show a significant effect estimate. The indication for revascularization procedures might vary within the sites in a single trial and among trials. The ADVANCE trial contributed the most events, which were reported as peripheral vascular events.

The relative risk of microvascular complications as a composite outcome was reduced when targeting intensive glycaemic control. Subgroup analyses stratifying the trials according to the intervention could only be done for trials exclusively dealing with glycaemic control in usual care settings, which also showed a significant effect estimate in favour of targeting intensive glycaemic control. Definitions of the composite microvascular outcome varied between trials. The composite microvascular outcome from the Steno-2 trial included both severe and non-severe microvascular events; whereas the ACCORD, ADVANCE, and UKPDS trials reported more severe microvascular events. Trial sequential analysis suggested that firm evidence was reached for a 10% relative risk reduction when targeting intensive glycaemic control in all trials, but not in the trials exclusively dealing with glycaemic control in the usual care setting.

Meta-analysis of all trials reporting retinopathy showed that the risk of retinopathy was significantly reduced. Subgroup analysis of trials exclusively dealing with glycaemic control in usual care settings also showed a significant effect estimate. We reported retinopathy graded using a scale, which was the Early Treatment of Diabetic Retinopathy Study scale for most of the trials. By ex-

cluding the UGDP and the UKPDS trials, which included only participants with short duration diabetes, from the analysis of trials exclusively dealing with glycaemic control in usual care settings the effect estimate revealed a larger risk reduction. Heterogeneity was substantial. Trial sequential analysis showed that more trials are needed before firm evidence for a 10% relative risk reduction is established from randomised clinical trials.

A meta-analysis of all trials using both the random-effects and fixed-effect models showed significant benefit of targeting intensive glycaemic control for retinal photocoagulation. Analysing the trials exclusively dealing with glycaemic control in usual care settings resulted in a significant effect estimate favouring targeting intensive glycaemic control only when applying the fixed-effect model. The indication for retinal photocoagulation may vary between sites in a single clinical trial as well as between the sites of the different included trials. Most of the retinal photocoagulation was reported by a single trial (UKPDS). Trial sequential analysis suggested that more trials are needed before firm evidence of a 10% relative risk reduction is reached.

A significant effect estimate was shown for nephropathy for all trials in a random-effects model but not in the fixed-effect model. Subgroup analysis stratifying the trials according to the intervention was only possible for the trials exclusively dealing with glycaemic control in usual care settings, which was not significant. The reported nephropathy events were primarily from the ACCORD trial, because of an increase in glomerular filtration rate (GFR) that was observed in more than half of the participants. The definition of nephropathy varied between trials, from surrogate markers (for example, developing microalbuminuria) to hard clinical outcomes (for example, renal transplantation). Heterogeneity was considerable.

The effect estimate for end-stage renal disease showed no significance. Stratifying trials according to the intervention was only possible for trials exclusively dealing with glycaemic control in usual care settings, with no significant difference in effect. Some trials reported end-stage renal disease and death due to renal disease as part of the nephropathy outcome. Some trials provided separate data on end-stage renal disease and nephropathy. The extractable data for end-stage renal disease varied.

The risk of serious adverse events was significantly increased when applying the fixed-effect model to all the included trials, but not when applying the random-effects model. This was also the case analysing the trials exclusively dealing with glycaemic control in usual care settings. No significant effect was shown for glycaemic control as part of an acute intervention. The test of interaction between trials exclusively dealing with glycaemic control in usual care settings and the trials assessing glycaemic control as part of an acute intervention showed no significance. Meta-analysis of a multimodal intervention in usual care settings was not possible due to lack of data. Adverse event reporting varied between trials, and some trials reported cardiovascular complications as a serious adverse event whereas other did not. More than half of the serious adverse events were from the ADVANCE trial.

Neither the data for congestive heart failure nor drop-outs due to adverse events were driven by a single trial. No significant effect estimates were evident for drop-outs due to adverse events or to congestive heart failure.

The risk of mild hypoglycaemia was increased when targeting intensive glycaemic control, assessing all trials together. Separate analyses for trials exclusively dealing with glycaemic control in usual care settings showed increased risk of mild hypoglycaemia when targeting intensive glycaemic control. Trials with glycaemic control as a part of acute intervention did not show a significant increase in mild hypoglycaemia. The test of interaction between trials exclusively dealing with glycaemic control in usual care settings and the trials assessing glycaemic control as a part of acute intervention showed no significance. It was not possible to analyse trials with multimodal intervention in usual care settings separately due to lack of data. Definitions of mild hypoglycaemia varied among trials. The lack of blinding of the participants and the investigators might influence the reporting of mild hypoglycaemia. Heterogeneity was considerable, so the results should be interpreted extremely cautiously.

Severe hypoglycaemia was significantly more frequent when assessing all trials together, as well as when assessing the trials exclusively dealing with glycaemic control in usual care settings. Analysis of glycaemic control as part of an acute intervention and multimodal intervention in usual care settings could not be performed due to lack of data. A definition of severe hypoglycaemia was given for most trials providing data on this outcome. The definitions often included assistance from another person, without further specification. The grade of assistance from another person may vary from handling a juice to giving glucagon injections. The design of the included trials made it impossible to blind the participants, which in turn may bias the reporting of severe hypoglycaemia. Heterogeneity was considerable, which may reflect differences in both the included trials and the definition of severe hypoglycaemia. Trial sequential analysis suggested a 30% relative risk increase when targeting intensive glycaemic control. Meta-regression for all trials and the subgroup of trials exclusively dealing with glycaemic control in usual care settings showed a positive correlation between the relative risk of severe hypoglycaemia and the duration of disease, indicating that the relative risk of severe hypoglycaemia with targeted intensive glycaemic control versus conventional glycaemic control increases with longer disease duration. A negative correlation between the relative risk of severe hypoglycaemia and the duration of the intervention was found for all trials and for the subgroup of trials exclusively dealing with glycaemic control in usual care settings, indicating a lower relative risk of severe hypoglycaemia with increased duration of the intervention for targeting intensive glycaemic control versus conventional glycaemic control. Meta-regression for all trials showed no influence of HbA1c or fasting blood glucose level at baseline on the risk of severe hypoglycaemia, whereas a positive correlation

was found for the subgroup of trials exclusively dealing with glycaemic control in usual care settings. Heterogeneity between trials was considerable and the results should be interpreted extremely cautiously.

We assessed health-related quality of life and well-being. It was not possible to pool the data. Three larger trials (ACCORD 2008; ADVANCE 2008; VADT 2009) had quality of life as a predefined outcome but the results are not yet published.

Cost data from two trials were pooled (Kumamoto 2000; UKPDS 1998). Based on these data we could not conclude whether targeting intensive glycaemic control is economical efficient. The results might be specific to the countries in which the trials were undertaken (Japan, United Kingdom) because of differences between the public health systems.

Overall completeness and applicability of evidence

We conducted an extensive search for trials, included publications in all languages, and had no restriction on the outcomes reported in the trials. We have included trials with large ranges for duration of T2D, duration of the interventions, age, different groups according to risk of cardiovascular disease, and finally different assessments of glycaemic control. Our primary objective was to assess all-cause as well as cardiovascular mortality.

The participants of the included trials represented a very diverse sampling of the population with T2D. The results of our review should therefore be interpreted with caution. The diagnosis of T2D varied between trials, and some trials used a definition of T2D which may have included participants with impaired glucose tolerance. Some of the trials only included participants with newly diagnosed T2D, whereas others included patients with a longer duration of T2D. Moreover, the cardiovascular risk profile may have differed significantly because of differences in inclusion criteria, for example inclusion of participants with acute cardiovascular events, microvascular disease, or at high risk of cardiovascular disease. However, it should be kept in mind that participants with existing co-morbidities, especially renal or hepatic disease, were excluded from many of the included trials. Detailed information about the participants was presented in most trials. Many of the trials were conducted in Europe or Northern America. Age, body mass index (BMI), glycaemic control, and diabetes duration of participants were in keeping with what might be expected in clinical practice. Even though we have included a large range of patients with T2D, and due to potential selection bias for instance more healthy and motivated patients in a clinical trial, it is difficult to say how typical the participants in each clinical trial may be compared with the wider population with T2D. Nevertheless, the heterogeneity in this review might indeed reflect the well-known heterogeneity in clinical practice.

The glycaemic targets in the intensive and the conventional treatment groups, as well as the anti-diabetic interventions used to achieve the targets, differed among the trials. Based on the included trials, it is neither possible to estimate the 'optimal' glycaemic intervention target nor the optimal treatment regimen necessary to receive that target. These were not part of our objectives. Thus, our review cannot provide evidence of superiority or inferiority of specific glucose-lowering regimens or of specific glycaemic targets.

Quality of the evidence

Among the 20 trials included in this analysis, only eight trials were classified as having low risk of bias. Stratifying the trials according to risk of bias did not influence the effect estimates on our primary outcomes. We were able to assess some of the predefined outcomes in all but one of the included trials. All of the larger included trials described randomisation, allocation, and blinding adequately. Because of the design of the trials, comparing intensive glycaemic control with conventional glycaemic control, it was not feasible to require double blinding of investigators and participants. This might have influenced the reporting from both the participants and the investigators. Reporting of hypoglycaemia in particular might have been prone to reporting bias. We defined blinding of outcome assessors as adequate blinding.

Certain potential limitations of this review warrant special consideration, one being that we were dealing with a very heterogeneous group of trials. The heterogeneity might to some extent be due to the differences in baseline characteristics of the participants of the included trials (for example age, diabetes duration). This meta-analysis is limited by an inability to use individual patient data to assess whether certain characteristics (for example, history of cardiovascular events, degree of HbA1c reduction, duration of disease at baseline) affect the degree of cardiovascular risk. We explored heterogeneity by sensitivity analyses, subgroup analyses, and meta-regression. Diagnostic criteria and definitions of outcomes differed among the trials and were not always well-defined. The anti-diabetic intervention also varied among trials. Moreover, the outcomes we assessed were diabetic complications, both macro- and microvascular, which might have different aetiologies. The effects of intensive glycaemic control were assessed in patients with newly diagnosed T2D, participants with T2D and microvascular disease, participants with elevated risk for cardiovascular disease, and participants with T2D combined with an acute coronary event. The variable risk of developing the outcomes we assessed might have influenced the results. We have tried to take the differences between trials into account by performing sensitivity analyses and subgroup analyses. Many of the included trials were not designed or powered to detect our predefined outcomes, which might have resulted in insufficient data from these trials. Besides, when prespecifying a certain primary outcome, the outcome might be more systematically and uniformly collected in the trial. We tried in all cases to ask for supplementary information from the authors. However, outcome reporting bias could influence the results of our meta-analysis. Adverse events outcome reporting in particular

was lacking and varied among trials.

Reporting outcomes that were not predefined in the trials gives rise to other concerns beside reporting bias. Both macrovascular and microvascular complications usually evolve over a long time period. It might therefore be that some of the included trials reported on outcomes where the duration of the trials was too short to influence the outcome (for example, retinopathy reported from the VA CSDM).

We have not evaluated the glucose-lowering drugs that were used to achieve the glycaemic target. In the included trials a wide range of glucose-lowering drugs were often used to achieve the glycaemic goal. The treatment protocols for the prescription of glucose-lowering drugs were not identical for the intensive glycaemic group and the conventional glycaemic group in all trials, for example, gliclazide prescribed for all participants in the intensive treatment group in the ADVANCE and the REMBO trials (ADVANCE 2008; REMBO 2008). Besides predefined differences in the anti-diabetic treatment, other differences might appear. In the ACCORD and the ADVANCE trials a greater proportion of the participants randomised to intensive glycaemic control received rosiglitazone compared with the conventional therapy group (ACCORD 2008; ADVANCE 2008). We have not taken such differences in anti-diabetic treatments between the intervention groups into account despite the fact that some anti-diabetic interventions are suspected of causing some of our reported outcomes. Therefore, the most suitable way to assess the objective of this review would be if all the included trials only used one glucose-lowering drug in both intervention arms to achieve glycaemic target. This was done to some extent in the DCCT study in patients with type 1 diabetes mellitus (DCCT/EDIC 2005) and in the Kumamoto trial in patients with T2D (Kumamoto 2000). However, not only did the glycaemic target differ between the intervention groups in these trials but so did the insulin regimen (for example number of daily injections) thus limiting the conclusions that can be drawn about the effect of the glycaemic target per se. A trial design that only used insulin would, however, probably not be applicable to current clinical practice for patients with T2D as a large range of glucose-lowering drugs are currently being used.

A relatively large proportion of the trials received funding from the pharmaceutical industry. When stratifying all-cause and cardiovascular mortality by source of funding, this did not cause any significant changes in the effect estimates.

To assess whether differences in targeted or achieved glycaemic control caused differences in the investigated outcomes, the respective groups would have to be similar for every known and unknown risk factor that influences the outcome. For the glucose target this should be true at baseline, and for the achieved glycaemic control other confounders during follow-up should be controlled for. We included only randomised trials to best protect against differences in baseline variables (and, in fact, also during follow-up) that may influence the outcomes differently between intervention groups. Potential blinding of participants and investigators would also confer some protection against confounding during follow-up. Unfortunately, however, such blinding is probably not possible when investigating glucose targets. On the contrary, there are probably few, if any, possible ways of protecting against confounding influences during follow-up for the effect of the achieved glycaemic control to influence other outcomes, for example, mortality or cardiovascular risk. Short of blinded trials, we therefore believe that our approach of identifying randomised trials with different predefined glycaemic targets between the intervention groups was the best way to assess the question of possible causality between glucose control and clinical outcomes. For our review, some trials assessed multimodal intervention in usual care settings, of blood pressure and cholesterol control together with intensive glycaemic control. To take these differences into account, we planned to conduct separate analysis of these trials.

The method for assessing glucose control varied between the included trials. Some trials defined the target glucose values using blood glucose. However, the levels of blood glucose only provide a 'snapshot' of the overall degree of glycaemic control. Most of the included trials expressed glycaemic control and the glycaemic goal in levels of HbA1c, which are determined by the blood glucose levels over several weeks. In spite of differences in the timeline for blood glucose and HbA1c determinations, we chose to include trials irrespective of the way glycaemic control was assessed.

Potential biases in the review process

Despite an extensive search of major diabetes conference abstracts and correspondence with authors of the included trials and relevant medical companies, we did not retrieve any additional trials.

Some of the included trials are of a relatively small size, which increases the risk of providing a more unrealistic estimate of the intervention effects due to bias (systematic errors) and chance (random errors). We have tried to clarify systematic errors. All authors were contacted for clarification if one of the bias domains was not adequately reported. We divided the analyses for the primary outcomes into high risk of bias trials and low risk of bias trials to reveal any influence of bias on the effect estimates of our primary outcomes. To reduce the risk of random errors we have conducted trial sequential analysis on the primary outcomes and all secondary outcomes which showed significant effect estimates applying both the random-effects and fixed-effect models.

Heterogeneity among trials was partly caused by differences in included participants among trials, intervention targets, and anti-diabetic agents used. For each outcome we made efforts to explain the cause of the heterogeneity. Moreover, we conducted all analyses using both the random-effects model and fixed-effect model. Due to large heterogeneity, we by default reported the outcomes using the random-effects model, and the fixed-effect model if the results differed. The fixed-effect model assumes that the true intervention effect is the same in every randomised trial, that is, the effect is fixed across trials. On the contrary, the random-effects

model allows for the effects being estimated to differ across trials. When the heterogeneity increases, the estimated intervention effect may differ between the random-effects model and the fixed-effect model, and the confidence interval increases in the random-effects model. When there is no heterogeneity (I^2 = 0%), the two models tend to give the same result. By adopting the random-effects model we were therefore able to pool a broader population of studies than by only relying on the results of the fixed-effect model. On the other hand, the random-effects model reduces the weight of the large trials, which might be more representative of a true intervention effect.

Agreements and disagreements with other studies or reviews

The oldest trial we retrieved, the UGDP, did not reveal any benefit of intensive glycaemic control compared with conventional glycaemic control (UGDP 1975). The participants in both groups were exclusively treated with insulin. At the time the UGDP was designed, there was no single definition of T2D that had general acceptance. However, the participants of the UGDP were more likely to be diagnosed with impaired glucose tolerance than diabetes, according to modern diagnostic criteria. The UKPDS trial was initiated 10 to 15 years later, in 1977 (UKPDS 1998). By using the fasting plasma glucose criterion of 6.0 mmol/L, about 85% of all UKPDS patients would have fulfilled the 1985 WHO criteria for diabetes (fasting plasma glucose above 7.8 mmol/L). The findings of the UKPDS were more positive with respect to the effect of intensive versus conventional glucose control on complications of diabetes than the findings of the UGDP. Observational data from the UKPDS trial showed a 14% risk reduction of myocardial infarction for each 1% decrease in HbA1c (UKPDS-35 2000). A longer follow-up period, after the completion of the randomised UKPDS trial, revealed a reduction in both all-cause mortality and myocardial infarction for all participants receiving regimens targeting intensive glycaemic control during the intervention period. This was observed despite differences between the groups in their use of glucose-lowering therapies, as well as in stopping the intensive glycaemic control intervention (UKPDS-80 2008). The participants in both the UGDP and UKPDS represented patients with T2D with relatively mild abnormalities in glucose metabolism. The data from the UGDP have not been included in other meta-analyses of intensive versus conventional glucose control because of the diagnostic criteria for T2D in the trial (Kelly 2009; Ma 2009; Mannucci 2009; Marso 2010; Ray 2009; Stettler 2006; Turnbull 2009; Wang 2009; Wu 2010; Zhang 2010). Excluding UGDP from the analyses did not influence our results.

The Steno-2 trial reported a benefit of targeting multiple cardiovascular risk factors, including glycaemia in patients with T2D and microalbuminuria (Steno-2 2008). The intensive glucose regimen was combined with aggressively targeting other well-known risk factors of cardiovascular disease. Unfortunately, this trial was not designed to assess the influence of each component of the treatment regimen. It remains uncertain how much of the improvement was caused by intensive glucose control as an isolated target. In addition, the included participants represented a heterogeneous and relatively selected population. A longer follow-up period of the Steno-2 population indicated a possible benefit of intensive intervention for multiple risk factors, including glycaemic control, after the end of the intervention period. Like the long-term follow-up of the UKPDS, the differences in HbA1c disappeared. The observational post-trial data from both the Steno-2 and the UKPDS trials indicate a long-term benefit of early targeted intensive glycaemic control that may or may not be supported in future randomised trials. However, because of incomplete follow-up for some participants in the UKPDS post-trial analysis, and the observational design of the post-trial period, the data should be interpreted cautiously (UKPDS-80 2008).

Randomised clinical trials have shown that lipid- and blood pressure lowering treatments reduce the prevalence of cardiovascular disease and mortality in patients with T2D (Collins 2003; Haffner 1999; Patel 2007). We could not perform separate analyses of trials assessing multimodal intervention in usual care settings for all-cause mortality and cardiovascular mortality because we only had data from the Steno-2 trial (Steno-2 2008). The benefit in the intensive intervention group that was reported in the Steno-2 trial is probably caused by the aggressive approach to blood pressure control, aspirin use, and lipid lowering rather than the glycaemic control (Steno-2 2008). Moreover, the glycaemic targets were identical in the two interventions groups for the last two years of the intervention period.

The DIGAMI 2 trial was conducted exclusively in participants with T2D and acute coronary events (DIGAMI 2 2005). The trial was designed to answer the question of whether an intensive glucose-insulin regimen followed by intensive insulin therapy reduced mortality and cardiovascular morbidity compared with insulin-glucose infusion followed by conventional treatment, or conventional treatment alone. The first DIGAMI trial indicated lower mortality when applying intensive glycaemic control after a myocardial infarction in patients with diabetes (DIGAMI 1996). The DIGAMI 2 was an attempt to replicate and extend the findings of the first DIGAMI trial. In the DIGAMI 2 trial, the level of blood glucose ended up being identical in all treatment groups and the trial had to be stopped early due to slow patient recruitment. Other trials of smaller scale and shorter follow-up periods were not sufficiently powered to answer the question (Melidonis 2000; Stefanidis 2003). Subgroup analyses did not show any benefit of intensive glycaemic control for the primary outcomes in the trials with glycaemic control as a part of acute intervention.

Recently, two large trials were conducted to answer the question whether intensive glycaemic control is superior to conventional glycaemic control (ADVANCE 2008; ACCORD 2008). Worries arose as the results from the ACCORD trial in 2008 showed increased all-cause mortality and cardiovascular mortality with in-

tensive glycaemic intervention compared with conventional glycaemic intervention. The increased mortality caused early termination of the ACCORD trial. Explanations for this finding have been sought by the authors of the ACCORD trial but no firm evidence was found. Post-hoc analyses of the ACCORD trial suggest that elevated levels of baseline HbA1c (above 8.5%) influence the risk of mortality with intensive glycaemic control compared with conventional glycaemic control (Calles-Escandon 2010). Meta-regression of our data on trials exclusively dealing with glycaemic control in usual care settings showed a positive correlation between HbA1c and fasting blood glucose at baseline and the risk ratio of all-cause mortality. However, we did not find any association between baseline HbA1c and all-cause mortality using the data from all included trials. On the other hand, the ACCORD trial showed a reduction in the risk of non-fatal myocardial infarction when targeting intensive glycaemic control. It might be that the myocardial infarctions in the ACCORD trial were for some reason more severe and caused death. The question remains why the ACCORD trial reported increased deaths but reduced risk of non-fatal myocardial infarction. However, this reflects a very important clinical problem that may be difficult to solve. Recently, data from the follow-up period, after termination of the intensive glycaemic intervention arm, have been published. It was shown that the increased risk of mortality and reduced risk of non-fatal myocardial infarction have persisted (ACCORD 2011). These data will be included in further updates. The ADVANCE trial did not find any increased mortality in the treatment arm targeting intensive glycaemic control. The reasons for the differences in the mortality results for these trials have been debated. Several differences exist between the population of the ACCORD trial and the ADVANCE trial (a slightly longer duration of T2D and more patients on insulin at baseline in the ACCORD trial), which indicate that the participants of the ACCORD might have a more progressive T2D. Besides, there was a difference in the anti-diabetic drugs prescribed to reach the glycaemic target. A larger proportion of the participants were prescribed glitazones in the ACCORD trial; in the ADVANCE trial all participants in the intensive treatment group received gliclazide.

The different interventions applied to achieve glycaemic control in the different trials may influence mortality, and it has specifically been debated whether the glitazones increase the risk of myocardial infarction (Nissen 2010; Singh 2007). We conducted a sensitivity analysis on non-fatal myocardial infarctions by excluding the trials (ACCORD 2008; ADVANCE 2008) using more glitazones in the intensive intervention group, which changed the statistically significant effect estimate in favour of targeting intensive glycaemic control into not being significant, applying both the random-effects and fixed-effect models. As mentioned previously, it was not an objective of this review to assess the effect of the different anti-diabetic interventions used, and it might well be that some of the reported effects of intensive glycaemic control are due to the differences in the anti-diabetic interventions used and not to differences in the glycaemic target (for example metformin in the UKPDS, gliclazide in the ADVANCE trial). To ensure comparability between the interventions with different glycaemic targets, the number of anti-diabetic drug combinations should be limited and the treatment algorithm should be identical for both anti-diabetic interventions as well as for cardiovascular risk factors.

Epidemiological analyses of the data from the ACCORD trial observed that severe hypoglycaemia was associated with increased risk of death irrespective of the intervention group (Bonds 2010). However, experience of severe hypoglycaemia did not explain the increased risk of mortality in the intensive intervention group.

Our results for mortality and macrovascular outcomes in the present and more comprehensive meta-analysis are in accordance with the results of recent meta-analyses (Kelly 2009; Ma 2009; Mannucci 2009; Marso 2010; Ray 2009; Turnbull 2009; Wang 2009; Wu 2010; Zhang 2010).

Glycaemic control is a fundamental part of managing T2D. Today, HbA1c is commonly used in daily clinical practice to assess average glycaemia over several months. A recently published retrospective cohort study with data from the 'General Practice Research Database' somewhat unexpected showed in 48,000 patients with T2D that both low and high mean values of HbA1c were associated with increased all-cause mortality and macrovascular events (Currie 2010); and that the HbA1c value with the lowest hazard ratio for all-cause mortality was HbA1c 7.5%. The specific reasons for death were not reported. Notably, a recent large-scale cohort study in non-diabetic people demonstrated an association between lower levels of HbA1c and increased mortality (a J-shaped curve), that is with levels of HbA1c usually not considered to have a risk (Selvin 2010). Hence, any potential causal or non-causal relationship between lower levels of HbA1c and mortality might not necessarily be specific to the diabetic state, its treatments, or other associated conditions (for example hypoglycaemia).

The beneficial effect of targeting intensive glycaemic control on the composite microvascular outcome in our review may be in accordance with results from both randomised clinical trials and observational studies (ADVANCE 2008; Ohkubo 1995; UKPDS-33 1998; UKPDS-35 2000). Observational data from the UKPDS showed a 37% risk reduction of microvascular complications for each 1% decrease in HbA1c (UKPDS-35 2000). The ADVANCE trial found a 14% relative risk reduction of major microvascular events when targeting intensive glycaemic control (ADVANCE 2008). The UKPDS 33 showed a 25% risk reduction in microvascular outcomes when targeting intensive glycaemic control (UKPDS-33 1998). We found an 11% relative risk reduction applying both the random-effects model and the fixed-effect model for the composite microvascular outcome, and a 1% to 2% absolute risk reduction in favour of intensive glycaemic control for all included trials. For the trials exclusively dealing with glycaemic control in usual care setting a relative risk reduction of 11% to 12% was found, and a 1% absolute risk reduction in favour of

targeting intensive glycaemic control. However, the confidence interval for the absolute risk reduction included zero.

The Kumamoto trial showed a pronounced reduction in the incidence of nephropathy in both the primary prevention cohort (11.5% versus 43.5%) as well as in the secondary intervention cohort (16% versus 40%) when targeting intensive glycaemic control (Kumamoto 2000). The ADVANCE trial showed a 21% relative risk reduction in nephropathy when targeting intensive glycaemic control, whereas this could not be shown in ACCORD (ACCORD 2008; ADVANCE 2008). We found a 22% relative risk reduction for nephropathy for all included trials in favour to intensive glycaemic control when the random-effects model was applied, but no significant benefit with the fixed-effect model. However, we found no significant effect in the meta-analysis of the group of trials exclusively dealing with glycaemic control in usual care settings. The risk of end-stage renal disease did not significantly differ between the two intervention groups of the included trials.

We found a 21% relative risk reduction in retinopathy in favour of intensive glycaemic control in a meta-analysis of all included trials. The absolute risk reduction was 4%. The subgroup of trials exclusively dealing with glycaemic control in usual care settings also showed a 20% relative risk reduction, and a 3% absolute risk reduction. The UKPDS 33 showed a 29% relative risk reduction for retinal photocoagulation when targeting intensive glycaemic control (UKPDS-33 1998). Retinal photocoagulation showed a 23% relative risk reduction in favour of intensive glycaemic control in our meta-analysis. The absolute risk reduction was 2% in the fixed-effect model. However, the confidence interval for the random-effects model included zero. The group of trials exclusively dealing with glycaemic control in usual care settings only showed a 18% relative risk reduction and was only significant in the fixed-effect model.

We report both microvascular disease with surrogate markers (for example retinopathy initiation and progression expressed on a scale) and hard clinical outcomes (for example end-stage renal disease). Microvascular data from the ACCORD trial and the UKPDS indicate that the beneficial effects of intensive glycaemic glucose control on microvascular disease takes more than five years to emerge, and the benefits on microvascular disease achieved by intensive glycaemic control are less pronounced for patients with advanced T2D (ACCORD) compared with patients with new onset T2D (UKPDS) (ACCORD 2008; UKPDS 1998). On the other hand, the meta-analysis for retinopathy indicated that patients with more advanced stages of T2D (ACCORD, VADT) might benefit more from intensive glycaemic control compared with newly diagnosed patients with T2D (UKPDS, UGDP) (ACCORD 2008; UGDP 1975; UKPDS 1998; VADT 2009). Most of the recent meta-analyses have not included microvascular disease as an outcome (Kelly 2009; Mannucci 2009; Marso 2010; Ray 2009; Turnbull 2009; Wu 2010; Zhang 2010). However, Ma et al analysed the included trials according to the HbA1c target in the intensive intervention group and included microvascular disease including nephropathy, retinopathy, and neuropathy. For the trials with a HbA1c target less than 7% Ma et al found no significant reduction in the risk of microvascular disease with strict glycaemic control. For trials with a HbA1 target level of 7% to 7.9% in the intensive intervention group a significant reduction was found for nephropathy and retinopathy in favour of intensive glycaemic control (Ma 2009). Wang et al, which included trials without predefined differences in glycaemic target (for example, 'Prospective Pioglitazone Clinical Trial in Macrovascular Events' (PROactive) and ' Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes' (RECORD)), and showed a 26% reduction in the odds for microvascular events when targeting intensive glycaemic control (Wang 2009).

We identified both mild and severe hypoglycaemia as an adverse effect strongly associated with intensive glucose control, which is in accordance with established knowledge and other meta-analyses (Kelly 2009; Ma 2009; Mannucci 2009; Ray 2009; Turnbull 2009; Zhang 2010). We did not have access to in-trial data at the patient level, and therefore we could not investigate whether there was any correlation between severe hypoglycaemic events and the risk of sudden unexpected death. For the same reason, we were not able to investigate the effect of pre-existing cardiovascular disease on the outcomes. Meta-regression for all trials and the subgroup of trials exclusively dealing with glycaemic control in usual care showed a positive correlation between disease duration and the risk ratio for severe hypoglycaemia. An explanation for the increased risk of severe hypoglycaemia with time might be that the glucagon response to hypoglycaemia decreases with the longer duration of diabetes alongside the reduction in endogenous insulin secretion (Cryer 2008). On the other hand, we also found a negative correlation between the risk ratio of severe hypoglycaemia and the duration of the intervention, which could imply that the patients and clinicians become more familiar with the treatment over time, for example, with the prevention of adverse events.

When targeting intensive glycaemic control, quality of life might be reduced as a consequence of the increased number of finger pricks, insulin injections as well as an increased risk of hypoglycaemia. In the present meta-analysis we were not able to pool the quality of life data and we cannot therefore draw firm conclusions about this. The possible reduced quality of life with intensive glycaemic control, as described above, contrasts with its potential to reduce the risk of microvascular complications as a composite outcome, as suggested from our present meta-analysis. It also contrasts with the observed beneficial effects of other interventions, for example antihypertensive treatment or lipid-lowering therapy, which influence other patient relevant outcomes such as mortality and cardiovascular disease. That is, the quality of life is also likely to be influenced by the presence of complications (UKPDS 1998). Results of large-scale randomised clinical trials addressing this are not published yet and might help to reveal the influence of intensive glycaemic control on the quality of life.

The American Diabetes Association published in January 2010 a guideline recommending an HbA1c goal of less than 7% to reduce microvascular complications (ADA 2010). Treatment targets of HbA1c at 7% have only been used in five of the relatively small included trials involving 543 participants (Bagg 2001; Guo 2008; Kumamoto 2000; REMBO 2008; Yang 2007). However, only three of these exclusively assessed the effects of glycaemic control. One of these trials had a duration of more than one year (Kumamoto 2000). Besides, most of the included trials had sparse data on the number of participants achieving the glycaemic target at the end of follow-up and, when reported, the proportion of participants achieving the glycaemic target was relatively low. The American Diabetes Association, however, recommends less stringent goals in patients with a history of severe hypoglycaemia (ADA 2010).

Implications for research

For safety purposes, and with the aim of identifying the general optimal glycaemic target, it would be preferable to have more randomised clinical trials assessing cardiovascular disease and mortality in patients with type 2 diabetes mellitus, for example in younger patients with type 2 diabetes mellitus without complications and older patients with complications. Considering the combined evidence on the influence of intensive glycaemic control on mortality, a 10% relative risk reduction or more of all-cause mortality seems unlikely, and therefore very large randomised clinical trials with the ability to detect or reject less than a 10% relative risk reduction are warranted. We suggest that more uniform treatment regimens should be used in the interventions arms. We also suggest a more uniform and rigorous reporting of outcomes in upcoming trials to ease the comparisons between different glycaemic intervention targets. Future trials ought to be reported according to the CONSORT (CONsolidated Standards of Reporting Trials) statement.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to demonstrate whether targeting intensive glycaemic control influences all-cause or cardiovascular mortality. Intensive glycaemic control may reduce the occurrence of some patient important outcomes such as non-fatal myocardial infarction, lower extremity amputation, and microvascular disease as a composite outcome. Targeting intensive glycaemic control compared with conventional glycaemic control increases the risk of severe adverse events including both mild and severe hypoglycaemia. Although we were not able to pool quality of life data, it is conceivable that targeting intensive compared with conventional glycaemic control may negatively affect quality of life for patients aiming to cope with sometimes very complex and time consuming treatment modalities and combinations. The glycosylated haemoglobin A1c (HbA1c) target level must therefore be evaluated individually for different patients with type 2 diabetes mellitus and should take both the potential benefits and harms into account.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACCORD 2008

Methods	2x2 factorial randomised clinical trial.
Participants	SEX: Intensive: Female: 1985; male: 3143 Conventional: Female: 1967; male: 3156 AGE (mean years (SD)): Intensive: 62.2 (6.8) Conventional: 62.2 (6.8) DURATION OF DISEASE (mean years (SD)): Intensive (median): 10 years Conventional (median): 10 years GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 8.3 (1.1) Conventional: 8.3 (1.1) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 9.7 (3.1) Conventional: 9.8 (3.1) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 32.2 (5.5) Conventional: 32.2 (5.5) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 1826 Conventional: 1783 INCLUSION CRITERIA: 1. Type 2 diabetes mellitus defined according to the 1997 ADA criteria for ≥ 3 months; 2. HbA1c level (obtained < 3 months before anticipated date of randomisation) of a. 7.5%-11%: (i) If on insulin < 1 U/kg and on 0 or 1 oral anti-diabetic agent or (ii) If not on insulin, and on 0, 1, or 2 oral anti-diabetic agents; b. 7.5%-9%: (i) If on insulin < 1 U/kg and on 2 oral anti-diabetic agents, (ii) If on insulin > 1 U/kg and 0 oral anti-diabetic agents, or (iii) If not on insulin and on 3 oral anti-diabetic agents; 3. Stable diabetes therapy for > 3 months; 4. Age at randomisation; a. 40-79 years (inclusive) for anyone with a history of clinical cardiovascular disease, or b. 55-79 years (inclusive) for anyone without a history of clinical cardiovascular disease (the age eligibility was modified on the basis of the results of the vanguard phase, so some participants were aged ≥ 80 years at randomisation) 5. At high risk for cardiovascular disease events, defined as a. Presence of clinical cardiovascular disease (prior myocardial infarction, stroke, arterial revascularization, angina with ischaemic changes on electrocardiogram at rest, changes on a graded exercise test, or positive cardiac imaging test results); b. If no clinical cardiovascular disease, evidence in the past 2 years suggesting high likelihood of cardiovascular disease (1 risk factor: microalbuminuria, ankle-brachial index < 0.9, left ventricular hypertrophy by electrocardiogram or echocardiography, or > 50%

	stenosis of a coronary, carotid, or lower extremity artery), or c. Presence of ≥ 2 of the following factors that increase cardiovascular disease risk: LDL-cholesterol > 130 mg/dL (1 mg/dL = 0.02586 mmol/L) treated with lipid-lowering medication or untreated, low HDL-cholesterol (< 40 mg/dL for men and < 50 mg/dL for women), systolic blood-pressure > 140 mmHg or diastolic blood pressure > 95 mmHg treated with blood pressure-lowering medication or untreated, current cigarette smoking, or BMI > 32 kg/m^2; 6. In addition, all participants must be eligible for either the blood pressure trial or the lipid trial EXCLUSION CRITERIA: 1. History of hypoglycaemic coma/seizure within last 12 months; 2. Hypoglycaemia requiring third party assistance in last 3 months with concomitant glucose < 60 mg/dL (3.3 mmol/L); 3. History consistent with type 1 diabetes mellitus; 4. Unwilling to do frequent capillary blood glucose self-monitoring or unwilling to inject insulin several times a day; 5. BMI > 45 kg/m^2; 6. Serum creatinine > 1.5 mg/dL (132.6μ mol/L) obtained within the previous 2 months; 7. Transaminase > 2 times upper limit of normal or active liver disease; 8. Any ongoing medical therapy with known adverse interactions with the glycaemic interventions (e.g., corticosteroids, protease inhibitors); 9. Cardiovascular event or procedure (as defined for study entry) or hospitalisation for unstable angina within last 3 months; 10. Current symptomatic heart failure, history of NYHA class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25%; 11. A medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years; 12. Any factors likely to limit adherence to interventions; 13. Failure to obtain informed consent from participant; 14. Currently participating in another clinical trial; 15. Living in the same household as an already randomised ACCORD participant; 16. Any organ transplant; 17. Weight loss > 10% in last 6 months; 18. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practicing birth control; 19. Participants with recurrent requirements for phlebotomy or transfusion of red blood cells DIAGNOSTIC CRITERIA: Type 2 diabetes mellitus defined according to the 1997 ADA criteria: • Fasting plasma glucose > 126 mg/dL (> 7.0 mmol/L), or • Symptoms of hyperglycaemia with casual plasma glucose > 200 mg/dL (>11.1 mmol/L), or • 2 hour plasma glucose > 200 mg/dL (> 11.1 mmol/L) after a 75 gram oral glucose load.
Interventions	NUMBER OF STUDY CENTRES: 77 COUNTRY/ LOCATION: USA and Canada SETTING: Outpatient INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED):

	TARGET: HbA1c < 6 %. (fasting self monitored blood glucose < 5.6 mmol/L (100 mg/dL) or 2 hours blood glucose < 7.8 mmol/L (140 mg/dL) were also "action required threshold") ANTIDIABETIC INTERVENTIONS: The treatment algorithm depends on how many antidiabetic drugs the patient enters the trial with. Therapeutic regimens were individualised on the basis of group assignment and the response to therapy. When the glycaemic target was not achieved with 3 oral anti-diabetic drugs, insulin therapy was initiated. The following anti-diabetic drugs were available: biguanides, insulin secretagogues, thiazolidinediones, alpha-glucosidase inhibitors and insulins (for detailed description, please see study protocol p 62-63). Diet and lifestyle advice CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c 7%-7.9%. (fasting self monitored blood glucose > 5.0 mmol/L (90 mg/dL) was also "action required threshold") ANTIDIABETIC INTERVENTIONS: The therapeutic regimes were individualised. See above. Diet and lifestyle advice CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: About 5800 participants were randomised in the lipid component of the ACCORD trial. Eligible participants were randomised to fenofibrate or placebo; all participants were treated with simvastatin. The participants, who were not enrolled in the lipid portion of the ACCORD were treated by their usual physician. About 4200 participants were randomised to the blood pressure part of the ACCORD, where many classes of antihypertensives and combinations may be used (protocol p 70) . The participants who were not in the blood pressure trial were treated by their usual physician. ACE-inhibitors were prescribed to all participants with previously cardiovascular disease or one cardiovascular risk factor (besides type 2 diabetes mellitus) CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: All participants were advised to take aspirin daily. Lipid-lowering: For the participants not randomised to the lipid-lowering part of the ACCORD the recommended LDL-cholesterol goals were based on the National Cholesterol Education Program (NCEP) 2001 guidelines (initiation of pharmacologic treatment: LDL-cholesterol > 130 mg/dL, treatment goal: < 100 mg/dL (2.59 mmol/L)). The same LDL goal was stated for both arms in the lipid-lowering part of the trial. Blood pressure: In the blood pressure part of the trial the treatment goal in the intense group was: systolic blood pressure < 120 mmHg. In the less intense treatment arm of the blood pressure trial, the treatment target was a systolic blood pressure < 140 mmHg. For participants not in the blood pressure part of ACCORD, were treated by their usual physician. For participants not in the blood pressure trial the recommended blood pressure goal was 140/85 mmHg
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death SECONDARY OUTCOMES (as stated in the publication): • An expanded macrovascular outcome, specifically the combination of the primary

	endpoint plus any revascularization plus hospitalisation for congestive heart failure; • total mortality; • cardiovascular mortality; • major coronary heart disease event, specifically fatal events, non-fatal myocardial infarction, and unstable angina; • total stroke, specifically fatal strokes and non-fatal strokes; • congestive heart failure death or hospitalisation for congestive heart failure; • health-related quality of life; • cost-effectiveness; • the main microvascular outcome of the ACCORD trial is the primary outcome of the ACCORD Eye Substudy, namely: "the combined outcome of progression of diabetic retinopathy of at least 3 stages on the Early Treatment of Diabetic Retinopathy Study scale, photocoagulation, or vitrectomy for diabetic retinopathy"; • second composite microvascular endpoint will be examined in the entire ACCORD population: fatal or non-fatal renal failure, or retinal photocoagulation, or vitrectomy for diabetic retinopathy. ADDITIONAL OUTCOMES: • All cardiovascular revascularization procedures; • unstable angina; • total cancer mortality. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): NR.
Study details	DURATION OF INTERVENTION: Mean of 3.5 years (median 3.4 years). DURATION OF FOLLOW-UP: Median of 5.0 years. TITRATION PERIOD: When metformin was initiated, it was titrated to maximum dose over 4 weeks RUN-IN PERIOD: Potential participants will be asked to monitor capillary blood sugars 2 to 4 weeks pre-randomisation STUDY TERMINATED BEFORE REGULAR END: Yes.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Companies provided study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough NON-COMMERCIAL FUNDING: National Heart, Lung, and Blood Institute; by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the Centers for Disease Control and Prevention; and by General Clinical Research Centers
Stated aim for study	"The overall goal of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is to address this challenge by testing three complementary medical treatment strategies for type 2 diabetes to enhance the options for reducing the still very high rate of major CVD morbidity and mortality in this disease."
Notes	Values for fasting blood glucose are calculated from mg/dL to mmol/L by dividing with 18

ACCORD 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "An internet-based, web browser randomization procedure will be employed in ACCORD. Clinical Sites access the study web site and initiate the interactive randomization page. Entry into this area is password protected and encrypted."
Allocation concealment (selection bias)	Low risk	Quote: "An internet-based, web browser randomization procedure will be employed in ACCORD. Clinical Sites access the study web site and initiate the interactive randomization page. Entry into this area is password protected and encrypted."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "...classify the occurrence of clinical events in a masked fashion and to monitor event ascertainment/classification quality control."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the Appendix it is described; a total of 37 patients refused the approach they were randomised to, 50 were lost to follow-up and 688 discontinued intervention (a total of 775 participants). In the main publication it is described that 162 participants withdrew consent. It is unclear whether the 162 participants are calculated together with the other number reported in the Appendix
Selective reporting (reporting bias)	Low risk	Some of the predefined outcomes are still not published, as the analysis might not be finish yet
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Companies provided study medications, equipment or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough

ACCORD 2008 (*Continued*)

Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

ADVANCE 2008

Methods	Factorial randomised clinical trial.
Participants	SEX: Intensive: Female: 2376; male: 3195 Conventional: Female: 2357; male: 3212 AGE (mean years (SD)): Intensive: 66 (6) Conventional: 66 (6) DURATION OF DISEASE (mean years (SD)): Intensive: 7.9 (6.3) Conventional: 8.0 (6.4) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 7.5 (1.7) Conventional: 7.5 (1.6) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 8.5 (2.8) Conventional: 8.5 (2.8) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 28 (5) Conventional: 28 (5) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 1794 Conventional: 1796 INCLUSION CRITERIA: • 55 years or older at entry; • elevated risk of vascular disease (high risk for vascular disease was defined by a diagnosis of type 2 diabetes mellitus made 10 or more years earlier; or age 65 years or older at entry; or a history of any of the following: major macrovascular disease (including myocardial infarction, stroke, hospitalisation for transient ischaemic attack or unstable angina, or revascularization procedure)), major microvascular disease (including macroalbuminuria, proliferative retinopathy or retinal photocoagulation, or macular oedema), or another major risk factor for vascular disease (current cigarette smoking, total cholesterol > 6.0 mmol/L, HDL-cholesterol < 1.0 mmol/L or microalbuminuria); • diagnosis of type 2 diabetes mellitus first made at age 30 years or older. EXCLUSION CRITERIA: • Definite indication for, or contraindication to any of the study treatments; • a definite indication for long-term insulin therapy at the time of study entry. DIAGNOSTIC CRITERIA: NR.
Interventions	NUMBER OF STUDY CENTRES: 215. COUNTRY/ LOCATION: 20 countries from Asia, Australia, Europe, and North America

	SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c $\leq$ 6.5%. ANTIDIABETIC INTERVENTIONS: All participants were given gliclazide (modified release, 30 to 120 mg daily) and were required to discontinue any other sulphonylurea. On the basis of the HbA1c at each visit, this protocol initially advised increasing the dose of gliclazide (modified release), with the sequential addition or increase in dose of metformin, glitazones, acarbose, or insulin (advising the initial use of basal insulin, with the addition of short-acting insulin at meals) CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Strategy of standard glucose control with HbA1c target levels defined on the basis of local guidelines. ANTIDIABETIC INTERVENTIONS: Participants using gliclazide (modified release) when they entered the study were required to substitute this drug with another sulphonylurea, if continued therapy was required CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Participants were also assigned to placebo or preterax (a combination of perindopril and indapamide) CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: No prespecified target level of blood pressure.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): The primary endpoint was a composite of: • Major macrovascular complications; non-fatal stroke, non-fatal acute coronary syndrome, and death from any cardiovascular cause; • major microvascular complications; new or worsening nephropathy (defined as development of macroalbuminuria, doubling of serum creatinine to $\geq$ 200 μmol/L, the need for dialysis, transplantation or death from renal disease) or microvascular eye disease (defined as the need for retinal photocoagulation therapy, development of proliferative retinopathy, macular oedema, or diabetes-related blindness) SECONDARY OUTCOMES (as stated in the publication): • Death from any cause; • death from cardiovascular causes; • major coronary events (death due to coronary heart disease (including sudden death) or non-fatal myocardial infarction); total coronary events (major coronary events, silent myocardial infarction, coronary revascularization, or hospital admission for unstable angina); • major cerebrovascular events (death due to cerebrovascular disease or non-fatal stroke); • total cerebrovascular events (major cerebrovascular events, transient ischaemic attack, or subarachnoid haemorrhage); • heart failure (death due to heart failure, hospitalisation for heart failure, or worsening NYHA class); • peripheral vascular events; • new or worsening nephropathy; • new or worsening retinopathy;

	• development of microalbuminuria; • visual deterioration; • new or worsening neuropathy; • decline in cognitive function (reduction in the Mini-Mental State Examination score by at least 3 points, as compared with the baseline score); • dementia (satisfying the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition); • cost-effectiveness; • health-related quality of life; • hospitalisation for 24 hours or more; • hypoglycaemia. ADDITIONAL OUTCOMES: • Identifying genotypic predictors of vascular complications (specifically heart attack, stroke and nephropathy; substudy); • heart function (substudy); • retinopathy (ADVANCE Retinal Measurements, AdRem) MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Laboratories participating in ADVANCE underwent a standardization process using the Wales External Quality Assurance Scheme (WEQAS). Target values for all samples were assigned for Diabetes Control and Complications Trial (DCCT) and the International Federation of Clinical Chemistry (IFCC) reference methods
Study details	DURATION OF INTERVENTION: 5 years. DURATION OF FOLLOW-UP: Median duration 5 years. TITRATION PERIOD: None described, but titration is assumed to have been done when initiating some of the oral anti-diabetic drugs (e.g., metformin). RUN-IN PERIOD: Potentially eligible participants entered a 6-week run-in period, during which they continued their usual methods of glucose control and received a fixed combination of perindopril and indapamide STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Supported by grants from Servier (the major financial sponsor). Servier manufactures gliclazide (modified release) and the fixed combination of perindopril and indapamide NON-COMMERCIAL FUNDING: The National Health and Medical Research Council of Australia
Stated aim for study	"The aim of ADVANCE is to see if treatment to lower blood pressure and control glucose levels more tightly than usual reduces the risk of all complications in adults with type 2 diabetes"
Notes	The participants will be followed after the intervention period in an ongoing follow-up study (timeframe 2014)
Risk of bias	

ADVANCE 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A central, computer-based randomisation service will assign patients to treatments stratified by the study centre, history of CVD or microvascular disease and background use of perindopril at baseline."
Allocation concealment (selection bias)	Low risk	Quote: "A central, computer-based randomisation service will assign patients to treatments stratified by the study centre, history of CVD or microvascular disease and background use of perindopril at baseline."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "An independent End Point Adjudication Committee, unaware of the group assignments, reviewed source documentation for all suspected primary end points and deaths."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 7 (intensive) and 10 (conventional) were lost to follow-up
Selective reporting (reporting bias)	Low risk	Some of the predefined outcomes are still not published, as the analysis might not be finish yet
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Servier.
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

Bagg 2001

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 12; male: 9 Conventional: Female: 12; male: 10 AGE (mean years (SD)): Intensive: 57.2 (7.4) Conventional: 54.5 (9.2) DURATION OF DISEASE (mean years (SD)): Intensive: 7.9 (4.5) Conventional: 5.9 (3.2) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 10.8 (0.2)

	Conventional: 10.5 (0.2) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 13.7 (0.6) Conventional: 13.2 (0.6) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 31.9 (1.1) Conventional: 29.4 (1.1) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 2 Conventional: 2 INCLUSION CRITERIA: • Type 2 diabetes mellitus of < 15 years duration • HbA1c > 8.9%. EXCLUSION CRITERIA: • Age > 75 or < 40 years; • body mass index (BMI) > 40 kg/m^2; • current diastolic blood pressure > 100 mmHg; • creatinine > 0.16 mmol/L; • any severe concurrent illness; • left ventricular failure, myocardial infarction, or unstable angina in the 6 months prior to enrolment; • recent (< 6 weeks) commencement of vasoactive cardiac medications. DIAGNOSTIC CRITERIA: • Age at diagnosis > 35 years; • no episodes of ketoacidosis in the past; • insulin independence for more than 12 months or fasting plasma C-peptide > 0.21 pmol/L if duration of disease less than 12 months.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: New Zealand. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTION USED): TARGET: HbA1c < 7%. Medication adjusted to following targets: Before meal capillary glucose: 4-7 mmol/L, 2 hour after meal < 10 mmol/L. ANTIDIABETIC INTERVENTIONS: Initially oral hypoglycaemic agents before commencing insulin. In patients treated with diet only at baseline the initial primary therapy with oral hypoglycaemic drug was determined by the BMI: (1) BMI < 32 kg/m^2: A sulphonylurea was chosen as the initial therapy. BMI > 32 kg/m^2: metformin was chosen as initial therapy. (2) Once the initial oral hypoglycaemic drug had reached the maximum tolerated dose (glipizide 10 mg twice a day or metformin 1 g three times a day), the secondary drug was added and increased to the maximum tolerated dose. (3) Bedtime intermediate-acting insulin was started at 2 U/kg and increased to twice a day if glycaemic targets were not met. Premixed or short-acting insulin could be instituted if necessary to meet glycaemic targets. Patients taking insulin were continued on one oral hypoglycaemic agent, defined by the BMI as in (1).

	Dietary and nursing advice at least one time during the intervention period CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Avoid symptomatic hyperglycaemia and fortnightly fasting capillary glucose tests of > 17 mmol/L. ANTIDIABETIC INTERVENTIONS: Similar stepped care as intensive group if they were persistent hyperglycaemic. Patients received dietary and nursing advice in at least one occasion if this had not been provided in the 12 month before enrolment in the study CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Change in flow mediated dilatation of the brachial artery SECONDARY OUTCOMES (as stated in the publication): The effects of improved metabolic control on blood pressure, weight, lipids, haemorrheology, and body composition ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c was measured by a commercial ion exchange assay adapted in the Variant2 high-performance liquid chromatography analyser BioRad, Hercules, CA, USA
Study details	DURATION OF INTERVENTION: 20 weeks. DURATION OF FOLLOW-UP: 20 weeks. TITRATION PERIOD: We assume metformin was titrated, when initiated RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: The AMP Society of New Zealand, Health Research Council of New Zealand, Auckland Medical Research Foundation and University of Auckland Staff Research Fund.
Stated aim for study	"The aims of this study were to elucidate the factors that contribute to endothelial activation and fibrinolytic abnormalities in patients with poorly controlled type 2 diabetes and to determine whether improved glycaemic control reduces endothelial activation." "To examine the effects of improved glycaemic control over 20 weeks on the type and distribution of weight change in patients with type 2 diabetes who at baseline have poor glycaemic control."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Bagg 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised on the basis of gender, age and smoking status to either a usual control (n = 22) or improved control (n = 21)." The author recalls the trial as randomised by computer generated sequence, but is not able to confirm this
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Two observers were blinded to the intervention and the sequence in which the images were acquired performed all measurements in duplicate."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Four patients in IC were withdrawn after randomization: one suffered a brainstem cerebrovascular accident after 2 weeks, one developed unstable angina after 6 weeks and two other patients developed nonvascular illness requiring hospitalization."
Selective reporting (reporting bias)	Low risk	All predefined primary and secondary outcomes were assessed.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Becker 2003

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 50; male: 56 Conventional: Female: 60; male: 48 AGE (mean years (SD)): Intensive: 63.3 (8.4) Conventional: 63.3 (8.3) DURATION OF DISEASE (mean years (SD)): Intensive (median): 3.4 Conventional (median): 3.2 GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: NR Conventional: NR FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 9.4 (2.8) Conventional: 9.7 (3.3)

	BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 28.0 (4.8) Conventional: 29.1 (4.3) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 21 Conventional: 23 INCLUSION CRITERIA: • Type 2 diabetes mellitus; • age between 40 and 75 years; • Caucasian ethnicity. EXCLUSION CRITERIA: • No established diagnosis of diabetes according to WHO criteria in the absence of glucose-lowering medication; • carcinoma; • other comorbidity preventing three monthly visits to the study centre or seriously impairing well-being; • language problems; • psychological problems. DIAGNOSTIC CRITERIA: WHO criteria.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Netherlands. SETTING: Outpatient and general practitioners. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting capillary blood glucose < 6.5 mmol/L. ANTIDIABETIC INTERVENTIONS: Regimen: Oral anti-diabetic agents in increasing doses up to their usual maximum before other anti-diabetic agents were added In patients with a BMI $\geq$ 27 kg/m^2, metformin was the first step. If the assigned target values for glycaemic control were not reached either glibenclamide, gliclazide, or glipizide was added In patients with a BMI < 27 kg/m^2, sulphonylurea was the first step. If the assigned target values were not reached on tablets alone, bedtime intermediate-acting insulin was added (and metformin, if any, discontinued). If target values were not reached with this combination therapy, sulphonylurea was discontinued and twice-daily injections of a mixture of short- and intermediate-acting insulin was initiated If glycaemic control remained poor, multiple insulin injection therapy was considered CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting capillary blood glucose < 8.5 mmol/L. ANTIDIABETIC INTERVENTIONS: Same treatment algorithm as for intensive glycaemic control. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR.

Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Changes in lipidaemia, blood pressure, proinsulin, insulinaemia, plasma fibrinogen, plasma von Willenbrand factor, and the urinary albumin-creatinine ratio SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: Assessment of general well-being. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c was determined in EDTA plasma by ion exchange high-performance liquid chromatography (reference range: 4.3 to 6.1%; Modular Diabetes Monitoring System, BioRad, the Netherlands)
Study details	DURATION OF INTERVENTION: Mean of 22 months. DURATION OF FOLLOW-UP: Mean of 22 months. TITRATION PERIOD: We assume metformin was titrated, when initiated RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Univé Health Insurance. NON-COMMERCIAL FUNDING: None.
Stated aim for study	"...the association between on the one hand changes in glycaemic control and on the other hand within-subject changes of both classic cardiovascular risk factors and less conventional cardiovascular risk indicators that are typically associated with type 2 diabetes (proinsulin, insulin, fibrinogen, von Willebrand factor and the urinary albumin creatinine ratio)."
Notes	There is discrepancy in the number of participants between the two publications. In the article published in the Netherlands Journal of Medicine 372 participants were invited of which 232 gave informed consent. The data presented in the article from Netherlands Journal of Medicine included 214 patients with type 2 diabetes mellitus. The recruitment period was from June 1992 until December 1993. In the article published in Diabetes Care, 296 patients with type 2 diabetes mellitus were potentially eligible, of which 229 gave informed consent and 199 patients were randomised. The recruitment period was June 1992 to February 1994. We corresponded with two of the authors, who unfortunately were not able to clarify the discrepancy between the publications. We used baseline data from the publication from the Netherlands Journal of Medicine because the baseline characteristics of the participants were reported according to the groups the participants were randomised to. The publication from the Diabetes Care reported baseline characteristics according to the (percentage) achieved decrease in HbA1c

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After the baseline assessment, patients were randomly assigned to..."
Allocation concealment (selection bias)	Unclear risk	Not described.

Becker 2003 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants in the two articles of the trial, does not harmonise
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	Univé Health Insurance.
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

DIGAMI 2 2005

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 156; male: 318 Conventional: Female: 97; male: 209 AGE (mean years (SD)): Intensive: 68.1 (11.4) Conventional: 68.4 (11.2) DURATION OF DISEASE (mean years (SD)): Intensive: 7.9 (8.2) Conventional: 8.3 (8.3) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 7.2 (1.7) Conventional: 7.3 (1.7) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 12.8 (4.5) Conventional: 12.9 (4.6) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 28.3 (4.9) Conventional: 28.4 (4.4) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 474 Conventional: 306 INCLUSION CRITERIA: • Patients with established type 2 diabetes mellitus or an admission blood glucose > 11.0 mmol/L, admitted to participating coronary care units; • suspect acute myocardial infarction due to symptoms (chest pain > 15 min during the preceding 24 hour) and/or recent electrocardiogram signs (new Q-waves and/or ST-segment deviations in two or more leads).

	EXCLUSION CRITERIA: • Inability to cope with insulin treatment or to receive information on the study; • residence outside the hospital catchment area; • participation in other studies, or previous participation in DIGAMI 2. DIAGNOSTIC CRITERIA: Known type 2 diabetes mellitus was based on case history, record based information on diabetes and that the patient had been prescribed diabetes related therapy (lifestyle oriented and/or glucose-lowering drugs). Those with glucose > 11 mmol/L were accepted as having diabetes based on this elevated glucose level and subsequently higher than normal glucose values
Interventions	NUMBER OF STUDY CENTRES: 44 COUNTRY/ LOCATION: Sweden, Finland, Norway, Denmark, The Netherlands, and the UK SETTING: Hospital (coronary care units). INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting blood glucose level of 5 to 7 mmol/L and a non-fasting level of < 10 mmol/L. ANTIDIABETIC INTERVENTIONS: A 24 hour insulin-glucose infusion (for further details see Malmberg 1995) followed by a subcutaneous insulin-based long-term glucose control. Insulin was given as short-acting insulin before meals and intermediate long-acting insulin in the evening CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: No predefined target values, standard care. ANTIDIABETIC INTERVENTIONS: Routine metabolic management according to local practice CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Patients without contraindications were prescribed aspirin, thrombolytic agents, beta-blockers, lipid-lowering drugs, ACE- inhibitors, and revascularization procedures when appropriate CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): To compare total mortality between treatment groups 1 and 2 during the time of follow-up SECONDARY OUTCOMES (as stated in the publication): To compare the total mortality between groups 2 and 3 ADDITIONAL OUTCOMES: To compare morbidity, such as non-fatal reinfarction, congestive heart failure, and stroke, among the three groups MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c was analysed by high-performance liquid chromatography in a core laboratory (Department of Laboratory Medicine, Malmö Hospital, Sweden) on capillary blood applied on filter paper with an upper normal limit of 5.3%
Study details	DURATION OF INTERVENTION: The median study duration was 2.1 years (IQR 1.03-3.00 years).

	RUN-IN PERIOD: None. TITRATION PERIOD: None. DURATION OF FOLLOW-UP: 2.1 years. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Aventis Sweden and Novo Nordic Denmark, and AFA Insurance Denmark NON-COMMERCIAL FUNDING: The Swedish Heart-Lung Foundation.
Stated aim for study	"In DIGAMI 2, three treatment strategies were compared: group 1, acute insulin-glucose infusion followed by insulin-based long-term glucose control; group 2, insulin-glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice."
Notes	There are three intervention groups in the DIGAMI 2 trial. We have chosen to report two of the groups in our analyses: the one with the most intensive treatment strategy (group 1) and the group with standard care (group 3)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The computer-based randomization was centralized to the study coordinating office open 24 h/day (Karolinska Hospital, Stockholm, Sweden). An attempt for balanced randomization was performed directly after a patient had been evaluated for inclusion, given informed consent, and after baseline variables had been collected. Telecommunicated information about baseline variables were transferred into the computer and the subsequent randomization was based on an algorithm including important prognostic markers in the first DIGAMI trial...."
Allocation concealment (selection bias)	Low risk	Quote: "The computer-based randomization was centralized to the study coordinating office open 24 h/day (Karolinska Hospital, Stockholm, Sweden). An attempt for balanced randomization was performed directly after a patient had been evaluated for inclusion, given informed consent, and after baseline variables had been collected. Telecommunicated information about baseline variables were transferred into the computer and the subsequent randomization was based on an algorithm including important prognostic markers in the first DIGAMI trial...."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "An independent committee comprising three experienced cardiologists adjudicated all events blindly and could, as indicated, ask for any type of information felt

DIGAMI 2 2005 (*Continued*)

		needed to ensure a correct classification of the events and the reasons for mortality."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	High risk	DIGAMI 1996.
Free from sponsor bias?	High risk	Aventis, Sweden, and Novo Nordic, Denmark.
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

Guo 2008

Methods	Randomised clinical trial.
Participants	SEX: Both groups: Female: 92; male: 128 Intensive: Female: NR; male: NR Conventional: Female: NR ;male: NR AGE (mean years (SD)): Intensive: 49.3 (8.8) Conventional: 48.3 (8.7) DURATION OF DISEASE (mean years (SD)): Both groups: All participants had duration less than 1 year. GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 7.1 (1.9) Conventional: 7.7 (2.5) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 8.2 (2.6) Conventional: 9.0 (2.5) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 25.7 (3.1) Conventional: 25.3 (4.1) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: NR Conventional: NR INCLUSION CRITERIA: • Duration of type 2 diabetes mellitus less than 1 year; • age 30-70 years; • informed consent for the participation and regular monthly visit at diabetic clinic. EXCLUSION CRITERIA: • Other types of diabetes; • liver disease;

	• coronary heart disease; • cerebral or peripheral vascular disease; • renal disease except diabetic renal disease; • carotis intima-media thickness < 1.3 mm at baseline. DIAGNOSTIC CRITERIA: WHO 1999.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: China. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting plasma glucose 4.0 to 7.0 mmol/L, HbA1c < 7%. ANTIDIABETIC INTERVENTIONS: The hypoglycaemic agents included: • Glipizide (max 15 mg daily); • metformin (max 2250 mg daily); • α-Glucosidase inhibitors (max of 150 mg daily); • bedtime intermediate-acting insulin was added if HbA1c concentrations $\geq$ 7% after maximum oral hypoglycaemic treatment was reached. Advice on diet and physical exercise. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: No treatment goal. ANTIDIABETIC INTERVENTIONS: Routine outpatient service, dosage of their medications were adjusted if needed General health and diabetes-related advice. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: INTENSIVE: • Hypertension; Captopril and/or extended release Nifedipine were used. • Simvastatin was used for hypercholesterolaemia. • Delayed-release aspirin was given as a secondary prevention. CONVENTIONAL: Standard care, not specified. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: Intensive intervention group: Systolic blood pressure (mmHg): < 130; Diastolic blood pressure (mmHg): < 80; Total cholesterol (mmol/L): < 4.5; LDL-cholesterol (mmol/L): < 3.0; HDL-cholesterol (mmol/L): > 1.1; Triglycerides (mmol/L): < 1.5. Conventional intervention group: Standard care, not specified
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Progression of carotis intima-media thickness SECONDARY OUTCOMES (as stated in the publication): None found ADDITIONAL OUTCOMES: Body weight, BMI, blood pressure, urine albumin excretion rate (μg/min) MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c was determined

	by means of high-performance liquid chromatography
Study details	DURATION OF INTERVENTION: 6 months. DURATION OF FOLLOW-UP: 6 months. TITRATION PERIOD: When metformin was initiated we assume it was titrated RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: NR. NON-COMMERCIAL FUNDING: NR.
Stated aim for study	"We sought to determine whether a 6-month intensive multitherapy program resulted in better goal attainment than usual care and its effect on the development of cIMT among patients with newly diagnosed type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "All patients in this study were randomly assigned by computer program to receive intensive multitherapy or to serve as controls in a proportion of 3:1."
Allocation concealment (selection bias)	Low risk	Quote: "All patients in this study were randomly assigned by computer program to receive intensive multitherapy or to serve as controls in a proportion of 3:1."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Unclear risk	No funding described.
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, unclear blinding

IDA 2009

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 10; male: 29 Conventional: Female: 10; male: 33 AGE (mean years (SD)): Intensive (median): 66 (9.6) Conventional (median): 62 (6.7) DURATION OF DISEASE (mean years (SD)): Intensive: 6.4 (5.8) Conventional: 6.5 (7.4) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 6.5 (1.4) Conventional: 6.5 (1.3) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (median): 7.0 (1.9) Conventional (median): 7.3 (1.6) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: NR Conventional: NR NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 51 Conventional: 51 INCLUSION CRITERIA: Type 2 diabetes mellitus, and accepted for percutaneous coronary intervention as treatment for coronary artery disease EXCLUSION CRITERIA: • Acute myocardial infarction within 48 hours before the intervention; • inability to participate for physical or psychological reasons; • residency outside the hospital catchment areas. DIAGNOSTIC CRITERIA: All patients had previously known diabetes accepted as type 2 if the patient was > 35 years of age at onset of disease and without any demand of insulin during at least two years thereafter
Interventions	NUMBER OF STUDY CENTRES: 2. COUNTRY/ LOCATION: Sweden. SETTING: Hospital and outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c < 6.5%, fasting blood glucose 5-7 mmol/L and blood glucose before meals < 10 mmol/L. ANTIDIABETIC INTERVENTIONS: Elective patients: Attempts were made to optimise glycaemic control during three weeks preceding the percutaneous coronary intervention. Acute patients: Patients, in whom revascularization was deemed necessary within few days, were immediately brought to the best possible glucose control by means of a glucose-insulin infusion aiming at a blood glucose level of 4-9 mmol/L. The infusion continued for at least 12 hours after the percutaneous coronary intervention. Thereafter the treatment was identical for elective and acute patients. Both elective and acute patients: Treatment with fast-acting meal insulin three times

	daily and long-acting insulin at bedtime. This treatment was initiated by bed-time insulin with the dose adjusted to obtain fasting blood glucose of 5-7 mmol/L. If blood glucose still exceeded 10 mmol/L insulin human or insulin lispro was added before meals CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Standard treatment. ANTIDIABETIC INTERVENTIONS: Continuation of ongoing antidiabetic treatment, or changes assessed by physician CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: All participants received optimal medical care and use of aspirin, statins, beta-blocker, and antihypertensive treatment were recommended CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): If improved glucose control, achieved by insulin, reduces the rate of restenosis after percutaneous coronary intervention in patients with type 2 diabetes mellitus SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c was analysed by high-performance liquid chromatography in a core laboratory on capillary blood with an upper normal limit of 5.3%
Study details	DURATION OF INTERVENTION: 6 months and 3 weeks (attempts were made to optimise glycaemic control during three weeks preceding the percutaneous coronary intervention in the intensive intervention group). DURATION OF FOLLOW-UP: 6 months and 3 weeks. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: Yes.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: AFA insurance. NON-COMMERCIAL FUNDING: The Swedish Heart Lung foundation.
Stated aim for study	"The primary objective was to test the hypothesis that improved glucose control, achieved by adding or optimising insulin treatment, will reduce the rate of restenosis after PCI in patients with type 2 diabetes."
Notes	The baseline characteristics (except for previous cardiovascular disease) are only reported for 82 patients (intensive: 39, standard: 43), who completed follow-up The SD for age, average duration of diabetes, glycaemic control and fasting blood glucose is calculated from IQR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

IDA 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Central computer-generated. Quote: "…subsequently randomised to an intensified insulin-based glucose control (I-group) or to continue ongoing glucose-lowering treatment (C-group). "
Allocation concealment (selection bias)	Low risk	Central computer-generated. Quote: "…subsequently randomised to an intensified insulin-based glucose control (I-group) or to continue ongoing glucose-lowering treatment (C-group). "
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "...by two blinded interventionists."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The planned PCI was not performed in three patients and six withdrew their original consent to participation in the study. The final study group, in which restenosis could be assessed, consisted of 82 patients (I-group = 39; C-group = 43)." Quote: "Six patients did not undergo the angiogram due to unwillingness and five for medical reasons including cancer, salmonella and Addison's disease."
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	AFA Insurance
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

Jaber 1996

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 12; male: 5 Conventional: Female: 15; male: 7 AGE (mean years (SD)): Intensive: 59 (12) Conventional: 65 (12) DURATION OF DISEASE (mean years (SD)): Intensive: 6.8 (6.5) Conventional: 6.2 (4.8) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 11.5 (2.9)

	Conventional: 12.2 (3.5) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 11.1 (4.0) Conventional: 12.7 (4.7) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 34 (7) Conventional: 33 (7) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: NR Conventional: NR INCLUSION CRITERIA: Not specified. Only description in text: "Urban African-American patients with NIDDM currently attending a university affiliated general internal medicine outpatient clinic were considered for inclusion." EXCLUSION CRITERIA: • Insulin-dependent diabetes mellitus; • renal dysfunction (serum creatinine > 133 μmol/L); • hepatic disorder (concentration of serum aminotransferases 3 times above normal); • significant cardiac complications within the last 6 months; • mental incompetence; • history of non-compliance with regular clinical visits within the last 2 years. DIAGNOSTIC CRITERIA: NR.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: USA. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Regimens were adjusted or titrated to achieve fasting blood glucose $\leq$ 6.6 mmol/L and 2 hour post-prandial glucose concentrations of < 10 mmol/L or to reach maximum daily doses of the sulphonylurea. ANTIDIABETIC INTERVENTIONS: Advice about diabetes and lifestyle. Sulphonylurea. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Not defined. ANTIDIABETIC INTERVENTIONS: Standard care. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Fasting plasma glucose and glycated haemoglobin concentrations SECONDARY OUTCOMES (as stated in the publication): Blood pressure, serum creatinine, creatinine clearance, microalbumin to creatinine ratio, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein concentrations ADDITIONAL OUTCOMES: • Patient compliance;

	• hypo- and hyperglycaemic episodes; • quality of life. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Described as glycated haemoglobin, unknown whether it is HbA1c. Glycated haemoglobin concentrations were determined with the Isolab Glyc-Affin test kit (Isolab, Akron, OH). The normal range was 4.0% to 8.0% (mean: 6% SD: 1%)
Study details	DURATION OF INTERVENTION: 4 months. DURATION OF FOLLOW-UP: 4 months. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Upjohn. NON-COMMERCIAL FUNDING: Diabetes Research and Education Foundation
Stated aim for study	"To assess the effectiveness of a pharmaceutical care model on the management of non-insulin-dependent diabetes mellitus (NIDDM) in urban African-American patients."
Notes	The baseline characteristics are from the participants, who completed the trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized, parallel fashion..."
Allocation concealment (selection bias)	Unclear risk	Quote: "A randomized, parallel fashion..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six patients in the intervention group dropped out or were discharged from the study. Of those, 4 found it difficult to comply with the frequency of the visits, 1 discharged by the study investigators because of unstable angina within the first 2 weeks of the study, and 1 was lost to follow up."
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Grant from Upjohn.

Jaber 1996 (*Continued*)

Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

Kumamoto 2000

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 27; male: 28 Conventional: Female: 29; male: 26 AGE (mean years (SD)): Intensive: 48.2 (11) Conventional: 50.9 (14) DURATION OF DISEASE (mean years (SD)): Intensive: 8.6 (5.4) Conventional: 8.5 (5.2) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 9.4 (1.6) Conventional: 8.9 (1.4) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 9.4 (1.8) Conventional: 9.0 (1.9) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 20.5 (2.1) Conventional: 20.4 (2.6) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 0 Conventional: 0 INCLUSION CRITERIA: • No retinopathy or simple retinopathy determined by clinical funduscopic evaluation; • urinary albumin excretion < 300 mg/24 hour and serum creatinine level < 1.5 mg/dL; • absence of diabetic somatic or autonomic neuropathy severe enough to require treatment; • < 70 years of age; • otherwise healthy (no other findings such as hypertension, hypercholesterolaemia, severe diabetic complications, or other severe medical conditions). EXCLUSION CRITERIA: None described. DIAGNOSTIC CRITERIA: All of the patients were diagnosed as being affected with type 2 diabetes mellitus by their characteristics of no history of ketoacidosis, negative islet cell antibody, and daily urinary C-peptide excretion more than 20 pg
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Japan. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED):

	TARGET: • fasting blood glucose concentration (< 140 mg/dL); • 2 hour postprandial blood glucose concentration < 200 mg/dL; • HbA1c < 7.0%; • mean amplitude of glycaemic excursions < 100 mg/dL. ANTIDIABETIC INTERVENTIONS: The group was administered insulin 3 or more times daily (rapid-acting insulin at each meal and intermediate-acting insulin at bedtime). The dosage was adjusted according to the self-monitored results of blood glucose. Adjustment doses of insulin were usually 2-4 U at each point. Diet and exercise advice. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Glycaemic control as close to the fasting blood glucose concentration of < 140 mg/dL without symptoms of hyperglycaemia or hypoglycaemia. ANTIDIABETIC INTERVENTIONS: The group was administered 1 or 2 daily injections of intermediate-acting insulin. Diet and exercise advice. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: All attending physicians were asked to achieve good treatment of cardiovascular risk factors. No prespecified target values
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Primary prevention: The development of diabetic microangiopathy in patients with type 2 diabetes mellitus with no retinopathy and urinary albumin excretion < 30 mg/24 hour. Secondary prevention: The progression of microangiopathy in patients with type 2 diabetes mellitus with simple retinopathy and urinary albumin excretion < 300 mg/24 hour SECONDARY OUTCOMES (as stated in the publication): Macrovascular complications ADDITIONAL OUTCOMES: Cost-effectiveness, diabetes-related death MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1c value was assayed using high performance liquid chromatography (normal range: 4.8 to 6.4%)
Study details	DURATION OF INTERVENTION: 10 years. DURATION OF FOLLOW-UP: 10 years. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: The publication of one of the articles was made possible by an unrestricted educational grant from Aventis Pharma NON-COMMERCIAL FUNDING: Diabetes Mellitus Research Grants, the Ministry of Health and Welfare, Japan

Stated aim for study	"The Kumamoto study was a randomized clinical trial, designed to compare intensive insulin therapy, using the multiple insulin injection therapy with the conventional insulin injection therapy, to evaluate their effects on the development and the progression of the microvascular complications in NIDDM patients in both the primary-prevention cohort and the secondary-intervention cohort."
Notes	Fasting blood glucose is read from figure and converted from mg/dL to mmol/L by dividing with 18 All patients were stratified to a primary-prevention cohort (patients with no retinopathy and urinary albumin excretion < 30 mg/24 hour) and a secondary-intervention cohort (patients were required to have simple retinopathy and urinary albumin excretion < 300 mg/24 hour) After 6 years, the selection of insulin treatment regimens were left to the patients. Only two patients in the conventional insulin injection treatment group selected multiple insulin injection therapy, all other patients in both the conventional insulin injection treatment group and multiple insulin injection treatment group wanted to adhere to the same treatment regimens. Therefore, the follow-up study was initiated by the patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described. Quote: "One hundred and ten patients were divided into 2 cohorts - the primary-prevention cohort (n = 55) and the secondary-intervention cohort (n = 55)."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "After 10 years, 97 patients remained in the study, nine patients died (three in the MIT group and six in the CIT group) and four patients moved to other cities (two in each of the MIT and CIT groups)."
Selective reporting (reporting bias)	Unclear risk	The prolongation of the intervention period (8 and 10 years of follow-up) was initiated by the patients and the outcomes not predefined in previous publication
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	The publication of one of the articles was made possible by an unrestricted educational grant from Aventis Pharma

Kumamoto 2000 (*Continued*)

Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

Lu 2010

Methods	Randomised controlled clinical trial.
Participants	SEX: Intensive: Female: 7; male: 14 Conventional: Female: 6; male: 14 AGE (mean years (SD)): Intensive: 57.5 (11.0) Conventional: 61.5 (10.4) DURATION OF DISEASE (mean years (SD)): Intensive: 8.0 (4.0) Conventional: 8.3 (4.7) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 8.8 (4.4) Conventional: 9.1 (2.6) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 9.2 (4.3) Conventional: 9.4 (3.8) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 24.5 (3.6) Conventional: 24.2 (4.2) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: NR. Conventional: NR. INCLUSION CRITERIA: • Type 2 diabetes mellitus for at least two years; • treated with hypoglycaemic agents and/or diet; • microalbuminuria. EXCLUSION CRITERIA: • Glumerular nephritis • nephritic syndrome; • urinary tract infections: • chronic diarrhoea; • heart failure; • tuberculosis; • recent medication of nephrotoxic drugs • severe diabetic complications; • severe diseases of other systems. DIAGNOSTIC CRITERIA: NR.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: China. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTION USED)

	:TARGET: Fasting blood glucose < 6.1 mmol/L, postprandial 2 hour glucose < 7.8 mmol/L. ANTIDIABETIC INTERVENTIONS: Diet and hypoglycaemic agents. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting blood glucose < 7.0 mmol/L, postprandial 2 hour glucose < 10.0 mmol/L. ANTIDIABETIC INTERVENTIONS: Diet and hypoglycaemic agents. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Prohibited drugs: ACE-inhibitors, angiotensin receptor blockers, antiplatelet drugs, anticoagulants, vasodilators and antihyperlipidaemic drugs CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Systolic blood pressure (mmHg): < 130; diastolic blood pressure (mmHg): < 80.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Changes of microalbuminuria SECONDARY OUTCOMES (as stated in the publication): Levels of serum lipids and coagulation indices ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): NR.
Study details	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: 12 weeks. TITRATION PERIOD: None described. RUN-IN PERIOD: None described. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: Shaanxi Provincial Science and Technology Plan projects
Stated aim for study	"This clinical trial was designed to investigate the therapeutic effect of intensive glycemic control on type 2 diabetes patients with early DN"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 41 patients were divided into two groups randomly..."
Allocation concealment (selection bias)	Unclear risk	Quote: "... 21 of them were allocated in intensive glycemic control group (Group A) and the other 20 patients were enrolled into regular glycemic

Lu 2010 (*Continued*)

		control group (Group B)."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described if there was any drop-outs.
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

Melidonis 2000

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 11; male: 13 Conventional: Female: 8; male: 16 AGE (mean years (SD)): Intensive: 66.6 (6.7) Conventional: 66.5 (9.6) DURATION OF DISEASE (mean years (SD)): Intensive: 10.5 (4.4) Conventional: 12.4 (range: 3-38) GLYCAEMIC CONTROL (mean HbA1c (standardized level) (SD)): Intensive: 7.6 (0.6) Conventional: 7.9 (0.8) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 13.2 (3.6) Conventional: 13.9 (3.9) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 26.3 (4.0) Conventional: 27.4 (5.0) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 24 Conventional: 24 INCLUSION CRITERIA: • Acute coronary event (unstable angina or acute myocardial infarction) within the preceding 24 hours; • type 2 diabetes mellitus.

	EXCLUSION CRITERIA: • Inability or refusal to give informed consent for the methods of the study; • patients with type 1 and insulin-treated patients with type 2 diabetes mellitus. DIAGNOSTIC CRITERIA: WHO 1985.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Greece. SETTING: Hospital (coronary care unit). INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Blood glucose between 8.3 to 11.0 mmol/L in the first 48 hours after an acute coronary event, thereafter normoglycaemia. ANTIDIABETIC INTERVENTIONS: Patients received insulin by infusion for at least 48 hours according to a predefined protocol (please see publication for further details). Subcutaneous insulin treatment four times daily was started immediately after insulin infusion cessation until the end of hospitalisation to maintain normoglycaemia (three doses of soluble insulin administered subcutaneously before meals, plus a dose of intermediate-acting insulin in the evening) CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: No specified target. ANTIDIABETIC INTERVENTIONS: Not specified. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: All patients were treated with the optimal anti-anginal therapy for their ischaemic event. Thrombolytic treatment was administered when there were no contraindications in patients with onset of symptoms within 10 hours (streptokinase (1. 5 X 10-6 U over 60 min)) CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Fibrinolytic profile/function (parameters: Fibrinogen tissue plasminogen activator (t-PA), plasminogen activator inhibitor- 1 (PAI-1)) SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): HbA1C was determined by high performance liquid chromatography
Study details	DURATION OF INTERVENTION: BOTH GROUPS: 6 days. DURATION OF FOLLOW-UP: BOTH GROUPS: 6 days. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: Funded by the department in which the trial was

Melidonis 2000 (*Continued*)

	conducted
Stated aim for study	"In our study, we tested the hypothesis that intensive insulin treatment during an evolving acute coronary event (UA or AMI) improves the fibrinolytic function in diabetic patients. "
Notes	The number reported for fasting blood glucose is the mean daily plasma glucose (determined by at least four pre meal glucose values)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was made by using a table of random number
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "All samples were analyzed blinded to the clinical data." Blinding of clinical outcomes not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Description of all participants at the end of follow-up.
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Unclear risk	Adequate sequence generation. Unclear allocation concealment, and blinding

REMBO 2008

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 10; male: 31 Conventional: Female: 14; male: 26 AGE (mean years (SD)): Intensive (median): 64 (11.9) Conventional (median): 64 (7.4) DURATION OF DISEASE (mean years (SD)): Intensive (median): 5.0 (7.4) Conventional (median): 6.0 (8.5)

	GLYCAEMIC CONTROL (mean HbA1c (standardized level) (SD)): Intensive (median): 7.1 (1.2) Conventional (median): 7.2 (1.4) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (median): 6.5 (1.3) Conventional (median): 6.6 (1.9) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 31.6 (5.0) Conventional: 30.1 (4.4) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 41 Conventional: 40 INCLUSION CRITERIA: • Age 18 to 80 years; • NYHA classification II-III; • stable chronic heart insufficiency with unchanged medications at least two weeks before entry to trial; • left ventricular ejection fraction ≤ 45%; • type 2 diabetes mellitus. EXCLUSION CRITERIA: • Myocardial infarction (< 3 months before the randomisation); • unstable angina pectoris; • congenital coronary artery disease; • acquired myocardial infarction with substantial haemodynamic stenosis; • hypertrophic or restrictive cardiomyopathy; • chronic pulmonary heart disease; • arterial hypertension with systolic pressure > 180 mmHg and diastolic pressure >110 mmHg despite antihypertensive treatment; • acute inflammatory disease; • kidney insufficiency (plasma creatinine > 160 micromol/L); • active liver disease (alanine aminotransferase and aspartate aminotransferase levels > 3 times normal level); • electrolyte disruptions; • decompensated chronic heart insufficiency. DIAGNOSTIC CRITERIA: NR.
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Russia. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c < 7% in participants receiving sulphonylurea; HbA1c < 6.5% in participants receiving insulin. ANTIDIABETIC INTERVENTIONS: All participants received gliclazide, extended release. As a second step, metformin was added. If these two agents did not fulfil the glycaemic target, insulin was initiated CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED):

	TARGET: Not specified, standard care. ANTIDIABETIC INTERVENTIONS: Not specified, standard care. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: All participants were receiving optimal treatment for chronic heart failure (e.g., ACE-inhibitors, diuretics) CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Progression of heart insufficiency SECONDARY OUTCOMES (as stated in the publication): NR. ADDITIONAL OUTCOMES: Biochemical variables and quality of life MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): A1C is measured by turbidometric immuno inhibition
Study details	DURATION OF INTERVENTION: 12 months. DURATION OF FOLLOW-UP: 12 months. TITRATION PERIOD: We assume metformin was titrated, when initiated RUN-IN PERIOD: 2 weeks. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: Russian. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: NR. NON-COMMERCIAL FUNDING: NR.
Stated aim for study	"..to evaluate the influence of strict glycaemic control on chronic heart disease in patients with type 2 diabetes mellitus." [Translated from Russia]
Notes	All SD, except for the BMI, is calculated from IQR.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (from English abstract): "As a result of randomization 2 groups were performed - active with achievement of target levels of glycemia (n=41) and usual treatment (n=40) ."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up.

REMBO 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Unclear risk	No funding sources described.
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

Service 1983

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 3; male: 5 Conventional: Female: 3; male: 7 AGE (mean years (SD)): Intensive (median): 44 Conventional (median): 56 DURATION OF DISEASE (mean years (SD)): Intensive (median): 0.1 Conventional (median): 0.8 GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive (median): 11.4 Conventional (median): 11.4 FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (median): 9.9 Conventional (median): 7.7 BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: NR Conventional: NR NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: NR Conventional: NR INCLUSION CRITERIA: Recent onset (2 years or less) of insulin-requiring diabetes EXCLUSION CRITERIA: None described. DIAGNOSTIC CRITERIA: Participants were stratified as having type 1 or type 2 diabetes mellitus by basal and postprandial C-peptide values of less than 1 (type 1 diabetes mellitus) and more than 1 (type 2 diabetes mellitus) ng/ml
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: USA. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c to normal range and to maintain 80 minute postprandial plasma glucose well below 150 mg/dL (8.3 mmol/L).

	ANTIDIABETIC INTERVENTIONS: Complex insulin treatment tailored to each individual and all methods available at the time the trial started CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Eliminate symptoms, but not to a degree to reduce 80 minute postprandial plasma glucose below 150 mg/dL. ANTIDIABETIC INTERVENTIONS: A single daily injection of intermediate acting insulin CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: NR.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Neurological symptoms and a neurological disability score SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Boronate affinity chromatography
Study details	DURATION OF INTERVENTION: INTENSIVE: 1.5 years. CONVENTIONAL: 2.0 years. DURATION OF FOLLOW-UP: INTENSIVE (median): 1.5 years. CONVENTIONAL (median): 2.0 years. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: NINCDS, Heerick Funds and Borchard, Upton.
Stated aim for study	"A prospective, stratified, randomized 3-year clinical trial was conducted on the effect of rigorous versus conventional glucose control on peripheral nerve function....."
Notes	The trial included both patients with type 1 diabetes mellitus and type 2 diabetes mellitus, but the participants were stratified prior to randomisation. Two patients with type 2 diabetes mellitus randomised to intensive glucose control dropped out early in the trial. The baseline characteristics for these participants are not reported. The baseline characteristics above are from the 18 participants with type 2 diabetes mellitus, who completed the trial

Risk of bias

Bias	Authors' judgement	Support for judgement

Service 1983 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "After stratification, each patient was randomly assigned by a table of random numbers to conventional glucose control by continuation of the currently used insulin treatment or to rigorous glucose control."
Allocation concealment (selection bias)	Unclear risk	Not described, but the trial was randomised (see above).
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "...every 6 months, each patient was examined by the same neurologist (who was unaware of the patients treatment group)...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients were excluded from analysis; 2: Treatment was no longer required; 1: Treatment was not followed; 4: Early dropouts (< 6 months)
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Unclear risk	Adequate sequence generation and blinding. Unclear allocation concealment

Stefanidis 2003

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 14; male: 22 Conventional: Female: 18; male: 21 AGE (mean years (SD)): Intensive: 66 (11) Conventional: 68 (9) DURATION OF DISEASE (mean years (SD)): Intensive: 16 (7) Conventional: 15 (9) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 8.0 (1.0) Conventional: 8.2 (1.2) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (plasma glucose): 15.4 (5.2) Conventional (plasma glucose): 14.8 (5.6) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 28 (3.1) Conventional: 27.5 (3.2) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE:

	Intensive: 36 Conventional: 39 INCLUSION CRITERIA: Patients with type 2 diabetes mellitus admitted to coronary care unit with non-ST segment elevation acute coronary syndromes within the preceding 24 hours EXCLUSION CRITERIA: • Insulin-treated diabetes mellitus; • pathologic Q waves on the baseline electrocardiogram; • evolution in persistent ST-segment elevation myocardial infarction; • arrhythmias, and atrioventricular and intraventricular conduction disturbances that might have influenced either the global cardiac contractility or Doppler time intervals measurements; • septal or free left ventricular end-diastolic wall thickness > 12 mm; • Doppler evidence of more than a mild degree of left or right valvular regurgitation or stenosis; • use of inotropes; • revascularization intervention during the study period. DIAGNOSTIC CRITERIA: Type 2 diabetes mellitus was defined based on patient history or when plasma glucose levels were > 200 mg/dL at admission
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Greece. SETTING: Hospital. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Near normal glycaemia defined as 6.6 to 8.2 mmol/L. ANTIDIABETIC INTERVENTIONS: Soluble insulin by infusion, immediately after the first echocardiographic examination and subsequent randomisation, for 72 hours, according to a predefined protocol CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: No specific glucose target. ANTIDIABETIC INTERVENTIONS: Usual protocols, with oral hypoglycaemic drugs or 2 daily doses of intermediate acting insulin. Supplementary small doses of short-acting insulin were administered subcutaneously only if glucose levels were > 250 mg/dL CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: All participants were treated with an optimal anti-anginal regimen CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: No predefined targets
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Global myocardial performance SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Not described.
Study details	DURATION OF INTERVENTION: 72 hours. DURATION OF FOLLOW-UP: 72 hours.

	TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: The trial was conducted as a part of a PhD-thesis
Stated aim for study	"In this context, this open-label, randomised study assessed the impact of insulin administration on global myocardial performance during acute coronary syndromes, using a new Doppler-derived index (DI) that combines elements of systolic and diastolic phase periods of the cardiac cycle"
Notes	Fasting blood glucose is converted from mg/dL to mmol/L by dividing with 18

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomised to receive..." The randomisation procedure was done by using a table of random number
Allocation concealment (selection bias)	Unclear risk	Not described, but the trial was randomised (see above).
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Videotape recordings were analyzed by 1 investigator without knowledge of the clinical data, or whether the study was performed at admission or after 72 hours."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients from both groups were excluded from the analysis because there was objective evidence of development of persistent ST-elevation myocardial infarction. Two patients from group A and 1 from group B underwent percutaneous coronary intervention during the study period for intractable ischemia and were also excluded from the study."
Selective reporting (reporting bias)	Low risk	The predefined primary outcome is reported.
Free from academic bias (assessed from primary author)?	High risk	The primary author has written another publication about the same intervention (Melidonis 2000).
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Unclear risk	Adequate sequence generation and blinding. Unclear allocation concealment

Steno-2 2008

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 17; male: 63 Conventional: Female: 24; male: 56 AGE (mean years (SD)): Intensive: 54.9 (7.2) Conventional: 55.2 (7.2) DURATION OF DISEASE (mean years (SD)): Intensive (median): 5.5 (5.0) Conventional (median): 6.0 (4.4) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 8.4 (1.6) Conventional: 8.8 (1.7) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 10.1 (3.1) Conventional: 10.5 (3.0) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 29.7 (3.8) Conventional: 29.9 (4.9) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 18 Conventional: 21 INCLUSION CRITERIA: • Type 2 diabetes mellitus; • urine albumin excretion rates of 30-300 mg in a 24 hour urine sample. EXCLUSION CRITERIA: • Age older than 65 or younger than 40; • a stimulated serum C-peptide concentration less than 600 pmol/L 6 min after intravenous injection of 1 mg glucagon; • pancreatic insufficiency or diabetes secondary to pancreatitis; • alcohol abuse; • non-diabetic kidney disease; • malignancy; • life-threatening disease with death probable within 4 years. DIAGNOSTIC CRITERIA: WHO criteria (1985).
Interventions	NUMBER OF STUDY CENTRES: 1. COUNTRY/ LOCATION: Denmark. SETTING: Out-patient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c < 6.5%. ANTIDIABETIC INTERVENTIONS: • If patients were unable to maintain glycosylated haemoglobin values below 6.5% by means of diet and increased physical activity alone after three months, an oral hypoglycaemic agent was started: • Overweight patients (BMI > 25) received metformin (maximum, 1 gm twice daily); • lean patients, or overweight patients who had contraindications to metformin

	therapy, received gliclazide (maximum, 160 mg twice daily). • As the second step, metformin was added to the regimen of lean patients and gliclazide to that of overweight patients if hyperglycaemia was not controlled. • If the HbA1c exceeded 7.0% despite maximal doses of oral agents, the addition of neutral protamine Hagedorn (NPH) insulin at bedtime was recommended. When insulin was started, lean patients stopped metformin treatment and overweight patients stopped gliclazide therapy unless it was the only oral hypoglycaemic agent given. The insulin dose was adjusted on the basis of the morning fasting blood glucose concentration. If the daily dose of insulin exceeded 80 U at bedtime or there was no decrease in the HbA1c, patients were switched to regimens in which regular and NPH insulin was given two to four times a day. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c < 7.5% (1993-1999), HbA1c < 6.5% (2000-2001). ANTIDIABETIC INTERVENTIONS: Treatment according to the 1988 recommendations of the Danish Medical Association CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: Intensive: Treatment with ACE-inhibitor irrespective of blood pressure: Yes (1993-2001) Aspirin therapy: • For patients with known ischaemia: Yes (1993-2001). • For patients with peripheral vascular disease: Yes (1993-2001). • For patients without coronary heart disease or peripheral vascular disease: No (1993-1999); yes (2000-2001). Vitamin E and vitamin C. Non-medical interventions: Exercise at least 30 min/day and invitation to smoking cessation Conventional: Treatment with ACE-inhibitor irrespective of blood pressure: No (1993-1999); yes (2000-2001) Aspirin therapy: • For patients with known ischaemia: Yes (1993-2001). • For patients with peripheral vascular disease: No (1993-2001). • For patients without coronary heart disease or peripheral vascular disease: No (1993-1999); no (2000-2001). CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: Intensive: Systolic blood pressure (mmHg): < 140 (1993-1999); < 130 (2000-2001) Diastolic blood pressure (mmHg): < 85 (1993-1999); < 80 (2000-2001) Total cholesterol (mmol/L): < 4.9 (1993-1999); < 4.5 (2000-2001) Triglycerides (mmol/L): < 1.7 (1993-1999); < 1.7 (2000-2001) Conventional: Systolic blood pressure (mmHg): < 160 (1993-1999); < 135 (2000-2001) Diastolic blood pressure (mmHg): < 95 (1993-1999); < 85 (2000-2001) Total cholesterol (mmol/L): < 6.5 (1993-1999); < 4.9 (2000-2001) Triglycerides (mmol/L): < 2.2 (1993-1999); < 2.0 (2000-2001)
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): The study protocol specified two major analyses, a microvascular analysis in which the

	development of diabetic nephropathy after four years of intervention was the primary outcome and a macrovascular analysis after eight years of intervention The primary macrovascular outcome was a composite of: • Death from cardiovascular causes; • non-fatal myocardial infarction; • coronary-artery bypass grafting; • percutaneous coronary intervention; • non-fatal stroke; • amputation as a result of ischaemia; • vascular surgery for peripheral atherosclerotic artery disease. In follow-up trial: The time to death from any cause. SECONDARY OUTCOMES (as stated in the publication): Four years of intervention: The incidence or progression of diabetic retinopathy and neuropathy. Eight years of intervention: The incidence of diabetic nephropathy or the development or progression of diabetic retinopathy or neuropathy. Follow-up trial: Death from cardiovascular causes and a composite of cardiovascular disease events that included death from cardiovascular causes, non-fatal stroke, non-fatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention or revascularization for peripheral atherosclerotic arterial disease, and amputation as a result of ischaemia ADDITIONAL OUTCOMES: Four years of intervention: Macrovascular events and death were tertiary outcomes MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Ion-exchange high-performance liquid chromatography (Bio-Rad VARIANT, California, USA) and the non-diabetic reference range was 4.1 to 6.4%
Study details	DURATION OF INTERVENTION: 7.8 years. DURATION OF FOLLOW-UP: 13.3 years. TITRATION PERIOD: None. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Novo Nordisk A/S. NON-COMMERCIAL FUNDING: The Danish Health Research Council.
Stated aim for study	"Our randomised trial was designed to find out whether intensive multifactorial intervention that includes changes in behaviour and pharmacological therapy, slows the initiation and progression of microvascular complications in microalbuminuric patients with type 2 diabetes compared with a standard multifactorial treatment."
Notes	The SD for duration of diabetes is calculated from IQR. The number used for previously cardiovascular disease is the number of ischaemia on resting or stress electrocardiogram
Risk of bias	

Steno-2 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence was computer generated.
Allocation concealment (selection bias)	Low risk	Allocation was performed with the use of sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All events were defined a priori and evaluated by an Endpoint Committee unaware of patient treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Description of all participants at the end of follow-up.
Selective reporting (reporting bias)	Low risk	All predefined outcomes were assessed.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Supported by grants from Novo Nordisk A/S.
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

UGDP 1975

Methods	Randomised clinical trial
Participants	SEX: Intensive: Female: 158; male: 46 Conventional: Female: 153; male: 57 AGE (mean years (SD)): Only available for all treatments group: 52.7 (11.2) Intensive: NR. Conventional: NR. DURATION OF DISEASE (mean years (SD)): Both groups: All patients were diagnosed with type 2 diabetes within 12 months prior to enrolment in the study GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Both group: Not able to measure HbA1c at study time. FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 7.8 Conventional: 7.9 BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: NR Conventional: NR NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE:

	Intensive: 7 Conventional: 16 INCLUSION CRITERIA: • Maturity onset diabetes diagnosed within 12 months prior to enrolment in the study (the time of diagnosis was determined by the date of the first glucose tolerance test or by the time which hypoglycaemic treatment had been first initiated); • free of life-endangering diseases and a minimal life expectancy of five years at entry into the study in the clinician´ s judgement; • a diagnostic glucose tolerance test in which the sum of the four individual blood glucose values was ≥ 500 mg/100 mL; • free of ketoacidosis and other major diabetic symptoms on diet alone during a four-week observation period immediately preceding entry into the study; • patient willing and able to participate in the study. EXCLUSION CRITERIA: A prior history of ketoacidosis. DIAGNOSTIC CRITERIA: The results of the glucose tolerance test provided the primary basis for the diagnosis of diabetes for patients admitted to the study. A sum of four glucose values from glucose tolerance test had to be equal or greater than 500 mg/100 mL
Interventions	NUMBER OF STUDY CENTRES: 12. COUNTRY/ LOCATION: USA. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Maintain blood glucose in normal range. Normal defined as: fasting blood glucose level below 110 mg/100 mL and a level of less than 210 mg/100 mL one hour after ingestion of 50 gm of glucose and one and one-half hours after the morning insulin injection. ANTIDIABETIC INTERVENTIONS: The insulin variable treatment group: In the event that both above limits were exceeded at a scheduled test, the insulin dose was to be raised by at least two units. The investigators were to decrease the insulin dosage when it appeared necessary in order to prevent hypoglycaemic episodes. A minimum of five units per day was stipulated in the low end of the dosage scale. Diet. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Minimize the likelihood of hypoglycaemic reactions without reducing the insulin dose to pharmacologically inactive amounts. ANTIDIABETIC INTERVENTIONS: The insulin standard treatment group: The only scheduled modifications in the number of units of insulin prescribed for patients in the insulin standard group that were permitted after initiation of treatment were those which resulted from a change of the patient´ s weight which in turn led to changes in the patient´ s body surface and corresponding dosage category: Units of insulin/body surface in square meters: (10 U/ under 1.5); (12 U/ 1.5-1.69);

	(14 U/ 1.7-1.89); (16U/ 1.9 and over). Diet. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: Both groups: NR. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: NR
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): • Evaluation of the efficacy of various hypoglycaemic treatments in the prevention of vascular complications in patients with mild diabetes; • study of the natural history of a group of patients with maturity onset, non insulin dependent diabetes; • development of methods applicable to cooperative clinical trials. SECONDARY OUTCOMES (as stated in the publication): None described ADDITIONAL OUTCOMES: None described. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): NR.
Study details	DURATION OF INTERVENTION: mean 12 years (range 10-14.5 years). DURATION OF FOLLOW-UP: 12 years. TITRATION PERIOD: None. RUN-IN PERIOD: Four weeks on diet. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None. NON-COMMERCIAL FUNDING: The National Institute of Arthritis, Metabolism, and Digestive Diseases of the Public Health Service
Stated aim for study	"The University Group Diabetes Program is a long-term prospective clinical trial designed to evaluate the effects of various hypoglycemic agents on vascular complications in patients with asymptomatic adult-onset diabetes."
Notes	Patients were randomised to five different therapeutic regimes: Insulin variable, insulin standard, tolbutamide, phenformin, and placebo. We have chosen the IVAR (Insulin Variable) group as an intensive group and ISTD (Insulin Standard) as the conventional group At the time the study was conducted HbA1c was not used to measure glycaemic control Fasting blood glucose calculated from mg/dL to mmol/L by dividing with 18 Sixty-nine of the patients enrolled did not meet the diagnostic criterion of the glucose tolerance test (17 in insulin standard, 13 in insulin variable) The age is only reported for all treatments group, i.e., 1027 participants, whereof only 414 participants are of relevance for this review Previous cardiovascular disease is reported as a history of angina pectoris

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

UGDP 1975 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Patients enrolled in the UGDP were randomly assigned to one of the five treatment groups." Quote: "Separate allocation schedules were used for each of the participating Clinical Centers. These schedules were prepared using a table of random numbers and were designed to insure a specified number of patients in each of the treatment groups in a given clinic at periodic intervals throughout the course of the recruitment."
Allocation concealment (selection bias)	Low risk	Quote: "All assignments were made by the UGDP coordinating centre."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "....blind evaluation long-term observation of patients, and central collection, editing, and monitoring of the observed data."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patients who indicated that they were no longer willing or able to participate in the UGDP or who had missed four consecutive quarterly examinations were classified as dropouts. A patient classified as dropout remained classified in this way until he/she returned to the clinic for follow-up examination or until the date of death." Quote: ".....the percentage of patients classified as dropouts was 15.0 for PLBO, 18.0 for ISTD and 18.0 for IVAR."
Selective reporting (reporting bias)	Low risk	All predefined primary and secondary outcomes were reported.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	No industry funding.
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

UKPDS 1998

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 1260; male: 1811 Conventional: Female: 433; male: 705 AGE (mean years (SD)): Intensive: 53.2 (8.6) Conventional: 53.4 (8.6) DURATION OF DISEASE (mean years (SD)): Intensive: All participants were newly diagnosed with type 2 diabetes mellitus.

	Conventional: All participants were newly diagnosed with type 2 diabetes mellitus GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 7.1 (1.5) Conventional: 7.1 (1.4) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (median): 8.1 (1.9) Conventional (median): 8.0 (2.0) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 27.5 (5.1) Conventional: 27.8 (5.5) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Both groups: 77 INCLUSION CRITERIA: Newly-diagnosed patients with type 2 diabetes mellitus aged 25-65 years inclusive and had fasting plasma glucose greater than 6 mmol/L on two mornings, 1-3 weeks apart, were eligible for the study Every participant randomised in the UKPDS-33 1998 or UKPDS-34 1998 had a fasting plasma glucose of 6.1 to 15.0 mmol/L after three months diet (body weight > 120% of ideal body weight for the entry in the UKPDS-34 1998). EXCLUSION CRITERIA: • Ketonuria more than 3 mmol/L; • serum creatinine greater than 175 μ mol/L; • myocardial infarction in the previous year; • current angina or heart failure; • more than one major vascular event; • retinopathy requiring laser treatment; • malignant hypertension; • uncorrected endocrine disorder; • occupation that precluded insulin therapy (e.g., driver of heavy goods vehicle); • severe concurrent illness that would limit life or require extensive systemic treatment; • inadequate understanding; • unwillingness to enter the study. DIAGNOSTIC CRITERIA: Main criterion for type 2 diabetes mellitus was fasting plasma glucose > 6 mmol/L on two mornings 1-3 weeks apart
Interventions	NUMBER OF STUDY CENTRES: 23. COUNTRY/ LOCATION: United Kingdom. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting plasma glucose less than 6 mmol/L and, in insulin-treated patients; pre-meal glucose concentrations of 4 to 7 mmol/L. ANTIDIABETIC INTERVENTIONS: One of the following sulphonylureas: chlorpropamide 100-500 mg, glibenclamide 2.5-20 mg or glipizide 2.5-40 mg.

	Metformin up to 2550 mg, distributed on two doses a day. Patients assigned insulin started on once daily ultralente insulin or isophane insulin. If the daily dose was more than 14 U or pre-meal or bed-time home blood glucose measurements were more than 7 mmol/L, a short-acting insulin, usually soluble (regular) insulin was added (basal/bolus regimen) All participants had to continue their assigned treatment as long as possible. Additional therapies for participants assigned to sulphonylurea/metformin were metformin/glibenclamide, and if hyperglycaemia recurred then initiating of insulin The protocol was amended to allow the early addition of metformin when fasting plasma glucose was greater than 6 mmol/L on maximum doses of sulphonylurea in symptomless patients in the intensive group. Patients were changed to insulin therapy if marked hyperglycaemia recurred. In the last eight centres recruited in 1988, patients allocated to sulphonylurea had insulin added early, rather than metformin, when fasting plasma glucose was greater than 6 mmol/L on maximum doses of sulphonylurea Dietary advice. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: To maintain fasting plasma glucose below 15 mmol/L without symptoms of hyperglycaemia. ANTIDIABETIC INTERVENTIONS: If marked hyperglycaemia or symptoms occurred, patients were secondarily randomised to treatment with sulphonylurea or insulin therapy (UKPDS-34 1998, also metformin). If marked hyperglycaemia recurred in participants secondarily allocated sulphonylurea, metformin was added. In those secondarily allocated metformin, glibenclamide was added. Patients with marked hyperglycaemia or symptoms on both agents were changed to insulin. Throughout, the aim of fasting plasma glucose below 15 mmol/L without symptoms was maintained Dietary advice. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Regular aspirin therapy was only advised, if there was a specific indication such as a recent myocardial infarction. Blood pressure lowering and lipid-lowering - se below. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Lipid-lowering treatment was initiated if total cholesterol were greater than 8.5 mmol/L or triglyceride were greater than 4.0 mmol/L, if dietary advice not could reduce these values satisfactorily The Hypertension in Diabetes Study randomly allocated patients with blood pressure $\geq$ 160/90 mmHg to tight control aiming for < 150/85 mmHg with either an ACE-inhibitor or a beta-blocker or to less tight control aiming for < 200/105 mmHg. In all 1148 patients were also included in the Hypertension Diabetes Study
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Time to the first occurrence of: • Any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinal

	photocoagulation, blindness in one eye, or cataract extraction); • diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death); • all-cause mortality. These aggregates were used to assess the difference between conventional and intensive treatment SECONDARY OUTCOMES (as stated in the publication): Single clinical outcomes ADDITIONAL OUTCOMES: Surrogate clinical outcomes. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): High-performance liquid chromatography (normal range is 4.5 to 6.2%)
Study details	DURATION OF INTERVENTION: Median of 10.0 years (IQR 7.7-12.4). For the participants taking part in the UKPDS 34, the median was 10.7 years. DURATION OF FOLLOW-UP: The median follow-up for endpoint analyses was 10. 0 years (IQR 7.7-12.4). For UKPDS 34 the median follow-up was 10.7 years TITRATION PERIOD: Metformin was titrated. RUN-IN PERIOD: Patients with newly-diagnosed diabetes were initially treated with diet for 3 months. Those who remained symptom-free but who had continuing fasting hyperglycaemia, plasma glucose > 6.0 and < 15.0 mmol/L were randomly allocated to active policy or to diet policy in the main randomisation (UKPDS 33 and UKPDS 34) STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Hoechst, Lilly, Novo-Nordisk and Lipha. NON-COMMERCIAL FUNDING: The Oxford Medical School Research Fund, the Charles Wolfson Charitable Trust, Clothworker's Foundation and the Alan and Babette Sainsbury Charitable Fund (grants for the pilot study). British Diabetic Association, Medical Research Council, National Eye Institute and National Institute of Digestive, Diabetes and Kidney Disease of the National Institutes of Health, USA, The Health Promotion Research Trust
Stated aim for study	"We compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial." (UKPDS 33 1998) "This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage." (UKPDS 34 1998)
Notes	Rury Holman confirmed a total overlap between the conventional group in the UKPDS 33 and the UKPDS 34. As UKPDS 33 had a larger number of participants; age, duration of disease, glycaemic control, fasting blood glucose, BMI, previously cardiovascular disease, duration of intervention, duration of follow-up are only taken from the participants of the UKPDS 33. The two baseline characteristics in which the UKPDS 34 1998 are particular different from the data noted above are HbA1c and BMI The number of patients with previous cardiovascular disease is taken from the meta-analyses by Turnbull et al. (Turnbull 2009). The number of males and females is calculated as the number of patients randomised to the UKPDS 33 1998, plus the number randomised to intensive control in UKPDS 34

UKPDS 1998 (*Continued*)

	1998 Fasting glycaemic control: SD is calculated from IQR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation of patients was computer generated..."
Allocation concealment (selection bias)	Low risk	Quote: "...allocations in sealed opaque envelopes, with a check maintained on numerical sequence, dates of opening and results."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Members of the UKPDS end-point committee, who were unaware of assignments to study groups, adjudicated outcomes exactly as they had during the original trial. " Quote from UKPDS 80 (UKPDS-80 2008).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "At the end of the trial, the vital status of 76 (2.0%) patients who had emigrated was not known; 57 and 19 in intensive and conventional groups, respectively, which reflects the 70/30 randomisation. A further 91 (2.4%) patients (65 in the intensive group) could not be contacted in the last year of the study for assessment of clinical endpoints."
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Hoechst, Lilly, Novo-Nordisk and Lipha.
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

VA CSDM 1995

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 0; male: 75 Conventional: Female: 0; male: 78 AGE (mean years (SD)): Intensive: 60.4 (6.4) Conventional: 59.9 (6.7)

	DURATION OF DISEASE (mean years (SD)): Intensive: 8.0 (3.6) Conventional: 7.7 (4.3) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 9.3 (0.2) Conventional: 9.5 (0.2) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 11.4 (0.4) Conventional: 12.4 (0.4) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 30.7 (4.4) Conventional: 31.3 (5.5) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 31 Conventional: 27 INCLUSION CRITERIA: • Men; • age from 40 to 69 years; • elevated HbA1c values (> 3 SD above the normal mean (5.05% + 3 x 0.50 = > 6. 55%); • insulin treatment or maximum dose of sulphonylurea. EXCLUSION CRITERIA: • Documented type 2 diabetes mellitus of > 15 years duration; • history of more than one myocardial infarction or a myocardial infarction within 6 months before entry; • angina pectoris class III or IV (Canadian Heart Association), refractory to medical therapy; • congestive heart failure class III or IV (NYHA), refractory to medical treatment, or any patient currently in need of digitalis; • transient cerebral ischaemic attacks first appearing within 1 year before entry; • documented cerebrovascular attack in the last 6 months or cerebrovascular attacks with more than minor functional impairment, preventing protocol adherence; • malignancies or other life-threatening diseases, if likely to cause death within 7 years; • autonomic neuropathy defined as orthostatic hypotension, gastroparesis, or diabetic diarrhoea; • symptomatic, documented pancreatic insufficiency, pancreatic diabetes, or other documented malabsorptive disease; • history of hypoglycaemic reactions with loss of consciousness or any clinical condition with seizure disorders; • history of ketoacidosis or other evidence of insulin dependency; • current endocrine disease, except corrected hypothyroidism, or mild primary hypogonadism not requiring medication; • currently taking beta-blockers that cannot be discontinued or replaced by cardioselective agents (i.e., metoprolol in doses $\leq$ 100 mg/day); • current participation in any other clinical trial; • allergies or intolerance to sulphonylureas; • albuminuria > 65 mg/ 3 hour (0.52 gm/24 hour) and/or albumin/creatinine > 0.

	33; • serum creatinine > 1.6 mg/dL; • ongoing diabetic gangrene or previous amputation from documented diabetic gangrene; • fasting C-peptide level < 0.21 pmol/mL; • uncooperative or unreliable, including alcoholism, or unable to follow instructions as decided by investigator; • severe obesity (> 60% above ideal body weight); • haemoglobinopathy, i.e., sickle-cell trait or haematological conditions interfering with HbA1c monitoring; • liver disease (transaminase > 3 times normal or serum bilirubin > 1.9 mg/dL); • living alone, without regular access to a person who can assist or be called in emergency; • any underlying condition(s) that the physician feels may prevent adherence to protocol therapy. DIAGNOSTIC CRITERIA: Fasting plasma C-peptide > 0.21 pmol/L.
Interventions	NUMBER OF STUDY CENTRES: 5. COUNTRY/ LOCATION: USA. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Maintain mean HbA1c < 7.5%. Treament is adjusted with home blood glucose monitoring aiming, at fasting blood glucose of 4.48 to 6.44 mmol/L and other preprandial levels ≤ 7.28 mmol/L. ANTIDIABETIC INTERVENTIONS: Participants moved to the next step if the HbA1c goal was not met: • One injection of evening intermediate or long-acting insulin; • continued evening insulin combined with daytime glipizide in step increments of 2.5-5.0 mg/week until HbA1c goal or maximum dose is reached; • two injections of insulin alone, no glipizide; • multiple daily insulin injections, no glipizide. CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Avoiding excessive hyperglycaemia, or symptoms of excessive glycosuria, ketonuria, or hypoglycaemia, consistent with conventional therapy provided patients with type 2 diabetes mellitus in the medical community. (Alert HbA1c < 12.9%). ANTIDIABETIC INTERVENTIONS: One injection of insulin. If treatment aims cannot be met by diet, exercise, or insulin adjustments, including mixtures, a maximum of two daily injections can be prescribed for patients in this group CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Hypertension, dyslipidaemia, smoking, and obesity were treated similarly in all patients following the guidelines of the ADA CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: Values from the guidelines of the ADA
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Statistically significant separation of HbA1c between both groups (feasibility trial) SECONDARY OUTCOMES (as stated in the publication):

	• To assess the adequacy of accrual, patient acceptance of therapy arms, and ability to measure the diabetic complications with precision and accuracy; • to evaluate side effects arising from either arm of treatment; • to assess differences between the two arms in subclinical predictors for morbidity and mortality; • to detect whether unintended differences occur between the two treatment groups in the covariables/risk factors of hyperlipidaemia and hypertension and their treatment, body weight, smoking, and exercise. ADDITIONAL OUTCOMES: Primary macrovascular endpoints: Non-fatal myocardial infarction, stroke, amputation, and cardiovascular death. Primary microvascular endpoints: Appearance and progression of retinopathy Silent cardiac events, ventricular function, peripheral vascular disease, neuropathy, and nephropathy Quality of life. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): High-pressure liquid chromatography
Study details	DURATION OF INTERVENTION: 27 months. DURATION OF FOLLOW-UP: 27 months. TITRATION PERIOD: Oral anti-diabetic drugs were titrated. RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: Roerig/Pfizer Pharmaceuticals. NON-COMMERCIAL FUNDING: Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service
Stated aim for study	"The relative risks and benefits of intensive therapy in NIDDM are not well defined. Accordingly, we designed a feasibility study that compared standard therapy and intensive therapy in a group of NIDDM men who required insulin due to sustained hyperglycaemia."
Notes	The Veteran Affairs Diabetes Feasibility Trial was conducted as a pilot study and was a precursor for the subsequent VADT Fasting blood glucose is calculated from mg/dL to mmol/L by dividing with 18

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised into..."

VA CSDM 1995 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "An End-Points Committee of consultants external to the study and masked to treatment assignment used predetermined criteria to decide whether an event occurred and to categorize it."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The participation of three patients on intensive therapy was terminated at 14, 17, and 24 months for causes apparently unrelated to diabetic treatment: one moved to unknown address, one had septicaemia leading to irreversible coma, and one developed psychotic depression. A fourth patient in the intensive group voluntarily withdrew at the 7th month."
Selective reporting (reporting bias)	Low risk	All predefined primary and secondary outcomes were reported.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	Roerig/Pfizer Pharmaceuticals.
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment. Adequate blinding

VADT 2009

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: 26; male: 866 Conventional: Female: 26; male: 873 AGE (mean years (SD)): Intensive: 60.5 (9.0) Conventional: 60.3 (9.0) DURATION OF DISEASE (mean years (SD)): Intensive: 11.5 (8.0) Conventional: 11.5 (7.0) GLYCAEMIC CONTROL (mean HbA1c (standardized level, %) (SD)): Intensive: 9.4 (2.0) Conventional: 9.4 (2.0) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive (median): 10.8 (4.0) Conventional (median): 11.0 (3.7) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 31.3 (3.0) Conventional: 31.2 (4.0) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: 355

	Conventional: 368 INCLUSION CRITERIA: • Male and female veterans; • > 41 years old; • nonresponsive to a maximum dose of at least one oral agent and/or daily insulin injections (Nonresponsiveness is defined as having centrally measured HbA1c level > 4 SD above the normal mean, that is, > 7.5%, or else local HbA1c > 8.3%). EXCLUSION CRITERIA: • Angina pectoris class III or IV (Canadian Heart Association); • congestive heart failure class III or IV (NYHA); • stroke, myocardial infarction, invasive revascularization within the past 6 months; • ongoing diabetic gangrene; • severe obesity (BMI $\geq$ 40 kg/m^2); • haemoglobinopathy interfering with HbA1c monitoring; • serum creatinine > 1.6 mg/dL; • transaminase > 3 times the upper limit of normal or serum bilirubin > 1.9 mg/dL; • conditions likely to cause death within 7 years; • autonomic neuropathy (orthostatism, gastroparesis, or diabetic diarrhoea); • type 1 diabetes or pancreatic insufficiency, pancreatic diabetes, or other malabsorptive disease; • recurrent seizures (within the past year) while on anti seizure medication; • hypopituitarism; • pregnancy, lactation, or planning a pregnancy; • active psychosis, alcoholism, or other substance abuse; • living alone, without access to a person who can assist in an emergency; • conditions that may prevent adherence to protocol (unable to self-care or a severe illness or treatment); • current participation in another trial. DIAGNOSTIC CRITERIA: Fasting plasma C-peptide > 0.21 pg per cc
Interventions	NUMBER OF STUDY CENTRES: 20. COUNTRY/ LOCATION: USA. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: HbA1c $\leq$ 6%. A priority is to avoid hypoglycaemia, even if asymptomatic. The goal for HbA1c level was an absolute reduction of 1.5 percentage points in the intensive intervention group, as compared with conventional intervention group. ANTIDIABETIC INTERVENTIONS: For obese patients (BMI $\geq$ 27 kg/m^2) entering on oral agents alone, the following algorithm was used: 1. Metformin starts at 500 mg and increases up to 2000 mg and rosiglitazone 4 mg twice a day; 2. initiate insulin, or if on insulin, adjust to one evening injection of intermediate or long-acting preparation targeted to normal fasting glucose (i.e., 80-115 mg/dL); 3. add morning insulin and may add alpha-glucosidase inhibitors; 4. multiple daily insulin injections with retention of oral agents (at least one oral sensitizer); 5. any necessary combination.

	For lean patients entering on oral agents alone, Step 1 is different in that glimepiride (8 mg) is used in combination with rosiglitazone. Steps 2-5 are the same as for obese patients. All patients entering on insulin proceed directly to Step 2. The treatment protocol may be changed if new modalities become available during the intervention period CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Well-being, avoidance of deterioration of HbA1c, keeping levels at 8-9% and preventing symptoms of glycosuria, hypoglycaemia, and ketonuria. ANTIDIABETIC INTERVENTIONS: The treatment outline is not rigid For obese patients (BMI $\geq$ 27 kg/m^2) entering on oral agents alone, the pharmacological steps are as follows: • Metformin 500 mg and up to 1000 mg and rosiglitazone 4 mg; • add intermediate or long-acting insulin, 1 U/9 lb, for subjects not previously on insulin; • increase metformin to 1000 mg twice a day; • increase rosiglitazone to 8 mg/day; • increase insulin dose (may add alpha-glucosidase inhibitors); • any necessary combination, including nateglinide or glimepiride. For lean patients entering on oral agents alone, the steps are as follows: • Glimepiride 2 mg and rosiglitazone 4 mg; • add intermediate or long-acting insulin, 1 U/9 lb; • increase glimepiride to 8 mg daily before noon; • increase rosiglitazone to 8 mg daily before noon; • the two last intervention opportunities are the same as in obese patients. Patients on insulin at entry proceed to Step 2. The treatment protocol may be changed if new modalities become available CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Basic tenets in type 2 diabetes mellitus are instructed and enforced in both treatment arms for education, diet, blood pressure, and lipid control CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: Blood pressure < 130/80 mmHg; LDL-cholesterol < 2.6 mmol/L; HDL-cholesterol > 1.2 mmol/L for men and > 1.4 mmol/L for women; Aspirin: 81-325 mg.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): The time to the first occurrence of any of a composite of cardiovascular events • Cardiovascular events were; • myocardial infarction; • stroke; • new or worsening congestive heart failure; • amputation for ischaemic diabetic gangrene; • invasive intervention for coronary artery disease, peripheral vascular disease, or cerebrovascular disease; • inoperable coronary artery disease; • cardiovascular death. SECONDARY OUTCOMES (as stated in the publication): The secondary objectives are to assess differences between treatment groups in other cardiovascular outcomes:

	• New or worsening angina; • new transient ischaemic attacks; • new intermittent claudicatio confirmed by Doppler; • new critical limb ischaemia; • total mortality; • nephropathy; • neuropathy. ADDITIONAL OUTCOMES: • Adverse events (including hypoglycaemia); • quality of life; • cost analysis; • cognitive changes; • dyslipidaemia and treatment for dyslipidaemia, hypertension and treatment for hypertension, plasma fibrinogen, plasminogen-activating inhibitor I (PAI-I), weight, and smoking. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): Turbidometric immuno inhibition assay (periodically calibrated by Washington University Core Laboratory for Clinical Studies, a National Glycohemoglobin Standardization Program)
Study details	DURATION OF INTERVENTION: 5.6 years. DURATION OF FOLLOW-UP: Median 5.6 years (up to 7.5 years). TITRATION PERIOD: When metformin is initiated, the dose is titrated RUN-IN PERIOD: None. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: English. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: GlaxoSmithKline, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis, Amylin, and Kos Pharmaceuticals NON-COMMERCIAL FUNDING: The Veterans Affairs Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, the American Diabetes Association, and the National Eye Institute
Stated aim for study	"The primary goal of the Veterans Affairs Diabetes Trial (VADT) was to compare the effects of intensive and standard glucose control on cardiovascular events."
Notes	Cholesterol is converted from mg/dL to mmol/L by dividing by 39 SD deviation of fasting blood glucose is calculated from IQR. Value of fasting blood glucose is converted from mg/dL to mmol/L by dividing with 18

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned with the use of a permuted-block design with a block size of six and stratified according to study site, the previous occurrence of a macrovascular event, and current insulin use. The randomization codes were generated by the study's biostatistician

VADT 2009 (*Continued*)

		at the Hines Cooperative Studies Program Coordinating Center. Study sites did not have access to the codes."
Allocation concealment (selection bias)	Low risk	See above.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Primary and secondary CV endpoints (see Objectives) are determined by the independent Endpoints Committee, masked to treatment assignment, by evaluation of supporting documentation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Main reasons for exclusion were that patients had low glycated hemoglobin levels (34% of patients), were not receiving a maximal dose of an oral antidiabetic medication or insulin (16%), did not want to participate (12%), or had a high serum creatinine level (8%)."
Selective reporting (reporting bias)	Low risk	Cerebrovascular disease and inoperable coronary artery disease are not listed as a part of the primary composite outcome in the design article of the trial, but is reported in the main publication of the results. These outcomes were, however, a part of the operations manual for the trial, which preceded the actual inception of the trial according to the investigators
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	High risk	GlaxoSmithKline, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis, Amylin, and Kos Pharmaceuticals
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment, and blinding

Yang 2007

Methods	Randomised clinical trial.
Participants	SEX: Intensive: Female: NR; Male: NR Conventional: Female: NR; Male: NR AGE (mean years (SD)): Intensive: 50 (8) Conventional: 53 (9). DURATION OF DISEASE (mean years (SD)): Intensive: 1 Conventional: 1 GLYCAEMIC CONTROL (mean HbA1c (standardized level) (SD)): Intensive: 7.4 (1.7)

	Conventional: 6.9 (1.2) FASTING BLOOD GLUCOSE (mean mmol/L (SD)): Intensive: 7.2 (1.7) Conventional: 7.33 (1.86) BODY MASS INDEX (mean kg/m^2 (SD)): Intensive: 26 (3.4) Conventional: 25.6 (3.5) NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE: Intensive: NR Conventional: NR INCLUSION CRITERIA: • 35-75 years old; • diagnoses of type 2 diabetes mellitus within one year before entry to trial. EXCLUSION CRITERIA: • Severe liver and renal dysfunction; • acute or chronic infectious diseases, • cancer; • people with endocrine disease and long-term hormone use; • macrovascular lesions. DIAGNOSTIC CRITERIA: WHO 1999.
Interventions	NUMBER OF STUDY CENTRES: 1 COUNTRY/ LOCATION: China. SETTING: Outpatient. INTENSIVE (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Fasting blood glucose < 7.0 mmol/L, 2 hour postprandial glucose < 10 mmol/L, HbA1c < 7.0% ANTIDIABETIC INTERVENTIONS: Mainly by multiple subcutaneous insulin injections CONVENTIONAL (GLYCAEMIC TARGET, ANTIDIABETIC INTERVENTIONS USED): TARGET: Not specified. ANTIDIABETIC INTERVENTIONS: Routine outpatient treatment. CONCOMITANT TREATMENT OF CARDIOVASCULAR RISK FACTORS: BOTH GROUPS: Not specified. CONCOMITANT TARGET VALUES OF CARDIOVASCULAR RISK FACTORS: Intensive: Total cholesterol (mmol/L): < 4.7 LDL-cholesterol (mmol/L): < 2.7 HDL-cholesterol (mmol/L): > 1.1 Triglycerides (mmol/L): < 1.7 Conventional: Not specified, routine outpatient.
Outcomes	PRIMARY OUTCOME(S) (as stated in the publication): Carotis intima thickness SECONDARY OUTCOMES (as stated in the publication): None. ADDITIONAL OUTCOMES: None. MEASUREMENT OF GLYCAEMIC CONTROL (HbA1c): NR.

Study details	DURATION OF INTERVENTION: 1 year. DURATION OF FOLLOW-UP: 1 year. TITRATION PERIOD: NR. RUN-IN PERIOD: NR. STUDY TERMINATED BEFORE REGULAR END: No.
Publication details	LANGUAGE OF PUBLICATION: Chinese. PUBLICATION STATUS: Peer-reviewed journal. COMMERCIAL FUNDING: None reported. NON-COMMERCIAL FUNDING: Supported by the national program for Key Science and Technology Projects
Stated aim for study	"To investigate whether long-term intensive glycemic and lipid control would ameliorate the carotid intima medial thickness (IMT) in patients with type 2 diabetes mellitus (T2DM)."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "89 patients who were willing to sign informed consent were randomly allocated into intense group and conventional group."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals or drop-outs reported.
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available.
Free from academic bias (assessed from primary author)?	Low risk	No academic bias.
Free from sponsor bias?	Low risk	Supported by the National Program for Key Science and Technology Projects (2001BA702B01)
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, and blinding

Abbreviations: ACE: angiotensin-converting-enzyme, ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, ADA: American Diabetes Association, ADVANCE: Action in Diabetes and Vascular disease - PreterAx and DiamicroN MR Controlled Evaluation, BMI: body mass index, DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction, DN: diabetic nephropathy; EDTA: ethylenediaminetetraacetic acid, HbA1c: glycosylated haemoglobin A1c, HDL: High density lipoprotein, IDA: Insulin Diabetes Angioplasty, IQR: interquartile range, LDL: low density lipoprotein, NR: not reported, NYHA: New York Heart Association. REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, U: units, UGDP: University Group Diabetes Program, UKPDS: United Kingdom Prospective Diabetes Study, VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, VADT: Veterans Affairs Diabetes Trial, WHO: World Health Organisation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ADOPT 2010	No predefined differences in glycaemic target.
Barbosa 1983	Not including participants with type 2 diabetes mellitus.
BARI 2D 2009	No predefined differences in glycaemic target.
Barnett 2008	Not a randomised controlled clinical trial.
Blaha 2009	Patients with type 2 diabetes mellitus are reported together with patients without diabetes
Brocco 2001	Not a randomised controlled clinical trial.
Chan 2009	No predefined differences in glycaemic target.
Clark 1985	Not a randomised controlled clinical trial.
Cleveringa 2010	No predefined differences in glycaemic target.
Corpus 2004	Not a randomised controlled clinical trial.
DIGAMI 1996	Patients with type 1 and type 2 diabetes mellitus reported together
Du 2009	No predefined differences in glycaemic target.
Eastman 1997	Not a randomised controlled clinical trial.
Eibl 2004	Not a randomised controlled clinical trial.
Evans 1982	Not a randomised controlled clinical trial.
Furnary 1999	Not a randomised controlled clinical trial.
Hanefeld 2010	No predefined differences in glycaemic target.

(*Continued*)

HEART 2D 2009	Randomised into two groups targeting the same HbA1c with different strategies (basal versus prandial)
Johansen 2007	No predefined differences in glycaemic target.
Joss 2002	No predefined differences in glycaemic target.
Lazar 2004	Patients with type 1 and type 2 diabetes mellitus reported together
Leibowitz 2010	Not a randomised controlled clinical trial.
Menard 2005	No predefined differences in glycaemic target.
Olivarius 2001	No predefined differences in glycaemic target.
Piatt 2010	No predefined differences in glycaemic target.
PROactive 2005	No predefined differences in glycaemic target.
Retnakaran 2010	Not a randomised controlled clinical trial.
Ryan 2004	Not a randomised controlled clinical trial.
Shi 2010	No predefined differences in glycaemic target.
UKPDS-44 1999	No predefined differences in glycaemic target.
van Bruggen 2009	No predefined differences in glycaemic target.

ADOPT: a Diabetes Outcome Progression Trial, BARI 2D: The Bypass Angioplasty Revascularization Investigation 2 Diabetes, DIGAMI: Diabetes Insulin-Glucose in Acute Myocardial Infarction, HEART 2D: Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus, PROactive: PROspective pioglitAzone Clinical Trial In macroVascular Events, UKPDS: United Kingdom Prospective Diabetes Study

Characteristics of ongoing studies *[ordered by study ID]*

ADDITION 2001

Trial name or title	ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In PeOple With screeN Detected Diabetes in Primary Care)
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus.

ADDITION 2001 (*Continued*)

Interventions	Intensified multifactorial treatment of cardiovascular risk factors versus conventional treatment of cardiovascular risk factors
Outcomes	The primary outcome for the 5-year follow-up is a composite cardiovascular outcome (cardiovascular mortality, myocardial infarction, non-fatal stroke, revascularizations, and amputations)
Starting date	January 2001.
Contact information	tl@alm.au.dk
Estimated study completion data	December 2009.
Notes	The ADDITION consist of a screening study and an intervention trial. Publication of primary outcome will be published early 2011

ADVANCE-ON

Trial name or title	Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study (ADVANCE-ON)
Methods	Observational (post-randomisation).
Participants	Patients with type 2 diabetes mellitus.
Interventions	No intervention given. Only follow-up.
Outcomes	Primaty outcomes: Major macrovascular events, death from any cause. Secondary outcomes: Death from cardiovascular cause, major clinical microvascular events, major microvascular and macrovascular events assessed composite, stroke, requirement for renal replacement therapy, death from renal disease, development of severe diabetes eye disease, major hypoglycaemia, and myocardial infarction
Starting date	January 2010.
Contact information	hmonaghan@george.org.au
Estimated study completion data	December 2013.
Notes	

CABG USCDP

Trial name or title	United States Coronary Artery Bypass Surgery (CABG) Diabetes Project (USCDP) Pilot Study
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus undergoing coronary by-pass surgery (CABG)
Interventions	Intervention: Extends the intensive glucose control beyond the third postoperative day to one full year. Once discharged from the hospital following the CABG procedure, the intense glucose control is done using subcutaneous insulin (a shot under the skin), oral medications, and by measuring blood sugar levels frequently Standard care: strict control of blood sugar (glucose) levels for 3 days after CABG. This is done through frequent monitoring of blood sugar levels and by giving insulin continuously through a needle into a vein (intravenously)
Outcomes	Primary outcome: The purpose of this study is to see how safe and effective strict glucose control is when extended beyond 3 days and hospital discharge for one year. Secondary outcome: Another purpose is to see how well patients can comply with the daily management of intensive glucose control for one-year as well as the study follow-up schedule
Starting date	March 2009.
Contact information	eric.johnson@providence.org
Estimated study completion data	December 2012.
Notes	

Chen 2009

Trial name or title	The Benefits of Intensive Glycemic Control in Elderly Patients With Type 2 Diabetes
Methods	Randomised clinical trial.
Participants	Elderly patients with type 2 diabetes mellitus.
Interventions	Intensive glycaemic control versus conventional glycaemic control
Outcomes	Primary outcomes: The primary study outcomes are a composite of macrovascular events and a composite of microvascular events, considered both jointly and separately. Secondary outcomes: Death from any cause, disability from any cause, total coronary events, total cerebrovascular events, heart failure, peripheral vascular events, all cardiovascular events, and hospitalisation for 24 hours or more
Starting date	February 2009.
Contact information	chenhs@vghtpe.gov.tw
Estimated study completion data	December 2010.

Notes	

DARE

Trial name or title	DARE: Diabetes in cArdiac REhabilitation
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus and recent myocardial infarction
Interventions	Intensive treatment group: The patients will treated by insulin under a basal-bolus regimen with strict glycaemic control; conventional treatment group, in which the previous anti-diabetic treatment will be continued
Outcomes	Primary outcomes: Improvement of peak VO2, peak workload, ventilatory threshold . Secondary outcomes: Number of patients, in each group of treatment, having improved from at least 20% their peak VO2, after cardiac rehabilitation. Influence of improvement of glycaemic control on cardiac rehabilitation on exercise capacities
Starting date	July 2005.
Contact information	bruno.verges@chu-dijon.fr
Estimated study completion data	January 2012.
Notes	According to the completion data on ClinicalTrials.gov, then the trial should be completed. However, the trial is currently recruiting participants. Contact has been taken

GLUCOSURG1

Trial name or title	GLUCOSURG1 (Resolution of Type 2 Diabetes Mellitus: Intensive vs. Conventional Glycaemic Control After Obesity Surgery)
Methods	Randomised clinical trial.
Participants	Patients with Type 2 Diabetes Mellitus who have been approved for obesity surgery
Interventions	Intensive glycaemic control (fasting capillary glucose levels between 5-7 mmol/L) versus conventional glycaemic control (7-9 mmol/L)
Outcomes	Primary outcomes: Percentage of patients with type 2 diabetes mellitus who achieve fasting blood glucose of less than 5.6 mmol/L and/or HbA1c of less than 6%. Secondary outcomes: Percentage of type 2 diabetes mellitus patients with a reduction in the doses/number of diabetes medications used preoperatively, microvascular events
Starting date	December 2010.

GLUCOSURG1 (*Continued*)

Contact information	a.miras@nhs.net
Estimated study completion data	December 2013.
Notes	

HFDM

Trial name or title	HFDM (Optimized Glycemic Control in Heart Failure Patients With DM2: "Effect on Left Ventricular Function and Skeletal Muscle")
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus and heart failure.
Interventions	Intensive glycaemic control versus conventional glycaemic control
Outcomes	Primary outcomes: Left ventricular function, muscle strength and mass. Secondary outcomes: Hormonal and metabolic profile, 6-minutes hall walk test, exercise capacity and peak oxygen consumption
Starting date	March 2010.
Contact information	roni.r.nielsen@gmail.com
Estimated study completion data	March 2012.
Notes	

LIMBISCH

Trial name or title	LIMBISCH (Normalization of Fasting Glucose and the Incidence of Restenosis After Peripheral Angioplasty)
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus and limb ischaemia.
Interventions	Insulin therapy incorporating the target of normal fasting glucose (< 5.5 mmol/L) and glycated haemoglobin < 6.5% compared with standard care to achieve a glycated haemoglobin < 7.0% in patients with type 2 diabetes mellitus and limb ischaemia
Outcomes	Primary outcome: Reduction of restenosis after peripheral angioplasty. Secondary outcome: Identification of new peripheral markers predictive of restenosis
Starting date	December 2008.

Contact information	piatti.piermarco@hsr.it
Estimated study completion data	June 2010.
Notes	

REMIT Pilot Trial

Trial name or title	REMIT Pilot Trial (Remission Evaluation of Metabolic Interventions in Type 2 Diabetes)
Methods	Randomised clinical trial.
Participants	Patients with type 2 diabetes mellitus diagnosed by a physician within 3 years prior to enrolment
Interventions	Intensive glycaemic control versus conventional glycaemic control
Outcomes	Primary outcomes: Proportion of participants achieving normoglycaemia in the experimental group 1 compared to the control group, proportion of participants achieving normoglycaemia in the experimental group 2 compared to the control group. Secondary outcomes: Proportion of participants with normal glucose tolerance, proportion of participants with normal fasting plasma glucose, change in fasting plasma glucose from baseline, HbA1C, change in weight from baseline, rate of symptomatic hypoglycaemic episodes, rate of severe hypoglycaemic episodes
Starting date	September 2010.
Contact information	gerstein@mcmaster.ca
Estimated study completion data	August 2013.
Notes	

VADT-FS 2008

Trial name or title	The VA Diabetes Trial Follow-up Study (VADT-FS).
Methods	Observational follow-up study.
Participants	Patients with type 2 diabetes mellitus.
Interventions	No intervention given. Only follow-up of the participants from the VADT
Outcomes	Primary outcome: Long-term effect of intensive glycaemic control in type 2 diabetes mellitus on major cardiovascular complications. Secondary outcomes: Long-term effects of intensive glycaemic control in type 2 diabetes mellitus on: a) cardiovascular mortality, b) major microvascular complications, c) health-related quality of life, and d) total mortality

VADT-FS 2008 (*Continued*)

Starting date	February 2008.
Contact information	Tamara.Paine@va.gov
Estimated study completion data	May 2017.
Notes	This is an observational follow-up study of VADT (VADT 2009).

HbA1c: glycosylated haemoglobin A1c

DATA AND ANALYSES

Comparison 1. Intensive glycaemic control versus conventional glycaemic control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2 All-cause mortality; stratified after risk of bias	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
2.1 Low risk of bias	8	28847	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
2.2 High risk of bias	10	884	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.65]
3 All-cause mortality; stratified after study duration	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
3.1 Long duration (> 2.0 years)	9	29008	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
3.2 Short duration (≤ 2 years)	9	723	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.34, 2.96]
4 All-cause mortality; stratified after diagnostic criteria	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
4.1 Diagnostic criteria described	14	18376	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
4.2 Diagnostic criteria not described	4	11355	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.05]
5 All-cause mortality; stratified after source of funding	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
5.1 Industry-funded	13	29131	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
5.2 Non-industry-funded	5	600	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.43]
6 All-cause mortality; stratified after intervention	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
6.1 Exclusively dealing with glycaemic control in usual care setting	12	28359	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.13]
6.2 Glycaemic control as a part of acute intervention	3	903	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.92, 1.60]
6.3 Multimodal intervention in usual care setting	3	469	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.40, 0.90]
7 All-cause mortality; hazard ratio	5		Hazard Ratio (Random, 95% CI)	0.96 [0.74, 1.23]
8 All-cause mortality; available case	18	29382	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
9 All-cause mortality; best-case scenario	18	29731	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
10 All-cause mortality; worst-case scenario	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.42]
11 Cardiovascular mortality	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.26]
12 Cardiovascular mortality; stratified after risk of bias	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.17]
12.1 Low risk of bias	7	28745	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.17]
12.2 High risk of bias	11	986	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.33, 2.42]

13 Cardiovascular mortality; stratified after study duration	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.17]
13.1 Long duration (> 2 years)	9	29008	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.17]
13.2 Short duration (≤ 2 years)	9	723	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.30]
14 Cardiovascular mortality; stratified after diagnostic criteria	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.26]
14.1 Diagnostic criteria described	14	18376	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.02, 1.35]
14.2 Diagnostic criteria not described	4	11355	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.03]
15 Cardiovascular mortality; stratified after source of funding	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.17]
15.1 Industry funding	12	29050	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.17]
15.2 Non-industry funding	6	681	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.50]
16 Cardiovascular mortality; stratified after intervention	18	29731	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.26]
16.1 Exclusively dealing with glycaemic control in usual care setting	12	28359	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.92, 1.35]
16.2 Glycaemic control as a part of acute intervention	3	903	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.44]
16.3 Multimodal intervention in usual care setting	3	469	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.98]
17 Cardiovascular mortality; hazard ratio	4		Hazard Ratio (Random, 95% CI)	0.88 [0.56, 1.38]
18 Cardiovascular mortality; available case	18	29382	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
19 Cardiovascular mortality; worst-case scenario	18	29731	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.20, 1.45]
20 Cardiovascular mortality; best-case scenario	18	29731	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.01]
21 Macrovascular complications	10	28509	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
22 Macrovascular complications; stratified after intervention	10	28509	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.05]
22.1 Exclusively dealing with glycaemic control in usual care setting	8	27569	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.01]
22.2 Glycaemic control as a part of acute intervention	1	780	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.96, 1.44]
22.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.36, 0.75]
23 Non-fatal myocardial infarction	12	29174	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
24 Non-fatal myocardial infarction; stratified after study duration	12	29174	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
24.1 Long duration (≤ 2 years)	9	29008	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.02]

24.2 Short duration (> 2 years)	3	166	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.23, 2.78]
25 Non-fatal myocardial infarction; stratified after risk of bias	12	29174	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
25.1 Low risk of bias	7	28745	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.03]
25.2 High risk of bias	5	429	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.34, 1.99]
26 Non-fatal myocardial infarction; stratified after source of funding	12	29174	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
26.1 Industry-funded	8	28594	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.02]
26.2 Non-industry-funded	4	580	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.62, 1.51]
27 Non-fatal myocardial infarction; stratified after diagnostic criteria	11	18034	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.74, 0.94]
27.1 Diagnostic criteria described	11	18034	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.74, 0.94]
28 Non-fatal myocardial infarction; stratified after intervention	12	29174	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
28.1 Exclusively dealing with glycaemic control in usual care setting	8	28111	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
28.2 Glycaemic control as a part of acute intervention	3	903	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.88, 1.80]
28.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.18, 0.81]
29 Non-fatal myocardial infarction; available case	12	27332	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.78, 0.96]
30 Non-fatal myocardial infarction; worst-case scenario	12	29174	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.94, 2.31]
31 Non-fatal myocardial infarction; best-case scenario	12	29174	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.34, 0.41]
32 Non-fatal stroke	11	28760	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.80, 1.16]
33 Non-fatal stroke; stratified after intervention	11	28757	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.80, 1.16]
33.1 Exclusively dealing with glycaemic control in usual care setting	7	27697	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.16]
33.2 Glycaemic control as a part of acute intervention	3	900	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.62, 2.30]
33.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.80]
34 Amputation of lower extremity	8	6960	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.43, 0.95]
35 Amputation of lower extremity; stratified after intervention	8	6960	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.43, 0.95]
35.1 Exclusively dealing with glycaemic control in usual care setting	5	6677	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.09]
35.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

35.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.06]
36 Cardiac revascularization	5	2289	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.05]
37 Cardiac revascularization; stratified after intervention	5	2289	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.05]
37.1 Exclusively dealing with glycaemic control in usual care setting	3	2054	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.67, 1.07]
37.2 Glycaemic control as a part of acute intervention	1	75	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.21, 22.89]
37.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.40]
38 Peripheral revascularization	7	13477	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
39 Peripheral revascularization; stratified after intervention	7	13477	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.06]
39.1 Exclusively dealing with glycaemic control in usual care setting	4	13194	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
39.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
39.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.23, 1.57]
40 Microvascular complications	4	25760	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.83, 0.95]
41 Microvascular complications; stratified after intervention	4	25760	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.97]
41.1 Exclusively dealing with glycaemic control in usual care setting	3	25600	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.97]
41.2 Glycaemic control as a part of acute intervention	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
41.3 Multimodal intervention in usual care setting	1	160	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.12, 1.01]
42 Nephropathy	9	27929	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 0.99]
43 Nephropathy; stratified after intervention	9	27929	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 0.99]
43.1 Exclusively dealing with glycaemic control in usual care setting	8	27769	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.06]
43.2 Glycaemic control as a part of acute intervention	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
43.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.35, 0.85]
44 End-stage renal disease	7	28075	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.06]
45 End-stage renal disease; stratified after intervention	7	28075	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.06]
45.1 Exclusively dealing with glycaemic control in usual care setting	6	27915	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.07]
45.2 Glycaemic control as a part of acute intervention	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

45.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.35]
46 Retinopathy	8	10230	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.92]
47 Retinopathy; stratified after intervention	8	10230	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.92]
47.1 Exclusively dealing with glycaemic control in usual care setting	7	10070	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.94]
47.2 Glycaemic control as a part of acute intervention	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 0.99]
48 Retinal photocoagulation	7	11142	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.97]
49 Retinal photocoagulation; stratified after intervention	7	11142	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.97]
49.1 Exclusively dealing with glycaemic control in usual care setting	6	10982	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.03]
49.2 Glycaemic control as a part of acute intervention	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
49.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.91]
50 Adverse events	12	36745	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.14]
50.1 Serious adverse events	10	24069	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.13]
50.2 Drop-outs due to adverse events	9	12676	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.89, 2.87]
51 Serious adverse events; stratified after intervention	10	24069	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.13]
51.1 Exclusively dealing with glycaemic control in usual care setting	7	23786	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.14]
51.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.41, 2.18]
51.3 Multifactorial intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.56]
52 Drop-outs due to adverse events; stratified after intervention	9	12676	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.89, 2.87]
52.1 Exclusively dealing with glycaemic control in usual care setting	6	12393	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.86, 3.26]
52.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.39, 4.65]
52.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
53 Congestive heart failure	9	27792	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]
54 Congestive heart failure; stratified after intervention	8	27710	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]

54.1 Exclusively dealing with glycaemic control in usual care setting	6	27587	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.17]
54.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.26, 2.13]
54.3 Multimodal intervention in usual care setting	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
55 Hypoglycaemia	14	47050	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.46, 2.13]
55.1 Mild hypoglycaemia	11	18923	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.31, 1.72]
55.2 Severe hypoglycaemia	12	28127	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.39, 3.02]
56 Mild hypoglycaemia; stratified after intervention	11	18923	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.31, 1.72]
56.1 Exclusively dealing with glycaemic control in usual care setting	7	17860	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.35, 1.82]
56.2 Glycaemic control as a part of acute intervention	3	903	Risk Ratio (M-H, Random, 95% CI)	2.13 [0.83, 5.50]
56.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.95, 1.37]
57 Severe hypoglycaemia; stratified after intervention	12	28127	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.39, 3.02]
57.1 Exclusively dealing with glycaemic control in usual care setting	9	27844	Risk Ratio (M-H, Random, 95% CI)	2.39 [1.71, 3.34]
57.2 Glycaemic control as a part of acute intervention	2	123	Risk Ratio (M-H, Random, 95% CI)	7.00 [0.38, 128.61]
57.3 Multimodal intervention in usual care setting	1	160	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.34, 1.51]
58 Cost of treatment	2	4319	Mean Difference (IV, Random, 95% CI)	543.85 [-985.46, 2073.16]

Analysis 1.1. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 1 All-cause mortality.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 1 All-cause mortality

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**1.01 [0.90, 1.13]**

Total events: 1597 (Intensive control), 1212 (Conventional control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.19$, df = 11 (P = 0.08); $I^2 = 40\%$

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

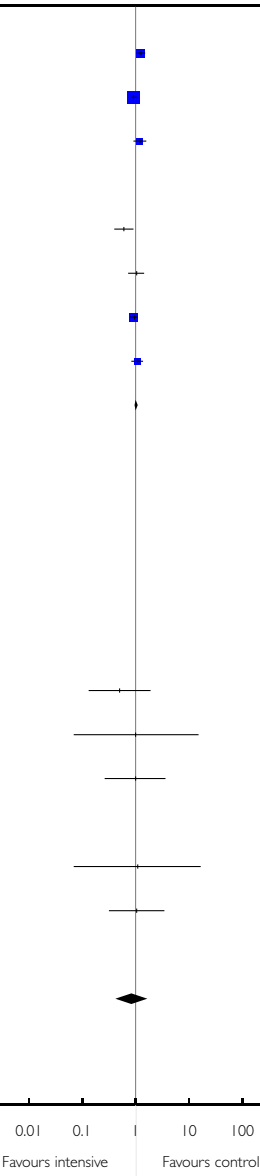
Analysis 1.2. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 2 All-cause mortality; stratified after risk of bias.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 2 All-cause mortality; stratified after risk of bias

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias				
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Subtotal (95% CI)	**15471**	**13376**		**1.01 [0.94, 1.08]**
Total events: 1583 (Intensive control), 1195 (Conventional control)				
Heterogeneity: Chi² = 17.15, df = 6 (P = 0.01); I² =65%				
Test for overall effect: Z = 0.17 (P = 0.87)				
2 High risk of bias				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**508**	**376**		**0.83 [0.42, 1.65]**
Total events: 14 (Intensive control), 17 (Conventional control)				
Heterogeneity: Chi² = 0.80, df = 4 (P = 0.94); I² =0.0%				



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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.53 (P = 0.60)				
Total (95% CI)	**15979**	**13752**		**1.00 [0.93, 1.08]**
Total events: 1597 (Intensive control), 1212 (Conventional control)				
Heterogeneity: Chi^2 = 18.19, df = 11 (P = 0.08); I^2 =40%				
Test for overall effect: Z = 0.11 (P = 0.92)				
Test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59), I^2 =0.0%				

Analysis 1.3. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 3 All-cause mortality; stratified after study duration.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 3 All-cause mortality; stratified after study duration

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Long duration (> 2.0 years)				
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Subtotal (95% CI)	**15550**	**13458**		**1.00 [0.93, 1.08]**

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total events: 1591 (Intensive control), 1206 (Conventional control)				
Heterogeneity: Chi² = 18.19, df = 8 (P = 0.02); I² =56%				
Test for overall effect: Z = 0.11 (P = 0.92)				
2 Short duration (≤ 2 years)				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**429**	**294**		**1.00 [0.34, 2.96]**
Total events: 6 (Intensive control), 6 (Conventional control)				
Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.01 (P = 1.0)				
Total (95% CI)	**15979**	**13752**		**1.00 [0.93, 1.08]**
Total events: 1597 (Intensive control), 1212 (Conventional control)				
Heterogeneity: Chi² = 18.19, df = 11 (P = 0.08); I² =40%				
Test for overall effect: Z = 0.11 (P = 0.92)				
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² =0.0%				

Analysis 1.4. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 4 All-cause mortality; stratified after diagnostic criteria.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 4 All-cause mortality; stratified after diagnostic criteria

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Diagnostic criteria described				
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Subtotal (95% CI)	**10287**	**8089**		**1.05 [0.96, 1.15]**
Total events: 1095 (Intensive control), 675 (Conventional control)				
Heterogeneity: Chi^2 = 16.32, df = 9 (P = 0.06); I^2 =45%				
Test for overall effect: Z = 1.09 (P = 0.28)				
2 Diagnostic criteria not described				
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**5692**	**5663**		**0.93 [0.83, 1.05]**
Total events: 502 (Intensive control), 537 (Conventional control)				
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%				

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.15 (P = 0.25)				
Total (95% CI)	**15979**	**13752**		**1.00 [0.93, 1.08]**
Total events: 1597 (Intensive control), 1212 (Conventional control)				
Heterogeneity: Chi^2 = 18.19, df = 11 (P = 0.08); I^2 =40%				
Test for overall effect: Z = 0.11 (P = 0.92)				
Test for subgroup differences: Chi^2 = 2.49, df = 1 (P = 0.11), I^2 =60%				

Analysis 1.5. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 5 All-cause mortality; stratified after source of funding.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 5 All-cause mortality; stratified after source of funding

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Industry-funded				
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**15684**	**13447**		**1.00 [0.93, 1.08]**
Total events: 1543 (Intensive control), 1158 (Conventional control)				
Heterogeneity: Chi^2 = 18.15, df = 8 (P = 0.02); I^2 =56%				
Test for overall effect: Z = 0.07 (P = 0.94)				
2 Non-industry-funded				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
Subtotal (95% CI)	**295**	**305**		**1.03 [0.74, 1.43]**
Total events: 54 (Intensive control), 54 (Conventional control)				
Heterogeneity: Chi^2 = 0.00, df = 2 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.18 (P = 0.86)				
Total (95% CI)	**15979**	**13752**		**1.00 [0.93, 1.08]**
Total events: 1597 (Intensive control), 1212 (Conventional control)				
Heterogeneity: Chi^2 = 18.19, df = 11 (P = 0.08); I^2 =40%				
Test for overall effect: Z = 0.11 (P = 0.92)				
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%				

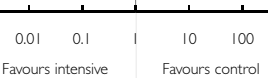
Analysis 1.6. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 6 All-cause mortality; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 6 All-cause mortality; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	257/5128	203/5123		1.26 [1.06, 1.51]
ADVANCE 2008	498/5571	533/5569		0.93 [0.83, 1.05]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	6/55		0.50 [0.13, 1.90]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
UGDP 1975	52/204	52/210		1.03 [0.74, 1.44]
UKPDS 1998	539/3071	213/1138		0.94 [0.81, 1.08]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Subtotal (95% CI)	**15142**	**13217**		**1.02 [0.91, 1.13]**
Total events: 1460 (Intensive control), 1111 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.07, df = 7 (P = 0.18); I^2 =30%				
Test for overall effect: Z = 0.33 (P = 0.74)				
2 Glycaemic control as a part of acute intervention				
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Subtotal (95% CI)	**534**	**369**		**1.21 [0.92, 1.60]**
Total events: 113 (Intensive control), 61 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 2 (P = 0.99); I^2 =0.0%				
Test for overall effect: Z = 1.35 (P = 0.18)				
3 Multimodal intervention in usual care setting				
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]



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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**303**	**166**		**0.60 [0.40, 0.90]**
Total events: 24 (Intensive control), 40 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 2.50 (P = 0.012)				
Total (95% CI)	**15979**	**13752**		**1.01 [0.90, 1.13]**
Total events: 1597 (Intensive control), 1212 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 18.19, df = 11 (P = 0.08); I^2 =40%				
Test for overall effect: Z = 0.10 (P = 0.92)				
Test for subgroup differences: Chi^2 = 8.16, df = 2 (P = 0.02), I^2 =75%				

Analysis 1.7. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 7 All-cause mortality; hazard ratio.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 7 All-cause mortality; hazard ratio

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
ACCORD 2008	0.1989 (0.1148)		21.5 %	1.22 [0.97, 1.53]
ADVANCE 2008	-0.0726 (0.0587)		24.5 %	0.93 [0.83, 1.04]
DIGAMI 2 2005	0.2311 (0.2041)		15.8 %	1.26 [0.84, 1.88]
Steno-2 2008	-0.6162 (0.1454)		19.5 %	0.54 [0.41, 0.72]
VADT 2009	0.0677 (0.1556)		18.8 %	1.07 [0.79, 1.45]
Total (95% CI)			**100.0 %**	**0.96 [0.74, 1.23]**
Heterogeneity: Tau^2 = 0.07; Chi^2 = 22.46, df = 4 (P = 0.00016); I^2 =82%				
Test for overall effect: Z = 0.35 (P = 0.72)				
Test for subgroup differences: Not applicable				

Analysis 1.8. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 8 All-cause mortality; available case.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 8 All-cause mortality; available case

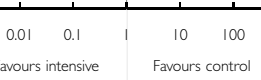
Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ACCORD 2008	257/5018	203/5021		1.27 [1.06, 1.52]
ADVANCE 2008	498/5564	533/5559		0.93 [0.83, 1.05]
Bagg 2001	0/17	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/17	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/53	6/51		0.48 [0.13, 1.82]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/8	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/31	1/35		1.13 [0.07, 17.30]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/191	52/206		1.08 [0.78, 1.50]
UKPDS 1998	539/3014	213/1119		0.94 [0.81, 1.08]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15773**	**13609**		**1.01 [0.94, 1.08]**

Total events: 1597 (Intensive control), 1212 (Conventional control)

Heterogeneity: Chi^2 = 18.57, df = 11 (P = 0.07); I^2 =41%

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 9 All-cause mortality; best-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 9 All-cause mortality; best-case scenario

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	257/5128	305/5123		0.84 [0.72, 0.99]
ADVANCE 2008	498/5571	543/5569		0.92 [0.82, 1.03]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	3/55	10/55		0.30 [0.09, 1.03]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	5/39		0.22 [0.03, 1.77]
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	52/204	56/210		0.96 [0.69, 1.32]
UKPDS 1998	539/3071	232/1138		0.86 [0.75, 0.99]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**0.90 [0.81, 1.00]**
Total events: 1597 (Intensive control), 1355 (Conventional control)				

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.01; Chi² = 16.36, df = 11 (P = 0.13); I² =33%				
Test for overall effect: Z = 1.90 (P = 0.058)				
Test for subgroup differences: Not applicable				

Analysis 1.10. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 10 All-cause mortality; worst-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 10 All-cause mortality; worst-case scenario

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	367/5128	203/5123		1.81 [1.53, 2.13]
ADVANCE 2008	505/5571	533/5569		0.95 [0.84, 1.06]
Bagg 2001	4/21	0/22		9.41 [0.54, 164.74]
DIGAMI 2 2005	111/474	59/306		1.21 [0.92, 1.61]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	6/23	0/22		12.46 [0.74, 208.81]
Kumamoto 2000	5/55	6/55		0.83 [0.27, 2.57]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	4/41	4/40		0.98 [0.26, 3.64]
Service 1983	2/10	0/10		5.00 [0.27, 92.62]
Stefanidis 2003	6/36	1/39		6.50 [0.82, 51.41]

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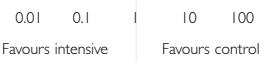
Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Steno-2 2008	24/80	40/80		0.60 [0.40, 0.90]
UGDP 1975	65/204	52/210		1.29 [0.94, 1.75]
UKPDS 1998	596/3071	213/1138		1.04 [0.90, 1.19]
VA CSDM 1995	5/75	5/78		1.04 [0.31, 3.45]
VADT 2009	102/892	95/899		1.08 [0.83, 1.41]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**1.15 [0.93, 1.42]**

Total events: 1803 (Intensive control), 1212 (Conventional control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 60.49$, df = 14 ($P<0.00001$); $I^2 = 77\%$

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 11 Cardiovascular mortality.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 11 Cardiovascular mortality

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	31/204	32/210		1.00 [0.63, 1.57]
UKPDS 1998	301/3071	91/1138		1.23 [0.98, 1.53]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**1.06 [0.90, 1.26]**

Total events: 863 (Intensive control), 619 (Conventional control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 17.52$, df = 11 (P = 0.09); $I^2 = 37\%$

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

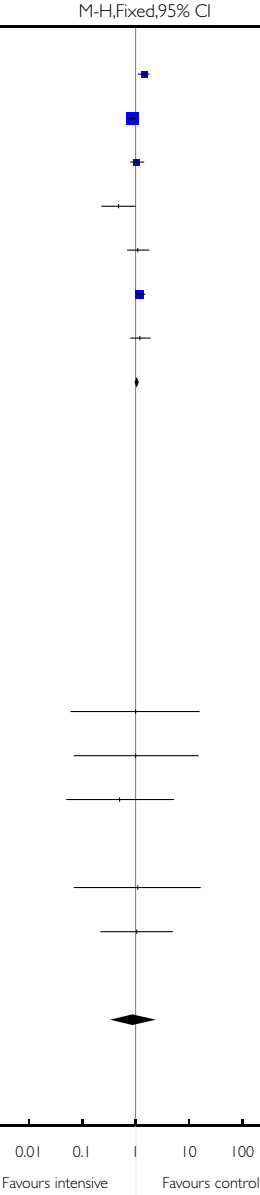
Analysis 1.12. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 12 Cardiovascular mortality; stratified after risk of bias.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 12 Cardiovascular mortality; stratified after risk of bias

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias				
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	29/204	27/210		1.11 [0.68, 1.80]
UKPDS 1998	301/3071	91/1138		1.23 [0.98, 1.53]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Subtotal (95% CI)	**15420**	**13325**		**1.06 [0.95, 1.17]**
Total events: 854 (Intensive control), 606 (Conventional control)				
Heterogeneity: Chi^2 = 17.09, df = 6 (P = 0.01); I^2 =65%				
Test for overall effect: Z = 1.08 (P = 0.28)				
2 High risk of bias				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**559**	**427**		**0.89 [0.33, 2.42]**
Total events: 7 (Intensive control), 8 (Conventional control)				
Heterogeneity: Chi^2 = 0.32, df = 4 (P = 0.99); I^2 =0.0%				



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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.22 (P = 0.83)				
Total (95% CI)	**15979**	**13752**		**1.06 [0.95, 1.17]**
Total events: 861 (Intensive control), 614 (Conventional control)				
Heterogeneity: Chi^2 = 17.50, df = 11 (P = 0.09); I^2 =37%				
Test for overall effect: Z = 1.05 (P = 0.29)				
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%				

Analysis 1.13. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 13 Cardiovascular mortality; stratified after study duration.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 13 Cardiovascular mortality; stratified after study duration

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Long duration (> 2 years)				
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	31/204	32/210		1.00 [0.63, 1.57]
UKPDS 1998	301/3071	91/1138		1.23 [0.98, 1.53]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Subtotal (95% CI)	**15550**	**13458**		**1.05 [0.95, 1.17]**

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total events: 860 (Intensive control), 615 (Conventional control)				
Heterogeneity: Chi^2 = 17.11, df = 8 (P = 0.03); I^2 =53%				
Test for overall effect: Z = 1.00 (P = 0.32)				
2 Short duration ($\leq$ 2 years)				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**429**	**294**		**0.76 [0.18, 3.30]**
Total events: 3 (Intensive control), 4 (Conventional control)				
Heterogeneity: Chi^2 = 0.24, df = 2 (P = 0.89); I^2 =0.0%				
Test for overall effect: Z = 0.37 (P = 0.71)				
Total (95% CI)	**15979**	**13752**		**1.05 [0.95, 1.17]**
Total events: 863 (Intensive control), 619 (Conventional control)				
Heterogeneity: Chi^2 = 17.52, df = 11 (P = 0.09); I^2 =37%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Test for subgroup differences: Chi^2 = 0.19, df = 1 (P = 0.66), I^2 =0.0%				

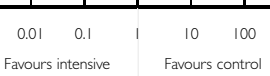
Analysis 1.14. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 14 Cardiovascular mortality; stratified after diagnostic criteria.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 14 Cardiovascular mortality; stratified after diagnostic criteria

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Diagnostic criteria described				
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	31/204	32/210		1.00 [0.63, 1.57]
UKPDS 1998	301/3071	91/1138		1.23 [0.98, 1.53]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Subtotal (95% CI)	**10287**	**8089**		**1.17 [1.02, 1.35]**
Total events: 609 (Intensive control), 328 (Conventional control)				
Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.36, df = 9 (P = 0.40); I^2 =4%				
Test for overall effect: Z = 2.28 (P = 0.023)				
2 Diagnostic criteria not described				
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**5692**	**5663**		**0.87 [0.74, 1.03]**
Total events: 254 (Intensive control), 291 (Conventional control)				



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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.0; Chi² = 0.23, df = 1 (P = 0.63); I² =0.0%				
Test for overall effect: Z = 1.63 (P = 0.10)				
Total (95% CI)	**15979**	**13752**		**1.06 [0.90, 1.26]**
Total events: 863 (Intensive control), 619 (Conventional control)				
Heterogeneity: Tau² = 0.02; Chi² = 17.52, df = 11 (P = 0.09); I² =37%				
Test for overall effect: Z = 0.74 (P = 0.46)				
Test for subgroup differences: Chi² = 7.35, df = 1 (P = 0.01), I² =86%				

Analysis 1.15. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 15 Cardiovascular mortality; stratified after source of funding.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 15 Cardiovascular mortality; stratified after source of funding

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Industry funding				
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]

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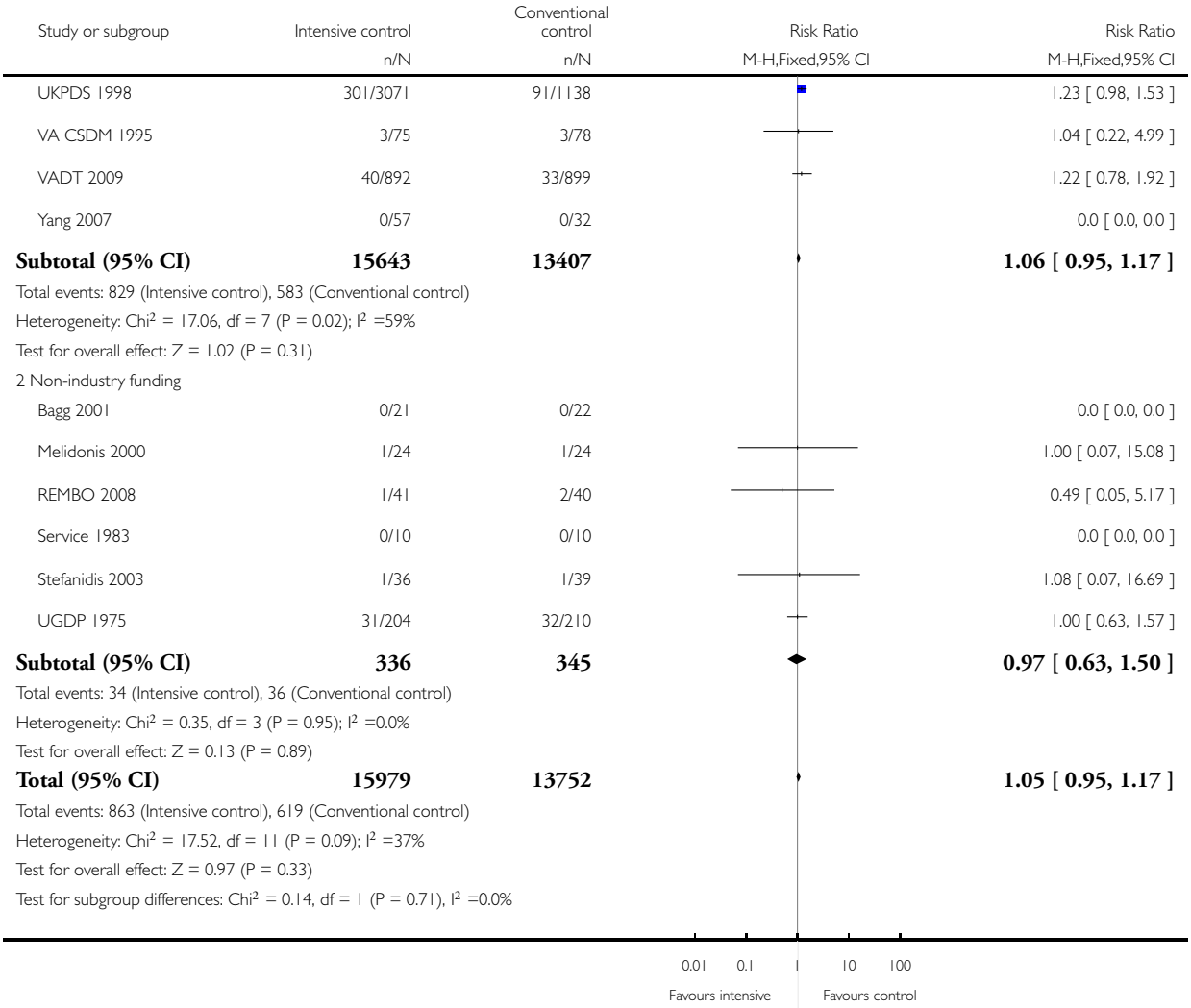

Analysis 1.16. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 16 Cardiovascular mortality; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 16 Cardiovascular mortality; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	135/5128	94/5123		1.43 [1.11, 1.86]
ADVANCE 2008	253/5571	289/5569		0.88 [0.74, 1.03]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	1/55		1.00 [0.06, 15.59]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
UGDP 1975	31/204	32/210		1.00 [0.63, 1.57]
UKPDS 1998	301/3071	91/1138		1.23 [0.98, 1.53]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Subtotal (95% CI)	**15142**	**13217**		**1.11 [0.92, 1.35]**
Total events: 765 (Intensive control), 545 (Conventional control)				
Heterogeneity: Tau^2 = 0.03; Chi^2 = 12.86, df = 7 (P = 0.08); I^2 =46%				
Test for overall effect: Z = 1.11 (P = 0.27)				
2 Glycaemic control as a part of acute intervention				
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Subtotal (95% CI)	**534**	**369**		**1.06 [0.78, 1.44]**
Total events: 89 (Intensive control), 55 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 2 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.37 (P = 0.71)				
3 Multimodal intervention in usual care setting				
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**303**	**166**		**0.47 [0.23, 0.98]**
Total events: 9 (Intensive control), 19 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 2.01 (P = 0.045)				
Total (95% CI)	**15979**	**13752**		**1.06 [0.90, 1.26]**
Total events: 863 (Intensive control), 619 (Conventional control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 17.52, df = 11 (P = 0.09); I^2 =37%				
Test for overall effect: Z = 0.74 (P = 0.46)				
Test for subgroup differences: Chi^2 = 4.94, df = 2 (P = 0.08), I^2 =59%				

Analysis 1.17. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 17 Cardiovascular mortality; hazard ratio.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 17 Cardiovascular mortality; hazard ratio

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
ACCORD 2008	0.3001 (0.1837)		25.9 %	1.35 [0.94, 1.94]
ADVANCE 2008	-0.1278 (0.0765)		30.1 %	0.88 [0.76, 1.02]
Steno-2 2008	-0.844 (0.1913)		25.6 %	0.43 [0.30, 0.63]
VADT 2009	0.2776 (0.3393)		18.5 %	1.32 [0.68, 2.57]
Total (95% CI)			**100.0 %**	**0.88 [0.56, 1.38]**
Heterogeneity: Tau^2 = 0.17; Chi^2 = 20.82, df = 3 (P = 0.00011); I^2 =86%				
Test for overall effect: Z = 0.55 (P = 0.58)				
Test for subgroup differences: Not applicable				

Analysis 1.18. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 18 Cardiovascular mortality; available case.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 18 Cardiovascular mortality; available case

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	135/5018	94/5021		1.44 [1.11, 1.86]
ADVANCE 2008	253/5564	289/5559		0.87 [0.74, 1.03]
Bagg 2001	0/17	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/17	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/53	1/51		0.96 [0.06, 14.98]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/8	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/31	1/35		1.13 [0.07, 17.30]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	31/191	32/206		1.04 [0.66, 1.64]
UKPDS 1998	301/3014	91/1119		1.23 [0.98, 1.54]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15773**	**13609**		**1.07 [0.91, 1.26]**

Total events: 863 (Intensive control), 619 (Conventional control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 17.61$, df = 11 (P = 0.09); $I^2 = 38\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 19 Cardiovascular mortality; worst-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 19 Cardiovascular mortality; worst-case scenario

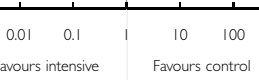
Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ACCORD 2008	245/5128	94/5123		2.60 [2.06, 3.29]
ADVANCE 2008	260/5571	289/5569		0.90 [0.76, 1.06]
Bagg 2001	4/21	0/22		9.41 [0.54, 164.74]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	6/23	0/22		12.46 [0.74, 208.81]
Kumamoto 2000	3/55	1/55		3.00 [0.32, 27.96]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	2/10	0/10		5.00 [0.27, 92.62]
Stefanidis 2003	6/36	1/39		6.50 [0.82, 51.41]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	44/204	32/210		1.42 [0.94, 2.14]
UKPDS 1998	358/3071	91/1138		1.46 [1.17, 1.82]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**1.32 [1.20, 1.45]**

Total events: 1069 (Intensive control), 619 (Conventional control)

Heterogeneity: $Chi^2 = 72.56$, df = 14 ($P<0.00001$); $I^2 = 81\%$

Test for overall effect: $Z = 5.58$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 20 Cardiovascular mortality; best-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 20 Cardiovascular mortality; best-case scenario

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	135/5128	196/5123		0.69 [0.55, 0.85]
ADVANCE 2008	253/5571	299/5569		0.85 [0.72, 1.00]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	87/474	53/306		1.06 [0.78, 1.44]
Guo 2008	0/166	0/54		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	1/55	5/55		0.20 [0.02, 1.66]
Melidonis 2000	1/24	1/24		1.00 [0.07, 15.08]
REMBO 2008	1/41	2/40		0.49 [0.05, 5.17]
Service 1983	0/10	0/10		0.0 [0.0, 0.0]
Stefanidis 2003	1/36	5/39		0.22 [0.03, 1.77]
Steno-2 2008	9/80	19/80		0.47 [0.23, 0.98]
UGDP 1975	31/204	36/210		0.89 [0.57, 1.38]
UKPDS 1998	301/3071	110/1138		1.01 [0.82, 1.25]
VA CSDM 1995	3/75	3/78		1.04 [0.22, 4.99]
VADT 2009	40/892	33/899		1.22 [0.78, 1.92]
Yang 2007	0/57	0/32		0.0 [0.0, 0.0]
Total (95% CI)	**15979**	**13752**		**0.87 [0.74, 1.01]**
Total events: 863 (Intensive control), 762 (Conventional control)				

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.02; Chi² = 17.00, df = 11 (P = 0.11); I² =35%				
Test for overall effect: Z = 1.82 (P = 0.069)				
Test for subgroup differences: Not applicable				

Analysis 1.21. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 21 Macrovascular complications.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 21 Macrovascular complications

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ACCORD 2008	352/5128	371/5123		18.4 %	0.95 [0.82, 1.09]
ADVANCE 2008	557/5571	590/5569		19.9 %	0.94 [0.85, 1.05]
Bagg 2001	3/21	0/22		0.2 %	7.32 [0.40, 133.66]
Becker 2003	5/106	6/108		1.3 %	0.85 [0.27, 2.70]
DIGAMI 2 2005	177/474	97/306		15.2 %	1.18 [0.96, 1.44]
Kumamoto 2000	5/55	10/55		1.7 %	0.50 [0.18, 1.37]
Steno-2 2008	25/80	48/80		8.4 %	0.52 [0.36, 0.75]
UKPDS 1998	169/2729	87/1138		12.9 %	0.81 [0.63, 1.04]
VA CSDM 1995	21/75	13/78		4.0 %	1.68 [0.91, 3.11]
VADT 2009	235/892	264/899		17.9 %	0.90 [0.77, 1.04]
Total (95% CI)	**15131**	**13378**		**100.0 %**	**0.92 [0.80, 1.05]**
Total events: 1549 (Intensive control), 1486 (Conventional control)					

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.02; Chi² = 23.16, df = 9 (P = 0.01); I² =61%					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Not applicable					

Analysis 1.22. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 22 Macrovascular complications; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 22 Macrovascular complications; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	352/5128	371/5123		18.4 %	0.95 [0.82, 1.09]
ADVANCE 2008	557/5571	590/5569		19.9 %	0.94 [0.85, 1.05]
Bagg 2001	3/21	0/22		0.2 %	7.32 [0.40, 133.66]
Becker 2003	5/106	6/108		1.3 %	0.85 [0.27, 2.70]
Kumamoto 2000	5/55	10/55		1.7 %	0.50 [0.18, 1.37]
UKPDS 1998	169/2729	87/1138		12.9 %	0.81 [0.63, 1.04]
VA CSDM 1995	21/75	13/78		4.0 %	1.68 [0.91, 3.11]
VADT 2009	235/892	264/899		17.9 %	0.90 [0.77, 1.04]
Subtotal (95% CI)	**14577**	**12992**		**76.4 %**	**0.93 [0.85, 1.01]**
Total events: 1347 (Intensive control), 1341 (Conventional control)					
Heterogeneity: Tau² = 0.00; Chi² = 8.52, df = 7 (P = 0.29); I² =18%					
Test for overall effect: Z = 1.70 (P = 0.089)					

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 Glycaemic control as a part of acute intervention					
DIGAMI 2 2005	177/474	97/306		15.2 %	1.18 [0.96, 1.44]
Subtotal (95% CI)	**474**	**306**		**15.2 %**	**1.18 [0.96, 1.44]**
Total events: 177 (Intensive control), 97 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
3 Multimodal intervention in usual care setting					
Steno-2 2008	25/80	48/80		8.4 %	0.52 [0.36, 0.75]
Subtotal (95% CI)	**80**	**80**		**8.4 %**	**0.52 [0.36, 0.75]**
Total events: 25 (Intensive control), 48 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.45 (P = 0.00057)					
Total (95% CI)	**15131**	**13378**		**100.0 %**	**0.92 [0.80, 1.05]**
Total events: 1549 (Intensive control), 1486 (Conventional control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 23.16, df = 9 (P = 0.01); I^2 =61%					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Chi^2 = 14.65, df = 2 (P = 0.00), I^2 =86%					

Analysis 1.23. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 23 Non-fatal myocardial infarction.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 23 Non-fatal myocardial infarction

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
ADVANCE 2008	153/5571	156/5569		0.98 [0.79, 1.22]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Total (95% CI)	**15631**	**13543**		**0.87 [0.76, 1.00]**

Total events: 729 (Intensive control), 655 (Conventional control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.49$, df = 9 (P = 0.19); $I^2 = 28\%$

Test for overall effect: Z = 1.93 (P = 0.054)

Test for subgroup differences: Not applicable

Analysis 1.24. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 24 Non-fatal myocardial infarction; stratified after study duration.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 24 Non-fatal myocardial infarction; stratified after study duration

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Long duration (≤ 2 years)				
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
ADVANCE 2008	153/5571	156/5569		0.98 [0.79, 1.22]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Subtotal (95% CI)	**15550**	**13458**		**0.87 [0.74, 1.02]**
Total events: 725 (Intensive control), 650 (Conventional control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 12.43, df = 7 (P = 0.09); I^2 =44%				
Test for overall effect: Z = 1.71 (P = 0.087)				
2 Short duration (> 2 years)				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Subtotal (95% CI)	**81**	**85**		**0.81 [0.23, 2.78]**
Total events: 4 (Intensive control), 5 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 0.34 (P = 0.74)				
Total (95% CI)	**15631**	**13543**		**0.87 [0.76, 1.00]**
Total events: 729 (Intensive control), 655 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 12.49, df = 9 (P = 0.19); I^2 =28%				
Test for overall effect: Z = 1.93 (P = 0.054)				
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 =0.0%				

Analysis 1.25. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 25 Non-fatal myocardial infarction; stratified after risk of bias.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 25 Non-fatal myocardial infarction; stratified after risk of bias

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Low risk of bias				
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
ADVANCE 2008	153/5571	156/5569		0.98 [0.79, 1.22]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Subtotal (95% CI)	**15420**	**13325**		**0.87 [0.74, 1.03]**
Total events: 721 (Intensive control), 645 (Conventional control)				
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.42$, df = 6 (P = 0.05); $I^2 = 52\%$				
Test for overall effect: Z = 1.62 (P = 0.11)				
2 High risk of bias				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
Subtotal (95% CI)	**211**	**218**		**0.82 [0.34, 1.99]**
Total events: 8 (Intensive control), 10 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 2 (P = 0.97); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.44 (P = 0.66)				
Total (95% CI)	**15631**	**13543**		**0.87 [0.76, 1.00]**
Total events: 729 (Intensive control), 655 (Conventional control)				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.49$, df = 9 (P = 0.19); $I^2 = 28\%$				
Test for overall effect: Z = 1.93 (P = 0.054)				
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.90), $I^2 = 0.0\%$				

Analysis 1.26. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 26 Non-fatal myocardial infarction; stratified after source of funding.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 26 Non-fatal myocardial infarction; stratified after source of funding

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Industry-funded				
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
ADVANCE 2008	153/5571	156/5569		0.98 [0.79, 1.22]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Subtotal (95% CI)	**15346**	**13248**		**0.86 [0.72, 1.02]**
Total events: 696 (Intensive control), 620 (Conventional control)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 12.08, df = 6 (P = 0.06); I^2 =50%				
Test for overall effect: Z = 1.71 (P = 0.088)				
2 Non-industry-funded				
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
Subtotal (95% CI)	**285**	**295**		**0.97 [0.62, 1.51]**
Total events: 33 (Intensive control), 35 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.15, df = 2 (P = 0.93); I^2 =0.0%				
Test for overall effect: Z = 0.14 (P = 0.89)				
Total (95% CI)	**15631**	**13543**		**0.87 [0.76, 1.00]**
Total events: 729 (Intensive control), 655 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 12.49, df = 9 (P = 0.19); I^2 =28%				
Test for overall effect: Z = 1.93 (P = 0.054)				
Test for subgroup differences: Chi^2 = 0.25, df = 1 (P = 0.62), I^2 =0.0%				

Analysis 1.27. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 27 Non-fatal myocardial infarction; stratified after diagnostic criteria.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 27 Non-fatal myocardial infarction; stratified after diagnostic criteria

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Diagnostic criteria described				
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Total (95% CI)	**10060**	**7974**		**0.83 [0.74, 0.94]**

Total events: 576 (Intensive control), 499 (Conventional control)

Heterogeneity: Chi^2 = 10.90, df = 8 (P = 0.21); I^2 =27%

Test for overall effect: Z = 3.05 (P = 0.0023)

Test for subgroup differences: Not applicable

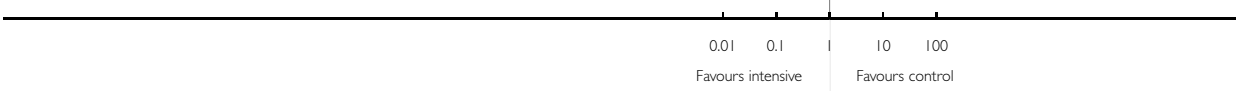
Analysis 1.28. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 28 Non-fatal myocardial infarction; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 28 Non-fatal myocardial infarction; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	186/5128	235/5123		0.79 [0.65, 0.95]
ADVANCE 2008	153/5571	156/5569		0.98 [0.79, 1.22]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
UGDP 1975	29/204	30/210		1.00 [0.62, 1.60]
UKPDS 1998	221/3071	101/1138		0.81 [0.65, 1.02]
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	66/899		0.78 [0.55, 1.11]
Subtotal (95% CI)	**15017**	**13094**		**0.85 [0.76, 0.95]**
Total events: 644 (Intensive control), 593 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.02, df = 5 (P = 0.70); I^2 =0.0%				
Test for overall effect: Z = 2.88 (P = 0.0039)				
2 Glycaemic control as a part of acute intervention				
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	1/39		1.08 [0.07, 16.69]
Subtotal (95% CI)	**534**	**369**		**1.26 [0.88, 1.80]**
Total events: 77 (Intensive control), 41 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.59, df = 2 (P = 0.74); I^2 =0.0%				
Test for overall effect: Z = 1.26 (P = 0.21)				
3 Multimodal intervention in usual care setting				
Steno-2 2008	8/80	21/80		0.38 [0.18, 0.81]
Subtotal (95% CI)	**80**	**80**		**0.38 [0.18, 0.81]**
Total events: 8 (Intensive control), 21 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.51 (P = 0.012)				
Total (95% CI)	**15631**	**13543**		**0.87 [0.76, 1.00]**
Total events: 729 (Intensive control), 655 (Conventional control)				



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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.01; Chi^2 = 12.49, df = 9 (P = 0.19); I^2 =28%				
Test for overall effect: Z = 1.93 (P = 0.054)				
Test for subgroup differences: Chi^2 = 8.89, df = 2 (P = 0.01), I^2 =77%				

Analysis 1.29. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 29 Non-fatal myocardial infarction; available case.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 29 Non-fatal myocardial infarction; available case

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ACCORD 2008	186/4725	235/4751		0.80 [0.66, 0.96]
ADVANCE 2008	153/5326	156/5274		0.97 [0.78, 1.21]
Bagg 2001	0/17	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/53	0/51		0.0 [0.0, 0.0]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/31	1/35		1.13 [0.07, 17.30]
Steno-2 2008	8/79	21/78		0.38 [0.18, 0.80]
UGDP 1975	29/167	30/172		1.00 [0.63, 1.58]
UKPDS 1998	221/2949	101/1093		0.81 [0.65, 1.02]
VA CSDM 1995	4/71	5/78		0.88 [0.25, 3.14]
VADT 2009	51/772	66/760		0.76 [0.54, 1.08]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	**14688**	**12644**		**0.86 [0.78, 0.96]**
Total events: 729 (Intensive control), 655 (Conventional control)				
Heterogeneity: Chi^2 = 12.55, df = 9 (P = 0.18); I^2 =28%				
Test for overall effect: Z = 2.78 (P = 0.0054)				
Test for subgroup differences: Not applicable				

Analysis 1.30. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 30 Non-fatal myocardial infarction; worst-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 30 Non-fatal myocardial infarction; worst-case scenario

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACCORD 2008	589/5128	235/5123		33.1 %	2.50 [2.16, 2.90]
ADVANCE 2008	398/5571	156/5569		22.0 %	2.55 [2.13, 3.06]
Bagg 2001	4/21	0/22		0.1 %	9.41 [0.54, 164.74]
DIGAMI 2 2005	73/474	36/306		6.2 %	1.31 [0.90, 1.90]
Kumamoto 2000	2/55	0/55		0.1 %	5.00 [0.25, 101.81]
Melidonis 2000	3/24	4/24		0.6 %	0.75 [0.19, 3.00]
Stefanidis 2003	5/36	1/39		0.1 %	5.42 [0.66, 44.18]
Steno-2 2008	9/80	21/80		3.0 %	0.43 [0.21, 0.88]
UGDP 1975	66/204	30/210		4.2 %	2.26 [1.54, 3.33]
UKPDS 1998	343/3071	101/1138		20.8 %	1.26 [1.02, 1.55]
VA CSDM 1995	8/75	5/78		0.7 %	1.66 [0.57, 4.86]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VADT 2009	171/892	66/899		9.3 %	2.61 [2.00, 3.42]
Total (95% CI)	**15631**	**13543**		**100.0 %**	**2.12 [1.94, 2.31]**

Total events: 1671 (Intensive control), 655 (Conventional control)

Heterogeneity: Chi^2 = 64.82, df = 11 (P<0.00001); I^2 =83%

Test for overall effect: Z = 17.05 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.31. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 31 Non-fatal myocardial infarction; best-case scenario.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 31 Non-fatal myocardial infarction; best-case scenario

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ACCORD 2008	186/5128	607/5123		0.31 [0.26, 0.36]
ADVANCE 2008	153/5571	451/5569		0.34 [0.28, 0.41]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
DIGAMI 2 2005	73/474	36/306		1.31 [0.90, 1.90]
Kumamoto 2000	0/55	4/55		0.11 [0.01, 2.02]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	1/36	4/39		0.27 [0.03, 2.31]
Steno-2 2008	8/80	23/80		0.35 [0.17, 0.73]
UGDP 1975	29/204	68/210		0.44 [0.30, 0.65]
UKPDS 1998	221/3071	146/1138		0.56 [0.46, 0.68]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
VA CSDM 1995	4/75	5/78		0.83 [0.23, 2.98]
VADT 2009	51/892	205/899		0.25 [0.19, 0.34]
Total (95% CI)	**15631**	**13543**		**0.38 [0.34, 0.41]**

Total events: 729 (Intensive control), 1553 (Conventional control)
Heterogeneity: Chi² = 77.65, df = 10 (P<0.00001); I² =87%
Test for overall effect: Z = 21.58 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.32. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 32 Non-fatal stroke.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 32 Non-fatal stroke

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	67/5128	61/5123		1.10 [0.78, 1.55]
ADVANCE 2008	214/5571	209/5569		1.02 [0.85, 1.23]
Bagg 2001	1/21	0/22		3.14 [0.13, 72.96]
DIGAMI 2 2005	24/474	13/306		1.19 [0.62, 2.30]
Kumamoto 2000	1/55	0/55		3.00 [0.12, 72.08]
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Steno-2 2008	6/80	18/80		0.33 [0.14, 0.80]
UKPDS 1998	120/3071	44/1138		1.01 [0.72, 1.42]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
VA CSDM 1995	2/75	5/78		0.42 [0.08, 2.08]
VADT 2009	22/892	30/899		0.74 [0.43, 1.27]
Total (95% CI)	**15427**	**13333**		**0.96 [0.80, 1.16]**

Total events: 457 (Intensive control), 380 (Conventional control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.01$, df = 8 (P = 0.26); $I^2 = 20\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 1.33. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 33 Non-fatal stroke; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 33 Non-fatal stroke; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	67/5128	61/5123		1.10 [0.78, 1.55]
ADVANCE 2008	214/5571	209/5569		1.02 [0.85, 1.23]
Bagg 2001	1/21	0/22		3.14 [0.13, 72.96]
Kumamoto 2000	1/55	0/55		3.00 [0.12, 72.08]
UKPDS 1998	120/3071	44/1138		1.01 [0.72, 1.42]
VA CSDM 1995	2/75	5/78		0.42 [0.08, 2.08]
VADT 2009	22/892	30/899		0.74 [0.43, 1.27]

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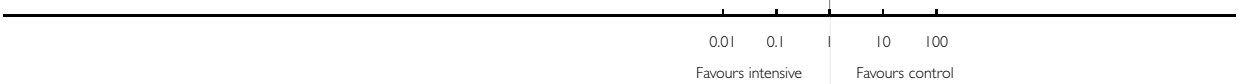
Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**14813**	**12884**	◆	**1.01 [0.87, 1.16]**
Total events: 427 (Intensive control), 349 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.63, df = 6 (P = 0.73); I^2 =0.0%				
Test for overall effect: Z = 0.11 (P = 0.91)				
2 Glycaemic control as a part of acute intervention				
DIGAMI 2 2005	24/474	13/306	■	1.19 [0.62, 2.30]
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**534**	**366**	◆	**1.19 [0.62, 2.30]**
Total events: 24 (Intensive control), 13 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.52 (P = 0.60)				
3 Multimodal intervention in usual care setting				
Steno-2 2008	6/80	18/80	─	0.33 [0.14, 0.80]
Subtotal (95% CI)	**80**	**80**	◆	**0.33 [0.14, 0.80]**
Total events: 6 (Intensive control), 18 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.47 (P = 0.013)				
Total (95% CI)	**15427**	**13330**	◆	**0.96 [0.80, 1.16]**
Total events: 457 (Intensive control), 380 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.01, df = 8 (P = 0.26); I^2 =20%				
Test for overall effect: Z = 0.41 (P = 0.68)				
Test for subgroup differences: Chi^2 = 6.37, df = 2 (P = 0.04), I^2 =69%				



Analysis 1.34. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 34 Amputation of lower extremity.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 34 Amputation of lower extremity

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Steno-2 2008	6/80	14/80		0.43 [0.17, 1.06]
UGDP 1975	3/204	1/210		3.09 [0.32, 29.45]
UKPDS 1998	33/3071	18/1138		0.68 [0.38, 1.20]
VA CSDM 1995	0/75	1/78		0.35 [0.01, 8.37]
VADT 2009	11/892	17/899		0.65 [0.31, 1.38]
Total (95% CI)	**4437**	**2523**		**0.64 [0.43, 0.95]**

Total events: 53 (Intensive control), 51 (Conventional control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.82$, df = 4 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 2.22 (P = 0.026)

Test for subgroup differences: Not applicable

Analysis 1.35. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 35 Amputation of lower extremity; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 35 Amputation of lower extremity; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
UGDP 1975	3/204	1/210		3.09 [0.32, 29.45]
UKPDS 1998	33/3071	18/1138		0.68 [0.38, 1.20]
VA CSDM 1995	0/75	1/78		0.35 [0.01, 8.37]
VADT 2009	11/892	17/899		0.65 [0.31, 1.38]
Subtotal (95% CI)	**4297**	**2380**		**0.70 [0.45, 1.09]**
Total events: 47 (Intensive control), 37 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 3 (P = 0.59); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.58 (P = 0.11)				
2 Glycaemic control as a part of acute intervention				
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Multimodal intervention in usual care setting				
Steno-2 2008	6/80	14/80		0.43 [0.17, 1.06]
Subtotal (95% CI)	**80**	**80**		**0.43 [0.17, 1.06]**
Total events: 6 (Intensive control), 14 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.84 (P = 0.066)				
Total (95% CI)	**4437**	**2523**		**0.64 [0.43, 0.95]**
Total events: 53 (Intensive control), 51 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.82$, df = 4 (P = 0.59); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.22 (P = 0.026)				
Test for subgroup differences: $Chi^2 = 0.92$, df = 1 (P = 0.34), $I^2 = 0.0\%$				

Analysis 1.36. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 36 Cardiac revascularization.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 36 Cardiac revascularization

Study or subgroup	Intensive control	Conventional control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Kumamoto 2000	1/55	0/55		0.3 %	3.00 [0.12, 72.08]
Stefanidis 2003	2/36	1/39		0.7 %	2.17 [0.21, 22.89]
Steno-2 2008	8/80	13/80		8.9 %	0.62 [0.27, 1.40]
VA CSDM 1995	3/75	5/78		3.4 %	0.62 [0.15, 2.52]
VADT 2009	107/892	127/899		86.7 %	0.85 [0.67, 1.08]
Total (95% CI)	**1138**	**1151**		**100.0 %**	**0.84 [0.67, 1.05]**

Total events: 121 (Intensive control), 146 (Conventional control)

Heterogeneity: $Chi^2 = 1.96$, df = 4 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 1.55 (P = 0.12)

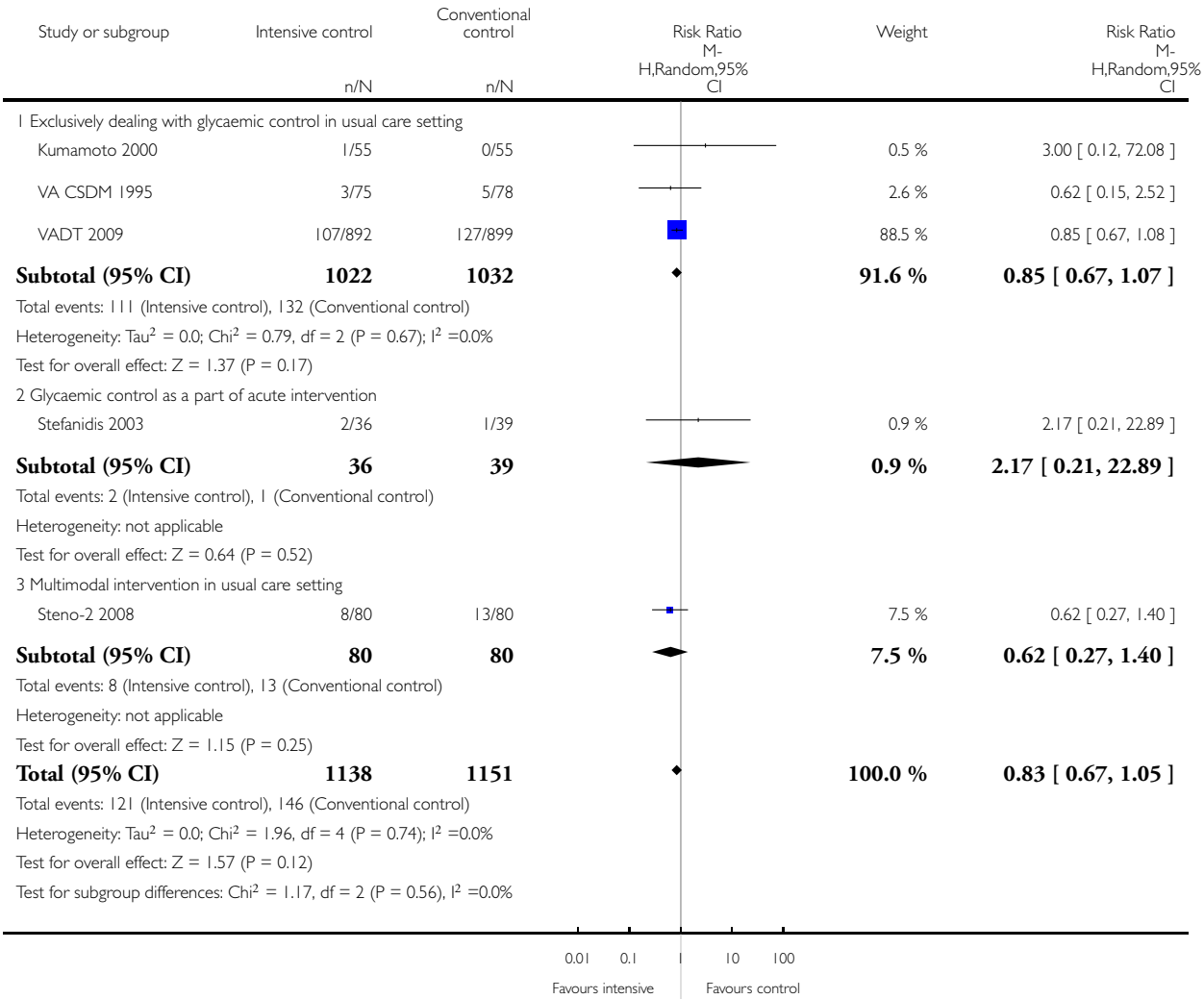
Test for subgroup differences: Not applicable

Analysis 1.37. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 37 Cardiac revascularization; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 37 Cardiac revascularization; stratified after intervention



Analysis 1.38. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 38 Peripheral revascularization.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 38 Peripheral revascularization

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ADVANCE 2008	343/5571	366/5569		0.94 [0.81, 1.08]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Steno-2 2008	6/80	10/80		0.60 [0.23, 1.57]
VA CSDM 1995	0/75	0/78		0.0 [0.0, 0.0]
VADT 2009	20/892	23/899		0.88 [0.48, 1.58]
Total (95% CI)	**6733**	**6744**		**0.92 [0.81, 1.06]**

Total events: 369 (Intensive control), 399 (Conventional control)

Heterogeneity: $Chi^2 = 0.84$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 1.39. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 39 Peripheral revascularization; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 39 Peripheral revascularization; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ADVANCE 2008	343/5571	366/5569		0.94 [0.81, 1.08]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
VA CSDM 1995	0/75	0/78		0.0 [0.0, 0.0]
VADT 2009	20/892	23/899		0.88 [0.48, 1.58]
Subtotal (95% CI)	**6593**	**6601**		**0.93 [0.81, 1.07]**
Total events: 363 (Intensive control), 389 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.97 (P = 0.33)				
2 Glycaemic control as a part of acute intervention				
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Multimodal intervention in usual care setting				
Steno-2 2008	6/80	10/80		0.60 [0.23, 1.57]
Subtotal (95% CI)	**80**	**80**		**0.60 [0.23, 1.57]**
Total events: 6 (Intensive control), 10 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.04 (P = 0.30)				
Total (95% CI)	**6733**	**6744**		**0.93 [0.81, 1.06]**
Total events: 369 (Intensive control), 399 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.84$, df = 2 (P = 0.66); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.11 (P = 0.27)				
Test for subgroup differences: $Chi^2 = 0.79$, df = 1 (P = 0.37), $I^2 = 0.0\%$				

Analysis 1.40. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 40 Microvascular complications.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 40 Microvascular complications

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ACCORD 2008	556/5128	586/5123		30.5 %	0.95 [0.85, 1.06]
ADVANCE 2008	526/5571	605/5569		29.9 %	0.87 [0.78, 0.97]
Steno-2 2008	67/80	75/80		29.4 %	0.89 [0.80, 1.00]
UKPDS 1998	249/3071	121/1138		10.1 %	0.76 [0.62, 0.94]
Total (95% CI)	**13850**	**11910**		**100.0 %**	**0.89 [0.83, 0.95]**

Total events: 1398 (Intensive control), 1387 (Conventional control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.61$, df = 3 (P = 0.31); $I^2 = 17\%$

Test for overall effect: Z = 3.43 (P = 0.00061)

Test for subgroup differences: Not applicable

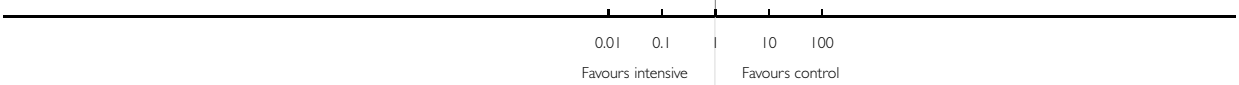
Analysis 1.41. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 41 Microvascular complications; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 41 Microvascular complications; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	556/5128	586/5123		38.1 %	0.94 [0.83, 1.06]
ADVANCE 2008	526/5571	605/5569		38.1 %	0.86 [0.76, 0.97]
UKPDS 1998	249/3071	121/1138		22.2 %	0.74 [0.59, 0.93]
Subtotal (95% CI)	**13770**	**11830**		**98.4 %**	**0.87 [0.77, 0.97]**
Total events: 1331 (Intensive control), 1312 (Conventional control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.50$, df = 2 (P = 0.17); $I^2 = 43\%$					
Test for overall effect: Z = 2.49 (P = 0.013)					
2 Glycaemic control as a part of acute intervention					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Multimodal intervention in usual care setting					
Steno-2 2008	67/80	75/80		1.6 %	0.34 [0.12, 1.01]
Subtotal (95% CI)	**80**	**80**		**1.6 %**	**0.34 [0.12, 1.01]**
Total events: 67 (Intensive control), 75 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.053)					
Total (95% CI)	**13850**	**11910**		**100.0 %**	**0.85 [0.74, 0.97]**
Total events: 1398 (Intensive control), 1387 (Conventional control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.35$, df = 3 (P = 0.10); $I^2 = 53\%$					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: $Chi^2 = 2.77$, df = 1 (P = 0.10), $I^2 = 64\%$					



Analysis 1.42. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 42 Nephropathy.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 42 Nephropathy

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ACCORD 2008	3056/5128	3077/5123		23.9 %	0.99 [0.96, 1.02]
ADVANCE 2008	230/5571	292/5569		21.6 %	0.79 [0.67, 0.93]
Bagg 2001	4/21	1/22		1.3 %	4.19 [0.51, 34.50]
Kumamoto 2000	9/55	24/55		8.6 %	0.38 [0.19, 0.73]
Steno-2 2008	20/80	37/80		13.3 %	0.54 [0.35, 0.85]
UGDP 1975	11/204	4/210		3.9 %	2.83 [0.92, 8.75]
UKPDS 1998	11/2729	11/1138		6.4 %	0.42 [0.18, 0.96]
VA CSDM 1995	3/75	10/78		3.3 %	0.31 [0.09, 1.09]
VADT 2009	78/892	78/899		17.7 %	1.01 [0.75, 1.36]
Total (95% CI)	**14755**	**13174**		**100.0 %**	**0.78 [0.61, 0.99]**

Total events: 3422 (Intensive control), 3534 (Conventional control)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 35.10$, df = 8 (P = 0.00003); $I^2 = 77\%$

Test for overall effect: Z = 2.03 (P = 0.043)

Test for subgroup differences: Not applicable

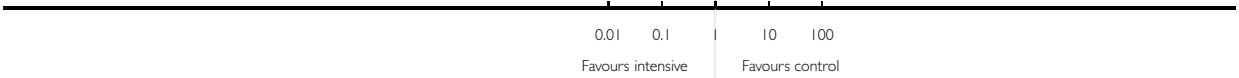
Analysis 1.43. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 43 Nephropathy; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 43 Nephropathy; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	3056/5128	3077/5123		23.9 %	0.99 [0.96, 1.02]
ADVANCE 2008	230/5571	292/5569		21.6 %	0.79 [0.67, 0.93]
Bagg 2001	4/21	1/22		1.3 %	4.19 [0.51, 34.50]
Kumamoto 2000	9/55	24/55		8.6 %	0.38 [0.19, 0.73]
UGDP 1975	11/204	4/210		3.9 %	2.83 [0.92, 8.75]
UKPDS 1998	11/2729	11/1138		6.4 %	0.42 [0.18, 0.96]
VA CSDM 1995	3/75	10/78		3.3 %	0.31 [0.09, 1.09]
VADT 2009	78/892	78/899		17.7 %	1.01 [0.75, 1.36]
Subtotal (95% CI)	**14675**	**13094**		**86.7 %**	**0.83 [0.64, 1.06]**
Total events: 3402 (Intensive control), 3497 (Conventional control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 28.09, df = 7 (P = 0.00021); I^2 =75%					
Test for overall effect: Z = 1.51 (P = 0.13)					
2 Glycaemic control as a part of acute intervention					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Multimodal intervention in usual care setting					
Steno-2 2008	20/80	37/80		13.3 %	0.54 [0.35, 0.85]
Subtotal (95% CI)	**80**	**80**		**13.3 %**	**0.54 [0.35, 0.85]**
Total events: 20 (Intensive control), 37 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.70 (P = 0.0070)					
Total (95% CI)	**14755**	**13174**		**100.0 %**	**0.78 [0.61, 0.99]**
Total events: 3422 (Intensive control), 3534 (Conventional control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 35.10, df = 8 (P = 0.00003); I^2 =77%					
Test for overall effect: Z = 2.03 (P = 0.043)					
Test for subgroup differences: Chi^2 = 2.64, df = 1 (P = 0.10), I^2 =62%					



Analysis 1.44. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 44 End-stage renal disease.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 44 End-stage renal disease

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008	140/5128	152/5123		0.92 [0.73, 1.15]
ADVANCE 2008	22/5571	33/5569		0.67 [0.39, 1.14]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Steno-2 2008	1/80	6/80		0.17 [0.02, 1.35]
UGDP 1975	0/204	0/210		0.0 [0.0, 0.0]
UKPDS 1998	28/3071	11/1138		0.94 [0.47, 1.89]
VADT 2009	2/892	3/899		0.67 [0.11, 4.01]
Total (95% CI)	**15001**	**13074**		**0.87 [0.71, 1.06]**

Total events: 193 (Intensive control), 205 (Conventional control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.71$, df = 4 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

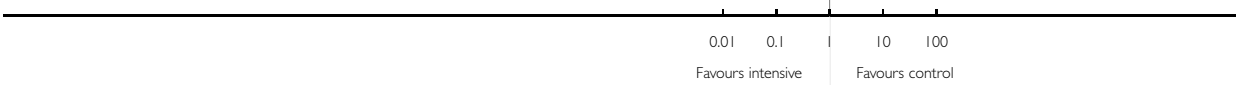
Analysis 1.45. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 45 End-stage renal disease; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 45 End-stage renal disease; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	140/5128	152/5123		0.92 [0.73, 1.15]
ADVANCE 2008	22/5571	33/5569		0.67 [0.39, 1.14]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
UGDP 1975	0/204	0/210		0.0 [0.0, 0.0]
UKPDS 1998	28/3071	11/1138		0.94 [0.47, 1.89]
VADT 2009	2/892	3/899		0.67 [0.11, 4.01]
Subtotal (95% CI)	**14921**	**12994**		**0.88 [0.72, 1.07]**
Total events: 192 (Intensive control), 199 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.30$, df = 3 (P = 0.73); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.27 (P = 0.20)				
2 Glycaemic control as a part of acute intervention				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
3 Multimodal intervention in usual care setting				
Steno-2 2008	1/80	6/80		0.17 [0.02, 1.35]
Subtotal (95% CI)	**80**	**80**		**0.17 [0.02, 1.35]**
Total events: 1 (Intensive control), 6 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.68 (P = 0.094)				
Total (95% CI)	**15001**	**13074**		**0.87 [0.71, 1.06]**
Total events: 193 (Intensive control), 205 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.71$, df = 4 (P = 0.45); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.43 (P = 0.15)				
Test for subgroup differences: $Chi^2 = 2.40$, df = 1 (P = 0.12), $I^2 = 58\%$				



Analysis 1.46. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 46 Retinopathy.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 46 Retinopathy

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ACCORD 2008	81/1429	126/1427		13.7 %	0.64 [0.49, 0.84]
ADVANCE 2008	88/791	99/811		13.7 %	0.91 [0.70, 1.19]
Kumamoto 2000	13/55	34/55		6.1 %	0.38 [0.23, 0.64]
Steno-2 2008	41/80	54/80		14.1 %	0.76 [0.58, 0.99]
UGDP 1975	44/204	45/210		9.8 %	1.01 [0.70, 1.45]
UKPDS 1998	363/2729	172/1138		19.3 %	0.88 [0.74, 1.04]
VA CSDM 1995	21/75	22/78		6.3 %	0.99 [0.60, 1.65]
VADT 2009	123/534	154/534		17.1 %	0.80 [0.65, 0.98]
Total (95% CI)	**5897**	**4333**		**100.0 %**	**0.79 [0.68, 0.92]**

Total events: 774 (Intensive control), 706 (Conventional control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.80$, df = 7 (P = 0.04); $I^2 = 53\%$

Test for overall effect: Z = 3.14 (P = 0.0017)

Test for subgroup differences: Not applicable

Analysis 1.47. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 47 Retinopathy; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 47 Retinopathy; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	81/1429	126/1427		13.6 %	0.64 [0.49, 0.84]
ADVANCE 2008	88/791	99/811		13.5 %	0.91 [0.70, 1.19]
Kumamoto 2000	13/55	34/55		6.0 %	0.38 [0.23, 0.64]
UGDP 1975	51/204	53/210		10.9 %	0.99 [0.71, 1.38]
UKPDS 1998	363/2729	172/1138		19.1 %	0.88 [0.74, 1.04]
VA CSDM 1995	21/75	22/78		6.2 %	0.99 [0.60, 1.65]
VADT 2009	123/534	154/534		16.9 %	0.80 [0.65, 0.98]
Subtotal (95% CI)	**5817**	**4253**		**86.1 %**	**0.80 [0.67, 0.94]**
Total events: 740 (Intensive control), 660 (Conventional control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 14.61, df = 6 (P = 0.02); I^2 =59%					
Test for overall effect: Z = 2.67 (P = 0.0076)					
2 Glycaemic control as a part of acute intervention					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Multimodal intervention in usual care setting					
Steno-2 2008	41/80	54/80		13.9 %	0.76 [0.58, 0.99]
Subtotal (95% CI)	**80**	**80**		**13.9 %**	**0.76 [0.58, 0.99]**
Total events: 41 (Intensive control), 54 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.040)					
Total (95% CI)	**5897**	**4333**		**100.0 %**	**0.79 [0.69, 0.92]**
Total events: 781 (Intensive control), 714 (Conventional control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 14.87, df = 7 (P = 0.04); I^2 =53%					
Test for overall effect: Z = 3.15 (P = 0.0016)					
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.77), I^2 =0.0%					

Analysis 1.48. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 48 Retinal photocoagulation.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 48 Retinal photocoagulation

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ACCORD 2008	33/1429	34/1427		15.0 %	0.97 [0.60, 1.56]
ADVANCE 2008	16/791	22/811		9.9 %	0.75 [0.39, 1.41]
Kumamoto 2000	3/55	12/55		3.3 %	0.25 [0.07, 0.84]
Steno-2 2008	14/80	27/80		11.8 %	0.52 [0.29, 0.91]
UGDP 1975	2/204	2/210		1.4 %	1.03 [0.15, 7.24]
UKPDS 1998	229/3071	117/1138		30.2 %	0.73 [0.59, 0.90]
VADT 2009	119/892	121/899		28.5 %	0.99 [0.78, 1.25]
Total (95% CI)	**6522**	**4620**		**100.0 %**	**0.77 [0.61, 0.97]**

Total events: 416 (Intensive control), 335 (Conventional control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.55$, df = 6 (P = 0.10); $I^2 = 43\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

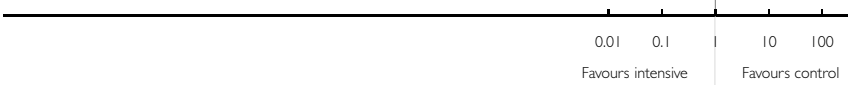
Analysis 1.49. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 49 Retinal photocoagulation; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 49 Retinal photocoagulation; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	33/1429	34/1427		15.0 %	0.97 [0.60, 1.56]
ADVANCE 2008	16/791	22/811		9.9 %	0.75 [0.39, 1.41]
Kumamoto 2000	3/55	12/55		3.3 %	0.25 [0.07, 0.84]
UGDP 1975	2/204	2/210		1.4 %	1.03 [0.15, 7.24]
UKPDS 1998	229/3071	117/1138		30.2 %	0.73 [0.59, 0.90]
VADT 2009	119/892	121/899		28.5 %	0.99 [0.78, 1.25]
Subtotal (95% CI)	**6442**	**4540**		**88.2 %**	**0.82 [0.65, 1.03]**
Total events: 402 (Intensive control), 308 (Conventional control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.09$, df = 5 (P = 0.15); $I^2 = 38\%$					
Test for overall effect: Z = 1.71 (P = 0.088)					
2 Glycaemic control as a part of acute intervention					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Multimodal intervention in usual care setting					
Steno-2 2008	14/80	27/80		11.8 %	0.52 [0.29, 0.91]
Subtotal (95% CI)	**80**	**80**		**11.8 %**	**0.52 [0.29, 0.91]**
Total events: 14 (Intensive control), 27 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
Total (95% CI)	**6522**	**4620**		**100.0 %**	**0.77 [0.61, 0.97]**
Total events: 416 (Intensive control), 335 (Conventional control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.55$, df = 6 (P = 0.10); $I^2 = 43\%$					
Test for overall effect: Z = 2.18 (P = 0.029)					
Test for subgroup differences: $Chi^2 = 2.16$, df = 1 (P = 0.14), $I^2 = 54\%$					



Analysis 1.50. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 50 Adverse events.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 50 Adverse events

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Serious adverse events				
ACCORD 2008	113/5128	82/5123		1.38 [1.04, 1.82]
ADVANCE 2008	2501/5571	2381/5569		1.05 [1.01, 1.10]
Bagg 2001	4/21	0/22		9.41 [0.54, 164.74]
IDA 2009	51/51	51/51		1.00 [0.96, 1.04]
Jaber 1996	2/23	2/22		0.96 [0.15, 6.21]
Melidonis 2000	3/24	4/24		0.75 [0.19, 3.00]
Stefanidis 2003	6/36	6/39		1.08 [0.38, 3.06]
Steno-2 2008	1/80	0/80		3.00 [0.12, 72.56]
UGDP 1975	14/204	13/210		1.11 [0.53, 2.30]
VADT 2009	139/892	130/899		1.08 [0.86, 1.34]
Subtotal (95% CI)	**12030**	**12039**		**1.05 [0.98, 1.13]**
Total events: 2834 (Intensive control), 2669 (Conventional control)				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 16.21$, df = 9 (P = 0.06); $I^2 = 44\%$				
Test for overall effect: Z = 1.30 (P = 0.20)				
2 Drop-outs due to adverse events				
ACCORD 2008	11/5128	10/5123		1.10 [0.47, 2.59]
Bagg 2001 (1)	4/21	0/22		9.41 [0.54, 164.74]
Jaber 1996	1/23	0/22		2.88 [0.12, 67.03]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	0/24	0/24		0.0 [0.0, 0.0]
Stefanidis 2003	5/36	4/39		1.35 [0.39, 4.65]
Steno-2 2008	0/80	0/80		0.0 [0.0, 0.0]
VA CSDM 1995	2/75	0/78		5.20 [0.25, 106.50]
VADT 2009	7/892	3/899		2.35 [0.61, 9.07]
Subtotal (95% CI)	**6334**	**6342**		**1.60 [0.89, 2.87]**

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 30 (Intensive control), 17 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.39$, df = 5 (P = 0.64); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.56 (P = 0.12)				
Total (95% CI)	**18364**	**18381**		**1.06 [0.98, 1.14]**
Total events: 2864 (Intensive control), 2686 (Conventional control)				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 22.91$, df = 15 (P = 0.09); $I^2 = 35\%$				
Test for overall effect: Z = 1.47 (P = 0.14)				
Test for subgroup differences: $Chi^2 = 1.94$, df = 1 (P = 0.16), $I^2 = 49\%$				

(1) Three of these events are macrovascular disease, and are therefore also as macrovascular disease as well.

Analysis 1.51. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 51 Serious adverse events; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 51 Serious adverse events; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ACCORD 2008	113/5128	82/5123		5.7 %	1.38 [1.04, 1.82]
ADVANCE 2008	2501/5571	2381/5569		41.3 %	1.05 [1.01, 1.10]
Bagg 2001	4/21	0/22		0.1 %	9.41 [0.54, 164.74]
IDA 2009	51/51	51/51		42.4 %	1.00 [0.96, 1.04]
Jaber 1996	2/23	2/22		0.1 %	0.96 [0.15, 6.21]
UGDP 1975	14/204	13/210		0.9 %	1.11 [0.53, 2.30]
VADT 2009	139/892	130/899		8.6 %	1.08 [0.86, 1.34]

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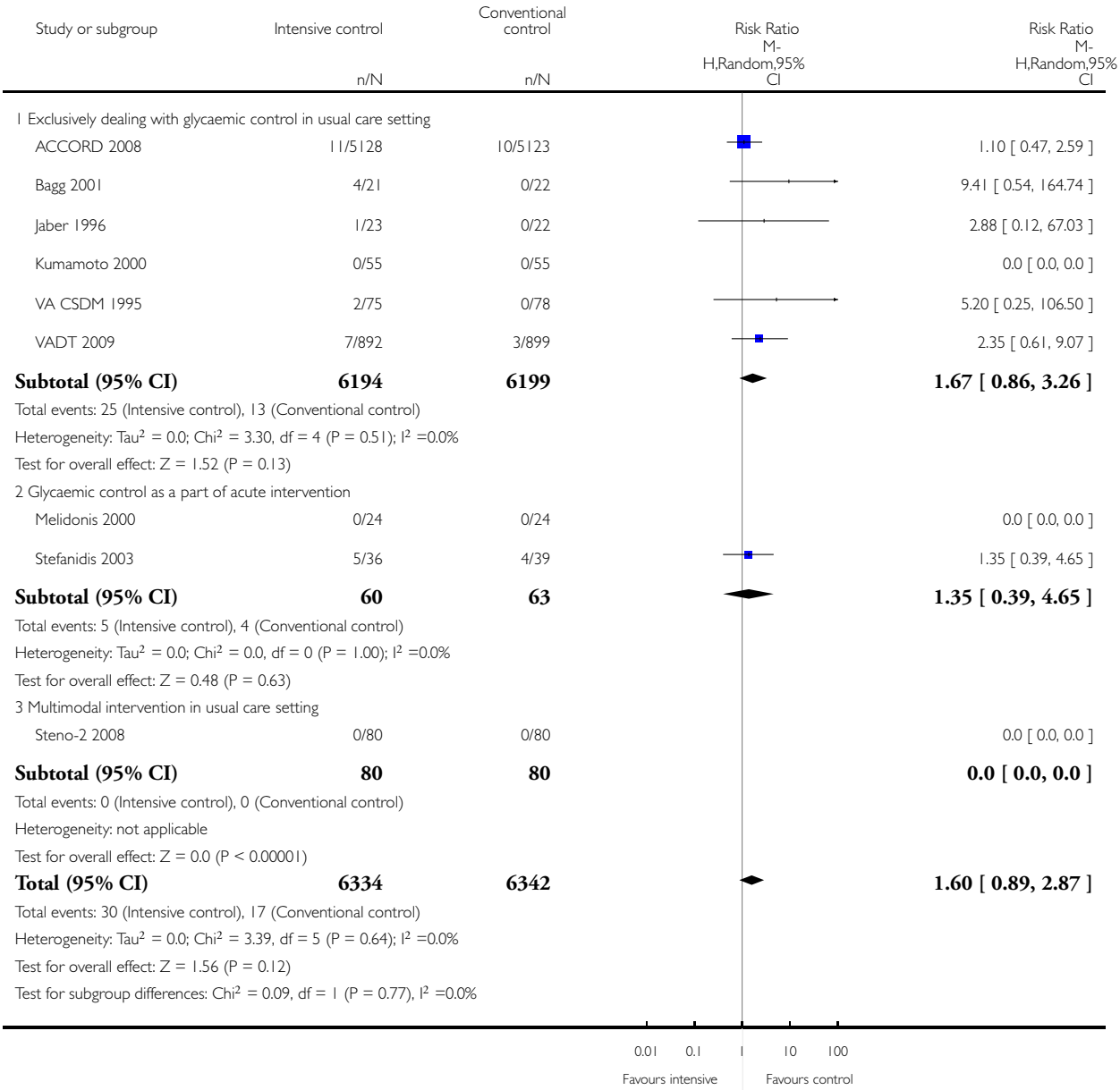
Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**11890**	**11896**		**99.2 %**	**1.05 [0.97, 1.14]**
Total events: 2824 (Intensive control), 2659 (Conventional control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.57$, df = 6 (P = 0.02); $I^2 = 61\%$					
Test for overall effect: Z = 1.28 (P = 0.20)					
2 Glycaemic control as a part of acute intervention					
Melidonis 2000	3/24	4/24		0.3 %	0.75 [0.19, 3.00]
Stefanidis 2003	6/36	6/39		0.5 %	1.08 [0.38, 3.06]
Subtotal (95% CI)	**60**	**63**		**0.7 %**	**0.95 [0.41, 2.18]**
Total events: 9 (Intensive control), 10 (Conventional control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.12 (P = 0.90)					
3 Multifactorial intervention in usual care setting					
Steno-2 2008	1/80	0/80		0.1 %	3.00 [0.12, 72.56]
Subtotal (95% CI)	**80**	**80**		**0.1 %**	**3.00 [0.12, 72.56]**
Total events: 1 (Intensive control), 0 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Total (95% CI)	**12030**	**12039**		**100.0 %**	**1.05 [0.98, 1.13]**
Total events: 2834 (Intensive control), 2669 (Conventional control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 16.21$, df = 9 (P = 0.06); $I^2 = 44\%$					
Test for overall effect: Z = 1.30 (P = 0.20)					
Test for subgroup differences: $Chi^2 = 0.47$, df = 2 (P = 0.79), $I^2 = 0.0\%$					

Analysis 1.52. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 52 Drop-outs due to adverse events; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 52 Drop-outs due to adverse events; stratified after intervention



Analysis 1.53. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 53 Congestive heart failure.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 53 Congestive heart failure

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACCORD 2008 (1)	152/5128	124/5123		1.22 [0.97, 1.55]
ADVANCE 2008	220/5571	231/5569		0.95 [0.79, 1.14]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
Melidonis 2000	4/24	5/24		0.80 [0.24, 2.62]
REMBO 2008	14/41	19/41		0.74 [0.43, 1.26]
Stefanidis 2003	1/36	2/39		0.54 [0.05, 5.72]
UKPDS 1998	91/3071	36/1138		0.94 [0.64, 1.37]
VA CSDM 1995	1/75	4/78		0.26 [0.03, 2.27]
VADT 2009	76/892	82/899		0.93 [0.69, 1.26]
Total (95% CI)	**14859**	**12933**		**0.99 [0.88, 1.12]**

Total events: 559 (Intensive control), 503 (Conventional control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.58$, df = 7 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

(1) Death or hospitalisation for congestive heart failure.

Analysis 1.54. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 54 Congestive heart failure; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 54 Congestive heart failure; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	152/5128	124/5123		1.22 [0.97, 1.55]
ADVANCE 2008	220/5571	231/5569		0.95 [0.79, 1.14]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
UKPDS 1998	91/3071	36/1138		0.94 [0.64, 1.37]
VA CSDM 1995	1/75	4/78		0.26 [0.03, 2.27]
VADT 2009	76/892	82/899		0.93 [0.69, 1.26]
Subtotal (95% CI)	**14758**	**12829**		**1.01 [0.87, 1.17]**
Total events: 540 (Intensive control), 477 (Conventional control)				
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.93, df = 4 (P = 0.29); I^2 =19%				
Test for overall effect: Z = 0.13 (P = 0.90)				
2 Glycaemic control as a part of acute intervention				
Melidonis 2000	4/24	5/24		0.80 [0.24, 2.62]
Stefanidis 2003	1/36	2/39		0.54 [0.05, 5.72]
Subtotal (95% CI)	**60**	**63**		**0.74 [0.26, 2.13]**
Total events: 5 (Intensive control), 7 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 1 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 0.56 (P = 0.58)				
3 Multimodal intervention in usual care setting				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Intensive control), 0 (Conventional control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**14818**	**12892**		**1.01 [0.89, 1.14]**
Total events: 545 (Intensive control), 484 (Conventional control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.35, df = 6 (P = 0.50); I^2 =0.0%				
Test for overall effect: Z = 0.10 (P = 0.92)				
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.57), I^2 =0.0%				

Analysis 1.55. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 55 Hypoglycaemia.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 55 Hypoglycaemia

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Mild hypoglycaemia				
ADVANCE 2008	2898/5571	2077/5569		1.39 [1.34, 1.46]
Bagg 2001	15/21	5/22		3.14 [1.39, 7.11]
DIGAMI 2 2005	16/474	10/306		1.03 [0.47, 2.25]
Kumamoto 2000	6/55	4/55		1.50 [0.45, 5.02]
Melidonis 2000	11/24	3/24		3.67 [1.17, 11.52]
Stefanidis 2003	7/36	2/39		3.79 [0.84, 17.07]
Steno-2 2008	64/80	56/80		1.14 [0.95, 1.37]
UGDP 1975	82/204	32/210		2.64 [1.84, 3.78]
UKPDS 1998	478/3071	106/1138		1.67 [1.37, 2.04]
VA CSDM 1995	69/75	44/78		1.63 [1.33, 2.00]
VADT 2009	833/892	694/899		1.21 [1.16, 1.26]
Subtotal (95% CI)	**10503**	**8420**		**1.50 [1.31, 1.72]**
Total events: 4479 (Intensive control), 3033 (Conventional control)				
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 75.90$, df = 10 (P<0.00001); $I^2 = 87\%$				
Test for overall effect: Z = 5.89 (P < 0.00001)				
2 Severe hypoglycaemia				
ACCORD 2008	830/5128	261/5123		3.18 [2.78, 3.63]
ADVANCE 2008	150/5571	81/5569		1.85 [1.42, 2.42]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000 (1)	0/55	0/55		0.0 [0.0, 0.0]
Melidonis 2000	3/24	0/24		7.00 [0.38, 128.61]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Steno-2 2008	10/80	14/80		0.71 [0.34, 1.51]

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
UKPDS 1998	33/3071	8/1138		1.53 [0.71, 3.30]
VA CSDM 1995	5/75	2/78		2.60 [0.52, 12.99]
VADT 2009	76/892	28/899		2.74 [1.79, 4.18]
Subtotal (95% CI)	**15027**	**13100**		**2.05 [1.39, 3.02]**
Total events: 1107 (Intensive control), 394 (Conventional control)				
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 27.92$, df = 6 (P = 0.00010); $I^2 = 79\%$				
Test for overall effect: Z = 3.60 (P = 0.00031)				
Total (95% CI)	**25530**	**21520**		**1.76 [1.46, 2.13]**
Total events: 5586 (Intensive control), 3427 (Conventional control)				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 318.11$, df = 17 (P<0.00001); $I^2 = 95\%$				
Test for overall effect: Z = 5.89 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 2.14$, df = 1 (P = 0.14), $I^2 = 53\%$				

(1) Number reported after 8 years of follow-up

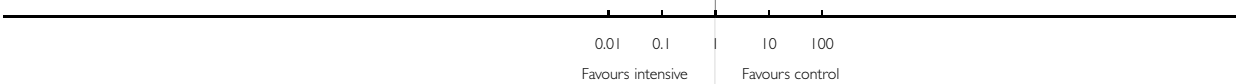
Analysis 1.56. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 56 Mild hypoglycaemia; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 56 Mild hypoglycaemia; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting					
ADVANCE 2008	2898/5571	2077/5569		20.0 %	1.39 [1.34, 1.46]
Bagg 2001	15/21	5/22		2.4 %	3.14 [1.39, 7.11]
Kumamoto 2000	6/55	4/55		1.2 %	1.50 [0.45, 5.02]
UGDP 1975	82/204	32/210		8.4 %	2.64 [1.84, 3.78]
UKPDS 1998	478/3071	106/1138		14.2 %	1.67 [1.37, 2.04]
VA CSDM 1995	69/75	44/78		13.9 %	1.63 [1.33, 2.00]
VADT 2009	833/892	694/899		20.1 %	1.21 [1.16, 1.26]
Subtotal (95% CI)	**9889**	**7971**		**80.2 %**	**1.57 [1.35, 1.82]**
Total events: 4381 (Intensive control), 2962 (Conventional control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 67.31, df = 6 (P<0.00001); I^2 =91%					
Test for overall effect: Z = 5.80 (P < 0.00001)					
2 Glycaemic control as a part of acute intervention					
DIGAMI 2 2005	16/474	10/306		2.7 %	1.03 [0.47, 2.25]
Melidonis 2000	11/24	3/24		1.3 %	3.67 [1.17, 11.52]
Stefanidis 2003	7/36	2/39		0.8 %	3.79 [0.84, 17.07]
Subtotal (95% CI)	**534**	**369**		**4.8 %**	**2.13 [0.83, 5.50]**
Total events: 34 (Intensive control), 15 (Conventional control)					
Heterogeneity: Tau^2 = 0.38; Chi^2 = 4.39, df = 2 (P = 0.11); I^2 =54%					
Test for overall effect: Z = 1.56 (P = 0.12)					
3 Multimodal intervention in usual care setting					
Steno-2 2008	64/80	56/80		15.0 %	1.14 [0.95, 1.37]
Subtotal (95% CI)	**80**	**80**		**15.0 %**	**1.14 [0.95, 1.37]**
Total events: 64 (Intensive control), 56 (Conventional control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Total (95% CI)	**10503**	**8420**		**100.0 %**	**1.50 [1.31, 1.72]**
Total events: 4479 (Intensive control), 3033 (Conventional control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 75.90, df = 10 (P<0.00001); I^2 =87%					
Test for overall effect: Z = 5.89 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 7.67, df = 2 (P = 0.02), I^2 =74%					



Analysis 1.57. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 57 Severe hypoglycaemia; stratified after intervention.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 57 Severe hypoglycaemia; stratified after intervention

Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Exclusively dealing with glycaemic control in usual care setting				
ACCORD 2008	830/5128	261/5123		3.18 [2.78, 3.63]
ADVANCE 2008	150/5571	81/5569		1.85 [1.42, 2.42]
Bagg 2001	0/21	0/22		0.0 [0.0, 0.0]
IDA 2009	0/51	0/51		0.0 [0.0, 0.0]
Jaber 1996	0/23	0/22		0.0 [0.0, 0.0]
Kumamoto 2000	0/55	0/55		0.0 [0.0, 0.0]
UKPDS 1998	33/3071	8/1138		1.53 [0.71, 3.30]
VA CSDM 1995	5/75	2/78		2.60 [0.52, 12.99]
VADT 2009	76/892	28/899		2.74 [1.79, 4.18]
Subtotal (95% CI)	**14887**	**12957**		**2.39 [1.71, 3.34]**
Total events: 1094 (Intensive control), 380 (Conventional control)				
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 15.01$, df = 4 (P = 0.005); $I^2 = 73\%$				
Test for overall effect: Z = 5.10 (P < 0.00001)				
2 Glycaemic control as a part of acute intervention				
Melidonis 2000	3/24	0/24		7.00 [0.38, 128.61]
Stefanidis 2003	0/36	0/39		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**63**		**7.00 [0.38, 128.61]**
Total events: 3 (Intensive control), 0 (Conventional control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.31 (P = 0.19)				
3 Multimodal intervention in usual care setting				
Steno-2 2008	10/80	14/80		0.71 [0.34, 1.51]
Subtotal (95% CI)	**80**	**80**		**0.71 [0.34, 1.51]**
Total events: 10 (Intensive control), 14 (Conventional control)				
Heterogeneity: not applicable				

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Study or subgroup	Intensive control n/N	Conventional control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.88 (P = 0.38)				
Total (95% CI)	**15027**	**13100**	◆	**2.05 [1.39, 3.02]**
Total events: 1107 (Intensive control), 394 (Conventional control)				
Heterogeneity: Tau^2 = 0.15; Chi^2 = 27.92, df = 6 (P = 0.00010); I^2 =79%				
Test for overall effect: Z = 3.60 (P = 0.00031)				
Test for subgroup differences: Chi^2 = 9.03, df = 2 (P = 0.01), I^2 =78%				

Analysis 1.58. Comparison 1 Intensive glycaemic control versus conventional glycaemic control, Outcome 58 Cost of treatment.

Review: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus

Comparison: 1 Intensive glycaemic control versus conventional glycaemic control

Outcome: 58 Cost of treatment

Study or subgroup	Intensive control N	Mean(SD)	Conventional control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kumamoto 2000 (1)	55	30310 (8118)	55	31525 (10812)	←	16.4 %	-1215.00 [-4788.19, 2358.19]
UKPDS 1998 (2)	3071	15874 (14530)	1138	14984 (17888)	←	83.6 %	890.00 [-269.41, 2049.41]
Total (95% CI)	**3126**		**1193**		◆	**100.0 %**	**543.85 [-985.46, 2073.16]**
Heterogeneity: Tau^2 = 378720.48; Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%							
Test for overall effect: Z = 0.70 (P = 0.49)							
Test for subgroup differences: Not applicable							

(1) Cost expressed in 1998 US$

(2) Cost expressed in 2004

ADDITIONAL TABLES

Table 1. Glycaemic control in trials

Trial	glycaemic target, intensive treatment	glycaemic target, conventional treatment	Glycaemic control at the end of follow-up, HbA1c (%) or other used glycaemic measurement (mmol/L) (mean(SD))	Number of participants achieved treatment goal	Comment
ACCORD 2008	HbA1c < 6% Fasting SMBG[1] < 5.6 mmol/L (100 mg/dL) or 2 hour blood glucose < 7.8 mmol/L (140 mg/dL).	HbA1c 7%-7.9% Fasting SMBG[1] > 5.0 mmol/L (90 mg/dL).	I: 7.4 (0.7) C: 7.5 (0.8)	I: NR C: NR	Data are from the end of the intervention period. SD is calculated from IQR.
ADVANCE 2008	HbA1c ≤ 6.5%	Glycaemic target of HbA1c defined from local guidelines.	I: HbA1c: 6.5 (1.0) C: HbA1c: 7.2 (1.4)	I: 3133 (at the end of follow-up) C: No specified target	
Bagg 2001	HbA1c < 7% Before meal capillary glucose: 4-7 mmol/L, 2 hour blood glucose < 10 mmol/L	Avoid symptomatic hyperglycaemia and fortnightly fasting capillary glucose test > 17 mmol/L	I: HbA1c: 7.0 (0.4) C: HbA1c: 10.2 (0.2)	I: 3 C: No specific target	
Becker 2003	Fasting capillary blood glucose < 6.5 mmol/L.	Fasting capillary blood glucose < 8.5 mmol/L.	I: 7.2 (1.2) C: 7.4 (1.4)	I: NR C: NR	
DIGAMI 2 2005	Insulin infusion until stable normoglycaemia and at least for 24 hours. Subcutaneous insulin was initiated at the cessation of the infusion. The treatment goal for patients in group 1 was a fasting blood glucose level of 5-7 mmol/L and a non-fasting level of < 10 mmol/L	Standard glucose control.	I: HbA1c: 7.0 (1.0) FBG (target): 8.0 (2.0) C: HbA1c: 7.0 (1.3) FBG: 8.6 (3.0)	I: NR C: NR	HbA1c and fasting blood glucose is read from figure.

Table 1. Glycaemic control in trials (*Continued*)

Guo 2008	HbA1c < 7.0% Fasting plasma glucose 4-7 mmol/L.	No treatment goal.	I: HbA1c: 6.3 (0.9) FPG (target): 7.1 (1.7) C: HbA1c: 7.1 (0.9) FPG: 8.3 (2.6)	I: 142 C: No specific target	
IDA 2009	HbA1c < 6.5% Fasting blood glucose 5-7 mmol/L, before meal < 10 mmol/L.	Standard treatment.	I: HbA1c (median): 6.3 (1.5) C: HbA1c (median) : 6.6 (0.9)	I: 37 (HbA1c) C: No specific target	SD is calculated from IQR.
Jaber 1996	Fasting blood glucose ≤ 6.6 mmol/L, 2 hour postprandial glucose < 10 mmol/L, or to reach maximum daily doses of sulphonylurea	Not defined.	I: 9.2 (2.1) FBG (target): 8.5 (2.3) C: 12.1 (3.7) FBG: 11.0 (3.9)	I: NR C: NR	Measurement of glycated haemoglobin is not further specified
Kumamoto 2000	HbA1c < 7.0% Fasting blood glucose (< 140 mg/dL), 2 hour postprandial glucose < 200 mg/dL, mean amplitude of glycaemic excursions < 100 mg/dL	Fasting blood glucose close to < 140 mg/dL without symptoms of hyperglycaemia or hypoglycaemia	I: 7.2 (1.0) FBG (target): 6.3 (1.6) C: 9.4 (1.3) FBG (target): 7.4 (1.6)	I: 14 C: 3	
Lu 2010	Fasting blood glucose < 6.1 mmol/L, postprandial 2 hour glucose < 7.8 mmol/L	Fasting blood glucose < 7.0 mmol/L, postprandial 2 hour glucose < 10.0 mmol/L	I: 6.1 (0.5) C: 7.8 (0.7)	I: NR C: NR	
Melidonis 2000	Blood glucose 8.3-11.0 mmol/L in the first 48 hours after an acute coronary event, thereafter normoglycaemia	No specific target.	I: HbA1c not measured. Plasma glucose (target): 6.6 mmol/L (0.5) C: HbA1c not measured. Plasma glucose: 10.5 mmol/L (2.1)	I: NR C: NR	The reported plasma glucose value is for the last day of hospitalisation
REMBO 2008	HbA1c < 7% in participants receiving sulphonylurea; HbA1c < 6.5% in	Not specified, standard care.	I (median): 6.7 (1.2) C (median): 6.7 (1.2)	I: NR C: NR	SD is calculated from IQR.

Table 1. Glycaemic control in trials (*Continued*)

	participants receiving insulin.				
Service 1983	HbA1c to normal range, and to maintain 80 minute postprandial plasma glucose below 150 mg/dL (8.3 mmol/L)	Eliminate symptoms, but not to a degree to reduce 80 minute postprandial plasma glucose below 150 mg/dL	I (median): 8.7 C (median): 9.4	I: 3 C: 4	
Stefanidis 2003	Near normal glycaemia (defined as 6.6-8.2 mmol/L).	No specific target.	I: 8 (1.1) Plasma glucose (target): 6.9 mmol/L (1.8) C: 8 (1.0) Plasma glucose: 9.9 mmol/L (1.7)	I: 31 C: NR	We assume HbA1c is unchanged at the end of follow-up due to the short intervention period The reported plasma glucose value is for the last day of hospitalisation
Steno-2 2008	HbA1c < 6.5%	HbA1c < 7.5% (1993-1999), HbA1c < 6.5% (2000-2001).	I: 7.9 (1.2) C: 9.0 (1.8)	I: 13 C: 3	Data are from the end of the intervention period (7.8 years of follow-up) Number of patients achieved glycaemic target is read from figure
UGDP 1975	Maintain blood glucose in normal range (defined as fasting blood glucose < 110mg/100 mL, blood glucose < 210 mg/100 mL one hour after ingestion of 50 gm glucose and one and one-half hours after the morning insulin injection)	Minimize the likelihood of hypoglycaemic reactions without reducing the insulin dose to pharmacologically inactive amounts	I: FBG (target): 6.7 C: FBG: 9.7	I: NR C: NR	Value for fasting blood glucose is calculated from text. mg/dL is calculated to mmol/L by dividing with 18 SD calculated from SE.
UKPDS 1998	Fasting blood glucose < 6 mmol/L In insulin treated patients; pre-meal glucose 4-7 mmol/L.	Fasting blood glucose < 15 mmol/L without symptoms of hyperglycaemia	I (median): 8.1 (1.8) FPG (target, median): 8.6 mmol/L C (median): 8.7 (1.6) FPG (target, me-	I: NR C: NR	HbA1c used is the median for the last 5 years follow-up period. SD calculated from IQR Fasting plasma glu-

Table 1. Glycaemic control in trials (*Continued*)

			dian): 9.8 mmol/L		cose read from figure, 10 years after randomisation Data are from the UKPDS 33.
VA CSDM 1995	Maintain mean HbA1c < 7.5%. Treament is adjusted with home blood glucose monitoring aiming, at fasting blood glucose of 4. 48 to 6.44 mmol/L and other preprandial levels ≤ 7.28 mmol/L	Avoiding excessive hyperglycaemia, or symptoms of excessive glucosuria, ketonuria, or hypoglycaemia (Alert HbA1c < 12.9 %)	I: HbA1c: 7.1 (0.7) C: HbA1c: 9.2 (0.8)	I: 7 (maintained target) C: No specified target	The value of HbA1c is estimated from figure after 24 months of follow-up The SD for HbA1c is calculated from SE.
VADT 2009	HbA1c ≤ 6%. The goal for HbA1c level was an absolute reduction of 1.5 percentage points in the intensive-therapy group, as compared with conventional intervention group	Well-being, avoidance of deterioration of HbA1c, keeping levels at 8-9% and preventing symptoms of glycosuria, hypoglycaemia, and ketonuria	I (median): 6.9 (0.9) C (median): 8.4 (1. 2)	I: NR C: NR	HbA1c estimated from figure. Data from glycaemic control are medians. SD calculated from IQR
Yang 2007	Fasting blood glucose < 7.0 mmol/L, 2 hour postprandial glucose < 10 mmol/L, HbA1c < 7.0%	Not specified.	I: 6.5 (1.1) C: 6.8 (1.4)	I: NR C: NR	

[1]In the ACCORD trial, SMBG targets were defined as "action required" thresholds (see protocol at http://www.accordtrial.org/public/protocol˙2005-05-11.pdf)

Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes, ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction, HbA1c: glycosylated haemoglobin A1c, IDA: Insulin Diabetes Angioplasty; IQR: Interquartile range, REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, SE: Standard error, SMBG: self monitoring of blood glucose; UGDP: University Group Diabetes Program, UKPDS: United Kingdom Prospective Diabetes Study, VA CSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitu, VADT: Veterans Affairs Diabetes Trial.

Table 2. Overview of study populations

study ID	[n] screened	[n] randomised	[n] finishing study (mortality)	[n] finishing study (other outcomes)	[n] Lost to follow-up (mortality)	[n] Lost to follow-up (other outcomes)	[%] of randomised participants finishing study	comments
ACCORD 2008	T: 19,716	I: 5128 C: 5123 T: 10,251	I: 5018 C: 5021 T: 10,039	I: 4725 C: 4751 T: 9476	I: 110 C: 102 T: 212	I: 403 C: 372 T: 775	I: 97.9 C: 98.0 T: 97.9	
ADVANCE 2008	T: 12,877	I: 5571 C: 5569 T: 11,140	I: 5564 C: 5559 T: 11,123	I: 5326 C: 5274 T: 10,600	I: 7 C:10 T:17	I: 245 C: 295 T: 540	I: 99.9 C: 99.8 T: 99.8	
Bagg 2001	T: more than 1000 patients	I: 21 C: 22 T: 43	I: 17 C: 22 T: 39	I: 17 C: 22 T: 39	I: 4 C: 0 T: 4	I: 4 C: 0 T: 4	I: 81.0 C: 100 T: 90.7	
Becker 2003	T: 296	I: 106 C: 108 T: 231 (214)	I: - C: - T: 191	I: - C: - T: 188	I: - C: - T: 40	I: - C: - T: 43	I: NA C: NA T: 82.7	"During the first year, ten patients found participation too much of a burden, six moved and one died (7%). One outlier (a woman with a BMI of 59) was excluded from the analyses. Thus, 106 patients in group 6 and 108 patients in group 8 were included in the analyses."

Table 2. Overview of study populations (*Continued*)

								It means 231 patients were randomised. It is not possible from the articles to find out which group they were randomised to Of all randomised patients 43 did not make the visit after 2 years
DIGAMI 2 2005	T: -	I: 474 C: 306 T: 780	I: 474 C: 306 T: 780	I: 474 C: 306 T: 780	I: 0 C: 0 T: 0	I: 0 C: 0 T: 0	I: 100 C: 100 T: 100	
Guo 2008	T: -	I: 166 C: 54 T: 220	I: 166 C: 54 T: 220	I: 166 C: 54 T: 220	I: 0 C: 0 T: 0	I: 0 C: 0 T: 0	I: 100 C: 100 T: 100	
IDA 2009	T: -	I: 51 C: 51 T: 102	I: 51 C: 51 T: 102	I: 51 C: 51 T: 102	I: 0 C: 0 T: 0	I: 12 C: 8 T: 20	I: 100 C: 100 T: 100	
Jaber 1996	T: 892	I: 23 C: 22 T: 45	I:17 C:22 T: 39	I:17 C:22 T: 39	I: 6 C: 0 T: 6	I: 6 C: 0 T: 6	I: 73.9 C: 100 T: 86.7	
Kumamoto 2000	T: -	I: 55 C: 55 T: 110	I: 53 C: 51 T: 104	I: 53 C: 51 T: 104	I: 2 C: 4 T: 6	I: 2 C: 4 T: 6	I: 96.4 C: 92.7 T: 94.5	
Lu 2010	T: -	I: 21 C: 20 T: 41	-	-	-	-	-	
Melidonis 2000	T: 179	I: 24 C: 24 T: 48	I: 24 C: 24 T: 48	I: 24 C: 24 T: 48	I: 0 C: 0 T: 0	I: 0 C: 0 T: 0	I: 100 C: 100 T: 100	
REMBO 2008	T: -	I: 41 C: 40 T: 81	I: 41 C: 40 T: 81	I: 41 C: 40 T: 81	I: 0 C: 0 T: 0	I: 0 C: 0 T: 0	I: 100 C: 100 T: 100	

Table 2. Overview of study populations (*Continued*)

Service 1983	T: -	I: 10 C: 10 T: 20	I: 8 C: 10 T: 18	I: 8 C: 10 T: 18	I: 2 C: 0 T: 2	I: 2 C: 0 T: 2	I: 80 C: 100 T: 90	
Stefanidis 2003	T: 239	I: 36 C: 39 T: 75	I: 31 C: 35 T: 66	I: 31 C: 35 T: 66	I: 5 C: 4 T: 9	I: 5 C: 4 T: 9	I: 86.1 C: 89.7 T: 88	
Steno-2 2008	T: 315	I: 80 C: 80 T: 160	I: 80 C: 80 T: 160	I: 79 C: 78 T: 157	I: 0 C: 0 T: 0	I: 1 C: 2 T: 3	I: 100 C: 100 T: 100	The number is taken after 13.3 years of follow-up.
UGDP 1975	T: -	I: 204 C: 210 T: 414	I: 191 C: 206 T: 397	I: 167 C: 182 T: 349	I:13 C: 4 T: 17	I: 37 C: 28 T: 65	I: 93.6 C: 98.1 T: 95.9	
UKPDS 1998	T: 5102	I: 3071 C: 1138 T: 4209	I: 3014 C: 1119 T: 4133	I: 2949 C: 1093 T: 4042	I: 57 C: 19 T: 76	I: 122 C: 45 T: 167	I: 98.1 C: 98.3 T: 98.2	"At the end of the trial, the vital status of 76 (2.0%) patients who had emigrated was not known; 57 and 19 in intensive and conventional groups, respectively, which reflects the 70/30 randomisation. A further 91 (2.4%) patients (65 in the intensive group) could not be contacted in the last year of the

Table 2. Overview of study populations (*Continued*)

								study for assessment of clinical endpoints." The n [finishing study] is calculated from the lost to follow-up (mortality) from the UKPDS 33 It is not clear from the UKPDS 34 1998 to clarify how the participants lost to follow-up are distributed. It is reported that 13 participants had unknown vital status, and that the number lost to follow-up for other outcomes is 56. Therefore only data for the UKPDS 33 1998 are used
VA CSDM 1995	T: 289	I: 75 C: 78 T: 153	I: 75 C: 78 T: 153	I: 71 C: 78 T: 149	I: 0 C: 0 T: 0	I: 4 C: 0 T: 4	I: 100 C: 100 T: 100	Mortality data were assessed on the participants lost to follow-up

Table 2. Overview of study populations (*Continued*)

VADT 2009	T: 2239	I: 892 C: 899 T: 1791	I: 892 C: 899 T: 1791	I: 772 C: 760 T: 1532	I: 0 C: 0 T: 0	I: 120 C: 139 T: 259	I: 100 C: 100 T: 100	Deaths occurring after withdrawal from the study were included in the analysis
Yang 2007	T: 116	I: 57 C: 32 T: 89	I: 57 C: 32 T: 89	I: 57 C: 32 T: 89	I: 0 C: 0 T: 0	I: 0 C: 0 T: 0	I: 100 C: 100 T: 100	
Total	Total: (more than) 43, 260	***I: 16,106*** ***C: 13,880*** ***T: 29,986***	*I: 15,773* *C: 13,609* *T: 29,573*	***I: 15,028*** ***C: 12,863*** ***T: 28,079***	*I: 206* *C: 143* *T: 389*	*I: 951* *C: 889* *T: 1883*	*I: 97.9* *C: 98* *T: 98.6*	Totals are not the sum of I and C for all columns, because not all trials provided data on the two intervention groups, but only the total

"-" denotes not reported

Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE: Action in Diabetes and Vascular disease - PreterAx and DiamicroN MR Controlled Evaluation; C (control): targeting conventional glycaemic control; DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; I (intervention): targeting intensive glycaemic control; DA: Insulin Diabetes Angioplasty; REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP: University Group Diabetes Program; UKPDS: United Kingdom Prospective Diabetes Study; VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus; VADT: Veterans Affairs Diabetes Trial

APPENDICES

Appendix 1. Search strategies

Search terms
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent
MEDLINE
1. exp Blood Glucose/
2. exp Hyperglycemia/
3. exp Hemoglobin A, Glycosylated/
4. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti.
5. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
6. (glycosylated adj6 h?emoglobin$).ab,ti.
7. (glucos$ adj3 management$).ab,ti.
8. or/1-7
9. exp Diabetes Mellitus, Type 2/
10. exp Diabetes Complications/
11. (MODY or NIDDM or T2DM).tw,ot.
12. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend).tw,ot.
13. ((typ$ 2 or typ$ II) adj3 diabet$).tw,ot.
14. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
15. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ab,ti.
16. or/9-15
17. exp Diabetes Insipidus/
18. diabet$ insipidus.tw,ot.
19. 17 or 18
20. 16 not 19
21. 8 or 20
22. ((intensi$ or conventional$ or regular or tight or usual or routin$ or or standard) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti.
23. 21 and 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi?ed.ab,ti.
27. placebo$.ab,ti.
28. drug therapy.fs.
29. randomly.ab,ti.
30. trial$.ab,ti.
31. group$.ab,ti.
32. or/24-31
33. Meta-analysis.pt.
34. exp Technology Assessment, Biomedical/
35. exp Meta-analysis/
36. exp Meta-analysis as topic/
37. hta.tw,ot.
38. (health technology adj6 assessment$).tw,ot.
39. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.

(*Continued)*

40. ((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.
41. or/33-40
42. (comment or editorial or historical-article).pt.
43. 41 not 42
44. 32 or 43
45. 23 and 44
46. (animals not (animals and humans)).sh.
47. 45 not 46

EMBASE

1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. impaired glucose toleranc$.ab,ti,ot.
4. glucose intoleranc$.ab,ti,ot.
5. insulin$ resistanc$.ab,ti,ot.
6. (obes$ adj diabet$).ab,ti,ot.
7. (MODY or NIDDM or TDM2).ab,ti,ot.
8. (non insulin$ depend$ or noninsulin depend$ or noninsulin?depend$ or non insulin?depend$).ab,ti,ot.
9. ((typ$ 2 or typ$ II) adj diabet$).ab,ti,ot.
10. (diabet$ adj (typ$ 2 or typ$ II)).ab,ti,ot.
11. ((keto?resist$ or non?keto$) adj diabet$).ab,ti,ot.
12. ((adult$ or matur$ or late or slow or stabl$) adj diabet$).ab,ti,ot.
13. (insulin$ defic$ adj relativ$).ab,ti,ot.
14. pluri?metabolic$ syndrom$.ab,ti,ot.
15. or/1-14
16. exp Diabetes Insipidus/
17. diabet$ insipidus.ab,ti,ot.
18. 16 or 17
19. 15 not 18
20. exp Glucose Blood Level/
21. exp Hyperglycemia/
22. exp Glycosylated Hemoglobin/
23. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti,ot.
24. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
25. (glycosylated adj6 h?emoglobin$).ab,ti,ot.
26. (glucos$ adj3 management$).ab,ti,ot.
27. or/20-25
28. 19 or 27
29. ((intensiv$ or conventional$ or regular or tight or usual or routin$) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti,ot.
30. 28 and 29
31. Randomized Controlled Trial/
32. exp Controlled Clinical Trial/
33. randomi?ed.ab,ti.
34. placebo$.ab,ti.
35. exp Drug Therapy/
36. randomly.ab,ti.
37. trial$.ab,ti.
38. group$.ab,ti.

(*Continued)*

39. or/31-38
40. exp meta analysis/
41. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
42. ((review$ 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$)).ab,ti,ot.
43. exp Literature/
44. exp Biomedical Technology Assessment/
45. hta.tw,ot.
46. (health technology adj6 assessment$).tw,ot.
47. or/40-46
48. (comment or editorial or historical-article).pt.
49. 47 not 48
50. 39 or 49
51. 30 and 50
52. limit 51 to human

The Cochrane Library

1. MeSH descriptor Diabetes mellitus, type 2explode all trees
2. MeSH descriptor Insulin resistanceexplode all trees
3. ((impaired in All Text and glucosein All Text and toleranc* in All Text) or (glucosein All Text and intoleranc* in All Text) or (insulin*in All Text and resistanc* in All Text))
4. (obes* in All Text near/6 diabet*in All Text)
5. (MODY in All Text or NIDDMin All Text or TDM2 in All Text)
6. ((non in All Text and insulin*in All Text and depend* in All Text) or (noninsulin*in All Text and depend* in All Text) or (nonin All Text and insulindepend* in All Text) or noninsulindepend*in All Text)
7. (typ* in All Text and (2in All Text near/6 diabet* in All Text))
8. (typ* in All Text and (IIin All Text near/6 diabet* in All Text))
9. (non in All Text and (keto*in All Text near/6 diabet* in All Text))
10. (nonketo* in All Text near/6 diabet*in All Text)
11. (adult* in All Text near/6 diabet*in All Text)
12. (matur* in All Text near/6 diabet*in All Text)
13. (late in All Text near/6 diabet*in All Text)
14. (slow in All Text near/6 diabet*in All Text)
15. (stabl* in All Text near/6 diabet*in All Text)
16. (insulin* in All Text and (defic*in All Text near/6 diabet* in All Text)
17. (plurimetabolic in All Text and syndrom*in All Text)
18. (pluri in All Text and metabolicin All Text and syndrom* in All Text)
19. (#1 or #2 or #3or #4 or #5 or #6 or #7or #8 or #9 or #10)
20. (#11 or #12 or #13or #14 or #15 or #16 or #17or #18)
21. (#19 or #20)
22. MeSH descriptor Diabetes insipidusexplode all trees
23. (diabet* in All Text and insipidusin All Text)
24. (#22 or #23)
25. (#21 and not #24)
26. MeSH descriptor Blood glucoseexplode all trees
27. MeSH descriptor Hyperglycemiaexplode all trees
28. MeSH descriptor Hemoglobin A, glycosylatedexplode all trees
29. ((blood in All Text and glucos*in All Text) or hyperglycaemi* in All Text or hyperglycemi*in All Text or (haemoglobin* in All Text and Ain All Text) or (hemoglobin* in All Text and Ain All Text))
30. (HbA1C in All Text or (Hbin All Text and A in All Text) or (HbA in All Text and 1c in All Text) or HbA in All Text or A1Cs in

(*Continued)*

All Text)
31. (glycosylated in All Text near/6 haemoglobin*in All Text)
32. (glycosylated in All Text near/6 hemoglobin*in All Text)
33. (glucos* in All Text near/3 management*in All Text)
34. (#26 or #27 or #28or #29 or #30 or #31 or #32or #33)
35. (#25 or #34)
36. (intensi* in All Text near/3 control*in All Text)
37. (intensi* in All Text near/3 therap*in All Text)
38. (intensi* in All Text near/3 treatment*in All Text)
39. (intensi* in All Text near/3 intervention*in All Text)
40. (intensi* in All Text near/3 management*in All Text)
41. (conventional* in All Text near/3 control*in All Text)
42. (conventional* in All Text near/3 therap*in All Text)
43. (conventional* in All Text near/3 treatment*in All Text)
44. (conventional* in All Text near/3 intervention*in All Text)
45. (conventional in All Text near/3 management*in All Text)
46. (regular in All Text near/3 control*in All Text)
47. (regular in All Text near/3 therap*in All Text)
48. (regular in All Text near/3 treatment*in All Text)
49. (regular in All Text near/3 intervention*in All Text)
50. (regular in All Text near/3 management*in All Text)
51. (usual in All Text near/3 control*in All Text)
52. (usual in All Text near/3 therap*in All Text)
53. (usual in All Text near/3 treatmentin All Text)
54. (usual in All Text near/3 intervention*in All Text)
55. (usual in All Text near/3 management*in All Text)
56. (routin* in All Text near/3 control*in All Text)
57. (routin* in All Text near/3 therap*in All Text)
58. (routin* in All Text near/3 treatment*in All Text)
59. (routin* in All Text near/3 intervention*in All Text)
60. (routin* in All Text near/3 management*in All Text)
61. (tight in All Text near/3 control*in All Text)
62. (tight in All Text near/3 therap*in All Text)
63. (tight in All Text near/3 treatment*in All Text)
64. (tight in All Text near/3 intervention*in All Text)
65. (tight in All Text near/3 management*in All Text)
66. (#36 or #37 or #38or #39 or #40 or #41 or #42or #43 or #44 or #45 or #46or #47 or #48 or #49 or #50or #51 or #52 or #53 or #54or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65)
67. (#35 and #66)

LILACS

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

CINAHL

1. MM "Blood Glucose"
2. MM "Glycemic Control"
3. MM "Hyperglycemia+"

(*Continued*)

4. MM "Hemoglobin A, Glycosylated"
5. TI (blood glucos* OR hyperglyc?emi* OR h?emoglobin A) or AB (blood glucos* OR hyperglyc?emi* OR h?emoglobin A)
6. TI (HbA1C or Hb A or HbA 1c or HbA or A1Cs) or AB (HbA1C or Hb A or HbA 1c or HbA or A1Cs)
7. TI glycosylated N6 h?emoglobin* or AB glycosylated N6 h?emoglobin*
8. TI glucos* N3 management* or AB glucos* N3 management*
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. MM "Diabetes Mellitus, Non-Insulin-Dependent"
11. TX Diabetes Complications
12. TX MODY or NIDDM or T2DM
13. TX non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend
14. TX diabet* AND (typ* 2 or typ* II)
15. TX diabet* AND (keto*resist* or non*keto*)
16. TI (onset AND (late or adult* or matur* or slow or stabl*)) and TI diabet*
17. AB (onset N3 (late or adult* or matur* or slow or stabl*)) and AB diabet*
18. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. MM "Diabetes Insipidus"
20. TX diabet* insipidus
21. #19 or #20
22. #18 NOT #21
23. #9 or #22
24. TI (control* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (control* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
25. TI (therap* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (therap* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
26. TI (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
27. TI (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
28. TI (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
29. #24 or #25 or #26 or #27 or #28
30. #23 and #29
31. TX random* OR blind* OR placebo* OR group*
32. TX animal* NOT (animal* AND human*)
33. #31 NOT #32
34. #30 and #33

Science Citation Index Expanded

1. TS=(blood glucos* or glyc?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=(MODY or NIDDM or T2DM)
7. TS=(non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*)
8. TS=(diabet* SAME (typ* 2 or typ* II))
9. TS=(diabet* SAME (keto*resist* or non*keto*))
10. TS=((onset SAME (late or adult* or matur* or slow or stabl*)) and diabet*)
11. #10 OR #9 OR #8 OR #7 OR #6
12. #11 NOT TS=(diabet* insipidus)

(*Continued*)

13. #12 OR #5
14. TS=((intensi* or tight or conventional* or regular or usual or routin* or standard) SAME (control* or therap* or treatment* or intervention* or management*))
15. #14 AND #13
16. TS=(random* OR blind* OR placebo* OR group*)
17. TS=(animal* NOT (animal* AND human*))
18. #16 NOT #17
19. #18 AND #15

Appendix 2. Interventions in trials

Study ID	Number of units of insulin/day [mean (SD)]	Number of units of insulin/day/kg body weight [mean (SD)]	Monotherapy used	Combination therapy used	Comments
ACCORD 2008	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
ADVANCE 2008	I: 37.3 (28.4) C: 39.8 (27.2)	I: 0.5 (0.3) C: 0.5 (0.3)	I: Yes C: Yes	I: Yes C: Yes	
Bagg 2001	I: - C: -	I: 0.8 (0.1) C: 0.4 (0.1)	I: Yes C: Yes	I:Yes C:Yes	
Becker 2003	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
DIGAMI 2 2005	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
Guo 2008	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
IDA 2009	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
Jaber 1996	I: - C: -	I: - C: -	I: Yes C: Yes	I: No? C: Yes	It is not explicit in the text whether monotherapy was used only or combination therapy in the intensive treatment group.

(*Continued*)

Kumamoto 2000	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
Lu 2010	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
Melidonis 2000	I: - C: -	I: - C: -	I: Yes C: Yes	I: No C: Yes	
REMBO 2008	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	
Service 1983	I: - C: -	I: - C: -	I: Yes C: Yes	I: Yes? C: Yes?	It is not explicit in the text whether monotherapy was used only or if combination therapy also was allowed in the intensive and conventional treatment group
Stefanidis 2003	I: 38 (10) C: -	I: - C: -	I: Yes C: No	I: Yes C: Yes	
Steno-2 2008	I: 75 (57) C: 75 (61)	I: 0.7 (0.5) C: 0.8 (0.5)	I: Yes C: Yes	I: Yes C: Yes	All numbers are from the end of the intervention period (7.8 years of follow-up) The doses of insulin did not have a normal distribution.
UGDP 1975	I: 47.0 (38.0) C: 13.9 (1.7)	I: - C: -	I: Yes C: Yes	I: No C: No	SD calculated from SE.
UKPDS 1998	I (median): 36 (22.2) C: -	I: - C: -	I: Yes C: Yes	I: Yes C: Yes	SD for number of units of insulin/day calculated from IQR. Data are from the UKPDS 33.
VA CSDM 1995	I: 97.5 (26) C: 57.5 (44.2)	I: 1.0 C: 0.6	I:Yes C:Yes	I: Yes C: No	The number of units of insulin/day is estimated from figure after 24

(*Continued*)

					months of follow-up. The SD for insulin doses is calculated from SE.
VADT 2009	I (median): 56 (48.1) C (median): 45 (40.7)	I: 0.5 C: 0.5	I: Yes C: Yes	I: Yes C: Yes	Data from insulin doses are medians. SD calculated from IQR. Data on insulin doses only available after 4 years of follow-up
Yang 2007	I: - C: -	I: - C: -	I: Yes C: Yes	I: - C: Yes	

Footnotes
"-" denotes not reported
Abbreviations: C: control (targeting conventional glycaemic control); I: intervention (targeting intensive glycaemic control); T: total

Appendix 3. Cardiovascular risk factors and body mass index at the end of follow-up

Study ID	Values of CVD risk factors	Number of patients treated with medication against cardiovascular disease	BMI [kg/m^2]	Comments
ACCORD 2008	I: Systolic blood pressure (mean mmHg (SD)):128 (16.3) Diastolic blood pressure (mean mmHg (SD)): 68 (10.4) Total cholesterol (mean mmol/L (SD)): 4.0 (0.9) LDL-cholesterol (mean mmol/L (SD)): 2.1 (0.7) HDL-cholesterol (mean mmol/L (SD)): 1.1 (0.3) C: Systolic blood pressure (mean mmHg (SD)): 128 (15.6)	I: Aspirin: 3736 Antihypertensiva: 4664 Lipid-lowering (statin): 4432 C: Aspirin: 3753 Antihypertensiva: 4714 Lipid-lowering (statin): 4425	I: 33 (5.9) C: 32 (5.9)	Mean is approximated median. SD is calculated from interquartile ranges.

(*Continued*)

	Diastolic blood pressure (mean mmHg (SD)): 67 (9.6) Total cholesterol (mean mmol/L (SD)): 4.1 (0.9) LDL-cholesterol (mean mmol/L (SD)): 2.1 (0.7) HDL-cholesterol (mean mmol/L (SD)): 1.1 (0.1)			
ADVANCE 2008	I: Systolic blood pressure (mean mmHg (SD)): 135.5 (17.6) Diastolic blood pressure (mean mmHg (SD)): 73.5 (9.8) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): 2.64 (0.97) HDL-cholesterol (mean mmol/L (SD)): 1.24 (0.35) C: Systolic blood pressure (mean mmHg (SD)): 137.9 (18.4) Diastolic blood pressure (mean mmHg (SD)): 74.3 (9.9) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): 2.65 (1.06) HDL-cholesterol (mean mmol/L (SD)): 1.25 (0.35)	I: Aspirin: 2665 Antihypertensiva: 4291 Lipid-lowering (statin): 2131 C: Aspirin: 2503 Antihypertensiva: 4190 Lipid-lowering (statin): 2174	I: 28 (5) C: 28 (5)	
Bagg 2001	I: Systolic blood pressure (mean mmHg (SD)): 134 (3.8) Diastolic blood pressure (mean mmHg (SD)): 79 (2.0) Total cholesterol (mean	I: Aspirin: 1 Antihypertensiva: 6 Lipid-lowering: 3 C: Aspirin: 4 Antihypertensiva: 5 Lipid-lowering: 3	I: 33.1 (1.1) C: 29.4 (1.1)	

(*Continued*)

	mmol/L (SD)): 5.2 (0.3) LDL-cholesterol (mean mmol/L (SD)): 3.3 (0.2) HDL-cholesterol (mean mmol/L (SD)): 1.1 (0.1) C: Systolic blood pressure (mean mmHg (SD)): 130 (3.6) Diastolic blood pressure (mean mmHg (SD)): 78 (1.9) Total cholesterol (mean mmol/L (SD)): 5.1 (0.2) LDL-cholesterol (mean mmol/L (SD)): 3.0 (0.2) HDL-cholesterol (mean mmol/L (SD)): 1.2 (0.1)			
Becker 2003	I: Systolic blood pressure (mean mmHg (SD)): 149 (23) Diastolic blood pressure (mean mmHg (SD)): 83 (11) Total cholesterol (mean mmol/L (SD)): 5.9 (1.2) LDL-cholesterol (mean mmol/L (SD)): 3.9 (1.0) HDL-cholesterol (mean mmol/L (SD)): 1.0 (0.3) C: Systolic blood pressure (mean mmHg (SD)): 145 (24) Diastolic blood pressure (mean mmHg (SD)): 82 (12) Total cholesterol (mean mmol/L (SD)): 6.0 (1.0) LDL-cholesterol (mean mmol/L (SD)): 4.0 (0.9) HDL-cholesterol (mean mmol/L (SD)): 1.06 (0.27)	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: 28.4 (4.9) C: 29.4 (4.7)	Medication against cardiovascular disease is only available for both intervention groups together: Antihypertensiva: 52 Lipid-lowering: 36
DIGAMI 2 2005	I: Systolic blood pressure	I: Aspirin:191	I: - C: -	

(*Continued*)

	(mean mmHg (SD)):137 Diastolic blood pressure (mean mmHg (SD)):77 Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)):139 Diastolic blood pressure (mean mmHg (SD)):79 Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	Antihypertensiva: Not possible to find suitable data. Lipid-lowering:173 C: Aspirin: 119 Antihypertensiva: Not possible to find suitable data. Lipid-lowering: 102		
Guo 2008	I: Systolic blood pressure (mean mmHg (SD)): 117.2 (16.8) Diastolic blood pressure (mean mmHg (SD)): 78.8 (8.8) Total cholesterol (mean mmol/L (SD)): 4.3 (1.1) LDL-cholesterol (mean mmol/L (SD)): 2.5 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.2 (0.6) C: Systolic blood pressure (mean mmHg (SD)): 116.6 (15.9) Diastolic blood pressure (mean mmHg (SD)): 73.9 (7.6) Total cholesterol (mean mmol/L (SD)): 5.0 (1.0) LDL-cholesterol (mean mmol/L (SD)): 2.8 (0.7) HDL-cholesterol (mean mmol/L (SD)): 1.4 (0.6)	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: 25.9 (3.0) C: 25.8 (4.5)	

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IDA 2009	I: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: - C: -	
Jaber 1996	I: Systolic blood pressure (mean mmHg (SD)): 140 (20) Diastolic blood pressure (mean mmHg (SD)): 82 (10) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): 3.5 (0.3) HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: - C: -	

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Kumamoto 2000	I: Systolic blood pressure (mean mmHg (SD)):129 (16) Diastolic blood pressure (mean mmHg (SD)): 70 (12) Total cholesterol (mean mmol/L (SD)): 5.3 (0.7) LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): 1.3 (0.4) C: Systolic blood pressure (mean mmHg (SD)): 130 (17) Diastolic blood pressure (mean mmHg (SD)): 72 (11) Total cholesterol (mean mmol/L (SD)): 5.3 (0.7) LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): 1.3 (0.4)	I: Aspirin: - Antihypertensiva: 7 Lipid-lowering: 6 C: Aspirin: - Antihypertensiva: 10 Lipid-lowering: 8	I: 21.5 (2.0) C: 21.3 (2.6)	All data after 8 years of follow-up. Cholesterol values are converted from mg/dL to mmol/L by dividing with 39.
Lu 2010	I: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): 4.6 (1.1) LDL-cholesterol (mean mmol/L (SD)): 2.6 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.3 (0.4) C: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): 4.6 (0.8) LDL-cholesterol (mean mmol/L (SD)): 2.8 (0.3) HDL-cholesterol (mean mmol/L (SD)): 1.2 (0.3)	I: Aspirin: - Antihypertensiva: - Lipid-lowering: Prohibited. C: Aspirin: - Antihypertensiva: - Lipid-lowering: Prohibited.	I: - C: -	ACE-inhibitors, angiotensin receptor blockers, antiplatelet drugs, anticoagulants, vasodilators and antihyperlipidaemic drug were prohibited.

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Melidonis 2000	I: Systolic blood pressure (mean mmHg (SD)): 132 (16) Diastolic blood pressure (mean mmHg (SD)): 88 (11) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): 136 (12) Diastolic blood pressure (mean mmHg (SD)): 89 (10) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin: 19 Antihypertensiva: 22 Lipid-lowering: 20 C: Aspirin: 21 Antihypertensiva: 21 Lipid-lowering: 21	I: 26.3 C: 26.3	
REMBO 2008	I: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: 33.0 (4.8) C: 31.5 (4.6)	

(*Continued*)

Service 1983	I: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): - Diastolic blood pressure (mean mmHg (SD)): - Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: - C: -	
Stefanidis 2003	I: Systolic blood pressure (mean mmHg (SD)): 126 (13) Diastolic blood pressure (mean mmHg (SD)): 87 (6) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): 123 (13) Diastolic blood pressure (mean mmHg (SD)): 84 (8) Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -	I: Aspirin (platelet inhibitors): 29 Antihypertensiva: 29 Lipid-lowering: 11 C: Aspirin (platelet inhibitors): 33 Antihypertensiva: 30 Lipid-lowering: 16	I: - C: -	

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Steno-2 2008	I: Systolic blood pressure (mean mmHg (SD)): 131 (13) Diastolic blood pressure (mean mmHg (SD)): 73 (11) Total cholesterol (mean mmol/L (SD)): 4.1 (0.9) LDL-cholesterol (mean mmol/L (SD)): 2.1 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.2 (0.4) C: Systolic blood pressure (mean mmHg (SD)): 146 (18) Diastolic blood pressure (mean mmHg (SD)): 78 (10) Total cholesterol (mean mmol/L (SD)): 5.6 (1.3) LDL-cholesterol (mean mmol/L (SD)): 3.3 (0.93) HDL-cholesterol (mean mmol/L (SD)): 1.2 (0.3)	I: Aspirin: 58 Antihypertensiva: 66 Lipid-lowering: 57 C: Aspirin: 35 Antihypertensiva: 52 Lipid-lowering: 14	I: 30.9 (5.2) C: 30.6 (5.3)	All data are from the end of the intervention period (7.8 years of follow-up). Cholesterol values are converted from mg/dL to mmol/L by dividing with 39.
UGDP 1975	I: Systolic blood pressure (mean mmHg (SD)): 145.3 (28.6) Diastolic blood pressure (mean mmHg (SD)): 81.9 (17.1) Total cholesterol (mean mmol/L (SD)): 6.0 (1.9) LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): 149.3 (31.9) Diastolic blood pressure (mean mmHg (SD)): 83.8 (14.5) Total cholesterol (mean mmol/L (SD)): 6.2 (1.9)	I: Aspirin: -, but reported anticoagulants: 6. Antihypertensiva: 68 Lipid-lowering: - C: Aspirin: -, but reported anticoagulants: 5. Antihypertensiva: 71 Lipid-lowering: -	I: - C: -	SD calculated from SE. Cholesterol values are converted from mg/dL to mmol/L by dividing with 39.

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	LDL-cholesterol (mean mmol/L (SD)): - HDL-cholesterol (mean mmol/L (SD)): -			
UKPDS 1998	I: Systolic blood pressure (mean mmHg (SD)): 139 Diastolic blood pressure (mean mmHg (SD)): 77 Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): 3.26 HDL-cholesterol (mean mmol/L (SD)):1.09 C: Systolic blood pressure (mean mmHg (SD)): 138 Diastolic blood pressure (mean mmHg (SD)): 77 Total cholesterol (mean mmol/L (SD)): - LDL-cholesterol (mean mmol/L (SD)): 3.26 HDL-cholesterol (mean mmol/L (SD)): 1.11	I: Aspirin/other antiplatelet: 104 Antihypertensiva: 648 Lipid-lowering: - C: Aspirin/other antiplatelet: 51 Antihypertensiva: 258 Lipid-lowering: -	I: 29 C: 29	Number of concomitant treatment of risk factors is taken from the meta-analyses by Turnbull et al. (Turnbull 2009). Data are truncated after 5 years. BMI, blood pressure and cholesterol values are taken from meta-analyses by Kelly et al. (Kelly 2009) All data are from the UKPDS 33.
VA CSDM 1995	I: Systolic blood pressure (mean mmHg (SD)): 137.2 (17.5) Diastolic blood pressure (mean mmHg (SD)): 80.2 (8.8) Total cholesterol (mean mmol/L (SD)): 5.2 (1.0) LDL-cholesterol (mean mmol/L (SD)): 3.4 (0.9) HDL-cholesterol (mean mmol/L (SD)): 1.0 (0.3) C: Systolic blood pressure (mean mmHg (SD)): 138.7 (16.8) Diastolic blood pressure (mean mmHg (SD)): 82.6 (8.1) Total cholesterol (mean	I: Aspirin: - Antihypertensiva: 50 Lipid-lowering: 12 C: Aspirin: - Antihypertensiva: 54 Lipid-lowering: 16	I: 31.5 (3.3) C: 31.8 (3.4)	BMI is estimated from figure after 24 months of follow-up. SD for BMI is calculated from SE.

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	mmol/L (SD)): 5.2 (1.0) LDL-cholesterol (mean mmol/L (SD)): 3.3 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.0 (0.3)			
VADT 2009	I: Systolic blood pressure (mean mmHg (SD)): 127 (16) Diastolic blood pressure (mean mmHg (SD)): 68 (10) Total cholesterol (mean mmol/L (SD)): 3.8 (1.0) LDL-cholesterol (mean mmol/L (SD)): 2.1 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.0 (0.3) C: Systolic blood pressure (mean mmHg (SD)): 125 (15) Diastolic blood pressure (mean mmHg (SD)): 69 (10) Total cholesterol (mean mmol/L (SD)): 3.9 (1.0) LDL-cholesterol (mean mmol/L (SD)): 2.1 (0.8) HDL-cholesterol (mean mmol/L (SD)): 1.1 (0.3)	I: Aspirin: 658 Antihypertensiva: 656 Lipid-lowering: 609 C: Aspirin (and other antiplatelet): 662 Antihypertensiva: 652 Lipid-lowering: 590	I:33.8 (6.0) C: 32.5 (5.0)	Data for lipid-lowering treatment, antihypertensive treatment and aspirin are taken from meta-analysis by Turnbull et al. (Turnbull 2009). Cholesterol values are converted from mg/dL to mmol/L by dividing with 39
Yang 2007	I: Systolic blood pressure (mean mmHg (SD)): 121 Diastolic blood pressure (mean mmHg (SD)): 77 Total cholesterol (mean mmol/L (SD)): 4.4 LDL-cholesterol (mean mmol/L (SD)): 2.5 HDL-cholesterol (mean mmol/L (SD)): - C: Systolic blood pressure (mean mmHg (SD)): 121 Diastolic blood pressure (mean mmHg (SD)): 75	I: Aspirin: - Antihypertensiva: - Lipid-lowering: - C: Aspirin: - Antihypertensiva: - Lipid-lowering: -	I: 25.7 (3.6) C: 26.1 (3.2)	

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	Total cholesterol (mean mmol/L (SD)): 4.9 LDL-cholesterol (mean mmol/L (SD)): 2.9 HDL-cholesterol (mean mmol/L (SD)):-			

Footnotes
"-" denotes not reported
Abbreviations: BMI: body mass index; C: control (targeting conventional glycaemic control); CVD: cardiovascular disease; I: intervention (targeting intensive glycaemic control); T: total

Appendix 4. Definition of mortality and cardiovascular outcomes in study or as reported

Study	Cardiovascular mortality	Macrovascular complications (composite outcome)	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity	Cardial revascularization	Peripheral revascularization	Comments
ACCORD 2008	Unexpected death and death due to myocardial infarction, congestive heart failure, after invasive cardiovascular interventions, arrhythmia, stroke, cardiovascular causes after non-cardiovascular surgery, other cardiovascular diseases (e.g. , pulmonary emboli or abdominal	Non-fatal myocardial infarction or non-fatal stroke or death from cardiovascular causes	Prolonged ischaemic symptoms > 20 minutes and or raised cardiac enzymes (Troponin T or I and/or serum CK-MB) , included Q-wave myocardial infarction, non Q-wave myocardial infarction, silent myocardial infarction, probable non Q-wave myocardial	Included ischaemic stroke, primary intracerebral haemorrhage, subarachnoid haemorrhage, stroke of unknown aetiology, non-fatal stroke after cardiovascular invasive interventions, and non-fatal stroke after non-cardiovascular surgery	Limb amputation: including partial or digit amputation due to vascular disease (a part of cardiovascular revascularization procedures)	A part of cardiovascular revascularization procedures: 1. Percutaneous transluminal coronary angioplasty (balloon); 2. Percutaneous transluminal coronary angioplasty with stent; 3. coronary-artery bypass grafting.	A part of cardiovascular revascularization procedures: Peripheral angioplasty with or without stent and peripheral vascular surgery (including aortic aneurysm repair)	

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	aortic rupture), and presumed cardiovascular death (every component described in details in study protocol p 87-88)		infarction, myocardial infarction after coronary bypass graft surgery, myocardial infarction after cardiovascular invasive interventions, and myocardial infarction after non-cardiovascular surgery	(more details of each component, see study protocol p 89)				
ADVANCE 2008	Death from cardiovascular causes.	Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke	Non-fatal myocardial infarction.	Non-fatal stroke.	ND	A part of total cardiovascular disease events (major coronary events, silent myocardial infarction, coronary revascularization, or hospital admission for unstable angina)	Peripheral vascular events.	
Bagg 2001	ND	Non-fatal stroke, unstable angina.	Non-fatal myocardial infarction.	Non-fatal stroke.	ND	ND	ND	"One suffered a brainstem cerebrovascular accident after 2 weeks, one developed unstable angina. One further

(*Continued*)

								patient in IC developed exertional angina during the study but was able to complete the study."
Becker 2003	ND	Myocardial infarction, angina pectoris, stroke, transient ischaemic attack, and intermittent claudication	ND	ND	ND	ND	ND	For macrovascular complications, the definition of previously cardiovascular disease is used
DIGAMI 2 2005	Sudden cardiovascular deaths were those that occurred within 24 hour following onset of symptoms and without any other obvious reason for the fatal outcome. Deaths were labelled as cardiovascular or non-cardiovascular, and those without any obvious non-cardiovascular cause were considered cardiovascular	Death, reinfarction, or stroke.	Myocardial infarction was diagnosed according to the joint recommendations of the European Society of Cardiology and the American College of Cardiology A reinfarction was defined as a new event > 72 hour from the index infarction	Stroke was defined as unequivocal signs of focal or global neurological deficit of sudden onset and a duration of > 24 hour that were judged to be of vascular origin	ND	Not possible to divide the revascularizations into thrombolysis or invasive surgical intervention	ND	An inclusion criteria was previously myocardial infarction. Therefore we have recorded the number from reinfarction as myocardial infarction

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Guo 2008	ND	ND	ND	ND	ND	ND	ND	
IDA 2009	ND	New percutaneous coronary intervention, coronary bypass surgery, angina	ND	ND	ND	ND	ND	The macrovascular disease is not clearly defined in text.
Jaber 1996	ND	ND	ND	ND	ND	ND	ND	
Kumamoto 2000	Sudden death (probably myocardial infarction) and death due to cerebral vascular disease	Cardiovascular events (angina pectoris or myocardial infarction), cerebrovascular events (stroke), and peripheral vascular events (intermittent claudication, gangrene, or amputation)	Non-fatal myocardial infarction.	Non-fatal ischaemic stroke, non-fatal haemorraghic stroke.	Amputation of lower extremity.	Cardial revascularization.	Peripherial revascularization.	
Lu 2010	ND	ND	ND	ND	ND	ND	ND	
Melidonis 2000	ND	ND	The diagnosis of AMI required fulfilment of at least two of the following criteria: 1. Anginal chest pain of at least 30 min duration; 2. development of new Q waves in 2 of	Non-fatal stroke.	Amputation of lower extremity.	Cardial revascularization.	Peripheral revascularization.	The number of myocardial infarction reported in analysis is the number of reinfarction. Reinfarction was not defined in trial

(*Continued*)

			the 12 electrocardiogram leads; 3. serum levels of creatine phosphokinase and creatine phosphokinase-MB fraction to more than twice the upper limit of normal 10-16 hour after the onset of symptoms Reinfarction reported.					
REMBO 2008	Stroke, heart failure.	ND	ND	ND	ND	ND	ND	
Service 1983	ND	ND	ND	ND	ND	ND	ND	
Stefanidis 2003	Reported as death due to myocardial infarction.	ND	Reinfarction reported.	Non-fatal stroke.	Amputation of lower extremity.	Cardial revascularization.	Peripheral revascularization.	The number of myocardial infarction reported is the number of reinfarction. Reinfarction was not defined in trial
Steno-2 2008	Death from cardiovascular causes.	Death from cardiovascular causes, non-fatal myocardial infarction, coronary-artery by-	WHO criteria.	WHO criteria.	Amputation because of ischaemia.	Coronary-artery bypass grafting.	Surgical interventions for peripheral atherosclerotic artery disease	

(*Continued*)

		pass grafting, percutaneous coronary intervention, non-fatal stroke, amputation as a result of ischaemia, or vascular surgery for peripheral atherosclerotic artery disease						
UGDP 1975	Death due to: Sudden death; defined as a death occurring within three hours of the onset of symptoms in an otherwise clinically stable patient and in a manner consistent with a cardiovascular event. Myocardial infarction; this diagnosis was made from electrocardiogram changes and changes in serum enzymes observed	ND	Patients hospitalised with a diagnosis of non-fatal myocardial infarction or changes from a less severe finding for Q/QS and T patterns on the baseline ECG to a more severe finding for these abnormalities on a follow-up ECG	ND	Amputation of all or part of lower limb.	ND	ND	

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	during the terminal course of illness, or if the events leading to death were clinically compatible with the diagnosis and autopsy findings provided evidence that an myocardial infarction was the principal cause of death. Other heart disease, included deaths due to congestive heart failure, valvular heart disease, atherosclerotic heart disease, and hypertensive heart disease. Extracardiac Vascular Disease: cerebral vascular disease, pulmonary embolism, and peripheral vascular							

(*Continued*)

UKPDS 1998	Fatal myocardial infarction, fatal stroke, death from peripheral vascular disease, and sudden death	Is not reported separately in trial. Is reported as a part of the aggregate outcome; any diabetes-related endpoint	WHO clinical criteria with associated electrocardiogram/ enzyme changes or new pathological Q wave (ICD 9 Code 410)	Major strokes with symptoms that persisted for more than one month (ICD 430 to 434.9 and 436)	Major limb complications- requiring amputation of digit or limb for any reason (ICD codes 5.845 to 5.848)	ND	ND	Defintion of major cardiovascular events from Turnbull et al. (Turnbull 2009): cardiovascular death or non-fatal stroke or non-fatal myocardial infarction, stroke (fatal or non-fatal), myocardial infarction (fatal or non-fatal) and heart failure resulting in hospitalisationor death.
VA CSDM 1995	Cardiovascular death is classified as sudden death, coronary heart disease, cerebrovascular attack, or other cardiovascular causes (pulmonary embolism, cardiomyopathy, etc)	Myocardial infarction, stroke, congestive heart failure, amputation for gangrene, new angina and/or coronary artery disease, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, ischaemic	Myocardial infarctions are classified by the CERLab using the Minnesota code. Patients with suspected acute myocardial infarction, treated with thrombolytic therapy or with acute coronary angioplasty (within 24	Non-fatal stroke.	Limb ulcers or amputation were computed end points only if diagnosed as ischaemic	Coronary revascularization.	Peripheral revascularization.	

(*Continued*)

		ulcer, transient ischaemic attack, new intermittent claudication	hour of the onset of symptoms) , who do not meet the electrocardiogram criteria, also are counted					
VADT 2009	In appendix listed as death caused by: myocardial infarction, congestive heart failure, coronary revascularization, stroke, cerebral revascularization, complications of occlusions, peripheral revascularization, sudden death, and pulmonary embolism	Acute myocardial infarction, death from cardiovascular disease, stroke, congestive heart failure, amputation from peripheral vascular disease, surgical intervention for coronary or peripheral vascular disease, and critical limb ischaemia	Q wave in 2 consecutive leads or a new R-wave in V1 of at least 50% accompanied with motion abnormality in MUGA scan or echocardiography; or ST depression over 1 mm or new T-wave in 2 consecutive leads with injury changes in creatine phosphokinase over 2 times and elevated CK-MB or troponins	Non-haemorragic stroke: sudden onset of focused symptoms over 24 hours; intracranial haemorraghic stroke: with meningeal symptoms in the absence of focal signs, and bloody spinal fluid with increased pressure; embolic stroke: rapid onset, localized symptoms, presence of embolic condition	Amputation for ischaemic diabetic gangrene.	Coronary revascularization.	Peripheral revascularization.	Myocardial infarction, stroke, coronary revascularization, and peripheral revascularization are listed in appendix in the same table as death due to cardiovascular disease. Therefore we assume the number of these events is the non-fatal events
Yang 2007	ND	ND	ND	ND	ND	ND	ND	

Footnotes

Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, ADVANCE: Action in Diabetes and Vascular disease - PreterAx and DiamicroN MR Controlled Evaluation, DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction, ICD: International Classification of Diseases, IDA: Insulin Diabetes Angioplasty, MUGA scan: multiple-gated acquisition scan, ND: Not defined, REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, UGDP: University Group Diabetes Program, UKPDS: United Kingdom Prospective Diabetes Study, VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, VADT: Veterans Affairs Diabetes Trial, WHO: World

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Health Organisation

Appendix 5. Definition of microvascular outcomes in study or as reported

Study ID	Microvascular complications (composite outcome)	Nephropathy	End-stage renal disease	Retinopathy	Retinal photocoagulation	Comments
ACCORD 2008	Fatal or non-fatal renal failure (initiation of dialysis or end-stage renal disease, renal transplantation, or rise of serum creatinine > 291.7 μmol/L) or retinal photocoagulation or vitrectomy for diabetic retinopathy	Composite nephropathy outcome: Doubling of serum creatinine or a 20 mL/min/1.73m^2 or decrease in estimated glomerular filtration rate, development of macroalbuminuria (albumin/creatinine ratio > 300 mg albumin per gram creatinine in random urine sample), development of renal failure (renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dL in the absence of an acute reversible cause)	Development of renal failure as defined by renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dL in the absence of an acute reversible cause. Death due to renal failure.	Progression of diabetic retinopathy of at least 3 stages the Early Treatment of Diabetic Retinopathy Study scale	Photocoagulation.	
ADVANCE 2008	New or worsening nephropathy or retinopathy (development of proliferative retinopathy, macular edema or dia-	Development of macroalbuminuria, defined as a urinary albumin: creatinine ratio of more than 300 μg of albumin per milligram of	Renal-replacement therapy or death from renal causes.	Progression of $\geq$2 steps in Early Treatment of Diabetic Retinopathy Study classification with laser coagulation therapy during	Laser coagulation therapy.	

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	betes-related blindness, or the use of retinal photocoagulation therapy)	creatinine (33.9 mg per millimole), or doubling of the serum creatinine level to at least 200 μmol/L, the need for renal-replacement therapy, or death due to renal disease		follow-up as the final step in Early Treatment of Diabetic Retinopathy Study classification, including both incidence and progression of retinopathy.		
Bagg 2001	ND	Macroalbuminuria.	ND	ND	ND	The urine assessment at the end of the follow-up period was a single albumin creatinine ratio
Becker 2003	ND	ND	ND	ND	ND	
DIGAMI 2 2005	ND	ND	ND	ND	ND	
Guo 2008	ND	ND	ND	ND	ND	
IDA 2009	ND	ND	ND	ND	ND	
Jaber 1996	ND	ND	ND	ND	ND	
Kumamoto 2000	ND	The patients with nephropathy were divided into three stages depending on their urinary albumin excretion: normoalbuminuria (< 30 mg/24 hour), microalbuminuria (30-300 mg/24 hour), or albuminuria (> 300 mg/24 hour) Reported for the primary prevention population	End-stage renal disease.	The degree of retinopathy for each patient was determined by the two eye examiners using the modified Early Treatment of Diabetic Retinopathy Study classification with a scale of 19 stages. The development and progression of retinopathy were defined as a change of	Retinal photocoagulation.	

(*Continued*)

		as participants developing nephropathy. Reported for the secondary intervention population as participants progressing to nephropathy		at least two steps up from stage 1 in the primary prevention population and as a change of two or more steps up from stages 2 to 5 in the secondary intervention population		
Lu 2010	ND	WHO 1999 criteria.	ND	ND	ND	
Melidonis 2000	ND	ND	ND	ND	ND	
REMBO 2008	ND	ND	ND	ND	ND	
Service 1983	ND	ND	ND	ND	ND	
Stefanidis 2003	ND	ND	ND	ND	ND	
Steno-2 2008	Progression of microvascular complications (incident diabetic nephropathy or the development or progression of diabetic retinopathy or neuropathy).	Nephropathy was defined as median albumin excretion rates greater than 300 mg/24 hour in at least one of the two-yearly examinations	End-stage renal disease requiring dialysis.	Diabetic retinopathy was graded according to the six-level grading scale of the European Community - funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes	ND	
UGDP 1975	ND	Urine protein ≥ 1 gm/L.	Renal dialysis.	Mild retinal abnormalities: hard exudates, soft exudates, and/or haemorrhages or microaneurysms	ND	The authors have not defined nephropathy in the articles, but we have chosen to report urine protein ≥1 gram/L as nephropathy

(*Continued*)

UKPDS 1998	Retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure	Two-fold plasma-creatinine increase.	Renal failure dialysis and/or plasma creatinine > 250 μ mol/L not ascribable to any acute intercurrent illness. Death from renal disease	Retinopathy was defined as one microaneurysm or more in one eye or worse retinopathy, and progression of retinopathy as a two-step change in Early Treatment of Diabetic Retinopathy Study grade	Retinal photocoagulation.	
VA CSDM 1995	ND	Overt nephropathy was defined as an albumin: creatinine ratio > 0.30	Serum creatinine > 265 μ M (without a reversible cause), and/or need for dialysis or kidney transplant	Seven-field fundus photograph and ophthalmological examination. The first two photographic end points is the presence of at least 3 counts of microaneurysms for the two eyes, and the second is the worsening of retinopathy as defined by a progression of two or more levels in the final Early Treatment of Diabetic Retinopathy Study scale	ND	
VADT 2009	Retinopathy, nephropathy, and neuropathy	Severe nephropathy was defined as a doubling of the serum creatinine level, a creatinine level of more than 3 mg per deciliter (265 μmol/L), or a glomerular filtra-	Death due to renal failure.	The 23-point Early Treatment Diabetic Retinopathy Study grading scale was used to define progression to new proliferative diabetic retinopa-	ND	

(*Continued*)

		tion rate of less than 15 ml per minute		thy. The progression of retinopathy was defined as a 2-point increase on the scale		
Yang 2007	ND	ND	ND	ND	ND	

Footnotes
Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, ADVANCE: Action in Diabetes and Vascular disease - PreterAx and DiamicroN MR Controlled Evaluation, DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction, ICD: International Classification of Diseases, IDA: Insulin Diabetes Angioplasty, MUGA scan: multiple-gated acquisition scan, ND: Not defined, REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, UGDP: University Group Diabetes Program, UKPDS: United Kingdom Prospective Diabetes Study, VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, VADT: Veterans Affairs Diabetes Trial, WHO: World Health Organisation

Appendix 6. Definition of hypoglycaemia in study or as reported

Study ID	Hypoglycaemia (when not further specified)	Mild hypoglycaemia	Moderate hypoglycaemia	Severe hypoglycaemia	Comments
ACCORD 2008	Hypoglycaemia specified after severeness in trial.	Mild hypoglycaemia is defined as self-reported transient symptoms, such as light headedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating, and so on, that resolve after self-treatment with the ingestion of simple carbohydrates	ND	Severe hypoglycaemia is defined as hypoglycaemia with documented blood glucose < 2.8 mmol/L (50 mg/dL) or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require the assistance of medical or paramedical personnel	
ADVANCE 2008	Hypoglycaemia was defined as a blood glucose level of less than 2.8 mmol/L	Minor hypoglycaemia.	ND	Patients with transient dysfunction of the central nervous system who were un-	

(*Continued*)

	(50 mg/dL) or the presence of typical symptoms and signs of hypoglycaemia without other apparent cause			able to treat themselves (requiring help from another person) were considered to have severe hypoglycaemia	
Bagg 2001	Hypoglycaemic episodes were defined as any capillary glucose record < 4 mmol/L, or symptoms of hypoglycaemia relieved by treatment expected to raise the level of blood glucose in the absence of a capillary glucose test	Mild hypoglycaemia.	ND	Severe hypoglycaemia was defined as the presence of impaired consciousness requiring the help of another person, coma or seizure and the presence of low blood glucose	
Becker 2003	ND	ND	ND	ND	
DIGAMI 2 2005	Hypoglycaemia was defined as a blood glucose < 3.0 mmol/L and was recorded as with or without symptoms	ND	ND	ND	
Guo 2008	ND	ND	ND	ND	
IDA 2009	ND	ND	ND	Severe hypoglycaemic episodes.	
Jaber 1996	ND	Mild to moderate: classic autonomic symptoms, recognised by the patients and successfully self-treated	ND	ND	
Kumamoto 2000	Hypoglycaemia specified after severeness in trial.	Mild hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia (sweating, palpitations, hunger, or blurred	ND	Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the patient required the assistance of an-	

(*Continued*)

		vision) in which the patient did not require the assistance of another person and which was associated with a blood glucose level < 50 mg/dL by self-monitoring		other person and which was associated with a blood glucose level < 50 mg/dL and a prompt recovery after intravenous glucose loading	
Lu 2010	ND	ND	ND	ND	
Melidonis 2000	ND	Mild hypoglycaemic episodes.	Moderate hypoglycaemic episodes.	Severe hypoglycaemic episodes.	
REMBO 2008	ND	ND	ND	ND	
Service 1983	ND	ND	ND	ND	
Stefanidis 2003	ND	Mild hypoglycaemic episodes.	Moderate hypoglycaemic episodes.	Severe hypoglycaemic episodes.	
Steno-2 2008	ND	Minor episode of symptomatic hypoglycaemia.	ND	Major hypoglycaemic event that impaired consciousness and required help from another person	
UGDP 1975	Suspected or observed period of hypoglycaemia (Fasting values below 50 mg/100mL.)	ND	ND	ND	
UKPDS 1998	Hypoglycaemia specified after severeness in trial.	Hypoglycaemic episodes were defined as minor if the patient was able to treat the symptoms unaided	ND	Hypoglycaemia requiring third-party help or medical intervention.	The number of hypoglycaemia is on intention-to-treat percentages from UKPDS 33 and UKPDS 34. We assumed the number being reported is the number of patients with at least one episode of hypoglycaemia over 10 years of follow-up

(*Continued*)

VA CSDM 1995	Hypoglycaemia specified after severeness in trial.	Mild hypoglycaemia is defined as serum glucose < 2.8 mmol/L, with or without symptoms, or consistent symptoms (sweating, palpitations, blurred vision etc.) relieved by treatments that raise blood glucose	Symptoms that caused substantial discomfort and interfered with normal activity but that did not meet the criteria for either mild or severe hypoglycaemia	Coma, seizure, or impaired consciousness requiring assistance	
VADT 2009	Hypoglycaemia specified after severeness in trial.	Relieved by food or sugar intake.	ND	Defined with as a serious adverse event i.e., life threatening, death, hospitalisation, disability or incapacity, cancer or other important event requiring medical intervention/treatment	
Yang 2007	ND	ND	ND	ND	

Footnotes
Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, ADVANCE: Action in Diabetes and Vascular disease - PreterAx and DiamicroN MR Controlled Evaluation, DIGAMI: Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction, ICD: International Classification of Diseases, IDA: Insulin Diabetes Angioplasty, MUGA scan: multiple-gated acquisition scan, ND: Not defined, REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, UGDP: University Group Diabetes Program, UKPDS: United Kingdom Prospective Diabetes Study, VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, VADT: Veterans Affairs Diabetes Trial, WHO: World Health Organisation

Appendix 7. Quality of life and assessment of well-being

Name of trial	Becker 2003	Jaber 1996	REMBO 2008	Steno-2 2008	UKPDS 1998	VA CSDM 1995
Dimensions (sub scales)	Composite scale consisting of The type 2 diabetes symptom checklist (DSC-type 2), The Dutch shortened	Health Status Questionare version 2.0 (derived from the Short Form-36)	Minnesota Living With Heart Failure Questionaire (consist of 21 items each having a response	Quality adjusted life expectancy.	Quality of life assessed in two ways: 1) questionnaire examining specific quality-of-life domains	20-question version of the Medical Outcome Study instrument, consist of six scales (general health,

(*Continued*)

	version of mood states (POMS) , and The effect balance scale (ABS) (DSC- type 2 measures the presence and perceived burden of type 2 diabetes symptom (DSC-type 2). If symptom is present then measured on a frequency scale and a discomfort scale. Consist of 34 items divided over 8 scales The Dutch shortened version of mood states (POMS) was used to measure emotional well-being. 32 items consist of 4 negative scales and one positive scale The affect balance scale (ABS) was used to measure happiness. 10 item scale measures) Five-point Likert scale ("How would you describe your current state of health? ", "How did you feel, all things considered? ", "How satisfied were you,		scale of 0-5; two subscales reflects bet- ter health related quality of life (8 items) and emotional (5 items) impairment)		(cognitive mistakes, mood disturbances, symptoms, and work satisfaction). 2) EQ-5D Consisted of two parts: a) five questions about mobility, self- care, usual activities, pain, anxiety. b) A 100-point scale assessing their health state.	pain, physical function, transition or perceived change in function, social function, and mental health)

(*Continued*)

	all things considered, with your life?") Four-point Likert-scale (perceived burden of their diabetes treatment)					
Validated instrument	Composite scale: No (DSC-type 2: Yes. POMS (brief): Yes (Wald 1990). ABS: Yes (McDowell 1982)). 4-and 5-point Likert scale: No.	Yes.	Yes (Minnesota Living with Heart Failure Questionnaire).	Yes.	1) Yes. 2) Yes.	Yes.
Possible answers	DSC-type 2: How often a symptom (divided into: hyperglycaemic, hypoglycaemic, neuropathic pain, sensibility, fatigue, cognitive distress, cardiovascular, and ophthalmological) is present and description on discomfort scale (range 1-4) POMS: The respondent rates each item on a 5-point Likert scale ranging from "Not at all" to "Extremely" ABS: particularly excited or inter-	Twelfe different questions with value with answer options in number	6-point Likert scale (range 0-5): 0-No, 1-Very Little, 5-Very Much	Health state utilities for each patient were calculated by adjusting there baseline utility scores depending on their history of complications	Questionaire: • Cognitive failure:frequency of 25 cognitive failures on a 5 point scale (never-very often). • Mood state: 5-point Likert scale. • Symptoms: frequency of 40 symptoms (not at all-extremely). • Work satisfaction: 7-point Likert scale. EQ-5D: a) For each dimension patients should report one of the following statements: no	Responses were measured by Likert-scales.

(*Continued*)

	ested in something (during the past weeks)?				problems - some problems - severe problems. b) The health state was assessed with a number.	
Minimum score	Composite scale: 0. (Because of skewed distributions and/or substantial proportions of 0 scores, the level of well-being were transformed to a dichotomous scale: 0 indicating a score below the median, 1 a score above the median) Likert scale: 1.	1	0	0 (Quality of life for dialyses intervention).	Questionaire: • Cognitive failure: 0. • Mood state: -40. • Symptoms: 0. • Work satisfaction: 7. EQ-5D: a) -0.594. b) 0.	0
Maximum score	Composite scale: 10. (Because of skewed distributions and/or substantial proportions of 0 scores, the level of well-being were transformed to a dichotomous scale: 0 indicating a score below the median, 1 a score above the median) Likert scale: 4 or 5.	6	105	0.814 (Uncomplicated type 2 diabetes).	Questionaire: • Cognitive failure: 100. • Mood state: 192. • Symptoms: 160. • Work satisfaction: 49. EQ-5D: a) 1. b) 100.	100.
Weighting of the scores/ calculating the scores	Composite scale: not described. Likert scale: weighting not described.	Average of the scores for the each item.	Summing the responses to all 21 items.	Multiplication/ addition.	Questionaire: • Cognitive failure:adding the scores for each component of the question. • Mood	The six scales were not combined, but analysed separately.

(*Continued*)

					state: sum of the scores for tension, depression, anger, fatigue, and confusion minus the score for vigour. • Symptoms: sum of the scores. • Work satisfaction: The scores were added for each component. EQ-5D: a) Responses of the five dimensions were expressed as a tariff score. b) a value for their health.	
Direction of scale	Composite scale: Higher levels indicates higher levels of well-being Likert scale: Not described.	The higher scores, the better health status.	The lower scores, the better quality of life.	The higher scores, the better quality of life.	Questionaire: • Cognitive failure: the higher number, the more cognitive failures. • Mood state: larger score indicate greater mood disturbances, except in the case of vigour score, in which smaller scores imply reduced vigour. • Symptoms: The higher score, the more symptoms. • Work	With exception of pain, the higher score, the better perceived health

(*Continued*)

					satisfaction: The higher number, the lower quality of life. EQ-5D: a) The higher score, the better health. b) the higher scores, the better health.	
Minimal important difference	Composite scale: Not defined. Likert scale: Not defined.	Not defined.	Not defined.	Not defined.	Questionaire: Not defined. EQ-5D: Not defined.	Not described.

Appendix 8. Adverse events

Study ID	Non-serious adverse events [number (percentage)]	Serious adverse events [number (percentage)]	Hospitalisation [number (percentage)]	Drop-outs due to adverse events [number (percentage)]	Congestive heart failure [number (percentage)]
ACCORD 2008	-	I: 113/5128 (2.2) C: 82/5123 (1.6) T:195/10,251 (1.9)	I/C/T: part of left reported	I: 11/5128 (0.2) C: 10/5123 (1.2) T: 21/10,251 (0.2)	I: 152/5128 (3.0) C: 124/5123 (2.4) T: 276/10,251 (2.7)
ADVANCE 2008	-	-	I: 2501/5571 (44.9) C: 2381/5569 (42.8) T: 4882/11,140 (43.8)	-	I: 220/5571 (3.9) C: 231/5569 (4.1) T: 451/11,140 (4.0)
Bagg 2001	-	I: 4/21 (19.0) C: 0/22 (0.0) T: 4/43 (9.3)	I: 4/21 (19.0) C: 0/22 (0.0) T: 4/43 (9.3)	I: 4/21 (19.0) C: 0/22 (0.0) T: 4/43 (9.3)	I: 0/21 (0.0) C: 0/22 (0.0) T: 0/43 (0.0)
Becker 2003	-	-	-	-	-
DIGAMI 2 2005	-	-	I: 474/474 (100.0) C: 306/306 (100.0) T: 780/780 (100.0)	-	-
Guo 2008	-	-	-	-	-

(*Continued*)

IDA 2009	-	-	I: 51/51 (100.0) C: 51/51 (100.0) T: 102/102 (100.0)	-	-
Jaber 1996	-	I: 2/23 (8.7) C: 2/22 (9.1) T: 4/45 (8.9)	I: 1/23 (4.3) C: 2/22 (9.0) T: 3/45 (6.7)	I: 1/23 (4.3) C: 0/22 (0.0) T: 1/43 (2.3)	-
Kumamoto 2000	-	-	-	-	-
Lu 2010	-	-	-	-	-
Melidonis 2000	-	I: 6/24 (25.0) C: 4/24 (16.7) T: 10/48 (20.8)	I: 24/24 (100.0) C: 24/24 (100.0) T: 48/48 (100.0)	I: 0/24 (0.0) C: 0/24 (0.0) Tl: 0/48 (0.0)	I: 4/24 (16.7) C: 5/24 (20.8) T: 9/48 (18.8)
REMBO 2008	-	-	-	-	-
Service 1983	-	-	-	-	I: 14/41 (34.1) C: 19/40 (47.5) T: 33/81 (40.7)
Stefanidis 2003	-	I: 6/36 (16.7) C: 6/39 (15.4) T: 12/75 (16.0)	I: 36/36 (100.0) C: 39/39 (100.0) T: 75/75 (100.0)	I: 5/36 (13.9) C: 4/39 (10.3) T: 9/75 (12.0)	I: 1/36 (2.8) C: 2/39 (5.1) T: 3/75 (4.0)
Steno-2 2008	I: 7/80 (8.8) C: 5/80 (6.3) T: 12/160 (7.5)	I: 1/80 (1.3) C: 0/80 (0.0) T: 1/160 (0.6)	I: 1/80 (1.3) C: 0/80 (0.0) T: 1/160 (0.6) (same patient as left)	I: 0/80 (0.0) C: 0/80 (0.0) T: 0/160 (0.0)	-
UGDP 1975	-	-	I: 14/204 (6.9) C: 13/210 (6.2) T: 27/414 (6.5)	-	-
UKPDS 1998	-	-	-	-	I: 91/3071 (3.0) C: 36/1138 (3.2) T: 127/4209 (3.0)
VA CSDM 1995	-	-	-	I: 2/75 (2.7) C: 0/78 (0.0) T: 2/153 (1.3)	I: 1/75 (1.3) C: 4/78 (5.1) T: 5/153 (3.3)
VADT 2009	-	I: 139/892 (15.6) C: 130/899 (14.5) T: 269/1791 (15.0)	-	I: 7/892 (0.8) C: 3/899 (0.3) T: 10/1791 (0.6)	I: 76/892 (8.5) C: 82/899 (9.1) T:158/1791 (8.8)
Yang 2007	-	-	-	-	-

(*Continued*)

Footnotes
"-" denotes not reported
Abbreviations: C: control (targeting conventional glycaemic control); I: intervention (targeting intensive glycaemic control); T: total

WHAT'S NEW

Last assessed as up-to-date: 8 December 2010.

Date	Event	Description
22 December 2011	Amended	The data for retinopathy trials were corrected. This only results in minor changes. The risk of selective outcome reporting for some of the included trials was corrected

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 6, 2011

Date	Event	Description
24 August 2011	Amended	Originally, we published that there was firm evidence for a 10% relative risk reduction of the composite microvascular outcome for trials exclusively dealing with glycaemic control in the usual care setting. It is now changed into: Trial sequential analysis does not show firm evidence for a 10% relative risk reduction in the trial sequential analysis of the composite microvascular outcome for trials exclusively dealing with glycaemic control in the usual care setting

CONTRIBUTIONS OF AUTHORS

BIANCA HEMMINGSEN: development of protocol, undertaking of searches, selection of trials, data extraction, quality assessment of trials, data analysis, contact person, development of final review.

SØREN S LUND: development of protocol, selection of trials, development of final review.

CHRISTIAN GLUUD: development of protocol, selection of trials, advised on statistical methods to be used, development of final review.

ALLAN VAAG: development of protocol, selection of trials, development of final review.

THOMAS ALMDAL: development of protocol, selection of trials, data extraction, quality assessment of trials, development of final review.

CHRISTINA HEMMINGSEN: selection of trials, data extraction, quality assessment of trials, development of final review, and data analyses.

JØRN WETTERSLEV: developed the initial idea for the review, development of protocol, selection of trials, advised on statistical methods to be used, development of final review, and data analyses.

DECLARATIONS OF INTEREST

Søren Søgaard Lund, Allan Vaag and Thomas Almdal have reported equity in Novo Nordisk A/S. Søren Søgaard Lund and Allan Vaag have received fees from Novo Nordisk A/S for speaking. Thomas Almdal is employed at Steno Diabetes Center, Gentofte, Denmark. Allan Vaag and Søren Søgaard Lund were employed at Steno Diabetes Center at the time the review was written. Steno Diabetes Center is an academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation. Christina Hemmingsen has been employed at Novo Nordisk A/S after completion of the data extraction.

SOURCES OF SUPPORT

Internal sources

- Copenhagen Trial Unit, Rigshospitalet, Denmark.
- Cochrane Metabolic and Endocrine Disorders Group, Germany.

External sources

- The Copenhagen Insulin and Metformin Therapy Group, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Christina Hemmingsen joined as an author after publication of the protocol.

Originally we defined in our protocol to report the effect estimates primarily by means of a fixed-effect model. Because of large heterogeneity of the included trials, it was changed to primarily reporting the effect estimates by means of a random-effects model.

Components of macrovascular complications and of microvascular complications were both assessed individually and as composite endpoints.

Non-fatal haemorrhagic stroke and non-fatal ischaemic stroke were assessed as composite endpoints.

We added to assess end-stage renal disease.

Congestive heart failure was assessed separately.

It was added to the risk of bias for incomplete data that trials with a clear description of reasons for drop-outs or withdrawals were classified as low risk of bias.

We originally planned to judge heterogeneity of 50% or more as substantial. This was changed to be graded exactly like the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) where I^2 between 0% to 40% was graded as heterogeneity that might not be important, I^2 between 30% to 60% was graded as moderate, I^2 between 50% to 90% was graded as substantial heterogeneity, and I^2 between 75% to 100% was graded as considerable heterogeneity.

Internet searches for additional information of included trials were conducted.

'Available case analysis', 'worst-best' and 'best-worst' scenario analyses were planned for the primary and secondary outcomes. These analyses were performed for our primary outcomes and for non-fatal myocardial infarction.

We have conducted an available case analysis and not a per-protocol analysis for the primary outcomes and for non-fatal myocardial infarction.

We originally planned to use the 'uncertainty method' but it was not performed because the method only corrects the confidence interval and not the point estimate.

Because some of the trials did not report HbA1c at baseline, we added fasting blood glucose at baseline as a variable in the meta-regression.

In the trial sequential analysis of severe hypoglycaemia we used 30% relative risk reduction (number needed to harm being approximately 50) instead of 10% relative risk reduction (number needed to treat being approximately 100) as this seems to be a more reasonable analysis with in fact an obtainable required information size for harm.

We applied trial sequential monitoring boundaries according to an information size suggested by the intervention effect estimated from all trials and not just the low risk of bias trials.

We predefined to assess baseline imbalance and early stopping bias. As a result of the recommendations from the Cochrane Colloquium 2010 we chose not to report these variables as sources of bias. Factorial design bias was deleted as well.

Subgroup analyses for all outcomes stratifying the trials after how the intensive glycaemic control was applied were not predefined in the protocol.

We deleted the subgroup analysis stratifying the trials into achievement of glycaemic intervention targets.

In the protocol we incorrectly chose to assess the following as sensitivity analyses, which actually are subgroup analyses:

- comparing trials with low risk of bias sequence generation, allocation concealment, and blinding to trials with high risk of bias regarding sequence generation, allocation concealment, and blinding;
- comparing the trials with long study duration (more than two years) to the trials with short study duration (equal or less than two years);
- comparing the trials using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other).

Appendix 2 is modified, as it would give raise to the data being written twice (see 'Data and analyses section').

Karla Bergerhoff extended the MEDLINE and EMBASE search strategy to include health technology assessments reports and meta-analyses.

Sarah Klingenberg changed the N3 and N6 in front of parentheses in the CINAHL search strategy to AND.

NOTES

Additional figures may be inspected at www.ctu.dk.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Glucose [analysis]; Cardiovascular Diseases [mortality]; Cause of Death; Diabetes Mellitus, Type 2 [blood; *drug therapy; mortality]; Hyperglycemia [complications; *drug therapy; mortality]; Hypoglycemia [chemically induced; mortality]; Hypoglycemic Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans; Middle Aged

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RESEARCH

Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

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Abstract

Objective To assess the effect of targeting intensive glycaemic control versus conventional glycaemic control on all cause mortality and cardiovascular mortality, non-fatal myocardial infarction, microvascular complications, and severe hypoglycaemia in patients with type 2 diabetes.

Design Systematic review with meta-analyses and trial sequential analyses of randomised trials.

Data sources Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL to December 2010; hand search of reference lists and conference proceedings; contacts with authors, relevant pharmaceutical companies, and the US Food and Drug Administration.

Study selection Randomised clinical trials comparing targeted intensive glycaemic control with conventional glycaemic control in patients with type 2 diabetes. Published and unpublished trials in all languages were included, irrespective of predefined outcomes.

Data extraction Two reviewers independently assessed studies for inclusion and extracted data related to study methods, interventions, outcomes, risk of bias, and adverse events. Risk ratios with 95% confidence intervals were estimated with fixed and random effects models.

Results Fourteen clinical trials that randomised 28 614 participants with type 2 diabetes (15 269 to intensive control and 13 345 to conventional control) were included. Intensive glycaemic control did not significantly affect the relative risks of all cause (1.02, 95% confidence interval 0.91 to 1.13; 28 359 participants, 12 trials) or cardiovascular mortality (1.11, 0.92 to 1.35; 28 359 participants, 12 trials). Trial sequential analyses rejected a relative risk reduction above 10% for all cause mortality and showed insufficient data on cardiovascular mortality. The risk of non-fatal myocardial infarction may be reduced (relative risk 0.85, 0.76 to 0.95; P=0.004; 28 111 participants, 8 trials), but this finding was not confirmed in trial sequential analysis. Intensive glycaemic control showed a reduction of the relative risks for the composite microvascular outcome (0.88, 0.79 to 0.97; P=0.01; 25 600 participants, 3 trials) and retinopathy (0.80, 0.67 to 0.94; P=0.009; 10 793 participants, 7 trials), but trial sequential analyses showed that sufficient evidence had not yet been reached. The estimate of an effect on the risk of nephropathy (relative risk 0.83, 0.64 to 1.06; 27 769 participants, 8 trials) was not statistically significant. The risk of severe hypoglycaemia was significantly increased when intensive glycaemic control was targeted (relative risk 2.39, 1.71 to 3.34; 27 844 participants, 9 trials); trial sequential analysis supported a 30% increased relative risk of severe hypoglycaemia.

Conclusion Intensive glycaemic control does not seem to reduce all cause mortality in patients with type 2 diabetes. Data available from randomised clinical trials remain insufficient to prove or refute a relative risk reduction for cardiovascular mortality, non-fatal myocardial infarction, composite microvascular complications, or retinopathy at a magnitude of 10%. Intensive glycaemic control increases the relative risk of severe hypoglycaemia by 30%.

Introduction

Observational studies suggest an association between the extent of hyperglycaemia and the risk of death and of macrovascular and microvascular disease in patients with type 2 diabetes.[1-3] Three recent randomised clinical trials in patients with type 2 diabetes were not able to detect (or reject the possibility of) reduced cardiovascular disease or mortality with intensive compared with conventional glycaemic control.[4-6] Worries arose as the results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in 2008 showed increased all cause

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Extra material supplied by the author (see http://www.bmj.com/content/343/bmj.d6898?tab=related#webextra)

mortality and cardiovascular mortality in the intensive treatment group compared with conventional treatment.[4] The increased mortality led to early termination of the ACCORD trial.[4] On the other hand, randomised clinical trials have indicated a beneficial effect on microvascular complications of intensive versus conventional glycaemic control in patients with type 2 diabetes. However, inconsistencies exist among the trials with respect to which type of microvascular complications are prevented and the magnitude of the effect of intensive glycaemic control.[5 7 8] The price of intensive glycaemic control may be an increased risk of hypoglycaemia. Achieving intensive glycaemic control in patients with type 2 diabetes requires enormous effort from the patient as well as resources from the healthcare system, particularly compared with the well documented beneficial effects of lipid and blood pressure lowering treatment.[9]

The definition of intensive glycaemic control varies among trials and guidelines. The ACCORD trial and the Veterans Affairs Diabetes Trial (VADT) used a target of glycated haemoglobin A_{1c} (HbA_{1c}) below 6.0% for intensive glycaemic control compared with a target of HbA_{1c} below 6.5% in the Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. The results from these trials have created a debate about the optimal choice of glycaemic target. The American Diabetes Association recommends an HbA_{1c} level of less than 7.0% as the standard glycaemic treatment goal, whereas the International Diabetes Federation recommends a level of less than 6.5%.[10-12]

In our 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 but higher glycaemic target.[13] The difference in treatment strategy between the groups was clearly defined either as values of HbA_{1c} or as intensifying glycaemic control. The intensive glycaemic targets varied across the trials, but the trials compared the results of trying to achieve a distinct lower target with those of aiming for a higher one. We believe that the existence of a "gold threshold" target remains to be established and that the hypothesis so far has been that targeting/lowering the HbA_{1c} may have a beneficial effect along the entire scale of measurements of HbA_{1c} unless hypoglycaemia is reached. In this sense, we have included all trials comparing an intensified glycaemic target with a more "relaxed" glycaemic target, often reflecting usual clinical practice for a given place and time.

This systematic review reanalyses current evidence of the effect of targeting intensive glycaemic control on all cause mortality, cardiovascular mortality, cardiovascular disease, and microvascular disease in patients with type 2 diabetes. We consider the effects of intensive glycaemic control irrespective of differences among trials in individual targets or achieved glycaemic control.[13]

As well as assessing the effect of intensive glycaemic control on the outcomes reported in this systematic review (all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, composite microvascular complications, retinopathy, and nephropathy), we assessed macrovascular complications as a composite outcome, non-fatal stroke, peripheral and cardiac revascularisation, retinal photocoagulation, end stage renal disease, congestive heart failure, adverse events, the cost of the intervention, and quality of life. The results for these supplemental outcomes are published elsewhere.[14]

Methods

This review follows the recommendations of the Cochrane Collaboration.[15] It is based on our published Cochrane protocol.[13]

We included all randomised trials that compared the targeting of intensive glycaemic versus conventional glycaemic control in patients with type 2 diabetes.[13 14] We analysed trials according to the setting of the intensive glycaemic intervention. We analysed trials of targeting intensive glycaemic control in patients without acute events at entry or without concomitant treatments targeting other cardiovascular risk factors as "trials exclusively dealing with glycaemic control in usual care setting."[13] The data in the review reported here are from this group of trials, representing 28 614 (95%) of 29 986 participants included in our review.[13 14] We excluded three trials assessing multimodal interventions,[16-18] as well as three trials assessing intensive glycaemic control as part of an acute intervention.[19-21] For the vast majority of estimated effects of intervention, these exclusions did not cause noticeable changes.[13]

We analysed trials of targeting intensive glycaemic control as part of an acute intervention and trials with multimodal interventions separately.[13 14] We also did an overall meta-analysis combining data from all included trials irrespective of the setting in which intensive glycaemic control was applied.[13 14] We refer only to data from the analyses of trials exclusively dealing with glycaemic control in usual care setting in this paper, but the Cochrane version gives a full presentation.[14]

Search strategy

We did a search in the Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL in December 2010 for randomised clinical trials of targeting intensive glycaemic control versus targeting conventional glycaemic control in patients with type 2 diabetes. Web appendix 1 describes the search terms and strategies for each database. We also searched abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes congresses. We contacted relevant drug companies and the US Food and Drug Administration for unpublished randomised trials relevant to our review. We searched reference lists of included trials and (systematic) reviews, meta-analyses, and health technology assessment reports. We did internet searches for all trials to find additional information about the included trials. We contacted authors for information about additional trials.

Study selection

Two authors (BH and AV, CG, CH, SSL, or TA) 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 targeting conventional glycaemic control, and was done in patients with type 2 diabetes. We included trials irrespective of duration, language, publication status, or predefined outcomes.

Data extraction and risk of bias assessment

Two authors (BH and CH or TA) independently extracted information from each included trial by using standard data extraction forms and assessed the risk of bias as advised in the Cochrane Handbook of Systematic Reviews of Interventions.[15] We assessed the following risk of bias domains: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.[15] We classified each domain as adequate, unclear, or

inadequate. Web appendix 2 gives details. Discrepancies between authors' assessments were resolved by involvement of a third author (JW). Translators extracted data from all relevant non-English articles.

We extracted data on several baseline characteristics of the participants (such as age, duration of disease, HbA_{1c}) and outcomes. The predefined outcomes reported in this review are all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, microvascular disease reported as a composite outcome, retinopathy, nephropathy, and severe hypoglycaemia.[13] We sought any relevant missing information from the original author(s) of the randomised trial.

When we identified more than one publication of an original trial, we assessed these together to maximise data collection. In case of substantial disagreements between older and newer publications, we contacted the authors.

Statistical analysis

We used Review Manager version 5.0.25 for statistical analysis.[22] We summarised data on all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and severe hypoglycaemia statistically as relative risks with 95% confidence intervals. We used both a random effects model and a fixed effect model.[23 24] In case of discrepancy between the two models, we report both results; otherwise, we report the random effects model.

We examined heterogeneity with the I^2 statistic, quantifying the proportion of between trial variance to the sum of the between trial variance and a common sampling error.[25] We graded values of I^2 between 0% to 40% as "heterogeneity might not be important," values between 30% and 60% as "moderate heterogeneity," values between 50% and 90% as "substantial heterogeneity," and values between 75% and 100% as "considerable heterogeneity."[25] When we found heterogeneity, we attempted to determine potential reasons by examining characteristics of individual trials.

We did subgroup analyses stratifying trials according to risk of bias, length of study, diagnostic criteria for type 2 diabetes, language of publication, and source of funding for all cause mortality, cardiovascular mortality, and non-fatal myocardial infarction.

We did trial sequential analyses.[26 27] 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 no reason exists 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.[28-30] Cumulative meta-analyses of trials are at risk of producing random errors because of sparse data and repetitive testing of accumulating data when the required information size (analogous to the sample size of an optimally powered clinical trial) has not been met. Trial sequential analysis depends on the quantification of the required information size (the meta-analysis sample size). 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. We calculated a heterogeneity (I^2) adjusted required information size. We did 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. On the basis of pre-determined criteria,[13] we initially 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%). We chose a 10% relative risk reduction equivalent to a number needed to treat of approximately 100 patients, because even this decrease in mortality is likely to be clinically meaningful. For severe hypoglycaemia, however, we chose a 30% increase in relative risk equivalent to a number needed to harm of 50. We also provide the 95% confidence intervals adjusted for sparse data and repetitive testing, which we describe as the trial sequential analysis adjusted 95% confidence intervals. We used TSA version 0.9 beta (www.ctu.dk/tsa) for these analyses.

Results

Results of the search and trial, participant, and intervention characteristics

Figure 1⇓ summarises the results of the search. We excluded 42 references after further evaluation. The main reasons for exclusion were that the trial was not randomised (11 references),[31-41] participants were not patients with type 2 diabetes or we could not separate data on patients with type 2 diabetes (four references),[42-45] or no predefined differences in glycaemic intervention target existed (16 references).[46-61] In addition, we excluded trials that assessed intensive glycaemic control as a part of an acute intervention (five references, three trials) or had concomitant targeting of several cardiovascular risk factors in the glycaemic intervention arm (six references, three trials).[16-21 62-66] Table 1⇓ gives a list of excluded trials.

We included 20 randomised trials, of which 14 exclusively dealt with glycaemic control in the usual care setting in patients without acute events at entry.[4-8 67-111] Thirteen of the trials were published in English and one in Russian.[85] The 14 included trials were described in 51 publications. We noted a discrepancy in the number of participants in two publications of one trial.[83 84] We used baseline data from the publication in the *Netherlands Journal of Medicine*.[83]

The trials included 28 614 participants, of whom 15 269 were randomised to intensive glycaemic control and 13 345 to conventional glycaemic control. Table 2⇓ shows key characteristics of the included trials, and table 3⇓ shows characteristics of trials' participants. The included trials were mainly done in North America and Europe. The number of randomised patients in each trial ranged from 20 to 11 140.[5 87] All 14 included trials were randomised clinical trials.

Two of the trials had a factorial design.[4 5] The UK Prospective Diabetes Study (UKPDS) had a substudy in which some of the participants were randomised to intensive blood pressure control versus conventional blood pressure control.[102] The University Group Diabetes Program (UGDP) randomised participants to five different treatment regimens.[88] We chose to report the "insulin variable" group as the intensive group and the "insulin standard" group as the conventional group.

The Kumamoto trial had a planned length of intervention of six years.[7] Only two of the included 110 participants changed their glycaemic intervention regimen after the predefined intervention period. The trial therefore continued on the initiative of the participants. We have reported all outcomes in this analysis after 10 years of follow-up, except for severe hypoglycaemia (reported after eight years of follow-up).[95]

Ten trials described how the diagnosis of type 2 diabetes was established (see web appendix 3).[4 6-8 82 83 87 88 92 106] Four trials did not describe how the diagnosis was established.[5 85 86 94] Most exclusion criteria consisted of liver disease, kidney disease, or other severe concurrent illnesses.

The anti-diabetes interventions used in the trials often included add-on regimens consisting of several oral drugs. If participants could not reach the glycaemic target with these regimens, insulin was started. The usual add-on regimen was identical in the intensive and conventional intervention groups of the single trials, except in the ADVANCE trial and the Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure (REMBO) trial, in which participants targeting intensive glucose control were given gliclazide.[5 85] Most trials allowed combination of oral anti-diabetes interventions and insulin. Two trials allowed only monotherapy (insulin) in both the intensive intervention group and conventional intervention group.[7 88]

The treatment targets for glycaemic control varied between trials in both the intensive treatment group and the conventional treatment group (table 2⇓). The ACCORD trial and the VADT had the lowest target for HbA_{1c} in the intensive intervention groups (both less than 6%).[4 6] Some of the trials did not predefine the glycaemic target in values of HbA_{1c} but used fasting glucose concentration as a target for treatment.[8 83 86 88 94]

Bias risk assessment

We divided the trials into those with a low risk of bias and those with a high risk of bias on the basis of assessment of sequence generation, concealment of allocation, and blinding according to the Cochrane Handbook risk of bias tool.[15] When we judged all three domains to have a low risk of bias, we designated the trial as having a low risk of bias. Table 4⇓ reports the bias risk assessments of the included trials. We considered six trials to have a low risk of bias.[4-6 8 88 92]

Clinical outcomes

All cause mortality

Twelve trials provided information on all cause mortality in a total of 28 359 participants (fig 2⇓). Meta-analysis showed no significant effect of intensive glycaemic control (relative risk 1.02, 95% confidence interval 0.91 to 1.13; P=0.74; 28 359 participants, 12 trials) compared with conventional glycaemic control. Heterogeneity was moderate (I^2=30%; P=0.18).

Subgroup analyses of the trials according to risk of bias, length of study, diagnostic criteria for type 2 diabetes, and source of funding showed no statistically significant differences between subgroups (that is, no significant interaction). Subgroup analyses for language of publication could not be done.

Trial sequential analysis showed that only 28 149 of the heterogeneity adjusted required information size of 46 677 patients were accrued. The cumulative Z curve did not cross any boundaries for benefit or harm (trial sequential analysis adjusted 95% confidence interval 0.88 to 1.18) (fig 3⇓). However, the cumulative Z curve crossed the futility boundaries, suggesting that a relative risk reduction of 10% or greater could be rejected.

Cardiovascular mortality

Twelve trials provided information on cardiovascular mortality and were included in the analyses. Web appendix 3 gives details of the definitions and reporting of cardiovascular mortality in the trials. The meta-analysis of the 12 trials did not show a statistically significant effect of the intervention on cardiovascular mortality (relative risk 1.11, 0.92 to 1.35; P=0.27; 28 359 participants, 12 trials). Figure 4⇓ shows the forest plot analysis of cardiovascular mortality. Heterogeneity was present (I^2=46%; P=0.08).

Subgroup analyses of the trials according to risk of bias, length of study, and source of funding showed no statistically significant differences between subgroups. Subgroup analyses for language of publication could not be done. Including only trials that described the diagnostic criteria for type 2 diabetes changed the effect estimate to a significant value in favour of conventional glycaemic control (relative risk 1.26, 1.08 to 1.46; P=0.002; 17 093 participants, 9 trials). The test for interaction showed a statistically significant difference between the two estimates (P=0.001).

Trial sequential analysis showed that barely 22% of the heterogeneity adjusted required information size to detect or reject a 10% relative risk reduction was actually accrued (trial sequential analysis adjusted 95% confidence interval 0.70 to 1.76). None of the boundaries for benefit, harm, or futility was crossed, showing too little evidence to allow us to conclude whether the intervention was beneficial, harmful, or without any effect on this outcome (fig 5⇓).

Non-fatal myocardial infarction

A total of 1237 non-fatal myocardial infarctions were recorded in 28 111 participants from eight trials. The details of how the diagnosis of myocardial infarction was defined varied among the trials (web appendix 3). The effect estimate showed a significant benefit of targeting intensive glycaemic control in a conventional meta-analysis (relative risk 0.85, 0.76 to 0.95; P=0.004; 28 111 participants, 8 trials). Heterogeneity was absent (I^2=0%; P=0.70). Figure 6⇓ shows the forest plot.

Subgroup analyses of the trials according to low risk of bias did not change the effect estimates. Meta-analysis of trials with a high risk of bias changed the effect estimate to a statistically non-significant value (relative risk 0.83, 0.23 to 2.98; P=0.78; 306 participants, 3 trials). A test for interaction showed no statistically significant difference in the effect estimates. We could not do the subgroup analyses for language of publication, duration of intervention, funding source, and diagnostic criteria owing to lack of data.

Trial sequential analysis showed a lack of sufficient evidence of a benefit of targeting intensive glycaemic control for the reduction of non-fatal myocardial infarction (trial sequential analysis adjusted 95% confidence interval 0.71 to 1.02). Only 27 958 (44%) of the heterogeneity adjusted required information size of 63 446 patients required to detect a 10% relative risk reduction for non-fatal myocardial infarction were accrued (fig 7⇓).

Composite outcome of microvascular complications

We assessed a composite outcome of microvascular complications, consisting of manifestation and progression of nephropathy, end stage renal disease, manifestation and progression of retinopathy, and retinal photocoagulation. We could extract usable data from three trials that had a predefined composite microvascular outcome.[4 5 8] The definitions of the reported composite outcome varied among the included trials (web appendix 2).

For the composite outcome of microvascular complications, we found a benefit of targeting intensive glycaemic control compared with targeting conventional glycaemic control (relative risk 0.88, 0.79 to 0.97; P=0.01; 25 600 participants, 3 trials) (fig 8⇓). The I^2 statistic was 45% (P=0.16). We found an absolute risk reduction of about 1% (risk difference −0.01, 95% confidence interval −0.02 to 0.00; P=0.006). However, trial sequential analysis did not show sufficient evidence for a 10%

relative risk reduction for the composite outcome of microvascular complications (trial sequential analysis adjusted 95% confidence interval 0.76 to 1.01) (fig 9⇓).

Retinopathy

Retinopathy was primarily reported with the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale (web appendix 3). The effect estimate showed significant benefit in favour of intensive glycaemic control (relative risk 0.80, 0.67 to 0.94; P=0.009; 10 793 participants, 7 trials) (fig 10⇓). Heterogeneity was substantial (I^2=59%; P=0.02). Trial sequential analysis showed a lack of sufficient evidence for a 10% or greater relative risk reduction in retinopathy (trial sequential analysis adjusted 95% confidence interval 0.54 to 1.17) (fig 11⇓).

Nephropathy

The definition of nephropathy varied among trials (web appendix 3). We found no statistically significant effect of intensive glycaemic control on nephropathy (relative risk 0.83, 0.64 to 1.06; P=0.13; 27 769 participants, 8 trials) (fig 12⇓). Heterogeneity was substantial (I^2=75%, P<0.001).

Severe hypoglycaemia

The definition of severe hypoglycaemia varied among trials (web appendix 3). The ACCORD trial reported the number of hypoglycaemic events in two ways—requiring any assistance and requiring medical assistance. We have reported the number requiring any assistance, as this definition accords best with the definition in the other included trials.[5] Five trials, besides the ACCORD trial, had the assistance of a third person as a part of their definition of serious hypoglycaemia.[5 7 8 80 109]

Meta-analysis of intensive versus conventional control showed a statistically significant estimate of effect on severe hypoglycaemia (relative risk 2.39, 1.71 to 3.34; P<0.001; 27 844 participants, 9 trials). Heterogeneity was substantial (I^2=73%, P=0.005) (fig 13⇓).

For the application of trial sequential analysis to severe hypoglycaemia, the protocol assumed an increase in relative risk of 30%, equivalent to a number needed to harm of 50, to construct the trial sequential monitoring boundaries. The cumulative Z curve crossed the trial sequential monitoring boundary for harm, indicating that sufficient evidence exists for a 30% increase in relative risk of severe hypoglycaemia when intensive glycaemic control is targeted (fig 14⇓).

Discussion

Our key finding is that whether the clinician is targeting an intensive or conventional glycaemic value does not seem to change the risk of all cause mortality or cardiovascular mortality. However, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction, microvascular complications (on the basis of a composite outcome), and retinopathy. The risk of nephropathy does not seem to change with the glycaemic target. The price of intensive glycaemic control is an increased risk of severe hypoglycaemia. However, among these conclusions, only that for hypoglycaemia seems to be based on a sufficient information size at this stage. A reduced risk of microvascular disease with intensive versus conventional glucose control has been found in several individual trials and is consistent with findings in patients with type 1 diabetes. However, our meta-analysis suggests that data on microvascular outcomes in patients with type 2 diabetes are still insufficient. Absence of evidence cannot be taken as evidence of absence, however, and an effect at the size of the point estimates found in our meta-analyses may eventually be shown when further trials are done.[112]

Strengths and limitations

This is the first and most comprehensive systematic review with meta-analyses of targeting intensive versus conventional glycaemic control in patients with type 2 diabetes that focuses on mortality and macrovascular as well as microvascular complications. The strengths of this review are a published protocol, a comprehensive search strategy, and rigid inclusion criteria for the randomised trials.[13]

We have included trials with large differences in the average duration of type 2 diabetes, length of the interventions, patients' age and risk of cardiovascular disease, and assessment of glycaemic control, as well as pre-specified targets of glycaemic control. We included trials irrespective of the language of publication and outcomes reported. Two authors independently extracted data and obtained data from or confirmed data with corresponding authors of the included trials.

Several meta-analyses have recently been published on this topic.[113-121] However, many of the meta-analyses claiming to assess the effect of targeting intensive glycaemic control versus conventional glycaemic control have included trials on the basis of achieved (that is, during follow-up) rather than targeted (that is, as randomly allocated) differences in glycaemic control.[113 115 116 120 121] For example, they included head to head comparisons of anti-diabetes drugs with a similar target of HbA_{1c} below 6.5% in both intervention groups, such as the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial of add-on pioglitazone versus placebo.[50] Boussageon et al applied the same approach in a recently published meta-analysis.[113] This chosen strategy of selection is potentially problematic, as the levels of glycaemic control targeted and achieved in a clinical trial represent different chosen variables. To some extent, the achieved glycaemic control represents observational data precluding inferences about causality with respect to its influence on other outcomes. In contrast, target levels, as part of the randomised intervention strategy, can support inferences about causality. Therefore, to optimally assess the clinical effect of aiming for intensive glycaemic control, which is probably the relevant question for the clinician as well as people trying to establish evidence based guidelines, trials need to be meta-analysed primarily on the basis of predefined differences in glycaemic targets.

The previous meta-analyses that dealt exclusively with trials in which the patients were randomised to different glycaemic targets included only four to six trials.[114 117-119] We included 14 trials, which is at least eight more trials than in the previous meta-analysis. All of the meta-analyses investigating the effect of targeting intensive glycaemic control have included the four major trials,[4 5 6 8] which contributed the greatest number of the participants in our analysis (27 391 of 28 614 participants). However, none of the previous meta-analyses included trials published in languages other than English or tested for the risk of having false positive P values or unrealistically narrow confidence intervals. Furthermore, none of the previous meta-analyses was done as a Cochrane systematic review.[15]

The weaknesses of our analyses and conclusions mirror the weaknesses in the individual included trials. Most importantly, only six of the 14 trials included were classified as trials with a low risk of bias. However, we found no statistically significant association between the risk of bias and the effect estimates in subgroup analyses. Analysing cardiovascular mortality by

diagnostic criteria suggested a negative effect estimate for intensive versus conventional glycaemic control in the trials with a clear description of the diagnosis. However, analysis of trials describing diagnostic criteria excluded the ADVANCE trial, which is the largest trial included in this systematic review (11 140 participants, about one third of the total information size). Excluding the ADVANCE trial, which reported a neutral effect of intensive versus conventional glycaemic control on cardiovascular mortality, substantially increased the weight of some other trials in the analysis. This applies in particular to the ACCORD trial, which included a marginally lower number of participants than did the ADVANCE trial. Unlike the ADVANCE trial, the ACCORD trial reported an increased risk of cardiovascular death for targeting intensive versus conventional glycaemic control. Apart from diagnostic criteria, subgroup analyses for other variables supported the conclusions from the primary overall analysis. Given the somewhat arbitrary criteria for type 2 diabetes, the progressive nature of the disease, and, perhaps in particular, the inclusion of trials in this analysis with different glycaemic targets and clinical outcomes, we find it most likely that the reduced cardiovascular mortality with conventional glycaemic control of the subgroup analysis according to diagnostic criteria represents a chance finding, possibly arising from confounding by the ACCORD trial.

We evaluated the strength of the available evidence by comprehensive analyses of the risk of sparse data and repetitive testing with trial sequential analysis. We did this for outcomes that showed significance in the cumulative meta-analysis, calculating heterogeneity adjusted required information sizes and applying trial sequential monitoring boundaries of benefit, harm, and futility.[26 27] The result of the trial sequential analysis rules out an effect of intensive glycaemic control on all cause mortality larger than a 10% reduction in relative risk. Even though the conventional meta-analyses of non-fatal myocardial infarction, composite microvascular complications, and retinopathy indicated a statistically significant effect estimate, trial sequential analysis showed that sufficient evidence was not yet available for a conclusion to be reached.

In addition to the differences between the glycaemic targets among the trials, the conventional treatment groups as well as the anti-diabetes interventions used to achieve the targets differed among the trials. Furthermore, the measurement used to assess the levels of glycaemic control varied among the included trials. Some trials defined the target glucose values by using blood glucose, providing only a "snapshot" of the overall glycaemic control. Most of the included trials expressed glycaemic control and glycaemic targets in values of HbA_{1c}, reflecting an average of the blood glucose concentration over several weeks. We were unable to evaluate the effects of the specific anti-diabetes drugs used to achieve the glycaemic targets. A wide range of glucose lowering interventions were used to achieve the glycaemic goal within and among the trials. In the ACCORD and the ADVANCE trials, a greater proportion of the participants randomised to intensive glycaemic control received rosiglitazone compared with the conventional treatment group.[4 5] We have not been able to quantify any drug specific effects on our outcomes that may counteract or contribute to both benefits and harms of glycaemic control. The most suitable way to answer the specific question of whether the target in itself affects outcomes important to patients would be to include only trials that used one blood glucose lowering drug exclusively to receive a predefined glycaemic target. However, such a design would seem to be inapplicable to clinical practice.

The participants in the included trials represented a diverse population with type 2 diabetes. The results of our review should be interpreted with this in mind. The diagnosis of type 2 diabetes varied among the trials, and some trials used a definition of type 2 diabetes that may have included participants with impaired glucose tolerance. Some of the trials included only participants with newly diagnosed type 2 diabetes, whereas others included patients with longer duration of type 2 diabetes. Participants' age, body mass index, glycaemic control, and duration of diabetes were in keeping with what might be expected in clinical practice. In spite of this, for several effects of the intervention on outcomes, we found no or only moderate heterogeneity. Furthermore, we found no significant subgroup differences when we stratified for the diagnostic criteria used for inclusion in the trials. Although we included a broad spectrum of patients with type 2 diabetes and, owing to potential selection bias—for instance, towards healthier and more motivated patients volunteering in a clinical trial compared with the background population of patients—saying how typical the participants in each clinical trial may be compared with the wider general population of patients with type 2 diabetes is difficult. On the other hand, the heterogeneity in this review might indeed reflect the well known heterogeneity in clinical practice.

The reporting of severe hypoglycaemia is problematic in several ways; first of all, the definitions of severe hypoglycaemia were diverse. Many of the trials included assistance from another person, without further specification. The grade of assistance from another person may vary from handing a juice to giving glucagon injections. In addition, the design of the included trials made blinding the participants impossible, which may in turn lead to reporting bias.[15]

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.[15]

Relation to other studies and reviews

The UGDP was the first "large scale," multicentre clinical trial on the topic. It did not find any differences in mortality and cardiovascular outcomes between targeting intensive or conventional glycaemic control with insulin.[88] The much larger UKPDS also failed to show a benefit on mortality or cardiovascular outcomes for targeting intensive glycaemic control with insulin or a sulfonylurea.[8] However, a small subgroup of 753 overweight patients randomly assigned to intensive glycaemic control with metformin showed a benefit of intensive glycaemic control.[100] Post hoc observational data from the UKPDS suggested that a 1% decrease in HbA_{1c} reduced the risk of non-fatal myocardial infarction by 14%.[1] A 10 year follow-up of the initial randomised groups in the UKPDS suggested long term beneficial effects of intensive glucose control on cardiovascular disease and mortality with both metformin and sulfonylurea-insulin regimens. Our analysis indicated a significant 15% reduction in relative risk of non-fatal myocardial infarction in favour of intensive glycaemic control. However, this was not confirmed when challenged for a 10% relative risk reduction in trial sequential analysis with adjustment for repetitive testing on accumulating and sparse data. A potential explanation for the magnitude of beneficial effects of lower glucose concentrations being more pronounced in observational studies than in randomised trials and prospective studies is the effects of confounding by indication in the observational studies.

Recently, two large trials attempted to answer the question of whether intensive glycaemic control is superior to conventional

glycaemic control.[4 5] Worries arose as the results from the ACCORD trial in 2008 showed increased all cause mortality and cardiovascular mortality with intensive glycaemic control compared with conventional glycaemic control. The increased mortality led to early termination of the ACCORD trial. On the other hand, the ACCORD trial showed a reduction in the risk of non-fatal myocardial infarction with intensive glycaemic control. The question remains why the ACCORD trial reported increased mortality but a reduced risk of non-fatal myocardial infarction. Recently, data from the follow-up period, after termination of the intensive glycaemic intervention arm, have been published and reported that the increased risk of mortality and reduced risk of non-fatal myocardial infarction have persisted.[122] Explanations for this finding have been sought by the authors of the ACCORD trial, but no firm evidence has been found.

Observational data from the UKPDS showed a 37% reduction in the risk of microvascular complications for each 1% decrease in HbA_{1c}.[1] The ADVANCE trial found a 14% relative risk reduction for major microvascular events when targeting intensive glycaemic control.[75] The UKPDS 33 showed a 25% risk reduction in microvascular outcomes when targeting intensive glycaemic control.[8] We found a 12% relative risk reduction for the composite microvascular outcome. We found a 20% relative risk reduction for retinopathy in favour of intensive glycaemic control. The absolute risk reduction was 3%.

The Kumamoto trial showed a pronounced reduction in the incidence of nephropathy in both the primary prevention cohort (11.5% *v* 43.5%) and the secondary intervention cohort (16% *v* 40%) when targeting intensive glycaemic control.[7] The ADVANCE trial showed a 21% relative risk reduction for nephropathy when targeting intensive glycaemic control, whereas this could not be shown in ACCORD.[5 74] We found no significant effect of glycaemic intervention on the risk of nephropathy.

Microvascular data from the ACCORD trial and the UKPDS indicate that the beneficial effects of intensive glycaemic control on microvascular disease take more than about five years to emerge or that the benefits on microvascular disease achieved by intensive glycaemic control are less pronounced for patients with advanced type 2 diabetes (ACCORD) than for patients with new onset of type 2 diabetes (UKPDS).[8 74] On the other hand, the meta-analysis of retinopathy indicated that patients with more advanced stages of type 2 diabetes (ACCORD, VADT) might benefit more from intensive glycaemic control than do patients newly diagnosed as having type 2 diabetes (UKPDS, UGDP).[6 8 74 91]

We identified severe hypoglycaemia as a serious adverse effect strongly associated with intensive glucose control, which seems to be in accordance with established knowledge and other meta-analyses.[114 116 117] We did not have access to trial data at the level of the patient, so we could not explore whether an association exists between severe hypoglycaemic events and the risk of sudden unexpected death.

In January 2010 the American Diabetes Association published a guideline recommending an HbA_{1c} goal of less than 7% to reduce microvascular complications.[10] Treatment targets of HbA_{1c} at 7% have been used in only three trials exclusively dealing with glycaemic control in usual care setting, and they are all of relatively small sample size, consisting in total of 234 participants.[7 82 85] Only one of these trials had a duration of more than one year.[7]

Conclusion

We found evidence to refute the suggestion that intensive compared with conventional glycaemic control reduces all cause mortality with a relative risk reduction of 10% or more. We found insufficient information to confirm or exclude a 10% relative risk reduction in cardiovascular mortality and non-fatal myocardial infarction with intensive glycaemic control. We found insufficient evidence for a reduction in risk of composite microvascular complications, retinopathy, and nephropathy. Conversely, we confirmed a 30% increase in relative risk of severe hypoglycaemia with intensive compared with conventional glycaemic control. Accordingly, treatment and choice of a glycaemic target for patients with type 2 diabetes need to take both harms and benefits into account.

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Contributors: BH 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. SSL developed the protocol, selected trials, and developed the final review. CG developed the protocol, selected trials, advised on statistical methods, and developed the final review. AV developed the protocol, selected trials, and developed the final review. TA developed the protocol, selected trials, extracted data, assessed risk of bias of trials, and developed the final review. CH selected trials, extracted data, assessed risk of bias of trials, analysed data, and developed the final review. JW developed the initial idea for the review, developed the protocol, selected trials, advised on statistical methods, analysed data, and developed the final review. All authors read and approved the final manuscript. BH and JW are the guarantors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that SSL, AV, and TA have reported equity in Novo Nordisk A/S; SSL and AV have received fees from Novo Nordisk A/S for speaking; TA is employed at Steno Diabetes Center, Gentofte, Denmark; AV and SSL were employed at Steno Diabetes Center at the time the review was written. Steno Diabetes Center is an academic institution owned by Novo Nordisk A/S. CH has been employed at Novo Nordisk after completion of the data extraction.

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What is already known on this topic

Patients with type 2 diabetes are at increased risk of macrovascular and microvascular disease

Uncertainty exists as to whether intensive glycaemic control reduces the risk of death, macrovascular disease, or microvascular disease

Only a few meta-analyses with a high risk of bias have estimated the effect of intensive glycaemic control on microvascular complications

What this study adds

Sufficient evidence exists for an absence of a 10% relative risk reduction in all cause mortality with intensive glycaemic control versus conventional glycaemic control in patients with type 2 diabetes

Insufficient evidence exists for a 10% relative risk reduction in cardiovascular mortality and non-fatal myocardial infarction

Insufficient evidence exists to support the conclusions that intensive glycaemic control prevents the occurrence of microvascular disease assessed as a composite outcome, retinopathy, or nephropathy

Sufficient evidence exists that intensive glycaemic control increases the risk of severe hypoglycaemia by 30% compared with conventional glycaemic control

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Tables

Table 1| Excluded trials

Trial	Reason for exclusion
ADOPT 2010[46]	No predefined differences in glycaemic target
Barbosa et al 1983[42]	Did not include participants with type 2 diabetes
BARI 2D 2009[47]	No predefined differences in glycaemic target
Barnett et al 2008[31]	Not a randomised clinical trial
Blaha et al 2009[43]	Patients with type 2 diabetes reported together with patients without diabetes
Brocco et al 2001[32]	Not a randomised clinical trial
Chan et al 2009[48]	No predefined differences in glycaemic target
Clark et al 1985[33]	Not a randomised clinical trial
Cleveringa et al 2010[49]	No predefined differences in glycaemic target
Corpus et al 2004[34]	Not a randomised clinical trial
DIGAMI 1996[45]	Patients with type 1 diabetes and type 2 diabetes reported together
DIGAMI 2 2005[19 65]	Intensive glycaemic control applied as a part of acute intervention
Du et al 2009[51]	No predefined differences in glycaemic target
Eastman et al 1997[35]	Not a randomised clinical trial
Eibl et al 2004[36]	Not a randomised clinical trial
Evans et al 1982[37]	Not a randomised clinical trial
Furnary et al 1999[38]	Not a randomised clinical trial
Guo et al 2008[17]	Intensive glycaemic control applied as part of multimodal intervention
Hanefeld et al 2010[52]	No predefined differences in glycaemic target
HEART 2D 2009[59]	Randomised into two groups targeting same HbA_{1c} with different strategies (basal *v* prandial)
Johansen et al 2007[54]	No predefined differences in glycaemic target
Joss et al 2002[55]	No predefined differences in glycaemic target
Lazar et al 2004[44]	Patients with type 1 diabetes and type 2 diabetes reported together
Leibowitz et al 2010[41]	Not a randomised clinical trial
Melidonis et al 2000[20]	Intensive glycaemic control applied as part of acute intervention
Menard et al 2005[56]	No predefined differences in glycaemic target
Olivarius et al 2001[57]	No predefined differences in glycaemic target
Piatt et al 2010[58]	No predefined differences in glycaemic target
PROactive et al 2005[50]	No predefined differences in glycaemic target
Retnakaran et al 2010[39]	Not a randomised clinical trial
Ryan et al 2004[40]	Not a randomised clinical trial
Shi et al 2010[60]	No predefined differences in glycaemic target
Stefanidis et al 2003[21 66]	Intensive glycaemic control applied as part of acute intervention
Steno 2 2008[16 62-64]	Intensive glycaemic control applied as part of multimodal intervention
UKPDS-44 1999[53]	No predefined differences in glycaemic target
Van Bruggen et al 2009[61]	No predefined differences in glycaemic target
Yang et al 2007[18]	Intensive glycaemic control applied as part of multimodal intervention

ADOPT=A Diabetes Outcome Progression Trial; BARI 2D=Bypass Angioplasty Revascularization Investigation 2 Diabetes; DIGAMI=Diabetes Insulin-Glucose in Acute Myocardial Infarction; HbA_{1c}=glycated haemoglobin A_{1c}; HEART 2D=Hyperglycaemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus; PROactive=PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS=United Kingdom Prospective Diabetes Study.

Table 2| **Key characteristics of included trials**

Trial	Location	Design	No of intensive/conventional (total) participants	Length of follow-up*	Intensive glycaemic control	Conventional glycaemic control
ACCORD 2008[4 67-74]	77 centres; USA and Canada	Randomised, 2×2 factorial design	5128/5123 (10 251)	3.5 years	HbA_{1c} <6%; fasting SMBG <5.6 mmol/L or 2 hour blood glucose <7.8 mmol/L	HbA_{1c} 7.0-7.9%; fasting SMBG >5.0 mmol/L
ADVANCE 2008[75-78]	215 centres; 20 countries	Randomised, factorial design	5571/5569 (11 140)	5.0 years	HbA_{1c} ≤6.5%	Glycaemic target of HbA_{1c} defined from local guidelines
Bagg et al 2001[79-82]	1 centre; New Zealand	Randomised	21/22 (43)	20 weeks	HbA_{1c} <7%; before meal capillary glucose 4-7 mmol/L; 2 hour blood glucose <10 mmol/L	Avoid symptoms of hyperglycaemia and fortnightly fasting capillary glucose test >17 mmol/L
Becker et al 2003[83 84]	1 centre; Netherlands	Randomised	106/108 (231)	22 months	Fasting capillary blood glucose <6.5 mmol/L	Fasting capillary blood glucose <8.5 mmol/L
IDA 2009[92 93]	2 centres; Sweden	Randomised	51/51 (102)	6 months and 3 weeks	HbA_{1c} <6.5%; fasting blood glucose 5-7 mmol/L; before meal <10 mmol/L	Standard treatment
Jaber et al 1996[94]	1 centre; USA	Randomised	23/22 (45)	4 months	Fasting blood glucose ≤6.6 mmol/L; 2 hour postprandial glucose <10 mmol/L, or to reach maximum daily dose of sulfonylurea	Not defined
Kumamoto 2000[7 95 96]	1 centre; Japan	Randomised	55/55 (110)	10 years	HbA_{1c} <7.0%; fasting blood glucose <140 mg/dL; 2 hour postprandial glucose <200 mg/dL; mean amplitude of glycaemic excursions <100 mg/dL	Fasting blood glucose close to <140 mg/dL without symptoms of hyperglycaemia or hypoglycaemia
Lu et al 2010[86]	1 centre; China	Randomised	21/20 (41)	12 weeks	Fasting blood glucose <6.1 mmol/L, postprandial 2 hour glucose <7.8 mmol/L	Fasting blood glucose <7.0 mmol/L; postprandial 2 hour glucose <10.0 mmol/L
REMBO 2008[85]	1 centre; Russia	Randomised	41/40 (81)	12 months	HbA_{1c} <7% in participants receiving sulfonylurea; HbA_{1c} <6.5% in participants receiving insulin	Not specified
Service et al 1983[87]	1 centre; USA	Randomised	10/10 (20)	1.75 years	HbA_{1c} to normal range, and to maintain 80 minute postprandial plasma glucose <8.3 mmol/L	Eliminate symptoms, but not to degree to reduce 80 minute postprandial plasma glucose below 150 mg/dL
UGDP 1978[88-91]	12 centres; USA	Randomised	204/210 (414)	12 years	Maintain blood glucose in normal range (defined as fasting blood glucose <110 mg/100 mL, blood glucose <210 mg/100 mL 1 hour after ingestion of 50 g glucose and 1 and 1.5 hours after morning insulin injection)	Minimise likelihood of hypoglycaemic reactions without reducing insulin dose to pharmacologically inactive amounts
UKPDS 1998[1 8 97-102]	23 centres, UK	Randomised (some participants randomised to blood pressure arm)	3071/1138 (4209)	UKPDS 33 10.0 years; UKPDS 34 10.7 years	Fasting blood glucose <6 mmol/L in insulin treated patients; pre-meal glucose 4-7 mmol/L	Fasting blood glucose <15 mmol/L without symptoms of hyperglycaemia
VA CSDM 1995[103-109]	5 centres; USA	Randomised	75/78 (153)	27 months	Maintain mean HbA_{1c} <7.5%; treatment adjusted with home blood glucose monitoring, aiming at fasting blood glucose 4.48-6.44 mmol/L and other pre-prandial levels ≤7.28 mmol/L	Avoid excessive hyperglycaemia or symptoms of excessive glucosuria, ketonuria, or hypoglycaemia (alert HbA_{1c} <12.9%)
VADT 2009[6 110 111]	20 centres; USA	Randomised	892/899 (1791)	5.6 years	HbA_{1c} ≤6%; goal for HbA_{1c} was absolute reduction of 1.5 percentage points in intensive therapy group, compared with conventional intervention group	Wellbeing, avoidance of deterioration of HbA_{1c}, keeping levels at 8-9%, and preventing symptoms of glycosuria, hypoglycaemia, and ketonuria

ACCORD=Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE=Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; HbA_{1c}=glycated haemoglobin A_{1c}; IDA=Insulin Diabetes Angioplasty; REMBO=Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; SMBG=self monitoring of blood glucose; UGDP=University Group Diabetes Program; UKPDS=United Kingdom Prospective Diabetes Study; VACSDM=Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus; VADT=Veterans Affairs Diabetes Trial.

Table 2 (continued)

Trial	Location	Design	No of intensive/conventional (total) participants	Length of follow-up*	Intensive glycaemic control	Conventional glycaemic control

*Mean or median.

Table 3| Key characteristics of participants

Trial	Age (years)*	Duration of disease at baseline (years)*	HbA_{1c} at baseline (%)*	Fasting blood glucose at baseline (mmol/L)*†	Previous cardiovascular disease, intensive/conventional (No)
ACCORD 2008[4 67-74]	62.2	10	8.3	9.8	1826/1783
ADVANCE 2008[75-78]	66.0	8.0	7.5	8.5	1794/1796
Bagg et al 2001[79-82]	55.9	6.9	10.7	13.5	2/2
Becker et al 2003[83 84]	63.3	3.3	NR	9.6	21/23
IDA 2009[92 93]	64.0	6.5	6.5	7.2	51/51
Jaber et al 1996[94]	62.4	6.5	11.9‡	12.0	NR
Kumamoto 2000[7 95 96]	49.6	8.6	9.2	9.2	0/0
Lu et al 2010[86]	59.5	8.2	9.0	9.3	NR
REMBO 2008[85]	64	5.5	7.2	6.6	41/40
Service et al 1983[87]	50.7	0.5	11.4	8.7	NR
UGDP 1978[88-91]	52.7§	Newly diagnosed	NR	7.9	7/16¶
UKPDS 1998[1 8 97-102]	53.2**	Newly diagnosed	7.1**	8.1**	77††
VA CSDM 1995[103-109]	60.1	7.8	9.4	11.9	31/27
VADT 2009[6 110 111]	60.4	11.5	9.4	10.9	355/368

ACCORD=Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE=Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; IDA=Insulin Diabetes Angioplasty; NR=not reported; REMBO=Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP=University Group Diabetes Program; UKPDS=United Kingdom Prospective Diabetes Study; VACSDM=Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus; VADT=Veterans Affairs Diabetes Trial.

*Mean or median.

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

‡Described as glycated haemoglobin.

§Age reported for all treatment groups together.

¶Previous cardiovascular disease reported as history of angina.

**Number for baseline characteristics taken from UKPDS 33.

††Number taken from meta-analysis by Turnbull et al.[114]

Table 4| Risk of bias assessments of included trials

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Free from other bias
ACCORD 2008[4 67-74]	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate
ADVANCE 2008[75-78]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Bagg et al 2001[79-82]	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate
Becker et al 2003[83 84]	Unclear	Unclear	Unclear	Unclear	Adequate	Adequate
IDA 2009[92 93]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Jaber et al 1996[94]	Unclear	Unclear	Unclear	Adequate	Adequate	Inadequate
Kumamoto 2000[7 95 96]	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate
Lu et al 2010[86]	Unclear	Unclear	Unclear	Unclear	Adequate	Adequate
REMBO 2008[85]	Unclear	Unclear	Unclear	Adequate	Adequate	Unclear
Service et al 1983[87]	Adequate	Unclear	Adequate	Adequate	Adequate	Adequate
UGDP 1978[88-91]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
UKPDS 1998[1 8 97-102]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
VA CSDM 1995[103-109]	Unclear	Unclear	Adequate	Adequate	Adequate	Inadequate
VADT 2009[6 110 111]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate

ACCORD=Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE=Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; IDA=Insulin Diabetes Angioplasty; REMBO=Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP=University Group Diabetes Program; UKPDS=United Kingdom Prospective Diabetes Study; VACSDM=Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus; VADT=Veterans Affairs Diabetes Trial.

Figures

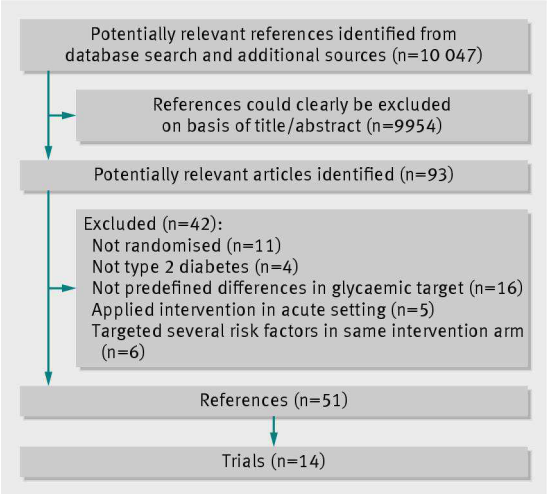

Fig 1 Flow diagram of identification of randomised trials for inclusion

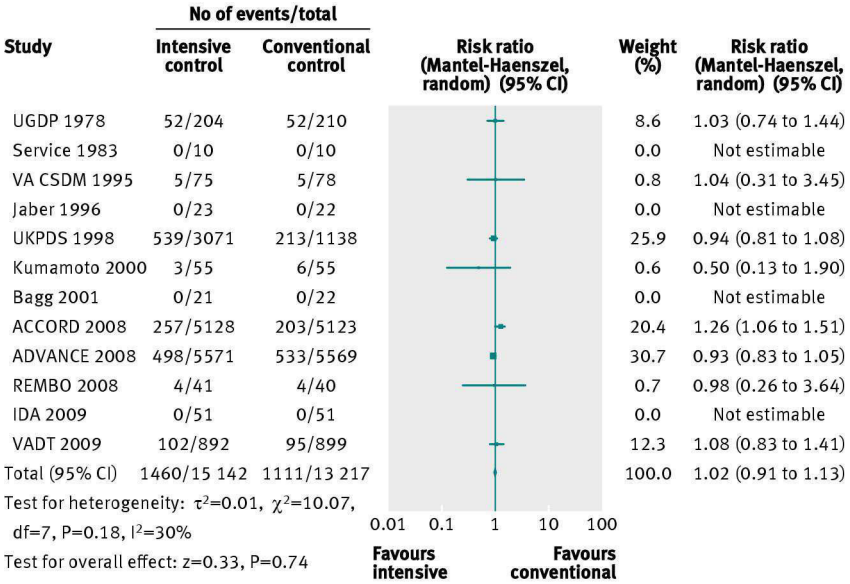

Fig 2 Forest plot for all cause mortality

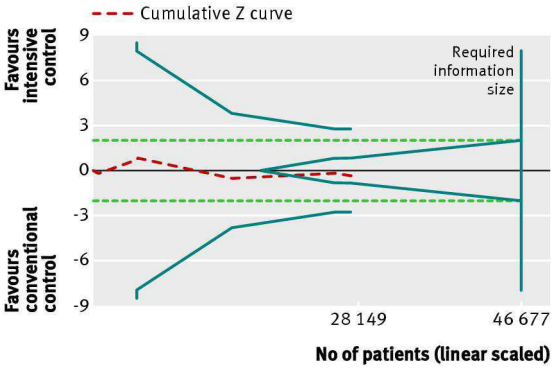

Fig 3 Trial sequential analysis of all cause mortality. Heterogeneity adjusted required information size of 46 677 participants calculated on basis of proportion of mortality of 8.4% in conventional glucose control group, relative risk reduction of 10%, α=5%, β=20%, and I^2=30%. Actually accrued No of participants was 28 149, 60% of required information size. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm, but boundaries for futility (blue inner wedge boundaries) are crossed. Horizontal dotted green lines illustrate traditional level of statistical significance (P=0.05)

Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
UGDP 1978	31/204	32/210		11.8	1.00 (0.63 to 1.57)
Service 1983	0/10	0/10		0.0	Not estimable
VA CSDM 1995	3/75	3/78		1.4	1.04 (0.22 to 4.99)
Jaber 1996	0/23	0/22		0.0	Not estimable
UKPDS 1998	301/3071	91/1138		23.9	1.23 (0.98 to 1.53)
Kumamoto 2000	1/55	1/55		0.5	1.00 (0.06 to 15.59)
Bagg 2001	0/21	0/22		0.0	Not estimable
ACCORD 2008	135/5128	94/5123		21.5	1.43 (1.11 to 1.86)
ADVANCE 2008	253/5571	289/5569		28.2	0.88 (0.74 to 1.03)
REMBO 2008	1/41	2/40		0.6	0.49 (0.05 to 5.17)
IDA 2009	0/51	0/51		0.0	Not estimable
VADT 2009	40/892	33/899		11.9	1.22 (0.78 to 1.92)
Total (95% CI)	765/15 142	545/13 217		100.0	1.11 (0.92 to 1.35)

Test for heterogeneity: τ^2=0.03, χ^2=12.86, df=7, P=0.08, I^2=46%

Test for overall effect: z=1.11, P=0.27

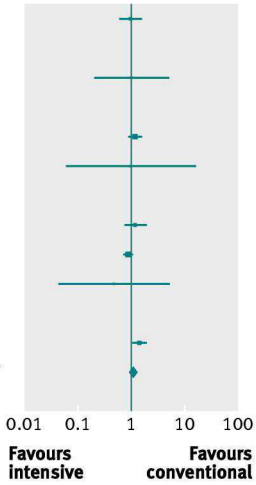

Fig 4 Forest plot for cardiovascular mortality

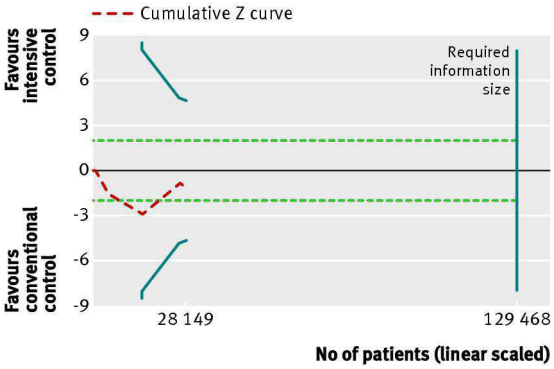

Fig 5 Trial sequential analysis for cardiovascular mortality. Heterogeneity adjusted required information size of 129 468 participants calculated on basis of proportion of cardiovascular mortality of 4.1% in conventional glucose control group, relative risk reduction of 10%, α=5%, a β=20%, and I^2=46%. Actually accrued No of participants was 28 149, 22% of required information size. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm. Horizontal dotted green lines illustrate the traditional level of statistical significance (P=0.05)

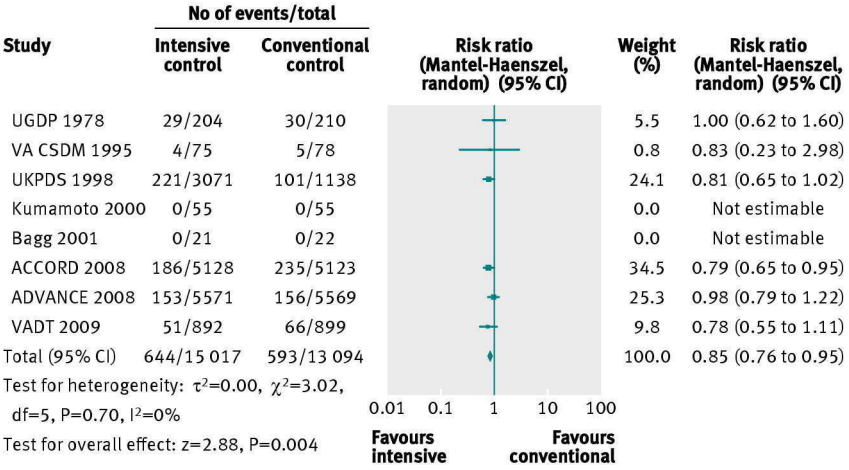

Fig 6 Forest plot for non-fatal myocardial infarction

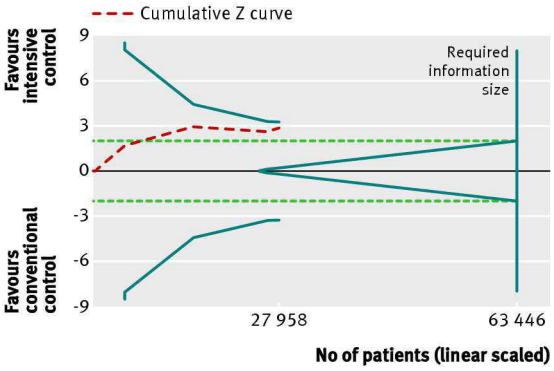

Fig 7 Trial sequential analysis for non-fatal myocardial infarction. Heterogeneity adjusted required information size of 63 446 participants calculated on basis of proportion of non-fatal myocardial infarction of 4.5% in conventional glucose control group, relative risk reduction of 10%, α=5%, β=20%, and I^2=0%. Actually accrued No of participants was 27 958, 44% of required information size. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm. Horizontal dotted green lines illustrate the traditional level of statistical significance (P=0.05)

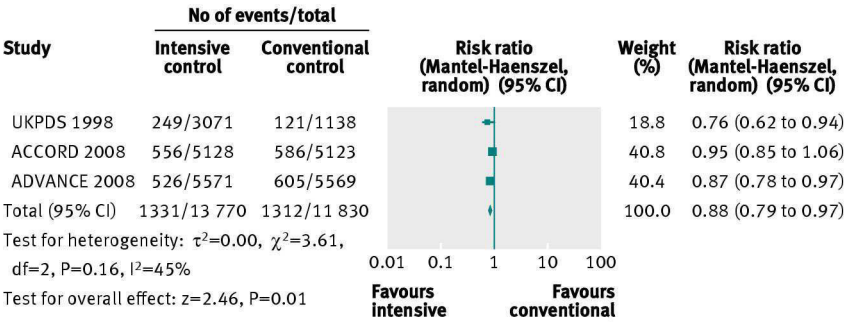

Fig 8 Forest plot for composite microvascular outcome

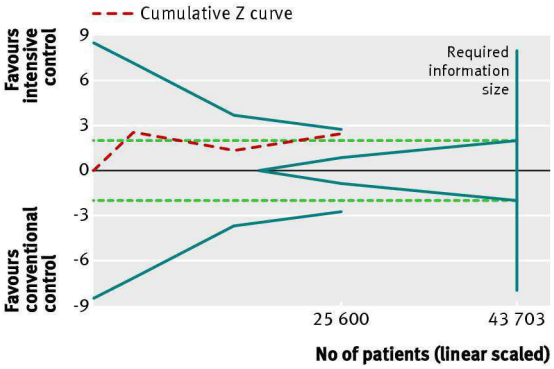

Fig 9 Trial sequential analysis for composite microvascular outcome. Heterogeneity corrected required information size of 43 703 participants calculated on basis of proportion of composite microvascular outcome of 11.1% in conventional glucose control group, relative risk reduction of 10%, α=5%, β=20%, and I^2=45%. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm. Horizontal dotted green lines illustrate the traditional level of statistical significance (P=0.05)

Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
UGDP 1978	51/204	53/210		13.1	0.99 (0.71 to 1.38)
VA CSDM 1995	21/75	22/78		7.9	0.99 (0.60 to 1.65)
UKPDS 1998	363/2729	172/1138		21.1	0.88 (0.74 to 1.04)
Kumamoto 2000	13/55	34/55		7.6	0.38 (0.23 to 0.64)
ACCORD 2008	81/1429	126/1427		15.9	0.64 (0.49 to 0.84)
ADVANCE 2008	88/791	99/811		15.9	0.91 (0.70 to 1.19)
VADT 2009	123/892	154/899		18.5	0.80 (0.65 to 1.00)
Total (95% CI)	740/6175	660/4618		100.0	0.80 (0.67 to 0.94)
Test for heterogeneity: τ^2=0.03, χ^2=14.58, df=6, P=0.02, I^2=59%					
Test for overall effect: z=2.63, P=0.009					

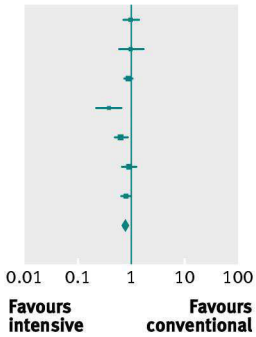

Fig 10 Forest plot for retinopathy

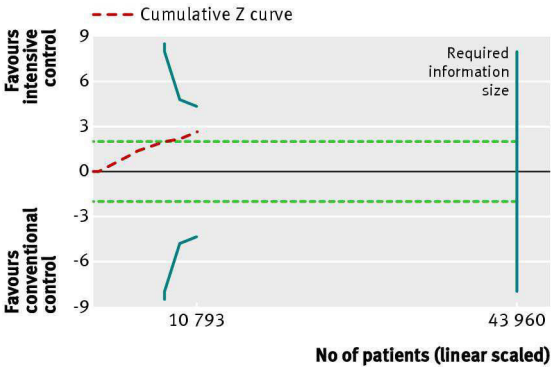

Fig 11 Trial sequential analysis for retinopathy. Heterogeneity corrected required information size of 43 960 participants calculated on basis of proportion of retinopathy of 14.3% in conventional glucose control group, relative risk reduction of 10%, α=5%, β=20%, and I^2=59%. Actually accrued No of participants was 10 793, 25% of required information size. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm. Horizontal dotted green lines illustrate the traditional level of statistical significance (P=0.05)

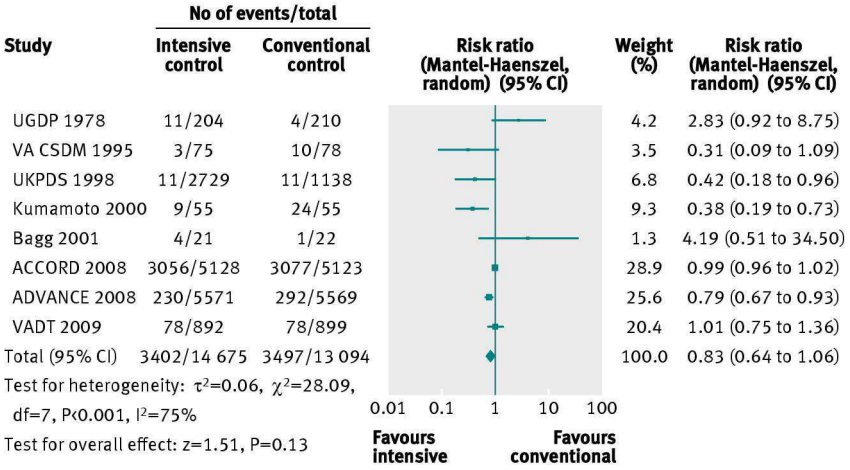

Fig 12 Forest plot for nephropathy

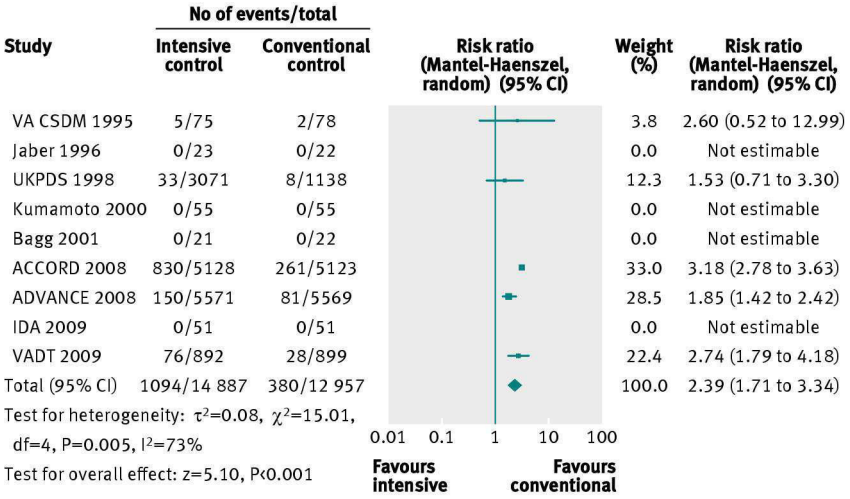

Fig 13 Forest plot for severe hypoglycaemia

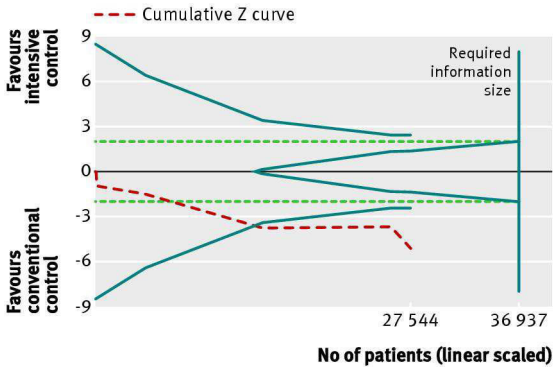

Fig 14 Trial sequential analysis for severe hypoglycaemia. Heterogeneity adjusted required information size of 36 937 participants calculated on basis of proportion of severe hypoglycaemia of 2.9% in conventional glucose control group, relative risk reduction of 30%, α=5%, β=20%, and I^2=73%. Cumulative Z curve crosses trial sequential monitoring boundary, showing sufficient evidence reached for 30% increase in relative risk with targeted intensive glycaemic control. Horizontal dotted green lines illustrate the traditional level of statistical significance (P=0.05)

Appendix 1. Search strategies

The Cochrane Library

1. MeSH descriptor Diabetes mellitus, type 2explode all trees
2. MeSH descriptor Insulin resistanceexplode all trees
3. ((impaired in All Text and glucosein All Text and toleranc* in All Text) or (glucosein All Text and intoleranc* in All Text) or (insulin*in All Text and resistanc* in All Text))
4. (obes* in All Text near/6 diabet*in All Text)
5. (MODY in All Text or NIDDMin All Text or TDM2 in All Text)
6. ((non in All Text and insulin*in All Text and depend* in All Text) or (noninsulin*in All Text and depend* in All Text) or (nonin All Text and insulindepend* in All Text) or noninsulindepend*in All Text)
7. (typ* in All Text and (2in All Text near/6 diabet* in All Text))
8. (typ* in All Text and (IIin All Text near/6 diabet* in All Text))
9. (non in All Text and (keto*in All Text near/6 diabet* in All Text))
10. (nonketo* in All Text near/6 diabet*in All Text)
11. (adult* in All Text near/6 diabet*in All Text)
12. (matur* in All Text near/6 diabet*in All Text)
13. (late in All Text near/6 diabet*in All Text)
14. (slow in All Text near/6 diabet*in All Text)
15. (stabl* in All Text near/6 diabet*in All Text)
16. (insulin* in All Text and (defic*in All Text near/6 diabet* in All Text)
17. (plurimetabolic in All Text and syndrom*in All Text)
18. (pluri in All Text and metabolicin All Text and syndrom* in All Text)
19. (#1 or #2 or #3or #4 or #5 or #6 or #7or #8 or #9 or #10)
20. (#11 or #12 or #13or #14 or #15 or #16 or #17or #18)
21. (#19 or #20)
22. MeSH descriptor Diabetes insipidusexplode all trees
23. (diabet* in All Text and insipidusin All Text)
24. (#22 or #23)
25. (#21 and not #24)
26. MeSH descriptor Blood glucoseexplode all trees
27. MeSH descriptor Hyperglycemiaexplode all trees
28. MeSH descriptor Hemoglobin A, glycosylatedexplode all trees
29. ((blood in All Text and glucos*in All Text) or hyperglycaemi* in All Text or hyperglycemi*in All Text or (haemoglobin* in All Text and Ain All Text) or (hemoglobin* in All Text and Ain All Text))
30. (HbA1C in All Text or (Hbin All Text and A in All Text) or (HbA in All Text and 1c in All Text) or HbA in All Text or A1Cs in All Text)
31. (glycosylated in All Text near/6 haemoglobin*in All Text)
32. (glycosylated in All Text near/6 hemoglobin*in All Text)
33. (glucos* in All Text near/3 management*in All Text)
34. (#26 or #27 or #28or #29 or #30 or #31 or #32or #33)
35. (#25 or #34)
36. (intensi* in All Text near/3 control*in All Text)
37. (intensi* in All Text near/3 therap*in All Text)
38. (intensi* in All Text near/3 treatment*in All Text)
39. (intensi* in All Text near/3 intervention*in All Text)
40. (intensi* in All Text near/3 management*in All Text)

41. (conventional* in All Text near/3 control*in All Text)
42. (conventional* in All Text near/3 therap*in All Text)
43. (conventional* in All Text near/3 treatment*in All Text)
44. (conventional* in All Text near/3 intervention*in All Text)
45. (conventional in All Text near/3 management*in All Text)
46. (regular in All Text near/3 control*in All Text)
47. (regular in All Text near/3 therap*in All Text)
48. (regular in All Text near/3 treatment*in All Text)
49. (regular in All Text near/3 intervention*in All Text)
50. (regular in All Text near/3 management*in All Text)
51. (usual in All Text near/3 control*in All Text)
52. (usual in All Text near/3 therap*in All Text)
53. (usual in All Text near/3 treatmentin All Text)
54. (usual in All Text near/3 intervention*in All Text)
55. (usual in All Text near/3 management*in All Text)
56. (routin* in All Text near/3 control*in All Text)
57. (routin* in All Text near/3 therap*in All Text)
58. (routin* in All Text near/3 treatment*in All Text)
59. (routin* in All Text near/3 intervention*in All Text)
60. (routin* in All Text near/3 management*in All Text)
61. (tight in All Text near/3 control*in All Text)
62. (tight in All Text near/3 therap*in All Text)
63. (tight in All Text near/3 treatment*in All Text)
64. (tight in All Text near/3 intervention*in All Text)
65. (tight in All Text near/3 management*in All Text)
66. (#36 or #37 or #38or #39 or #40 or #41 or #42or #43 or #44 or #45 or #46or #47 or #48 or #49 or #50or #51 or #52 or #53 or #54or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65)
67. (#35 and #66)

MEDLINE

1. exp Blood Glucose/
2. exp Hyperglycemia/
3. exp Hemoglobin A, Glycosylated/
4. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti.
5. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
6. (glycosylated adj6 h?emoglobin$).ab,ti.
7. (glucos$ adj3 management$).ab,ti.
8. or/1-7
9. exp Diabetes Mellitus, Type 2/
10. exp Diabetes Complications/
11. (MODY or NIDDM or T2DM).tw,ot.
12. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend).tw,ot.
13. ((typ$ 2 or typ$ II) adj3 diabet$).tw,ot.
14. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
15. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ab,ti.
16. or/9-15
17. exp Diabetes Insipidus/
18. diabet$ insipidus.tw,ot.

19. 17 or 18
20. 16 not 19
21. 8 or 20
22. ((intensi$ or conventional$ or regular or tight or usual or routin$ or or standard) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti.
23. 21 and 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi?ed.ab,ti.
27. placebo$.ab,ti.
28. drug therapy.fs.
29. randomly.ab,ti.
30. trial$.ab,ti.
31. group$.ab,ti.
32. or/24-31
33. Meta-analysis.pt.
34. exp Technology Assessment, Biomedical/
35. exp Meta-analysis/
36. exp Meta-analysis as topic/
37. hta.tw,ot.
38. (health technology adj6 assessment$).tw,ot.
39. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
40. ((review$ 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.
41. or/33-40
42. (comment or editorial or historical-article).pt.
43. 41 not 42
44. 32 or 43
45. 23 and 44
46. (animals not (animals and humans)).sh.
47. 45 not 46

EMBASE

1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. impaired glucose toleranc$.ab,ti,ot.
4. glucose intoleranc$.ab,ti,ot.
5. insulin$ resistanc$.ab,ti,ot.
6. (obes$ adj diabet$).ab,ti,ot.
7. (MODY or NIDDM or TDM2).ab,ti,ot.
8. (non insulin$ depend$ or noninsulin depend$ or noninsulin?depend$ or non insulin?depend$).ab,ti,ot.
9. ((typ$ 2 or typ$ II) adj diabet$).ab,ti,ot.
10. (diabet$ adj (typ$ 2 or typ$ II)).ab,ti,ot.
11. ((keto?resist$ or non?keto$) adj diabet$).ab,ti,ot.
12. ((adult$ or matur$ or late or slow or stabl$) adj diabet$).ab,ti,ot.
13. (insulin$ defic$ adj relativ$).ab,ti,ot.
14. pluri?metabolic$ syndrom$.ab,ti,ot.

15. or/1-14
16. exp Diabetes Insipidus/
17. diabet$ insipidus.ab,ti,ot.
18. 16 or 17
19. 15 not 18
20. exp Glucose Blood Level/
21. exp Hyperglycemia/
22. exp Glycosylated Hemoglobin/
23. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti,ot.
24. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
25. (glycosylated adj6 h?emoglobin$).ab,ti,ot.
26. (glucos$ adj3 management$).ab,ti,ot.
27. or/20-25
28. 19 or 27
29. ((intensiv$ or conventional$ or regular or tight or usual or routin$) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti,ot.
30. 28 and 29
31. Randomized Controlled Trial/
32. exp Controlled Clinical Trial/
33. randomi?ed.ab,ti.
34. placebo$.ab,ti.
35. exp Drug Therapy/
36. randomly.ab,ti.
37. trial$.ab,ti.
38. group$.ab,ti.
39. or/31-38
40. exp meta analysis/
41. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
42. ((review$ 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$)).ab,ti,ot.
43. exp Literature/
44. exp Biomedical Technology Assessment/
45. hta.tw,ot.
46. (health technology adj6 assessment$).tw,ot.
47. or/40-46
48. (comment or editorial or historical-article).pt.
49. 47 not 48
50. 39 or 49
51. 30 and 50
52. limit 51 to human

Science Citation Index Expanded

1. TS=(blood glucos* or glyc?emic* control or hyperglyc?emi* or h?emoglobin* A)
2. 2. TS=(HbA1C or Hb A or HbA 1c or HbA or A1Cs)
3. 3. TS=(glycosylated SAME h?emoglobin*)
4. 4. TS=(glucos* SAME management*)
5. 5. #4 OR #3 OR #2 OR #1
6. 6. TS=(MODY or NIDDM or T2DM)

7. 7. TS=(non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*)
8. 8. TS=(diabet* SAME (typ* 2 or typ* II))
9. 9. TS=(diabet* SAME (keto*resist* or non*keto*))
10. 10. TS=((onset SAME (late or adult* or matur* or slow or stabl*)) and diabet*)
11. 11. #10 OR #9 OR #8 OR #7 OR #6
12. 12. #11 NOT TS=(diabet* insipidus)
13. 13. #12 OR #5
14. 14. TS=((intensi* or tight or conventional* or regular or usual or routin* or standard) SAME (control* or therap* or treatment* or intervention* or management*))
15. 15. #14 AND #13
16. 16. TS=(random* OR blind* OR placebo* OR group*)
17. 17. TS=(animal* NOT (animal* AND human*))
18. 18. #16 NOT #17
19. 19. #18 AND #15

LILAC

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

CINAHL

1. MM “Blood Glucose”
2. MM “Glycemic Control”
3. MM “Hyperglycemia+”
4. MM “Hemoglobin A, Glycosylated”
5. TI (blood glucos* OR hyperglyc?emi* OR h?emoglobin A) or AB (blood glucos* OR hyperglyc?emi* OR h?emoglobin A)
6. TI (HbA1C or Hb A or HbA 1c or HbA or A1Cs) or AB (HbA1C or Hb A or HbA 1c or HbA or A1Cs)
7. TI glycosylated N6 h?emoglobin* or AB glycosylated N6 h?emoglobin*
8. TI glucos* N3 management* or AB glucos* N3 management*
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. MM “Diabetes Mellitus, Non-Insulin-Dependent”
11. TX Diabetes Complications
12. TX MODY or NIDDM or T2DM
13. TX non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend
14. TX diabet* AND (typ* 2 or typ* II)
15. TX diabet* AND (keto*resist* or non*keto*)
16. TI (onset AND (late or adult* or matur* or slow or stabl*)) and TI diabet*
17. AB (onset N3 (late or adult* or matur* or slow or stabl*)) and AB diabet*
18. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. MM “Diabetes Insipidus”
20. TX diabet* insipidus
21. #19 or #20

22. #18 NOT #21
23. #9 or #22
24. TI (control* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (control* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
25. TI (therap* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (therap* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
26. TI (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
27. TI (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
28. TI (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
29. #24 or #25 or #26 or #27 or #28
30. #23 and #29
31. TX random* OR blind* OR placebo* OR group*
32. TX animal* NOT (animal* AND human*)
33. #31 NOT #32
34. #30 and #33

Appendix 2. Description of bias assessment

Risk of bias components based on the Cochrane risk of bias tool classification:

Sequence generation

- Low risk of bias, if the allocation sequence was generated by a computer or a random number table or similar.
- Uncertain risk of bias, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- High risk of bias, if a system involving dates, names, or admittance number was used for the allocation of patients (quasi-randomised). Such trials were not found, but would have been excluded.

Allocation concealment

- Low risk of bias, if the allocation of patients involved a central independent unit, on-site locked computer, or consecutively numbered sealed envelopes.
- Uncertain risk of bias, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- High risk of bias, if the allocation sequence was known to the investigators, who assigned participants or if the study was quasi-randomised. Such trials were not found, but would have been excluded.

Blinding

It was not possible to blind the health-care provider and patients in the treatment groups. Blinding was therefore considered adequate if the outcome assessors were blinded, although we were aware of the fact that even such trials may be subject to bias.

- Low risk of bias, if the outcome assessors were blinded and the method of blinding was described.
- Uncertain risk of bias, if the outcome assessors were blinded and the method of blinding was not described.
- High risk of bias, if the outcome assessors were not blinded.

Incomplete data outcomes

- Low risk of bias, if it was clearly described if there were any post-randomisation drop-outs or withdrawals and the reason for these drop-outs was described.
- Uncertain risk of bias, if it was not clear whether there were any drop-outs or withdrawals or if the reasons for these drop-outs were not clear.
- High risk of bias, if the reasons for missing data were likely to be related to true outcomes; (1) ‘as-treated’ analysis were performed, (2) potentially inappropriate application of simple imputation, (3) potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Low risk of bias, if all the pre-defined (primary and secondary) outcomes mentioned in the trial´s protocol or in the design article were reported and the reporting had been done in the pre-specified way.

- Uncertain risk of bias, if there was insufficient information to assess whether the risk of selective outcome reporting was present.
- High risk of bias, if not all the pre-specified outcomes were reported or if the primary outcomes were changed or if some of the important outcomes were incompletely reported.

Other Bias

Sponsor bias

- Low risk of bias, if the trial was unfunded or was not funded by an instrument or equipment or drug manufacturer.
- Uncertain risk of bias, if the source of funding was not clear.
- High risk of bias, if the trial was funded by an instrument or equipment or drug manufacturer.

Academic bias

- Low risk of bias, if the author of the trial had not conducted previous trials addressing the same interventions.
- Uncertain risk of bias, if it was not clear if the author had conducted previous trials addressing the same interventions.
- High risk of bias, if the author of the trial had conducted previous trials addressing the same interventions.

Besides investigating each bias domain, we also evaluated the overall risk of bias. When sequence generation, allocation concealment, and blinding were judged adequately, the trial was classified as a trial with low-risk of bias.

Appendix 3. Definitions or Reporting in Trials

Trial	Type 2 diabetes	Cardiovascular Mortality	Non-fatal myocardial infarction	Severe hypoglycaemmia
ACCORD[a], 2008[4;67-74]	American Diabetes Association criteria	Unexpected death and death due to myocardial infarction, congestive heart failure, after invasive cardiovascular interventions, arrhythmia, stroke, cardiovascular causes after non-cardiovascular surgery, other cardiovascular diseases (eg, pulmonary emboli or abdominal aortic rupture) and presumed cardiovascular death (every component described in details in study protocol p 87-88)	Prolonged ischemic symptoms > 20 minutes and or raised cardiac enzymes (Troponin T or I and/or serum creatine kinase-MB), included Q-wave myocardial infarction, non Q-wave myocardial infarction, silent myocardial infarction, probable non Q-wave myocardial infarction, myocardial infarction after coronary bypass graft surgery, myocardial infarction after cardiovascular invasive interventions and myocardial infarction after non-cardiovascular surgery	Severe hypoglycaemia is defined as hypoglycaemia with documented blood glucose < 2.8 mmol/L (50 mg/dL) or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require the assistance of medical or paramedical personnel
ADVANCE[b], 2008[75-78;123]	Type 2 diabetes	Death from cardiovascular causes	Non-fatal myocardial infarction	Patients with transient dysfunction of the central nervous system who were unable to treat themselves (requiring help from another person) were considered to have severe hypoglycaemia
Bagg et al, 2001[79-82]	1) Age at diagnosis > 35 years; 2) no episodes of ketoacidosis in the past; 3) insulin independence for more than 12 months or fasting plasma C-peptide > 0.21 pmol/L if duration of disease less than 12	ND[c]	Non-fatal myocardial infarction	Severe hypoglycaemia was defined as the presence of impaired consciousness requiring the help of another person, coma or seizure, and the presence of low blood glucose

	months			
Becker et al, 2003[83;84]	World Health Organisation criteria	ND	ND	ND
IDA[d], 2009[92;93]	All patients had previously known diabetes accepted as type 2 if the patient was > 35 years of age at onset of disease and without any demand of insulin during at least two years thereafter	ND	ND	Severe hypoglycaemic episodes
Jaber et al, 1996[94]	Type 2 diabetes	ND	ND	ND
Kumamoto, 2000[7;95;96]	All of the patients were diagnosed as being affected with type 2 diabetes mellitus by their characteristics of no history of ketoacidosis, negative islet cell antibody and daily urinary C-peptide excretion more than 20 pg	Sudden death (probably myocardial infarction) and death due to cerebral vascular disease	Non-fatal myocardial infarction	Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the patient required the assistance of another person and which was associated with a blood glucose level < 50 mg/dL and a prompt recovery after intravenous glucose loading
Lu et al, 2010[86]	Type 2 diabetes	ND	ND	ND
REMBO[e], 2008[85]	Type 2 diabetes	Stroke, heart failure	ND	ND
Service et al, 1983[87]	Participants were stratified as having type 1 or type 2 diabetes by basal and postprandial C-peptide values of less than 1 (type 1 diabetes mellitus) and more than 1	ND	ND	ND

	(type 2 diabetes mellitus) ng/ml			
UGDP[†], 1978[88-91]	The results of the glucose tolerance test provided the primary basis for the diagnosis of diabetes for patients admitted to the study. A sum of four glucose values from glucose tolerance test had to be equal or greater than 500 mg/100 mL	Death due to: Sudden death; defined as a death occurring within three hours of the onset of symptoms in an otherwise clinically stable patient and in a manner consistent with a cardiovascular event. Myocardial infarction; this diagnosis was made from electrocardiogram changes and changes in serum enzymes observed during the terminal course of illness, or if the events leading to death were clinically compatible with the diagnosis and autopsy findings provided evidence that an myocardial infarction was the principal cause of death. Other heart disease, included deaths due to congestive heart failure, valvular heart disease, atherosclerotic heart disease and hypertensive heart disease. Extracardiac vascular disease: cerebral vascular disease, pulmonary embolism and peripheral vascular	Patients hospitalised with a diagnosis of non-fatal myocardial infarction or changes from a less severe finding for Q/QS and T patterns on the baseline electrocardiogram to a more severe finding for these abnormalities on a follow-up electrocardiogram	ND
UKPDS[g],	Main criterion	Fatal myocardial	World Health Organisation	Hypoglycaemia

1998[1;8;97-102]	for type 2 diabetes mellitus was fasting plasma glucose > 6 mmol/L on two mornings 1-3 weeks apart	infarction, fatal stroke, death from peripheral vascular disease and sudden death	clinical criteria with associated electrocardiogram/enzyme changes or new pathological Q wave (ICD[h] 9 Code 410)	requiring third-party help or medical intervention
VA CSDM[i], 1995[103-109]	Fasting plasma C-peptide > 0.21 pmol/L	Cardiovascular death is classified as sudden death, coronary heart disease, cerebrovascular attack, or other cardiovascular causes (pulmonary embolism, cardiomyopathy, etc)	Myocardial infarctions are classified by the CER-Lab using the Minnesota code. Patients with suspected acute myocardial infarction, treated with thrombolytic therapy or with acute coronary angioplasty (within 24 hour of the onset of symptoms), who do not meet the electrocardiogram criteria, also are counted	Coma, seizure, or impaired consciousness requiring assistance
VADT[j], 2009[6;110;111]	Fasting plasma C-peptide > 0.21 pgrams per cc	In appendix listed as death caused by: Myocardial infarction, congestive heart failure, coronary revascularisation, stroke, cerebral revascularisation, complications of occlusions, peripheral revascularisation, sudden death and pulmonary embolism	Q wave in 2 consecutive leads or a new R-wave in V1 of at least 50% accompanied with motion abnormality in MUGA[k] scan or echocardiography; or ST depression over 1 mm or new T-wave in 2 consecutive leads with injury changes in creatine phosphokinase over 2 times and elevated creatine kinase-MB or troponins	Defined with as a serious adverse event ,i.e., life threatening, death, hospitalisation, disability or incapacity, cancer or other important event requiring medical intervention/treatment

[a]ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, [b]ADVANCE: Action in Diabetes and Vascular disease – PreterAx and DiamicroN MR Controlled Evaluation, [c]ND:Not defined, [d]IDA:Insulin Diabetes Angioplasty, [e]REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, [f]UGDP: University Group Diabetes Program, [g]UKPDS: United Kingdom Prospective Diabetes Study, [h]ICD: International Classification of Diseases, [i]VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, [j]VADT: Veterans Affairs Diabetes Trial, [k]MUGA scan: multiple-gated acquisition scan

Trial	Microvascular complications (composite outcome)	Retinopathy	Nephropathy
ACCORD[a], 2008[4;67-74]	Fatal or non-fatal renal failure (initiation of dialysis or end-stage renal disease, renal transplantation, or rise of serum creatinine > 291.7 µmol/L) or retinal photocoagulation or vitrectomy for diabetic retinopathy	Progression of diabetic retinopathy of at least 3 stages the Early Treatment of Diabetic Retinopathy Study scale	Composite nephropathy outcome: Doubling of serum creatinine or a 20 mL/min/1.73m^2 or decrease in estimated glomerular filtration rate, development of macroalbuminuria (albumin/creatinine ratio > 300 mg albumin per gram creatinine in random urine sample), development of renal failure (renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dL in the absence of an acute reversible cause)
ADVANCE[b], 2008[75-78;123]	New or worsening nephropathy or retinopathy (development of proliferative retinopathy, macular edema or diabetes-related blindness, or the use of retinal photocoagulation therapy)	Progression of ≥2 steps in Early Treatment of Diabetic Retinopathy Study classification with laser coagulation therapy during follow-up as the final step in Early Treatment of Diabetic Retinopathy Study classification, including both incidence and progression of retinopathy	Development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300 µg of albumin per milligram of creatinine (33.9 mg per millimole), or doubling of the serum creatinine level to at least 200 µmol/L, the need for renal-replacement therapy, or death due to renal disease
Bagg et al, 2001[79-82]	Not defined	Not defined	Macroalbuminuria
Becker et al, 2003[83;84]	Not defined	Not defined	Not defined
IDA[c], 2009[92;93]	Not defined	Not defined	Not defined
Jaber et al, 1996[94]	Not defined	Not defined	Not defined
Kumamoto, 2000[7;95;96]	Not defined	The degree of retinopathy for each patient was determined by the two eye examiners using the modified Early Treatment of Diabetic Retinopathy Study classification with a scale of 19 stages. The development and progression of retinopathy were	The patients with nephropathy were divided into three stages depending on their urinary albumin excretion: normoalbuminuria (< 30 mg/24 hour), microalbuminuria (30-300 mg/24 hour), or albuminuria (> 300 mg/24 hour). Reported for the primary prevention population as

		defined as a change of at least two steps up from stage 1 in the primary prevention population and as a change of two or more steps up from stages 2 to 5 in the secondary intervention population	participants developing nephropathy. Reported for the secondary intervention population as participants progressing to nephropathy
Lu et al, 2010[86]	Not defined	Not defined	World Health Organization 1999 criteria
REMBO[d], 2008[85]	Not defined	Not defined	Not defined
Service et al, 1983[87]	Not defined	Not defined	Not defined
UGDP[e], 1975[88-91]	Not defined	Mild retinal abnormalities: hard exudates, soft exudates, and/or haemorrhages or microaneurysms	Urine protein ≥ 1 gm/L.
UKPDS[f], 1998[1;8;97-102]	Retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure	Retinopathy was defined as one microaneurysm or more in one eye or worse retinopathy, and progression of retinopathy as a two-step change in Early Treatment of Diabetic Retinopathy Study grade	Two-fold plasma-creatinine increase (ICD 9: 250.3 and 585 to 586)
VA CSDM[g], 1995[103-109]	Not defined	Seven-field fundus photograph and ophthalmological examination The first two photographic end points is the presence of at least 3 counts of microaneurysms for the two eyes, and the second is the worsening of retinopathy as defined by a progression of two or more levels in the final Early Treatment of Diabetic Retinopathy Study	Overt nephropathy was defined as an albumin:creatinine ratio > 0.30

		scale	
VADT[h], 2009[6;110;111]	Retinopathy, nephropathy, and neuropathy	The 23-point Early Treatment Diabetic Retinopathy Study grading scale was used to define progression to new proliferative diabetic retinopathy. The progression of retinopathy was defined as a 2-point increase on the scale	Severe nephropathy was defined as a doubling of the serum creatinine level, a creatinine level of more than 3 mg per deciliter (265 µmol/L), or a glomerular filtration rate of less than 15 ml per minute

[a]ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, [b]ADVANCE: Action in Diabetes and Vascular disease – PreterAx and DiamicroN MR Controlled Evaluation, [c]ND:Not defined, [d]IDA:Insulin Diabetes Angioplasty, [e]REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, [f]UGDP: University Group Diabetes Program, [g]UKPDS: United Kingdom Prospective Diabetes Study, [h]ICD: International Classification of Diseases, [i]VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, [j]VADT: Veterans Affairs Diabetes Trial,

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CORRECTIONS

Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

In the final stages of production, the authors of this paper, Bianca Hemmingsen and colleagues, made some late changes to data in the 14 figures, resulting in some errors in the published article (*BMJ* 2011;343:d6898, doi:10.1136/bmj.d6898). Additionally, after publication they also noticed some further errors. In the abstract and results section, the P value for retinopathy should be 0.008 [rather than 0.009] and the number of participants should be 10 070 [not 10 793]. The trial sequential analysis adjusted 95% confidence interval for retinopathy should be 0.55 to 1.15 [not 0.54 to 1.17]. Figure 10⇓ and figure 11⇓ have been corrected; and in the legend to fig 11, the heterogeneity adjusted required information size is 40 021 [not 43 960] participants calculated on the basis of proportion of retinopathy of 15.5% [not 14.3%] in the conventional glucose control group, and the number of participants is as above. In table 2, the conventional glycaemic control column for Jaber et al 1996 and REMBO 2008 should read “Standard treatment” [rather than “Not specified”]. Table 4⇓ contained incorrect information for selective outcome reporting bias and had been corrected. Finally, in appendix 3 of the webextra (original re-posted here), the retinopathy outcome for UGDP 1975 should be “Fundus abnormalities excluding exudates.”

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Extra material supplied by the author (see http://www.bmj.com/content/344/bmj.d8277?tab=related#webextra)

Web extra file, as originally published

Table

Table 4 (Corrected)| Risk of bias assessments of included trials

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Free from other bias
ACCORD 2008[4 67-74]	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate
ADVANCE 2008[75-78]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Bagg et al 2001[79-82]	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate
Becker et al 2003[83 84]	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate
IDA 2009[92 93]	Adequate	Adequate	Adequate	Adequate	Unclear	Inadequate
Jaber et al 1996[94]	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate
Kumamoto 2000[7 95 96]	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate
Lu et al 2010[86]	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate
REMBO 2008[85]	Unclear	Unclear	Unclear	Adequate	Unclear	Unclear
Service et al 1983[87]	Adequate	Unclear	Adequate	Adequate	Unclear	Adequate
UGDP 1978[88-91]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
UKPDS 1998[1 8 97-102]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
VA CSDM 1995[103-109]	Unclear	Unclear	Adequate	Adequate	Adequate	Inadequate
VADT 2009[6 110 111]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate

ACCORD=Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE=Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; IDA=Insulin Diabetes Angioplasty; REMBO=Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP=University Group Diabetes Program; UKPDS=United Kingdom Prospective Diabetes Study; VACSDM=Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus; VADT=Veterans Affairs Diabetes Trial.

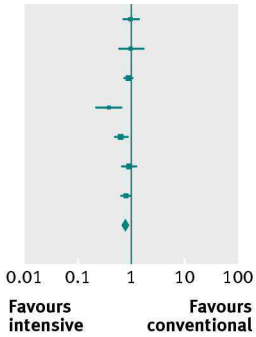
Figures

Corrected Figure 10

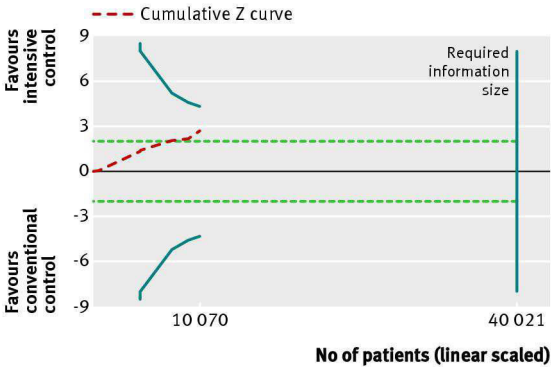
Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
UGDP 1978	51/204	53/210		13.0	0.99 (0.71 to 1.38)
VA CSDM 1995	21/75	22/78		7.8	0.99 (0.60 to 1.65)
UKPDS 1998	363/2729	172/1138		21.0	0.88 (0.74 to 1.04)
Kumamoto 2000	13/55	34/55		7.5	0.38 (0.23 to 0.64)
ACCORD 2008	81/1429	126/1427		15.8	0.64 (0.49 to 0.84)
ADVANCE 2008	88/791	99/811		15.8	0.91 (0.70 to 1.19)
VADT 2009	123/534	154/534		19.1	0.80 (0.65 to 0.98)
Total (95% CI)	740/5817	660/4253		100.0	0.80 (0.67 to 0.94)

Test for heterogeneity: τ^2=0.03, χ^2=14.61, df=6, P=0.02, I^2=59%

Test for overall effect: z=2.67, P=0.008



Corrected Figure 11



Sulphonylurea monotherapy for patients with type 2 diabetes mellitus (Review)

Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, Sonne DP, Lundstrøm LH, Almdal T

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[Intervention Review]

Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

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ABSTRACT

Background

Type 2 diabetes mellitus (T2DM) is a growing health problem worldwide. Whether sulphonylureas show better, equal or worse therapeutic effects in comparison with other antidiabetic interventions for patients with T2DM remains controversial.

Objectives

To assess the effects of sulphonylurea monotherapy versus placebo, no intervention or other antidiabetic interventions for patients with T2DM.

Search methods

We searched publications in *The Cochrane Library,* MEDLINE, EMBASE, Science Citation Index Expanded, LILACS and CINAHL (all until August 2011) to obtain trials fulfilling the inclusion criteria for our review.

Selection criteria

We included clinical trials that randomised patients 18 years old or more with T2DM to sulphonylurea monotherapy with a duration of 24 weeks or more.

Data collection and analysis

Two authors independently assessed the risk of bias. The primary outcomes were all-cause and cardiovascular mortality. Secondary outcomes were other patient-important outcomes and metabolic variables. Where possible, we used risk ratios (RR) with 95% confidence intervals (95% CI) to analyse the treatment effect of dichotomous outcomes. We used mean differences with 95% CI to analyse the treatment effect of continuous outcomes. We evaluated the risk of bias. We conducted trial sequential analyses to assess whether firm evidence could be established for a 10% relative risk reduction (RRR) between intervention groups.

Main results

We included 72 randomised clinical trials (RCTs) with 22,589 participants; 9707 participants randomised to sulphonylureas versus 12,805 participants randomised to control interventions. The duration of the interventions varied from 24 weeks to 10.7 years. We judged none of the included trials as low risk of bias for all bias domains. Patient-important outcomes were seldom reported.

First-generation sulphonylureas (FGS) versus placebo or insulin did not show statistical significance for all-cause mortality (versus placebo: RR 1.46, 95% CI 0.87 to 2.45; P = 0.15; 2 trials; 553 participants; high risk of bias (HRB); versus insulin: RR 1.18, 95% CI 0.88 to 1.59; P = 0.26; 2 trials; 1944 participants; HRB). FGS versus placebo showed statistical significance for cardiovascular mortality in favour of placebo (RR 2.63, 95% CI 1.32 to 5.22; P = 0.006; 2 trials; 553 participants; HRB). FGS versus insulin did not show statistical significance for cardiovascular mortality (RR 1.36, 95% CI 0.68 to 2.71; P = 0.39; 2 trials; 1944 participants; HRB). FGS versus alpha-glucosidase inhibitors showed statistical significance in favour of FGS for adverse events (RR 0.63, 95% CI 0.52 to 0.76; P = 0.01; 2 trials; 246 participants; HRB) and for drop-outs due to adverse events (RR 0.28, 95% CI 0.12 to 0.67; P = 0.004; 2 trials; 246 participants; HRB).

Second-generation sulphonylureas (SGS) versus metformin (RR 0.98, 95% CI 0.61 to 1.58; P = 0.68; 6 trials; 3528 participants; HRB), thiazolidinediones (RR 0.92, 95% CI 0.60 to 1.41; P = 0.70; 7 trials; 4955 participants; HRB), insulin (RR 0.96, 95% CI 0.79 to 1.18; P = 0.72; 4 trials; 1642 participants; HRB), meglitinides (RR 1.44, 95% CI 0.47 to 4.42; P = 0.52; 7 trials; 2038 participants; HRB), or incretin-based interventions (RR 1.39, 95% CI 0.52 to 3.68; P = 0.51; 2 trials; 1503 participants; HRB) showed no statistically significant effects regarding all-cause mortality in a random-effects model. SGS versus metformin (RR 1.47; 95% CI 0.54 to 4.01; P = 0.45; 6 trials; 3528 participants; HRB), thiazolidinediones (RR 1.30, 95% CI 0.55 to 3.07; P = 0.55; 7 trials; 4955 participants; HRB), insulin (RR 0.96, 95% CI 0.73 to 1.28; P = 0.80; 4 trials; 1642 participants; HRB) or meglitinide (RR 0.97, 95% CI 0.27 to 3.53; P = 0.97; 7 trials, 2038 participants, HRB) showed no statistically significant effects regarding cardiovascular mortality. Mortality data for the SGS versus placebo were sparse. SGS versus thiazolidinediones and meglitinides did not show statistically significant differences for a composite of non-fatal macrovascular outcomes. SGS versus metformin showed statistical significance in favour of SGS for a composite of non-fatal macrovascular outcomes (RR 0.67, 95% CI 0.48 to 0.93; P = 0.02; 3018 participants; 3 trials; HRB). The definition of non-fatal macrovascular outcomes varied among the trials. SGS versus metformin, thiazolidinediones and meglitinides showed no statistical significance for non-fatal myocardial infarction. No meta-analyses could be performed for microvascular outcomes. SGS versus placebo, metformin, thiazolidinediones, alpha-glucosidase inhibitors or meglitinides showed no statistical significance for adverse events. SGS versus alpha-glucosidase inhibitors showed statistical significance in favour of SGS for drop-outs due to adverse events (RR 0.48, 95% CI 0.24 to 0.96; P = 0.04; 9 trials; 870 participants; HRB). SGS versus meglitinides showed no statistical significance for the risk of severe hypoglycaemia. SGS versus metformin and thiazolidinediones showed statistical significance in favour of metformin (RR 5.64, 95% CI 1.22 to 26.00; P = 0.03; 4 trials; 3637 participants; HRB) and thiazolidinediones (RR 6.11, 95% CI 1.57 to 23.79; P = 0.009; 6 trials; 5660 participants; HRB) for severe hypoglycaemia.

Third-generation sulphonylureas (TGS) could not be included in any meta-analysis of all-cause mortality, cardiovascular mortality or non-fatal macro- or microvascular outcomes. TGS versus thiazolidinediones showed statistical significance regarding adverse events in favour of TGS (RR 0.88, 95% CI 0.78 to 0.99; P = 0.03; 3 trials; 510 participants; HRB). TGS versus thiazolidinediones did not show any statistical significance for drop-outs due to adverse events. TGS versus other comparators could not be performed due to lack of data.

For the comparison of SGS versus FGS no meta-analyses of all-cause mortality, cardiovascular mortality, non-fatal macro- or microvascular outcomes, or adverse events could be performed.

Health-related quality of life and costs of intervention could not be meta-analysed due to lack of data.

In trial sequential analysis, none of the analyses of mortality outcomes, vascular outcomes or severe hypoglycaemia met the criteria for firm evidence of a RRR of 10% between interventions.

Authors' conclusions

There is insufficient evidence from RCTs to support the decision as to whether to initiate sulphonylurea monotherapy. Data on patient-important outcomes are lacking. Therefore, large-scale and long-term randomised clinical trials with low risk of bias, focusing on patient-important outcomes are required.

PLAIN LANGUAGE SUMMARY

Sulphonylurea as sole therapy for patients with type 2 diabetes mellitus

Sulphonylureas are widely used for patients with type 2 diabetes mellitus. Sulphonylureas lower blood glucose by stimulating insulin secretion from the pancreas thereby increasing the insulin levels in the blood. Seventy-two trials were included in the systematic review assessing the effects of sulphonylurea as sole therapy versus other comparators in patients with type 2 diabetes mellitus. A total of 22,589 participants were included. The number of participants randomised to a sulphonylurea was 9707 and the number of participants randomised to a comparator was 12,805. The duration of the interventions varied from 24 weeks to 10.7 years. All trials had deficiencies (risk of bias) and for the individual comparisons the number of participants were small, resulting in a high risk of random errors (play of chance). Data on mortality and diabetic complications were sparse and inconclusive. Stopping taking the antidiabetic drug due to adverse events were more common with alpha-glucosidase inhibitors (for example acarbose) compared with second-generation sulphonylureas (for example glibenclamide, glipizide, glibornuride and gliclazide), but the data were sparse. Severe hypoglycaemia was more common with second-generation sulphonylureas compared with metformin and thiazolidinediones (for example pioglitazone), but again the data were sparse. Due to lack of data we could not adequately evaluate health-related quality of life and costs.

There is insufficient evidence regarding patient-important outcomes from high-quality randomised controlled trials (RCTs) to support the decision as to whether to initiate sulphonylurea as sole therapy. Large-scale and long-lasting randomised clinical trials with low risk of bias, which focus on mortality, diabetic complications, adverse events and health-related quality of life, are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

First-generation sulphonylureas compared with controls for type 2 diabetes mellitus

Patient or population: participants with type 2 diabetes mellitus
Settings: outpatients
Intervention: first-generation sulphonylureas (acetohexamide, carbutamide, chlorpropamide, tolbutamide, tolazamide)
Comparison: placebo, active comparators

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality a. Intervention vs placebo [30 weeks to 4.75 years] b. Intervention vs insulin [4.75 years to 10.0 years]	a.**RR 1.46** (0.87 to 2.45) b. **RR 1.18** (0.88 to 1.59)	a. 553 (2) b. 1944 (2)	⊕⊕◯◯ **low**[a]	a. Small sample size (1. 5% of the diversity-adjusted required information size) b. Trial sequential analysis showed that 5.7% of the required information size to detect or reject a 10% RRR was accrued
Cardiovascular mortality a. Intervention vs placebo [30 weeks to 4.75 years] b. Intervention vs insulin [4.75 years to 10.0 years]	a.**RR 2.63** (1.32 to 5.22) b. **RR 1.36** (0.88 to 1.48)	a. 553 (2) b. 1944 (2)	⊕⊕◯◯ **low**[a]	a. Small sample size (0. 7% of the diversity-adjusted required information size) b. Trial sequential analysis showed that 1.1% of the required information size to detect or reject a 10% RRR was accrued
Non-fatal macrovascular outcomes 1. Composite 2. Non-fatal myocardial infarction Intervention vs insulin [4.75 years to 10.0 years]	1a. not estimable 2b. **RR 1.08** (0.81 to 1. 45)	1a. See comment 2b.1944 (2)	1a. See comment 2b. ⊕⊕◯◯ **low**[a]	1a. No meta-analysis possible
Microvascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Cancer Intervention vs insulin [4.75 years to 10.0 years]	**RR 0.81** (0.29 to 2.27)	1944 (2)	⊕⊕◯◯ **low**[a]	One study reported any cancer and the other death due to cancer

Adverse events 1. All adverse events 2. Drop-outs due to adverse events Intervention vs alpha-glucosidase inhibitors [30 weeks]	1. **RR 0.63** (0.52 to 0.76) 2. **RR 0.28** (0.12 to 0.67)	1. 246 (2) 1. 246 (2)	⊕⊕◯◯ **low**[a]	Trial sequential analysis showed that firm evidence was not established
Health-related quality of life	Not estimable	See comment	See comment	Not investigated

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Due to imprecision and results of trial sequential analysis.
RRR: relative risk reduction

BACKGROUND

Description of the condition

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide (King 1998). Insulin resistance in peripheral tissues and inadequate compensatory insulin secretion are essential elements in the pathogenesis of T2DM. Reduced insulin secretion is caused by a decrease in the β-cell mass, a dysfunction of existing β-cells, or both (LeRoith 2002). A consequence of these defects is chronic hyperglycaemia (elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy and the risk of cardiovascular disease.
For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'; MEDG 2007). For an explanation of methodological terms, please see the main glossary in *The Cochrane Library*.

Description of the intervention

All insulin secretagogues lower blood glucose by enhancing insulin secretion from β-cells. The insulin secretagogues are divided into different classes. The first-generation sulphonylureas (carbutamide, tolbutamide, acetohexamide, tolazamide and chlorpropamide) were introduced in diabetes treatment in the 1950s, but are now rarely used (Henquin 1992; Markkanen 1960; Nathan 2009). However, chlorpropamide was used in the United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS-33 1998). The second-generation sulphonylureas (e.g. glibenclamide, glipizide, glibornuride and gliclazide) and third-generation sulphonylureas (glimepiride, gliclazide modified release (MR) and glipizide gastrointestinal therapeutic system (GITS)) have almost replaced the first-generation sulphonylureas, as they are preferred because of their perceived greater potency and better safety profiles (Henquin 1992; Nathan 2009). The meglitinide analogues (repaglinide and nateglinide) are a relatively new class of oral hypoglycaemic agents. They are designed primarily to augment the early-phase insulin release from the β-cells and therefore target postprandial glucose levels (Dornhorst 2001). Despite different chemical structures, the mechanisms of action of the meglitinide analogues and sulphonylureas are very similar in binding to and activating the sulphonylurea receptor on the β-cell.
As T2DM is a progressive disease, the glucose-lowering interven-

tion will be adjusted over time to achieve and maintain glycaemic control (UKPDS-33 1998). All patients with T2DM are initially advised to follow 'lifestyle' interventions including weight loss and increased physical activity. However, with time, the large majority of the patients will need addition of pharmacological glucose-lowering interventions to control blood glucose levels. In the early stages of the disease the most commonly used glucose-lowering medications are metformin (which reduces hepatic glucose production and may increase insulin sensitivity) and insulin secretagogues (sulphonylureas, meglitinide analogues or incretin therapies - which stimulate insulin secretion) (Inzucchi 2012; Nathan 2009). Thus, sulphonylurea monotherapy is considered an option if dietary and exercise interventions fail.

If lifestyle changes and maximum tolerated doses of an oral glucose-lowering drug given as monotherapy fail to achieve the glycaemic goal, other oral glucose-lowering drugs may be added. The most often recommended choice of a combined intervention is metformin plus an insulin secretagogue or insulin (Inzucchi 2012; Nathan 2009).

In case of sub-optimal glycaemic control by use of oral glucose-lowering drugs, insulin can be initiated (Inzucchi 2012; Nathan 2009). In contrast to other glucose-lowering medications, theoretically there is no upper limit of the dose of insulin above which further glucose-lowering effects will be absent. Hence, insulin may be used at all stages of the disease.

Adverse effects of the intervention

All sulphonylureas have a potential to cause hypoglycaemia. The risk of hypoglycaemia seems more pronounced for the first-generation sulphonylureas than the newer generations of sulphonylureas (Harrower 2000). Other specific adverse effects are known, e.g. hyponatraemia with chlorpropamide treatment (Fine 1970; Harrower 2000). All sulphonylureas are bound to plasma proteins, which might cause interactions with other medical interventions. This is primarily seen in first-generation sulphonylureas (Gerich 1989). The University Group Diabetes Program (UGDP) trial reported an increased all-cause and cardiovascular mortality in patients treated with tolbutamide compared with placebo and insulin (UGDP 1970). The results gave rise to a debate whether sulphonylureas should be used in patients with T2DM with known ischaemic heart disease. Sulphonylureas increase pancreatic insulin release by closing of adenosine triphosphate-sensitive K^+ channels (K_{ATP}). Opening of the cardiac K_{ATP} channels is a key transduction pathway for heart ischaemic preconditioning, in which brief episodes of ischaemia and reperfusion renders the heart more resistant to a subsequent sustained ischaemic insult (i.e. reduction of infarct size). As individual sulphonylurea drugs differ in their affinities to extrapancreatic K_{ATP} channels, their effects on the signalling pathways of pre- and post-conditioning may differ. Cardioprotection with sulphonylurea, in terms of reducing infarct size in the acute setting of myocardial ischaemia, is theoretically possible through opening of K_{ATP} channels. However, it is unknown if chronic therapy with sulphonylurea can protect the myocardium (i.e. reduced ischaemia-reperfusion injury) after acute myocardial infarction (Henquin 1992; UGDP 1970; Yellon 2007). For example, the initial analysis from the UKPDS trial did not find any statistically significant differences in the risk of myocardial infarction between the groups treated with insulin, chlorpropamide or glibenclamide (UKPDS-33 1998). However, the risk of angina was more reduced in the glibenclamide group compared with the insulin or chlorpropamide groups (UKPDS-33 1998). Patients assigned to chlorpropamide did not have the same risk reduction as those assigned to glibenclamide or insulin for the progression of retinopathy. Also, combined intervention with metformin and sulphonylurea versus sulphonylurea monotherapy showed a significant increase in mortality (UKPDS-34 1998). However, in the 10-year post-study follow-up from the UKPDS trial, a statistically significant reduction in the risk of myocardial infarction was observed in the group with prior allocation to intensive therapy with either sulphonylurea or insulin versus conventional therapy with diet alone (Holman 2008).

How the intervention might work

In 1942 the efficacy of a sulphonamide was evaluated in the treatment of typhoid fever (Henquin 1992). It was noted that some of the patients died of hypoglycaemia. In the mid-1950s a sulphonamide was tested as treatment against bacterial infections. Hypoglycaemia was reported among the trial participants, and the drug was shortly thereafter tested in patients with T2DM (Henquin 1992). Tolbutamide was thereafter synthesised for use in patients with diabetes mellitus. In 1966 the second-generation sulphonamide, glibenclamide (in the United States: glyburide) was available for patients with T2DM. In the 1970s the first non-sulphonylurea insulin secretagogue was discovered. Shortly thereafter the first non-sulphonylurea rapid-acting insulin secretagogues, repaglinide and nateglinide, were developed for T2DM (Henquin 1992). This class of drug produces a rapid, short-acting insulin response (Landgraf 2000).

The differences in the pharmacokinetic profiles of the insulin secretagogues are primarily explained by different binding affinities to the K_{ATP} channels in the β-cells. The meglitinide analogues bind to the K_{ATP} channel at a distinct different site than the sulphonylureas (Landgraf 2000).

A relatively new class of antidiabetic intervention, the incretins, control blood glucose by increasing glucose-dependent insulin secretion and inhibition of glucagon secretion. This class of drugs works by a different mechanism than the other insulin secretagogues, and stimulate insulin secretion in a glucose-dependent manner (Drucker 2005).

Why it is important to do this review

Sulphonylureas are widely used in daily clinical practice (Nathan 2009). A Cochrane review investigated the effect of meglitinide analogues in patients with T2DM, but they did not find any trials assessing mortality and morbidity (Black 2007). A meta-analysis compared glibenclamide with other insulin secretagogues and with insulin (Gangji 2007). The conclusion from the authors was that glibenclamide caused more hypoglycaemia than the other sulphonylureas. This meta-analysis did only include trials published in English. Moreover, this meta-analysis only made comparisons of glibenclamide with other antidiabetic interventions and was unable to draw conclusions on the benefits and harms of the other sulphonylureas. We are unaware of any up-to-date systematic reviews looking into the effect of all sulphonylureas on clinical relevant outcomes in patients with T2DM. A Cochrane review compared metformin monotherapy with any other antidiabetic interventions (Saenz 2005). The authors concluded that metformin monotherapy may prevent some vascular complications and mortality in patients with T2DM with overweight. Three recent meta-analyses published outside The Cochrane Collaboration investigated the effect of oral glucose-lowering drugs (Bennett 2011; Bolen 2007; Selvin 2008). Selvin et al concluded that metformin seemed superior to other oral glucose-lowering drugs (Selvin 2008). Bolen et al concluded that older oral glucose-lowering agents (second-generation sulphonylurea and metformin) had equivalent or superior effects regarding glycaemic control compared with newer oral glucose-lowering drugs (Bolen 2007). Bolen et al and Selvin et al did not include studies published after January 2006. Therefore, the landmark study, the 'A Diabetes Outcome Progression Trial' (ADOPT) investigating time to treatment failure of glibenclamide, metformin and rosiglitazone during about four years in 4360 drug-naive patients with T2DM and published in December 2006, was not included in either of the reviews by Bolen et al and Selvin et al (ADOPT 2006). Bennett et al only found very sparse data on patient-important outcomes, and only included trials published in English (Bennett 2011). The ADOPT trial is the largest trial to date of monotherapy with oral glucose-lowering agents. In fact, the ADOPT trial suggested less cardiovascular risk with glibenclamide than with either metformin or rosiglitazone. An up-to-date review including the ADOPT trial might therefore add important information to existing reviews about oral glucose-lowering agents. Also, neither Bennett et al, Bolen et al nor Selvin et al used the 'Risk of bias' tools recommended by The Cochrane Collaboration (Bennett 2011; Bolen 2007; Selvin 2008). Cochrane reviews have also been published on both pioglitazone and rosiglitazone versus other antidiabetic interventions (Richter 2006; Richter 2007). Both reviews concluded that further knowledge about the glitazones should become available, to assess the benefit-harm risk ratio properly. None of the reviews or meta-analyses so far have estimated the required information size needed to draw sensible conclusions on the effect on patient-important outcomes.

OBJECTIVES

To assess the effects of sulphonylurea monotherapy versus placebo, no intervention or other antidiabetic interventions for patients with type 2 diabetes mellitus (T2DM).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials.

Types of participants

Adults of 18 years or more with T2DM.

Diagnostic criteria

To be consistent with changes in classification and diagnostic criteria of T2DM through the years, the diagnosis of T2DM should have been established using the standard criteria valid at the time of the beginning of the trial (e.g. ADA 1997; ADA 1999; ADA 2003; ADA 2008; NDDG 1979; WHO 1980; WHO 1985; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, we used the authors' definition of diabetes mellitus. We subjected diagnostic criteria to a sensitivity analysis.

Types of interventions

We investigated the allocation to sulphonylurea monotherapy (irrespective of whether the subsequent addition of other glucose-lowering drugs was permitted after randomisation, e.g. escape medicine).

First-generation sulphonylureas are carbutamide, tolbutamide, acetohexamide, tolazamide and chlorpropamide. Second-generation sulphonylureas are glibenclamide, glipizide, glibornuride and gliclazide. Third-generation sulphonylureas are glimepiride, gliclazide modified release (MR) and glipizide gastrointestinal therapeutic system (GITS).

Experimental intervention and control intervention

- First-, second- or third-generation sulphonylureas versus placebo, diet, metformin, thiazolidinediones, insulin or any other antidiabetic comparator.
- Second- or third-generation sulphonylureas versus first-generation sulphonylureas.

Other comparisons are being undertaken by other review teams within the Cochrane Metabolic and Endocrine Disorder Review Group. Their results are referenced in this review, in order to give a comprehensive overview. We did not conduct a predefined comparison of second-generation sulphonylureas versus third-generation sulphonylureas in order to reduce the number of comparisons.

Types of outcome measures

Primary outcomes

- All-cause mortality (death from any cause).
- Cardiovascular mortality (death from myocardial infarction, stroke, peripheral vascular disease and sudden death without known cause).

Secondary outcomes

- Non-fatal macrovascular outcomes assessed together and separately: non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity and cardial or peripheral revascularisation.
- Microvascular outcomes assessed together and separately: manifestation of nephropathy, manifestation and progression of retinopathy and retinal photocoagulation.
- Glycaemic control (as measured by the level of fasting plasma glucose and glycosylated haemoglobin A1c (HbA1c)).
- Body mass index (BMI).
- Weight.
- Adverse events (e.g. hypoglycaemia. Definitions may be heterogeneous between trials. Hypoglycaemia was defined as mild (controlled by patient), moderate (daily activities interrupted but self managed) or severe (requiring assistance)).
- Serious adverse events (ICH 1997).
- Health-related quality of life measured with validated instruments.
- Costs of treatment.
- Cancer.
- Need for an additional glucose-lowering drug (i.e. intervention failure).

Covariates, effect modifiers and confounders

- Disease duration.

Timing of outcome measurement

We divided the trials according to their intervention periods into short duration (equal to or greater than 24 weeks to less than two years) and long duration (equal to or greater than two years).

Search methods for identification of studies

Electronic searches

We used the following sources from inception until specified date for the identification of trials.

- *The Cochrane Library* (2011, Issue 3).
- MEDLINE (until August 2011).
- EMBASE (until August 2011).
- Science Citation Index Expanded (until August 2011).
- Latin American Caribbean Health Sciences Literature (LILACS) (until August 2011).
- Cumulative Index to Nursing & Allied Health Literature (CINAHL) (until August 2011).

For detailed search strategies please see under Appendix 1.
Additional key words of relevance were not detected during any of the electronic or other searches. If this had been the case, we would have modified the electronic search strategies to incorporate these terms. Trials published in any language were included.

Searching other resources

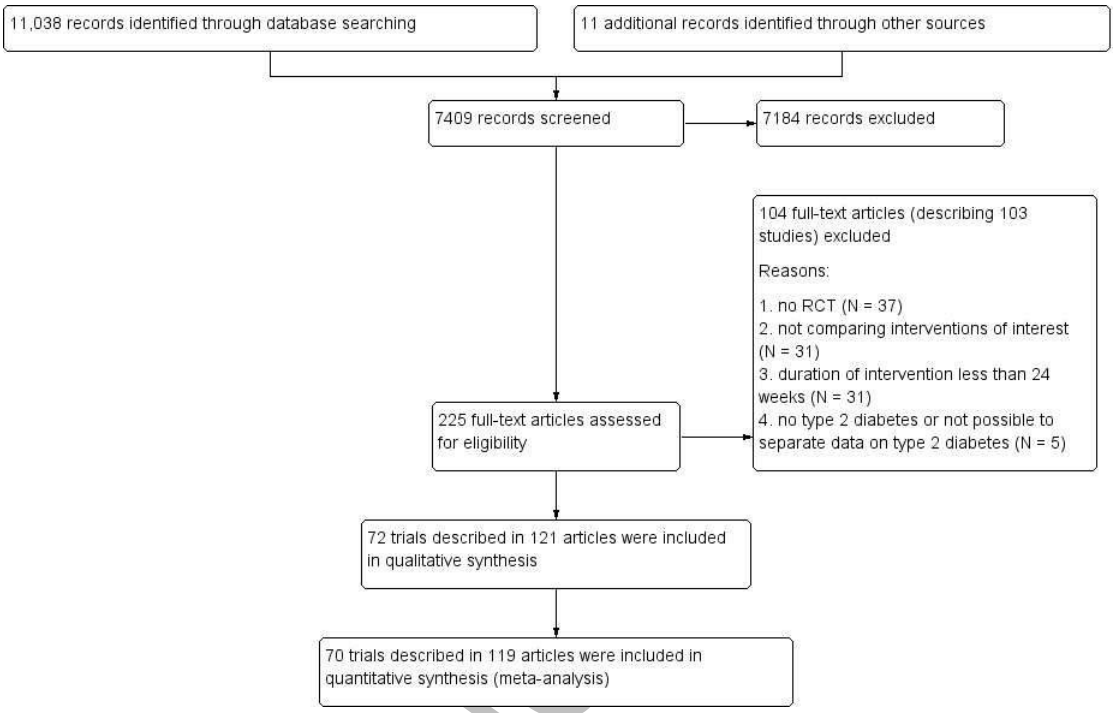
In addition, we handsearched abstracts of major diabetes conferences (American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD)) and checked the references from included trials and (systematic) reviews, meta-analyses and health technology assessment reports. The US Food and Drug Administration web site was searched for unpublished trials.
We obtained evaluations of all relevant non-English articles.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (BH and LL, TA or JS) independently scanned the abstract, title or both sections of every record retrieved. We investigated all potentially relevant articles as full text.
We measured interrater agreement for selection of potentially relevant studies using the kappa statistic (Cohen 1960). Where differences in opinion existed, they were resolved by a third party (JW or CG). If resolving disagreement was not possible, we contacted the authors for clarification.
The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow-chart of study selection (Liberati 2009) is attached (Figure 1).

Figure 1. Study flow diagram.N = number of references



Data extraction and management

For studies that fulfilled the inclusion criteria, two review authors (BH and LL, TA, JS or DS) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies and Table 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8, Appendix 9). Any disagreements were resolved by discussion, or if required by a third party (JW or CG). We sought any relevant missing information on the trial from the original author(s) of the article, if required.

We converted standard errors and confidence intervals to standard deviations (SD) (Higgins 2008). When no differences in means and SDs were reported from baseline, we used the end-of follow-up values (Higgins 2008). .

Dealing with duplicate publications

In the case of companion papers of a primary trial, we simultaneously evaluated all available papers together to maximise the information. In cases of doubt, we contacted the corresponding author(s). If no reply or explanation was given, we prioritised the original publication (usually the oldest version).

Assessment of risk of bias in included studies

Methodological quality is defined as the confidence that the design and the report of the randomised clinical trial will restrict bias in the comparisons of the intervention with controls (Moher 1998). According to empirical evidence, the methodological quality of trials is based on sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias (Gluud 2006; Higgins 2008; Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012; Schulz 1995; Wood 2008).

Since there is no sufficiently well-designed formal statistical method to combine the results of trials with high and low risk of bias, the major approach to incorporating risk of bias assessments in Cochrane reviews is to restrict meta-analyses to trials at low (or lower) risk of bias (Higgins 2008).

Two authors (BH and LL, TA, JS or DS) independently assessed the risk of bias in each trial (see Figure 2; Figure 3). Any differences in opinion were resolved through discussion with CG, AV, SL or JW. We calculated interrater agreement for allocation concealment.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

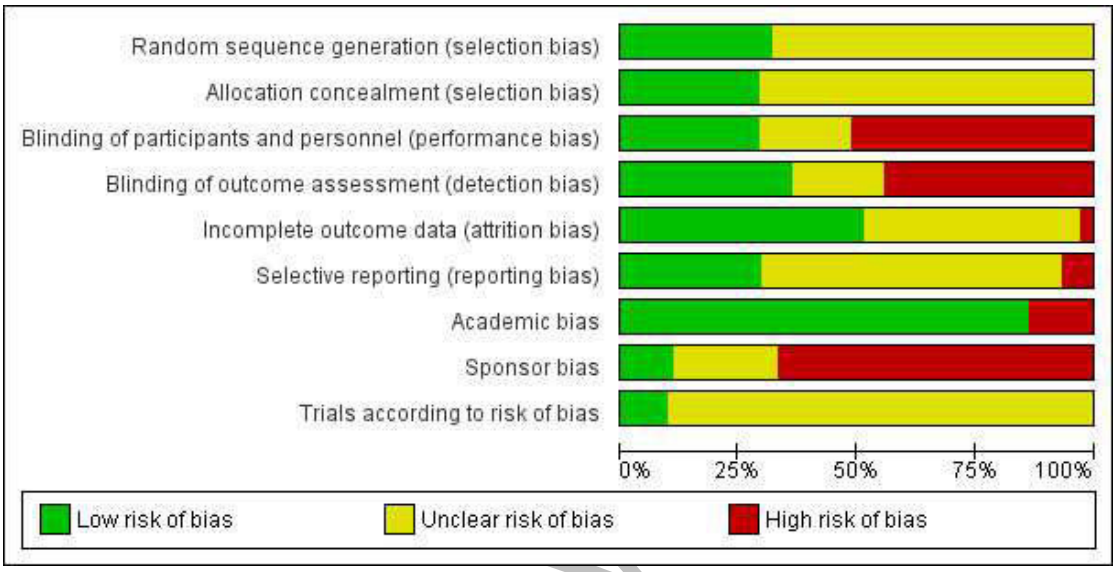
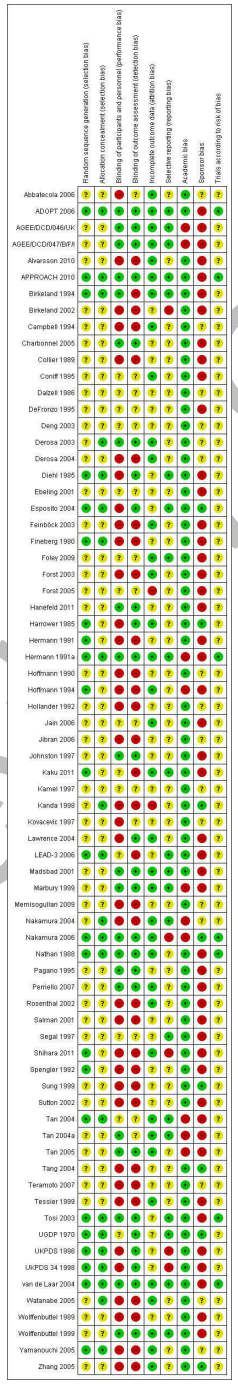


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



We classified risk of bias components as follows:

Sequence generation

- Low risk of bias, if the allocation sequence is generated by a computer or random number table or similar.
- Uncertain risk of bias, if the trial is described as randomised, but the method used for the allocation sequence generation was not described.
- High risk of bias, if a system involving dates, names or admittance numbers is used for the allocation of patients (quasi-randomised). Such studies were excluded.

Allocation concealment

- Low risk of bias, if the allocation of patients involves a central independent unit, on-site locked computer or consecutively numbered sealed envelopes.
- Uncertain risk of bias, if the trial is described as randomised, but the method used to conceal the allocation is not described.
- High risk of bias, if the allocation sequence is known to the investigators who assigned participants or if the study is quasi-randomised. Such studies were excluded.

Blinding

- Low risk of bias, if the method of blinding is described.
- Uncertain risk of bias, if the method of blinding is not described.
- High risk of bias, if the participants or investigators are not blinded.

Incomplete data outcomes

- Low risk of bias, if it is clearly described if there are any post-randomisation drop-outs or withdrawals and the reasons for these drop-outs are described.
- Uncertain risk of bias, if it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear.
- High risk of bias, if the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis is performed, there is potentially inappropriate application of simple imputation, or the potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Low risk of bias, if all the pre-defined (primary and secondary) outcomes are mentioned in the trial's protocol or in a design article have been reported in the pre-specified way.
- Uncertain risk of bias, if there is insufficient information to assess whether the risk of selective outcome reporting is present.
- High risk of bias, if not all the pre-specified outcomes are reported or if the primary outcomes are changed or if some of the important outcomes are incompletely reported.

Academic bias

- Low risk of bias, if the author of the trial has not conducted previous trials addressing the same interventions.
- Uncertain risk of bias, if it is not clear if the author has conducted previous trials addressing the same interventions.
- High risk of bias, if the author of the trial has conducted previous trials addressing the same interventions.

Sponsor bias

- Low risk of bias, if the trial is unfunded or is not funded by an instrument or equipment or drug manufacturer.
- Uncertain risk of bias, if the source of funding is not clear.
- High risk of bias, if the trial is funded by an instrument or equipment or drug manufacturer.

Unit of analysis issues

The unit of analysis was patient groups randomised to the interventions in the individual trials. We subjected different units of analysis to subgroup analyses or sensitivity analyses.

Dealing with missing data

We attempted to find missing data by contacting the trial authors and discussed the impact of any missing data.
Intention-to-treat analysis is recommended in order to minimise bias in design, follow-up and analysis of the efficacy of randomised clinical trials. It estimates pragmatically the benefit of a change in treatment policy rather than the potential benefit in patients who receive the treatment exactly as planned (Hollis 1999). Full application of intention-to-treat is possible when complete outcome data are available for all randomised participants. Despite the fact that about half of all published reports of randomised clinical trials state that intention-to-treat is used, handling of deviations from randomised allocation varies widely and many trials have missing data on the primary outcome variable (Hollis 1999). The methods used to deal with deviations from randomised allocation are generally inadequate, potentially leading to bias (Hollis 1999).
Performing an intention-to-treat analysis in a systematic review is not straightforward in practice since review authors must decide how to handle missing outcome data in the contributing trials (

Gamble 2005). No consensus exists about how missing data should be handled in intention-to-treat analysis, and different approaches may be appropriate in different situations (Higgins 2008; Hollis 1999).

We considered the potential impact of the missing data on the primary outcomes by applying the best-worst case scenario and the worst-best case scenario. The 'best-case' scenario is that all participants with missing outcomes in the experimental intervention group had good outcomes, and all those with missing outcomes in the control intervention group had poor outcomes; the 'worst-case' scenario is the converse (Higgins 2008).

Assessment of heterogeneity

We evaluated the clinical diversity of the included trials. We identified heterogeneity by visual inspection of the forest plots and by using a standard Chi^2 test with a significance level of α = 0.1. We specifically examined heterogeneity with diversity (D^2) (Wetterslev 2009) and inconsistency factor (I^2 statistic) (Higgins 2008), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2008). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual trial characteristics and those of subgroups of the main body of evidence. Diversity (D^2) is different from the common quantification of heterogeneity (I^2). We used D^2 for heterogeneity adjustment of the information size as it leads to a correct and robust estimate of the required information size, whereas I^2 used for this purpose may underestimate the required information size (Wetterslev 2009).

We assessed clinical heterogeneity by comparing the trials with regard to different clinical variables: patient characteristics, duration of disease, glycaemic target, targets of other metabolic variables and assessment of outcomes.

When significant clinical, methodological or statistical heterogeneity was found, we surveyed the individual trial in trying to determine potential reasons for it.

We used both the random-effects model (DerSimonian 1986) and the fixed-effect model (DeMets 1987). We reported the results for the random- and fixed-effect models for all outcomes. However, when heterogeneity was absent, we only reported the random-effects model.

Assessment of reporting biases

We used funnel plots to assess for the potential existence of small study bias for the primary outcomes. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001). Therefore, we carefully interpreted results (Lau 2006).

Data synthesis

We summarised data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analysis according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Trial sequential analysis

Cumulative meta-analyses are subject to random errors due to sparse data and repetitive testing of data (TSA Manual 2011). Trial sequential analysis is a methodology that combines an information size calculation for a meta-analysis with thresholds of statistical significance as data accumulate. Trial sequential analysis is a tool for quantifying the statistical reliability of data in a cumulative meta-analysis adjusting statistical significance levels for sparse data and repetitive testing on accumulating data. We conducted trial sequential analysis on the primary outcomes and the secondary outcomes showing statistical significance in both the random-effects model and fixed-effect model (Brok 2009; Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008).

Meta-analysis may result in type I errors due to random errors due to sparse data or repeated significance testing when updating meta-analysis with new trials (Brok 2009; Wetterslev 2008). Bias (systematic error) from trials with low methodological quality, outcome measure bias, publication bias and small trial bias may also result in spurious P values (Brok 2009; Higgins 2008; Wetterslev 2008).

In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value that is the cumulative Z-curve crosses the monitoring boundaries (Lan 1983). Sequential monitoring boundaries can be applied to meta-analysis as well, called trial sequential monitoring boundaries (Wetterslev 2008). The idea in trial sequential analysis is that if the cumulative Z-curve crosses the trial sequential alpha-spending boundary, a sufficient level of evidence is reached and no further trials may be needed (firm evidence). If the Z-curve does not cross the alpha-spending boundary then there is insufficient evidence to reach a conclusion about the difference between the interventions. Here the Z-curve may not reach or may cross the trial sequential beta-spending monitoring boundary. In the latter case futility may be declared. To construct the trial sequential monitoring boundaries, the required information size is needed and is calculated as the least number of participants needed in a well-powered single trial (Brok 2009; Pogue 1997; Pogue 1998; TSA Manual 2011; TSA Program 2011; Wetterslev 2008). Additionally, trial sequential analysis provides information regarding the need for additional trials and the sample size of such trials.

We applied trial sequential monitoring boundaries according to a diversity-adjusted required information size (Wetterslev 2009) suggested by the intervention effect estimated with a 10% relative

risk reduction (RRR) employing α = 0.05, ß = 0.20 and the incidence in the control intervention group (binary outcomes) from the cumulative meta-analysis. For the continuous outcomes we tested the evidence of the achieved difference in the cumulative meta-analysis. We used the diversity measured in the traditional meta-analysis to adjust the required information size.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses if one of the primary outcome measures demonstrated statistically significant differences between intervention groups. Subgroup analyses were clearly marked as a hypothesis-generating exercise.

We conducted the following subgroup analyses:

- Duration of the intervention (short (equal to or greater than 24 weeks and less than two years) compared to long (equal to or greater than two years)).
- Drug-naive patients compared to patients who had previously received glucose-lowering drugs.
- Trials with adequate sequence generation, allocation concealment and blinding compared to trials with inadequate sequence generation, allocation concealment or blinding.
- Trials not allowing the addition of other glucose-lowering drugs during follow-up compared to trials allowing addition of other glucose-lowering drugs during follow-up.

Tests of interaction determined the difference in intervention effects of subgroups (Altman 2003).

Sensitivity analysis

We planned to perform sensitivity analyses for the primary outcomes.

- Repeating the analysis excluding the trial with longest duration or the largest trial to establish how much they influence the results.
- Repeating the analysis using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other).
- Repeating the analysis excluding unpublished trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The initial search of the databases identified 7409 records after duplicates were removed. Most of the references were excluded on the basis of their titles and abstracts because they clearly did not meet the inclusion criteria (Figure 1). Two hundred and twenty-five of the references were evaluated as full text. After screening the full text, 72 randomised trials described in 121 publications met our inclusion criteria. One of the references was an approval letter (FDA 2000), which identified two unpublished trials (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I). Sixty-two trials were exclusively published in English. The remaining trials were exclusively or partly published in other languages: three in German (Hoffmann 1990; Rosenthal 2002; Spengler 1992), three in Chinese (Deng 2003; Tang 2004; Zhang 2005), one in Japanese (Kanda 1998) and one in Italian (Pagano 1995). For the two unpublished trials, we received a description from the sponsor in English (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I).

Abstracts from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) conferences provided no additional references. One additional reference was obtained from the US Food and Drug Administration (FDA) homepage (FDA 2000). The reference referred to an approval letter for repaglinide. Five phase III trials were described in the letter and were conducted by a pharmaceutical company comparing second-generation sulphonylureas with repaglinide. We asked the company for additional information. Three of the five trials described in the approval letter were already published and identified through the search in the databases (Madsbad 2001; Marbury 1999; Wolffenbuttel 1999). The remaining two trials were never published (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I).

No health technology assessment report was found for sulphonylureas. No previous meta-analysis has focused on the effects of sulphonylurea monotherapy. We screened a meta-analysis focusing on sulphonylureas for additional references (Gangji 2007), but no additional references were found. We retrieved one meta-analysis in Chinese about glimepiride (Liu 2009). This meta-analysis did not provide any additional information. We searched one comprehensive meta-analysis comparing all antidiabetic interventions, which did not provide additional references (Bolen 2007). We searched Cochrane reviews about antidiabetic interventions for additional references (Black 2007; Liu 2002; Ooi 2010; Richter 2006; Richter 2007; Richter 2008; Saenz 2005; Van de Laar 2005). Van de Laar et al provided an additional reference to one included trial (Mauersberger 2001), which described the trial from Rosenthal 2002 (Rosenthal 2002). Moreover, an additional reference to Spengler 1992 was retrieved (Spengler 1992) from van de Laar et al (Van de Laar 2005). The Cochrane review by Liu et al, which focused on the effects of Chinese herbs in T2DM (Liu 2002) provided a trial in Chinese comparing glibenclamide monotherapy with a Chinese herb (Deng 2003). Only the Cochrane review from van de Laar gave supplemental information, as they had retrieved some unpublished data from trials, where we could not get any

(Van de Laar 2005). Van de Laar et al had extracted two publications as one trial, as they had information from the authors of the publications that they were describing the same trial (Hoffmann 1990). The review from Saenz et al provided data from the United Kingdom Prospective Diabetes Study (UKPDS) 34 for end of follow-up values of fasting blood glucose, HbA1c and weight (Saenz 2005). We could not find these data, and through correspondence we were informed that they were read from a figure. We could, however, not find the same numbers in the figure, and the numbers were therefore not included.

We tried to retrieve protocols of all included trials from ClinicalTrials.gov (www.clinicaltrials.gov). Protocols for six trials were retrieved by this search or by a reference in the publication (ADOPT 2006; APPROACH 2010; Foley 2009; Kaku 2011; LEAD-3 2006; Shihara 2011).

A total of 225 references were finally evaluated in full text. Of these, 121 references described 72 included trials. One hundred and four references described 103 excluded trials (Figure 1). The remaining references could be excluded based on title or abstract (n = 7184).

We sent all authors of the included trials a reference list and a request for information on additional trials of relevance, if possible. Inter-rater agreement between the two trial selectors was 80.8%, using a kappa statistic (Cohen 1960).

Included studies

We included 72 trials, of which 70 trials provided data for meta-analyses. All were randomised clinical trials assessing the effect of sulphonylurea monotherapy versus a comparator in patients with T2DM. A total of 22,589 participants were included, of which 9707 were randomised to sulphonylurea monotherapy and 12,805 were randomised to a comparator (Table 1). For full details please see the table Characteristics of included studies.

Trial designs

All 72 included trials were randomised clinical trials. Four of the trials had a cross-over design (Diehl 1985; Hermann 1991; Tosi 2003; Wolffenbuttel 1989). The remaining trials had a parallel design. Twenty-eight of the trials were described as open-labelled (Alvarsson 2010; Birkeland 2002; Campbell 1994; Collier 1989; Derosa 2004; Esposito 2004; Feinböck 2003; Fineberg 1980; Forst 2003; Forst 2005; Harrower 1985; Hermann 1991; Hoffmann 1990; Hollander 1992; Kanda 1998; Lawrence 2004; Memisogullari 2009; Salman 2001; Shihara 2011; Spengler 1992; Sutton 2002; Tang 2004; Teramoto 2007; Tessier 1999; UKPDS 1998; UKPDS 34 1998; Wolffenbuttel 1989; Zhang 2005) and 28 trials were designed to blind investigators and participants (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; APPROACH 2010; Birkeland 1994; Charbonnel 2005; Coniff 1995; DeFronzo 1995; Deng 2003; Derosa 2003; Ebeling 2001; Foley 2009; Hanefeld 2011; Hermann 1991a; Jain 2006; Johnston 1997; Madsbad 2001; Marbury 1999; Nakamura 2006; Nathan 1988; Pagano 1995; Perriello 2007; Segal 1997; Tan 2004; Tan 2004a; Tosi 2003; van de Laar 2004; Wolffenbuttel 1999). Ten of the trials did not describe blinding (Abbatecola 2006; Dalzell 1986; Diehl 1985; Jibran 2006; Kamel 1997; Nakamura 2004; Rosenthal 2002; Sung 1999; Watanabe 2005; Yamanouchi 2005). One of the trials involved a placebo group, and we judged this trial to have blinded investigators and participants (Kamel 1997). We classified the remaining trials as open-label based on the interventions and how they were applied (Abbatecola 2006; Dalzell 1986; Diehl 1985; Jibran 2006; Nakamura 2004; Rosenthal 2002; Sung 1999; Watanabe 2005; Yamanouchi 2005).

Two trials had different blinding of the comparisons (glibenclamide, placebo and acarbose) (Hoffmann 1994; Kovacevic 1997). In both trials the participants and the investigators were blinded for the comparison of acarbose versus placebo, but the investigators were not blinded for glibenclamide (Hoffmann 1994; Kovacevic 1997). The University Group Diabetes Program (UGDP) trial had both investigators and participants blinded for the evaluation of tolbutamide versus placebo, but insulin was applied in an open-label design (UGDP 1970). One trial consisted of a trial period with blinding of investigators and participants for 24 weeks, followed by an open-label period (28 weeks) (Kaku 2011). Charbonnel blinded investigators and participants for 52 weeks (Charbonnel 2005). Some of the included trial centres in the Charbonnel 2005 trial were invited to continue for an additional 52 weeks (Tan 2005). The baseline data we report from Tan 2005 are taken after the participants have been included for 52 weeks of Charbonnel 2005 (Charbonnel 2005; Tan 2005). The Liraglutide Effect and Action in Diabetes-3 (LEAD-3) trial had investigators and participants blinded for the first 52 weeks and had a 91-week open-label extension period (LEAD-3 2006). Because of a large number of participants lost to follow-up during the extension period, we choose only to include data from the blinded period. A few of the outcomes were only reported after 104 weeks: non-fatal myocardial infarction, mild hypoglycaemic and adverse events.

The trials were primarily conducted in Europe. The number of clinical sites varied from 1 to 488 in the individual trials.

The duration of the intervention period varied from 24 weeks to 10.7 years (UKPDS 1998).

Trial participants

The definition of T2DM was not reported in most trials. In the UGDP trial, T2DM diagnosis was based on the sum of four glucose values from a glucose tolerance test. As a result of this definition, participants with impaired glucose tolerance were included in the trial (UGDP 1970). The main criterion for diagnosis in the UKPDS was based on two fasting glucose values (UKPDS 1998). This definition of T2DM was less stringent than the World Health

Organization (WHO) criteria (WHO 1985). All participants in the UGDP and UKPDS had a dietary run-in period of four weeks and three months, respectively. In the UGDP trial, participants who developed symptomatic hyperglycaemia were excluded. In the UKPDS trial, the participants with fasting blood glucose of 6.1 to 15.0 mmol/L after three months on a diet were randomised to the trial interventions (UKPDS 1998). The ADOPT trial did not clearly describe how the diagnosis of T2DM was established, but it had to be established within three years from screening to participation to the trial. Eligibility was determined on the fasting blood glucose, and if it was between 7 to 13 mmol/L, then the patient entered a four-week run-in period with diet and exercise reinforcement. If the fasting blood glucose was between 7 to 10 mmol/L after the four-week run-in period, then the participants were eligible for randomisation (ADOPT 2006).

The duration of T2DM at entry into the trials ranged from newly diagnosed diabetes to a mean disease duration of 17 years (Nakamura 2004).

Most exclusion criteria consisted of liver disease, kidney disease or other severe concurrent illnesses.

The mean age of the participants of the included trials varied from 40.3 years to 74.4 years (Abbatecola 2006; Kanda 1998).

Characteristics of the interventions

First-generation sulphonylureas were applied either as tolbutamide (six trials) (Coniff 1995; Dalzell 1986; Fineberg 1980; UGDP 1970; van de Laar 2004; Wolffenbuttel 1989) or chlorpropamide (four trials) (Diehl 1985; Harrower 1985; UKPDS 1998; UKPDS 34 1998).

A second-generation sulphonylurea was used in most trials (Abbatecola 2006; ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Alvarsson 2010; APPROACH 2010; Birkeland 1994; Birkeland 2002; Campbell 1994; Charbonnel 2005; DeFronzo 1995; Deng 2003; Ebeling 2001; Esposito 2004; Fineberg 1980; Foley 2009; Hanefeld 2011; Harrower 1985; Hermann 1991; Hermann 1991a; Hoffmann 1990; Hoffmann 1994; Hollander 1992; Jain 2006; Jibran 2006; Johnston 1997; Kaku 2011; Kanda 1998; Kamel 1997; Kovacevic 1997; Lawrence 2004; Madsbad 2001; Marbury 1999; Memisogullari 2009; Nakamura 2004; Nakamura 2006; Nathan 1988; Pagano 1995; Perriello 2007; Rosenthal 2002; Salman 2001; Segal 1997; Spengler 1992; Sung 1999; Sutton 2002; Tan 2004a; Tan 2005; Teramoto 2007; Tessier 1999; Tosi 2003; UKPDS 1998; UKPDS 34 1998; Watanabe 2005; Wolffenbuttel 1999; Zhang 2005). Glibenclamide was applied in most trials (Abbatecola 2006; ADOPT 2006; AGEE/DCD/046/UK; Alvarsson 2010; Birkeland 1994; Birkeland 2002; DeFronzo 1995; Deng 2003; Ebeling 2001; Esposito 2004; Forst 2003; Hanefeld 2011; Harrower 1985; Hermann 1991; Hermann 1991a; Hoffmann 1990; Hoffmann 1994; Hollander 1992; Jain 2006; Jibran 2006; Johnston 1997; Kaku 2011; Kamel 1997; Kovacevic 1997; Marbury 1999; Nakamura 2004; Nakamura 2006; Nathan 1988; Pagano 1995; Rosenthal 2002; Segal 1997; Spengler 1992; Sung 1999; Sutton 2002; Tan 2004a; Teramoto 2007 ; Tosi 2003; UKPDS 1998; UKPDS 34 1998; Watanabe 2005; Wolffenbuttel 1999). Glipizide was applied in nine trials (APPROACH 2010; Birkeland 1994; Campbell 1994; Feinböck 2003; Fineberg 1980; Harrower 1985; Madsbad 2001; UKPDS 1998; Zhang 2005). Gliclazide was applied in 13 trials (AGEE/DCD/047/B/F/I; Charbonnel 2005; Collier 1989; Foley 2009; Harrower 1985; Kamel 1997; Kanda 1998; Lawrence 2004; Memisogullari 2009; Perriello 2007; Salman 2001; Tan 2005; Tessier 1999). Four trials had more than one intervention group with a second-generation sulphonylurea (Birkeland 1994; Harrower 1985; Kamel 1997; UKPDS 1998).

A third-generation sulphonylurea was applied in nine trials (Derosa 2003; Derosa 2004; Feinböck 2003; Forst 2005; LEAD-3 2006; Shihara 2011; Tan 2004; Tang 2004; Yamanouchi 2005). All trials applied glimepiride as the third-generation sulphonylurea.

For the UKPDS trial we only included data from the intensive intervention group (allocated treatment with chlorpropamide, glibenclamide, glipizide, metformin or insulin), as the conventional intervention group had another glycaemic target. However, the fasting plasma glucose target was less than 6 mmol/L for the peroral antidiabetic intervention groups in the intensive intervention group, but the insulin-treated participants had a pre-meal glucose target of 4 to 7 mmol/L. We concluded that this difference was of minor importance (UKPDS 1998; UKPDS 34 1998).

The UKPDS 34 trial included overweight/obese participants with T2DM comparing intensive glycaemic control with metformin versus intensive glycaemic control with other antidiabetic interventions (chlorpropamide, glibenclamide and insulin) (UKPDS 34 1998). All the data were only reported as metformin versus the other interventions together in the main publication. However, data after 3 years of follow-up were included from another publication (UKPDS 34 1998). Data after one year of follow-up were used in the meta-analyses of mild and severe hypoglycaemia for both the UKPDS 33 and UKPDS 34 (UKPDS 1998; UKPDS 34 1998). . We included five different comparisons from the UKPDS trial: first-generation sulphonylurea versus metformin (UKPDS 34 1998), first-generation sulphonylurea versus insulin (UKPDS 1998), second-generation sulphonylurea versus metformin (UKPDS 34 1998), second-generation sulphonylurea versus insulin (UKPDS 1998) and second-generation sulphonylurea versus first-generation sulphonylurea (UKPDS 1998).

All the included trials randomised the participants to sulphonylurea monotherapy. Most of the included trials did not allow addition of glucose-lowering interventions to maintain the glycaemic intervention target and excluded such participants (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Alvarsson 2010; Birkeland 1994; Birkeland 2002; Charbonnel 2005; Coniff 1995; DeFronzo 1995; Derosa 2003; Derosa 2004; Feinböck 2003; Fineberg 1980; Hanefeld 2011; Jain 2006;

Johnston 1997; Kaku 2011; Lawrence 2004; LEAD-3 2006; Madsbad 2001; Marbury 1999; Segal 1997; Sutton 2002; Tan 2004; Tan 2004a; Tan 2005; Teramoto 2007; Tosi 2003; van de Laar 2004; Wolffenbuttel 1999; Yamanouchi 2005). However, some trials allowed the addition of an escape medicine of varying degrees (APPROACH 2010; Hermann 1991a; Hollander 1992; UGDP 1970; UKPDS 1998; UKPDS 34 1998; Wolffenbuttel 1989). In the UGDP trial addition of escape medicine was only allowed if the hyperglycaemia was associated with other clinical signs or symptoms, and the escape was one or more prescriptions for insulin during the trial (UGDP 1970). The sulphonylurea was continued unchanged. For the Glucose I trial half of the participants randomised to sulphonylurea were allocated to chlorpropamide (maximum 500 mg daily) and half to glibenclamide (maximum 10 mg twice daily) (UKPDS 1998). Until 1989, monotherapy was used if feasible but when maximal sulphonylurea doses were given and either the fasting plasma glucose rose to more than 15 mmol/L or symptoms developed, metformin was then added. From 1990 an amendment was made to maintain improved blood glucose control for a longer time in symptom-free sulphonylurea-allocated patients who developed fasting plasma glucose greater than 6 mmol/L on the maximal dose in the Glucose I trial. These patients were randomly allocated, half to the addition of metformin aiming for less than 6 mmol/L while the other half continued on sulphonylurea alone until the fasting plasma glucose was elevated to greater than 15 mmol/L or symptoms developed (UKPDS 1998). If the participants allocated to metformin monotherapy developed marked hyperglycaemia, glibenclamide was added with the aim of maintaining fasting plasma glucose below 6.0 mmol/L. If marked hyperglycaemia again developed, the patient was changed to insulin. For the participants in the Glucose II trial ultralente insulin was added if a patient on maximal sulphonylurea dose (chlorpropamide 500 mg once daily, glipizide 20 mg twice daily) had a mean of three successive fasting plasma glucose values above 108 mg/dl (6.0 mmol/L) (UKPDS 1998). In the Hollander 1992 trial, seven patients in the sulphonylurea group were switched to insulin due to poor glycaemic control (Hollander 1992). For the Hermann et al trial, 13 patients in both the sulphonylurea group and the metformin group required add-on therapy, but it was not further specified (Hermann 1991a). In the Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History (APPROACH) trial, 153 patients in the sulphonylurea and 152 in the pioglitazone group had metformin added (APPROACH 2010).

For the remaining included trials it was not clearly described if any of the participants had intervention failure to monotherapy, and what happened or would have happened in such case.

The APPROACH trial titrated all prior oral antidiabetic medications down by 50% at randomisation and they were discontinued one month after randomisation. The participants were therefore not exclusively treated with monotherapy at entry into the trial (APPROACH 2010).

The UGDP trial had a biguanide (phenformin) group that was not included in our analyses (UGDP 1970). The reason for not including the phenformin group from the UGDP trial was that this intervention was initiated later in the trial (after 18 months). The only insulin group included from the UGDP trial is the one from the 'insulin standard', as the 'insulin variable' was targeting a lower blood glucose level (UGDP 1970).

Excluded studies

Reasons for exclusion of studies are given in Characteristics of excluded studies. One hundred and three studies, described in 104 references, were excluded after further evaluation. The main reasons for exclusions were: the trial was not randomised (n = 37), not comparing interventions of interest (n = 31), duration of intervention less than 24 weeks (n = 31), participants were not patients with T2DM or we could not separate data on those patients with T2DM (n = 5). In three cases, we contacted the authors of the articles for clarification and received information (Chandra 2008; Mazzone 2006; Nissen 2008). For three other excluded studies we contacted the corresponding author to confirm the decision for exclusion, but never received an answer (Langenfeld 2005; Omrani 2005; Shinoda 2009). One of the trials was excluded because the duration of intervention was less than 24 weeks; the author wrote in the publication that data would be reported after one year, but we could not find the publication (Fuchs 1973).

Risk of bias in included studies

We performed the 'Risk of bias' assessment of the included trials using the previously described criteria (please see section, Assessment of risk of bias in included studies). For details of the judgements made for the individual trials, please see Risk of bias in included studies, Figure 2 and Figure 3. When a 'Risk of bias' domain could not be judged as low risk of bias, we asked the authors for additional information.

Random sequence generation

The generation of the allocation sequence was adequately described in 23 trials (ADOPT 2006; APPROACH 2010; Birkeland 1994; Diehl 1985; Esposito 2004; Fineberg 1980; Harrower 1985; Hermann 1991; Hermann 1991a; Hoffmann 1994; Kaku 2011; LEAD-3 2006; Nakamura 2006; Nathan 1988; Shihara 2011; Spengler 1992; Tan 2004; Tosi 2003; UGDP 1970; UKPDS 1998; UKPDS 34 1998; van de Laar 2004; Yamanouchi 2005). The remaining 49 trials were described as randomised but the method for sequence generation was not adequately described.

Allocation

The method used to conceal allocation was adequately described in 21 trials (ADOPT 2006; APPROACH 2010; Birkeland 1994; Derosa 2003; Diehl 1985; Esposito 2004; Fineberg 1980; Hermann 1991a; Kanda 1998; LEAD-3 2006; Nakamura 2004; Nakamura 2006; Nathan 1988; Tan 2004; Tosi 2003; UGDP 1970; UKPDS 1998; UKPDS 34 1998; van de Laar 2004; Watanabe 2005; Yamanouchi 2005). We judged the method for allocation concealment as unclear in the remaining 51 trials. There was agreement between the authors evaluating allocation concealment.

Blinding

The method of blinding of participants and investigators was adequate in 21 trials (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; APPROACH 2010; Birkeland 1994; Charbonnel 2005; Derosa 2003; Hanefeld 2011; Hermann 1991a; Johnston 1997; Madsbad 2001; Marbury 1999; Nakamura 2006; Nathan 1988; Pagano 1995; Perriello 2007; Tan 2004a; Tan 2005; Tosi 2003; van de Laar 2004; Wolffenbuttel 1999). We judged the method of blinding of participants and investigators as unclear or inadequate in the remaining 51 trials.

We judged the method of blinding of outcome assessors as adequate in 26 trials (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; APPROACH 2010; Charbonnel 2005; Derosa 2003; Diehl 1985; Esposito 2004; Hanefeld 2011; Harrower 1985; Hermann 1991a; Johnston 1997; Lawrence 2004; Madsbad 2001; Marbury 1999; Nakamura 2006; Nathan 1988; Pagano 1995; Perriello 2007; Tan 2005; Tosi 2003; UGDP 1970; UKPDS 1998; UKPDS 34 1998; van de Laar 2004; Wolffenbuttel 1999). For the remaining 46 trials we judged the blinding of outcome assessors as unclear or inadequate.

Incomplete outcome data

Incomplete data were addressed adequately in 37 trials (Abbatecola 2006; ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Alvarsson 2010; APPROACH 2010; Birkeland 1994; Campbell 1994; Coniff 1995; Derosa 2003; Derosa 2004; Feinböck 2003; Foley 2009; Forst 2003; Harrower 1985; Hermann 1991a; Hoffmann 1994; Jain 2006; Kaku 2011; Lawrence 2004; Madsbad 2001; Marbury 1999; Nakamura 2004; Nakamura 2006; Nathan 1988; Perriello 2007; Rosenthal 2002; Shihara 2011; Tan 2004; Tan 2004a; Tan 2005; Tessier 1999; van de Laar 2004; Watanabe 2005; Wolffenbuttel 1999; Yamanouchi 2005; Zhang 2005). For the remaining 35 trials we judged incomplete outcome data as unclear or inadequate.

Selective reporting

We judged selective outcome reporting as adequate in 21 trials (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; APPROACH 2010; Birkeland 1994; Diehl 1985; Esposito 2004; Foley 2009; Hermann 1991a; Kaku 2011; LEAD-3 2006; Madsbad 2001; Marbury 1999; Nakamura 2004; Segal 1997; Tan 2004; Tan 2004a; Tosi 2003; UGDP 1970; van de Laar 2004; Wolffenbuttel 1999). We judged five of the trials as high risk of selective outcome reporting (Birkeland 2002; Nakamura 2006; Shihara 2011; UKPDS 1998; UKPDS 34 1998). We judged the remaining 46 trials as unclear regarding selective outcome reporting.

Other potential sources of bias

We judged 62 of the trials as low risk of academic bias. We judged the risk of academic bias as high in 10 trials (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Hermann 1991a; Hoffmann 1994; Marbury 1999; Nakamura 2004; Nakamura 2006; Tan 2004; Tan 2004a; Tan 2005).

Only eight trials had not received funding from the pharmaceutical industry and we judged them as low risk of sponsor bias (Esposito 2004; Harrower 1985; Kanda 1998; Nakamura 2006; Sung 1999; Tang 2004; UGDP 1970; Zhang 2005). Sixteen of the trials did not report funding source and we judged them as unclear risk of sponsor bias (Abbatecola 2006; Campbell 1994; Dalzell 1986; Deng 2003; Derosa 2003; Derosa 2004; Hoffmann 1990; Hollander 1992; Jibran 2006; Kamel 1997; Kovacevic 1997; Memisogullari 2009; Nakamura 2004; Teramoto 2007; Watanabe 2005; Yamanouchi 2005). More than half of the trials received funding from the pharmaceutical industry (ADOPT 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Alvarsson 2010; APPROACH 2010; Birkeland 1994; Birkeland 2002; Charbonnel 2005; Collier 1989; Coniff 1995; DeFronzo 1995; Diehl 1985; Ebeling 2001; Feinböck 2003; Fineberg 1980; Foley 2009; Forst 2003; Forst 2005; Hanefeld 2011; Hermann 1991; Hermann 1991a; Hoffmann 1994; Jain 2006; Johnston 1997; Kaku 2011; Lawrence 2004; LEAD-3 2006; Madsbad 2001; Marbury 1999; Nathan 1988; Pagano 1995; Perriello 2007; Rosenthal 2002; Salman 2001; Segal 1997; Shihara 2011; Spengler 1992; Sutton 2002; Tan 2004; Tan 2004a; Tan 2005; Tessier 1999; Tosi 2003; UKPDS 1998; UKPDS 34 1998; van de Laar 2004; Wolffenbuttel 1989; Wolffenbuttel 1999).

Overall risk of bias

None of the trials was assessed as low risk of bias on all bias domains. We divided the trials according to our protocol into those with a lower risk of bias and those with high risk of bias based on the assessment of sequence generation, allocation concealment and blinding (participants, investigators and outcome assessors) - see 'Trials according to risk of bias' in Figure 2. These bias domains were all assessed as low risk of bias in only seven trials (ADOPT 2006; APPROACH 2010; Hermann 1991a; Nakamura 2006; Nathan 1988; Tosi 2003; van de Laar 2004).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings (first-generation sulphonylureas); **Summary of findings 2** Summary of findings (second-generation sulphonylureas); **Summary of findings 3** Summary of findings (third-generation sulphonylureas)

First-generation sulphonylureas versus placebo

Two trials included a comparison of a first-generation sulphonylurea versus placebo (Coniff 1995; UGDP 1970). Both trials were judged as high risk of bias (Coniff 1995; UGDP 1970). Both applied tolbutamide as the first-generation sulphonylurea. All-cause mortality was not significantly influenced by tolbutamide (random relative risk (RR) 1.46, 95% confidence interval (CI) 0.87 to 2.45; 553 participants, 2 trials, Analysis 1.1: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.65). Trial sequential analysis showed that only 1.5% of the diversity-adjusted required information size to detect or reject a 10% relative risk reduction (RRR) was accrued. Funnel plots could not be drawn. Best-worst case and worst-best case scenarios for all-cause mortality could not be performed, as it was not reported how many participants had unknown mortality status at the end of follow-up (Coniff 1995; UGDP 1970).

Cardiovascular mortality showed benefit in favour of placebo (random RR 2.63, 95% CI 1.32 to 5.22; P = 0.006; 553 participants, 2 trials, Analysis 1.4: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.93). Trial sequential analysis showed that only 0.7% of the diversity-adjusted required information size to detect or reject a 10% RRR was accrued. Funnel plots could not be drawn. Best-worst case and worst-best case scenarios could not be performed for cardiovascular mortality, as it was not reported how many participants had unknown mortality status at the end of follow-up (Coniff 1995; UGDP 1970).

We did not conduct subgroup analyses due to lack of data. Sensitivity analyses could not be performed due to lack of data.

Meta-analyses of the remaining outcomes could not be conducted due to lack of data. The UGDP trial reported 16 non-fatal myocardial infarctions in 204 participants allocated to tolbutamide and 20 non-fatal myocardial infarctions in 205 participants allocated to placebo (UGDP 1970). No participants in the tolbutamide or placebo group had any stroke (UGDP 1970). None of the participants from the tolbutamide group in the UGDP trial had amputation of lower extremity, whereas two participants in the placebo group had (UGDP 1970). In the UGDP trial five participants in the sulphonylurea group versus four participants in the placebo group had nephropathy during the trial (UGDP 1970). Fifty participants developed retinopathy in the sulphonylurea group and 54 developed retinopathy in the placebo group (UGDP 1970). Coniff 1995 reported a larger reduction in fasting blood glucose and HbA1c with tolbutamide compared with placebo (fasting blood glucose: mean -2.0 mmol/L; standard deviation (SD) 3.1 versus mean 0.1 mmol/L; SD 3.2; HbA1c: mean -0.9%; SD 1.04 versus 0.04%; SD 1.02) (Coniff 1995). The UGDP trial reported a rise in blood glucose for both the tolbutamide and the placebo group, but no SDs were provided, so the data could not be included in the analysis (UGDP 1970). The UGDP trial reported more participants with intervention failure from the placebo group (32 participants out of 205) compared with the sulphonylurea group (23 participants out of 204).

First-generation sulphonylureas versus diet

No trials assessed the effect of first-generation sulphonylureas versus diet.

First-generation sulphonylureas versus metformin

Three trials involved a comparison of first-generation sulphonylurea and a biguanide (Dalzell 1986; UGDP 1970; UKPDS 34 1998). Dalzell 1986 and UKPDS 34 were judged as high risk of bias (Dalzell 1986; UKPDS 34 1998). The only outcome reported from Dalzell 1986 was the fasting blood glucose (Dalzell 1986). The UKPDS trial reported data on the subgroup of overweight/obese participants randomised to chlorpropamide versus metformin (UKPDS 34 1998). Data from the UKPDS 34 are reported after three years of follow-up. The change in fasting blood glucose from baseline did not show any statistical significance (random mean difference (MD) 0.13 mmol/L, 95% CI -0.75 to 1.01; Fixed MD 0.03 mmol/L, 95% CI -0.31 to 0.37; 482 participants, 2 trials, Analysis 2.13: subgroup 1). Heterogeneity was present (I^2 = 84%; P = 0.01). The UKPDS 34 did not report the total number of participants who experienced a mild or severe hypoglycaemic episode at the end of the follow-up period. We therefore used the number of participants with hypoglycaemic episodes after one year of follow-up (UKPDS 34 1998). There were two patients experienced severe hypoglycaemia in the chlorpropamide group and one patient in the metformin group (UKPDS 34 1998). The UGDP trial had a phenformin group, which is not included in the analysis, as this intervention group was implemented in the trial 18 months after the other intervention groups (UGDP 1970).

First-generation sulphonylureas versus thiazolidinediones

No trials assessed the effect of first-generation sulphonylureas versus thiazolidinediones.

First-generation sulphonylureas versus insulin

Four trials investigated the effect of a first-generation sulphonylurea compared with insulin (Diehl 1985; UGDP 1970; UKPDS 1998; Wolffenbuttel 1989). All four trials were judged as high risk of bias (Diehl 1985; UGDP 1970; UKPDS 1998; Wolffenbuttel 1989). Two of the trials could not contribute any data to the

meta-analysis, as none of the outcomes were reported (Diehl 1985; Wolffenbuttel 1989). The UGDP trial applied tolbutamide and the UKPDS trial applied chlorpropamide as the first-generation sulphonylurea.

All-cause mortality was not significantly influenced by the interventions (random RR 1.18, 95% CI 0.88 to 1.59; fixed RR 1.14, 95% CI 0.95 to 1.37; 1944 participants, 2 trials, Analysis 4.1: subgroup 1). Funnel plots could not be drawn. Heterogeneity was moderate (I^2 = 32%; P = 0.23). D^2 was 61%. Trial sequential analysis showed that only 5.7% of the required information size to detect or reject a 10% RRR was accrued. Best-worst case and worst-best case scenarios for all-cause mortality could not be performed, as it was not reported how many participants had unknown mortality status at the end of follow-up (UGDP 1970; UKPDS 1998).

Cardiovascular mortality was not significantly influenced by the interventions (random RR 1.36, 95% CI 0.68 to 2.71; fixed RR 1.14, 95% CI 0.88 to 1.48; 1944 participants, 2 trials, Analysis 4.4: subgroup 1). Funnel plots could not be drawn. Heterogeneity was present (I^2 = 75%; P = 0.04). D^2 was 86%. Trial sequential analysis showed that only 1.1% of the required information size to detect or reject a 10% RRR was accrued. Best-worst case and worst-best case scenarios could not be performed for cardiovascular mortality, as it was not reported how many participants had unknown mortality status at the end of follow-up (UGDP 1970; UKPDS 1998).

We did not conduct subgroup analyses, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups. Sensitivity analysis could not be performed due to lack of data.

Non-fatal myocardial infarction was not significantly influenced by the interventions (random RR 1.08, 95% CI 0.81 to 1.45; 1944 participants, 2 trials, Analysis 4.5: subgroup 1). Heterogeneity was absent (I^2 = 0; P = 0.97). Non-fatal stroke was reported in 56 participants in the UKPDS trial and one participant in the UGDP trial. Meta-analysis did not show statistical significance (random RR 1.23, 95% CI 0.74 to 2.05; 1944 participants, 2 trials, Analysis 4.6; subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.43). None of the participants in the tolbutamide and insulin groups of the UGDP trial experienced amputation of the lower extremity, and therefore only the UKPDS trial provided data (five amputations in 619 participants allocated to chlorpropamide versus 15 amputations in 911 participants allocated to insulin) (UGDP 1970; UKPDS 1998). A composite microvascular outcome was reported in the UKPDS trial in 68 participants out of 619 randomised to chlorpropamide and in 77 participants out of 911 participants randomised to insulin (UKPDS 1998). Nephropathy was reported in the UGDP in five participants out of 204 in the tolbutamide group and in no participants of the 210 randomised to insulin (UGDP 1970). In the UGDP trial retinopathy was reported in 50 participants out of 204 randomised to tolbutamide and in 52 participants out of 210 randomised to insulin (UGDP 1970). In the UKPDS trial 55 participants out of 619 randomised to chlorpropamide and 72 participants out of 911 randomised to insulin experienced retinal photocoagulation (UKPDS 1998). The UKPDS trial reported the end of follow-up value after three years intervention for fasting blood glucose, HbA1c and weight (fasting blood glucose: mean 7.0 mmol/L; standard deviation (SD) 2.2 versus mean 7.4 mmol/L; SD 2.7; HbA1c: mean 6.8%; SD 1.6 versus 7.0%; SD 1.3; weight: mean 77.9 kg; SD 15.1 versus 80.2 kg; SD 15.3). The number of participants with one or more severe hypoglycaemic episode during the first year of intervention were 2 participants for chlorpropamide and 5 participants for insulin. The UGDP trial reported any cancer and the UKPDS trial reported death due to cancer. The effect estimate of cancer when meta-analysing the data did not show significant differences in the effect estimate (random RR 0.81, 95% CI 0.29 to 2.27; fixed RR 1.04, 95% CI 0.70 to 1.55; 1944 participants, 2 trials, Analysis 4.20: subgroup 1). The remaining outcomes could not be meta-analysed due to lack of data.

First-generation sulphonylureas versus other comparators

Alpha-glucosidase inhibitor

Two trials assessed the effect of tolbutamide versus an alpha-glucosidase inhibitor (Coniff 1995; van de Laar 2004). One trial was assessed as high risk of bias (Coniff 1995) and one trial was assessed as lower risk of bias (van de Laar 2004). One death was reported in 246 participants. The death was reported in Coniff 1995. No participants died in the van de Laar trial (van de Laar 2004). Meta-analysis could not be performed as only one trial reported fatal events. The same was the case for cardiovascular mortality.

The change in fasting blood glucose from baseline was significantly lower with tolbutamide compared with alpha-glucosidase inhibitor (random MD -1.16 mmol/L, 95% CI -1.92 to -0.41; P = 0.003; 208 participants, 2 trials, Analysis 5.15: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.53). Trial sequential analysis showed that firm evidence was established disregarding risk of bias. The change in HbA1c was also in favour of tolbutamide (random MD -0.50%, 95% CI -0.79 to -0.20; P = 0.0009; 208 participants, 2 trials, Analysis 5.16: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.35). Trial sequential analysis showed that firm evidence was established disregarding risk of bias.

The risk of adverse events was in favour of tolbutamide (random RR 0.63, 95% CI 0.52 to 0.76; P < 0.00001; 246 participants, 2 trials, Analysis 5.19: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.49). The risk of drop-outs due to adverse events was also increased in favour of the first-generation sulphonylurea (RR 0.28, 95% CI 0.12 to 0.67; P = 0.004; 246 participants, 2 trials, Analysis 5.21: subgroup 1). Heterogeneity was absent (I^2 = 0%; P = 0.34). Trial sequential analysis showed that firm evidence for a 10% RRR was not established.

The remaining outcomes could not be meta-analysed due to lack of data.

We did not identify other trials comparing first-generation sulphonylureas with other comparators.

Second-generation sulphonylureas versus placebo

Seven trials compared a second-generation sulphonylurea with placebo (Birkeland 1994; Ebeling 2001; Hoffmann 1994; Johnston 1997; Kamel 1997; Kovacevic 1997; Segal 1997). All of the trials were judged as high risk of bias. Two of the trials applied two second-generation sulphonylureas, which were combined. Birkeland 1994 had two groups with sulphonylureas (a glibenclamide group and a glipizide group) (Birkeland 1994), and Kamel 1997 had a gliclazide and glibenclamide group (Kamel 1997). Glibenclamide was used as the only second-generation sulphonylurea in the remaining trials (Ebeling 2001; Hoffmann 1994; Johnston 1997; Kovacevic 1997; Segal 1997).

Three trials reported all-cause mortality (Hoffmann 1994; Johnston 1997; Kovacevic 1997), but only one of the trials reported two deaths in the second-generation sulphonylurea group, and meta-analysis could therefore not be performed (Johnston 1997). Meta-analysis could not be performed for cardiovascular mortality for the same reason (only one death in one trial, Johnston 1997).

The macrovascular and microvascular outcomes could not be meta-analysed due to lack of data.

Fasting blood glucose was significantly lowered with second-generation sulphonylureas compared with placebo (random MD -1.20 mmol/L, 95% CI -1.94 to -0.46; P = 0.002; fixed MD -1.28 mmol/L, 95% CI -1.61 to -0.95; P < 0.00001, 214 participants, 5 trials, Analysis 1.10: subgroup 2). Heterogeneity was present (I^2 = 65%; P = 0.02). D^2 was 80%. Trial sequential analysis showed that firm evidence was established disregarding risk of bias. HbA1c was also significantly reduced with a second-generation sulphonylurea compared with placebo (random MD -1.02%, 95% CI -1.32 to -0.72; P < 0.00001; fixed MD -1.01%, 95% CI -1.19 to -0.83; P < 0.00001; 214 participants, 5 trials, Analysis 1.11: subgroup 2). Heterogeneity was present (I^2 = 39%; P = 0.16). D^2 was 66%. Trial sequential analysis showed that firm evidence was established disregarding risk of bias. There was no significant influence on the change of body mass index (BMI) from baseline with a second-generation sulphonylurea compared with placebo (random MD -0.09 kg/m^2, 95% CI -0.59 to 0.41; fixed MD -0.16 kg/m^2, 95% CI -0.45 to 0.14; 141 participants, 3 trials, Analysis 1.12: subgroup 2). Heterogeneity was present (I^2 = 8%, P = 0.34).

Two trials reported adverse events (Kovacevic 1997; Segal 1997). There was no significant difference in the incidence of adverse events between the interventions (random RR 0.91, 95% CI 0.51 to 1.62; 202 participants, 2 trials, Analysis 1.14: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.84). The number of drop-outs due to adverse events did not significantly differ between the interventions (random RR 0.62, 95% CI 0.24 to 1.57; fixed RR 0.62, 95% 0.29 to 1.31; 510 participants, 5 trials, Analysis 1.15: subgroup 2). Heterogeneity was present (I^2 = 15%; P = 0.32). Intervention failure was significantly changed in favour of second-generation sulphonylureas (RR 0.13, 95% CI 0.04 to 0.44; P = 0.001; 385 participants, 3 trials, Analysis 1.19: subgroup 2). Trial sequential analysis showed that firm evidence for a 10% RRR was not established. Heterogeneity was absent (I^2 = 0%; P = 0.80). The remaining meta-analyses could not be performed due to lack of data.

Second-generation sulphonylureas versus diet

Only one trial compared sulphonylurea therapy (gliclazide) versus diet (Memisogullari 2009). The trial was judged as high risk of bias (Memisogullari 2009). Meta-analyses for this comparison could not be performed. Both the participants in the intervention group and control group received diet. No participants in any of the intervention groups died. There were no data reported on any of the other outcomes of interest for our systematic review.

Second-generation sulphonylureas versus metformin

Eleven trials investigated the effect of second-generation sulphonylureas versus metformin (ADOPT 2006; Campbell 1994; Collier 1989; DeFronzo 1995; Hermann 1991; Hermann 1991a; Kamel 1997; Lawrence 2004; Tessier 1999; Tosi 2003; UKPDS 34 1998). Eight of the trials were judged as high risk of bias (Campbell 1994; Collier 1989; DeFronzo 1995; Hermann 1991; Kamel 1997; Lawrence 2004; Tessier 1999; UKPDS 34 1998) and only three of the trials were judged as lower risk of bias (ADOPT 2006; Hermann 1991a; Tosi 2003). Most of the trials applied glibenclamide as the second-generation sulphonylurea (ADOPT 2006; Hermann 1991; Hermann 1991a; DeFronzo 1995; Kamel 1997; Tosi 2003; UKPDS 34 1998). Four trials used gliclazide (Collier 1989; Kamel 1997; Lawrence 2004; Tessier 1999). One trial used glipizide (Campbell 1994). From the UKPDS 34 trial data were included after three years of follow-up, except for hypoglycaemia which were after one year of follow-up (UKPDS 34 1998). Data from the end of the intervention period of the UKPDS 34 trial could not be included in the analyses (UKPDS 34 1998).

The effect estimate of all-cause mortality was dominated by the A Diabetes Outcome Progression Trial (ADOPT) trial, which contributed 62 out of 65 fatal events (ADOPT 2006). All-cause mortality was not significantly influenced by the intervention (random RR 0.98, 95% CI 0.61 to 1.58; 6 trials, 3528 participants, Analysis 2.1: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.68). Funnel plots could not be drawn. Sensitivity analysis excluding the trial with the longest duration (ADOPT 2006) did not change the significance of the effect estimate (random RR 0.71, 95% CI 0.11 to 4.42; fixed RR 0.73, 95% CI 0.15 to 3.58). Analysis of the trials not describing how the diagnosis of type 2 diabetes

mellitus (T2DM) was established did not show any significance in the effect estimate (random RR 1.01, 95% CI 0.62 to 1.63). Heterogeneity was absent (I^2 = 0%; P = 0.59). Only one trial with fatal events stated how the diagnosis of T2DM was established (DeFronzo 1995). Sensitivity analysis according to the language of publication could not be performed, as all trials were published in English. All trials had received funding from the pharmaceutical industry or did not describe how they were funded. Sensitivity analysis according to funding source could therefore not be performed. None of the trials were unpublished, so sensitivity analysis according to publication status could not be performed. Trial sequential analysis showed that only 2.3% of the required information size to detect or reject a 10% RRR was accrued.

The best-worst case-scenario and worst-best case-scenario analyses were only based on two fatal events from two trials in which all participants had known vital status at the end of follow-up (Hermann 1991a; Lawrence 2004). The effect estimate did not show any statistical significance (best-worst case scenario and worst-best case scenario: random RR 1.02, 95% CI 0.10 to 10.25; fixed RR 1.03, 95% CI 0.15 to 6.87; 4 trials, 207 participants, Analysis 2.2: Analysis 2.3: subgroup 2). Heterogeneity was present (I^2 = 6%; P = 0.30).

The comparison of second-generation sulphonylurea versus metformin did not show statistical significance for cardiovascular mortality (random RR 1.47, 95% CI 0.54 to 4.01; 6 trials, 3528 participants, Analysis 2.4: subgroup 2). The total number of deaths due to cardiovascular disease was 15, of which 12 were from the ADOPT trial (ADOPT 2006). Heterogeneity was absent (I^2 = 0%; P = 0.52). Sensitivity analysis excluding the trial with the longest duration (ADOPT 2006) did not change the significance of the effect estimate (random RR 0.71, 95% CI 0.11 to 4.42). Heterogeneity was absent (I^2 = 0%; P = 0.50). Analysis of the trials not describing how the diagnosis of T2DM was established did not show any significance in the effect estimate (random RR 1.73, 95% CI 0.60 to 4.97). Heterogeneity was absent (I^2 = 0%; P = 0.51). Only one trial with fatal events due to cardiovascular disease stated how the diagnosis of T2DM was established (DeFronzo 1995). Sensitivity analysis according to the language of publication could not be performed, as all trials were published in English. All trials had received funding from the pharmaceutical industry or did not describe how they were funded. Sensitivity analysis according to funding source could therefore not be performed. None of the trials were unpublished, so sensitivity analysis according to publication status could not be performed. Trial sequential analysis showed that 2.7% of the required information size to detect or reject a 10% RRR was accrued.

Subgroup analyses were not conducted, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

Non-fatal macrovascular outcomes as a composite outcome were not reported in the way we predefined to assess the outcome. The ADOPT trial and Hermann 1991a were reported in a way which may involve other cardiac outcomes than those with arteriosclerotic origin (ADOPT 2006; Hermann 1991a). Tosi 2003 reported that no cardiovascular events were recorded during the trial (Tosi 2003). We meta-analysed the data as non-fatal macrovascular outcomes and found a statistical significance of the effect estimate in favour of second-generation sulphonylureas (random RR 0.67, 95% CI 0.48 to 0.93; P = 0.02; 3 trials, 3018 participants, Analysis 2.5: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.53). However, the macrovascular outcomes from the ADOPT trial included congestive heart failure (19 participants in the metformin group and nine participants in the glibenclamide group), which might not have an arteriosclerotic origin. Due to the way that 'cardiovascular disease' is reported in the ADOPT trial it is not possible to exclude the number with congestive heart failure. Trial sequential analysis showed that only 5% of the required information size to detect or reject a 10% RRR has been accrued. Thirty-nine non-fatal myocardial infarctions were reported, of which 36 were from the ADOPT trial (ADOPT 2006). The effect estimate did not show statistically significant differences (random RR 1.02, 95% CI 0.37 to 2.85; fixed RR 0.87, 95% CI 0.48 to 1.60; 4 trials, 3061 participants, Analysis 2.6: subgroup 2). Heterogeneity was present (I^2 = 15%; P = 0.31). The remaining macrovascular and microvascular outcomes could not be meta-analysed due to lack of data.

The change in fasting blood glucose from baseline showed statistical significance(random MD 0.43 mmol/L, 95% CI 0.10 to 0.75; P = 0.009; fixed MD 0.42 mmol/L, 95% CI 0.28 to 0.56; P < 0.00001; 11 trials, 3891 participants, Analysis 2.13: subgroup 2). Heterogeneity was present (I^2 = 44%; P = 0.06). Diversity was 81%. Trial sequential analysis showed that firm evidence for the achieved changes was not present. The change in HbA1c from baseline did not show statistical significance in the random-effects model, but showed statistical significance in favour of metformin in the fixed-effect model (random MD 0.17%, 95% CI -0.09 to 0.44; fixed MD 0.25%, 95% CI 0.18 to 0.33; P < 0.00001; 10 trials, 3351 participants; Analysis 2.14: subgroup 2). Heterogeneity was present (I^2 = 72%; P = 0.0002). One of the trials in the analyses of fasting blood glucose and HbA1c change from baseline allowed the addition of escape medicine when monotherapy failed, but we included only data on the participants who remained on monotherapy (Hermann 1991a). The UKPDS 34 trial also allowed addition of escape medicine in case of monotherapy failure (UKPDS 34 1998). Elimination of this trial from the analysis did not change the significance of the effect estimate for fasting blood glucose.

Change in BMI from baseline did not showstatistical significance in the random-effects model, but showed statistical significance in favour of metformin in the fixed-effect model (random MD 0.25 kg/m^2, 95% CI -1.21 to 1.70; fixed MD 0.54 kg/m^2, 95% CI 0.06 to 1.03; P = 0.03; 3 trials, 103 participants, Analysis 2.15: subgroup 2). Heterogeneity was present (I^2 = 71%; P = 0.03). However, only one of the trials included in the meta-analysis of

changes in BMI from baseline reported the actual change of the mean and standard deviation in each of the intervention groups (Tosi 2003). For the remaining two trials the end of follow-up values were used (Collier 1989; Lawrence 2004). Both of these trials had relatively small sample size and the sulphonylurea group had lower BMI compared with the metformin group at baseline and at the end of follow-up. The change in weight from baselineshowed statistical significance in favour of metformin (random MD 3.77 kg, 95% CI 3.06 to 4.47; P < 0.00001; fixed MD 3.76, 95% CI 3.35 to 4.48; P < 0.00001; 7 trials, 3497 participants, Analysis 2.16: subgroup 2). Heterogeneity was present (I^2 = 39%; P = 0.13); diversity was 65%. Trial sequential analysis showed firm evidence for the achieved reduction of weight disregarding risk of bias.

The effect estimate for adverse events was not significantly influenced by the interventions (random RR 0.99, 95% CI 0.97 to 1.01; 4 trials, 3042 participants, Analysis 2.17: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.71). The effect estimate of serious adverse events did not show any significance (random RR 0.94, 95% CI 0.82 to 1.07; 4 trials, 3011 participants, Analysis 2.18: subgroup 2). Six hundred and forty-one participants reported a serious adverse event, of which 639 were from the ADOPT trial. Heterogeneity was absent (I^2 = 0%; P = 0.99). Drop-outs due to adverse events were not significantly influenced by the interventions, but showed a tendency to favour metformin (random RR 1.19, 95% CI 0.99 to 1.42, 7 trials, 3567 participants, Analysis 2.19: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.54).

Mild hypoglycaemia was significantly increased in favour of metformin (random RR 2.95, 95% CI 2.13 to 4.07; P < 0.00001; fixed RR 3.24, 95% CI 2.80 to 3.76; P < 0.00001; 5 trials, 4056 participants, Analysis 2.20: subgroup 2). Heterogeneity was present (I^2 = 29%; P = 0.23). D^2 was 79%. Trial sequential analysis showed that only 2.9% of the required information size to detect or reject a 10% RRR was accrued so far. Severe hypoglycaemia showed statistical significant differences in favour of metformin (random RR 5.64, 95% CI 1.22 to 26.00; P = 0.03; 4 trials, 3637 participants, Analysis 2.22: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.62). Trial sequential analysis showed that only 0.1% of the required information size to detect or reject a 10% RRR was accrued. Due to a relatively large number of participants lost to follow-up for the hypoglycaemia data in the UKPDS trial, available case analysis was also performed with the UKPDS trial data, which did not change the statistical significance of mild or severe hypoglycaemia.

Intervention failure with monotherapy was not significantly influenced by the interventions in the random-effects model (random RR 0.97, 95% CI 0.60 to 1.57; 7 trials, 4143 participants, Analysis 2.24: subgroup 2), but showed significance in the fixed-effect model favouring metformin (fixed RR 1.35, 95% CI 1.17 to 1.55; P < 0.0001). Heterogeneity was present (I^2 = 69%; P = 0.006).

Second-generation sulphonylureas versus thiazolidinediones

Seventeen trials assessed the effect of a second-generation sulphonylurea versus thiazolidinediones (ADOPT 2006; APPROACH 2010; Charbonnel 2005; Ebeling 2001; Hanefeld 2011; Jain 2006; Lawrence 2004; Nakamura 2004; Nakamura 2006; Perriello 2007; Sung 1999; Sutton 2002; Tan 2004a; Tan 2005; Teramoto 2007; Watanabe 2005; Zhang 2005). Fourteen of the trials were assessed as high risk of bias (Charbonnel 2005; Ebeling 2001; Hanefeld 2011; Jain 2006; Lawrence 2004; Nakamura 2004; Perriello 2007; Sung 1999; Sutton 2002; Tan 2004a; Tan 2005; Teramoto 2007; Watanabe 2005; Zhang 2005). Only three of the trials were judged as lower risk of bias (ADOPT 2006; APPROACH 2010; Nakamura 2006). Charbonnel 2005 was a double-blind trial lasting for 52 weeks (Charbonnel 2005). Some of the included trial centres in Charbonnel were invited to continue the trial in double-blind manner for an additional 52 weeks (Tan 2005). The baseline data we report from Tan 2005 are taken after the participants have been included for 52 weeks of Charbonnel 2005 (Tan 2005). For outcomes where both Charbonnel 2005 and Tan 2005 were included, we conducted a sensitivity analysis, excluding Tan 2005 (Charbonnel 2005; Tan 2005).

Most of the trials applied glibenclamide as the second-generation sulphonylurea (ADOPT 2006; Ebeling 2001; Hanefeld 2011; Jain 2006; Nakamura 2004; Nakamura 2006; Sung 1999; Sutton 2002; Tan 2004a; Teramoto 2007; Watanabe 2005). Four of the trials applied gliclazide (Charbonnel 2005; Lawrence 2004; Perriello 2007; Tan 2005). However, Tan 2005 is an extension of Charbonnel 2005. Two trials applied glipizide (APPROACH 2010; Zhang 2005).

Three different kinds of thiazolidinediones were applied. Most of the trials applied pioglitazone (Charbonnel 2005; Ebeling 2001; Jain 2006; Lawrence 2004; Nakamura 2004; Nakamura 2006; Perriello 2007; Tan 2004a; Tan 2005; Teramoto 2007; Watanabe 2005). Five trials applied rosiglitazone (ADOPT 2006; APPROACH 2010; Hanefeld 2011; Sutton 2002; Zhang 2005) and one trial troglitazone (Sung 1999).

Most of the fatal events were reported by two trials (ADOPT 2006; APPROACH 2010). There was no statistically significant difference of second-generation sulphonylureas versus thiazolidinediones in the effect estimate of all-cause mortality (random RR 0.92, 95% CI 0.60 to 1.41; 7 trials, 4955 participants, Analysis 3.1: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.62). Sensitivity analysis excluding the trial with the longest duration (ADOPT 2006) did not change the effect estimate (random RR 0.92, 95% CI 0.37 to 2.29). Heterogeneity was absent (I^2 = 0%; P = 0.41). Only one trial described how the diagnosis of T2DM was established (APPROACH 2010). Excluding this trial from the analysis did not change the significance of the effect estimates (random RR 0.93, 95% CI 0.58 to 1.49). Heterogeneity was absent (I^2 = 0%; P = 0.42). All trials reporting all-cause mortality were published in English, so sensitivity analysis according to lan-

guage of publication could not be performed. Sensitivity analysis according to source of funding could not be performed, as all trials were either funded by the pharmaceutical industry or did not report their funding source. Sensitivity analysis according to publication status could not be performed as all trials were published. Trial sequential analysis showed that only 2.5% of the required information size to detect or reject a 10% RRR was accrued. Separate analysis for all-cause mortality of the trials applying rosiglitazone showed no statistical significance (random RR 0.91, 95% CI 0.59 to 1.40). Heterogeneity was absent (I^2 = 0%; P = 0.59). Three trials provided data for this analysis (ADOPT 2006; APPROACH 2010; Hanefeld 2011). For the analysis of the trials applying pioglitazone, only three fatal events were reported. The effect estimate did not show significance (random RR 1.23, 95% CI 0.07 to 20.96; fixed RR 1.39, 95% CI 0.24 to 7.88). Funnel plots could not be drawn. Best-worst case scenario analysis showed significance in favour of second-generation sulphonylurea (random RR 0.18, 95% CI 0.06 to 0.54; P = 0.002; fixed RR 0.19, 95% CI 0.09 to 0.38; P < 0.00001; 4 trials, 1252 participants, Analysis 3.2: subgroup 2). Worst-best case scenario analysis only showed statistical significance in the fixed-effect model (random RR 9.76, 95% CI 0.59 to 161.27; P = 11; fixed RR 6.09, 95% CI 2.98 to 12.45; P < 0.00001; 4 trials, 1252 participants, Analysis 3.3: subgroup 2).

Twenty-one events of cardiovascular mortality were reported. There was no statistical significance of second-generation sulphonylurea versus thiazolidinediones in the effect estimate of cardiovascular mortality (random RR 1.30, 95% CI 0.55 to 3.07; 7 trials, 4955 participants, Analysis 3.4: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.62). Analysis according to type of thiazolidinediones applied could not be performed as only one trial applying pioglitazone reported one event (Jain 2006). Sensitivity analysis excluding the longest trial (ADOPT 2006) did not change the significance of the effect estimate (random RR 0.95, 95% CI 0.25 to 3.65). Heterogeneity was absent (I^2 = 0%; P = 0.43). Only one trial described how the diagnosis of T2DM was established (APPROACH 2010). Excluding this trial from the analysis did not change the significance of the effect estimate (random RR 1.72, 95% CI 0.60 to 4.94). Heterogeneity was absent (I^2 = 0%; P = 0.72). All trials reporting cardiovascular mortality were published in English, so sensitivity analysis according to language of publication could not be performed. Sensitivity analysis according to source of funding could not be performed, as all trials were either funded by the pharmaceutical industry or did not report their funding source. Sensitivity analysis according to publication status could not be performed as all trials were published. Trial sequential analysis showed that only 0.3% of the required information size to detect or reject a 10% RRR was accrued.

We did not perform subgroup analyses.

The definition of the macrovascular outcome from the APPROACH trial included all-cause mortality; the remaining outcomes in the composite outcome were of atherosclerotic origin (APPROACH 2010). Data from the remaining trials were reported as cardiovascular events (ADOPT 2006; Jain 2006; Perriello 2007; Sutton 2002) (please see Appendix 7). The meta-analysis of the trials did not show statistical significance in the effect estimate of the interventions (random RR 0.91, 95% CI 0.62 to 1.33; fixed RR 0.87, 95% CI 0.68 to 1.11; 6 trials, 4600 participants, Analysis 3.5: subgroup 2). Heterogeneity was present (I^2 = 50%; P = 0.09). The risk of non-fatal myocardial infarction was not statistically significantly influenced by the interventions (random RR 0.68, 95% CI 0.41 to 1.14; 7 trials, 4956 participants, Analysis 3.6: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.94). Separate analysis of the trials applying rosiglitazone (ADOPT 2006; APPROACH 2010; Hanefeld 2011) did not change the statistical significance of the effect estimate (random RR 0.66, 95% CI 0.38 to 1.13). Heterogeneity was absent (I^2 = 0%; P = 0.87). The APPROACH trial reported one participant with non-fatal stroke in 339 participants randomised to sulphonylurea and five participants with non-fatal stroke in 333 participants randomised to thiazolidinediones (APPROACH 2010). Nakamura 2006 reported zero participants with non-fatal stroke in both intervention groups (Nakamura 2006). Meta-analysis of non-fatal stroke could therefore not be performed. Two trials reported zero participants in both intervention groups for amputation of lower extremity (APPROACH 2010; Nakamura 2006). Cardial revascularisation was reported in 27 participants out of 339 randomised to sulphonylurea and in 26 participants out of 333 randomised to thiazolidinediones in the APPROACH trial (APPROACH 2010). Nakamura reported zero participants with cardial revascularisation in both intervention groups (Nakamura 2006). The ADOPT trial reported 31 participants with peripheral revascularisation out of 1447 participants randomised to sulphonylurea and 36 participants with need of peripheral revascularisation in 1458 participants randomised to thiazolidinediones (ADOPT 2006). Two other trials reported zero participants with peripheral revascularisation in both intervention groups (APPROACH 2010; Nakamura 2006). Only one trial reported data for the composite microvascular outcome with one participant experiencing a microvascular outcome in each intervention group (Tan 2004a). Another trial reported zero participants in each intervention group exploring any microvascular outcomes (Nakamura 2006). Nephropathy was reported in zero of the 339 participants randomised to sulphonylurea and in four of the 333 participants randomised to thiazolidinediones in the APPROACH trial (APPROACH 2010). One participant in each intervention group of the APPROACH trial experienced diabetic retinopathy (APPROACH 2010). None of the participants in any of the intervention groups of the APPROACH trial had any retinal photocoagulation (APPROACH 2010).

The change in fasting blood glucose from baseline showed statistical significance of the effect estimate in favour of thiazolidinediones (random MD 0.56 mmol/L, 95% CI 0.33 to 0.79; P < 0.00001; fixed MD 0.75 mmol/L, 95% CI 0.64 to 0.85; P <

0.00001; 14 trials, 6076 participants, Analysis 3.15: subgroup 2). Heterogeneity was present (I^2 = 66%; P = 0.0002). Diversity was 79%. Trial sequential analysis showed that firm evidence was established disregarding risk of bias. Excluding Tan 2005, so that the participants who are analysed in Charbonnel 2005 were not counted twice did not change the statistical significance of the effect estimate (Charbonnel 2005; Tan 2005). Removing the APPROACH trial, which applied additional glucose-lowering drugs in case of intervention failure did also not change the statistical significance of the effect estimate (APPROACH 2010). The changes in HbA1c did not show statistical significance in the random-effects model (random MD 0.06%, 95% CI -0.090 to 0.20; 17 trials, 6776 participants, Analysis 3.16: subgroup 2). Statistical significance was present in the fixed-effect model in favour of thiazolidinediones (fixed MD 0.19%, 95% CI 0.14 to 0.24; P < 0.00001). Removing the APPROACH trial, which allowed addition of escape medicine did not change the significance of the effect estimate (APPROACH 2010). Heterogeneity was present (I^2 = 85%; P < 0.00001). Excluding Tan 2005, so that the participants in Charbonnel 2005 were not counted twice, did not change the statistical significance of the effect estimate (Charbonnel 2005; Tan 2005).

The change in BMI from baseline was changed in favour of second-generation sulphonylureas (random MD -1.00 kg/m^2, 95% CI -1.20 to -0.80; P < 0.00001; 4 trials, 121 participants, Analysis 3.17: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.98). Trial sequential analysis showed that firm evidence was not established. Weight change from baseline was changed in favour of second-generation sulphonylureas (random MD -1.90 kg, 95% CI -2.56 to -1.25; P < 0.00001; fixed MD -2.00 kg, 95% CI -2.24 to -1.76; P < 0.00001; 10 trials, 5779 participants, Analysis 3.18: subgroup 2). Heterogeneity was present (I^2 = 82%; P = 0.00001). Diversity was 87%. Trial sequential analysis showed firm evidence for the achieved reductions of weight disregarding risk of bias. As Tan 2005 is an extension for some of the participants in Charbonnel 2005 we performed a sensitivity analysis with and without the data from Tan 2005 (Charbonnel 2005; Tan 2005), which did not change the significance of the effect estimate.

A total of 5141 participants reported an adverse event. Adverse events did not show significant differences in the effect estimate between the two interventions (random RR 0.99, 95% CI 0.97 to 1.01; fixed RR 0.98, 95% CI 0.96 to 1.01; 10 trials, 6491 participants, Analysis 3.19: subgroup 2). Heterogeneity was low (I^2 = 2%; P = 0.42). Most of the participants reporting serious adverse events were from the ADOPT trial (654 out of 909). The effect estimate showed a non-significant effect in favour of second-generation sulphonylureas (random RR 0.90, 95% CI 0.80 to 1.01; 8 trials, 4979 participants, Analysis 3.20: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.81). Drop-outs due to adverse events did not show significant differences in the effect estimate in the random-effects model (random RR 1.15, 95% CI 0.98 to 1.36; 15 trials, 7433 participants, Analysis 3.21: subgroup 2), but showed significant differences in the fixed-effect model (fixed RR 1.17, 95% CI 1.01 to 1.35; P = 0.03). Heterogeneity was present (I^2 = 5%; P = 0.39).

Mild hypoglycaemia was experienced by more participants receiving second-generation sulphonylureas compared with thiazolidinediones (random RR 4.05, 95% 3.28 to 5.00; P < 0.00001; fixed RR 4.01, 95% CI 3.48 to 4.61; P < 0.00001; 8 trials, 6365 participants, Analysis 3.22: subgroup 2). Heterogeneity was present (I^2 = 21%; P = 0.27). Diversity was 55%. Trial sequential analysis showed firm evidence for a 10% RRR in favour of thiazolidinediones disregarding risk of bias. Severe hypoglycaemia was only reported in one participant receiving thiazolidinediones (ADOPT 2006). The risk of severe hypoglycaemia was significantly elevated for the participants receiving a second-generation sulphonylurea (random RR 6.11, 95% CI 1.57 to 23.79; P = 0.009; 6 trials, 5660 participants, Analysis 3.24: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.97). Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR was accrued.

Cancer was not significantly different between the two interventions (random RR 1.02, 95% CI 0.72 to 1.45; 6 trials, 4912 participants, Analysis 3.25: subgroup 2). Most cancers were reported from the ADOPT trial (110 out of 119), which besides being the largest trial also had a reporting of cancer that might have led to more events being reported compared with APPROACH trial which only reported death due to cancer (ADOPT 2006; APPROACH 2010). Heterogeneity was absent (I^2 = 0%; P = 0.79).

The incidence of intervention failure did not significantly differ between the thiazolidinediones and the second-generation sulphonylureas in the random-effects model (random RR 1.10, 95% CI 0.73 to 1.65; 8 trials, 6438 participants, Analysis 3.26: subgroup 2), but favoured thiazolidinediones in the fixed-effect model (fixed RR 1.43, 95% CI 1.28 to 1.59; P < 0.00001).

Nakamura 2006 reported that quality of life was improved in all intervention groups during the trial, but no scale was provided (Nakamura 2006).

Second-generation sulphonylureas versus insulin

Six trials included a comparison between a second-generation sulphonylurea versus insulin (Alvarsson 2010; Birkeland 2002; Forst 2003; Hollander 1992; Nathan 1988; UKPDS 1998). Five of the trials were judged as high risk of bias (Alvarsson 2010; Birkeland 2002; Forst 2003; Hollander 1992; UKPDS 1998) and only one of the trials was judged as lower risk of bias (Nathan 1988).

Four trials reported 309 fatal events, of which 98.7% were reported from the UKPDS trial. There was no statistically significant difference between second-generation sulphonylureas versus insulin in the effect estimate of all-cause mortality (random RR 0.96, 95% CI 0.79 to 1.18; 4 trials, 1642 participants, Analysis

4.1: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.64). Funnel plots could not be drawn. Sensitivity analysis excluding the largest trial (UKPDS 1998) did not change the statistical significance of the effect estimate (random RR 0.40, 95% CI 0.06 to 2.60). Heterogeneity was absent (I^2 = 0%; P = 0.89). Only one trial did not report how the diagnosis of T2DM was established (Alvarsson 2010). Excluding this trial did not change the significance of the effect estimate (RR 0.97, 95% CI 0.79 to 1.19). Heterogeneity was absent (I^2 = 0%; P = 0.50). All trials reporting all-cause mortality were published in English, so sensitivity analysis according to language of publication could not be performed. Sensitivity analysis according to source of funding could not be performed, as all the trials were funded by the pharmaceutical industry. Sensitivity analysis according to publication status could not be performed as all trials were published. Trial sequential analysis showed that only 12.8% of the required information size to detect or reject a 10% RRR for all-cause mortality was accrued. Worst-best case and best-worst case scenario analyses could not be performed due to lack of data.

There was no statistical significance of second-generation sulphonylurea versus insulin in the effect estimate of cardiovascular mortality (random RR 0.96, 95% CI 0.73 to 1.28; 4 trials, 1642 participants, Analysis 4.4: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.61). Sensitivity analysis excluding the largest trial (UKPDS 1998) did not change the significance of the effect estimate (random RR 0.31, 95% CI 0.03 to 2.91). Heterogeneity was absent (I^2 = 0%; P = 0.89). Only one trial did not report how the diagnosis of T2DM was established (Alvarsson 2010). Excluding this trial with one cardiovascular death did not change the significance of the effect estimate (RR 0.97, 95% CI 0.73 to 1.30). Heterogeneity was absent (I^2 = 0%; P = 0.50). All trials reporting cardiovascular mortality were published in English, so sensitivity analysis according to language of publication could not be performed. Sensitivity analysis according to source of funding could not be performed, as all the trials were funded by the pharmaceutical industry. Sensitivity analysis according to publication status could not be performed as all trials were published. Trial sequential analysis showed that only 6.6% of the required information size to detect or reject a 10% RRR was accrued. Funnel plots could not be drawn. Worst-best case and best-worst case scenario analyses could not be performed due to lack of data.

We did not conduct subgroup analyses, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

Only one trial reported macrovascular and microvascular outcomes (UKPDS 1998). Therefore, meta-analyses could not be performed.

Change in fasting blood glucose from baseline showed no statistical significance (random MD 0.29 mmol/L, 95% CI -0.02 to 0.61; 5 trials, 1301 participants, Analysis 4.12: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.56). Change in HbA1c from baseline also did not show significant differences (random MD -0.03%, 95% CI -0.17 to 0.10; 6 trials, 1444 participants, Analysis 4.13: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.51). Excluding the only trial that allowed addition of escape medicine did not change the statistical significance of the effect estimates for the changes in fasting blood glucose and HbA1c (UKPDS 1998). Change in weight from baseline showed no statistical significance (random MD -0.37 kg, 95% CI -2.39 to 1.65; fixed MD -0.02 kg, 95% CI -1.45 to 1.40; 5 trials, 1392 participants, Analysis 4.15: subgroup 2). Heterogeneity was present (I^2 = 27%; P = 0.24).

Meta-analyses of adverse events, serious adverse events and dropouts due to adverse events could not be performed due to lack of data. Mild hypoglycaemia was significantly changed in favour of insulin (random RR 1.41, 95% CI 1.13 to 1.76; P = 0.002; Analysis 4.18: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.50). However, the meta-analysis of mild hypoglycaemia was primarily based on data from the UKPDS 1998 trial, which only provided data after 1 year of follow-up. The number of participants with mild hypoglycaemia was 129 in the glibenclamide group the first year. However, the third year of the intervention period 71 participants experienced an mild hypoglycaemic episode in the glibenclamide group. Trial sequential analysis showed that only 8.6% of the required information size to confirm or reject a 10% RRR was accrued. Due to a relatively large number of participants lost to follow-up for the hypoglycaemia data in the UKPDS trial, available case analysis was also performed with the UKPDS trial data, which did not change the statistical significance of mild or severe hypoglycaemia.. Three trials reported zero events for severe hypoglycaemia (Alvarsson 2010; Birkeland 2002; Nathan 1988). As only one trial contributed with data, meta-analysis could not be performed (UKPDS 1998). Two trials provided data on cancer (Alvarsson 2010; UKPDS 1998). Alvarsson 2010 only reported one cancer in each intervention group, so this analysis was primarily based on the data from the UKPDS trial (random RR 0.95, 95% CI 0.61 to 1.49; 2 trials, 1575 participants, Analysis 4.20: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.96). Intervention failure was not statistically significant (random RR 1.96, 95% CI 0.80 to 4.76; fixed RR 1.21, 95% CI 0.97 to 1.63; 4 trials, 1670 participants, Analysis 4.21: subgroup 2). Heterogeneity was 65% (P = 0.04). If intervention failure occurred in the insulin intervention group in both of the included trials, the participants were treated with a more complex insulin regime (Birkeland 2002; UKPDS 1998).

Alvarsson assessed quality of life using the short-form 36 (SF 36), but did not find any significant differences between the interventions (Alvarsson 2010). The UKPDS trial reported quality of life for the intensive intervention versus the conventional interventions, but not for the different antidiabetic medications applied in the intensive regimen (UKPDS 1998).

Second-generation sulphonylureas versus other comparators

Alpha-glucosidase inhibitor

Twelve trials compared a second-generation sulphonylurea versus an alpha-glucosidase inhibitor (Hoffmann 1990; Hoffmann 1994; Kamel 1997; Kanda 1998; Kovacevic 1997; Nakamura 2004; Nakamura 2006; Pagano 1995; Rosenthal 2002; Salman 2001; Segal 1997; Spengler 1992). All of the trials, except one (Nakamura 2006), were judged as high risk of bias. Glibenclamide was applied in most trials (Hoffmann 1990; Hoffmann 1994; Kovacevic 1997; Nakamura 2004; Nakamura 2006; Pagano 1995; Rosenthal 2002; Spengler 1992). Gliclazide was applied in the remaining trials (Kanda 1998; Salman 2001; Segal 1997). One trial applied both glibenclamide and gliclazide (Kamel 1997).

All-cause mortality and cardiovascular mortality could not be meta-analysed due to lack of data. Only one trial reported any deaths, and the number of events was the same (two in each intervention group for all-cause mortality and one in each intervention group for cardiovascular mortality) (Johnston 1997).

None of the macrovascular or microvascular outcomes could be meta-analysed due to lack of data.

Change in fasting blood glucose from baseline showed no statistically significant difference (random MD -0.16 mmol/L, 95% CI -0.42 to 0.11; fixed MD -0.14 mmol/L, 95% CI -0.37 to 0.09; 8 trials, 488 participants, Analysis 5.15: subgroup 2). Heterogeneity was 15% (P = 0.31). Change in HbA1c from baseline did not show statistically significant differences (random MD -0.06%, 95% CI -0.36 to 0.24; fixed MD -0.05%, 95% CI -0.18 to 0.08; 10 trials, 541 participants, Analysis 5.16: subgroup 2). Heterogeneity was 74% (P < 0.0001).

Neither the changes in BMI or in weight from baseline showed significant differences (BMI: random MD -0.02 kg/m^2, 95% CI -0.20 to 0.16; I^2 = 10%; P = 0.35; fixed MD -0.04 kg/m^2, 95% CI -0.18 to 0.11; 5 trials, 232 participants, Analysis 5.17: subgroup 2; weight: random MD -0.22 kg, 95% CI -0.47 to 0.03; I^2 = 0%; P = 0.96; 5 trials, 338 participants, Analysis 5.18: subgroup 2).

The number of participants reporting adverse events was significantly lower in favour of second-generation sulphonylureas in a fixed-effect model, but not in a random-effects model (random RR 0.64, 95% CI 0.39 to 1.03; fixed RR 0.67, 95% CI 0.52 to 0.86; P = 0.002; 8 trials, 646 participants, Analysis 5.19: subgroup 2). Heterogeneity was 64% (P = 0.006). Serious adverse events could not be meta-analysed due to lack of data. Drop-outs due to adverse events were significantly changed in favour of second-generation sulphonylurea (random RR 0.48, 95% CI 0.24 to 0.96; P = 0.04; 9 trials, 870 participants, Analysis 5.21: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.90). Trial sequential analysis showed that only a minor fraction of the required information size to confirm or reject a 10% RRR was accrued.

Four trials reported data on mild hypoglycaemia, of which three reported zero events (Nakamura 2006; Rosenthal 2002; Spengler 1992). Meta-analysis could therefore not be performed. The three trials reporting severe hypoglycaemia had zero events in both intervention groups (Nakamura 2006; Rosenthal 2002; Spengler 1992).

Cancer could not be meta-analysed due to lack of data.

Intervention failure was significantly more common with alpha-glucosidase inhibitors than with second-generation sulphonylurea (random RR 0.25, 95% CI 0.07 to 0.92; P = 0.04; 3 trials, 514 participants, Analysis 5.26: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.85). Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR was accrued.

Nakamura 2006 reported that quality of life was improved in all intervention groups during the trial, but no scale was provided so the intervention effects could not be assessed (Nakamura 2006).

Incretin-based intervention

Two trials involved comparisons of second-generation sulphonylureas versus incretin-based interventions (Foley 2009; Kaku 2011). Both trials were judged as high risk of bias (Foley 2009; Kaku 2011). One trial applied glibenclamide (Kaku 2011) and one gliclazide (Foley 2009).

One of the trials involved a dipeptidyl peptidase-4 (DDP-4) inhibitor (Foley 2009) and the other a glucagon-like peptide 1 (GLP-1) analogue (Kaku 2011). All-cause mortality was not significantly influenced by the intervention (random RR 1.39, 95% CI 0.52 to 3.68; 2 trials, 1503 participants, Analysis 6.1: subgroup 2). Sensitivity and subgroup analyses were not performed due to lack of data. Funnel plots could not be drawn. Heterogeneity was absent (I^2 = 0%; P = 0.63). Trial sequential analysis showed that only 0.5% of the required information size to detect or reject a 10% RRR was accrued. Sensitivity and subgroup analysis could not be performed due to lack of data. The same was the case for best-worst case scenario and worst-best case scenario analyses.

Cardiovascular mortality, non-fatal macrovascular outcomes and microvascular outcomes could not be meta-analysed due to lack of data.

The change in fasting blood glucose from baseline was not significantly different (random MD 0.11 mmol/L, 95% CI -1.07 to 1.28; fixed MD 0.15 mmol/L, 95% CI -0.22 to 0.52; 2 trials, 1202 participants, Analysis 6.15: subgroup 2). Heterogeneity was present (I^2 = 90%; P = 0.002). Change in HbA1c from baseline did also not show significant differences in the random-effects model (random MD 0.26%, 95% CI -0.23 to 0.75; 2 trials, 1204 participants, Analysis 6.16: subgroup 2), but did so in favour of incretin-based therapies in the fixed-effect model (fixed MD 0.29%, 95% CI 0.12 to 0.47; P = 0.001). Heterogeneity was high (I^2 = 86%; P = 0.007).

Statistically significant change in weight from baseline was observed in favour of incretin-based interventions (random MD 1.31 kg, 95% CI 0.33 to 2.29; P = 0.009; fixed MD 1.34 kg, 95% CI 0.96 to 1.71; P < 0.0001; 2 trials, 1206 participants, Analysis 6.18: subgroup 2). Heterogeneity was high (I^2 = 85%; P = 0.009). Diversity was 85%. Trial sequential analysis showed that firm ev-

idence was not established. Change in BMI from baseline could not be meta-analysed due to lack of data.

Adverse events and serious adverse events could not be meta-analysed due to lack of data. Drop-outs due to adverse events did not differ significantly between the interventions (random RR 1.00, 95% CI 0.67 to 1.50; 2 trials, 1503 participants, Analysis 6.21: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.48).

Mild hypoglycaemia was registered in more participants receiving a second-generation sulphonylurea compared with incretin-based intervention (random RR 1.99, 95% CI 1.02 to 3.87; P = 0.04; fixed RR 1.78, 95% CI 1.34 to 2.38; 2 trials, 1503 participants, Analysis 6.22: subgroup 2). Heterogeneity was present (I^2 = 44%; P = 0.18). D^2 = 81%. Trial sequential analysis showed that only a minor fraction has been accrued so far before firm evidence for a 10% RRR can be established. The trials reported zero events of severe hypoglycaemia in both intervention groups (Foley 2009; Kaku 2011). In Kaku 2011 seven participants in the second-generation sulphonylurea group and three participants in the GLP-1 group experienced nocturnal hypoglycaemia (Kaku 2011).

The number of participants with intervention failure did not significantly differ between the interventions in the random-effects model (random RR 1.00, 95% CI 0.41 to 2.43; 2 trials, 1503 participants, Analysis 6.24: subgroup 2), but showed statistically significant differences in favour of second-generation sulphonylurea in the fixed-effect model (fixed RR 0.74, 95% CI 0.60 to 0.91; P = 0.004). Heterogeneity was 75% (P = 0.04).

Meglitinides

Nine trials compared second-generation sulphonylureas with meglitinide (Abbatecola 2006; AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Esposito 2004; Jibran 2006; Madsbad 2001; Marbury 1999; Nakamura 2006; Wolffenbuttel 1999). All of the trials, except for one (Nakamura 2006), were judged as high risk of bias. All of the trials, except for one using glipizide (Madsbad 2001) and one using gliclazide (AGEE/DCD/047/B/F/I), applied glibenclamide as the second-generation sulphonylurea. Two of the trials were unpublished (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I).

Thirteen fatal events were reported in seven trials (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Esposito 2004; Madsbad 2001; Marbury 1999; Nakamura 2006; Wolffenbuttel 1999). Statistical significance was not present (RR 1.44, 95% CI 0.47 to 4.42; 7 trials, 2038 participants, Analysis 7.1: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.70). The trial with the longest duration applied the intervention for 14 months and had a three-month post-intervention observational period (AGEE/DCD/047/B/F/I). Sensitivity analysis excluding the trial with the longest duration did not change the statistical significance of the effect estimate (RR 1.34, 95% CI 0.40 to 4.56). Heterogeneity was absent (I^2 = 0%; P = 0.55). Two of the trials reporting fatal events reported how the diagnosis of T2DM was established (Marbury 1999; Wolffenbuttel 1999). Excluding these trials from the meta-analysis of all-cause mortality did not change the significance of the effect estimate (RR 2.60, 95% CI 0.63 to 10.77). Heterogeneity was absent (I^2 = 0%; P = 0.82). Sensitivity analysis according to the language of publication could not be performed, as all trials were published in English. Two of the trials, both reporting zero fatal events, did not receive any funding from a pharmaceutical company (Esposito 2004; Nakamura 2006). Sensitivity analysis according to funding source could therefore not be performed. Sensitivity analysis only including data from the published trials did not change the significance of the effect estimate (RR 1.01, 95% CI 0.21 to 4.88). Heterogeneity was absent (I^2 = 0%; P = 0.41). Trial sequential analysis showed that 0.06% of the required information size to detect or reject a 10% RRR for all-cause mortality was accrued.

Ten fatal events due to cardiovascular disease were reported in seven trials (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I; Esposito 2004; Madsbad 2001; Marbury 1999; Nakamura 2006; Wolffenbuttel 1999). Statistical significance was not present (RR 0.97, 95% CI 0.27 to 3.53; 7 trials, 2038 participants, Analysis 7.4: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.93). The trial with the longest duration applied the intervention for 14 months and had a three-month post-intervention observational period (AGEE/DCD/047/B/F/I). Sensitivity analysis excluding the trial with the longest duration did not change the statistical significance of the effect estimate (RR 0.74, 95% CI 0.18 to 3.39). Heterogeneity was absent (I^2 = 0%; P = 0.96). Two of the trials reporting fatal events reported how the diagnosis of T2DM was established (Marbury 1999; Wolffenbuttel 1999). Excluding these trials from the meta-analysis of cardiovascular mortality did not change the significance of the effect estimate (RR 1.40, 95% CI 0.23 to 8.49). Heterogeneity was absent (I^2 = 0%; P = 0.71). Sensitivity analysis according to the language of publication could not be performed, as all trials were published in English. Two of the trials, both reporting zero fatal events, did not receive any funding from a pharmaceutical company (Esposito 2004; Nakamura 2006). Sensitivity analysis according to funding source could therefore not be performed. Sensitivity analysis only including data from the published trials did not change the significance of the effect estimate (RR 0.67, 95% CI 0.11 to 4.22). Heterogeneity was absent (I^2 = 0%; P = 0.99). Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR for cardiovascular mortality was accrued.

Funnel plots for the primary outcomes could not be drawn.

Best-worst case and worst-best case scenarios could not be performed for any of the primary outcomes due to lack of data.

We did not conduct subgroup analyses, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

Data for the composite non-fatal macrovascular outcome were reported in three trials (Madsbad 2001; Marbury 1999; Nakamura

2006), of which one reported zero events (Nakamura 2006). The definition of the reported composite outcome varied; one reported vascular extracardiac disorders (Madsbad 2001) and the other reported adverse cardiac events (Marbury 1999). Statistical significance was not shown (RR 0.50, 95% CI 0.20 to 1.20; 3 trials, 866 participants, Analysis 7.5: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.57).

Non-fatal myocardial infarction did not show any statistical significance (RR 1.03, 95% CI 0.26 to 4.08; 3 trials, 726 participants, Analysis 7.6: subgroup 2). An unpublished trial contributed with six out of nine events (AGEE/DCD/046/UK).

The remaining components of the non-fatal macrovascular outcome and the microvascular outcomes could not be meta-analysed as only one of the included trials reported data on these (Nakamura 2006). The trial reported zero events for all the macrovascular and microvascular outcomes in both intervention groups (Nakamura 2006).

The change in fasting blood glucose from baseline was significantly different between the interventions in favour of sulphonylurea (random MD -0.27 mmol/L, 95% CI -0.51 to -0.02; P = 0.03; fixed MD -0.25 mmol/L, 95% CI -0.40 to -0.10; P = 0.001; 9 trials, 2205 participants, Analysis 7.15: subgroup 2). Heterogeneity was present (I^2 = 52%; P = 0.03). Diversity was 60%. Trial sequential analysis showed that firm evidence for the achieved changes in fasting blood glucose from baseline was not established. Excluding data from the two unpublished trials changed the statistical significance of the effect estimate to non-significant values (random MD -0.20 mmol/L, 95% CI -0.44 to 0.04). The change in HbA1c from baseline was not significantly different between the interventions (random MD 0.07%, 95% CI -0.08 to 0.22; fixed MD 0.06%, 95% CI -0.04 to 0.15; 9 trials, 2221 participants, Analysis 7.16: subgroup 2). Heterogeneity was present (I^2 = 52%; P = 0.03). Excluding data from the two unpublished trials did not change the statistical significance of the effect estimate.

Two trials were included in the analysis of change in BMI from baseline, which did not show statistically significant differences (random MD 0.0 kg/m^2, 95% CI -0.19 to 0.20; fixed MD 0.02 kg/m^2, 95% CI -0.07 to 0.11; 2 trials, 209 participants, Analysis 7.17: subgroup 2). Heterogeneity was present (I^2 = 77%; P = 0.04). The change in weight from baseline did also not show significant differences (random MD 0.13 kg, 95% CI -0.50 to 0.76; fixed MD -0.05 kg, 95% CI -0.30 to 0.21; 4 trials, 1052 participants, Analysis 7.18: subgroup 2). Heterogeneity was present (I^2 = 38%; P = 0.19).

The number of participants reporting adverse events did not significantly differ (random RR 1.00, 95% CI 0.95 to 1.06; 5 trials, 1829 participants, Analysis 7.19: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.89). Excluding data from the two unpublished trials did not change the statistical significance of the effect estimate. Drop-outs due to adverse events did not show statistically significant differences (random RR 1.01, 95% CI 0.78 to 1.32; fixed RR 0.98, 95% CI 0.77 to 1.25; 7 trials, 2019 participants, Analysis 7.20: subgroup 2). Heterogeneity was 10% (P = 0.35). Excluding data from the two unpublished trials did not change the statistical significance of the effect estimate. None of the data in the meta-analysis of serious adverse events were published. Data from the three published trials in the meta-analysis of serious adverse events did not report the number of participants with a serious adverse event in each intervention group in the publication, and these data were provided by the sponsor (Madsbad 2001; Marbury 1999; Wolffenbuttel 1999). The effect estimate for serious adverse events did not show any statistical significance (random RR 1.02, 95% CI 0.74 to 1.39; fixed RR 0.99, 95% CI 0.74 to 1.32; 5 trials, 1829 participants, Analysis 7.21: subgroup 2).

The risk of mild hypoglycaemia was not significantly changed (random RR 1.20, 95% CI 0.96 to 1.49; 6 trials, 196 participants, Analysis 7.22: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.50). Excluding data from the two unpublished trials did not change the statistical significance of the effect estimate. The risk of severe hypoglycaemia did not show statistical significance (random RR 2.17, 95% CI 0.53 to 8.91; fixed RR 2.87, 95% CI 0.91 to 8.99; 6 trials, 1863 participants, Analysis 7.24: subgroup 2). Heterogeneity was low (I^2 = 4%; P = 0.37). Excluding data from the two unpublished trials did not change the statistical significance of the effect estimate.

Most of the participants reporting an intervention failure were from Marbury 1999 (96 out of 132) (Marbury 1999). The effect estimate did not show significant differences (random RR 0.98, 95% CI 0.69 to 1.38; 4 trials, 1524 participants, Analysis 7.26: subgroup 2). Heterogeneity was absent (I^2 = 0%; P = 0.40).

Cancer, quality of life and cost of intervention could not be meta-analysed due to lack of data.

Herbal medicine

One trial investigating the effect of glibenclamide versus a Chinese herb (xiaoyasan) was included (Deng 2003). Only the outcomes change in fasting blood glucose and change in HbA1c from baseline could be assessed. The observed decrease in both of these variables was very similar (fasting blood glucose from mean 10.28 mmol/L; standard deviation (SD) 1.01 to mean 6.08 mmol/L SD 0.32 for glibenclamide and mean 10.36 mmol/L SD 1.02 to mean 5.98 mmol/L SD 0.26 for Chinese herb; HbA1c from mean 8.98% SD 1.71 to mean 7.12% SD 0.59 for glibenclamide and mean 9.02% SD 1.62 to 7.12% SD 0.59 for Chinese herb). Meta-analysis was not possible due to lack of data.

Third-generation sulphonylureas versus placebo

No trials assessed the effects of a third-generation sulphonylurea versus placebo.

Third-generation sulphonylureas versus diet

No trials assessed the effects of a third-generation sulphonylurea versus diet.

Third-generation sulphonylureas versus metformin

Three trials compared the effect of monotherapy with a third-generation sulphonylurea versus metformin (Derosa 2004; Tang 2004; Yamanouchi 2005). One of the included trials reported that no participants experienced non-fatal macrovascular outcomes during the trial in both intervention groups (Yamanouchi 2005). Meta-analyses of non-fatal macrovascular outcomes and microvascular outcomes could not be meta-analysed due to lack of data. The reduction in fasting blood glucose and HbA1c from baseline showed no statistical significance (fasting blood glucose: random MD -0.22 mmol/L, 95% CI -0.52 to 0.08, I^2 = 0%; P = 0.42; 3 trials, 281 participants, Analysis 2.13: subgroup 3; HbA1c: random MD -0.18%, 95% CI -0.43 to 0.07; fixed MD -0.16%, 95% CI -0.37 to 0.04; I^2 = 19%; P = 0.29; 3 trials, 281 participants, Analysis 2.14: subgroup 3). Change in BMI from baseline did not show statistical significance (random MD -0.10 kg/m^2, 95% CI -1.06 to 0.86; I^2 = 0%; P = 0.1.00; 2 trials, 219 participants, Analysis 2.15: subgroup 3). The effect estimate for intervention failure showed no statistical significance (random RR 1.23, 95% CI 0.43 to 3.50; 2 trials, 240 participants, Analysis 2.24: subgroup 3).

Third-generation sulphonylureas versus thiazolidinediones

Four trials compared the effects of third-generation sulphonylureas versus thiazolidinediones (Forst 2005; Shihara 2011; Tan 2004; Yamanouchi 2005). All trials were judged as high risk of bias.

One of the included trials reported that no participants experienced non-fatal macrovascular outcomes during the trial in both intervention groups (Yamanouchi 2005). Meta-analyses for all-cause mortality, cardiovascular mortality, non-fatal macrovascular outcomes and microvascular outcomes could not be performed due to lack of data.

The changes in fasting blood glucose was not significantly different in the random-effects model (random MD 0.46 mmol/L, 95% CI -0.22 to 1.13; 4 trials, 655 participants, Analysis 3.15: subgroup 3), but showed significant differences in the fixed-effect model in favour of thiazolidinediones (fixed MD 0.40 mmol/L, 95% CI 0.07 to 0.73; P = 0.02). Heterogeneity was present (I^2 = 70%; P = 0.02). The change in HbA1c from baseline was not statistically significant (random MD -0.095%, 95% CI -0.31 to 0.14; fixed MD -0.10 %, 95% CI -0.26 to 0.07; 4 trials, 659 participants, Analysis 3.16: subgroup 3). Heterogeneity was present (I^2 = 44%; P = 0.15).

The effect estimate showed no significance for the change in BMI from baseline (random MD -0.75 kg/m^2, 95% CI -1.58 to 0.08; fixed MD -0.75 kg/m^2, 95% CI -1.56 to 0.07; 3 trials, 411 participants, Analysis 3.17: subgroup 3). Heterogeneity was present (I^2 = 4%; P = 0.35). Change in weight analysis could not be performed due to lack of data.

One hundred and ninety-nine of the 207 patients who reported an adverse event were from Tan 2004. Meta-analysis showed a significant difference in favour of third-generation sulphonylureas (random RR 0.88, 95% CI 0.78 to 0.99; P = 0.03; 3 trials, 510 participants, Analysis 3.19: subgroup 3). Heterogeneity was absent (I^2 = 0%; P = 0.43). Trial sequential analysis showed that firm evidence was not established. Serious adverse events could not be meta-analysed due to lack of data. Drop-outs due to adverse events were not significantly influenced by the interventions (random RR 0.54, 95% CI 0.15 to 1.97; 2 trials, 423 participants, Analysis 1.4: subgroup 3). Heterogeneity was absent (I^2 = 0%; P = 0.77).

We could not meta-analyse hypoglycaemic episodes due to lack of data.

The effect estimate of intervention failure showed significance in favour of third-generation sulphonylureas (random RR 0.24, 95% CI 0.08 to 0.75; P = 0.01; 2 trials, 319 participants, Analysis 3.26: subgroup 3). Heterogeneity was absent (I^2 = 0%; P = 0.81). Trial sequential analysis showed that firm evidence for a 10% RRR was not achieved.

Third-generation sulphonylureas versus other comparators

Alpha-glucosidase inhibitor

One trial compared third-generation sulphonylurea monotherapy with an alpha-glucosidase inhibitor (Feinböck 2003). The trial was judged as high risk of bias. The trial reported that 10 out of 111 participants in the glimepiride group versus 29 out of 108 in the acabose group had intervention failure. Mild hypoglycaemia was reported in 20 out of 111 participants in the glimepiride group versus 2 out of 108 in the acarbose group. The reductions in fasting blood glucose and HbA1c from baseline were greater in the glimepiride group than in the acarbose group (fasting blood glucose: mean -2.6 mmol/L SD 2.6 versus mean -1.4 mmol/L SD 2.8; HbA1c: mean -2.5% SD 2.2 versus mean -1.8% SD 2.2). The change in weight from baseline was changed in favour of acarbose (mean -0.4 kg SD 5.2 versus mean -1.9 kg SD 3.9). Meta-analyses could not be performed.

Incretin-based intervention

One trial compared third-generation sulphonylurea monotherapy with an incretin-based intervention (GLP-1 analogue) (LEAD-3 2006). The trial was judged as high risk of bias (LEAD-3 2006). Two hundred and forty-eight participants were randomised to a third-generation sulphonylurea versus 498 receiving an incretin-based intervention. The trial reported one cardiovascular death

in the group receiving a third-generation sulphonylurea. Non-fatal myocardial infarction was reported in three participants in the incretin-based intervention group and in one participant in the third-generation sulphonylurea group. Adverse events were reported in 364/498 participants receiving incretin-based intervention compared with 148/248 receiving third-generation sulphonylurea. The reporting of serious adverse events between the interventions was very similar (13 participants allocated to glimepiride reported serious adverse events out of 248, and 24 participants allocated to incretin-based intervention out of 498). The observed changes for fasting blood glucose, HbA1c and weight were in favour to incretin-based intervention (fasting blood glucose: mean -0.3 mmol/L SD 2.9 for third-generation sulphonylurea and mean -1.1 mmol/L SD 3 for incretin-based intervention; HbA1c: mean -0.5% SD 1.2 for third-generation sulphonylurea and mean -1% SD 1.2 for incretin-based intervention; weight: 1.1 kg SD 0.3 for third-generation sulphonylurea and mean -2.05 kg SD 4.4). Mild hypoglycaemia and intervention failure were more common in the participants receiving third-generation sulphonylurea compared with incretin-based intervention. Meta-analyses could not be performed.

Meglitinides

One trial compared third-generation sulphonylurea monotherapy with a meglitinide (Derosa 2003). The trial was judged as high risk of bias (Derosa 2003). The end of follow-up values for fasting blood glucose, HbA1c, BMI and weight were reported (fasting blood glucose: mean 6.9 mmol/L SD 1.1 for third-generation sulphonylurea and mean 6.7 mmol/L SD 1.3 for meglitinide; HbA1c: mean 6.7% SD 0.9 for third-generation sulphonylurea and mean 6.8% SD 0.8 for meglitinide; BMI: mean 25.9 kg/m^2 SD 1.2 for third-generation sulphonylurea and mean 26.2 kg/m^2; SD 0.8 for meglitinide; weight: mean 76.6 kg SD 5.3 for third-generation sulphonylurea and mean 76.5 kg SD 5.3 for meglitinide). Two drop-outs were reported in the trial (both in the third-generation sulphonylurea group). Intervention failure was experienced in two participants receiving a third-generation sulphonylurea and in three participants receiving a meglitinide. Meta-analysis could not be performed.

Second-generation sulphonylureas versus first-generation sulphonylureas

Three of the included trials compared a second-generation sulphonylurea versus a first-generation sulphonylurea (Fineberg 1980; Harrower 1985; UKPDS 1998). All of the trials were judged as high risk of bias.

In the UKPDS trial all-cause mortality was reported in 121 participants out of 615 participants randomised to second-generation sulphonylurea versus 136 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). Cardiovascular mortality was reported in 69 participants out of 615 participants randomised to second-generation sulphonylurea versus 71 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). In the UKPDS trial non-fatal myocardial infarction was reported in 46 participants out of 615 participants randomised to second-generation sulphonylurea versus 58 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). Non-fatal stroke was reported in 34 participants out of 615 participants randomised to second-generation sulphonylurea versus 26 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). The UKPDS trial reported five participants in each intervention group with an amputation of lower extremity (UKPDS 1998). The composite microvascular outcome was in the UKPDS trial reported in 49 participants out of 615 participants randomised to second-generation sulphonylurea versus 68 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). In the UKPDS trial retinal photocoagulation was reported in 45 participants out of 615 participants randomised to second-generation sulphonylurea versus 55 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998). All-cause mortality, cardiovascular mortality, non-fatal macrovascular outcomes and microvascular outcomes could not be meta-analysed due to lack of data.

The change in fasting blood glucose from baseline was significantly changed in favour of first-generation sulphonylurea (random MD 0.62 mmol/L, 95% CI 0.31 to 0.94; P < 0.0001; 2 trials, 936 participants, Analysis 8.9). Heterogeneity was absent (I^2 = 0; P = 0.79). The analysis was primarily based on data from the UKPDS trial (UKPDS 1998). Trial sequential analysis disregarding risk of bias showed that firm evidence for the achieved changes were established. The change in HbA1c from baseline was not statistical significant in random-effects model, but showed statistical significance in fixed-effect model (random MD -1.44%, 95% CI -4.48 to 1.60; fixed MD -0.31%, 95% CI -0.51 to -0.11; P = 0.002; 2 trials, 1014 participants, Analysis 8.9). Heterogeneity was high (I^2 = 99%; P < 0.00001). .

No trials reported change in BMI from baseline. Change in weight from baseline showed no significant differences in the random-effects model, but showed statistical significance in favour of first-generation sulphonylurea in the fixed-effect model (random MD 1.80 kg, 95% CI -0.63 to 4.23; fixed MD 1.21 kg, 95% CI 0.32 to 2.11; 2 trials, 1014 participants, Analysis 8.10).

Meta-analyses of adverse events and hypoglycaemic episodes could not be done due to lack of data. The UKPDS trial reported death due to cancer in 29 participants out of 615 participants randomised to second-generation sulphonylurea versus 36 participants out of 619 participants randomised to first-generation sulphonylurea (UKPDS 1998).

Intervention failure was not significantly changed in random-effects model, but was significantly changed in favour of first-generation sulphonylurea in fixed-effect model (random RR 1.96,

95% CI 0.67 to 5.75; fixed RR 1.62, 95% CI 1.62 to 3.29; P < 0.00001; 3 trials, 1364 participants, Analysis 8.14). Heterogeneity was present (I^2 = 20%; P = 0.26). Diversity was 89%. Trial sequential analysis showed that 0.3% of the required information size to confirm or reject a 10% RRR was accrued.

Third-generation sulphonylureas versus first-generation sulphonylureas

No trials assessed the effects of a third-generation sulphonylurea versus a first-generation sulphonylurea.

Sulphonylureas versus the included comparators

Due to lack of data for several outcomes in the systematic review, we decided post hoc to compare all generations of sulphonylureas with each of the included comparators. As the analyses of most of the outcomes were dominated by the second-generation sulphonylureas, there was only a few comparisons for which the significance for the second-generation sulphonylurea was different from an analysis of all classes of sulphonylureas. The change in fasting blood glucose from baseline, which showed significance for the comparison second-generation sulphonylurea versus metformin in a random-effects model (random MD 0.43 mmol/L, 95% CI 0.10 to 0.75; P = 0.009; 11 trials, 3891 participants), but showed no significance when all classes of sulphonylurea were compared with metformin in a random-effects model (random MD 0.20mmol/L, 95% CI -0.07 to 0.48; 16 trials, 4654 participants). Mild hypoglycaemia for the comparison second-generation sulphonylurea versus insulin showed statistical significance (random RR 1.37, 95% CI 1.10 to 1.69; P = 0.004; 2 trials, 1197 participants), but no significance was present when all classes of sulphonylureas were combined (random RR 0.94, 95% CI 0.45 to 1.95; 3 trials, 3105 participants). No changes in the significance of the effect estimates from the analyses of second-generation sulphonylureas were observed for the remaining comparisons.

For several outcomes there were no data available and no meta-analysis could be performed. Please see Appendix 10; Appendix 11; Appendix 12 for a complete overview of each outcome for each comparison.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Second-generation sulphonylureas compared with controls for type 2 diabetes mellitus

Patient or population: participants with type 2 diabetes mellitus
Settings: outpatients
Intervention: second-generation sulphonylureas (glibenclamide or glyburide, glibornuride, gliclazide, glipizide)
Comparison: placebo, active comparators

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality a. Intervention vs metformin [a. 24 weeks to 4 years] b. Intervention vs thiazolidinediones [b. 24 weeks to 4 years] c. Intervention vs insulin [c. 9 months to 10 years] d. Intervention vs incretin-based control [d. 52 weeks to 104 weeks] e. Intervention vs meglitinide [e. 12 months to 17 months]	a. **RR 0.98** (0.61 to 1.58) b. **RR 0.92** (0.60 to 1.41) c. **RR 0.96** (0.79 to 1.18) d. **RR 1.39** (0.52 to 3.68) e. **RR 1.44** (0.47 to 4.42)	a. 3528 (6) b. 4955 (7) c. 1642 (4) d. 1503 (2) e. 2038 (7)	⊕⊕◯◯ **low**[a]	a. Trial sequential analysis showed that 2.3% of the required information size to detect or reject a 10% RRR was accrued b. Results of the random-effects model. Trial sequential analysis showed that 2.5% of the required information size to detect or reject a 10% RRR was accrued c. Trial sequential analysis showed that 12.8% of the required information size to detect or reject a 10% RRR was accrued d. Trial sequential analysis showed that 0.5% of the required information size to detect or reject a 10% RRR was accrued e. Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR was accrued
Cardiovascular mortality a. Intervention vs metformin [a. 24 weeks to 4 years] b. Intervention vs thiazolidinediones [b. 24 weeks to 4 years] c. Intervention vs insulin [c. 9 months to 10 years]	a. **RR 1.47** (0.54 to 4.01) b. **RR 1.30** (0.55 to 3.07) c. **RR 0.96** (0.73 to 1.28) d. **RR 0.97** (0.27 to 3.53)	a. 3528 (6) b. 4955 (7) c. 1642 (4) d. 2038 (7)	⊕⊕◯◯ **low**[a]	a. Trial sequential analysis showed that 2.7% of the required information size to detect or reject a 10% RRR was accrued b. Trial sequential analysis showed that 0.3% of the required information size to detect or reject a

d. Intervention vs meglitinide [d. 12 months to 17 months]				10% RRR was accrued c. Trial sequential analysis showed that 6.6% of the required information size to detect or reject a 10% RRR was accrued d. Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR was accrued
Non-fatal macrovascular outcomes **1. Composite** a. Intervention vs metformin [1a. 6 months to 4 years] b. Intervention vs thiazolidinediones [1b. 52 weeks to 4 years] c. Intervention vs meglitinide [1c. 12 months to 15 months] **2. Non-fatal myocardial infarction** a. Intervention vs metformin [2a. 24 weeks to 4 years] b. Intervention vs thiazolidinediones [2b. 24 weeks to 4 years] c. Intervention vs meglitinide [2c. 12 months to 17 months]	1a. **RR 0.67** (0.48 to 0.93) 1b. **RR 0.91** (0.62 to 1.33) 1c. **RR 0.50** (0.20 to 1.20) 2a.**RR 1.02** (0.37 to 2.85) 2b. **RR 0.68** (0.41 to 1.14) 2c. **RR 1.03** (0.26 to 4.08)	1a. 3018 (3) 1b. 4600 (6) 1c. 866 (3) 2a. 3061 (4) 2b. 4956 (7) 2c. 726 (3)	⊕⊕◯◯ **low**[a]	1a. Non-fatal macrovascular outcomes as a composite outcome were not reported in the way we predefined to assess this outcome. Trial sequential analysis showed that 5% of the required information size to detect or reject a 10% RRR was accrued 1c. The definition of non-fatal macrovascular outcomes was heterogenous
Microvascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Adverse events **1. All adverse events** **2. Drop-outs due to adverse events** **3. Severe hypoglycaemia** a. Intervention vs placebo [1a. 24 weeks] [2a. 24 weeks to 56	1a. **RR 0.91** (0.51 to 1.62) 1b. **RR 0.99** (0.97 to 1.01) 1c. **RR 0.99** (0.97 to 1.01) 1d. **RR 0.64** (0.39 to 1.03) 1f. **RR 1.0** (0.95 to 1.06)	1a. 202 (2) 1b. 3042 (2) 1c. 6491 (10) 1d. 646 (8) 1f. 1829 (5) 2a. 510 (5) 2b. 3567 (7) 2c. 7433 (15)	⊕⊕◯◯ **low**[a]	1d. Results of the random-effects model. Fixed-effect model: RR 0.67 (0.52 to 0.86) 2c. Results of the random-effects model. Fixed-effect model: RR 1.17 (1.01 to 1.35)

weeks] b. Intervention vs metformin [1b. 6 months to 4 years] [2b. 24 weeks to 4 years] [3b. 24 weeks to 10.4 years] c. Intervention vs thiazolidinediones [1c. 6 months to 4 years] [2c. 24 weeks to 4 years] [3c. 6 months to 4 years] d. Intervention vs alpha-glucosidase inhibitors [1d. 24 weeks to 12 months] [2d. 24 weeks to 12 months] e. Intervention vs incretin-based control [2e. 52 weeks to 104 weeks] f. Intervention vs meglitinides [1f. 14 months to 17 months] [2f. 12 months to 17 months] [3f. 14 months to 17 months]	2a. **RR 0.62** (0.24 to 1. 57) 2b.**RR 1.19** (0.99 to 1. 42) 2c. **RR 1.15** (0.98 to 1. 36) 2d. **RR 0.48** (0.24 to 0. 96) 2e. **RR 1.00** (0.67 to 1. 50) 2f. **RR 1.01** (0.78 to 1. 32) 3b. **RR 5.64** (1.22 to 26. 00) 3c. **RR 6.11** (1.57 to 23. 79) 3f. **RR 2.17** (0.53 to 8. 91)	2d. 970 (9) 2e. 1503 (2) 2f. 2019 (7) 3b. 3637 (4) 3c. 5669 (6) 3f. 1863 (6)		2d. Trial sequential analysis showed that only a minor fraction of the required information size to confirm or reject a 10% RRR was accrued 3b. Trial sequential analysis showed that only 0. 1% of the required information size was accrued 3c. Trial sequential analysis showed that a minor fraction of the required information size was accrued
Cancer a. Intervention vs thiazolidinediones [52 weeks to 4 years] b. Intervention vs insulin [6 years to 10 years]	a. **RR 1.02** (0.72 to 1.45) b. **RR 0.95** (0.61 to 1.49)	a. 4192 (6) b. 1575 (2)	⊕⊕◯◯ **low**[a]	
Health-related quality of life a. Intervention vs thiazolidinediones [12 months] b. Intervention vs insulin [6 years] c. Intervention vs alpha-glucosidase inhibitors [12 months]	Not estimable	a. 35 (1) b. 49 (1) c. 35 (1)	⊕◯◯◯ **very low**[b]	a. Inadequately reported, no scale provided b. Authors used short-form 36 (SF 36), but did not find any significant differences between the interventions c. Inadequately reported, no scale provided

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Due to imprecision and results of trial sequential analysis.
[b] Due to small sample size and risk of bias.
RRR: relative risk reduction

Third-generation sulphonylureas compared with controls for type 2 diabetes mellitus

Patient or population: participants with type 2 diabetes mellitus
Settings: outpatients
Intervention: third-generation sulphonylureas (gliclazide modified release (MR), glimepiride, glipizide gastrointestinal therapeutic system (GITS))
Comparison: active comparators

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	Not estimable	See comment	See comment	No meta-analysis possible
Cardiovascular mortality	Not estimable	See comment	See comment	No meta-analysis possible
Macrovascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Microvascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Adverse events 1. All adverse events 2. Drop-outs due to adverse events Interventions vs thiazolidinediones [1. 6 months to 12 months] [2. 24 weeks to 52 weeks]	1. **RR 0.88** (0.78 to 0.99) 2. **RR 0.54** (0.15 to 1.97)	1. 510 (3) 2. 423 (2)	⊕⊕◯◯ **low**[a]	1. Trial sequential analysis showed that firm evidence was not established

Cancer	Not estimable	See comment	See comment	No meta-analysis possible
Health-related quality of life	Not estimable	See comment	See comment	No meta-analysis possible

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Due to imprecision/small sample size and results of trial sequential analysis.
RRR: relative risk reduction

DISCUSSION

Summary of main results

This Cochrane review is the first systematic review including all randomised trials assessing allocation to sulphonylurea monotherapy versus placebo or no intervention, or allocation to sulphonylurea monotherapy versus other comparators in patients with type 2 diabetes mellitus (T2DM). We included 72 trials with a total of 22,589 participants. All trials had an uncertain or high risk of bias in one or more risk of bias domain. Overall the amount of evidence on patient-important outcomes was low. For an overview of intervention effects please see Appendix 10; Appendix 11; Appendix 12.

Our two primary outcomes were all-cause mortality and cardiovascular mortality. After publication of the protocol, it was decided to meta-analyse change of weight from baseline, as it might be an important variable for most patients with T2DM.

We list below the comparisons showing statistically significant differences in the random-effects model.

- Cardiovascular mortality: for the comparison of first-generation sulphonylurea versus placebo, the effect estimate showed statistical significance in favour of placebo. However, this did not hold in the trial sequential analysis for a 10% relative risk reduction (RRR) as only 0.7% of the required information size has been accrued so far.
- Non-fatal macrovascular outcomes: for the comparison of second-generation sulphonylureas versus metformin, statistical significance in favour of second-generation sulphonylurea was found. However, the trials included in this meta-analysis also reported events of non-arteriosclerotic origin as cardiovascular disease. A trial sequential analysis did not confirm a 10% RRR.
- Fasting blood glucose: for the comparison of first-generation sulphonylureas versus alpha-glucosidase inhibitors, statistical significance in favour of first-generation sulphonylureas was observed. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylureas versus placebo, statistical significance was present in favour of second-generation sulphonylurea. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylurea versus metformin statistical significance was present in favour of metformin. The result was not confirmed in the trial sequential analysis. For the comparisons of second-generation sulphonylurea versus thiazolidinediones statistical significance was present in favour of the thiazolidinediones. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylureas versus meglitinides statistical significance was present in favour of second-generation sulphonylurea. The result was not confirmed in the trial sequential analysis. For the comparison of second-generation sulphonylurea versus first-generation sulphonylurea statistical significance was present in favour of first-generation sulphonylurea. The result was confirmed in the trial sequential analysis disregarding risk of bias.
- HbA1c: for the comparison of first-generation sulphonylurea versus alpha-glucosidase inhibitors, statistical

significance was shown in favour of first-generation sulphonylureas. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylureas versus placebo, statistical significance was present in favour of second-generation sulphonylurea. The result was confirmed in the trial sequential analysis disregarding risk of bias.

- BMI: For the comparison of second-generation sulphonylureas versus thiazolidinediones statistical significance was present in favour of second-generation sulphonylureas. The result was not confirmed in the trial sequential analysis disregarding risk of bias.
- Weight: for the comparison of second-generation sulphonylureas versus metformin, statistical significance was present in favour of metformin. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylureas versus thiazolidinediones, statistical significance was present in favour of second-generation sulphonylureas. The result was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison second-generation sulphonylurea versus incretin-based interventions statistical significance was found in favour of incretin-based intervention. The result was not confirmed in the trial sequential analysis..
- Adverse events: for the comparison of first-generation sulphonylureas versus alpha-glucosidase inhibitors, statistical significance was present in favour of first-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of third-generation sulphonylureas versus thiazolidinediones, statistical significance was present in favour of third-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR.
- Drop-out due to adverse events: for the comparison of first-generation sulphonylureas versus alpha-glucosidase inhibitors, statistical significance was present in favour of first-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of second-generation sulphonylureas versus alpha-glucosidase inhibitors, statistical significance was present in favour of second-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR.
- Mild hypoglycaemia: for the comparison of second-generation sulphonylureas versus metformin, statistical significance was present in favour of metformin. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of second-generation sulphonylureas versus thiazolidinediones, statistical significance was present in favour of thiazolidinediones. A 10% RRR was confirmed in the trial sequential analysis disregarding risk of bias. For the comparison of second-generation sulphonylureas versus insulin, statistical significance was present in favour of insulin. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of second-generation sulphonylureas versus incretin-based intervention, statistical significance was present in favour of incretin-based intervention. However, this did not hold in the trial sequential analysis for a 10% RRR.
- Severe hypoglycaemia: for the comparison of second-generation sulphonylureas versus metformin, statistical significance was present in favour of metformin. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of second-generation sulphonylureas versus thiazolidinediones, statistical significance was present in favour of thiazolidinediones. However, this did not hold in the trial sequential analysis for a 10% RRR.
- Intervention failure: for the comparison of second-generation sulphonylureas versus placebo, statistical significance was present in favour of second-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of second-generation sulphonylureas versus alpha-glucosidase inhibitors, statistical significance was present in favour of second-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison of third-generation sulphonylureas versus thiazolidinediones, statistical significance was present in favour of third-generation sulphonylureas. However, this did not hold in the trial sequential analysis for a 10% RRR. For the comparison second-generation sulphonylurea versus first-generation sulphonylurea statistical significance was present in favour of first-generation sulphonylurea. However, this did not hold in the trial sequential analysis for a 10% RRR. As for the definition of intervention failure to monotherapy, the strategy between the included trials varied (please see Included studies).

Conclusions when all sulphonylurea groups (first-, second- and third-generation) were analysed together were similar to those of second-generation sulphonylurea. The only exceptions were the change in fasting blood glucose from baseline, which in a random-effects model did not show statistical significance when all classes of sulphonylureas were combined compared with metformin, and mild hypoglycaemia for the comparison of second-generation sulphonylurea versus insulin, which showed statistical significance in favour of insulin in the random-effects model, but no statistical significance was present when all sulphonylureas were combined..

Overall completeness and applicability of evidence

We conducted an extensive search for trials, included publications in all languages and had no restriction on the outcomes reported in the trials. We have included trials with large variation in duration of T2DM and interventions, age and glycaemic targets in trials. Our

primary objective was to assess all-cause as well as cardiovascular mortality. We cross-checked our data with the data from other meta-analyses and Cochrane reviews of relevance (Black 2007; Bolen 2007; Liu 2002; Liu 2009; Ooi 2010; Richter 2006; Richter 2007; Richter 2008; Saenz 2005; Selvin 2008).

The participants of the included trials represented a very diverse sample of the population with T2DM. The results of our review should therefore be interpreted with caution. The diagnosis of T2DM varied among trials and some trials used a definition of T2DM which may have included participants with impaired glucose tolerance. Some of the trials only included participants with newly diagnosed T2DM, whereas others included patients with a longer duration of T2DM. The inclusion criteria varied among the trials, but almost all trials excluded participants with existing co-morbidities, especially renal or hepatic disease. Detailed information about the participants was presented in most trials. The majority of trials were conducted in Europe or North America. A potential selection bias exists as more healthy and motivated patients may participate in a clinical trial. However, a Cochrane systematic review has observed that clinical outcomes in patients that participate in randomised trials are comparable to similar patients outside trials (Vist 2008). All together, the participants of the included trials represented a heterogenous sample of the population with T2DM and the results should therefore be interpreted with some caution. However, the diversity of patient characteristics mirrors that seen in real life, which may justify the clinical relevance of the results.

The included trials applied sulphonylurea monotherapy with different intensities and with different types of sulphonylureas. All trials primarily focused on sulphonylurea monotherapy, however, a few trials allowed varying degrees of add-on to monotherapy in case of intervention failure. The fact that escape medicine was allowed to a varying degree makes it difficult to decide whether the intervention effects or adverse effects are ascribed to the intended (mono)therapy or arise from combination therapy.

Quality of the evidence

Among the 72 trials included in this analysis, we classified none of the trials as having low risk of bias according to all bias domains and we only classified seven trials as having a lower risk of bias according to a combined evaluation of sequence generation, allocation concealment and blinding. We would have stratified the trials according to risk of bias for our primary outcomes if statistical significance was present, but due to lack of statistical significance these analyses were not performed. Several of the included trials had an open-label design, which might have influenced the reporting from both the participants and the investigators. We were able to assess some of the predefined outcomes in 70 included trials. The outcome reporting in the individual trials varied grossly suggesting a high risk of outcome selection bias.

Certain potential limitations of this review warrant special consideration, one being that we were dealing with a very heterogeneous group of trials. The meta-analyses are limited by an inability to use individual patient data to assess whether distinct clinical characteristics may have influenced the effect estimates of the intervention effects. We tried to explore heterogeneity using sensitivity analyses for the primary outcomes. Diagnostic criteria and definitions of outcomes differed among trials and were not always well defined. Besides our primary outcomes (all-cause and cardiovascular mortality), we assessed other patient-important outcomes such as non-fatal macro- and microvascular outcomes. However, due to lack of data very few comparisons could be performed for these outcomes. Many of the included trials were not designed or powered to detect our predefined outcomes, which might have resulted in insufficient data from these trials. Cardiovascular outcomes were collected as adverse events in most trials. Additionally, when prespecifying a certain primary outcome, this outcome might be more systematically and uniformly collected in the trial. In all cases we asked for supplementary information from the authors. However, as stated above, outcome reporting bias could influence the results of our meta-analyses.

Several trials received funding from the pharmaceutical industry. We would have stratified all-cause and cardiovascular mortality by source of funding to see if it influenced the effect estimates, but were unable to do this.

The way sulphonylurea monotherapy or another comparator was applied to the participants varied among the trials. Some trials excluded the participants who could not achieve adequate glycaemic control on monotherapy, whereas other trials allowed varying degrees of escape medicine in order to maintain glycaemic control. Again, some trials did not describe what happened to the participants who could not maintain adequately glycaemic control on monotherapy. In our opinion, trials that permitted escape medicine, as well as those that did not, were relevant to include in the present meta-analysis. Thus, both types of trials allow for inferences regarding initial allocation to monotherapy. Taking into consideration whether or not escape medicine was allowed, we meta-analysed the trials for changes in fasting blood glucose levels and HbA1c for second-generation sulphonylurea versus metformin and for second-generation sulphonylurea versus thiazolidinediones.

Some of the included trials reported continuous outcomes by last observation carried forward, which is considered an outdated way of imputing missing data as this kind of single value imputation exaggerates the precision of the overall estimate in the analysis (Fleming 2011). Several trials did not report the changes from baseline for the continuous outcomes during the intervention period and in that case we entered the end of follow-up value into the meta-analyses. However, as several of the trials were relatively small it might be that the groups were not well-balanced at baseline.

Some of the included trials had a relatively small number of partic-

ipants, and the resulting information size in the meta-analyses was equally small. This increases the risk of providing a more unrealistic estimate of the intervention effects due to bias (systematic errors) and chance (random errors) (Savovic 2012; Thorlund 2011; Wetterslev 2008; Wood 2008). We have tried to clarify systematic errors. We contacted all authors for clarification if one of the bias domains was not adequately reported. We would have divided the analyses for the primary outcomes into high risk of bias trials versus lower risk of bias trials to reveal any influence of bias on the effect estimates of our primary outcomes, if the primary outcome had shown significance. To reduce the risk of random errors, we conducted trial sequential analysis on the primary outcomes and on those secondary outcomes showing statistical significance in both random-effects and fixed-effect models.

There was heterogeneity due to differences in patient characteristics, intervention targets and quality of the trials. For the continuous variables we preferably reported the change from baseline, and if the change was not reported, we applied the end of follow-up value. Heterogeneity was high, but we decided to perform the meta-analyses anyway. We conducted all meta-analyses using both the random-effects and the fixed-effect model. Due to expected large heterogeneity, we predefined by default that we would report the outcomes using the random-effects model, and only use the fixed-effect model if the results differed. The fixed-effect model assumes that the true intervention effect is the same in every randomised trial; that is, the effect is fixed across trials. On the contrary, the random-effects model allows for the effects being estimated to differ across trials. When the heterogeneity increases, the estimated intervention effect may differ between the random-effects model and the fixed-effect model, and the confidence interval increases in the random-effects model. In case of no heterogeneity (I^2 = 0%), the two models tend to give the same result, and we only reported the random-effects model. By adopting the random-effects model, we were therefore able to pool a broader population of trials than by only relying on the results of the fixed-effect model. On the other hand, the random-effects model reduces the weight of the large trials, which might be more representative of a true intervention effect.

Potential biases in the review process

We searched conference proceedings and contacted authors in order to obtain unpublished trials. On the US Food and Drug Administration homepage, we found an approval letter for repaglinide, in which five potential relevant phase III trials are described (FDA 2000). Through contact with the sponsor of the trials, it was clarified that two of them were unpublished (AGEE/DCD/046/UK; AGEE/DCD/047/B/F/I). A strength of our systematic review is that several authors kindly provided unpublished data. We were therefore able to include unpublished data for 18 of the included trials (please see Included studies).

Several trials were published in more than one publication, which for some trials made it difficult to separate the primary publication from companion papers (for details see Included studies).

The data extraction was done independently by two authors. However, the authors extracting the data were not blinded regarding which trial they were extracting.

We included trials with a minimum duration of 24 weeks of sulphonylurea monotherapy in order to have a chance to detect clinically relevant differences for the outcomes. Unfortunately, we had a severe lack of long-term trial data in this review. Especially, the reporting from the UKPDS trials was very poor and several outcomes were not reported to the longest follow-up (UKPDS 1998; UKPDS 34 1998).

The main limitations for interpreting the results of this review relate to the, in general, poor quality of the trials, such as including insufficient reporting of randomisation, allocation and blinding. In addition, several of the trials were funded by the pharmaceutical industry, which might influence the reported results.

Agreements and disagreements with other studies or reviews

The University Group Diabetes Program (UGDP) trial was one of the first multicentre clinical trials designed to evaluate widely used methods for T2DM in the late 1950s and early 1960s (UGDP 1970). The sulphonylurea explored in the UGDP trial was tolbutamide, which was discontinued in June 1969 due to excess of all-cause as well as cardiovascular mortality compared with placebo and insulin. A total of 89 deaths were reported in four intervention groups and it was decided to discontinue prescription of tolbutamide. To explore the reasons for the increased mortality, further analyses of the UGDP trial data have been done. Most of the excess mortality observed in the tolbutamide group appeared to be a result of increased mortality due to myocardial infarction (UGDP 1970). When monotherapy failed, one or more prescriptions of insulin were allowed to reduce blood glucose. At the time the UGDP trial was designed, there was no single definition of T2DM that had general acceptance. However, according to modern diagnostic criteria, the participants of the UGDP trial were more likely to be diagnosed with impaired glucose tolerance. Since the UGDP trial, only very few trials have compared first-generation sulphonylurea with placebo or insulin. Our results show that only two trials could be included in the meta-analysis of first-generation sulphonylurea versus placebo and in the analysis of first-generation sulphonylureas versus insulin. Besides, it is interesting that no meta-analysis of patient-important outcomes could be performed for the comparison of second-generation sulphonylurea versus first-generation sulphonylurea. The increased risk of adverse effects suggested with intervention of first-generation sulphonylurea compared with newer generation of sulphonylurea is primarily based on animal studies and non-randomised human studies (Fine 1970; Harrower 2000; Henquin 1992).

The United Kingdom Prospective Diabetes Study (UKPDS) trial started in 1977 (UKPDS 1998). By using the fasting plasma glucose criterion of 6.0 mmol/L, about 85% of all UKPDS participants would have fulfilled the 1985 World Health Organization (WHO) criteria for T2DM (fasting plasma glucose above 7.8 mmol/L). The UKPDS trial was a multicentre trial designed to assess the effect of intensive versus conventional glycaemic control. The participants in the intensive group were randomised to open-label intervention with first-generation sulphonylurea (chlorpropamide), second-generation sulphonylurea (glibenclamide and glipizide) or insulin as monotherapy as well as a goal of fasting plasma glucose below 6 mmol/L, and those in the conventional group to diet only and a goal of fasting blood glucose below 15 mmol/L. In a subgroup of overweight patients intensive glycaemic control was achieved with metformin and a goal of fasting plasma glucose below 6.0 mmol/L (UKPDS 34 1998). In case of monotherapy failure addition of other antidiabetic drugs was allowed when persistent hyperglycaemia was present. A subgroup of patients with asymptomatic failure with sulphonylurea alone was randomly allocated to addition of metformin or continued sulphonylurea. There was no evidence of any major detrimental effect on mortality of the drugs or insulin in monotherapy. Notably, increased mortality was not seen with first-generation sulphonylurea although the comparison against metformin was not reported. Unfortunately none of the outcomes for the comparison between sulphonylurea and metformin from the UKPDS trial could be included to the longest follow-up in our meta-analysis due to the way of reporting (UKPDS 34 1998). In the design article of the UKPDS trial it is stated that the obese participants allocated to metformin and sulphonylurea will be compared. However, these data are unfortunately not published, but would probably increase the number of patient-important meta-analyses (UKPDS 34 1998). Metformin appeared to have a favourable effect on mortality and cardiovascular outcomes compared with either the conventional group or with a combined group of the other intensive therapies (first and second-generation sulphonylureas and insulin). However, combined therapy of metformin and sulphonylurea appeared to have a harmful effect on mortality compared with sulphonylureas alone (UKPDS 34 1998). Neither are the patient-important outcomes from the participants randomised to glipizide and chlorpropamide in the Glucose II trial published (UKPDS 1998).

Recently, a large-scale, double-blind, randomised clinical trial, the A Diabetes Outcome Progression Trial (ADOPT), was published. The participants were randomised to monotherapy with metformin, glibenclamide or rosiglitazone (ADOPT 2006). If monotherapy failed, escape medicine was not allowed. The ADOPT trial demonstrated fewer macrovascular events with glibenclamide monotherapy compared with thiazolidinedione monotherapy. There were also nominally fewer events with glibenclamide than metformin, however, the statistical comparison of these groups was not reported for vascular outcomes. In addition, it should be noted that time to treatment failure, and not vascular outcomes, was the primary outcome in the ADOPT trial.

Besides the fear of cardiovascular adverse effects, other concerns have been raised regarding sulphonylurea intervention: the risk of beta-cell exhaustion with time, the risk of severe hypoglycaemia and weight gain. For the comparisons where we were able to meta-analyse intervention failure, none of them showed significance in favour of the comparators. On the other hand, the comparisons of second-generation sulphonylureas versus placebo, second-generation sulphonylurea versus alpha-glucosidase inhibitors and third-generation sulphonylureas versus thiazolidinediones, significantly favoured sulphonylurea. However, few trials were included in these meta-analyses and trial sequential analyses showed that firm evidence was far from being present. The ADOPT trial suggested, as its primary outcome, rosiglitazone treatment to be significantly better than glibenclamide (or metformin) in terms of intervention failure. However, we could only confirm such an effect of thiazolidinediones versus sulphonylurea in the fixed-effect model, and not in the random-effects model. Weight gain was more pronounced with a second-generation sulphonylurea compared with metformin, incretin-based interventions and first-generation sulphonylurea. However, it was less pronounced for second-generation sulphonylureas compared with thiazolidinediones. For the remaining comparisons in which meta-analyses were applicable, there was no significant difference in change of weight from baseline. The change in BMI from baseline did not show statistical significance for the comparison of second-generation sulphonylurea with metformin. We would have expected that change in BMI from baseline was in favour of metformin. The reason for lack of statistical significance is probably due to only a few trials contributing with data (Collier 1989; Lawrence 2004; Tosi 2003). Besides, two of these trials did not report change from baseline, but end of follow-up values (Collier 1989; Lawrence 2004). Both of these trials had a small sample size and a duration of six months and a higher BMI at baseline in the metformin group. This may explain the lack of statistical significance in this analysis.

For the comparison second-generation sulphonylurea versus metformin and thiazolidinediones we found statistical significant changes in fasting blood glucose from baseline and lower risk of mild as well as severe hypoglycaemia in favour of the comparators. However, the magnitude of the achieved differences in fasting blood glucose for the comparators compared with second-generation sulphonylurea was minor, and of doubtful clinical importance (second-generation sulphonylurea versus metformin: 0.43 mmol/L; second-generation sulphonylurea versus thiazolidinediones: 0.56 mmol/L). A Cochrane review of metformin monotherapy also found less hypoglycaemia with metformin compared with sulphonylurea and improved glycaemic control in terms of fasting blood glucose and HbA1c (Saenz 2005). However, we did only find statistical significance for a lower HbA1c in favour of metformin in the fixed-effect model. A Cochrane review about rosiglitazone also reported a lower risk of hypogly-

caemia with rosiglitazone compared with sulphonylurea (Richter 2007). However, this Cochrane review did not report the changes in fasting blood glucose between rosiglitazone and sulphonylurea (Richter 2007).

The conclusions in other Cochrane reviews about glucose-lowering interventions in patients with T2DM did also find sparse reporting of patient-important outcomes (Black 2007; Liu 2002; Ooi 2010; Richter 2006; Richter 2007; Richter 2008; Saenz 2005; Van de Laar 2005). Unlike our present review, a the Cochrane review of metformin monotherapy could include mortality and vascular outcomes from UKPDS - however, like our review, not for metformin versus sulphonylurea (Saenz 2005). The Cochrane review of metformin monotherapy made a pooled analysis of non-UKPDS trials having various comparators, which showed no significant difference for mortality or vascular outcomes as well as a separate analysis of UKPDS, which corroborated most of the previous conclusions from the UKPDS. The conclusion from that Cochrane review was that metformin might be beneficial regarding cardiovascular outcomes in obese patients with T2DM (Saenz 2005).

A Danish retrospective cohort study compared patients receiving monotherapy with insulin secretagogues, including the meglitinides, to metformin monotherapy (Schramm 2011). The median duration of follow-up was 3.3 years and a total of 107,806 patients were included in the analysis. The conclusion from the study was that monotherapy with most first- and second-generation sulphonylureas seems to be associated with increased mortality and cardiovascular risk compared to metformin (Schramm 2011). However, we could not confirm this finding in our analysis of prospective randomised trials, which could be due to low power in our analyses. On the other hand, there may be several confounding factors some of which may be undetected in the observational study (Deeks 2003).

The evidence supporting the use of sulphonylureas as monotherapy in patients with T2DM is limited, as is the case in fact with all existing glucose-lowering interventions. Current guidelines recommending metformin as first-line monotherapy are based mainly on the reduced risk of hypoglycaemia and weight gain with metformin compared to sulphonylureas (Inzucchi 2012; Nathan 2009). The rationale for recommending metformin monotherapy as first-line intervention is to a large extent based on the UKPDS trial, which allocated 342 overweight/obese participants to metformin monotherapy. However, the UKPDS trial having the longest follow-up comparing metformin with other comparators (including sulphonylureas and insulin) does not present cardiovascular outcomes allowing the differentiation between classes of sulphonylureas (UKPDS 34 1998). Moreover, there seems to be very limited evidence for announcing any intervention in this systematic review to be superior to another on patient-important outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to demonstrate whether sulphonylurea monotherapy versus other comparators influences all-cause or cardiovascular mortality. The assessments of patient-important outcomes such as non-fatal macrovascular and microvascular outcomes are very sporadic and sparsely assessed. Sulphonylureas increase the risk of mild hypoglycaemia compared with several other comparators, but the total amount of evidence is sparse. The same is the case for severe hypoglycaemia. Weight gain is more pronounced with second-generation sulphonylureas than with metformin, but less pronounced compared with thiazolidinediones. Therefore, it is hard to give specific advice regarding sulphonylureas in the treatment of type 2 diabetes mellitus.

Implications for research

For safety purposes, we need much more evidence from randomised clinical trials assessing cardiovascular disease and mortality in patients with type 2 diabetes mellitus treated with sulphonylurea monotherapy. Large randomised clinical trials are warranted. We also suggest a more uniform and rigorous reporting of outcomes in upcoming trials to ease the comparisons between different glycaemic intervention targets. Future trials ought to be reported according to the CONSORT (CONsolidated Standards of Reporting Trials) statement.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abbatecola 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: blinding not described, but we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • T2DM • treatment-naive • 60 to 78 years **EXCLUSION CRITERIA**: • severe macro- and microangiopathy • coronary heart disease • heart failure • medium/severe hypertension • cancer • chronic obstructive pulmonary disease • upper limb paresis or paralysis • dementia **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and exercise **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, postprandial glucose, cognition score, adverse events, hypoglycaemic episodes, Homeostasis Model of Assessment - Insulin Resistance, blood pressure, biochemical variables, carotid ultrasound, depression
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months + 3 weeks **DURATION OF FOLLOW-UP**: 12 months + 3 weeks **STUDY TERMINATED BEFORE REGULAR END**: no

Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We tested the hypothesis that an elevated PPG instability could be associated with both global cognitive functioning as well as executive and attention functioning neuropsychological tests."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After patient referral to our offices, participants who accepted to enroll in the study were randomly assigned to undergo monotherapy with repaglinide (initially started with 1 mg twice a day) or glibenclamide therapy (also known as glyburide in the United States and Canada; initially started with 2.5 mg twice a day)."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not described, but we assume open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All MRI evaluations were made by physicians not involved in the study and blind toward the study design." Blinding of participants for the other outcomes are not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up adequately described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding

ADOPT 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: rosiglitazone Control 2: metformin
Participants	**INCLUSION CRITERIA**: • T2DM within the last 3 years • 30 to 75 years • previously diet/exercise (exceptions: prior insulin use for gestational diabetes, short-term (≤1 months) insulin use to maintain glycaemic control for hospitalisation, medical procedure, or intervention; and ≤1 month use of any oral hypoglycaemic agent at least 2 months before screening) • FPG 7 to 13 mmol/L at screening and 7 to 10 mmol/L at randomisation **EXCLUSION CRITERIA**: • clinically significant hepatic disease • alanine aminotransferase ≥2.5 times the upper limit of the normal reference range • renal impairment indicated by serum creatinine concentration • anaemia • history of lactate acidosis • unstable or severe angina • congestive heart failure • uncontrolled hypertension • any chronic disease requiring continuous intermittent treatment with corticosteroids • any associated condition that could preclude completion of the study • active drug or alcohol abuse within the last 6 months • patients with variation in body weight ≥ 5% during the run-in period will also be excluded **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 247 Control 1: 231 Control 2: 269 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/753/370 Control 1: NR/744/378 Control 2: NR/737/377
Interventions	**NUMBER OF STUDY CENTRES**: 488 **COUNTRY/LOCATION**: North America, Europe and Canada **SETTING**: outpatients **TREATMENT BEFORE STUDY**: lifestyle interventions **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: FPG below 140 mg/dl (7.8 mmol/L)

ADOPT 2006 (*Continued*)

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: time to monotherapy failure, glycaemic control, islet beta-cell function, insulin sensitivity, progression of microalbuminuria, fibrinolytic markers, cardiovascular risk factors, renal function, health status, quality of life and safety parameters
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 4 years **DURATION OF FOLLOW-UP**: 4 years **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "Our goal was to evaluate, in patients recently diagnosed with type 2 diabetes (<3 years), the long term efficacy of monotherapy with rosiglitazone on glycemic control and on the progression of pathophysiological abnormalities associated with type 2 diabetes as compared with metformin or glyburide monotherapy."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A central laboratory will be used during the study. Samples will be collected and transferred under appropriate conditions to the central laboratory."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up adequately described

ADOPT 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	All predefined primary and secondary outcomes in the protocol are assessed
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

AGEE/DCD/046/UK

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • T2DM • 40 to 75 years • BMI $\geq$ 21 and $\leq$ 35 kg/m^2 • HbA1c $\geq$ 6.5 (diet-treated) and $\leq$ 10% (for patients previously on sulphonylurea) **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 26 **COUNTRY/LOCATION**: United Kingdom **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or sulphonylurea **TITRATION PERIOD**: 6 to 8 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, hypoglycaemia, adverse events, lipid metabolism and beta-cell status
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months + 6 to 8 weeks **DURATION OF FOLLOW-UP**: 12 months + 6 to 8 weeks + 3 months

AGEE/DCD/046/UK (*Continued*)

	STUDY TERMINATED BEFORE REGULAR END: no
Publication details	**LANGUAGE OF PUBLICATION**: not published, but the synopsis describing the trial is in English. Trial identified through approval letter of the US Food and Drug Administration (FDA 2000) **COMMERCIAL FUNDING** **PUBLICATION STATUS**: unpublished
Stated aim of study	Quote: "..to assess and compare the effect of repaglinide and glibenclamide on glycaemic control as measured by HbA1c and fasting plasma glucose (FPG) when administered to Type 2 diabetic patients for 12 months."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized to a treatment group in a 2:1 ratio of repaglinide and glibenclamide."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo: used to double-blind the trial; encapsulated tablets, orally"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded due to a double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up clearly described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes assessed as predefined
Academic bias	High risk	The data for the trial are provided from Novo Nordisk
Sponsor bias	High risk	Sponsored by pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear randomisation and allocation concealment, adequate blinding

AGEE/DCD/047/B/F/I

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • T2DM • 40 to 75 years • BMI $\geq$ 21 and $\leq$ 35 kg/m^2 • HbA1c $\geq$ 6.5 (diet-treated) and $\leq$ 12% (for patients previously on sulphonylurea) **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 41 **COUNTRY/LOCATION**: Belgium, France and Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or sulphonylurea **TITRATION PERIOD**: 6 to 8 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, hypoglycaemia, adverse events, lipid metabolism and beta-cell status
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months + 6 to 8 weeks **DURATION OF FOLLOW-UP**: 12 months + 6 to 8 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: not published, but the synopsis describing the trial is in English. Trial identified through approval letter of the US Food and Drug Administration (FDA 2000) **COMMERCIAL FUNDING** **PUBLICATION STATUS**: unpublished
Stated aim of study	Quote: "..to assess and compare the effect of repaglinide and gliclazide on glycaemic control as measured by HbA1c and fasting plasma glucose (FPG) when administered to Type 2 diabetic patients for 12 months."
Notes	

Risk of bias

AGEE/DCD/047/B/F/I (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized to a treatment group in a 2:1 ratio of repaglinide and gliclazide."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo: used to double-blind the trial; encapsulated tablets, orally"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded due to a double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up clearly described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes assessed as predefined
Academic bias	High risk	The data for the trial are provided from Novo Nordisk
Sponsor bias	High risk	Sponsored by pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear randomisation and allocation concealment, adequate blinding

Alvarsson 2010

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: insulin
Participants	**INCLUSION CRITERIA**: • T2DM diagnosed < 2 years previously were asked for participation • women and men • 35 to 70 years of age • FBG between 7.0 and 12.0 mmol/L during screening on one occasion when on diet alone for at least 1 month **EXCLUSION CRITERIA**: • pharmacological treatment for diabetes > 6 months • low fasting plasma C-peptide concentrations (< 0.2 nmol/L) • ketonuria (more than trace amounts)

	• BMI > 35 kg/m^2 • plasma creatinine > 150 µmol/L • severe retinopathy (proliferative or preproliferative) • severe cardiac disease (NYHA III-IV) • positivity for islet antibodies (islet cell antibodies, glutamic acid decarboxylase 65 antibodies and protein tyrosine phosphatase-like protein IA-2 antibodies) **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/2/2 Control: NR/1/1
Interventions	**NUMBER OF STUDY CENTRES**: 6 **COUNTRY/LOCATION**: Sweden **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated, but time period not reported **GLYCAEMIC TARGET**: HbA1c levels within target level, that is below or equal to 1% above the upper normal level of HbA1c of 6.2%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: retinopathy, quality of life, biochemical variables, effect on beta-cell function
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 6 years **DURATION OF FOLLOW-UP**: 6 years **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare effects of early insulin vs. glibenclamide treatment on beta-cell function, metabolic control and quality of life (QL) in recently diagnosed patients with type 2 diabetes."
Notes	Data for participants on antihypertensives are the number on angiotensin converting enzyme inhibitor or angiotensinogen receptor blocker

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to monotherapy with glibenclamide or insulin."

Alvarsson 2010 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design, we assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs clearly described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions. This trial is published in 3 publications
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, inadequate blinding

APPROACH 2010

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glipizide Control: rosiglitazone
Participants	**INCLUSION CRITERIA**: • 30 and 80 years of age • established T2DM undergoing clinically indicated coronary angiography or percutaneous coronary intervention with at least one atherosclerotic plaque in a non intervened coronary artery with 10% to 50% luminal narrowing • treated for T2DM with diet and exercise only, oral antidiabetic monotherapy or submaximal oral antidiabetic combination therapy (≤ 50% of maximal dose for each agent) • screening HbA1c > 7% and ≤ 10% (if treated with diet and exercise only) or > 6.5% and ≤ 8.5% (if treated with oral antidiabetic medications) **EXCLUSION CRITERIA**: • ST-segment elevation myocardial infarction in the prior 30 days • coronary artery bypass graft surgery • severe cardiac valvular disease • left ventricular ejection fraction < 40%

	• heart failure (NYHA I-IV) • uncontrolled hypertension (systolic blood pressure > 170 mm Hg or diastolic blood pressure > 100 mm Hg) • renal insufficiency (serum creatinine ≥ 1.5 mg/dl for men or ≥ 1.4 mg/dl for women) • hepatic enzyme elevation (alanine aminotransferases or aspartate aminotransferase > 2.5 × upper limit of normal or total bilirubin> 2 × upper limit of normal) **DIAGNOSTIC CRITERIA**: diagnosed with T2DM, established diagnosis of T2DM based on ADA, WHO or local national guidelines **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 339 Control: 333 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 279/238/262 Control: 280/237/248
Interventions	**NUMBER OF STUDY CENTRES**: 92 **COUNTRY/LOCATION**: 19 (Asia, Europe, North America, South America) **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or oral antidiabetics **TITRATION PERIOD**: 12 weeks **GLYCAEMIC TARGET**: HbA1c < 7% (target mean daily glucose < 126 mg/dl (7.0 mmol/L))
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: per cent atheroma volume, intravascular ultrasound efficacy parameters include change in normalised total atheroma volume and change in atheroma volume within the most diseased 10 mm sub-segment, change from baseline in vessel volume, change in biochemical variables, major adverse cardiovascular events (cardiovascular and non-cardiovascular death, non-fatal myocardial infarction and stroke, coronary revascularisation, and hospitalisation for recurrent myocardial ischaemia) and new or worsening heart failure
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 18.6 months **DURATION OF FOLLOW-UP**: 18.6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The aim of the APPROACH (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History) trial is to compare the glucose-independent effects of the thiazolidinedione rosiglitazone with the sulfonylurea glipizide on the progression of coronary atherosclerosis, as measured by IVUS, in participants with T2DM and coronary artery disease."

Notes	Number for antihypertensive treatment is the number of participants with ACE-inhibitor or angiotensin receptor blocker treatment. Number for lipid-lowering treatment is the number of participants on statins All prior oral antidiabetic medications are down titrated by 50% at randomisation and discontinued after 1 month as double-blind study medications were up titrated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants are randomized in a 1:1 ratio to rosiglitazone or glipizide treatment using an automated voice-response system."
Allocation concealment (selection bias)	Low risk	Quote: "Participants are randomized in a 1:1 ratio to rosiglitazone or glipizide treatment using an automated voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, study personnel, and core laboratory staff are blinded to treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, study personnel, and core laboratory staff are blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up described
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes described in protocol and assessed
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from the pharmaceutical industry
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

Birkeland 1994

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea 1: glibenclamide Sulphonylurea 2: glipizide Control: placebo
Participants	**INCLUSION CRITERIA**: • T2DM • non-pharmacological treated for T2DM • HbA1c between 7% and 11% • considerable residual beta-cell function (the C-peptid concentration 6 min after injection of 1 mg glucagon was > 0.7 nM) **EXCLUSION CRITERIA**: • severe concurrent illness • signs of chronic cardiac, hepatic, pulmonary or renal disease **DIAGNOSTIC CRITERIA**: without insulin for > 1 year after diabetes diagnosis **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Norway **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated during trial to achieve target **GLYCAEMIC TARGET**: FBG < 8 mmol/L and HbA1c < 7.5% without hypoglycaemia
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, insulin secretion and biochemical variables
Study details	**RUN-IN PERIOD**: 3 to 6 months **DURATION OF INTERVENTION**: 15 months **DURATION OF FOLLOW-UP**: 15 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The aim of the study was to assess and compare the long-term (15 months) effects of moderate doses of glipizide and glyburide on glycaemic control and insulin secretion in a randomized placebo-controlled double-blind fashion."
Notes	

Birkeland 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "…they were subjected to a stratified randomisation procedure…" Through correspondence it was clarified that the randomisation was done manually by drawing numbers
Allocation concealment (selection bias)	Low risk	Through correspondence it was clarified that the concealment was made with opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All tablets looked identical and contained either 1.75 mg glyburide, 2.5 mg glipizide, or placebo."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Through correspondence it was clarified that the outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up adequately described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes not clearly defined in the publication. However, the list of priority of outcomes was not corrected from the answer we received by correspondence
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Adequate sequence generation, allocation concealment and blinding of participants, inadequate blinding of outcome assessors

Birkeland 2002

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: insulin
Participants	**INCLUSION CRITERIA**: • T2DM • age of onset diabetes ≥ 35 years • HbA1c 7% to 10% • age 40 to 70 years • BMI < 35 kg/m^2 • duration of diabetes > 2 years without insulin treatment • glucagon-stimulated peptide > 0.7 nmol/L **EXCLUSION CRITERIA**: • diastolic blood pressure > 110 mmHg • islet call antibodies positive • proliferative retinopathy • proteinuria • myocardial infarction within the last 12 months • angina pectoris causing pain daily • heart failure • malignancy • collagenoses **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/4NR Control: NR/5/NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Norway **SETTING**: outpatients **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: FBG < 7 mmol/L and a postprandial blood glucose < 10 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: retinopathy, nephropathy, macrovascular disease, metabolic profile
Study details	**RUN-IN PERIOD**: at least 3 months **DURATION OF INTERVENTION**: 42 months **DURATION OF FOLLOW-UP**: 42 months **STUDY TERMINATED BEFORE REGULAR END**: yes. Planned duration of the trial was 5 years, but as almost all participants in the sulphonylurea group ended up on insulin the trial was stopped

Birkeland 2002 (*Continued*)

Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS:** peer-reviewed journal
Stated aim of study	Quote: "In our study, our aim was to investigate the long-term effects of insulin versus SU therapy in type 2 diabetic subjects on glycaemic control, insulin resistance, microalbuminuria and levels of Lp(a) lipoprotein, triglycerides (TG), total- and HDL cholesterol, and diastolic and systolic blood pressure."
Notes	Number treated with antihypertensives is the number of participants prescribed ACE-inhibitors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: ".., they were randomly assigned to treatment…."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up and their reasons not clearly described
Selective reporting (reporting bias)	High risk	Do not report primary outcome
Academic bias	Low risk	Primary author's first publication on the interventions. Have previously published trials with glibenclamide, but with other comparators (Birkeland 1994)
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Campbell 1994

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glipizide Control: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • 40 to 69 years old **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: FPG > 8 mmol/L on 2 occasions 2 weeks apart on diet **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 0/3/NR Control: 0/4/NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: United Kingdom **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: up to 6 weeks **GLYCAEMIC TARGET**: FPG < 8 mmol/L (but more than 4)
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion
Study details	**RUN-IN PERIOD**: 2 weeks **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING: NR** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This present study is a long term comparison of metformin and the second generation sulphonylurea, glipizide in diet failed type 2 diabetes subjects, unstratified for weight, assessing glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion over a 12 month period."
Notes	
Risk of bias	

Campbell 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…subjects were randomised in blocks of four (11) to receive…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Charbonnel 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: pioglitazone
Participants	**INCLUSION CRITERIA**: • T2DM inadequately treated with diet alone • HbA1c between 7.5% and 11% with stable or worsening glycaemic control over a period of at least 3 months • 35 to 75 years **EXCLUSION CRITERIA**: • previously use of glucose-lowering pharmacotherapy at any time • any specific contraindications to either drug • long-term treatment with corticosteroids and the start of ß-blockers were not permitted during the study or within 4 weeks prior to screening **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**:

Charbonnel 2005 (*Continued*)

	Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 209 **COUNTRY/LOCATION**: Europe, Australia, Canada, South Africa and Israel **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 16 weeks **GLYCAEMIC TARGET**: HbA1c < 8%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, insulin, lipids
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This study compared the effects of pioglitazone and gliclazide on metabolic control in drug-naïve patients with Type 2 diabetes mellitus."
Notes	This trial is the first 52 weeks of Tan 2005 (Tan 2005)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized in…."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "…, double-dummy, double-blind, …."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume they were blinded

Charbonnel 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some of the participants were randomised, but not included in the analysis: 8 participants were not treated; 12 participants had unreliable data. It is not described to which group they originally were randomised to
Selective reporting (reporting bias)	Unclear risk	No protocol or design article available
Academic bias	Low risk	Primary author has not previously conducted trials comparing the same interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Collier 1989

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • patients with HbA1c > 9% at the end of the dietary run-in period were randomised **EXCLUSION CRITERIA**: other medication **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 0/0/0 Control: 0/0/0
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: NR **SETTING**: outpatients **TREATMENT BEFORE STUDY**: no antidiabetic intervention **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: not clear, but HbA1c < 8% is specified as the normal range

Collier 1989 (*Continued*)

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: platelet density profiles, intraplatelet nucleotides, intraplatelet nucleotides, intraplatelet β-thromboglobulin, plasma β triglyceride levels, intraplatelet cyclic AMP levels, platelet release reaction, platelet thromboxane B_2 production and plasma fibrinogen levels
Study details	**RUN-IN PERIOD**: 3 to 6 weeks **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "In this study we investigated the changes in platelet density profiles, intraplatelet nucleotides, intraplatelet nucleotides, intraplatelet β-thromboglobulin (β), plasma βTG levels, intraplatelet cyclic AMP (cAMP) levels, platelet release reaction, platelet thromboxane (TX)B_2 production and plasma fibrinogen levels in 24 newly diagnosed non-insulin-dependent diabetic patients."
Notes	The group of 12 comparable aged controls are not included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "..,and were therefore randomized into either metformin (Glucophage) or gliclazide (Diamicron) treatment groups, .."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design, we assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Small study, no drop-outs reported
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions

Collier 1989 (*Continued*)

Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Coniff 1995

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: tolbutamide Control 1: acarbose Control 2: placebo
Participants	**INCLUSION CRITERIA**: • T2DM of at least 6 months' duration • 18 years of age • stable body weight (+/- 5 kg within the previous 3 months) • FPG of at least 140 mg/dL **EXCLUSION CRITERIA**: • significant diseases or conditions likely to alter the course of their diabetes or their ability to complete the study • documented gastrointestinal diseases likely to be associated with abnormal gut motility or altered absorption of nutrients • known or suspected lactose intolerance • severe and poorly controlled diabetes • concomitant treatment with sulphonylureas, insulin, hypolipaemic agents, glucocorticoids, • other investigational drugs, or medications that might significantly alter gastrointestinal motility or absorption • inability to swallow tablets • known hypersensitivity to tolbutamide • impairment of hepatic and/or renal function resulting in impaired metabolism and/or excretion of tolbutamide **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 0 Control 1: 0 Control 2: 0 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 0 Control 1: 0 Control 2: 0

Coniff 1995 (*Continued*)

Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet. Patients on sulphonylurea or insulin therapy had these medications discontinued at least 4 weeks prior to enrolment **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: 1 hour postprandial plasma glucose level < 200 mg/dl
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: change in HbA1c, full-meal test tolerance, adverse events (including hypoglycaemia), blood lipids, change in HbA1c from each scheduled visit
Study details	**RUN-IN PERIOD**: 6 weeks **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 30 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This multicenter, double-blind study compared the long-term efficacy and safety of treatment with placebo, acarbose alone, tolbutamide alone, and acarbose combined with tolbutamide in NIDDM patients treated with a standard diabetic diet."
Notes	The intervention group combining tolbutamide with acarbose is not included in the analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…, patients were stratified based on fasting glucose level (stratum I ≤1200 mg/dL versus stratum II > 200 mg/dL) and randomized to receive 24 weeks of treatment with acarbose, tolbutamide, acarbose-plus-tolbutamide, or placebo."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...was followed by a double-blind treatment for 24 weeks..." Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR

Coniff 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up adequately described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Dalzell 1986

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: blinding not described, but we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: tolbutamide Comparator: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • normal or overweight • FPG persistently above 11 mmol/L • managed with diet for at least 6 months **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Ireland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: plasma glucose, fasting lipids and dietary adherence

Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 1 year **DURATION OF FOLLOW-UP**: 1 year **STUDY TERMINATED BEFORE REGULAR END**: NR
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: abstract in peer-reviewed journal
Stated aim of study	Quote: "This study compares the effect of tolbutamide and metformin on plasma glucose and fasting lipids in the management of NIDDM with persistent severe hypoglycaemia despite good dietary adherence."
Notes	It was not possible to find any address of a corresponding author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…, were randomized to treatment with…."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

DeFronzo 1995

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: metformin
Participants	**INCLUSION CRITERIA**: • lack acceptable glycaemic control (FPG $\geq$ 140 mg per decilitre) after at least 4 weeks of dietary therapy plus 20 mg of glyburide per day • weight of 120 to 170 per cent of ideal (on the basis of 1983 Metropolitan Life Insurance tables) • age of 40 to 70 years • normal renal function (serum creatinine $\leq$ 1.4 mg per decilitre (124 μmol per litre) in men and $\leq$ 1.3 mg per decilitre (115 μmol per litre) in women; and $\leq$ 2+ proteinuria) • normal liver function **EXCLUSION CRITERIA**: • symptomatic diabetes (polyuria, polydipsia and weight loss) • symptomatic cardiovascular disease • diastolic blood pressure above 100 mm Hg during antihypertensive drug treatment • any concurrent medical illness • received insulin therapy within the previous 6 months • used medications known to affect glucose metabolism • drank 3 or more alcoholic drinks per day ($\geq$ 3 oz of alcohol per day) • used illicit drugs • previously received metformin therapy **DIAGNOSTIC CRITERIA**: The diagnosis of T2DM was based on clinical history and the finding of a fasting plasma glucose concentration above 140 mg per decilitre (7.8 mmol per litre) on 2 occasions **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR, but multicentre **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: 5 weeks **GLYCAEMIC TARGET**: FPG < 140 mg per decilitre
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: -
Study details	**RUN-IN PERIOD**: 5 weeks **DURATION OF INTERVENTION**: 29 weeks **DURATION OF FOLLOW-UP**: 29 weeks

DeFronzo 1995 (*Continued*)

	STUDY TERMINATED BEFORE REGULAR END: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This report describes the results of two randomized, placebo-controlled, multicenter trials in which moderately obese patients with NIDDM whose diabetes was poorly controlled with diet alone or with diet plus a sulfonylurea drug were treated with metformin for 29 weeks."
Notes	The intervention group with glibenclamide plus metformin combination therapy is not included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "....patients were randomly assigned to treatment with....."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blind, but the method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for withdrawals are not sufficient
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Deng 2003

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: xiaoyoasan jiajian
Participants	**INCLUSION CRITERIA**: T2DM **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: China **SETTING**: NR **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: FBG, 2-hour post-prandial blood glucose and HbA1c
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: NR
Publication details	**LANGUAGE OF PUBLICATION**: Chinese **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	According to Chinese extractor, NR
Notes	Extracted by a Chinese collaborator

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Is a randomised clinical trial. Generation of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	NR

Deng 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Derosa 2003

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control: repaglinide
Participants	**INCLUSION CRITERIA**: • T2DM ≥ 6 months • nonsmokers with normal blood pressure (WHO criteria: systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg, no coronary heart disease and normal renal function (serum creatinine < 1.5 mg/dl)) • receiving no antidiabetic medications at the time of enrolment and had not achieved satisfactory glycaemic control (HbA1c > 7.0%) with diet and exercise alone • low-density lipoprotein concentrations > 100 mg/dl • no hypolipidaemic drugs, diuretics, beta-blockers or thyroxin **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: ADA criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/0/0 Control: NR/0/0

Derosa 2003 (*Continued*)

Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: treatment-naive **TITRATION PERIOD**: 8 weeks **GLYCAEMIC TARGET**: FPG < 120 mg/dl; postprandial plasma glucose < 160 mg/dl 2 hours after meal; HbA1c < 7%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, lipoprotein (a), plasminogen activator inhibitor-1, homocysteine, biochemical variables, blood pressure
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 14 months **DURATION OF FOLLOW-UP**: 14 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The present study was designed to compare the effects of repaglinide and glimepiride on measures of glycemic control in patients with type 2 diabetes and to determine whether these agents have differing effects on levels of Lp(a), PAl-l, and Hcy"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization codes were prepared by a statistician and placed in envelopes; the statistician subsequently carried out randomization by drawing the envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization codes were prepared by a statistician and placed in envelopes; the statistician subsequently carried out randomization by drawing the envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "..., blinding of the investigators and patients was maintained through the use of identical numbered bottles prepared by the hospital pharmacy."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient description of patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Not published trials investigating the same interventions (in monotherapy) previously
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation, adequate allocation concealment and blinding

Derosa 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control: metformin
Participants	**INCLUSION CRITERIA**: • T2DM ≥ 6 months • nonsmokers with normal blood pressure (WHO criteria: systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg, no coronary heart disease and normal renal function (serum creatinine < 1.5 mg/dl) • no hypolipidaemic drugs, diuretics, beta-blockers or thyroxin **EXCLUSION CRITERIA**: • abnormal liver or kidney function • history of chronic insulin treatment • active cardiac problems • known contradictions to sulphonylurea or biguanides • pregnancy • breastfeeding • intending to get pregnant • systemic treatment with corticosteroids **DIAGNOSTIC CRITERIA**: ADA criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR/0/0 Control: NR/0/0

Interventions	**NUMBER OF STUDY CENTRES**: 3 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: 8 weeks **GLYCAEMIC TARGET**: FPG < 120 mg/dl; postprandial plasma glucose < 160 mg/dl 2 hours after meal
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: extraglycaemic parameters, specifically those associated with cardiovascular risk. Glycaemic efficacy
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months (+ 8 weeks titration period) **DURATION OF FOLLOW-UP**: 12 months (+ 8 weeks titration period) **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The aim of the study was to compare the metabolic effects of glimepiride and metformin in patients with T2DM."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...,randomised,.."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient description of patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available

Derosa 2004 (*Continued*)

Academic bias	Low risk	Not published trials investigating the same interventions (in monotherapy) previously
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment. Inadequate blinding

Diehl 1985

Methods	**CROSS-OVER RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: not described, we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: chlorpropamide Control: insulin
Participants	**INCLUSION CRITERIA**: • fasting serum glucose of 150 mg/dl or higher on 2 occasions • newly diagnosed or no hypoglycaemic medication the previous 12 months • > 30 years **EXCLUSION CRITERIA**: • history of ketoacidosis • serum creatinine > 1.5 mg/dl • pregnancy • taking more than 2 other medications daily • poor visual acuity • handicaps preventing using a syringe • major co-morbidities **DIAGNOSTIC CRITERIA**: fasting serum glucose of 150 mg/dl or higher on 2 occasions **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or antidiabetic interventions the previously 12 months **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: achieve fasting glucose levels of ≤ 140 mg/dl while avoiding hypoglycaemic symptoms
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: compliance

Diehl 1985 (*Continued*)

Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We compared compliance with insulin and chlorpropamide in patients newly beginning medication for NIDDM."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "…were randomly assigned using opaque sealed envelopes to therapy…" Through correspondence, the primary author informed us that randomisation was done with a table of random number
Allocation concealment (selection bias)	Low risk	Quote: "…were randomly assigned using opaque sealed envelopes to therapy…"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Through correspondence we were told that the outcome assessors were blinded for the primary outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs and reasons described, but not possible to judge whether from first or second treatment period
Selective reporting (reporting bias)	Low risk	No trial protocol or design article available, but the primary authors confirmed the predefined outcomes through correspondence
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry

Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding of participants, adequate blinding of outcome assessors

Ebeling 2001

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: pioglitazone Control 2: placebo
Participants	**INCLUSION CRITERIA**: • T2DM treated with diet and 1 oral medication or diet alone • BMI $\geq$ 25 kg/m^2 • 35 years or older and 75 years or younger • HbA1c $\geq$ 7.5% • fasting serum glucose $\geq$ 7.8 mmol/L **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Finland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet with or without one oral agent **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, acute phase proteins and the influence of complement activation
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no

Ebeling 2001 (*Continued*)

Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We wanted to study how these proteins are related to complement activation in type 2 diabetes and how improvement of glycemic control affects them or complement activation."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We wanted to study how these proteins are related to complement activation in type 2 diabetes and how improvement of glycemic control affects them or complement activation."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This study was performed in a randomized double-blind manner." Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Esposito 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • diagnosis of T2DM for < 3 years • 35 to 70 years of age • BMI $\geq$ 24 kg/m^2 • HbA1c $\geq$ 6.5% • treated with diet or oral drugs **EXCLUSION CRITERIA**: • need for insulin use • concomitant chronic diseases, including kidney, liver and cardiovascular diseases; recent acute illness or change in diet, treatment or lifestyle within the 3 months before the study • severe uncontrolled hypertension (blood pressure < 200/100 mmHg) • pregnant women or women who intended to become pregnant **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: treatment-naive or peroral antidiabetic drugs **TITRATION PERIOD**: 6 to 8 weeks **GLYCAEMIC TARGET**: • FBG < 110 mg/dL • postprandial glucose < 140 mg/dL • HbA1c < 6.5%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: carotis intima media thickness, biochemical variables, markers of systemic vascular inflammation
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 12 months plus 6 to 8 weeks (titration period) **DURATION OF FOLLOW-UP**: 12 months plus 6 to 8 weeks (titration period) **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal

Esposito 2004 (*Continued*)

Stated aim of study	Quote: "We compared the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in type 2 diabetic patients."
Notes	Non-diabetic control group not included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A total of 175 diabetic patients were randomly assigned to open-label treatment with either repaglinide or glyburide, through the use of a computer-generated random number sequence (Figure 1)."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed in sealed study folders that were held in a central, secured location until after informed consent was obtained."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The laboratory staff did not know the participants' group assignments."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly described reason for drop-outs in each intervention group
Selective reporting (reporting bias)	Low risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	No commercial funding
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding of participants and investigators, adequate blinding of outcome assessors

Feinböck 2003

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM not adequately controlled on diet alone • 36 to 80 years • HbA1c $\geq$ 7.8% • BMI between 24 and 35 kg/m^2 **EXCLUSION CRITERIA**: • previous antidiabetic drugs for more than 4 weeks during the last 3 months • serious late diabetic complications • serum glutamic oxalacetic transferase or serum glutamic pyruvic transaminase greater than 2 times the upper limit • creatinine levels > 132.6 µmol/L • pregnant or not using a reliable method of birth control during the study period **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 17 **COUNTRY/LOCATION**: Austria **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 6 weeks **GLYCAEMIC TARGET**: FBG 7.8 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: number of responders in each intervention group, change in HbA1c, weight, postprandial blood glucose and C-peptide levels from baseline, standard biochemical variables and C-peptide
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 26 weeks **DURATION OF FOLLOW-UP**: 26 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "In the present study the efficacy, compliance and safety of acarbose and glimepiride were compared in patients with T2DM over a period of 26 weeks in a multicentre trial in Austria."

Feinböck 2003 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomized (stratified by study center, blocked) to a dose-finding phase…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only describe that blood samples were analysed in a central laboratory
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up adequately described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Fineberg 1980

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glipizide Control: tolbutamide
Participants	**INCLUSION CRITERIA**: • above 30 years (female adults using contraceptives or unable to bear children) • life expectancy at least 5 years • diabetes as confirmed by an oral glucose tolerance test on admission • ability to adhere to diet and medication regimens **EXCLUSION CRITERIA**:

Fineberg 1980 (*Continued*)

	• juvenile-onset or unstable diabetes mellitus • hepatic or renal insufficiency • use of diabetogenic drugs • history of drug abuse or non-compliant behaviour • previous sulphonylurea therapy failure **DIAGNOSTIC CRITERIA**: United States Public Health Service criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or antidiabetic drugs **TITRATION PERIOD**: individual. Until max dose or satisfactory glycaemic control **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: fasting and 2-hour postprandial serum glucose levels, insulin secretion and dynamics and glucose disappearance rates
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "Insulin secretion and dynamics and glucose disappearance rates (Kg) were studied before and at the end of the sixth month of therapy"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients then entered the active drug titration phase and were assigned consecutive numbers which were matched with a corresponding list of computer generated random drug assignments."

Fineberg 1980 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Patients then entered the active drug titration phase and were assigned consecutive numbers which were matched with a corresponding list of computer generated random drug assignments."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported to which group the patients lost to follow-up belonged
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from a pharmaceutical industry
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding

Foley 2009

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: vildagliptin
Participants	**INCLUSION CRITERIA**: • T2DM • HbA1c 7.5% to 11% while receiving no pharmacologic treatment (patients who had taken no oral antidiabetic drug for at least 12 weeks prior to screening and no oral antidiabetic drug for > 3 consecutive months at any time in the past were considered to be representative of a drug naive population) • $\geq$ 18 years • with a BMI in the range of 22 to 45 kg/m^2 • FPG < 15 mmol/L **EXCLUSION CRITERIA**: • pregnant or lactating • history of type 1 diabetes

	• pancreatic injury • secondary forms of diabetes • symptomatic autonomic neuropathy • acute infections • congestive heart failure NYHA class III or IV • electrocardiogram abnormalities • cirrhosis • chronic active hepatitis **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 151 **COUNTRY/LOCATION**: 16 countries (Europe, Latin America and South Africa) **SETTING**: outpatients **TREATMENT BEFORE STUDY**: treatment-naive **TITRATION PERIOD**: 12 weeks **GLYCAEMIC TARGET**: FPG was < 7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: change in HbA1c from baseline, body weight, FPG, fasting plasma lipids, fasting proinsulin, fasting insulin, fasting proinsulin/insulin ratio and homeostasis model assessment of insulin resistance (HOMA IR), adverse events both by regular physical examination and measurement of blood chemistry, haematology and urinalysis
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 104 weeks **DURATION OF FOLLOW-UP**: 104 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "...designed to compare the efficacy and safety of two years of monotherapy with vildagliptin 50 mg bid and gliclazide up to 320 mg/day in drug-naïve patients with type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Foley 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote:"..,multi-center, double-blind, randomized, active-controlled study to compare…"
Allocation concealment (selection bias)	Unclear risk	Quote:"..,multi-center, double-blind, randomized, active-controlled study to compare…"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"..,multi-center, double-blind, randomized, active-controlled study to compare…" Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reason for loss to follow-up described
Selective reporting (reporting bias)	Low risk	All outcomes from clinicaltrials.gov reported
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received grant from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Forst 2003

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator: insulin lispro
Participants	**INCLUSION CRITERIA**: • T2DM • 35 to 70 years • HbA1c < 1.7 fold normal-upper limit • C-peptide response ≥ 0.4 nmol/L after intravenous injection of 1.0 mg glucagon **EXCLUSION CRITERIA**: insulin therapy **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**:

	Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVE/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR
Interventions	**NUMBER OF STUDY CENTRES**: 19 **COUNTRY/LOCATION**: Sweden, Germany and Switzerland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: drug naive or oral antidiabetic **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: postprandial blood glucose excursion, glycaemic control, biochemical variables, safety data
Study details	**RUN-IN PERIOD**: 6 weeks **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "In the present study the efficacy and safety of the preprandial injections of insulin lispro were compared with the oral administration of glibenclamide in patients with type 2 diabetes"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Seventy-five patients were randomized to…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded

Forst 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed the trial
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Forst 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Comparator: pioglitazone
Participants	**INCLUSION CRITERIA**: • T2DM • 40 to 75 years of age • HbA1c between 6.6% and 9.9% **EXCLUSION CRITERIA**: • type 1 diabetes • smoking • clinically significant cardiovascular, renal or hepatic disease **DIAGNOSTIC CRITERIA**: ADA criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: glimepiride Comparator: pioglitazone **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 26/41/13 Comparator: 25/52/18
Interventions	**NUMBER OF STUDY CENTRES**: 1, we assume **COUNTRY/LOCATION**: Germany **SETTING**: outpatients **TREATMENT BEFORE STUDY**: not specified **TITRATION PERIOD**: not described **GLYCAEMIC TARGET**: morning blood glucose levels less than 6.7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: heat-stimulated microvascular blood flow, biochemical variables

Study details	**RUN-IN PERIOD**: not described **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING: no** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The present study was performed to investigate the effect of improving glucose control and insulin sensitivity by activating PPAR-γ with pioglitazone, in comparison with glimepiride treatment, on metabolic control, insulin resistance, and microvascular function in patients with type 2 diabetes."
Notes	It is not clearly described whether the trial is open-label or not, but we assume it to be open-label, because the addition of other antidiabetic drugs, if intervention failure differed between the 2 interventions The number reported for patients with antihypertensive is the number of patients receiving angiotensin 2-antagonist or ACE-inhibitor. Number of lipid-lowering is the number of patients on statins

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After randomization, patients..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Probably open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	179 patients randomised, but only 173 reported. Unknown why the 6 patients did not complete the trial
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions

Forst 2005 (*Continued*)

Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Hanefeld 2011

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: rosiglitazone 4 mg Control 2: rosiglitazone 8 mg
Participants	**INCLUSION CRITERIA**: • T2DM with a C-peptide level ≥ 0.8 ng/ml and a fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/L) and ≤ 270 mg/dl (15.0 mmol/L) at 4 and 2 weeks before randomisation • men and women aged 40 to 80 years **EXCLUSION CRITERIA**: Patients who had diabetic complications requiring treatment, serious renal, hepatic or haematological impairment, women of childbearing potential and insulin use were excluded **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: 71 **COUNTRY/LOCATION**: France, Germany, Italy, UK, Belgium, Sweden, Ireland and Netherlands **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or oral therapy (withdrawn 6 months before randomisation) **TITRATION PERIOD**: 12 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, fructosamine, C-peptide, insulin, pro-insulin, 32-33 split pro-insulin, urinary albumin, albumin excretion rate and serum lipids

Study details	**RUN-IN PERIOD**: 4 to 6 weeks **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: one of the publications is an article in a peer-reviewed journal, the other is from the GlaxoSmithKline website
Stated aim of study	Quote: "Sulphonylureas (SU) act by increasing endogenous insulin secretion. Rosiglitazone (RSG) acts predominantly by increasing insulin sensitivity and this study was to determine if RSG was a viable alternative to glibenclamide in first-line therapy in patients with type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....patients who were randomised. ..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Rosiglitazone, glibenclamide and placebo capsules were matched for weight, shape and colour. A double-dummy system allowed "titration" of rosiglitazone without a change of dose."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume due to double-blind design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up sufficiently described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Sponsored by pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment, adequate blinding

Harrower 1985

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: second-generation sulphonylurea: glipizide, gliquidone, gliclazide and glibenclamide Control: chlorpropamide
Participants	**INCLUSION CRITERIA**: • T2DM • failed to be controlled on diet **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Scotland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR, describe normal range from 5.6% to 8.7%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: diabetic control, biochemical variables
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **NON-COMMERCIAL FUNDING**: not directly, but was sponsored by the medical unit of a general hospital in Scotland **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "Five currently available sulphonylureas were compared to see whether, in routine use for 1 year, they produced any major differences in diabetic control."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Harrower 1985 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly allocated to one of five concurrent treatment groups…" Correspondence with author: the patients were randomly allocated using a card system with the drugs named on each card and placed randomly in a box
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were blinded. Information through correspondence
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up sufficiently described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	No funding from pharmaceutical industry. Information through correspondence
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Hermann 1991

Methods	**CROSS-OVER RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • younger than 70 years • normal serum creatinine and transaminase • modest control on current therapy of glibenclamide (FPG < 9 mmol/L and HbA1c < 11%) **EXCLUSION CRITERIA**: Persistent high blood glucose level on maximally tolerated dose of glibenclamide (FBG

	> 12 mmol/L) and/or intolerable adverse effects **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 2 **COUNTRY/LOCATION**: Sweden **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or glibenclamide **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, lipids, C-peptide
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The purpose of the present study was to compare long-term metformin and glibenclamide treatment in their effects on glycaemic control, weight, lipids, lipoproteins and insulin secretion."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The participants were randomised to the 2 interventions by help of a table of random numbers (correspondence with author)
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design

Hermann 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants lost to follow-up. Not clearly reported in which group they belonged
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Adequate sequence generation, unclear allocation concealment, inadequate blinding

Hermann 1991a

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: metformin
Participants	**INCLUSION CRITERIA**: • FBG $\geq$ 6.7 mmol/L on at least 2 occasions and/or abnormal glucose tolerance according to WHO • if FBG $\geq$ 6.7 mmol/L after 2 months of diet alone, patients were randomised **EXCLUSION CRITERIA**: • ketonuria • pregnancy • impaired renal function (serum creatinine above normal) • impaired hepatic function (elevated liver enzymes and/or other liver function tests), i.e. liver disease of a certain severity • known alcoholism • significant cardiac insufficiency • severe hypertension • severe retinopathy • serious chronic disease (cancer etc.) • periodic intake of drugs influencing glucose tolerance. If the patient received chronic drug therapy it must be kept constant during the study • drugs that interact with sulphonylurea **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: 12% of all participants had coronary heart disease Sulphonylurea: NR

Hermann 1991a (*Continued*)

	Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: 40% of all participants received beta-blockers Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 5 **COUNTRY/LOCATION**: Sweden **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or oral antidiabetic agents (had to be withdrawn 2 to 3 weeks before study entry) **TITRATION PERIOD**: 2 to 12 weeks **GLYCAEMIC TARGET**: FBG < 6.7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: efficacy and safety, responders, additive effect of sulphonylurea and metformin, lipids, insulin
Study details	**RUN-IN PERIOD**: 8 weeks (6 weeks on diet followed by 2 weeks with placebo tablets) **DURATION OF INTERVENTION**: 6 months + 2 to 12 weeks **DURATION OF FOLLOW-UP**: 6 months + 2 to 12 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To assess and compare the therapeutic efficacy and safety of metformin (M) and sulfonylurea (glyburide, G), alone and in various combinations, in patients with non-insulin-dependent diabetes mellitus (NIDDM)."
Notes	The group of participants randomised to receive metformin and glibenclamide combination therapy from the start is not included in the meta-analysis After diet period the patients underwent a main randomisation, early randomisation or delayed randomisation according to the FBG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "., patients were randomized (Fig. 1) according to computer-generated lists…"
Allocation concealment (selection bias)	Low risk	Quote: "., patients were randomized (Fig. 1) according to computer-generated lists…"

Hermann 1991a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To obtain truly double-blind conditions, the study used a double dummy technique."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume due to double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up sufficiently described
Selective reporting (reporting bias)	Low risk	All predefined primary and secondary outcomes are clearly described in trial protocol and assessed
Academic bias	High risk	Published Hermann 1991 previous to this trial
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

Hoffmann 1990

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM • 50 to 70 years • not satisfactorily regulated on diet • 2 fasting blood glucose values of at least 140 mg/100 ml • HbA1c at least 8.8% **EXCLUSION CRITERIA**: • Broca index larger than 1.1 • pharmacological diabetes therapy for the last 8 weeks • need for insulin therapy • pregnancy and lactation • decompensated heart insuffiencey • liver and kidney disease • malignant tumours • enteropathy • angiopathy

	• fever infection • laxative or obstipation medicaments • taking part in another randomised trial **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR
Interventions	**NUMBER OF STUDY CENTRES**: 5 **COUNTRY/LOCATION**: Germany **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 4 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, fasting blood glucose, postprandial blood glucose, renal glucose excretion, subjective compatibility
Study details	**RUN-IN PERIOD**: NR, probably none **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: German **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING: NR** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "Comparison of acarbose and glibenclamide on efficacy and adverse effects in patients with type II diabetes" [from English abstract]
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Open, randomized study in over 24 weeks in five private practices." [from English abstract]
Allocation concealment (selection bias)	Unclear risk	NR

Hoffmann 1990 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Hoffmann 1994

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind regarding acarbose/placebo and single-blinded regarding glibenclamide **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: placebo Control 2: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM pretreated with diet alone • HbA1c 7% to 9% • 35 to 70 years • duration of diabetes $\geq$ 3 months • stable body weight • BMI $\leq$ 35 kg/m^2 **EXCLUSION CRITERIA**: • aspartate-aminotransferase $\geq$ 50 U/L • alanine-aminotransferase $\geq$ 50 U/L • creatinine $\geq$ 2 mg/dl • severe disturbances of the haematopoietic system • malignant tumours • enteropathies • febrile infections • pregnancy • excessive abuse of alcohol or nicotine

	• laxative and constipating drugs • lack of willingness to co-operate • simultaneous intake of other test substances **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: 4 **COUNTRY/LOCATION**: Germany **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: the drugs were titrated during the trial **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: postprandial insulin increase, HbA1c, blood glucose, insulin and urinary glucose
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare the different therapeutic principles of a α-glucosidase inhibitors and sulphonylureas as first line treatment in non-insulin-dependent diabetes mellitus (NIDDM) patients with primary dietary failure."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The random list was generated by electronic data processing for 16 balanced blocks of six patients."
Allocation concealment (selection bias)	Unclear risk	NR

Hoffmann 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "…double-blind with respect to acarbose/placebo treatment and single-blind with respect to the glibenclamide treatment." The glibenclamide intervention was made single-blind so the investigators could adjust it to metabolic necessities and to avoid hypoglycaemia
Blinding of outcome assessment (detection bias) All outcomes	High risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up reported
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	High risk	Published similar trials previously (Hoffmann 1990)
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Adequate sequence generation, unclear allocation concealment, inadequate blinding

Hollander 1992

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: insulin
Participants	**INCLUSION CRITERIA**: not specified, but all had T2DM **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR

Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: NR **SETTING**: NR **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FBG, stimulated C-peptide
Study details	**RUN-IN PERIOD**: 8 weeks **DURATION OF INTERVENTION**: 44 weeks **DURATION OF FOLLOW-UP**: 44 weeks **STUDY TERMINATED BEFORE REGULAR END**: NR
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING: NR** **PUBLICATION STATUS**: published as abstract from conference proceeding
Stated aim of study	Not clearly stated, but the title says, Quote: "A randomized clinical trial of glyburide versus insulin using staged diabetes management to achieve euglycemia in NIDDM"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized clinical trial of..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions

Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Jain 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: pioglitazone
Participants	**INCLUSION CRITERIA**: • recently diagnosed with T2DM (< 2 years) • treatment-naive men and non-pregnant, non-lactating women • 18 to 80 years of age • from USA or Puerto Rico • HbA1c between 7.5% and 11.5% • fasting C-peptide level of 1.0 ng/ml or greater • fasting glucose level above 120 mg/dl **EXCLUSION CRITERIA**: • previously treatment with rosiglitazone, pioglitazone or troglitazone within the last 3 months • previous alcohol or drug abuse • previous treatment with meglitinide analogue, alfa-glucosidase inhibitor, metformin, insulin or sulphonylurea treatment for 3 months or more • use of hydrochlorothiazide greater than 25 mg/day, glucocorticoids, steroid joint injections, niacin greater then 250 mg/day or antidiabetic agents other than the study drugs during the trial • concurrent participation or enrolment in another investigational study • serum creatinine level above 1.5 mg/dl for men and above 1.4 mg/dl for women • greater than 1+ dipstick proteinuria or equivalent • anaemia • hypertension • BMI < 20 or > 45 kg/m^2 • elevated liver enzymes • elevated triglycerides • NYHA 3 to 4 • chronic condition expected to require glucocorticoids use • acute cardiovascular event within 6 months before screening • acute or unstable chronic pulmonary disease or lesions at chest radiography • cancer not in remission for the last 5 years **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR

Jain 2006 (*Continued*)

	NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 65 **COUNTRY/LOCATION**: USA and Puerto Rico **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and exercise. Other antidiabetics than the one mentioned in the exclusion criteria **TITRATION PERIOD**: 16 weeks **GLYCAEMIC TARGET**: FPG between 69 and 141 mg/dl
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, adverse events and biochemical variables
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 56 weeks **DURATION OF FOLLOW-UP**: 56 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To evaluate the long-term safety and efficacy of glyburide versus pioglitazone in patients with a recent diagnosis of type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…, patients were enrolled and randomly assigned 1:1 by means of…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "....multicenter, double-blind trial. ..." Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up reported

Jain 2006 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Jibran 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: blinding not described, but we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • newly diagnosed T2DM who remained uncontrolled on diet and exercise • 30 to 70 years **EXCLUSION CRITERIA**: • patients with type 1 diabetes • T2DM already taking maximum or near maximum doses of sulphonylurea and whose diabetes was still not controlled (patients with secondary failure) • T2DM already on insulin • patients taking diabetogenic drugs • significant gastrointestinal, cardiovascular or renal disease by history, physical examination or laboratory evidence or having concurrent medical illness **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: 0 Control: 0
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Pakistan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and exercise **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: FBG < 130 mg/dl and postprandial blood glucose < 175 mg/dl

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: fasting blood glucose , 2 hour postprandial glucose, HbA1c, weight, adverse events, biochemical variables
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To evaluate the safety and efficacy (glycaemic control) provided by repaglinide compared with glibenclamide in newly diagnosed type 2 (non-insulin dependant) diabetic patients."
Notes	Patients taking medication against cardiovascular disease are set to zero as none of the patients were taking long-term medication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Fifty patients were randomly selected for each group."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not described, but we assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described, but we assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described
Selective reporting (reporting bias)	Unclear risk	No design article or study protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported

Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Johnston 1997

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: placebo Control 2: miglitol 25 mg Control 3: miglitol 50 mg
Participants	**INCLUSION CRITERIA**: • T2DM • 60 years and above (at least 60% of the patients at each centre were required to be age 65 or older) • treated with diet alone for their diabetes for at least 12 weeks before randomisation • HbA1c from 6.5% to 10% inclusive • FPG greater than 140 mg/dl 2 weeks before randomisation • able to understand and comply with diet and glucose monitoring guidelines **EXCLUSION CRITERIA**: Serious illness that would prevent satisfactory completing of the study **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR Control 3: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: Control 1: NR Control 2: NR Control 3: NR
Interventions	**NUMBER OF STUDY CENTRES**: 30 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated during trial until week 40 **GLYCAEMIC TARGET**: FPG < 140 mg/dl
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, plasma glucose, serum insulin, lipid levels, albumin and glucose excursions

Johnston 1997 (*Continued*)

Study details	**RUN-IN PERIOD**: 6 weeks **DURATION OF INTERVENTION**: 56 weeks **DURATION OF FOLLOW-UP**: 56 weeks **STUDY TERMINATED BEFORE REGULAR END**: yes
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The objective of this study was to determine the safety, efficacy, and tolerability of the a-glucosidase inhibitor miglitol *vs*. the sulfonylurea glyburide in the treatment of elderly patients with type 2 diabetes mellitus, inadequately controlled by diet alone."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Four hundred eleven (411) diet-treated patients age 60 yr or greater were randomized to receive…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Glyburide dose titration was doubly blinded by encapsulation of active tablets or inactive excipients, and by an automated, interactive (between investigators and sponsor) dispensing system that permitted upwards and downwards dose titration without the glyburide dose appearing on tablets or packaging."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not adequately described
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes not stated in published protocol or design article
Academic bias	Low risk	Primary author's first publication on the interventions

Johnston 1997 (*Continued*)

Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Kaku 2011

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind in the first trial period (24 weeks), thereafter open-label (28 weeks) **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: liraglutide
Participants	**INCLUSION CRITERIA**: • T2DM treated with diet therapy with or without oral antidiabetic monotherapy for no less than 8 weeks (oral antidiabetic drugs: biguanide, sulphonylurea, alpha-glucosidase inhibitor, insulin secretagogue or insulin sensitiser within the dose range approved in Japan. The dose of sulphonylureas was set to within a half of the maximum approved dose. The dose of glibenclamide in patients previously treated with oral antidiabetic drugs was set at 2.5 mg or lower in order to exclude participants who could not be controlled with glibenclamide within the dose range fixed in this trial). • HbA1C $\geq$ 7.0% and < 10% • BMI < 35.0 kg/m^2 • age $\geq$ 20 years **EXCLUSION CRITERIA**: • treated with insulin within 12 weeks of the start of the study • receiving or expecting to receive systemic corticosteroids • known hypoglycaemia unawareness or recurrent major hypoglycaemia • any serious medical condition • pregnant or breastfeeding **DIAGNOSTIC CRITERIA**: the diagnosis of T2DM was done clinically by each investigator **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 77 Control: 166 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: 5/47/36 Control: 13/101/94
Interventions	**NUMBER OF STUDY CENTRES**: 75 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet with or without oral antidiabetic monotherapy **TITRATION PERIOD**: 2 weeks **GLYCAEMIC TARGET**: HbA1c < 6.9%

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, postprandial glucose, body weight, waist circumference, lipids, biochemical variables, hypoglycaemia, adverse events
Study details	**RUN-IN PERIOD**: 4 to 6 weeks **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We compared the safety and efficacy of liraglutide vs glibenclamide in patients with poorly controlled (HbA1c, 7.4-10.4%) type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "**…,** the subjects were randomly assigned at a 1:2 ratio to receive 1-year treatment with glibenclamide 1.25-2.5 mg/day or liraglutide given as follows…" The patients were randomised according to a randomisation list. The list was generated by a person in Trans Cocmos, Inc (information through correspondence)
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial consisted of 2 periods; a double-blind period with adequate blinding of participants and investigators. Quote: "The trial utilised a double-dummy method whereby placebo liraglutide injections and placebo glibenclamide tablets were administered alongside active therapy." The second trial period was open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcomes assessors were not blinded. However, the data review and decision on handling data were performed before the data from the liraglutide antibodies were available (information from correspondence)

Kaku 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up sufficiently described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes clearly defined in protocol published at www.clinicaltrials.gov, and they are all assessed
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Adequate sequence generation, unclear allocation concealment and blinding

Kamel 1997

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: we assume double-blind, as a placebo group is included **INTERVENTIONS USED IN TRIALS**: Sulphonylurea 1: gliclazide Sulphonylurea 2: glibenclamide Control 1: acarbose Control 2: metformin Control 3: placebo
Participants	**INCLUSION CRITERIA**: • T2DM • 35 to 65 years of age • BMI < 35 kg/m^2 • HbAlc 7% to 9% • duration of diabetes > 6 months **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea 1: NR Sulphonylurea 2: NR Control 1: NR Control 2: NR Control 3: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea 1: NR Sulphonylurea 2: NR Control 1: NR Control 2: NR

	Control 3: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Turkey **SETTING**: NR **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: FPG, HbA1c, postprandial serum insulin level, fasting serum-insulin levels and C-peptide
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: NR
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: abstract in peer-reviewed journal
Stated aim of study	Quote: "This study was planned to compare the different oral antidiabetic agents in NIDDM patients with dietary failure."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "43 NIDDM patients (35-65 years of age, BMI< 35 kg/m^2, HbA1c 7-9%, duration of diabetes > 6 months) were randomized into five groups and treated for 24 weeks..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR, but we assume double-blinded because of placebo group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR

Kamel 1997 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No design article or protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Kanda 1998

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM • not responding to strict diet and exercise treatment • fasting glucose level was higher than 150 mg/dl • BMI $\geq$ 24.5 kg/m^2 • Fasting plasma insulin levels $\geq$ 10μU/ml **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Japan **SETTING**: NR **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: waist size, visceral and subcutaneous fat
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: NR

Kanda 1998 (*Continued*)

Publication details	**LANGUAGE OF PUBLICATION**: Japanese **COMMERCIAL FUNDING**: no **PUBLICATION STATUS**: peer-reviewed journal	
Stated aim of study	Quote: "To compare effects of sulphonylurea and alpha-glucosidase inhibitor (acarbose) on glucose and lipid metabolism in DM patients."	
Notes	Evaluated by Japanese extractor	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...randomised.." Method not described
Allocation concealment (selection bias)	Low risk	Envelope used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assume not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up not addressed
Selective reporting (reporting bias)	Unclear risk	No design article or protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	No funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, adequate allocation concealment and inadequate blinding

Kovacevic 1997

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: single-blind regarding acarbose versus glibenclamide, double-blind regarding acarbose versus placebo **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: acarbose Control 2: placebo
Participants	**INCLUSION CRITERIA**: • T2DM for more than 3 months • HbA1c between 7% to 11% • age 35 to 70 years • stable body weight • BMI $\leq$ 35 kg/m^2 **EXCLUSION CRITERIA**: • severe liver disease • severe kidney disease: • other severe disease • pregnancy • on concurrent laxative or obstipating medications • non-compliance **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Croatia **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, relative postprandial serum insulin increase, blood glucose (fasting, 1-hour postprandial) , fasting serum insulin, 1-hour postprandial serum insulin, urine glucose, biochemical parameters
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no

Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The study was designed as a multicentric, randomized group comparison between acarbose and placebo as a double-blind, and between acarbose and glibenclamide as single-blind trial."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "On entering the study, the patients were consecutively allocated a number and divided into groups."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "…between acarbose and placebo as a double-blind, and between acarbose and glibenclamide as single-blind trial." However, the prescription of tablets are different in the acarbose group (tablets given 3 times a day) compared to the placebo group (tablets given 2 times a day)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up adequately described
Selective reporting (reporting bias)	Unclear risk	No design article or study protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding of participants and investigators, unclear blinding of outcome assessors

Lawrence 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control 1: metformin Control 2: pioglitazone
Participants	**INCLUSION CRITERIA**: • 45 to 80 years • diet treated diabetes with an HbA1c > 7% or those on low-dose oral hypoglycaemic therapy (gliclazide up to 80 mg/day or equivalent or metformin 500 mg 3 times a day) with an HbA1c < 7.5 % • BMI > 27 kg/m^2 • women of childbearing age had to be sterilised or using reliable contraceptive **EXCLUSION CRITERIA**: • diet-treated with an HbA1c > 10% • currently taking lipid-lowering therapy • previous intolerant of any study medication • study medication would be contraindicated (alanine transaminase more than 3 times the upper limit of normal, a serum creatinine > 150 µmol/L or a history of heart failure) • resent acute myocardial infarction (< 3 months) • uncontrolled angina or uncontrolled hypertension **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: United Kingdom **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or low-dose oral hypoglycaemic drugs **TITRATION PERIOD**: 3 months **GLYCAEMIC TARGET**: FBG < 7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: lipids and biochemical variables
Study details	**RUN-IN PERIOD**: 3 months **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no

Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare effects of different oral hypoglycemic drugs as first-line therapy on lipoprotein subfractions in type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...patients were randomly assigned.."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Individual three-digit patient identification numbers ensured that the laboratory staff was blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All drop-outs sufficiently described
Selective reporting (reporting bias)	Unclear risk	No study protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding of participants and investigators, adequate blinding of outcome assessors

LEAD-3 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind in the first year, thereafter open-label extension **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control 1: liraglutide 1.2 mg Control 2: liraglutide 1.8 mg
Participants	**INCLUSION CRITERIA**: • T2DM • aged 18 to 80 years • BMI of 45 kg/m^2 or less • eligible patients had been treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy including sulphonylureas, meglitinide, aminoacid derivatives, biguanides, alpha-glucosidase inhibitors and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months • screening HbA1c value of 7% to 11% if treated with diet and exercise or 7% to 10% with oral antidiabetic monotherapy **EXCLUSION CRITERIA**: • insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness) • treatment with systemic corticosteroids • hypoglycaemia unawareness or recurrent severe hypoglycaemia • impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations $\geq$ 2.5 times upper normal range) **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR
Interventions	**NUMBER OF STUDY CENTRES**: 138 **COUNTRY/LOCATION**: USA and Mexico **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or half the highest dose of oral monotherapy for at least 2 months **TITRATION PERIOD**: 2 to 3 weeks **GLYCAEMIC TARGET**: HbA1c < 7%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, body weight, FPG, self measured 8-point plasma-glucose profiles (measured before each meal, 90 min after the start of each meal, at bedtime and at 0300 h), blood pressure, ß-cell function (proinsulin to insulin ratio and 2 models of B-cell function: homoeostasis model assessment -B and homoeostasis model assessment-insulin resistance), fasting glucagon and patients' reported assessment of quality of life

Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 195 weeks **DURATION OF FOLLOW-UP**: 195 weeks **STUDY TERMINATED BEFORE REGULAR END**: yes. The duration of the treatment period was planned to be 260 weeks (5 years) Quote: "The trial was terminated at week 195 due to an insufficient number of subjects remaining to obtain reasonable statistical power."
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We aimed to investigate the safety and efficacy of liraglutide as monotherapy for this disorder."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned to the lowest available number."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned to the lowest available number."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The first year of the trial had adequate blinding of participants and personnel. Blinding of participants and personnel was not possible in the open-label extension
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes are assessed in the open-label extension period and we therefore assume that the outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some patients were lost to follow-up, when the trial went from double-blind to open-label extension and between the open-label extensions without being clearly described. All loss to follow-up adequately described during the intervention periods
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes predefined in the study protocol are assessed

LEAD-3 2006 (*Continued*)

Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, unclear blinding of participants and investigators, inadequate blinding of outcome assessors

Madsbad 2001

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glipizide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • diet or oral hypoglycaemic agents treated patients with T2DM • aged 40 to 75 years • BMI > 21 and < 35 kg/m^2 • HbA1c > 6.5 (diet-treated) and < 10% (for patients previously on oral antidiabetic drugs) **EXCLUSION CRITERIA**: • serum-creatinine levels > 140 µmol/L • signs of liver disease • proliferative retinopathy • severe uncontrolled hypertension (defined as systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg) • pregnancy • use of corticosteroids **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 23 **COUNTRY/LOCATION**: Denmark, Sweden, Norway and Finland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or oral antidiabetic drugs **TITRATION PERIOD**: 6 weeks **GLYCAEMIC TARGET**: FPG between 4.4 and 7.8 mmol/L

Madsbad 2001 (*Continued*)

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FBG, fasting C-peptide, insulin, triglycerides, total cholesterol, HDL-cholesterol, safety endpoints
Study details	**RUN-IN PERIOD**: 1 week **DURATION OF INTERVENTION**: 12 months + 6 to 8 weeks **DURATION OF FOLLOW-UP**: 12 months + 6 to 8 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To evaluate the long-term effectiveness and safety of repaglinide, a novel prandial glucose regulator, in comparison with glipizide in the treatment of patients with Type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to treatment with repaglinide or glipizide at a 2:1 ratio (in order to test rigorously the safety of the relatively new agent repaglinide)" OR "One week later the patients were randomized to either repaglinide or glipizide following cessation of any previous antidiabetic medication."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo tablets were used in the glipizide group for lunch and dinner."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded due to a double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate description of patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes assessed as predefined

Madsbad 2001 (*Continued*)

Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Marbury 1999

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • age 37 to 75 years • BMI of 20 to 40 kg/m^2 • T2DM according to WHO criteria of at least 6 months' duration • diet/exercise or another oral antidiabetic agent • HbA1c 6.5% to 14.6% (diet-treated with HbA1c > 6.5%, oral hypoglycaemic treated with HbA1c < 12%) **EXCLUSION CRITERIA**: • chronic insulin use • severe, uncontrolled hypertension • cardiac disorders • proliferative retinopathy • elevated serum creatinine (> 1.6 mg/dl), aspartate aminotransferase (> 120 U/L) or alanine aminotransferase (> 195 U/L) levels. • contraindications to glyburide • previously receiving repaglinide or systemic corticosteroids **DIAGNOSTIC CRITERIA**: WHO criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 2 Control: 11
Interventions	**NUMBER OF STUDY CENTRES**: 21 **COUNTRY/LOCATION**: USA and Canada **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or oral antidiabetic (other than repaglinide) **TITRATION PERIOD**: 8 weeks **GLYCAEMIC TARGET**: FPG 80 to 140 mg/dl, HbA1c $\leq$ 7.5%

Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FPG, lipid metabolism, changes in body weight and safety profiles, including hypoglycaemic events
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 + 3 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This prospective, 1-year, multicenter, double-blind, randomized, parallel-group study was designed to show that repaglinide was at least equivalent to glyburide in patients with type 2 diabetes."
Notes	Number with previously cardiovascular disease is the number of participants with previously serious cardiac events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized within each study center in a 2:1 ratio of repaglinide and glyburide and discontinued OHAs on the morning of the first post randomization visit."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Glyburide patients received a starting dose of 2.5 mg before breakfast and placebo before lunch and dinner"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded due to a double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up sufficiently described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes assessed as predefined
Academic bias	High risk	First author has published similar trials (Damsbo 1999)

Marbury 1999 (*Continued*)

Sponsor bias	High risk	Received funding from pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Memisogullari 2009

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: nothing
Participants	**INCLUSION CRITERIA**: • T2DM • recently diagnosed **EXCLUSION CRITERIA**: • active inflammatory and infectious diseases • anti-inflammatory, antihyperlipidaemic or antihypertensive drugs **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR/0/0 Control: NR/0/0
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Turkey **SETTING**: outpatients **TREATMENT BEFORE STUDY**: NR **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, markers of inflammation
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal

Memisogullari 2009 (*Continued*)

Stated aim of study	Quote: "In this study, we aimed to investigate whether gliclazide or diet treatment has an effect on serum levels of acute phase reactants, markers of inflammation."
Notes	The group of healthy controls is not included in the analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Twenty-six patients were prospectively randomized to take gliclazide…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	No design article or study protocol
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	NR
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Nakamura 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: NR, we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator 1: pioglitazone Comparator 2: voglibose
Participants	**INCLUSION CRITERIA**: • no history of ketoacidosis • treatment by diet alone • fasting C-peptide level more than 0.33 mmol/L

	• HbA1c level more than 6.5% **EXCLUSION CRITERIA**: • serum creatinine in excess of 1.5 mg/dl • none of the patients had been given antihypertensive drugs, including angiotensin-converting enzyme inhibitors • no malignancy, heart disease, cerebrovascular disease, liver disease or collagen disease based on physical examinations, urine and blood examination, and radiography, electrocardiography, ultrasound cardiography, x-ray or computed tomography scan data • haematuria or casturia • history of nondiabetic renal disease **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/0/NR Comparator: NR/0/NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: urinary albumin excretion, intima-media thickness, pulse wave velocity, HbA1c
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The aim of the present study was to compare the effects of pioglitazone (amelioration of insulin resistance), sulfonylurea (augmentation of insulin supply), and voglibose (limitation of postprandial hyperglycemia) on UAE, IMT, and PWV in normotensive diabetes patients with microalbuminuria."
Notes	Group of healthy controls are not included in the analyses

Risk of bias

Bias	Authors' judgement	Support for judgement

Nakamura 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to 1 of 3 treatment groups by sealed envelop method: treatment with pioglitazone 30 mg/d (n = 15), treatment with glibenclamide 5 mg/d (n = 15), or treatment with voglibose 0.6 mg/d (n = 15)"
Allocation concealment (selection bias)	Low risk	Quote: "The patients were randomly assigned to 1 of 3 treatment groups by sealed envelop method: treatment with pioglitazone 30 mg/d (n = 15), treatment with glibenclamide 5 mg/d (n = 15), or treatment with voglibose 0.6 mg/d (n = 15)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported, we assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	NR, we assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were no dropouts throughout the study period"
Selective reporting (reporting bias)	Low risk	All outcomes reported
Academic bias	High risk	Nakamura 2000
Sponsor bias	Unclear risk	NR
Trials according to risk of bias	Unclear risk	Unclear sequence generation, adequate allocation concealment, unclear blinding

Nakamura 2006

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator 1: pioglitazone Comparator 2: voglibose Comparator 3: nateglinide
Participants	**INCLUSION CRITERIA**: • no history of ketoacidosis • treatment by diet alone • fasting C-peptide level of more than 0.33 mmol/L

	• HbA1c more than 6.5% • microalbuminuria **EXCLUSION CRITERIA**: • serum creatinine in excess of 1.5 mg/dL • none of the patients had been given antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blocker or anti-platelet drugs • no malignancy, heart disease, cerebrovascular disease, liver disease or collagen disease based on physical examinations, urine and blood examination, and radiography, electrocardiography, ultrasound cardiography, x-ray or computed tomography scan data • haematuria or casturia • known history of nondiabetic renal disease **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 0/0/0 Comparator: 0/0/0
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 3 months **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glucose, HbA1c, creatinine, urea nitrogen, total cholesterol, high density lipoprotein cholesterol, triglyceride and urinary albumin excretion
Study details	**RUN-IN PERIOD**: 3 months **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: no **NON-COMMERCIAL FUNDING**: Shinmatsudo Central General Hospital and Koto Hospital **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The aim of the present study was to determine whether pioglitazone affects urinary L-FABP levels in diabetic nephropathy patients with microalbuminuria."
Notes	Group of healthy controls are not included in the analyses
Risk of bias	

Nakamura 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The diabetes patients with microalbuminuria were randomly assigned to one of four treatment groups by the sealed envelope method: treatment with pioglitazone 30 mg/d (*n* = 17), with glibenclamide 5 mg/d (*n* = 18), with voglibose 0.6 mg/d (*n* = 17), or with nateglinide 270 mg/d (*n* = 16)." The randomisation sequence was made by computer
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded. Information through correspondence
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors were blinded. Information through correspondence
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "..., and there were no dropouts."
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes reported by author, but not described in publication
Academic bias	High risk	Nakamura 2000; Nakamura 2004
Sponsor bias	Low risk	No commercial funding
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

Nathan 1988

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: insulin
Participants	**INCLUSION CRITERIA**: • T2DM • 30 to 70 years • weight greater than 90% of ideal weight

	• willingness and ability to do self blood glucose monitoring • patients not achieving FBG less than 7.8 mmol/L and HbA1c less than 6.5% after 1 month of diet were randomised **EXCLUSION CRITERIA**: • treated with insulin or oral agents within the last 6 months or have ever been primary or secondary oral agents failures • women planning pregnancy • history of renal failure • active liver disease • allergy to insulin, sulphonylurea or other sulphonamide drugs **DIAGNOSTIC CRITERIA**: National Diabetes Data Group **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: FBG < 6.4 mmol/L without hypoglycaemia
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: efficacy and complications, lipid status and weight
Study details	**RUN-IN PERIOD**: 1 month **DURATION OF INTERVENTION**: 9 months **DURATION OF FOLLOW-UP**: 9 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare the relatively efficacy, risks, and benefits of insulin with glyburide in achieving normoglycaemia in non-insulin-dependent diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Nathan 1988 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "……were randomly assigned to either glyburide or NPH insulin therapy using a computer-generated list."
Allocation concealment (selection bias)	Low risk	Quote: "……were randomly assigned to either glyburide or NPH insulin therapy using a computer-generated list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Glyburide (5-mg tablets) and identical placebo tablets were supplied by the manufacturer..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The success of the double-blind treatment strategy was tested by asking the research nurse and patient to guess.." We assume that the nurses were the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No design article or study protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

Pagano 1995

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: miglitol
Participants	**INCLUSION CRITERIA**: • T2DM • treated with diet and/or biguanide (biguanide discontinued at least 2 months before inclusion) **EXCLUSION CRITERIA**: • age < 40 years or > 70 years • BMI > 30 kg/m^2

	• HbA1c < 7% or > 11% • previous antidiabetic treatment (except biguanides) • serum creatinine > 176.8 mmol/L • haemoglobin > 11 g/dl **DIAGNOSTIC CRITERIA**: National Diabetes Group Criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 4 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or biguanides (discontinued at least 2 months before inclusion in trial) **TITRATION PERIOD**: 6 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, meal-stimulated serum insulin and C-peptide, FBG, postprandial glucose, total and HDL cholesterol, triglycerides, side effects and compliance
Study details	**RUN-IN PERIOD**: 7 weeks **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English and Italian **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The purpose of the present study was to compare the effectiveness of miglitol and glibenclamide in reducing HbA1c during long-term (24 week) administration in Type 2 diabetic patients (5-7) as well as meal-stimulated serum insulin and C-peptide levels (8, 9)."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…, patients were randomly assigned to miglitol…."
Allocation concealment (selection bias)	Unclear risk	NR

Pagano 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The glibenclamide group received a breakfast placebo throughout the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume they were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described to which group patients lost to follow-up belonged
Selective reporting (reporting bias)	Unclear risk	No design article or protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Perriello 2007

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: pioglitazone
Participants	**INCLUSION CRITERIA**: • T2DM managed by diet alone or with a maximum of one glucose-lowering agent • aged 35 to 70 years • HbA1C > 7.5% • no history of major cardiovascular events (myocardial infarction or stroke) within the 12 months before enrolment **EXCLUSION CRITERIA**: described in inclusion criteria **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 0 Control: 0 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR

Interventions	**NUMBER OF STUDY CENTRES**: 33 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or maximum of 1 oral hypoglycaemic agent **TITRATION PERIOD**: drugs were titrated every month to achieve glycaemic target **GLYCAEMIC TARGET**: the dose of drugs was increased if FBG was > 7.5 mmol/L or HbA1c > 7.5%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FBG, insulin and homeostasis model assessment of insulin resistance, self monitoring blood glucose, changes in plasminogen activator-1, antithrombin-III, von Willebrand factor and platelets
Study details	**RUN-IN PERIOD**: 2 weeks **DURATION OF INTERVENTION**: 1 year **DURATION OF FOLLOW-UP**: 1 year **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare long-term (1 year) efficacy and safety of pioglitazone and gliclazide in patients with Type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive either pioglitazone 30-45 mg/day or gliclazide 80-320 mg/day for up to one year."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to assure the double-blindness, drugs or placebo were identical in weight, taste, colour and shape and kept in coloured bottles with increasing doses of drugs. The lower doses of pioglitazone (30 mg) or gliclazide (80 mg) were stored in red bottles along with the placebo; 45 mg of pioglitazone and placebo or 80 and 160 mg of gliclazide were kept in blue and yellow bottles."

Perriello 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind design. We assume the outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs sufficiently described
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes clearly defined and assessed in publication, but no design article or study protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received support from a pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Rosenthal 2002

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: blinding not described, but we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM • men: age 40 to 75 • female: age < 75 (postmenopausal) • overweight • mild hypertension **EXCLUSION CRITERIA**: • myocardial infarction within the last 3 months • type 1 diabetes • alcohol or drug abuse • severe liver disease • serum creatinine > 1.3 mg/dl • hypo/or hyperthyroidism **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR

	Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: oral antidiabetic intervention or diet **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: blood pressure, serum insulin and biochemical variables
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To investigate the relationship between hypertension and hyperinsulinaemia, the effects on blood pressure and insulin levels of two oral antidiabetic agents with different mechanisms of action, acarbose (an α-glucosidase inhibitor) and glibenclamide (an insulin promoter), were compared in patients with hypertension and type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This study had a randomised, controlled, parallel-group design"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	We assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	NR, we assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 patients excluded due to protocol deviations
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available

Rosenthal 2002 (*Continued*)

Academic bias	Low risk	First article
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Salman 2001

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM $\geq$ 3 months • age 35 to 70 years • previously treated by diet alone • BMI $\leq$ 35 kg/m^2 • stable body weight • HbA1c 8% to 10% • C-peptide > 0.2 nmol/L • capable and willing to give informed consent **EXCLUSION CRITERIA**: • hypersensitivity to acarbose or gliclazide • inability to complete the study because of any significant disease or condition • having severe and poorly controlled diabetes manifested by ketonuria or severe hyperglycaemia and progressive weight loss, or documented gastrointestinal disease which was likely to be associated with abnormal gut motility or altered absorption of nutrients • receiving any investigational drug or participating in any other clinical trial within the last 30 days • receiving medication that significantly alters gastrointestinal motility and/or absorption • under therapy with any medication known to affect glucose homeostasis • had impaired liver functions defined as alanine-aminotransferase or aspartate transaminase of more than twice the upper limits of normal • impaired kidney function (serum creatinine > 220 µmol/L) • woman of childbearing age not using contraception or who was either pregnant or nursing **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**:

	Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Turkey **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 4 weeks **GLYCAEMIC TARGET**: not directly described, but they use HbA1c levels < 8% as a success criteria in the results section
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: fasting and postprandial plasma insulin, C-peptide, glucose levels, HbA1C, lipid profiles, biochemical tests for evaluation of drug safety
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare the effect of acarbose and gliclazide on clinical findings, biochemical parameters and safety in type 2 diabetic patients insufficiently controlled with medical nutrition therapy (MNT)."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Seventy-two patients (age 35-70 years, BMI $\leq$ 35 kg/m2), who had not taken any oral antidiabetic drug previously, were randomised into two groups after a four-week placebo period, and treated for 24 weeks with acarbose (100 mg two to three times daily) and gliclazide (40-80 mg twice daily)."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design

Salman 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded due to open-label design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not adequately described
Selective reporting (reporting bias)	Unclear risk	Outcomes clearly defined in trial publication, but not in a published protocol or design article
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Segal 1997

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control 1: miglitol Control 2: placebo
Participants	**INCLUSION CRITERIA**: • 30 to 70 years of age • T2DM of at least 3 months' duration • stable body weight on diet alone • no other diabetes medication in the 3 months before randomisation • HbA1c between 7.5% and 9.5% • absence of other major illness **EXCLUSION CRITERIA**: NR **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control 1: NR Control 2: NR

Segal 1997 (*Continued*)

Interventions	**NUMBER OF STUDY CENTRES**: 18 **COUNTRY/LOCATION**: Austria, Germany, Israel and Czech Republic **SETTING**: outpatients **TREATMENT BEFORE STUDY**: treatment-naive **TITRATION PERIOD**: 4 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, biochemical variables
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare the therapeutic effects of the alpha-glucosidase inhibitor miglitol (BAY m 1099), the sulfonylurea glibenclamide, and placebo on parameters of metabolic control and safety in patients with NIDDM that is inadequately controlled by diet alone. "
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization of eligible patients into a miglitol, glibenclamide (Euglucon, Boehringer Mannheim), and placebo treatment groups took place after a 4-week single-blind double-placebo run-in period, if the patient was at least 80% compliant."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients randomized to the three treatment groups received double-blind, double-dummy treatment." However, the titration regimen and the opportunity to increase the dose differed for the investigator, depending on the randomised intervention

Segal 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were many drop-outs and a very sparse description of the reasons
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Several authors work in the pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation, allocation concealment and blinding

Shihara 2011

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control: pioglitazone
Participants	**INCLUSION CRITERIA**: • T2DM • 30 to 75 years • stable dietary and exercise regime at least 1 month before randomisation • HbA1c between 6.9% to 10.4% at randomisation and 1 month before randomisation with absolute difference < 1% between these measurements **EXCLUSION CRITERIA**: • type 1 diabetes • use of insulin or any oral antidiabetic intervention in the month before randomisation • heart failure • any serious intercurrent complication involving heart, kidney, liver, pancreas or other organs or haematological condition • women who are pregnant, wishing to become pregnant or lactating • excessive alcohol drinking • past history of drug allergies • participating in other clinical studies (excluding epidemiological studies) • determined inappropriate for the study by the investigator **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR

	Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 33 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: titrated during trial **GLYCAEMIC TARGET**: FBG < 120 mg/dL, but > 80 mg/dl
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: percentage of patients with HbA1c < 6.9 at the end of study, change in HbA1c at 6 months compared with baseline, fasting plasma glucose, insulin, lipids and plasma natriuretic peptide levels, body weight, BMI, safety of study medication, compliance
Study details	**RUN-IN PERIOD**: 1 month **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To compare first-line agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes uncontrolled by diet and exercise with respect to glycaemic control, safety and metabolic changes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by a central registration method."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	In protocol described that no one was blinded

Shihara 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up explained
Selective reporting (reporting bias)	High risk	Assessed primary and secondary outcomes, but had in protocol predefined per cent of patients achieving HbA1c < 6.5%, however only reports the per cent of patients achieving HbA1c < 6.9%
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Pharmaceutical funding
Trials according to risk of bias	Unclear risk	Inadequate sequence generation, unclear allocation concealment, inadequate blinding

Spengler 1992

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: acarbose
Participants	**INCLUSION CRITERIA**: • T2DM insufficiently treated with diet • FBG $\geq$ 7.8 mmol/L, 1 hour postprandial glucose $\geq$ 10 mmol/L • diabetes duration $\geq$ 2 months • age 40 to 70 years • Broca-index $\leq$ 1.3 **EXCLUSION CRITERIA**: • patients who could not co-operate • patients who were unlikely to complete the trial • previously treated with peroral antidiabetics or insulin • myocardial infarction within the last 6 months • severe liver or kidney disease (creatinine > 2 mg/dl) • disease in the haemopoietic system • malignant tumours • enteropathy • infections with fever • pregnancy • alcohol or nicotine abuse • taking part in another clinical trial **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR

Spengler 1992 (*Continued*)

	Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 7 **COUNTRY/LOCATION**: Germany **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: glibenclamide titrated during the trial, the dose of acarbose was doubled after 2 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: FBG and 1 hour after breakfast, HbA1c, triglycerides, cholesterol, body weight, blood pressure, subjective symptoms, biochemical variables
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English and German **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This was the rationale to investigate the efficacy of acarbose vs. glibenclamide in a 6 months group comparison."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were in each centre consecutively assigned to one of two treatment groups according to a list of random numbers (after principle of randomness)."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias)	High risk	We assume not blinded due to open-label design

Spengler 1992 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for drop-outs clearly described, but it is not possible to estimate to which intervention they were originally randomised. The participants lost to follow-up are not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes not clearly described. No design article or protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Sung 1999

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: not described, we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: troglitazone
Participants	**INCLUSION CRITERIA**: T2DM with fasting glucose ≥ to 7.8 mmol/L and < 16.7 mmol/L on > 2 separate occasions **EXCLUSION CRITERIA**: • smokers • hypertension • known cardiovascular disease **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: NR

	TITRATION PERIOD: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: haemodynamic mechanism of blood pressure lowering glucose, insulin, C-peptide and HbA1c. Resting and stress blood pressure, stroke volume and cardiac output
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The present study examined the hemodynamic mechanisms of blood pressure (BP) lowering by troglitazone in patients with type 2 diabetes mellitus (DM) at rest and during a mental arithmetic test (MAT)."
Notes	"This study was performed as a 2-part protocol. The first part was to compare BP response to a mental arithmetic test (MAT) in persons with and without DM. Twenty-two DM patients and 12 age- and gender-matched controls participated in this protocol. The second part was designed to compare metabolic and hemodynamic effects of troglitazone and glyburide in subjects with DM. The same 22 DM patients were randomized to either the troglitazone or glyburide group and treated for 6 months" The healthy controls are not included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The DM group was then randomized to receive…"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely, not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unlikely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No drop-outs accounted for. Due to the size of the study it is very likely that there were no drop-outs

Sung 1999 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	No funding from the pharmaceutical industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Sutton 2002

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator: rosiglitazone
Participants	**INCLUSION CRITERIA**: • T2DM with endogenous insulin production (fasting C-peptide $\geq$ 0.8 ng/ml) • 40 to 80 years • women had to be postmenopausal, surgically sterile or currently using hormonal contraceptives or intrauterine devices • FPG $\geq$ 140 mg/dl but $\leq$ 300 mg/dl after the run-in period **EXCLUSION CRITERIA**: • renal disease (serum creatinine level > 18 mg/dl) • hepatic disease • previous treatment of myocardial infarction • NYHA class III/IV, coronary insuffiencey, congestive heart failure • previous or existing treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers or calcium-channel blockers • echocardiographic evidence of marked left ventricular hypertrophy at baseline • uncontrolled blood pressure (> 160/> 100) • FPG not within 140 and 300 mg/dl after 2 weeks of placebo treatment were excluded **DIAGNOSTIC CRITERIA**: National Diabetes Data Group definition, with fasting C-peptide concentration $\geq$ 0.8 ng/ml **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR

Interventions	**NUMBER OF STUDY CENTRES**: 19 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: varied from diet, single oral antidiabetic drug or combination therapy **TITRATION PERIOD**: 8 weeks **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: change from baseline in Left Ventricular Mass Index at weeks 28 and 52, change from baseline in left ventricular end-diastolic volume, ejection fraction, blood pressure, heart rate, arterial pressure, pulse, glycaemic control, serum lipids at weeks 28 and 52, urinary albumin excretion
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This open-label, active-controlled study investigated the cardiac safety and antihyperglycemic effect of rosiglitazone (RSG) in patients with type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly assigned…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discrepancy in number lost to follow-up in publication
Selective reporting (reporting bias)	Unclear risk	No design article or protocol

Sutton 2002 (*Continued*)

Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received commercial funding
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Tan 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Comparator: pioglitazone
Participants	**INCLUSION CRITERIA**: • HbA1c > 7.5% to ≤ 11% in patients who were not receiving oral antidiabetic drugs, and > 7.5% to ≤ 9.5% in patients who were receiving oral antidiabetic drugs monotherapy • adequate trial of dietary and lifestyle interventions before enrolment, as determined by the investigator **EXCLUSION CRITERIA**: • treatment with a thiazolidinedione or insulin within the previous 3 months • current prescription for a maximum dose of an oral antidiabetic drugs or for combination • oral antidiabetic drugs therapy • treatment with systemic glucocorticoids (excluding topical and inhaled preparations) within the previous 30 days • cardiac disease with substantial limitation of functional capacity (NYHA Class III or IV) • serum triglycerides > 400 mg/dl (> 4.5 mmol/L) • serum creatinine > 2.0 mg/dl (> 177 μmol/L) • renal transplantation or current renal dialysis • alanine aminotransferase or aspartate aminotransferase levels > 2.5 times the upper limit of normal of the central laboratory • clinical signs or symptoms of liver disease • haemoglobin < 10.5 g/dl for women and 11.5 g/dl for men • previous human immunodeficiency virus infection • BMI < 25 kg/m^2 or > 35 kg/m^2 • signs or symptoms of substance abuse **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**:

	Sulphonylurea: NR/NR/14 Comparator: NR/NR/15
Interventions	**NUMBER OF STUDY CENTRES**: 19 **COUNTRY/LOCATION**: Mexico **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or monotherapy oral (not maximum dose) **TITRATION PERIOD**: 12 weeks **GLYCAEMIC TARGET**: FBG $\leq$ 7 mmol/L and a 1-hour postprandial blood glucose concentration $\leq$ 10 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, insulin sensitivity and safety assessment
Study details	**RUN-IN PERIOD**: 1 to 3 weeks **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The goals of this study were to compare changes in measures of glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes who received pioglitazone or glimepiride for 1 year."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients who met the inclusion criteria were randomized in equal proportions to receive pioglitazone or glimepiride during the titration period according to a central randomization table generated by the sponsor and administered by an automated interactive voice-response system."
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "All doses of both drugs were administered as a single capsule to ensure blinding." However, according to the titration regimen pioglitazone could be prescribed in 3

		tablets and glimepiride in 4 tablets. They have not reported use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Description of all patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported
Academic bias	High risk	First author has published similar trials (Tan 2004a)
Sponsor bias	High risk	Received commercial funding
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, unclear blinding

Tan 2004a

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator: pioglitazone
Participants	**INCLUSION CRITERIA**: • oral antidiabetic drug-naive or were currently receiving monotherapy for the treatment of their diabetes • HbA1c > 7.5% and < 11% for patients who were not receiving oral antidiabetic drugs, or > 7.5% and < 9.5% for patients receiving oral antidiabetic drug monotherapy • fasting serum C-peptide of 0.333 pmol/L (1.0 ng/ml) • received an adequate trial of dietary/lifestyle intervention **EXCLUSION CRITERIA**: • insulin treatment within 30 days • glucocorticoid therapy (excluding topical and inhaled preparations) within 4 weeks; current treatment with nicotinic acid • currently on a maximum dose of 1 oral antidiabetic drug or on combination oral antidiabetic drug therapy • cardiac disease with substantial limitation of functional capacity (NYHA Class III or IV cardiac status) • serum creatinine > 177 µmol/L (2.0 mg/dl) • renal transplant or current renal dialysis • clinical signs or symptoms of liver disease • alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal for the central laboratory

	• haemoglobin or haematocrit below the lower limit of normal for the central laboratory **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/47/28 Comparator: NR/45/29
Interventions	**NUMBER OF STUDY CENTRES**: 22 **COUNTRY/LOCATION**: Denmark, Norway, Sweden and Finland **SETTING**: outpatients **TREATMENT BEFORE STUDY**: oral monotherapy (not maximum dose) or diet **TITRATION PERIOD**: 12 weeks **GLYCAEMIC TARGET**: FBG of < 7 mmol/L (126 mg/dl) and 1-h PBG of < 10 mmol/L (180 mg/dl)
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: efficacy and safety
Study details	**RUN-IN PERIOD**: 1 to 3 weeks **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This study compared the effects of 52 weeks' treatment with pioglitazone, a thiazolidinedione that reduces insulin resistance, and glibenclamide, on insulin sensitivity, glycaemic control, and lipids in patients with Type 2 diabetes."
Notes	Not clearly reported in publication whether the trial is double-blind or open-label, but we assume open-label, based on the different doses in the titration period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive pioglitazone or micronized glibenclamide."
Allocation concealment (selection bias)	Unclear risk	NR

Tan 2004a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding not reported in the publication. Sponsor described the blinding; glibenclamide and pioglitazone tablets were put inside a capsule to ensure blinding. Dummy titration visit was made for pioglitazone to ensure blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a very high number of patients lost to follow-up. The reasons for all of them were not clear in the publication, but additional information from the sponsors provided us with sufficient information
Selective reporting (reporting bias)	Low risk	All outcomes predefined in study protocol and reported
Academic bias	High risk	First author has published similar trials (Tan 2004)
Sponsor bias	High risk	Received commercial funding
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding of participants and investigators, unclear blinding of outcome assessors

Tan 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind (extension of Charbonnel 2005) **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: pioglitazone
Participants	**INCLUSION CRITERIA**: extension of Charbonnel 2005 **EXCLUSION CRITERIA**: extension of Charbonnel 2005 **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control: NR

Interventions	**NUMBER OF STUDY CENTRES**: 98 centres (selected on basis on the number of patients selected for the parent study) **COUNTRY/LOCATION**: Australia, Canada, Finland, Poland, the Slovak Republic, United Kingdom and South Africa **SETTING**: outpatients **TREATMENT BEFORE STUDY**: before randomisation to initial double-blind treatment phase, the patients were drug-naive (Charbonnel 2005). The patients were receiving either gliclazide or pioglitazone before the extension trial **TITRATION PERIOD**: none for the extension period **GLYCAEMIC TARGET**: HbA1c < 8%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: time to intervention failure, HbA1c, FPG, fasting serum insulin, homeostasis model assessment for insulin sensitivity and for cell activity
Study details	**RUN-IN PERIOD**: none **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The hypothesis that pioglitazone treatment is superior to gliclazide treatment in sustaining glycemic control for up to 2 years in patients with type 2 diabetes was tested. "
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a randomized, multicenter..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...randomized, multicenter, double-blind, double-dummy, parallel-group,. .."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate description of patients lost to follow-up

Tan 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No published protocol or design article available
Academic bias	High risk	Published similar trial previously (Tan 2004; Tan 2004a)
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Tang 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: glimepiride Comparator: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • age 35 to 70 years • course of disease < 5 years, without ketosis in 6 months • BMI 22 to 29 kg/m^2 • been treated with fixed dose glimepiride and/or metformin for more than 4 weeks in order to elution the influence of other hypoglycaemic drugs • newly diagnosed patients with not ideal blood glucose control after diet and/or exercise therapy for 4 weeks (FBG $\geq$ 7.0 mmol/L and/or postprandial blood glucose $\geq$ 11.1 mmol/L) • not been treated with insulin • not been treated with lipid-lowering drugs, thiazide diuretics, sex hormones, thyroxine, β-blockers, etc. for at least 2 months • without complications of diabetes • without gastrointestinal, heart, liver or kidney diseases **EXCLUSION CRITERIA**: described in the inclusion criteria **DIAGNOSTIC CRITERIA**: WHO 1999 **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 13 Comparator: 13 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 0/NR/0 Comparator: 0/NR/0
Interventions	**NUMBER OF STUDY CENTRES**: NR, probably 1 **COUNTRY/LOCATION**: China **SETTING**: NR

	TREATMENT BEFORE STUDY: NR **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: Both groups: FBG ≤ 7.1mmol/L, postprandial blood glucose ≤ 11.1mmol/L, HbA1c ≤ 7.0%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: biochemical variables
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: Chinese **NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote "To investigate the effect of glimepiride and metformin on free fatty acid in patients with Type 2 diabetes mellitus and to further study the relationship between free fatty acid and insulin resistance in patients with Type 2 diabetes mellitus." [From English abstract]
Notes	The abstract described the trial as a prospective case-control study, where patients were divided into 3 groups. In the main text the author state that the patients were randomised Intervention group in trial, not included in the review: glimepiride plus metformin The number of patients with previous cardiovascular disease is the number of patients with hypertension

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"....randomised..." [translated from Chinese]
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up reported

Selective reporting (reporting bias)	Unclear risk	No related information provided
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	"Sponsored by 15th National Research Project (2001BAA702B04); Science and Technology research Project of Hunan Province (03ssy3069)." [Translated from Chinese]
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Teramoto 2007

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Comparator: pioglitazone
Participants	**INCLUSION CRITERIA**: • Japanese • T2DM • 20 to 79 years old • received dietary and exercise instructions, without antidiabetic and hypolipidaemic agents • they had ≥ 140 mg/dl of FPG levels, ≤180 mg/dl of high-density lipoprotein cholesterol levels and triglycerides levels between 150 mg/dl and 500 mg/dl **EXCLUSION CRITERIA**: • taking medications known to influence glucose metabolism • history of ketoacidosis or with an unstable progressive diabetic coma or pre-coma condition • impaired liver function, kidney function, abnormal lipid metabolism • allergy to thiazolidinediones and/or sulphonylurea • tumour therapy • alcohol abuse • myocardial infarction • cerebrovascular dysfunction • receiving insulin due to severe infection **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**:

	Sulphonylurea: NR/NR/0 Comparator: NR/NR/0
Interventions	**NUMBER OF STUDY CENTRES**: 18 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 8 weeks **GLYCAEMIC TARGET**: FPG < 126 mg/dl
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: biochemical variables
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The effects of pioglitazone hydrochloride monotherapy on abnormal lipid control were evaluated in Japanese patients with type 2 diabetes mellitus, comparing with glibenclamide monotherapy."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a randomized..."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not extensively described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available

Teramoto 2007 (*Continued*)

Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	NR
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Tessier 1999

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Comparator: metformin
Participants	**INCLUSION CRITERIA**: • ambulatory patients • no acute cardiological or neurological events in the prior 6 months • no previous treatment with gliclazide, metformin, thiazide, beta-blockers, steroids or insulin **EXCLUSION CRITERIA**: described within the inclusion criteria **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**INTERVENTIONS USED IN TRIALS**: Sulphonylurea: gliclazide Control: metformin **NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Canada **SETTING**: outpatients **TREATMENT BEFORE STUDY**: not gliclazide, metformin or insulin; other oral were withdrawn 30 days prior to randomisation **TITRATION PERIOD**: not reported, but the dose was gradually increased **GLYCAEMIC TARGET**: self monitoring less than 8.0 mmol/L fasting in the morning, less than 10 mmol/L after meals
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: efficacy, lipid peroxidation and side effects

Tessier 1999 (*Continued*)

Study details	**RUN-IN PERIOD**: 30 days **DURATION OF INTERVENTION**: 24 weeks **DURATION OF FOLLOW-UP**: 24 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "Consequently, the goal of this study is to compare gliclazide and metformin in patients with type 2 diabetes mellitus with regard to efficacy, side effects profile, and lipid peroxidation."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Each subject were then randomized to…"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 drop-outs, reasons explained
Selective reporting (reporting bias)	Unclear risk	No design article or protocol available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Tosi 2003

Methods	**CROSS-OVER RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • FPG greater than 140 mg/dl • HbA1c $\geq$ 6.3% **EXCLUSION CRITERIA**: • insulin-treated patients • ketonuria • concurrent medical illness • severe diabetic complications • severe cardiovascular, hepatic, renal, respiratory or pancreatic diseases **DIAGNOSTIC CRITERIA**: ADA criteria **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 0 Control: 0 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 1/8/1 Control: 0/8/3
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Italy **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or oral antidiabetic intervention **TITRATION PERIOD**: 4 weeks **GLYCAEMIC TARGET**: during both phases of the study, doses were titrated in 4 steps (at intervals of minimum 20 days) to achieve HbA1c $\leq$ 6.0% and fasting plasma glucose less than 140 mg/dL, in the absence of hypoglycaemic episodes
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, FBG, insulin resistance, BMI, lipids and side effects
Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 6 months, thereafter switch to combination therapy **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "In the present randomized, double-blind trial, efficacy and tolerability of metformin and glibenclamide given alone or in combination were compared in 88 type 2 diabetic patients,using a cross-over design."

Notes	The combination group of glibenclamide plus metformin is not included in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After a 4-week run-in period (T 0), eligible patients were randomized to 3 treatment groups…" The random allocation schedule was generated by the pharmaceutical technique department (from correspondence)
Allocation concealment (selection bias)	Low risk	Quote: "All tablets were supplied by Guidotti Laboratories, Pisa, Italy, which generated the allocation schedule and provided the blinding procedure." Each drug was prepared and labelled by sequential number according to the allocation schedule. Participants were assigned in numbers in a consecutive order by a physician, who was blinded to treatments (from correspondence)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All tablets were supplied by Guidotti Laboratories, Pisa, Italy, which generated the allocation schedule and provided the blinding procedure."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume outcome assessors were adequately blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Difficult to assess drop-outs and their reasons after the first intervention period
Selective reporting (reporting bias)	Low risk	Primary outcome very vaguely defined in publication, but clarified through communication with corresponding author
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company

Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

UGDP 1970

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind evaluation of oral intervention, open-label for insulin **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: tolbutamide Control 1: placebo Control 2: insulin
Participants	**INCLUSION CRITERIA**: • maturity onset diabetes diagnosed within 12 months prior to enrolment in the study (the time of diagnosis was determined by the date of the first glucose tolerance test or by the time which hypoglycaemic treatment had been first initiated) • free of life-endangering diseases and a minimal life expectancy of 5 years at entry into the study in the clinicians' judgement • a diagnostic glucose tolerance test in which the sum of the 4 individual blood glucose values was $\geq$ 500 mg per 100 ml • free of ketoacidosis and other major diabetic symptoms on diet alone during a 4-week observation period immediately preceding entry into the study • patient willing and able to participate in the study **EXCLUSION CRITERIA**: prior history of ketoacidosis **DIAGNOSTIC CRITERIA**: patients fulfilling the requirements got a diagnostic test. Diagnostic test: the sum of 4 glucose values from glucose tolerance test had to be equal or greater than 500 mg/100 ml in order to be eligible for the study) **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 14 Control 1: 10 Control 2: 16 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: 4/55/NR Control 1: 7/48/NR Control 2: 7/62/NR
Interventions	**NUMBER OF STUDY CENTRES**: 12 **COUNTRY/LOCATION**: USA **SETTING**: outpatients **TREATMENT BEFORE STUDY**: hypoglycaemic therapy, not further specified **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: vascular complications, natural history of diabetes

UGDP 1970 (*Continued*)

Study details	**RUN-IN PERIOD**: 4 weeks **DURATION OF INTERVENTION**: 4.75 years **DURATION OF FOLLOW-UP**: 4.75 years **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "The University Group Diabetes Program had three major objectives: (1) Evaluation of the efficacy of various hypoglycaemic treatments in the prevention of vascular complications in patients with mild diabetes. (2) Study of the natural history of a group of patients with maturity onset, noninsulin dependent diabetes. (3) Development of methods applicable to cooperative clinical trials."
Notes	The phenformin group is not included in the analysis as it was included in the trial 18 months after the other interventions groups. The insulin variable (IVAR) intervention group had a more strict glycaemic target and is therefore not included in the analysis The insulin data is from the insulin standard intervention group in trial. Data from this intervention group are reported after a duration of intervention of 5.75 years to make the data comparable with tolbutamide The number reported with previously cardiovascular disease is the number of participants with angina

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients enrolled in the UGDP were randomly assigned to one of the five treatment groups. All assignments were made by the UGDP coordinating center."
Allocation concealment (selection bias)	Low risk	Quote: "Separate allocation schedules were used for each of the participating Clinical Centers. These schedules were prepared using a table of random numbers and were designed to insure a specified number of patients in each of the treatment groups in a given clinic at periodic intervals throughout the course of the recruitment. The allocation procedure used in each of these clinics was designed to provide the same number of patients in each of these four treatments groups after every sixteenth allocation. (Another assignment ratio when phenformin was added)."

UGDP 1970 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The tolbutamide and placebo group is adequately blinded. Quote: "Lactose placebo was given in tablet form which was indistinguishable by inspection from tolbutamide. The dosage schedule chosen was the same as for tolbutamide." The insulin group was open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…blind evaluation long-term observation of patients, and central collection, editing, and monitoring of the observed data."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specifically described for each intervention group Quote: "A total of 654 out of 823 patients had 5 complete years of follow-up…"
Selective reporting (reporting bias)	Low risk	Outcomes predefined in design article and assessed
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	No pharmaceutical funding
Trials according to risk of bias	Unclear risk	Adequate sequence generation, allocation concealment and blinding of outcome assessors. Unclear blinding of participants and investigators

UKPDS 1998

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea 1: chlorpropamide Sulphonylurea 2: glibenclamide Sulphonylurea 3: glipizide Control: insulin
Participants	**INCLUSION CRITERIA**: • newly diagnosed T2DM patients • aged 25 to 65 years inclusive • FPG greater than 6 mmol/L on 2 mornings, 1 to 3 weeks apart **EXCLUSION CRITERIA**: • ketonuria > 3 mmol/L • history of myocardial infarction in the previous year

	• current angina or heart failure • more than 1 major vascular episode • serum creatinine > 175 µmol/L • severe retinopathy requiring photocoagulation • malignant hypertension • an uncorrected endocrine abnormality • an occupation which would not allow randomisation to insulin therapy (e.g. heavy goods vehicle driver) • severe concurrent illness likely to limit life (e.g. cancer) or requiring extensive systemic treatment (e.g. ulcerative colitis) • inadequate comprehension to allow co-operation **DIAGNOSTIC CRITERIA**: FPG > 6 mmol/L on 2 occasions **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea 1: 9/69/2 Sulphonylurea 2: 7/69/0 Sulphonylurea: NR/NR/NR Control: insulin: 16/97/2
Interventions	**NUMBER OF STUDY CENTRES**: 23 **COUNTRY/LOCATION**: United Kingdom **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: the antidiabetic interventions were up titrated during the intervention period to achieve/maintain glycaemic target **GLYCAEMIC TARGET**: the aim of intensive treatment was FPG less than 6 mmol/L and, in insulin-treated patients, pre-meal glucose concentrations of 4 to 7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: any diabetes-related outcome, diabetes-related death, all-cause mortality, single components of macrovascular and microvascular outcomes, surrogate clinical outcomes, hyperglycaemic, quality of life
Study details	**RUN-IN PERIOD**: 3 months **DURATION OF INTERVENTION**: 10.0 years **DURATION OF FOLLOW-UP**: 10.0 years **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial."

Notes	The number of patients treated with aspirin/antihypertensives/lipid-lowering are only for the participants in glucose study 1. The number for aspirin is the number taking more than one a day, the number for antihypertensives are other than diuretics We have not included data from the conventional intervention group in the UKPDS, as it had another glycaemic target

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes which were opened in sequence."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes which were opened in sequence."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design: "The trial was open once patients were randomised"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Members of the UKPDS endpoint committee, who were unaware of assignments to study groups, adjudicated outcomes.."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up for each of the antidiabetic drug groups is not clearly described
Selective reporting (reporting bias)	High risk	Quote: "A subsidiary comparison is between those allocated to insulin and those allocated to sulphonylurea in all the randomisation groups to assess whether either has a specific risk or advantage." Not all the participants randomised in the sulphonylurea group are reported in the major comparison, as the primary and secondary outcomes for the participants randomised to glipizide and chlorpropamide in the Glucose II trial are not reported
Academic bias	Low risk	Primary author's first publication on the interventions

UKPDS 1998 (*Continued*)

Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding of participants and investigators

UKPDS 34 1998

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea 1: chlorpropamide Sulphonylurea 2: glibenclamide Control 1: metformin Control 2: insulin
Participants	**INCLUSION CRITERIA**: • newly diagnosed T2DM patients • aged 25 to 65 years inclusive • FPG greater than 6 mmol/L on 2 mornings, 1 to 3 weeks apart • > 120% of ideal bodyweight **EXCLUSION CRITERIA**: • ketonuria > 3 mmol/L • history of myocardial infarction in the previous year • current angina or heart failure • more than 1 major vascular episode • serum creatinine > 175 µmol/L • severe retinopathy requiring photocoagulation • malignant hypertension • an uncorrected endocrine abnormality • an occupation which would not allow randomisation to insulin therapy (e.g. heavy goods vehicle driver) • severe concurrent illness likely to limit life (e.g. cancer) or requiring extensive systemic treatment (e.g. ulcerative colitis) • inadequate comprehension to allow co-operation **DIAGNOSTIC CRITERIA**: fasting plasma glucose > 6 mmol/L on 2 occasions **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea 1: NR Sulphonylurea 2: NR Control 1: NR Control 2: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea 1: 5/40/2 Sulphonylurea 2: 3/44/2 Control 1: 5/51/1 Control 2: 12/49/1

UKPDS 34 1998 (*Continued*)

Interventions	**NUMBER OF STUDY CENTRES**: 15 **COUNTRY/LOCATION**: United Kingdom **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: the antidiabetic interventions were up titrated during the intervention period to achieve/maintain glycaemic target **GLYCAEMIC TARGET**: the aim of intensive treatment was FPG less than 6 mmol/L and, in insulin-treated patients, pre-meal glucose concentrations of 4 to 7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: any diabetes-related outcome, diabetes-related death, all-cause mortality, single components of macrovascular and microvascular outcomes, surrogate clinical outcomes, hyperglycaemic, quality of life
Study details	**RUN-IN PERIOD**: 3 months **DURATION OF INTERVENTION**: 10.7 years **DURATION OF FOLLOW-UP**: 10.7 years **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage."
Notes	The number for aspirin is the number taken more than one a day, the number for antihypertensives are other than diuretics We have not included data from the conventional intervention group in the UKPDS, as it had another glycaemic target

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	We assume the same method was applied as in UKPDS 1998
Allocation concealment (selection bias)	Low risk	Quote: "....allocations in sealed, opaque envelopes which were opened in sequence."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the same method was applied as in UKPDS 1998

UKPDS 34 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up for each of the antidiabetic drug groups is not clearly described
Selective reporting (reporting bias)	High risk	Quote: "The response to metformin therapy in the obese subjects is assessed by comparison with those allocated to diet policy and to sulphonylurea therapy." However, this comparison has never been reported
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received funding from pharmaceutical company
Trials according to risk of bias	Unclear risk	Adequate sequence generation, allocation concealment and blinding of outcome assessors, inadequate blinding of participants and investigators

van de Laar 2004

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: tolbutamide Control: acarbose
Participants	**INCLUSION CRITERIA**: • participants either with symptoms suggestive of diabetes mellitus and a capillary FBG $\geq$ 6.7 mmol/L or patients in whom a raised blood glucose level was found coincidentally • for patients without symptoms more than 1 abnormal fasting blood glucose was needed • patients were eligible for the trial if their FBG levels were between 6.7 and 20.0 mmol/L after an 8-week dietary treatment period (see below), and they met the following criteria: age between 40 and 70 years • sufficient understanding of spoken Dutch to follow instructions **EXCLUSION CRITERIA**: • any significant disease or condition likely to prevent patients from completing the study • uncorrected endocrine disturbances • pregnancy or breast-feeding • women of childbearing age not using contraceptives • diseases with abnormal gut motility or altered absorption of nutrients or use of medications for such conditions • use of systemic glucocorticoids • hypersensitivity or other contraindications to acarbose or tolbutamide

	• habitual use of drugs or an alcohol intake > 10 units daily • lactose intolerance • participation in another experimental study • serum cholesterol > 10 mmol/L or a serum triglyceride > 4 mmol/L • use of lipid-lowering agents containing ionic-substitution resins (e.g. colestipol) • aspartate aminotransferase > 50 U/L, alanine aminotransferase > 50 U/L, gamma glutamyltransferase > 150 U/L • creatinine > 150 µmol/L • myocardial infarction within the last 6 months **DIAGNOSTIC CRITERIA**: Symptoms suggestive of diabetes mellitus and a capillary FBG ≥ 6.7 mmol/L or patients in whom a raised blood glucose level was found coincidentally For patients without symptoms more than 1 abnormal fasting blood glucose was needed **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/11/3 Control: NR/3/4
Interventions	**NUMBER OF STUDY CENTRES**: 46 **COUNTRY/LOCATION**: The Netherlands **SETTING**: outpatients, general practice **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: 6 weeks **GLYCAEMIC TARGET**: FBG less than 6.7 mmol/L
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, fasting and post-load blood glucose and insulin levels, lipids and adverse events
Study details	**RUN-IN PERIOD**: 8 weeks **DURATION OF INTERVENTION**: 30 weeks **DURATION OF FOLLOW-UP**: 30 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "We performed a double blind randomised controlled trial in general practice to assess equivalence between tolbutamide and acarbose with respect to the effect on mean HbA1c in newly diagnosed patients with type 2 diabetes."
Notes	Number of patients on antihypertensive is the number receiving agent acting on the renin-angiotensin system
Risk of bias	

van de Laar 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We performed a double blind randomised controlled trial in general practice to assess equivalence between tolbutamide and acarbose with respect to the effect on mean HbA1c in newly diagnosed patients with type 2 diabetes."
Allocation concealment (selection bias)	Low risk	Quote: "The clinical quality assurance manager kept the allocation schedule in a central study file not accessible to the participating general practitioners. The code was sent to the general practitioner in a sealed radio-opaque envelope that was only to be broken in case of a medical emergency. At the end of the study the envelope had to be returned unopened."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Because of the different sizes of the actual tablets it was necessary to use the so-called 'double dummy' technique to ensure blinding. All patients received two sets of pills, apparently acarbose and tolbutamide, but only one set contained an active substance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	We assume the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up described
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes reported
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Sponsored by pharmaceutical company
Trials according to risk of bias	Low risk	Adequate sequence generation, allocation concealment and blinding

Watanabe 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: not described, we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: pioglitazone
Participants	**INCLUSION CRITERIA**: • T2DM • HbA1c between 6.5% and 8.0% • naive to antidiabetic drugs **EXCLUSION CRITERIA**: • kidney disease **DIAGNOSTIC CRITERIA**: FPG > 126 mg/dL **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/11/13 Control: NR/8/14
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: decrease of plasma glucose level equivalent to a decline of 0. 6% in terms of HbA1c in 6 months
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: change in pulse-wave velocity, BMI, blood pressure, brachial-ankle pulse-wave velocity, FPG, HbA1c, fasting immunoreactive insulin, homeostasis model insulin resistance index, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "To investigate the anti-arteriosclerotic effects of pioglitazone in patients with diabetes mellitus using pulse wave velocity (PWV) as an index of efficacy"
Notes	Number of patients with antihypertensives reported are only ACE-inhibitors

Watanabe 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "They were randomly divided into two groups..."
Allocation concealment (selection bias)	Low risk	Quote: "They were randomly divided into two groups by the envelope method (when the patient was registered, we opened the envelope in which contained either a card printed for pioglitazone (PIO) or for glibenclamide (GC) and followed the instructions), and assigned to receive either PIO or GC."
Blinding of participants and personnel (performance bias) All outcomes	High risk	We assume open-label, no blinding described
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume open-label, no blinding described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In the PIO group, drug administration was discontinued in two patients because of the development of edema. In the GC group, drug administration was discontinued in one patient because of signs of hypoglycemia. Therefore, a total of three patients were excluded from the present study."
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Unclear sequence generation, adequate allocation concealment, inadequate blinding

Wolffenbuttel 1989

Methods	**CROSS-OVER RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: tolbutamide Control: insulin
Participants	**INCLUSION CRITERIA**: • T2DM • non-obese • islet-cell negative antibodies • no ketonuria • no family history of type 1 diabetes • FBG > 8 mmol/L • stable body weight and blood glucose control after run-in period **EXCLUSION CRITERIA**: • impaired kidney function • severe hypertension • elevated liver enzymes • intervention with corticosteroids **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Control: NR
Interventions	**NUMBER OF STUDY CENTRES**: 1 **COUNTRY/LOCATION**: The Netherlands **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet or exercise **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: FBG < 8.0 mmol/L, HbA1c < 9%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic control, beta-cell function and lipids
Study details	**RUN-IN PERIOD**: 3 months **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote: "In 13 non-obese patients with Type 2 diabetes mellitus who failed to achieve adequate blood glucose control on dietary treatment (fasting blood glucose 13.4 +/- 2.7 (+/- SD) mmol l^{-1}, glycosylated haemoglobin 13.0 +/- 1.7%), the effects of 6 months

Wolffenbuttel 1989 (*Continued*)

	insulin or sulphonylurea therapy on blood glucose control and lipid metabolism were compared in a randomized crossover study."
Notes	Group of healthy controls not included in the analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to start either therapy."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	We assume not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not adequately described
Selective reporting (reporting bias)	Unclear risk	No protocol or design article
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Received grant from industry
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

Wolffenbuttel 1999

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: double-blind **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glibenclamide Control: repaglinide
Participants	**INCLUSION CRITERIA**: • T2DM • oral blood glucose-lowering agents and/or diet • age 40 to 75 years • BMI of 21.0 to 35.0 kg/m^2

	• HbA1c > 6.5% when treated with diet only and < 12% when treated with diet plus oral blood glucose-lowering agents **EXCLUSION CRITERIA**: • abnormal kidney or liver function (elevated serum creatinine > 140 µmol/L, elevated • transaminases more than 2 times the upper limit of normal) • a medical history of chronic insulin treatment • active cardiac problems (i.e. congestive heart failure) • unstable angina pectoris • recent myocardial infarction • severe uncontrolled hypertension (systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 110 mmHg) either untreated or while on antihypertensive treatment; any other disease that could interfere with study participation or outcome were excluded from the study • contraindications to sulphonylureas • pregnant • breast-feeding • intended to become pregnant • systemic treatment with corticosteroids **DIAGNOSTIC CRITERIA**: WHO **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Comparator: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR
Interventions	**NUMBER OF STUDY CENTRES**: 42 **COUNTRY/LOCATION**: The Netherlands, Germany and Austria **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet and/or oral antidiabetic drugs **TITRATION PERIOD**: 6 to 8 weeks **GLYCAEMIC TARGET**: Targets for treatment were fasting blood glucose of 4.4 to 6.1 mmol/L and postprandial levels of 4.4 to 8.0 mmol/L and HbA1c < 6.5%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: glycaemic values, insulin, lipids, hypoglycaemia and adverse events
Study details	**RUN-IN PERIOD**: 1 week **DURATION OF INTERVENTION**: 12 months + 6 to 8 weeks **DURATION OF FOLLOW-UP**: 12 months + 6 to 8 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal

Stated aim of study	Quote: "This multicenter study was designed to compare the efficacy and safety of this drug with glyburide in a 1-year randomized double-blind study of outpatients with type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients visited the outpatient clinic 1 week later and were asymmetrically randomized into blocks of six patients per treatment group in a 2:1 ratio of repaglinide to glyburide."
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain the thrice-daily dosing regimen, the glyburide group received placebo tablets at meals where no glyburide was taken."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As the trial is double-blinded and we assume the doctor assessed the outcome, we judged blinding as outcome assessors as low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up not adequately described
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes assessed as predefined
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	High risk	Sponsored by pharmaceutical company
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, adequate blinding

Yamanouchi 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: NR, we assume open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glimepiride Control 1: pioglitazone Control 2: metformin
Participants	**INCLUSION CRITERIA**: • T2DM • never used antidiabetic drugs • HbA1c ≥ 7.0% and FPG ≥ 7.78 mmol/L at the end of the 1-month observation period **EXCLUSION CRITERIA**: • unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy • liver dysfunction (aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 1.5 upper limit of normal) • impaired kidney function (serum creatinine > 133 μmol/L) • anaemia • myocardial infarction • angina • congestive heart failure • cerebrovascular accident **DIAGNOSTIC CRITERIA**: NR **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: NR Control 1: NR **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVES/ LIPID-LOWERING**: Sulphonylurea: NR/18/0 Control 1: NR/16/0 Control 2: NR/18/0
Interventions	**NUMBER OF STUDY CENTRES**: NR **COUNTRY/LOCATION**: Japan **SETTING**: outpatients **TREATMENT BEFORE STUDY**: diet **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: HbA1c ≤ 7%
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: HbA1c, metabolic variables
Study details	**RUN-IN PERIOD**: 1 month **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING/NON-COMMERCIAL FUNDING**: NR **PUBLICATION STATUS**: peer-reviewed journal

Stated aim of study	Quote: "To compare the metabolic effects of pioglitazone, metformin, and glimepiride in the treatment of Japanese patients with newly diagnosed Type 2 diabetes."	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was determined by the biostatistician, who provided sealed sequentially numbered envelopes opened only at the time of randomization."
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment was determined by the biostatistician, who provided sealed sequentially numbered envelopes opened only at the time of randomization."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not described, we assume open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not described, we assume open-label design
Incomplete outcome data (attrition bias) All outcomes	Low risk	All loss to follow-up sufficiently described
Selective reporting (reporting bias)	Unclear risk	No trial protocol or design article available
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Unclear risk	Funding not reported
Trials according to risk of bias	Unclear risk	Adequate sequence generation and allocation concealment, inadequate blinding

Zhang 2005

Methods	**PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL** **DOUBLE-BLIND/OPEN-LABEL**: open-label **INTERVENTIONS USED IN TRIALS**: Sulphonylurea: glipizide Comparator: rosiglitazone
Participants	**INCLUSION CRITERIA**: • initial diagnosis of T2DM • male patients older than 65 years • all signed the informed consent **EXCLUSION CRITERIA**: • refused to participate • received hypoglycaemic treatment before participating in the trial • history of hypertension and coronary heart disease • taking lipid-lowering drugs during the trial or liver and kidney dysfunction before treatment **DIAGNOSTIC CRITERIA**: WHO criteria 1999 **NUMBER OF PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASE**: Sulphonylurea: 0 Comparator: 0 **NUMBER OF PATIENTS TREATED WITH ASPIRIN/ANTIHYPERTENSIVE/LIPID-LOWERING**: Sulphonylurea: NR Comparator: NR
Interventions	**NUMBER OF STUDY CENTRES**: 24 **COUNTRY/LOCATION**: China **SETTING**: outpatients **TREATMENT BEFORE STUDY**: treatment-naive **TITRATION PERIOD**: NR **GLYCAEMIC TARGET**: NR
Outcomes	**OUTCOME(S) (as stated in the protocol/registered trial documents)**: biochemical variables, carotis intima-media thickness
Study details	**RUN-IN PERIOD**: NR **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **STUDY TERMINATED BEFORE REGULAR END**: no
Publication details	**LANGUAGE OF PUBLICATION**: Chinese **NON-COMMERCIAL FUNDING** **PUBLICATION STATUS**: peer-reviewed journal
Stated aim of study	Quote "To study the effects of thiazolidinediones (TZDs) on anti-atherosclerosis in elder male patients with type 2 diabetes, and understand related factors induced this function. "
Notes	The 2 rosiglitazone groups are meta-analysed as 1 group

Zhang 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly allocated into 3 groups. "
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All of the included patients completed 6 months' follow-up."
Selective reporting (reporting bias)	Unclear risk	Not clearly stated
Academic bias	Low risk	Primary author's first publication on the interventions
Sponsor bias	Low risk	Quote: "This trial was supported by Chinese Medical Care Centre Foundation, No. HeiB055."
Trials according to risk of bias	Unclear risk	Unclear sequence generation and allocation concealment, inadequate blinding

ACE: angiotension converting enzyme; ADA: American Diabetes Association; ADOPT: A Diabetes Outcome Progression Trial; (cyclic) AMP: adenosine monophosphate;APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; BMI: body mass index; FBG: fasting blood glucose; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; LEAD-3: Liraglutide Effect and Action in Diabetes-3; NR: not reported; NYHA: New York Heart Association; PPG: postprandial plasma glucose; T2DM: type 2 diabetes mellitus; UKPDS: United Kingdom Prospective Diabetes Study; WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adetuyibi 1977	Duration of intervention less than 24 weeks
Adlung 1974	Not a randomised clinical trial
Ahuja 1973	Not a randomised clinical trial.
Akanuma 1988	Not comparing interventions of interest. Comparing gliclazide with a mixed group of sulphonylureas. Participants in diet group are not randomised
Almer 1984	Not a randomised clinical trial
Aman 1977	Not a randomised clinical trial
Baba 1983	Not comparing interventions of interest. Comparing glimepiride with glibenclamide
Balabolkin 1983	Not a randomised clinical trial
Balabolkin 1988	Not a randomised clinical trial
Banerji 1995	Not including patients with T2DM
BARI 2009	Not comparing interventions of interest. Patients are randomised to insulin provision regime (not only sulphonylureas)
Bellomo 2011	Duration of intervention less than 24 weeks
Belovalova 1990	Not a randomised clinical trial
Ben 1988	Not a randomised clinical trial
Berber 1982	Duration of intervention less than 24 weeks
Bernas 1992	Not a randomised clinical trial
Berry 1981	Not a randomised clinical trial
Blumenbach 1976	Not a randomised clinical trial
Bruns 1990	Duration of intervention less than 24 weeks
Calvagno 1983	Not a randomised clinical trial
Cefalu 1998	Duration of intervention less than 24 weeks
Ceriello 2005	Not a randomised clinical trial

(*Continued*)

Chan 1982	Not comparing interventions of interest. Comparing gliclazide with glibenclamide
Chandra 2008	Not a randomised clinical trial. Authors asked and replied.
Chen 1987	Not a randomised clinical trial
Cortinovis 1998	Not a randomised clinical trial
Derosa 2010	Not comparing the interventions of interest. Metformin is continued after the randomisation
Dills 1996	Not comparing interventions of interest. Comparing glimepiride with glibenclamide
Dowey 1979	Not a randomised clinical trial
Drouin 2000	Not comparing interventions of interest. Comparing 2 different formulas of gliclazide
Drouin 2004	Not comparing interventions of interest. Comparing 2 different formulas of gliclazide
Duprey 1971	Not a randomised clinical trial
Engelhardt 1965	Includes also patients with normal glucose tolerance
Ferner 1991	Not a randomised clinical trial
Forst 2011	Not a randomised clinical trial
Fuchs 1973	Duration of intervention in publication less than 24 weeks. Report that data after 1 year of intervention will be published, but publication could not be found. Attempt made to contact authors
Garber 2002	Duration of intervention less than 24 weeks
Garber 2003	Duration of intervention less than 24 weeks
Gargiolo 2001	Not a randomised clinical trial
Giles 2008	Not comparing the interventions of interest. Patients are not exclusively allocated to sulphonylurea monotherapy, but some of the patients receive insulin in combination with sulphonylurea
Giles 2010	Not comparing the interventions of interest. Metformin is continued after the randomisation
Goldberg 1996	Duration of intervention less than 24 weeks
Groop 1989	Not comparing the interventions of interest
Gudat 1998	Not a randomised clinical trial
Gurling 1970	Not a randomised clinical trial

(*Continued*)

Happ 1974	Duration of intervention less than 24 weeks
Haupt 1974	Not a randomised clinical trial
Hollander 2001	Duration of intervention less than 24 weeks
Howes 2000	Not a randomised clinical trial
Hristov 2002	Not a randomised clinical trial
Hussain 2007	Not comparing the interventions of interest. The 3 randomised groups receive glibenclamide
Inukai 2005	Not comparing the interventions of interest. Comparing glimepiride with glibenclamide/gliclazide
Irsigler 1979	Duration of intervention less than 24 weeks
Ishizuka 1994	Not a randomised clinical trial
Jackson 1969	Not a randomised clinical trial
Jerums 1987	Not comparing interventions of interest. The randomised groups receive gliclazide and glibenclamide
Johnston 1970	Duration of intervention less than 24 weeks
Josephkutty 1990	Duration of intervention less than 24 weeks
Joshi 2002	Duration of intervention less than 24 weeks
Kakhnovskii 1993	Not a randomised clinical trial
Kanoun 1996	Not a randomised clinical trial
Langenfeld 2005	Not comparing the interventions of interest. Metformin is continued after the randomisation
Lecomte 1977	Duration of intervention less than 24 weeks
Levy 1995	Duration of intervention less than 24 weeks
Li 2009	Not comparing the interventions of interest. The group randomised to insulin secretagogues receives both sulphonylurea and repaglinide
Lim 1970	Duration of intervention less than 24 weeks
Lindbjerg 1976	Duration of intervention less than 24 weeks
Liu 1985	Duration of intervention less than 24 weeks
Lomuscio 1994	Not a randomised clinical trial

(*Continued*)

Mafauzy 2002	Duration of intervention less than 24 weeks
Mazzone 2006	Not comparing the interventions of interest. Metformin is continued after the randomisation. Correspondence with author
Meneilly 2011	Duration of intervention less than 24 weeks
Mogensen 1976	Not comparing the interventions of interest. Comparing glibornuride with glibenclamide
Nakamura 2000	Duration of intervention less than 24 weeks
Nikkilä 1982	Not comparing the interventions of interest. Comparing glibenclamide with gliquidone
Nissen 2008	Not comparing the interventions of interest. Metformin is continued after the randomisation. Clarified after e-mailing with corresponding author
Noury 1991	Duration of intervention less than 24 weeks
Omrani 2005	Only published as abstract, and the patients described as divided. Attempt to contact primary author. We assume not a randomised clinical trial
Osei 2003	Not including patients with type 2 diabetes mellitus
Papa 2006	Duration of intervention less than 24 weeks for each randomised group in the cross-over trial
Perez 2006	Not comparing the interventions of interest. Metformin is continued after the randomisation
Quatraro 1990	Not randomising participants to the intervention of interest, but only randomising patients to placebo or hydroxychloroquine in addition to glibenclamide
Rao 2010	Not comparing the interventions of interest. Metformin is continued after the randomisation
RECORD	Not comparing the interventions of interest. Investigates the effect of combination therapy
Rosenstock 1993	Not comparing the interventions of interest. Comparing glibenclamide with glipizide
Rupprecht 1993	Not a randomised clinical trial
Saadatnia 2009	Not a randomised clinical trial
Sami 1996	Not comparing the interventions of interest. Comparing glibenclamide with glipizide
Sasahara 1999	Not a randomised clinical trial
Schernthaner 2004	Not comparing the interventions of interest. Metformin and alpha-glucose inhibitors are continued after the randomisation
Seck 2010	Not comparing the interventions of interest. Metformin is continued after the randomisation

(*Continued*)

Shinoda 2009	Only published as abstract, and the patients described as divided. Attempt to contact primary author. We assume not a randomised clinical trial
Speiser 1989	Duration of intervention less than 24 weeks
Tolman 2009	Not comparing the interventions of interest. Metformin is continued after the randomisation
Tovi 1998	Not comparing interventions of interest. Other antidiabetic intervention is not stopped at entry to trial
Toyota 1997	Duration of intervention less than 24 weeks
Tsumura 1995	Not comparing the interventions of interest. Comparing glimepiride with gliclazide
Umpierrez 1997	Not exclusively including patients with T2DM
Vray 1995	Duration of intervention less than 24 weeks
Wang 1994	Duration of intervention less than 24 weeks
Wu 2010	Duration of intervention less than 24 weeks
Yang 2009	Not including patients with T2DM
Zhou 1999	Duration of intervention less than 24 weeks

T2DM: type 2 diabetes mellitus

DATA AND ANALYSES

Comparison 1. Sulphonylureas versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	883	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.91, 2.52]
1.1 First-generation SU	2	553	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.87, 2.45]
1.2 Second-generation SU	3	330	Risk Ratio (M-H, Random, 95% CI)	4.86 [0.24, 99.94]
1.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality; best-worst case scenario	1	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	1	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	1	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	1	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cardiovascular mortality	5	883	Risk Ratio (M-H, Random, 95% CI)	2.64 [1.35, 5.17]
4.1 First-generation SU	2	553	Risk Ratio (M-H, Random, 95% CI)	2.63 [1.32, 5.22]
4.2 Second-generation SU	3	330	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.12, 70.71]
4.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal macrovascular outcomes	1	205	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.82, 2.13]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	1	205	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.82, 2.13]
5.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	1	409	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.43, 1.51]
6.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.43, 1.51]
6.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Amputation of lower extremity	1	409	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.16]
7.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.16]
7.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Nephropathy	1	409	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.34, 4.61]
8.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.34, 4.61]
8.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Retinopathy	1	409	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
9.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
9.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Change in fasting blood glucose from baseline (mmol/L)	6	342	Mean Difference (IV, Random, 95% CI)	-1.35 [-2.00, -0.69]
10.1 First-generation SU	1	128	Mean Difference (IV, Random, 95% CI)	-2.1 [-3.19, -1.01]
10.2 Second-generation SU	5	214	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.94, -0.46]

10.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Change in HbA1c from baseline (%)	6	342	Mean Difference (IV, Random, 95% CI)	1.00 [-1.21, -0.79]
11.1 First-generation SU	1	128	Mean Difference (IV, Random, 95% CI)	-0.94 [-1.29, -0.59]
11.2 Second-generation SU	5	214	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.32, -0.72]
11.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Change in BMI from baseline (kg/m^2)	3	141	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.59, 0.41]
12.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	3	141	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.59, 0.41]
12.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in weight from baseline (kg)	1	128	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.36, 0.56]
13.1 First-generation SU	1	128	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.36, 0.56]
13.2 Second-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Adverse events	3	346	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.92, 1.64]
14.1 First-generation SU	1	144	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.97, 1.88]
14.2 Second-generation SU	2	202	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.51, 1.62]
14.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Drop-outs due to adverse events	6	654	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.33, 1.36]
15.1 First-generation SU	1	144	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.17, 3.23]
15.2 Second-generation SU	5	510	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.24, 1.57]
15.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16 Mild hypoglycaemia	1	134	Risk Ratio (M-H, Random, 95% CI)	12.26 [0.70, 213.33]
16.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	1	134	Risk Ratio (M-H, Random, 95% CI)	12.26 [0.70, 213.33]
16.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Severe hypoglycaemia	1	46	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	1	46	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 Cancer	2	614	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.06, 5.05]
18.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.88]
18.2 Second-generation SU	1	205	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.12, 70.71]
18.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Intervention failure	4	794	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.07, 0.94]
19.1 First-generation SU	1	409	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.44, 1.19]
19.2 Second-generation SU	3	385	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.04, 0.44]
19.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Sulphonylureas versus metformin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	8	3768	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.61, 1.58]
1.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Second-generation SU	6	3528	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.61, 1.58]
1.3 Third-generation SU	2	240	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality; best-worst case scenario	5	283	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.12, 4.45]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	4	207	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.10, 10.25]
2.3 Third-generation SU	1	76	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.35]
3 All-cause mortality; worst-best case scenario	5	283	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.37, 8.71]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	4	207	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.10, 10.25]
3.3 Third-generation SU	1	76	Risk Ratio (M-H, Random, 95% CI)	3.16 [0.34, 29.06]
4 Cardiovascular mortality	8	3768	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.54, 4.01]
4.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Second-generation SU	6	3528	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.54, 4.01]
4.3 Third-generation SU	2	240	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal macrovascular outcomes	4	3094	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.93]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	3	3018	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.93]
5.3 Third-generation SU	1	76	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	4	3061	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.37, 2.85]
6.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Second-generation SU	4	3061	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.37, 2.85]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Non-fatal stroke	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Amputation of lower extremity	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Peripheral revascularisation	2	2946	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.69, 1.92]
9.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Second-generation SU	2	2946	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.69, 1.92]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Microvascular outcomes	1	44	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 20.49]
10.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 20.49]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Nephropathy	1	44	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.00]
11.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.00]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

12 Retinal photocoagulation	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in fasting blood glucose from baseline (mmol/L)	15	4654	Mean Difference (IV, Random, 95% CI)	0.20 [-0.07, 0.48]
13.1 First-generation SU	2	482	Mean Difference (IV, Random, 95% CI)	0.13 [-0.75, 1.01]
13.2 Second-generation SU	11	3891	Mean Difference (IV, Random, 95% CI)	0.43 [0.10, 0.75]
13.3 Third-generation SU	3	281	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.52, 0.08]
14 Change in HbA1c from baseline (%)	13	3632	Mean Difference (IV, Random, 95% CI)	0.06 [-0.16, 0.29]
14.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	10	3351	Mean Difference (IV, Random, 95% CI)	0.17 [-0.09, 0.44]
14.3 Third-generation SU	3	281	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.43, 0.07]
15 Change in BMI from baseline (kg/m^2)	5	322	Mean Difference (IV, Random, 95% CI)	0.13 [-0.69, 0.94]
15.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Second-generation SU	3	103	Mean Difference (IV, Random, 95% CI)	0.25 [-1.21, 1.70]
15.3 Third-generation SU	2	219	Mean Difference (IV, Random, 95% CI)	-0.10 [-1.06, 0.86]
16 Change in weight from baseline (kg)	7	3497	Mean Difference (IV, Random, 95% CI)	3.77 [3.06, 4.47]
16.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	7	3497	Mean Difference (IV, Random, 95% CI)	3.77 [3.06, 4.47]
16.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17 Adverse events	5	3118	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.01]
17.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	4	3042	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.01]
17.3 Third-generation SU	1	76	Risk Ratio (M-H, Random, 95% CI)	3.16 [0.13, 75.16]
18 Serious adverse events	5	3175	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
18.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Second-generation SU	4	3011	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
18.3 Third-generation SU	1	164	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Drop-outs due to adverse events	8	3731	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.98, 1.41]
19.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Second-generation SU	7	3567	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.99, 1.42]
19.3 Third-generation SU	1	164	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.20]
20 Mild hypoglycaemia	6	4827	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [2.74, 3.64]
20.1 First-generation SU	1	607	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.00, 3.58]
20.2 Second-generation SU	5	4056	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [2.80, 3.76]
20.3 Third-generation SU	1	164	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Moderate hypoglycaemia	1	44	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.87]
21.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 Second-generation SU	1	44	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.87]
21.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22 Severe hypoglycaemia	5	4408	Risk Ratio (M-H, Random, 95% CI)	4.50 [1.24, 16.31]
22.1 First-generation SU	1	607	Risk Ratio (M-H, Random, 95% CI)	2.58 [0.24, 28.31]
22.2 Second-generation SU	4	3637	Risk Ratio (M-H, Random, 95% CI)	5.64 [1.22, 26.00]
22.3 Third-generation SU	1	164	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23 Cancer	1	2902	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.61]
23.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Second-generation SU	1	2902	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.61]

23.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Intervention failure	9	4990	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.39]
24.1 First-generation SU	1	607	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.09]
24.2 Second-generation SU	7	4143	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.60, 1.57]
24.3 Third-generation SU	2	240	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.43, 3.50]

Comparison 3. Sulphonylureas versus thiazolidinediones

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	8	5030	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.41]
1.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Second-generation SU	7	4955	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.41]
1.3 Third-generation SU	1	75	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality; best-worst case scenario	5	1327	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.54]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	4	1252	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.54]
2.3 Third-generation SU	1	75	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	5	1327	Risk Ratio (M-H, Random, 95% CI)	7.49 [1.39, 40.18]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	4	1252	Risk Ratio (M-H, Random, 95% CI)	9.76 [0.59, 161.27]
3.3 Third-generation SU	1	75	Risk Ratio (M-H, Random, 95% CI)	7.18 [0.38, 134.45]
4 Cardiovascular mortality	8	5030	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.55, 3.07]
4.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Second-generation SU	7	4955	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.55, 3.07]
4.3 Third-generation SU	1	75	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal macrovascular outcomes	7	4675	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.33]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	6	4600	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.33]
5.3 Third-generation SU	1	75	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	7	4956	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.14]
6.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Second-generation SU	7	4956	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.14]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Non-fatal stroke	2	707	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.67]
7.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.67]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Amputation of lower extremity	2	707	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Cardial revascularisation	2	707	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.71]
9.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.61, 1.71]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

10 Peripheral revascularisation	3	3612	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.39]
10.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Second-generation SU	3	3612	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.39]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Microvascular outcomes	2	235	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.05, 13.16]
11.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Second-generation SU	2	235	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.05, 13.16]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Nephropathy	2	707	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.02]
12.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.02]
12.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy	2	707	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.64]
13.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.64]
13.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Retinal photocoagulation	2	707	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	2	707	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in fasting blood glucose from baseline (mmol/L)	18	6731	Mean Difference (IV, Random, 95% CI)	0.53 [0.31, 0.75]
15.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Second-generation SU	14	6076	Mean Difference (IV, Random, 95% CI)	0.56 [0.33, 0.79]
15.3 Third-generation SU	4	655	Mean Difference (IV, Random, 95% CI)	0.46 [-0.22, 1.13]
16 Change in HbA1c from baseline (%)	21	7435	Mean Difference (IV, Random, 95% CI)	0.03 [-0.10, 0.16]
16.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	17	6776	Mean Difference (IV, Random, 95% CI)	0.06 [-0.09, 0.20]
16.3 Third-generation SU	4	659	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.31, 0.14]
17 Change in BMI from baseline (kg/m^2)	7	532	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.18, -0.79]
17.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	4	121	Mean Difference (IV, Random, 95% CI)	1.00 [-1.20, -0.80]
17.3 Third-generation SU	3	411	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.58, 0.08]
18 Change in weight from baseline (kg)	11	5948	Mean Difference (IV, Random, 95% CI)	-1.86 [-2.50, -1.21]
18.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Second-generation SU	10	5779	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.56, -1.25]
18.3 Third-generation SU	1	169	Mean Difference (IV, Random, 95% CI)	0.20 [-3.75, 4.15]
19 Adverse events	13	7001	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.01]
19.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Second-generation SU	10	6491	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.01]
19.3 Third-generation SU	3	510	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
20 Serious adverse events	11	5605	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
20.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 Second-generation SU	8	4979	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
20.3 Third-generation SU	3	626	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.83]
21 Drop-outs due to adverse events	17	7856	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.00, 1.34]
21.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 Second-generation SU	15	7433	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.98, 1.36]

21.3 Third-generation SU	2	423	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.15, 1.97]
22 Mild hypoglycaemia	9	6556	Risk Ratio (M-H, Random, 95% CI)	3.95 [3.08, 5.06]
22.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22.2 Second-generation SU	8	6365	Risk Ratio (M-H, Random, 95% CI)	4.05 [3.28, 5.00]
22.3 Third-generation SU	1	191	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.47, 4.30]
23 Moderate hypoglycaemia	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Severe hypoglycaemia	8	6030	Risk Ratio (M-H, Random, 95% CI)	6.11 [1.57, 23.79]
24.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Second-generation SU	6	5660	Risk Ratio (M-H, Random, 95% CI)	6.11 [1.57, 23.79]
24.3 Third-generation SU	2	370	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Cancer	6	4912	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
25.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25.2 Second-generation SU	6	4912	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
25.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26 Intervention failure	10	6757	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.65, 1.45]
26.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 Second-generation SU	8	6438	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.73, 1.65]
26.3 Third-generation SU	2	319	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.08, 0.75]

Comparison 4. Sulphonylureas versus insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	3586	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.92, 1.21]
1.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.88, 1.59]
1.2 Second-generation SU	4	1642	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.18]
1.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality; best-worst case scenario	2	80	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.95]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	2	80	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.95]
2.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	2	80	Risk Ratio (M-H, Random, 95% CI)	3.54 [0.83, 15.00]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	2	80	Risk Ratio (M-H, Random, 95% CI)	3.54 [0.83, 15.00]
3.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cardiovascular mortality	5	3586	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.44]
4.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.68, 2.71]
4.2 Second-generation SU	4	1642	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.73, 1.28]
4.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal myocardial infarction	2	3470	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.79, 1.23]
5.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.81, 1.45]
5.2 Second-generation SU	1	1526	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.61, 1.22]
5.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal stroke	2	3470	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.02, 2.06]

6.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.74, 2.05]
6.2 Second-generation SU	1	1526	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.04, 2.71]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Amputation of lower extremity	2	3470	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.24, 1.00]
7.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.34]
7.2 Second-generation SU	1	1526	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.35]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Microvascular outcomes	1	3056	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.82, 1.53]
8.1 First-generation SU	1	1530	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.95, 1.77]
8.2 Second-generation SU	1	1526	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.67, 1.33]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Nephropathy	1	414	Risk Ratio (M-H, Random, 95% CI)	11.32 [0.63, 203.45]
9.1 First-generation SU	1	414	Risk Ratio (M-H, Random, 95% CI)	11.32 [0.63, 203.45]
9.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Retinopathy	1	414	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.39]
10.1 First-generation SU	1	414	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.39]
10.2 Second-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Retinal photocoagulation	1	3056	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.80, 1.31]
11.1 First-generation SU	1	1530	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.57]
11.2 Second-generation SU	1	1526	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.32]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Change in fasting blood glucose from baseline (mmol/L)	5	2423	Mean Difference (IV, Random, 95% CI)	0.12 [-0.37, 0.61]
12.1 First-generation SU	1	1122	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.69, -0.11]
12.2 Second-generation SU	5	1301	Mean Difference (IV, Random, 95% CI)	0.29 [-0.02, 0.61]
12.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in HbA1c from baseline (%)	6	2566	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.20, 0.03]
13.1 First-generation SU	1	1122	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.38, -0.02]
13.2 Second-generation SU	6	1444	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.17, 0.10]
13.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Change in BMI from baseline (kg/m^2)	1	34	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.10, 0.70]
14.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	1	34	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.10, 0.70]
14.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in weight from baseline (kg)	5	2514	Mean Difference (IV, Random, 95% CI)	1.00 [-2.82, 0.83]
15.1 First-generation SU	1	1122	Mean Difference (IV, Random, 95% CI)	-2.30 [-4.11, -0.49]
15.2 Second-generation SU	5	1392	Mean Difference (IV, Random, 95% CI)	-0.37 [-2.39, 1.65]
15.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 Adverse events	1	143	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.68, 1.65]
16.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	1	143	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.68, 1.65]
16.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Drop-outs due to adverse events	2	192	Risk Ratio (M-H, Random, 95% CI)	3.54 [0.43, 29.43]
17.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	2	192	Risk Ratio (M-H, Random, 95% CI)	3.54 [0.43, 29.43]
17.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

18 Mild hypoglycaemia	2	3105	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.45, 1.95]
18.1 First-generation SU	1	1530	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
18.2 Second-generation SU	2	1575	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.13, 1.76]
18.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Severe hypoglycaemia	4	3172	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.38, 4.24]
19.1 First-generation SU	1	1530	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.11, 3.02]
19.2 Second-generation SU	4	1642	Risk Ratio (M-H, Random, 95% CI)	2.07 [0.66, 6.50]
19.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20 Cancer	3	3519	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.36]
20.1 First-generation SU	2	1944	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.29, 2.27]
20.2 Second-generation SU	2	1575	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.61, 1.49]
20.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Intervention failure	4	3200	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.67, 2.27]
21.1 First-generation SU	1	1530	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.89]
21.2 Second-generation SU	4	1670	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.80, 4.76]
21.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Sulphonylureas versus alpha-glucosidase inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	6	714	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.43, 11.84]
1.1 First-generation SU	2	246	Risk Ratio (M-H, Random, 95% CI)	3.16 [0.13, 76.44]
1.2 Second-generation SU	4	468	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.28, 13.86]
1.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality; best-worst case scenario	2	90	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	2	90	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	2	90	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	2	90	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cardiovascular mortality	6	708	Risk Ratio (M-H, Random, 95% CI)	2.39 [0.30, 19.28]
4.1 First-generation SU	2	242	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.44]
4.2 Second-generation SU	4	466	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.13, 31.96]
4.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal macrovascular outcomes	2	345	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.06, 2.44]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	2	345	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.06, 2.44]
5.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	2	133	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.92]
6.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.92]
6.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Non-fatal stroke	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

7.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Amputation of lower extremity	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Cardial revascularisation	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Peripheral revascularisation	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Microvascular outcomes	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Nephropathy	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Retinal photocoagulation	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in fasting blood glucose from baseline (mmol/L)	11	915	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.80, -0.11]
15.1 First-generation SU	2	208	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.92, -0.41]
15.2 Second-generation SU	8	488	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.42, 0.11]
15.3 Third-generation SU	1	219	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.92, -0.48]
16 Change in HbA1c from baseline (%)	13	968	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.46, 0.06]
16.1 First-generation SU	2	208	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.79, -0.20]
16.2 Second-generation SU	10	541	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.36, 0.24]
16.3 Third-generation SU	1	219	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.28, -0.12]
17 Change in BMI from baseline (kg/m^2)	5	232	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.20, 0.16]
17.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	5	232	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.20, 0.16]
17.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18 Change in weight from baseline (kg)	7	689	Mean Difference (IV, Random, 95% CI)	0.81 [-0.61, 2.23]
18.1 First-generation SU	1	132	Mean Difference (IV, Random, 95% CI)	3.2 [2.29, 4.11]
18.2 Second-generation SU	5	338	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.47, 0.03]
18.3 Third-generation SU	1	219	Mean Difference (IV, Random, 95% CI)	1.5 [0.28, 2.72]
19 Adverse events	11	1111	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.51, 0.82]

19.1 First-generation SU	2	246	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.52, 0.76]
19.2 Second-generation SU	8	646	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.39, 1.03]
19.3 Third-generation SU	1	219	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.53, 0.78]
20 Serious adverse events	3	229	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.09, 3.03]
20.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.55]
20.2 Second-generation SU	2	131	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.81]
20.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Drop-outs due to adverse events	12	1335	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.22, 0.63]
21.1 First-generation SU	2	246	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.12, 0.67]
21.2 Second-generation SU	9	870	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.96]
21.3 Third-generation SU	1	219	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.64]
22 Mild hypoglycaemia	6	636	Risk Ratio (M-H, Random, 95% CI)	8.59 [2.62, 28.12]
22.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.12, 69.07]
22.2 Second-generation SU	4	319	Risk Ratio (M-H, Random, 95% CI)	12.63 [0.73, 219.86]
22.3 Third-generation SU	1	219	Risk Ratio (M-H, Random, 95% CI)	9.73 [2.33, 40.63]
23 Moderate hypoglycaemia	3	183	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Second-generation SU	3	183	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Severe hypoglycaemia	5	500	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Second-generation SU	3	183	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.3 Third-generation SU	1	219	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Cancer	3	443	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.11, 7.27]
25.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.67]
25.2 Second-generation SU	2	345	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.13, 31.35]
25.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26 Intervention failure	5	831	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.18, 0.57]
26.1 First-generation SU	1	98	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.67]
26.2 Second-generation SU	3	514	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.92]
26.3 Third-generation SU	1	219	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.17, 0.65]

Comparison 6. Sulphonylureas versus incretin-based intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	2249	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.62, 4.00]
1.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Second-generation SU	2	1503	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.52, 3.68]
1.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	6.01 [0.25, 147.05]
2 All-cause mortality; best-worst case scenario	1	1092	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.84]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	1	1092	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.84]
2.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	1	1092	Risk Ratio (M-H, Random, 95% CI)	3.67 [1.50, 8.97]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

3.2 Second-generation SU	1	1092	Risk Ratio (M-H, Random, 95% CI)	3.67 [1.50, 8.97]
3.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cardiovascular mortality	2	1157	Risk Ratio (M-H, Random, 95% CI)	6.01 [0.25, 147.05]
4.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	6.01 [0.25, 147.05]
5 Non-fatal macrovascular outcomes	1	411	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.82, 3.17]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.82, 3.17]
5.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	2	1157	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.10, 4.19]
6.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.03, 15.85]
6.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.07, 6.40]
7 Non-fatal stroke	1	411	Risk Ratio (M-H, Random, 95% CI)	3.91 [0.36, 42.79]
7.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	3.91 [0.36, 42.79]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Amputation of lower extremity	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Cardial revascularisation	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Peripheral revascularisation	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Microvascular outcomes	1	411	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.52, 2.29]
11.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.52, 2.29]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Nephropathy	1	411	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.09, 10.70]
12.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.09, 10.70]
12.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy	1	411	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.50, 2.43]
13.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.50, 2.43]
13.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Retinal photocoagulation	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in fasting blood glucose from baseline (mmol/L)	3	1948	Mean Difference (IV, Random, 95% CI)	0.34 [-0.44, 1.13]
15.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Second-generation SU	2	1202	Mean Difference (IV, Random, 95% CI)	0.11 [-1.07, 1.28]
15.3 Third-generation SU	1	746	Mean Difference (IV, Random, 95% CI)	0.8 [0.34, 1.26]

16 Change in HbA1c from baseline (%)	3	1950	Mean Difference (IV, Random, 95% CI)	0.35 [0.05, 0.64]
16.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	2	1204	Mean Difference (IV, Random, 95% CI)	0.26 [-0.23, 0.75]
16.3 Third-generation SU	1	746	Mean Difference (IV, Random, 95% CI)	0.5 [0.32, 0.68]
17 Change in BMI from baseline (kg/m^2)	1	400	Mean Difference (IV, Random, 95% CI)	0.7 [0.52, 0.88]
17.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	1	400	Mean Difference (IV, Random, 95% CI)	0.7 [0.52, 0.88]
17.3 Third-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18 Change in weight from baseline (kg)	3	1952	Mean Difference (IV, Random, 95% CI)	1.96 [0.63, 3.28]
18.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Second-generation SU	2	1206	Mean Difference (IV, Random, 95% CI)	1.31 [0.33, 2.29]
18.3 Third-generation SU	1	746	Mean Difference (IV, Random, 95% CI)	3.30 [2.64, 3.96]
19 Adverse events	2	1157	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.08]
19.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
19.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.73, 0.92]
20 Serious adverse events	2	1157	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.77, 1.94]
20.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 Second-generation SU	1	411	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.71, 2.63]
20.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.56, 2.10]
21 Drop-outs due to adverse events	3	2249	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.24]
21.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 Second-generation SU	2	1503	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.67, 1.50]
21.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.40, 1.24]
22 Mild hypoglycaemia	3	2249	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.44, 2.97]
22.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22.2 Second-generation SU	2	1503	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.02, 3.87]
22.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.71, 3.40]
23 Severe hypoglycaemia	3	2249	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Second-generation SU	2	1503	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Intervention failure	3	2249	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.56, 3.05]
24.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Second-generation SU	2	1503	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.41, 2.43]
24.3 Third-generation SU	1	746	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.22, 3.59]

Comparison 7. Sulphonylureas versus meglitinide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	7	2038	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.47, 4.42]
1.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Second-generation SU	7	2038	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.47, 4.42]
1.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

2 All-cause mortality; best-worst case scenario	2	209	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.16]
2.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Second-generation SU	2	209	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.16]
2.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality; worst-best case scenario	2	209	Risk Ratio (M-H, Random, 95% CI)	15.17 [0.88, 261.61]
3.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Second-generation SU	2	209	Risk Ratio (M-H, Random, 95% CI)	15.17 [0.88, 261.61]
3.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cardiovascular mortality	7	2038	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.27, 3.53]
4.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Second-generation SU	7	2038	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.27, 3.53]
4.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Non-fatal macrovascular outcomes	3	866	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.20]
5.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Second-generation SU	3	866	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.20]
5.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal myocardial infarction	3	726	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.26, 4.08]
6.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Second-generation SU	3	726	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.26, 4.08]
6.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Non-fatal stroke	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Amputation of lower extremity	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Cardial revascularisation	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Peripheral revascularisation	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Microvascular outcomes	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Nephropathy	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Retinal photocoagulation	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

14.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in fasting blood glucose from baseline (mmol/L)	10	2329	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]
15.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Second-generation SU	9	2205	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.51, -0.02]
15.3 Third-generation SU	1	124	Mean Difference (IV, Random, 95% CI)	0.20 [-0.22, 0.62]
16 Change in HbA1c from baseline (%)	10	2345	Mean Difference (IV, Random, 95% CI)	0.05 [-0.09, 0.19]
16.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Second-generation SU	9	2221	Mean Difference (IV, Random, 95% CI)	0.07 [-0.08, 0.22]
16.3 Third-generation SU	1	124	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.40, 0.20]
17 Change in BMI from baseline (kg/m^2)	3	333	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.25, 0.14]
17.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Second-generation SU	2	209	Mean Difference (IV, Random, 95% CI)	0.00 [-0.19, 0.20]
17.3 Third-generation SU	1	124	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.66, 0.06]
18 Change in weight from baseline (kg)	5	1176	Mean Difference (IV, Random, 95% CI)	0.05 [-0.40, 0.51]
18.1 First-generation SU	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Second-generation SU	4	1052	Mean Difference (IV, Random, 95% CI)	0.13 [-0.50, 0.76]
18.3 Third-generation SU	1	124	Mean Difference (IV, Random, 95% CI)	0.10 [-1.77, 1.97]
19 Adverse events	5	1829	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.95, 1.06]
19.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Second-generation SU	5	1829	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.95, 1.06]
19.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20 Drop-outs due to adverse events	8	2151	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.79, 1.33]
20.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 Second-generation SU	7	2019	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.32]
20.3 Third-generation SU	1	132	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.24, 102.19]
21 Serious adverse events	5	1829	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.39]
21.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 Second-generation SU	5	1829	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.39]
21.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22 Mild hypoglycaemia	6	1863	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.96, 1.49]
22.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22.2 Second-generation SU	6	1863	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.96, 1.49]
22.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23 Moderate hypoglycaemia	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Second-generation SU	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Severe hypoglycaemia	6	1863	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.91, 8.99]
24.1 First-generation SU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Second-generation SU	6	1863	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.91, 8.99]
24.3 Third-generation SU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Cancer	2	290	Risk Ratio (M-H, Random, 95% CI)	6.44 [0.27, 156.37]
25.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25.2 Second-generation SU	2	290	Risk Ratio (M-H, Random, 95% CI)	6.44 [0.27, 156.37]
25.3 Third-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

26 Intervention failure	5	1656	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.35]
26.1 First-generation SU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 Second-generation SU	4	1524	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.69, 1.38]
26.3 Third-generation SU	1	132	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.86]

Comparison 8. Second-generation sulphonylureas versus first-generation sulphonylureas

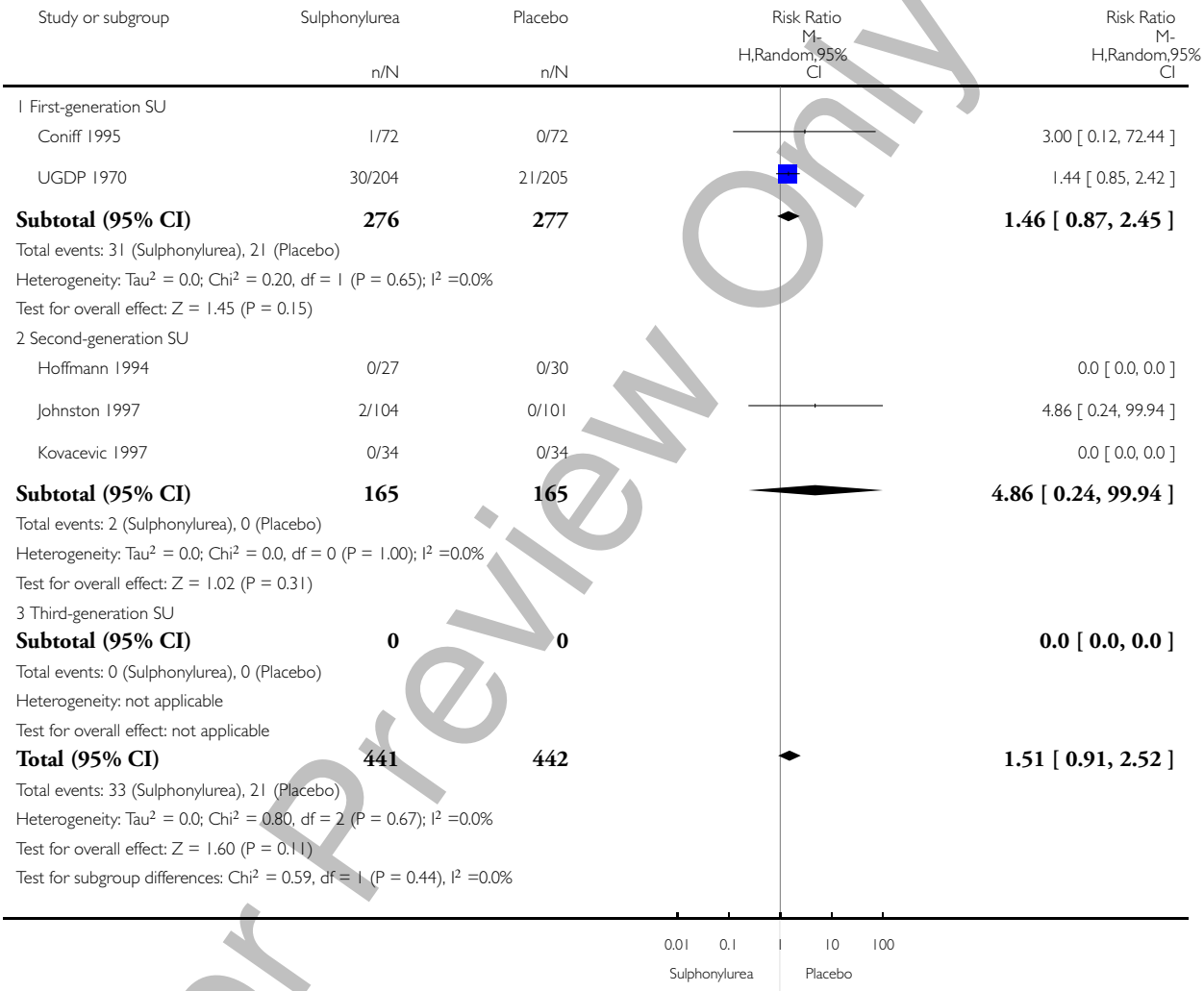
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1	1234	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.11]
2 Cardiovascular mortality	1	1234	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.34]
3 Non-fatal myocardial infarction	1	1234	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.16]
4 Non-fatal stroke	1	1234	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.80, 2.17]
5 Amputation of lower extremity	1	1234	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.29, 3.46]
6 Microvascular outcomes	1	1234	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.48, 1.03]
7 Retinal photocoagulation	1	1234	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.56, 1.20]
8 Change in fasting blood glucose from baseline (mmol/L)	2	936	Mean Difference (IV, Random, 95% CI)	0.62 [0.31, 0.94]
9 Change in HbA1c from baseline (%)	2	1014	Mean Difference (IV, Random, 95% CI)	-1.44 [-4.48, 1.60]
10 Change in weight from baseline (kg)	2	1014	Mean Difference (IV, Random, 95% CI)	1.80 [-0.63, 4.23]
11 Mild hypoglycaemia	1	1234	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.83, 3.42]
12 Severe hypoglycaemia	1	1234	Risk Ratio (M-H, Random, 95% CI)	3.52 [0.73, 16.89]
13 Cancer	1	1234	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.50, 1.31]
14 Intervention failure	3	1364	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.67, 5.75]

Analysis 1.1. Comparison 1 Sulphonylureas versus placebo, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 1 All-cause mortality



Analysis 1.2. Comparison 1 Sulphonylureas versus placebo, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Hoffmann 1994	0/27	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**27**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 1.3. Comparison 1 Sulphonylureas versus placebo, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 3 All-cause mortality; worst-best case scenario

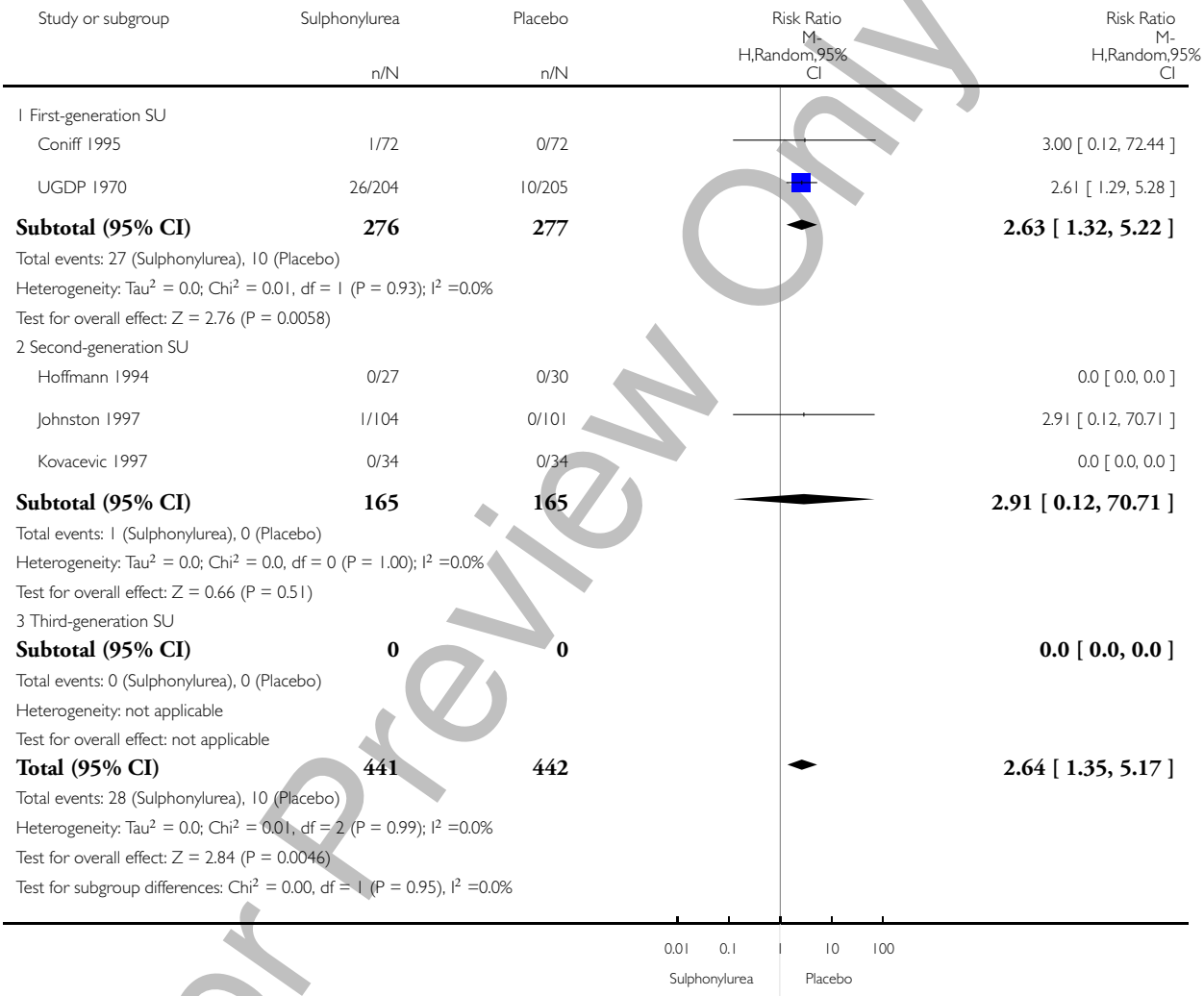
Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Hoffmann 1994	0/27	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**27**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 1.4. Comparison 1 Sulphonylureas versus placebo, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 4 Cardiovascular mortality



Analysis 1.5. Comparison 1 Sulphonylureas versus placebo, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 5 Non-fatal macrovascular outcomes

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Johnston 1997	30/104	22/101		100.0 %	1.32 [0.82, 2.13]
Subtotal (95% CI)	**104**	**101**		**100.0 %**	**1.32 [0.82, 2.13]**
Total events: 30 (Sulphonylurea), 22 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**104**	**101**		**100.0 %**	**1.32 [0.82, 2.13]**
Total events: 30 (Sulphonylurea), 22 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Not applicable					

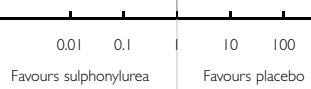
Analysis 1.6. Comparison 1 Sulphonylureas versus placebo, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 6 Non-fatal myocardial infarction

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	16/204	20/205		100.0 %	0.80 [0.43, 1.51]
Subtotal (95% CI)	**204**	**205**		**100.0 %**	**0.80 [0.43, 1.51]**
Total events: 16 (Sulphonylurea), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
2 Second-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**204**	**205**		**100.0 %**	**0.80 [0.43, 1.51]**
Total events: 16 (Sulphonylurea), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					



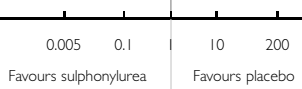
Analysis 1.7. Comparison 1 Sulphonylureas versus placebo, Outcome 7 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 7 Amputation of lower extremity

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	0/204	2/205		100.0 %	0.20 [0.01, 4.16]
Subtotal (95% CI)	**204**	**205**		**100.0 %**	**0.20 [0.01, 4.16]**
Total events: 0 (Sulphonylurea), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Second-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**204**	**205**		**100.0 %**	**0.20 [0.01, 4.16]**
Total events: 0 (Sulphonylurea), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Not applicable					

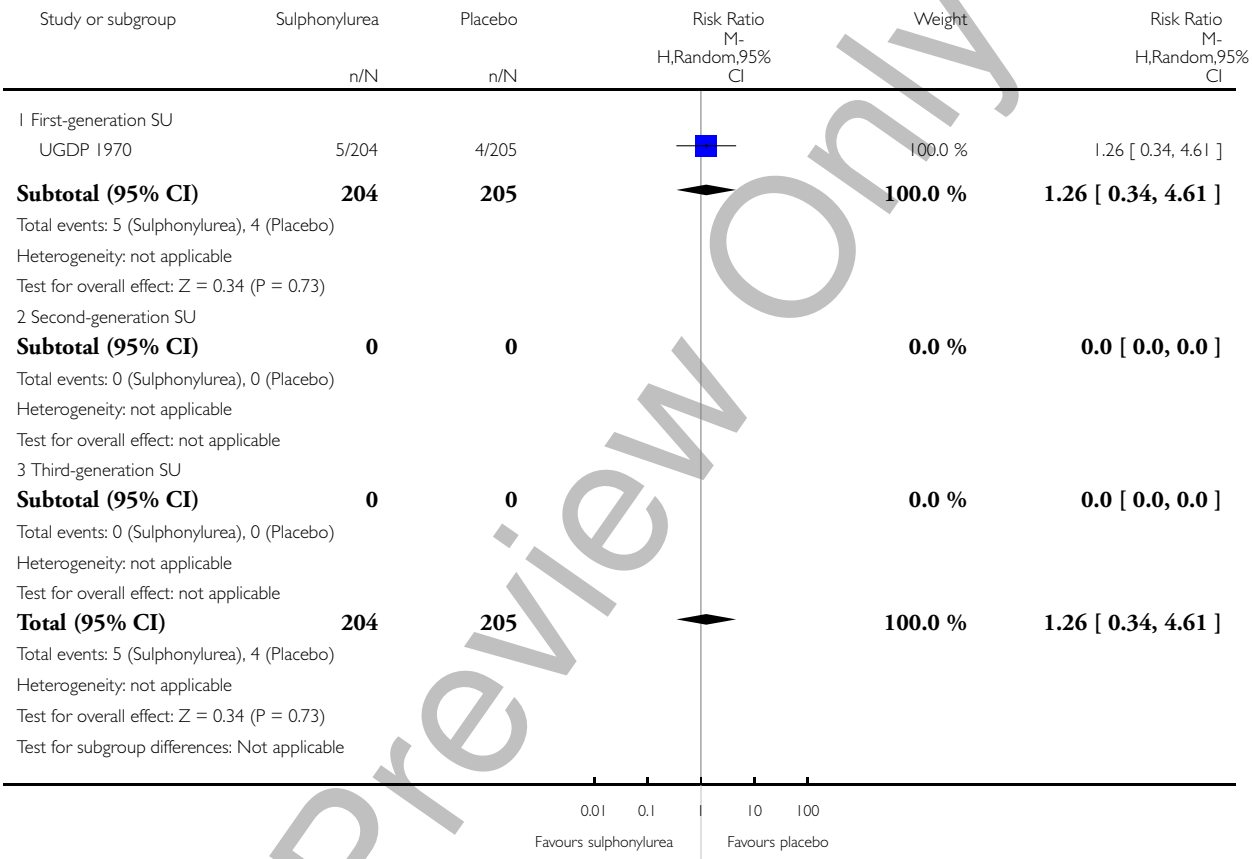


Analysis 1.8. Comparison 1 Sulphonylureas versus placebo, Outcome 8 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 8 Nephropathy



Analysis 1.9. Comparison 1 Sulphonylureas versus placebo, Outcome 9 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 9 Retinopathy

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	50/204	54/205		100.0 %	0.93 [0.67, 1.30]
Subtotal (95% CI)	**204**	**205**		**100.0 %**	**0.93 [0.67, 1.30]**
Total events: 50 (Sulphonylurea), 54 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
2 Second-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**204**	**205**		**100.0 %**	**0.93 [0.67, 1.30]**
Total events: 50 (Sulphonylurea), 54 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 1.10. Comparison 1 Sulphonylureas versus placebo, Outcome 10 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 10 Change in fasting blood glucose from baseline (mmol/L)

Study or subgroup	Sulphonylurea N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Coniff 1995 (1)	66	-2 (3.1)	62	0.1 (3.2)		16.7 %	-2.10 [-3.19, -1.01]
Subtotal (95% CI)	**66**		**62**			**16.7 %**	**-2.10 [-3.19, -1.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.77 (P = 0.00017)							
2 Second-generation SU							
Birkeland 1994	30	8.9 (2.8)	16	10.1 (3)		9.5 %	-1.20 [-2.98, 0.58]
Ebeling 2001	10	10.1 (1.9)	10	9.9 (0.9)		14.0 %	0.20 [-1.10, 1.50]
Hoffmann 1994 (2)	27	-1.3 (0.9)	30	0.2 (0.7)		27.5 %	-1.50 [-1.92, -1.08]
Kamel 1997 (3)	17	8.1 (0.9)	10	9 (0.8)		23.7 %	-0.90 [-1.55, -0.25]
Kovacevic 1997 (4)	33	-4 (4)	31	-0.7 (3.8)		8.6 %	-3.30 [-5.21, -1.39]
Subtotal (95% CI)	**117**		**97**			**83.3 %**	**-1.20 [-1.94, -0.46]**
Heterogeneity: Tau^2 = 0.39; Chi^2 = 11.59, df = 4 (P = 0.02); I^2 =65%							
Test for overall effect: Z = 3.17 (P = 0.0015)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**183**		**159**			**100.0 %**	**-1.35 [-2.00, -0.69]**
Heterogeneity: Tau^2 = 0.36; Chi^2 = 13.57, df = 5 (P = 0.02); I^2 =63%							
Test for overall effect: Z = 4.01 (P = 0.000061)							
Test for subgroup differences: Chi^2 = 1.80, df = 1 (P = 0.18), I^2 =44%							

(1) Data from van de Laar

(2) Data from van de Laar

(3) Not described in abstract if the values are standard deviations or standard errors

(4) Data from van de Laar

Analysis 1.11. Comparison 1 Sulphonylureas versus placebo, Outcome 11 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 11 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Coniff 1995 (1)	66	-0.9 (1.04)	62	0.04 (1)		23.6 %	-0.94 [-1.29, -0.59]
Subtotal (95% CI)	**66**		**62**			**23.6 %**	**-0.94 [-1.29, -0.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.21 (P < 0.00001)							
2 Second-generation SU							
Birkeland 1994	30	7.6 (1.1)	16	8.6 (1)		9.9 %	-1.00 [-1.63, -0.37]
Ebeling 2001	10	7.7 (0.6)	10	8.4 (0.9)		8.8 %	-0.70 [-1.37, -0.03]
Hoffmann 1994 (2)	27	-0.8 (0.4)	30	0.2 (0.4)		40.8 %	-1.00 [-1.21, -0.79]
Kamel 1997 (3)	17	7.3 (1.1)	10	8 (0.7)		8.6 %	-0.70 [-1.38, -0.02]
Kovacevic 1997 (4)	33	-1.6 (1.2)	31	0.2 (1.6)		8.3 %	-1.80 [-2.50, -1.10]
Subtotal (95% CI)	**117**		**97**			**76.4 %**	**-1.02 [-1.32, -0.72]**
Heterogeneity: Tau^2 = 0.05; Chi^2 = 6.58, df = 4 (P = 0.16); I^2 =39%							
Test for overall effect: Z = 6.67 (P < 0.00001)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**183**		**159**			**100.0 %**	**-1.00 [-1.21, -0.79]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.70, df = 5 (P = 0.24); I^2 =25%							
Test for overall effect: Z = 9.16 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.12, df = 1 (P = 0.72), I^2 =0.0%							

(1) Data from van de Laar

(2) Data from van de Laar

(3) Not described in abstract if the values are standard deviations or standard errors

(4) Data from van de Laar

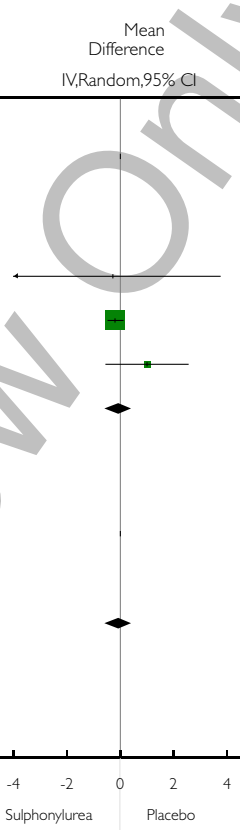
Analysis 1.12. Comparison 1 Sulphonylureas versus placebo, Outcome 12 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 12 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Ebeling 2001	10	31 (5.1)	10	31.3 (4.1)		1.5 %	-0.30 [-4.36, 3.76]
Hoffmann 1994 (1)	27	-0.3 (0.7)	30	-0.1 (0.4)		89.0 %	-0.20 [-0.50, 0.10]
Kovacevic 1997	33	0.4 (3.4)	31	-0.6 (3)		9.5 %	1.00 [-0.57, 2.57]
Subtotal (95% CI)	**70**		**71**			**100.0 %**	**-0.09 [-0.59, 0.41]**
Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.17, df = 2 (P = 0.34); I^2 =8%							
Test for overall effect: Z = 0.34 (P = 0.73)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**70**		**71**			**100.0 %**	**-0.09 [-0.59, 0.41]**
Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.17, df = 2 (P = 0.34); I^2 =8%							
Test for overall effect: Z = 0.34 (P = 0.73)							
Test for subgroup differences: Not applicable							



(1) Datafrom van de Laar

Analysis 1.13. Comparison 1 Sulphonylureas versus placebo, Outcome 13 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 13 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Coniff 1995 (1)	66	-1.8 (2.5)	62	-1.4 (3)		100.0 %	-0.40 [-1.36, 0.56]
Subtotal (95% CI)	**66**		**62**			**100.0 %**	**-0.40 [-1.36, 0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 Second-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**66**		**62**			**100.0 %**	**-0.40 [-1.36, 0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Not applicable							

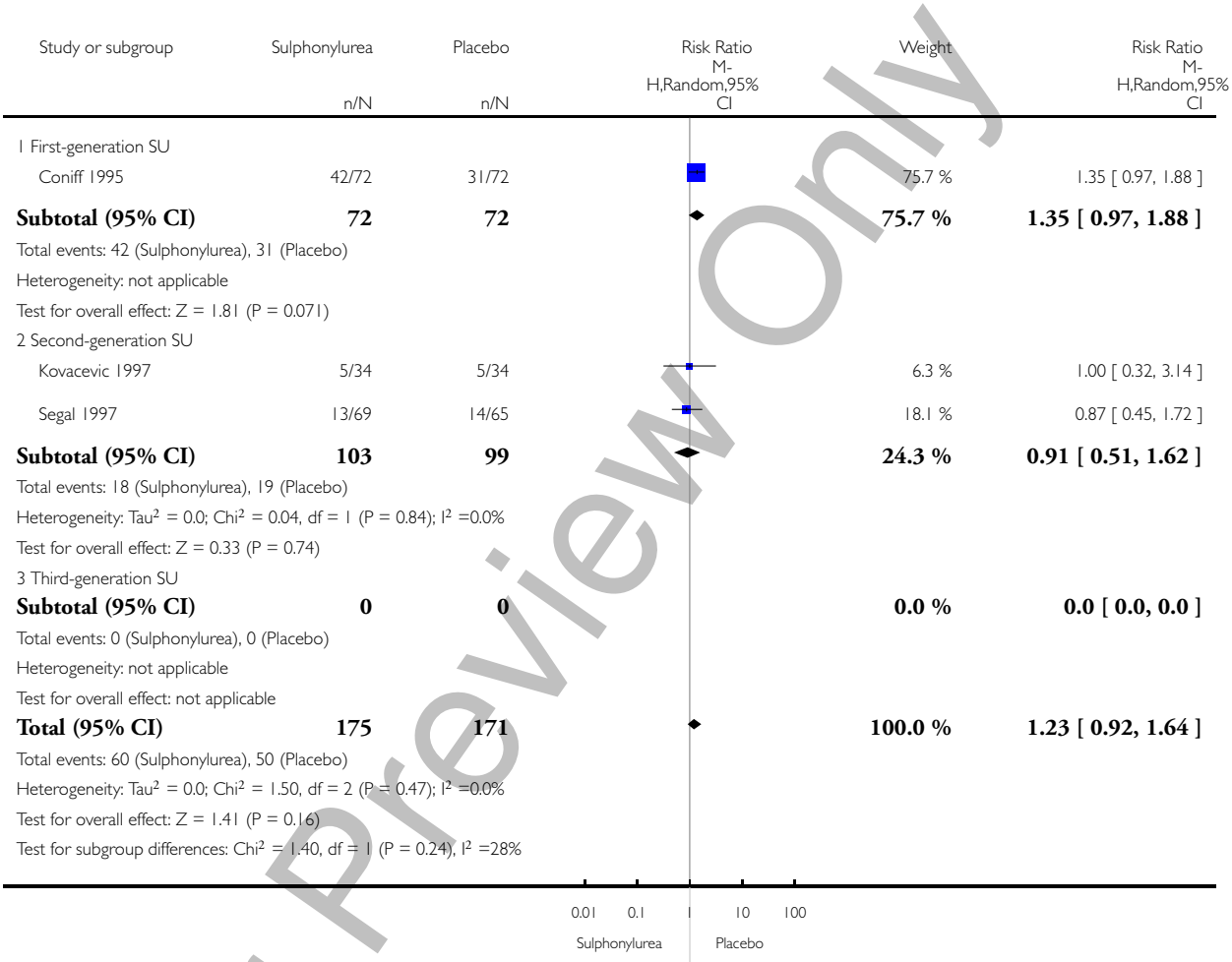
(1) Data read from graph

Analysis 1.14. Comparison 1 Sulphonylureas versus placebo, Outcome 14 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 14 Adverse events

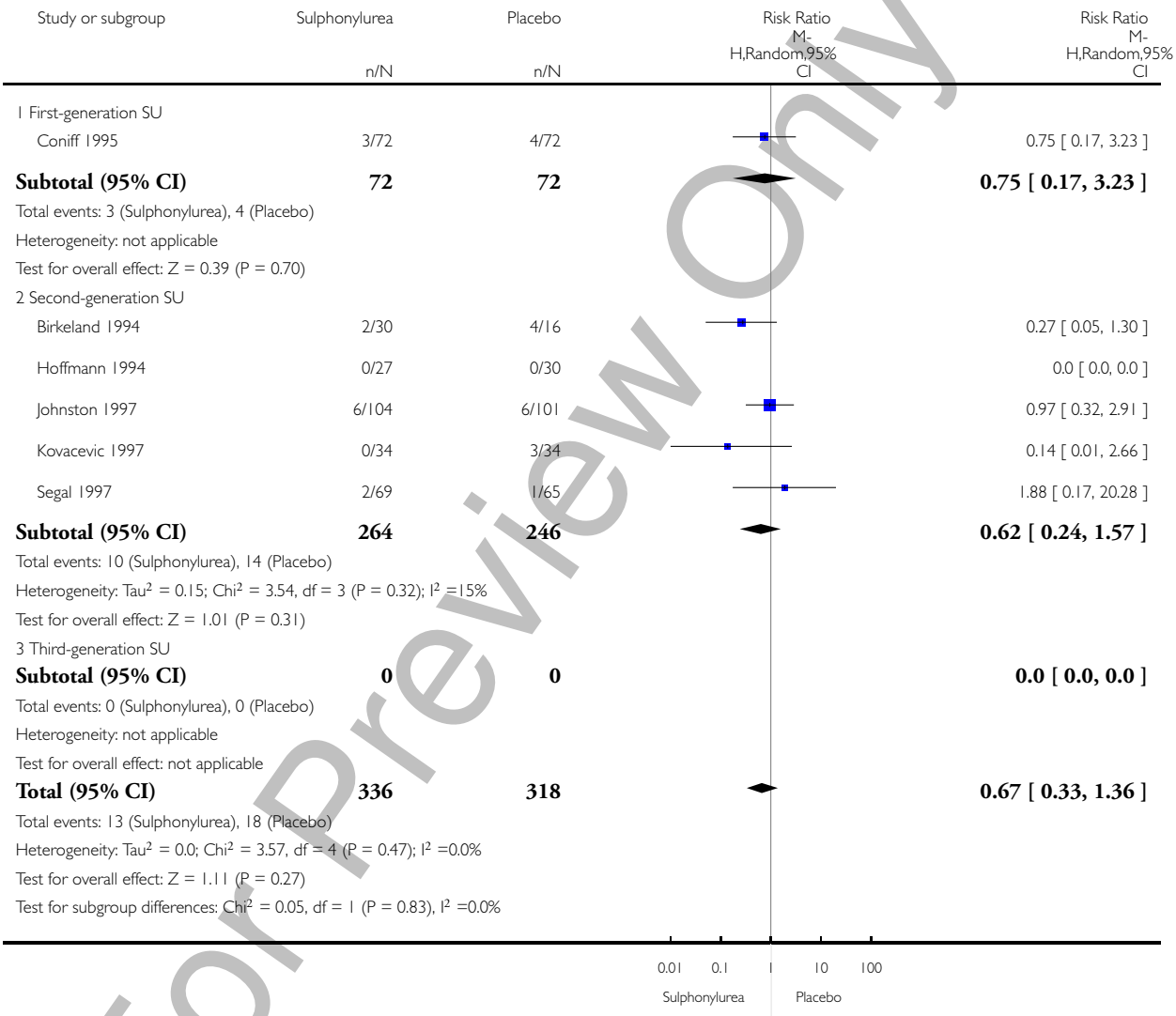


Analysis 1.15. Comparison 1 Sulphonylureas versus placebo, Outcome 15 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 15 Drop-outs due to adverse events

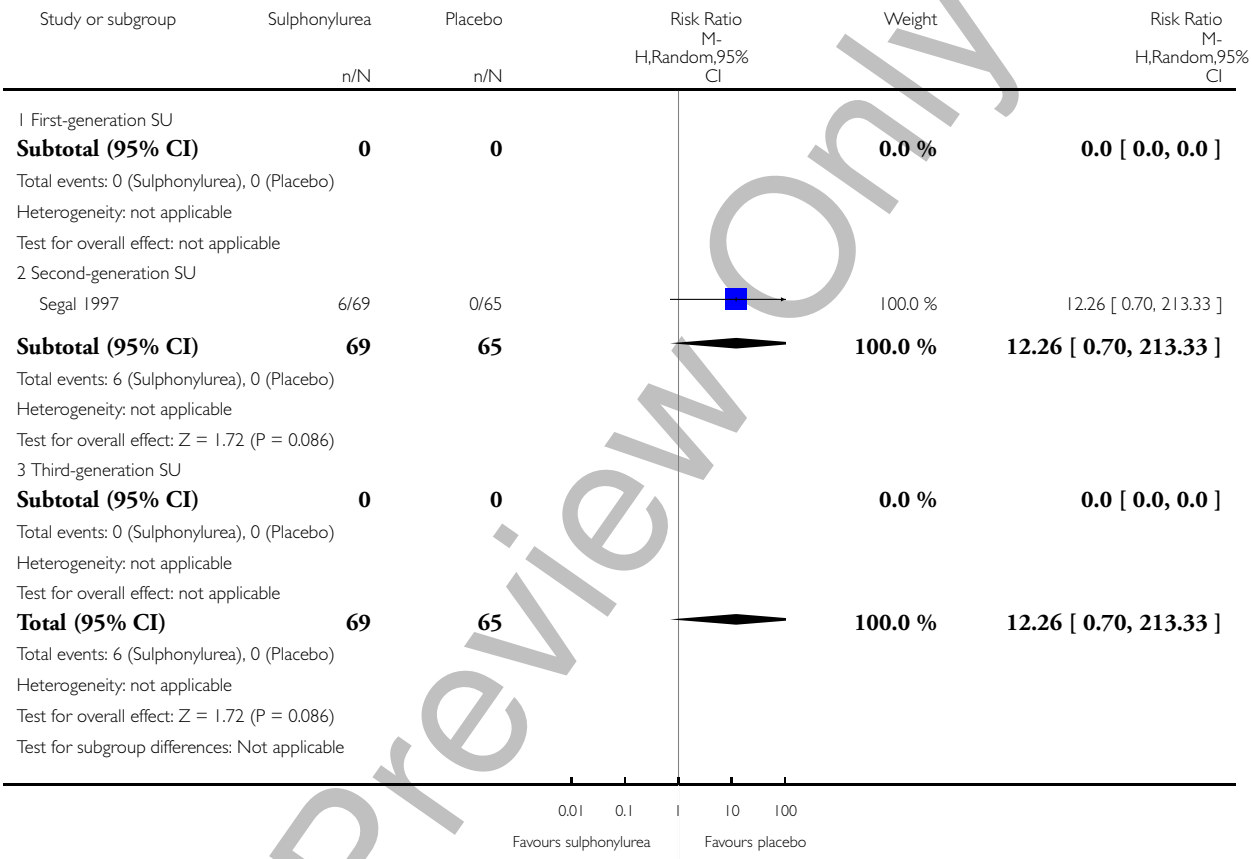


Analysis 1.16. Comparison 1 Sulphonylureas versus placebo, Outcome 16 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 16 Mild hypoglycaemia



Analysis 1.17. Comparison 1 Sulphonylureas versus placebo, Outcome 17 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 17 Severe hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Birkeland 1994	0/30	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**30**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**30**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 1.18. Comparison 1 Sulphonylureas versus placebo, Outcome 18 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 18 Cancer

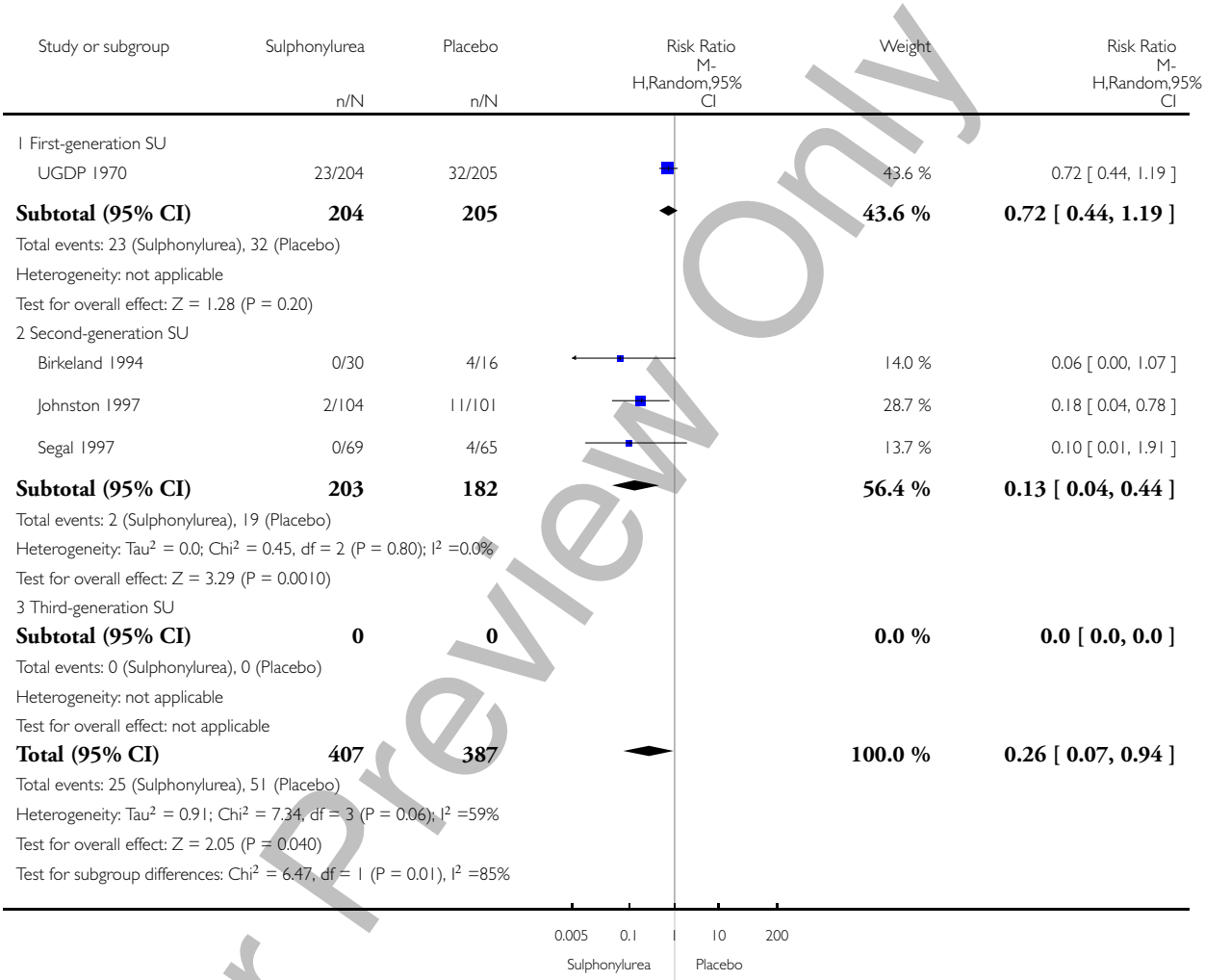
Study or subgroup	Sulphonylurea n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	3/204	12/205		68.6 %	0.25 [0.07, 0.88]
Subtotal (95% CI)	**204**	**205**		**68.6 %**	**0.25 [0.07, 0.88]**
Total events: 3 (Sulphonylurea), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 Second-generation SU					
Johnston 1997	1/104	0/101		31.4 %	2.91 [0.12, 70.71]
Subtotal (95% CI)	**104**	**101**		**31.4 %**	**2.91 [0.12, 70.71]**
Total events: 1 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**308**	**306**		**100.0 %**	**0.54 [0.06, 5.05]**
Total events: 4 (Sulphonylurea), 12 (Placebo)					
Heterogeneity: Tau^2 = 1.48; Chi^2 = 1.97, df = 1 (P = 0.16); I^2 =49%					
Test for overall effect: Z = 0.54 (P = 0.59)					
Test for subgroup differences: Chi^2 = 1.97, df = 1 (P = 0.16), I^2 =49%					

Analysis 1.19. Comparison 1 Sulphonylureas versus placebo, Outcome 19 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 1 Sulphonylureas versus placebo

Outcome: 19 Intervention failure



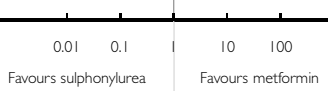
Analysis 2.1. Comparison 2 Sulphonylureas versus metformin, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 1 All-cause mortality

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	31/1447	31/1455		1.01 [0.61, 1.65]
Campbell 1994	0/24	0/24		0.0 [0.0, 0.0]
DeFronzo 1995	0/209	1/210		0.33 [0.01, 8.17]
Hermann 1991a	1/34	0/38		3.34 [0.14, 79.42]
Lawrence 2004	0/22	1/21		0.32 [0.01, 7.42]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1758**	**1770**		**0.98 [0.61, 1.58]**
Total events: 32 (Sulphonylurea), 33 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.51$, df = 3 (P = 0.68); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.07 (P = 0.94)				
3 Third-generation SU				
Derosa 2004	0/81	0/83		0.0 [0.0, 0.0]
Yamanouchi 2005	0/37	0/39		0.0 [0.0, 0.0]
Subtotal (95% CI)	**118**	**122**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1876**	**1892**		**0.98 [0.61, 1.58]**
Total events: 32 (Sulphonylurea), 33 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.51$, df = 3 (P = 0.68); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.07 (P = 0.94)				
Test for subgroup differences: Not applicable				



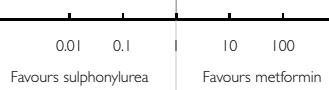
Analysis 2.2. Comparison 2 Sulphonylureas versus metformin, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Campbell 1994	0/24	0/24		0.0 [0.0, 0.0]
Hermann 1991a	1/34	0/38		3.34 [0.14, 79.42]
Lawrence 2004	0/22	1/21		0.32 [0.01, 7.42]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**102**	**105**		**1.02 [0.10, 10.25]**
Total events: 1 (Sulphonylurea), 1 (Metformin)				
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.06$, df = 1 (P = 0.30); $I^2 = 6\%$				
Test for overall effect: Z = 0.02 (P = 0.98)				
3 Third-generation SU				
Yamanouchi 2005	0/37	1/39		0.35 [0.01, 8.35]
Subtotal (95% CI)	**37**	**39**		**0.35 [0.01, 8.35]**
Total events: 0 (Sulphonylurea), 1 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.65 (P = 0.52)				
Total (95% CI)	**139**	**144**		**0.72 [0.12, 4.45]**
Total events: 1 (Sulphonylurea), 2 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.36$, df = 2 (P = 0.51); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.36 (P = 0.72)				
Test for subgroup differences: $Chi^2 = 0.29$, df = 1 (P = 0.59), $I^2 = 0.0\%$				



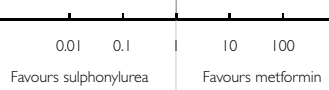
Analysis 2.3. Comparison 2 Sulphonylureas versus metformin, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 3 All-cause mortality; worst-best case scenario

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Campbell 1994	0/24	0/24		0.0 [0.0, 0.0]
Hermann 1991a	1/34	0/38		3.34 [0.14, 79.42]
Lawrence 2004	0/22	1/21		0.32 [0.01, 7.42]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**102**	**105**		**1.02 [0.10, 10.25]**
Total events: 1 (Sulphonylurea), 1 (Metformin)				
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.06$, df = 1 (P = 0.30); $I^2 = 6\%$				
Test for overall effect: Z = 0.02 (P = 0.98)				
3 Third-generation SU				
Yamanouchi 2005	3/37	1/39		3.16 [0.34, 29.06]
Subtotal (95% CI)	**37**	**39**		**3.16 [0.34, 29.06]**
Total events: 3 (Sulphonylurea), 1 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.02 (P = 0.31)				
Total (95% CI)	**139**	**144**		**1.81 [0.37, 8.71]**
Total events: 4 (Sulphonylurea), 2 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.56$, df = 2 (P = 0.46); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.74 (P = 0.46)				
Test for subgroup differences: $Chi^2 = 0.48$, df = 1 (P = 0.49), $I^2 = 0.0\%$				

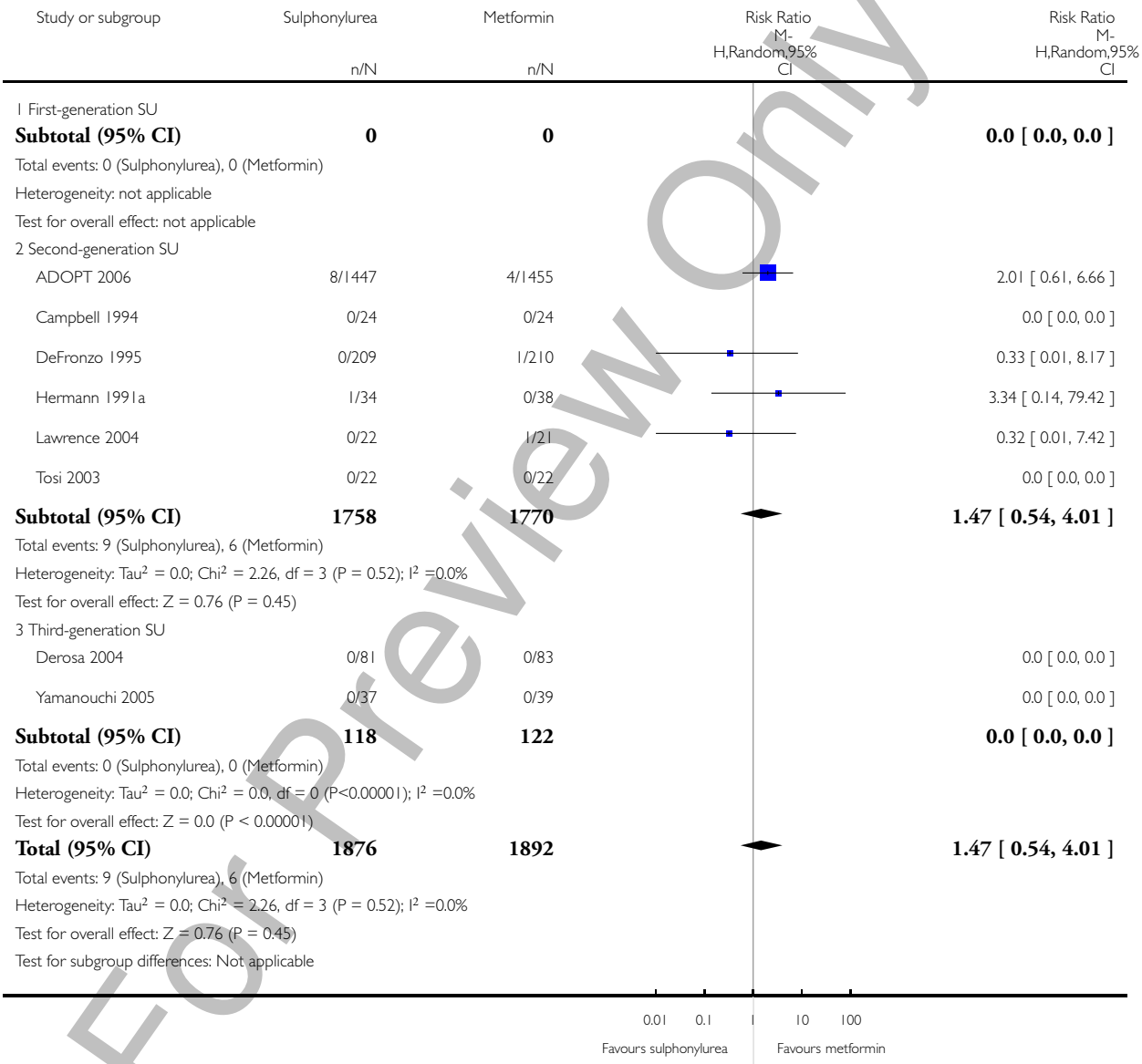


Analysis 2.4. Comparison 2 Sulphonylureas versus metformin, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 4 Cardiovascular mortality



Analysis 2.5. Comparison 2 Sulphonylureas versus metformin, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 5 Non-fatal macrovascular outcomes

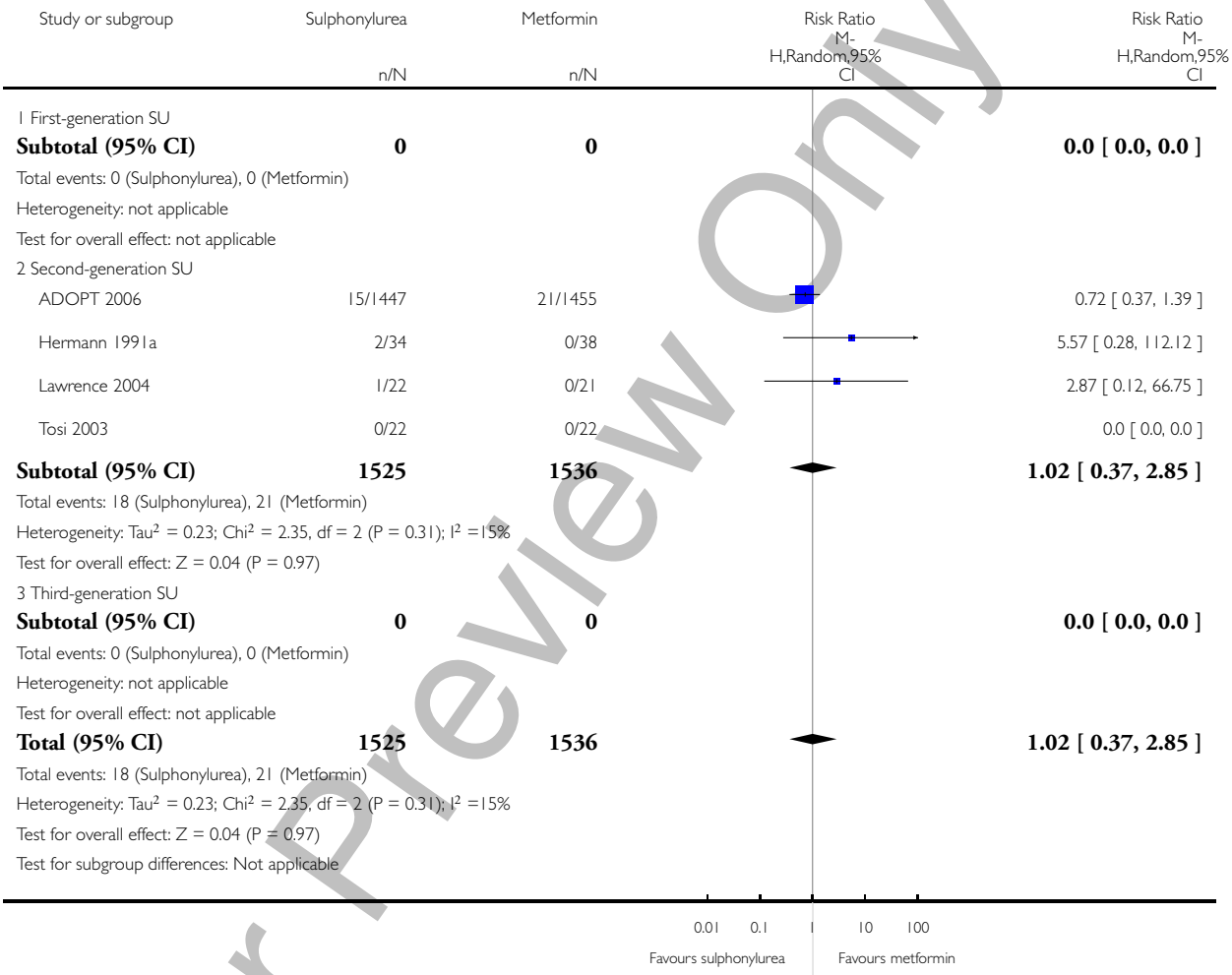
Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	41/1447	58/1455		0.71 [0.48, 1.05]
Hermann 1991a	9/34	18/38		0.56 [0.29, 1.07]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1503**	**1515**		**0.67 [0.48, 0.93]**
Total events: 50 (Sulphonylurea), 76 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.36 (P = 0.018)				
3 Third-generation SU				
Yamanouchi 2005	0/37	0/39		0.0 [0.0, 0.0]
Subtotal (95% CI)	**37**	**39**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1540**	**1554**		**0.67 [0.48, 0.93]**
Total events: 50 (Sulphonylurea), 76 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.36 (P = 0.018)				
Test for subgroup differences: Not applicable				

Analysis 2.6. Comparison 2 Sulphonylureas versus metformin, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 6 Non-fatal myocardial infarction



Analysis 2.7. Comparison 2 Sulphonylureas versus metformin, Outcome 7 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 7 Non-fatal stroke

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 2.8. Comparison 2 Sulphonylureas versus metformin, Outcome 8 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 8 Amputation of lower extremity

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 2.9. Comparison 2 Sulphonylureas versus metformin, Outcome 9 Peripheral revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 9 Peripheral revascularisation

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	31/1447	27/1455		1.15 [0.69, 1.92]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1469**	**1477**		**1.15 [0.69, 1.92]**
Total events: 31 (Sulphonylurea), 27 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.55 (P = 0.58)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**1469**	**1477**		**1.15 [0.69, 1.92]**
Total events: 31 (Sulphonylurea), 27 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.55 (P = 0.58)				
Test for subgroup differences: Not applicable				

Analysis 2.10. Comparison 2 Sulphonylureas versus metformin, Outcome 10 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 10 Microvascular outcomes

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Tosi 2003	2/22	1/22		100.0 %	2.00 [0.20, 20.49]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**2.00 [0.20, 20.49]**
Total events: 2 (Sulphonylurea), 1 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**22**	**22**		**100.0 %**	**2.00 [0.20, 20.49]**
Total events: 2 (Sulphonylurea), 1 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

Analysis 2.11. Comparison 2 Sulphonylureas versus metformin, Outcome 11 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 11 Nephropathy

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Tosi 2003	1/22	1/22		100.0 %	1.00 [0.07, 15.00]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**1.00 [0.07, 15.00]**
Total events: 1 (Sulphonylurea), 1 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**22**	**22**		**100.0 %**	**1.00 [0.07, 15.00]**
Total events: 1 (Sulphonylurea), 1 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

Analysis 2.12. Comparison 2 Sulphonylureas versus metformin, Outcome 12 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 12 Retinal photocoagulation

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**22**	**22**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 2.13. Comparison 2 Sulphonylureas versus metformin, Outcome 13 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 13 Change in fasting blood glucose from baseline (mmol/L)

Study or subgroup	Sulphonylurea N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Dalzell 1986 (1)	15	11.5 (0.9)	18	10.9 (0.7)		8.4 %	0.60 [0.04, 1.16]
UKPDS 34 1998 (2)	187	7.4 (2.4)	262	7.7 (2.1)		9.8 %	-0.30 [-0.73, 0.13]
Subtotal (95% CI)	**202**		**280**			**18.2 %**	**0.13 [-0.75, 1.01]**
Heterogeneity: Tau² = 0.34; Chi² = 6.29, df = 1 (P = 0.01); I² =84%							
Test for overall effect: Z = 0.29 (P = 0.77)							
2 Second-generation SU							
ADOPT 2006	1334	-0.09 (2.3)	1394	-0.5 (2)		12.3 %	0.41 [0.25, 0.57]
Campbell 1994 (3)	24	9.2 (3.7)	24	7.1 (1.3)		2.5 %	2.10 [0.53, 3.67]
Collier 1989	12	6.4 (1.5)	12	7.5 (1.7)		3.4 %	-1.10 [-2.38, 0.18]
DeFronzo 1995	209	0.8 (2.9)	210	-0.1 (4.3)		7.0 %	0.90 [0.20, 1.60]
Hermann 1991	10	7.2 (1)	12	7.2 (1.8)		3.7 %	0.0 [-1.19, 1.19]
Hermann 1991a	19	-2.1 (2.3)	19	-2 (1.7)		3.4 %	-0.10 [-1.39, 1.19]
Kamel 1997 (4)	17	8.1 (0.9)	6	7.8 (0.6)		7.5 %	0.30 [-0.34, 0.94]
Lawrence 2004	20	7.4 (1.4)	20	7.3 (1)		6.5 %	0.10 [-0.65, 0.85]
Tessier 1999	18	8 (3.1)	18	6.4 (1.1)		2.6 %	1.60 [0.08, 3.12]
Tosi 2003	20	-3.1 (2.4)	19	-2.8 (2.9)		2.2 %	-0.30 [-1.98, 1.38]
UKPDS 34 1998 (5)	212	8.5 (4.5)	262	7.7 (2.1)		7.4 %	0.80 [0.14, 1.46]
Subtotal (95% CI)	**1895**		**1996**			**58.4 %**	**0.43 [0.10, 0.75]**
Heterogeneity: Tau² = 0.10; Chi² = 17.85, df = 10 (P = 0.06); I² =44%							
Test for overall effect: Z = 2.59 (P = 0.0095)							
3 Third-generation SU							
Derosa 2004	73	6.8 (1.4)	75	6.9 (0.8)		10.4 %	-0.10 [-0.47, 0.27]
Tang 2004	33	6.3 (1.4)	29	6.9 (1.2)		7.5 %	-0.60 [-1.25, 0.05]
Yamanouchi 2005	34	8.8 (1.8)	37	9 (2)		5.5 %	-0.20 [-1.08, 0.68]
Subtotal (95% CI)	**140**		**141**			**23.4 %**	**-0.22 [-0.52, 0.08]**
Heterogeneity: Tau² = 0.0; Chi² = 1.73, df = 2 (P = 0.42); I² =0.0%							

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Sulphonylurea N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.43 (P = 0.15)							
Total (95% CI)	**2237**		**2417**		◆	**100.0 %**	**0.20 [-0.07, 0.48]**
Heterogeneity: Tau² = 0.15; Chi² = 42.23, df = 15 (P = 0.00021); I² =64%							
Test for overall effect: Z = 1.45 (P = 0.15)							
Test for subgroup differences: Chi² = 8.26, df = 2 (P = 0.02), I² =76%							

(1) Not described in abstract if the values are standard deviations or standard errors

(2) Data after three years of follow-up

(3) Numbers read from figure

(4) Not described in abstract if the values are standard deviations or standard errors

(5) Data after three years of follow-up

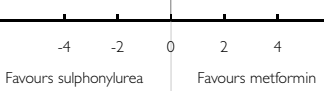
Analysis 2.14. Comparison 2 Sulphonylureas versus metformin, Outcome 14 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 14 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
ADOPT 2006	1310	0.07 (1.1)	1352	-0.2 (1.1)		13.5 %	0.27 [0.19, 0.35]
Campbell 1994	24	9.7 (1.9)	24	8.6 (1.2)		4.3 %	1.10 [0.20, 2.00]
Collier 1989	12	7 (0.8)	12	7.4 (0.8)		6.5 %	-0.40 [-1.04, 0.24]
DeFronzo 1995	209	0.2 (1.4)	210	-0.4 (1.4)		11.5 %	0.60 [0.33, 0.87]
Hermann 1991	10	7.9 (0.8)	12	7.9 (1.3)		4.3 %	0.0 [-0.89, 0.89]
Hermann 1991a	19	-1.3 (1.1)	19	-0.9 (1.1)		5.9 %	-0.40 [-1.10, 0.30]
Kamel 1997 (1)	17	7.3 (1.1)	6	6.9 (0.7)		5.3 %	0.40 [-0.37, 1.17]
Lawrence 2004	20	6.6 (0.5)	20	6.9 (0.5)		10.9 %	-0.30 [-0.61, 0.01]
Tessier 1999	18	6.8 (1.6)	18	6.1 (0.7)		4.9 %	0.70 [-0.11, 1.51]
Tosi 2003	20	-0.5 (1.3)	19	-0.5 (1.1)		5.4 %	0.0 [-0.75, 0.75]
Subtotal (95% CI)	**1659**		**1692**			**72.3 %**	**0.17 [-0.09, 0.44]**
Heterogeneity: Tau^2 = 0.09; Chi^2 = 31.65, df = 9 (P = 0.00023); I^2 =72%							
Test for overall effect: Z = 1.30 (P = 0.19)							
3 Third-generation SU							
Derosa 2004	73	6.9 (0.7)	75	7 (0.9)		11.6 %	-0.10 [-0.36, 0.16]
Tang 2004	33	6.1 (1)	29	6.7 (1.3)		7.1 %	-0.60 [-1.18, -0.02]
Yamanouchi 2005	34	7.7 (0.9)	37	7.8 (1)		8.9 %	-0.10 [-0.54, 0.34]
Subtotal (95% CI)	**140**		**141**			**27.7 %**	**-0.18 [-0.43, 0.07]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.46, df = 2 (P = 0.29); I^2 =19%							
Test for overall effect: Z = 1.43 (P = 0.15)							
Total (95% CI)	**1799**		**1833**			**100.0 %**	**0.06 [-0.16, 0.29]**
Heterogeneity: Tau^2 = 0.09; Chi^2 = 47.62, df = 12 (P<0.00001); I^2 =75%							
Test for overall effect: Z = 0.55 (P = 0.58)							
Test for subgroup differences: Chi^2 = 3.73, df = 1 (P = 0.05), I^2 =73%							



(1) Not described in abstract if the values are standard deviations or standard errors

Analysis 2.15. Comparison 2 Sulphonylureas versus metformin, Outcome 15 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 15 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Collier 1989	12	23.6 (1.4)	12	24.5 (1.6)		22.5 %	-0.90 [-2.10, 0.30]
Lawrence 2004	20	30.6 (8.8)	20	28.6 (3.5)		3.6 %	2.00 [-2.15, 6.15]
Tosi 2003	20	0.3 (0.9)	19	-0.5 (0.8)		37.0 %	0.80 [0.27, 1.33]
Subtotal (95% CI)	**52**		**51**			**63.1 %**	**0.25 [-1.21, 1.70]**
Heterogeneity: Tau^2 = 1.02; Chi^2 = 6.89, df = 2 (P = 0.03); I^2 =71%							
Test for overall effect: Z = 0.33 (P = 0.74)							
3 Third-generation SU							
Derosa 2004	73	-0.7 (3.4)	75	-0.6 (3.5)		24.2 %	-0.10 [-1.21, 1.01]
Yamanouchi 2005	34	25.4 (4)	37	25.5 (4.3)		12.7 %	-0.10 [-2.03, 1.83]
Subtotal (95% CI)	**107**		**112**			**36.9 %**	**-0.10 [-1.06, 0.86]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 0.20 (P = 0.84)							
Total (95% CI)	**159**		**163**			**100.0 %**	**0.13 [-0.69, 0.94]**
Heterogeneity: Tau^2 = 0.39; Chi^2 = 8.25, df = 4 (P = 0.08); I^2 =51%							
Test for overall effect: Z = 0.31 (P = 0.76)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							

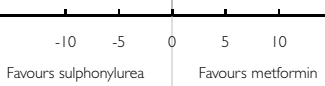
Analysis 2.16. Comparison 2 Sulphonylureas versus metformin, Outcome 16 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 16 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
ADOPT 2006	1441	1.6 (11.6)	1454	-2.9 (10.7)		27.9 %	4.50 [3.69, 5.31]
Campbell 1994	24	2.6 (3.9)	24	-2 (2.9)		10.1 %	4.60 [2.66, 6.54]
DeFronzo 1995	209	-0.3 (2.9)	210	-3.8 (2.9)		35.0 %	3.50 [2.94, 4.06]
Hermann 1991	10	73.2 (9.8)	12	76.5 (7.3)		0.9 %	-3.30 [-10.65, 4.05]
Hermann 1991a	19	2.8 (3.1)	19	-0.8 (2.2)		12.2 %	3.60 [1.89, 5.31]
Tessier 1999	18	81.5 (17.2)	18	82.3 (11.6)		0.5 %	-0.80 [-10.38, 8.78]
Tosi 2003	20	0.8 (2.7)	19	-2.3 (2.4)		13.4 %	3.10 [1.50, 4.70]
Subtotal (95% CI)	**1741**		**1756**			**100.0 %**	**3.77 [3.06, 4.47]**
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 9.84$, df = 6 (P = 0.13); $I^2 = 39\%$							
Test for overall effect: Z = 10.53 (P < 0.00001)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1741**		**1756**			**100.0 %**	**3.77 [3.06, 4.47]**
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 9.84$, df = 6 (P = 0.13); $I^2 = 39\%$							
Test for overall effect: Z = 10.53 (P < 0.00001)							
Test for subgroup differences: Not applicable							



Analysis 2.17. Comparison 2 Sulphonylureas versus metformin, Outcome 17 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 17 Adverse events

Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
ADOPT 2006	1321/1447	1341/1455		99.1 %	0.99 [0.97, 1.01]
Collier 1989	2/12	4/12		0.0 %	0.50 [0.11, 2.23]
Hermann 1991a	26/34	32/38		0.9 %	0.91 [0.72, 1.14]
Tosi 2003	3/22	3/22		0.0 %	1.00 [0.23, 4.42]
Subtotal (95% CI)	**1515**	**1527**		**100.0 %**	**0.99 [0.97, 1.01]**
Total events: 1352 (Sulphonylurea), 1380 (Metformin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.38$, df = 3 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.94 (P = 0.35)					
3 Third-generation SU					
Yamanouchi 2005	1/37	0/39		0.0 %	3.16 [0.13, 75.16]
Subtotal (95% CI)	**37**	**39**		**0.0 %**	**3.16 [0.13, 75.16]**
Total events: 1 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
Total (95% CI)	**1552**	**1566**		**100.0 %**	**0.99 [0.97, 1.01]**
Total events: 1353 (Sulphonylurea), 1380 (Metformin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.87$, df = 4 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: $Chi^2 = 0.51$, df = 1 (P = 0.47), $I^2 = 0.0\%$					

Analysis 2.18. Comparison 2 Sulphonylureas versus metformin, Outcome 18 Serious adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 18 Serious adverse events

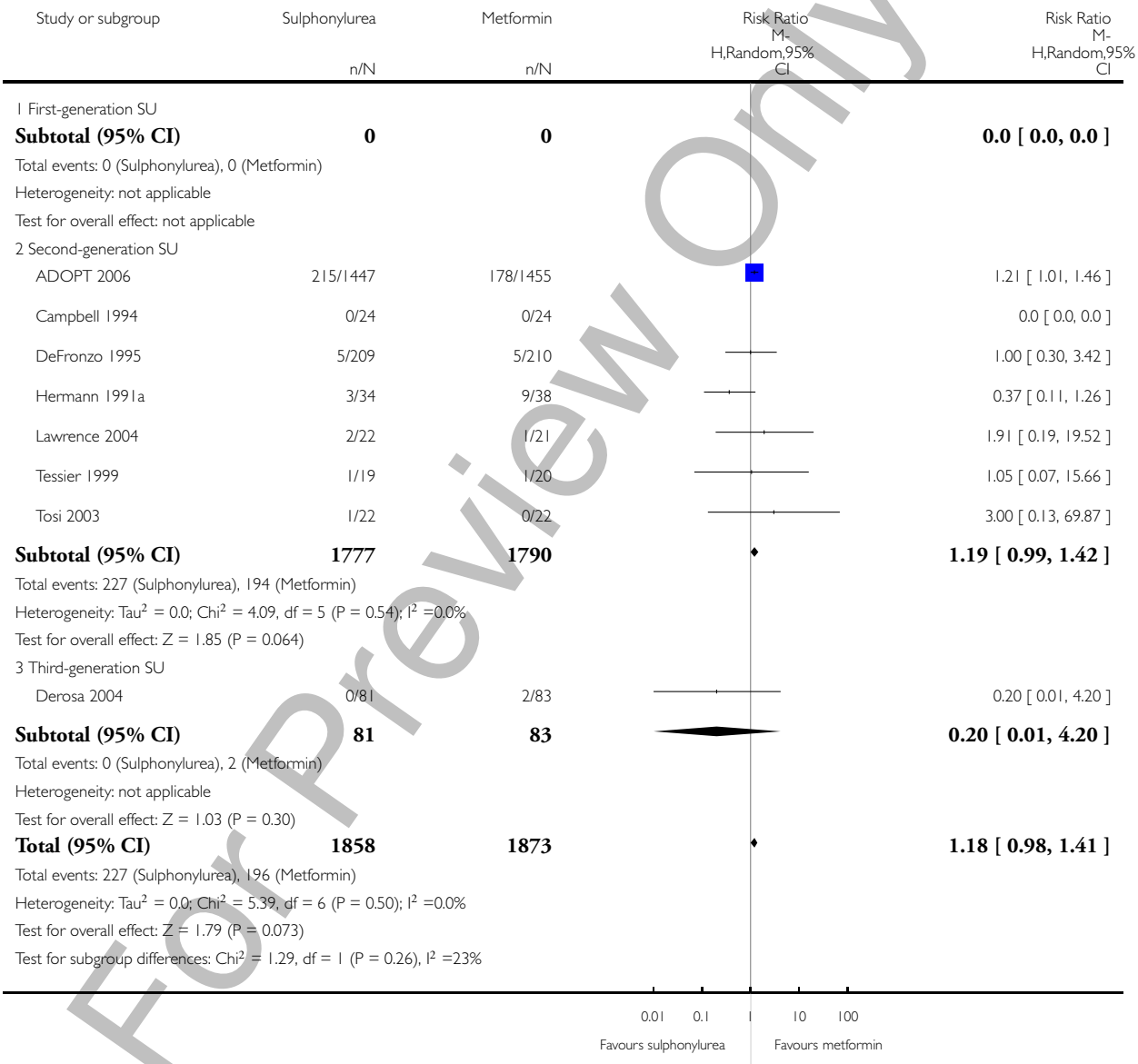
Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	308/1447	331/1455		0.94 [0.82, 1.07]
Hermann 1991	0/10	0/12		0.0 [0.0, 0.0]
Lawrence 2004	1/22	1/21		0.95 [0.06, 14.30]
Tosi 2003	0/22	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1501**	**1510**		**0.94 [0.82, 1.07]**
Total events: 309 (Sulphonylurea), 332 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.95 (P = 0.34)				
3 Third-generation SU				
Derosa 2004	0/81	0/83		0.0 [0.0, 0.0]
Subtotal (95% CI)	**81**	**83**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1582**	**1593**		**0.94 [0.82, 1.07]**
Total events: 309 (Sulphonylurea), 332 (Metformin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.95 (P = 0.34)				
Test for subgroup differences: Not applicable				

Analysis 2.19. Comparison 2 Sulphonylureas versus metformin, Outcome 19 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 19 Drop-outs due to adverse events

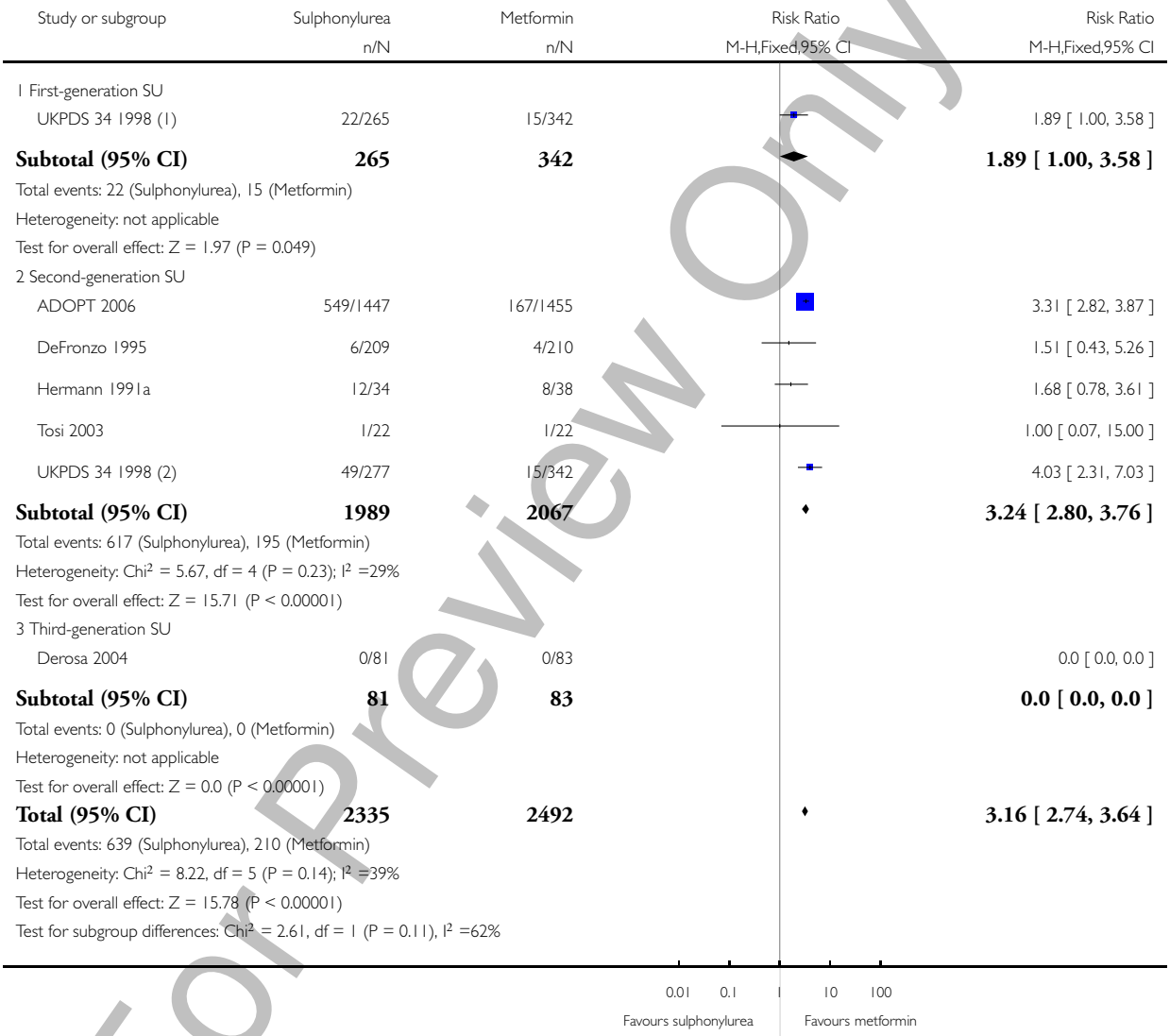


Analysis 2.20. Comparison 2 Sulphonylureas versus metformin, Outcome 20 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 20 Mild hypoglycaemia



(1) Data after one year of follow-up

(2) Data after one year of follow-up

Analysis 2.21. Comparison 2 Sulphonylureas versus metformin, Outcome 21 Moderate hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 21 Moderate hypoglycaemia

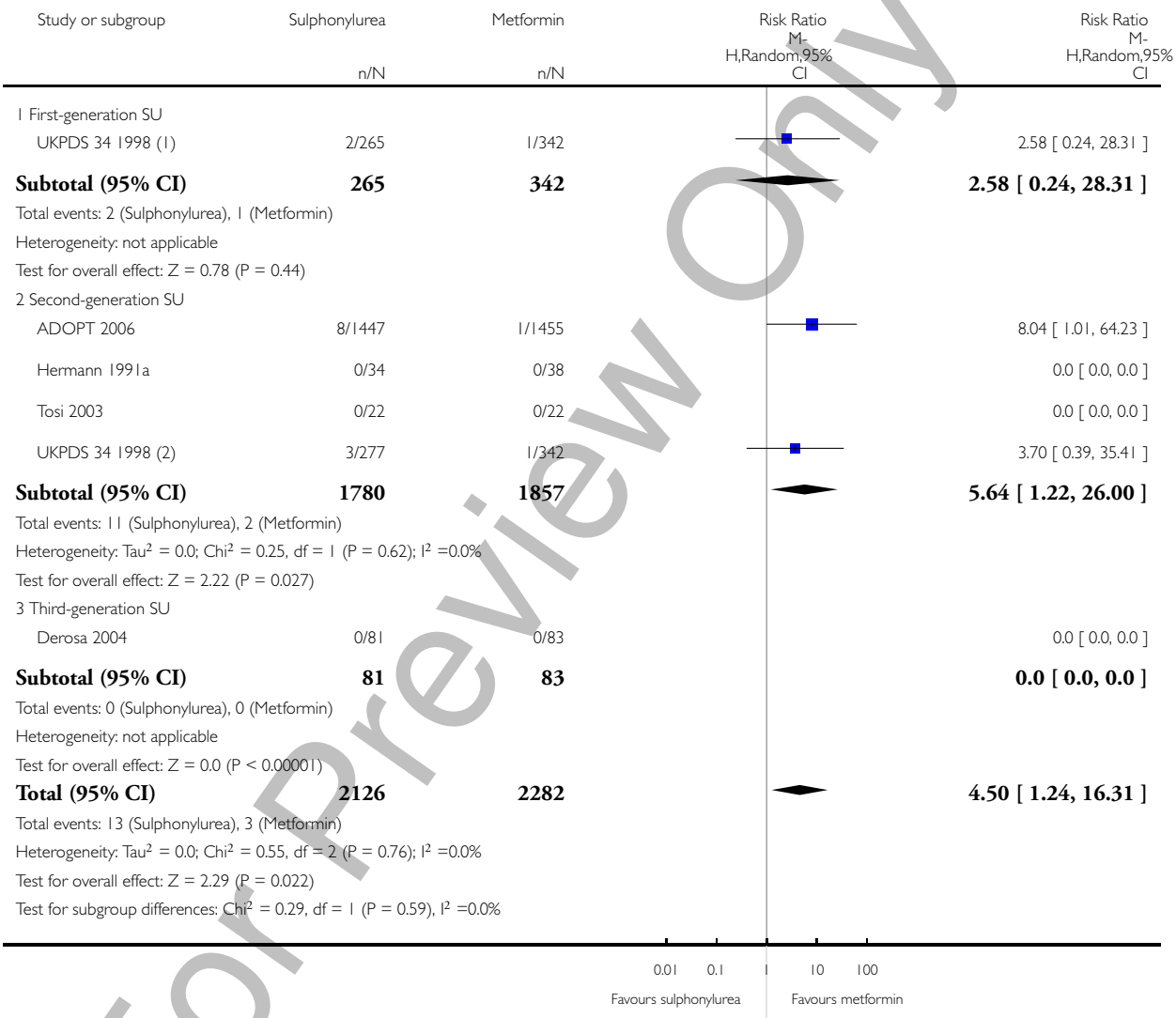
Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Tosi 2003	1/22	0/22		100.0 %	3.00 [0.13, 69.87]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**3.00 [0.13, 69.87]**
Total events: 1 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.49)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**22**	**22**		**100.0 %**	**3.00 [0.13, 69.87]**
Total events: 1 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.49)					
Test for subgroup differences: Not applicable					

Analysis 2.22. Comparison 2 Sulphonylureas versus metformin, Outcome 22 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 22 Severe hypoglycaemia



(1) Data after one year of follow-up

(2) Data after one year of follow-up

Analysis 2.23. Comparison 2 Sulphonylureas versus metformin, Outcome 23 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 23 Cancer

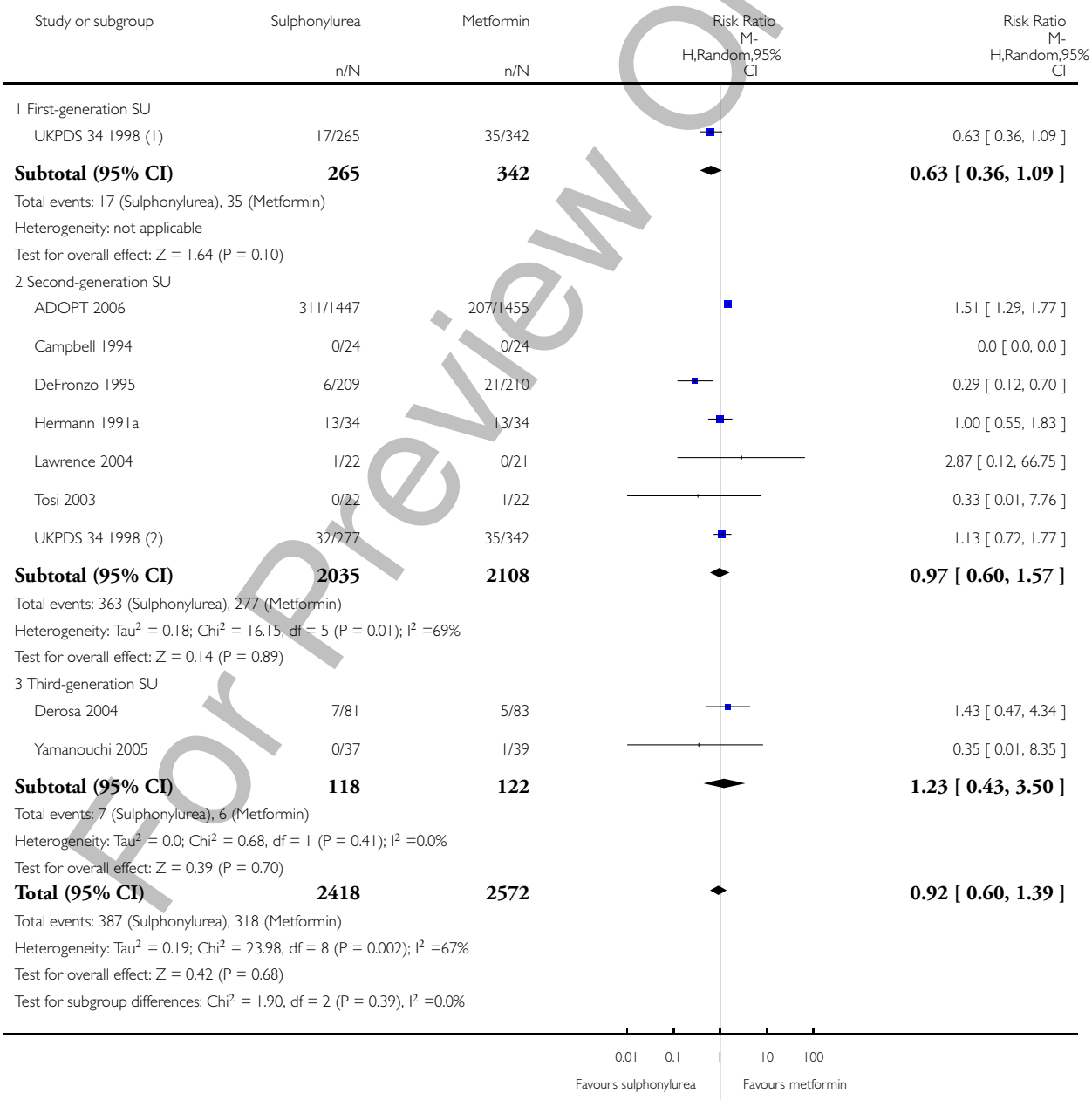
Study or subgroup	Sulphonylurea n/N	Metformin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
ADOPT 2006	55/1447	50/1455		100.0 %	1.11 [0.76, 1.61]
Subtotal (95% CI)	**1447**	**1455**		**100.0 %**	**1.11 [0.76, 1.61]**
Total events: 55 (Sulphonylurea), 50 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1447**	**1455**		**100.0 %**	**1.11 [0.76, 1.61]**
Total events: 55 (Sulphonylurea), 50 (Metformin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
Test for subgroup differences: Not applicable					

Analysis 2.24. Comparison 2 Sulphonylureas versus metformin, Outcome 24 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 2 Sulphonylureas versus metformin

Outcome: 24 Intervention failure



(1) Data after three years of follow-up

(2) Data after three years of follow-up

Analysis 3.1. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 1 All-cause mortality

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	31/1447	34/1458		0.92 [0.57, 1.49]
APPROACH 2010	7/339	8/333		0.86 [0.32, 2.34]
Hanefeld 2011	0/207	0/391		0.0 [0.0, 0.0]
Jain 2006	2/251	0/251		5.00 [0.24, 103.62]
Lawrence 2004	0/22	0/21		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	0/109	1/91		0.28 [0.01, 6.76]
Subtotal (95% CI)	**2393**	**2562**		**0.92 [0.60, 1.41]**
Total events: 40 (Sulphonylurea), 43 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.76$, df = 3 (P = 0.62); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.39 (P = 0.70)				
3 Third-generation SU				
Yamanouchi 2005	0/37	0/38		0.0 [0.0, 0.0]
Subtotal (95% CI)	**37**	**38**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**2430**	**2600**		**0.92 [0.60, 1.41]**
Total events: 40 (Sulphonylurea), 43 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.76$, df = 3 (P = 0.62); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.39 (P = 0.70)				
Test for subgroup differences: Not applicable				

Analysis 3.2. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 2 All-cause mortality; best-worst case scenario

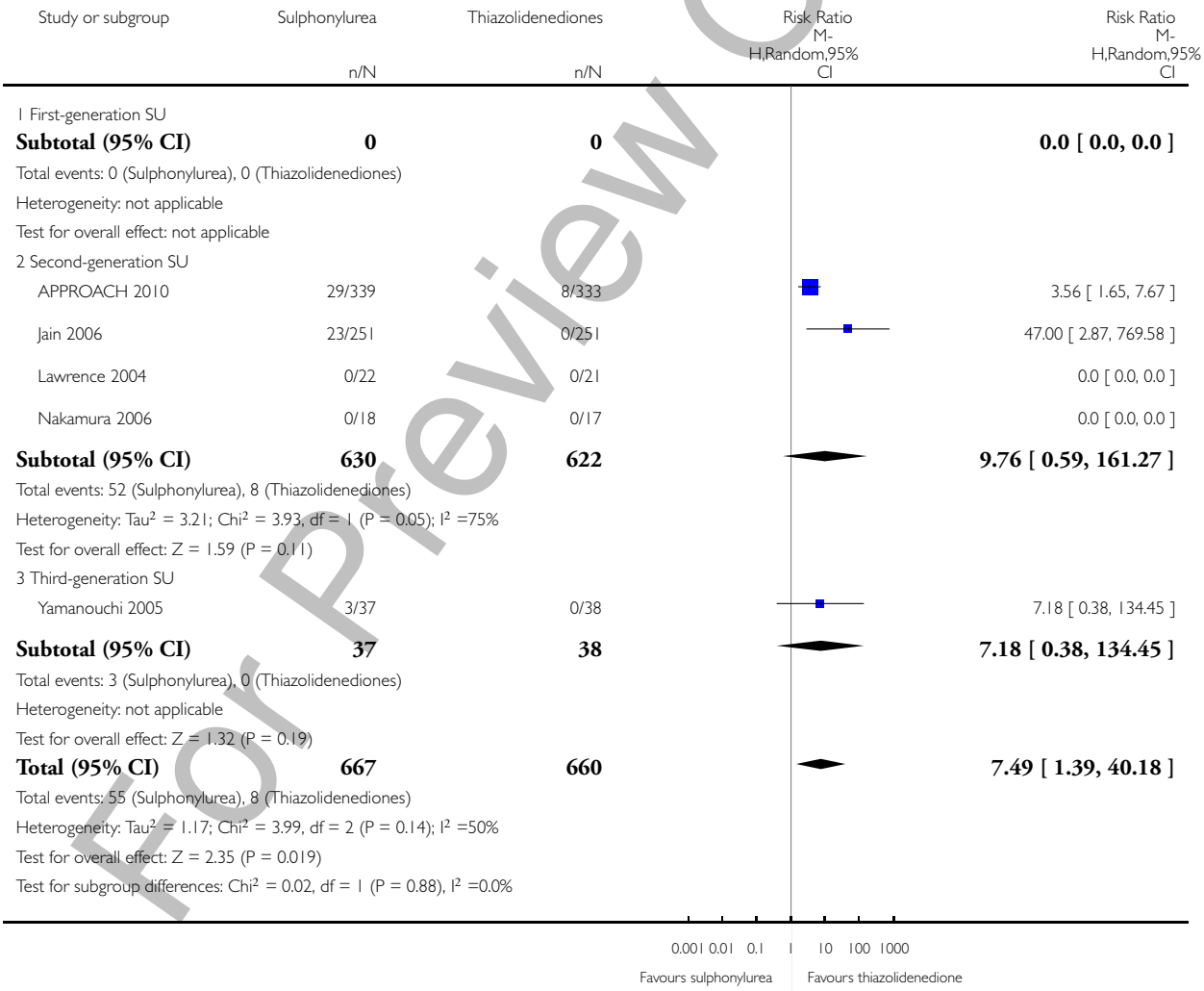
Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	7/339	25/333		0.28 [0.12, 0.63]
Jain 2006	2/251	22/251		0.09 [0.02, 0.38]
Lawrence 2004	0/22	0/21		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**630**	**622**		**0.18 [0.06, 0.54]**
Total events: 9 (Sulphonylurea), 47 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 1.79$, df = 1 (P = 0.18); $I^2 = 44\%$				
Test for overall effect: Z = 3.11 (P = 0.0019)				
3 Third-generation SU				
Yamanouchi 2005	0/37	0/38		0.0 [0.0, 0.0]
Subtotal (95% CI)	**37**	**38**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**667**	**660**		**0.18 [0.06, 0.54]**
Total events: 9 (Sulphonylurea), 47 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 1.79$, df = 1 (P = 0.18); $I^2 = 44\%$				
Test for overall effect: Z = 3.11 (P = 0.0019)				
Test for subgroup differences: Not applicable				

Analysis 3.3. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 3 All-cause mortality; worst-best case scenario



Analysis 3.4. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 4 Cardiovascular mortality

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	8/1447	5/1458		1.61 [0.53, 4.92]
APPROACH 2010	3/339	4/333		0.74 [0.17, 3.27]
Hanefeld 2011	0/207	0/391		0.0 [0.0, 0.0]
Jain 2006	1/251	0/251		3.00 [0.12, 73.29]
Lawrence 2004	0/22	0/21		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	0/109	0/91		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2393**	**2562**		**1.30 [0.55, 3.07]**
Total events: 12 (Sulphonylurea), 9 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 2 (P = 0.62); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.60 (P = 0.55)				
3 Third-generation SU				
Yamanouchi 2005	0/37	0/38		0.0 [0.0, 0.0]
Subtotal (95% CI)	**37**	**38**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**2430**	**2600**		**1.30 [0.55, 3.07]**
Total events: 12 (Sulphonylurea), 9 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 2 (P = 0.62); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.60 (P = 0.55)				
Test for subgroup differences: Not applicable				

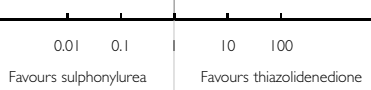
Analysis 3.5. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 5 Non-fatal macrovascular outcomes

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	41/1447	62/1458		0.67 [0.45, 0.98]
APPROACH 2010	38/339	39/333		0.96 [0.63, 1.46]
Jain 2006	22/251	11/251		2.00 [0.99, 4.04]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Perriello 2007	3/137	6/146		0.53 [0.14, 2.09]
Sutton 2002	12/99	16/104		0.79 [0.39, 1.58]
Subtotal (95% CI)	**2291**	**2309**		**0.91 [0.62, 1.33]**
Total events: 116 (Sulphonylurea), 134 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 7.98$, df = 4 (P = 0.09); $I^2 = 50\%$				
Test for overall effect: Z = 0.49 (P = 0.62)				
3 Third-generation SU				
Yamanouchi 2005	0/37	0/38		0.0 [0.0, 0.0]
Subtotal (95% CI)	**37**	**38**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**2328**	**2347**		**0.91 [0.62, 1.33]**
Total events: 116 (Sulphonylurea), 134 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 7.98$, df = 4 (P = 0.09); $I^2 = 50\%$				
Test for overall effect: Z = 0.49 (P = 0.62)				
Test for subgroup differences: Not applicable				

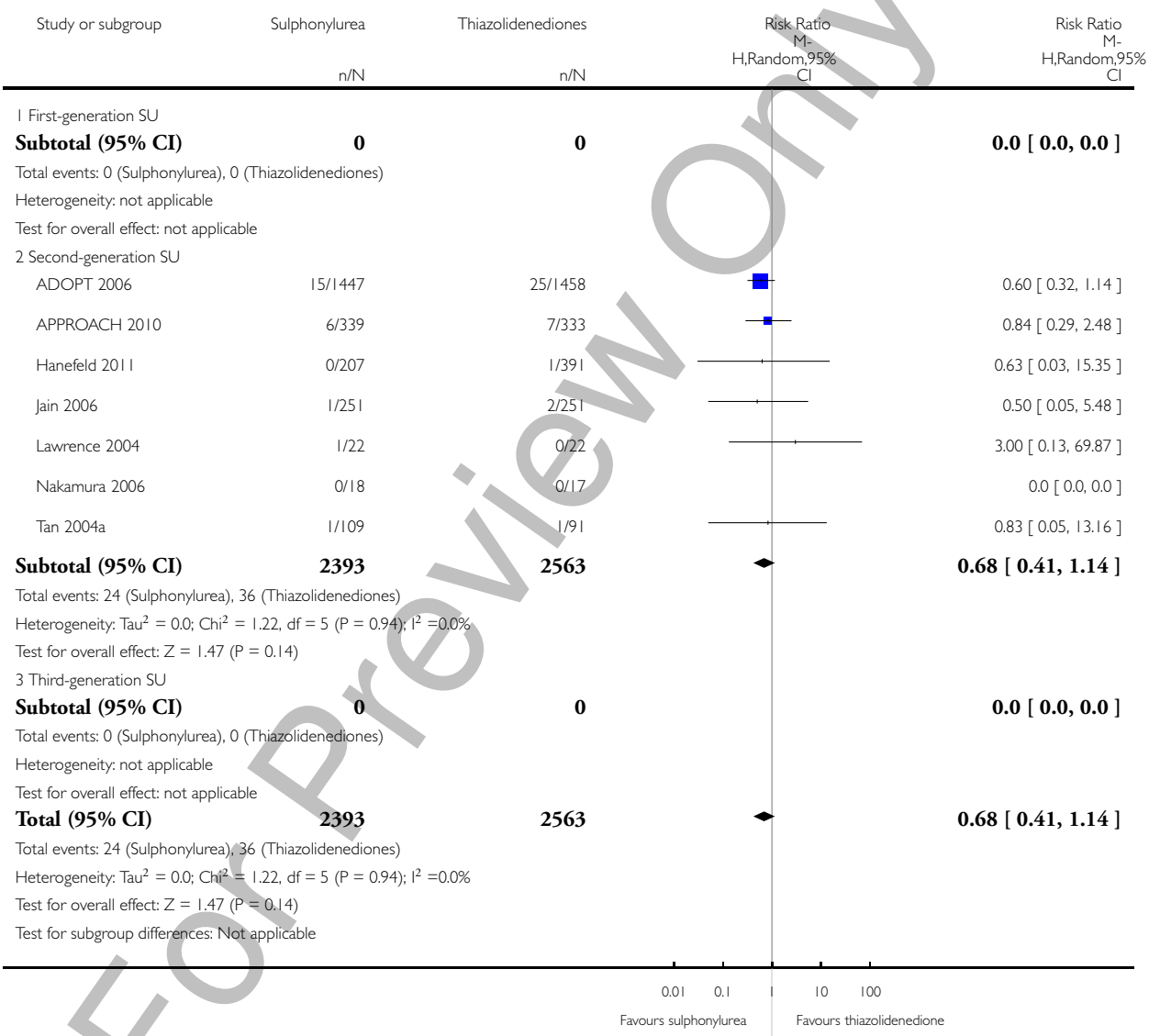


Analysis 3.6. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 6 Non-fatal myocardial infarction



Analysis 3.7. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 7 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 7 Non-fatal stroke

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	1/339	5/333		0.20 [0.02, 1.67]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**357**	**350**		**0.20 [0.02, 1.67]**
Total events: 1 (Sulphonylurea), 5 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.49 (P = 0.14)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**357**	**350**		**0.20 [0.02, 1.67]**
Total events: 1 (Sulphonylurea), 5 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.49 (P = 0.14)				
Test for subgroup differences: Not applicable				

Analysis 3.8. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 8 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 8 Amputation of lower extremity

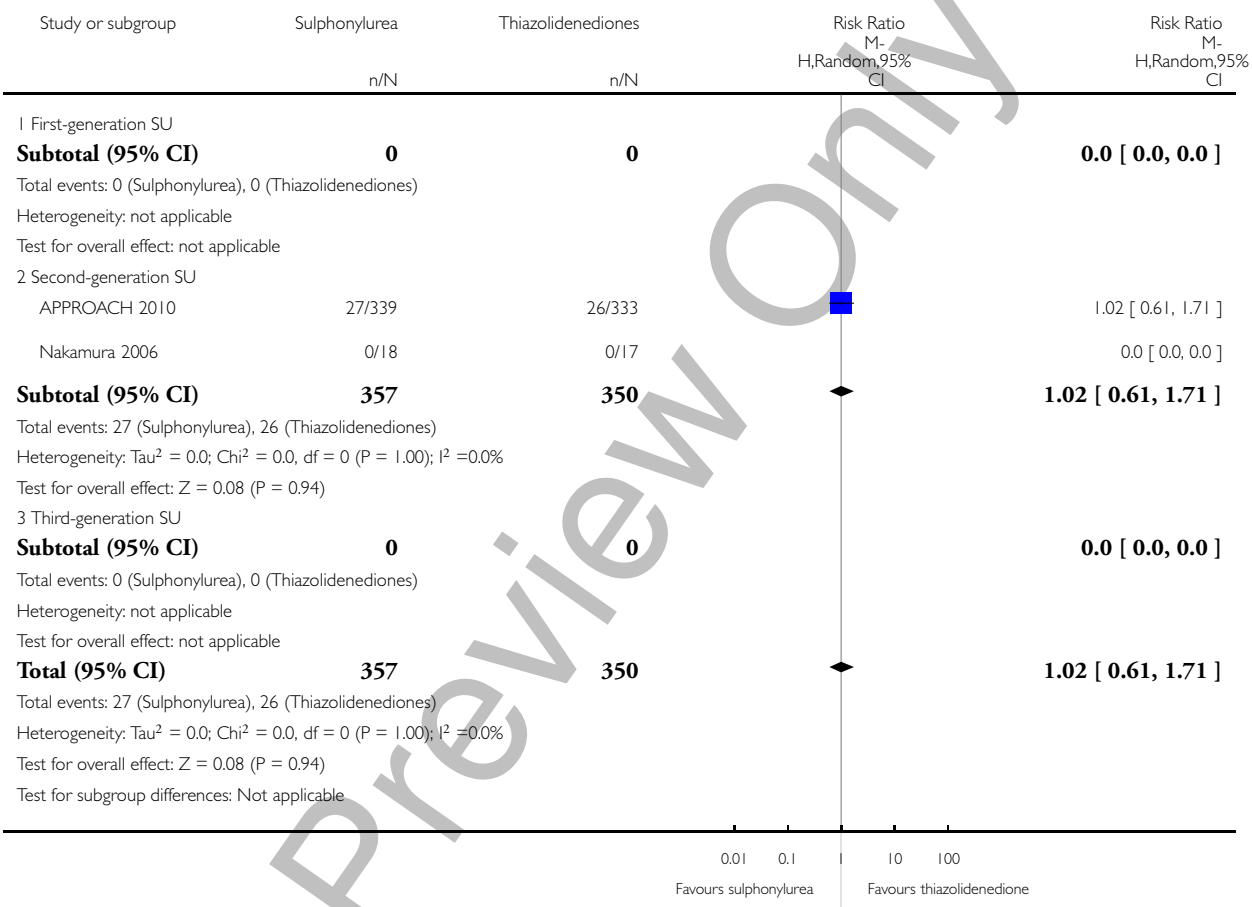
Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	0/339	0/333		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**357**	**350**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**357**	**350**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 3.9. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 9 Cardial revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 9 Cardial revascularisation



Analysis 3.10. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 10 Peripheral revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 10 Peripheral revascularisation

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	31/1447	36/1458		0.87 [0.54, 1.39]
APPROACH 2010	0/339	0/333		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1804**	**1808**		**0.87 [0.54, 1.39]**
Total events: 31 (Sulphonylurea), 36 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.59 (P = 0.56)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**1804**	**1808**		**0.87 [0.54, 1.39]**
Total events: 31 (Sulphonylurea), 36 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.59 (P = 0.56)				
Test for subgroup differences: Not applicable				

Analysis 3.11. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 11 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 11 Microvascular outcomes

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	1/109	1/91		0.83 [0.05, 13.16]
Subtotal (95% CI)	**127**	**108**		**0.83 [0.05, 13.16]**
Total events: 1 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.13 (P = 0.90)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**127**	**108**		**0.83 [0.05, 13.16]**
Total events: 1 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.13 (P = 0.90)				
Test for subgroup differences: Not applicable				

Analysis 3.12. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 12 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 12 Nephropathy

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	0/339	4/333		0.11 [0.01, 2.02]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**357**	**350**		**0.11 [0.01, 2.02]**
Total events: 0 (Sulphonylurea), 4 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.49 (P = 0.14)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**357**	**350**		**0.11 [0.01, 2.02]**
Total events: 0 (Sulphonylurea), 4 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.49 (P = 0.14)				
Test for subgroup differences: Not applicable				

Analysis 3.13. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 13 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 13 Retinopathy

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	1/339	1/333		0.98 [0.06, 15.64]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**357**	**350**		**0.98 [0.06, 15.64]**
Total events: 1 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.01 (P = 0.99)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**357**	**350**		**0.98 [0.06, 15.64]**
Total events: 1 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.01 (P = 0.99)				
Test for subgroup differences: Not applicable				

Analysis 3.14. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 14 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 14 Retinal photocoagulation

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
APPROACH 2010	0/339	0/333		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**357**	**350**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**357**	**350**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

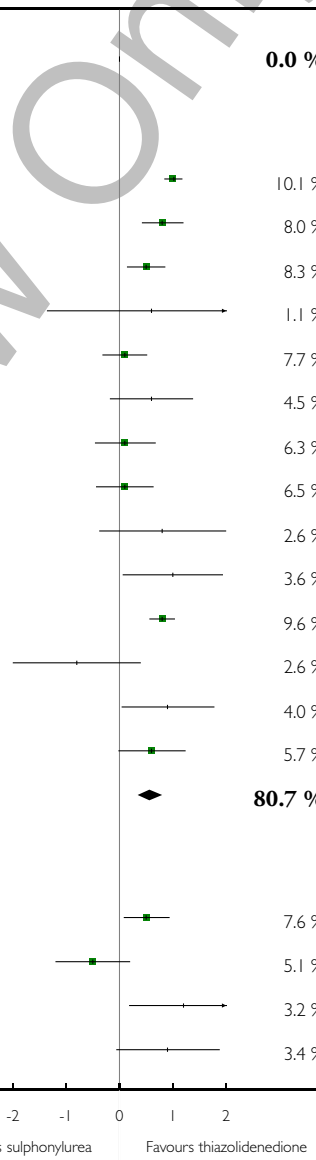
Analysis 3.15. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 15 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 15 Change in fasting blood glucose from baseline (mmol/L)

Study or subgroup	Sulphonylurea N	Mean(SD)	Thiazolidenediones N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
ADOPT 2006	1334	-0.09 (2.3)	1390	-1.1 (2.1)		10.1 %	1.01 [0.84, 1.18]
APPROACH 2010	273	-0.5 (2.3)	255	-1.3 (2.3)		8.0 %	0.80 [0.41, 1.19]
Charbonnel 2005 (1)	626	9.2 (3)	624	8.7 (3.5)		8.3 %	0.50 [0.14, 0.86]
Ebeling 2001	10	10.1 (1.9)	9	9.5 (2.4)		1.1 %	0.60 [-1.36, 2.56]
Hanefeld 2011	203	-1.7 (2.5)	384	-1.8 (2.4)		7.7 %	0.10 [-0.32, 0.52]
Lawrence 2004	20	7.4 (1.4)	20	6.8 (1.1)		4.5 %	0.60 [-0.18, 1.38]
Nakamura 2006	18	-1.6 (0.8)	17	-1.7 (0.9)		6.3 %	0.10 [-0.47, 0.67]
Perriello 2007	135	9.6 (2.5)	140	9.5 (2)		6.5 %	0.10 [-0.44, 0.64]
Sung 1999	12	9.2 (1.3)	10	8.4 (1.5)		2.6 %	0.80 [-0.39, 1.99]
Tan 2004a	96	0.3 (3.2)	83	-0.7 (3.2)		3.6 %	1.00 [0.06, 1.94]
Tan 2005	128	9.6 (1)	147	8.8 (1)		9.6 %	0.80 [0.56, 1.04]
Teramoto 2007	45	-2.9 (2.6)	46	-2.1 (3.2)		2.6 %	-0.80 [-2.00, 0.40]
Watanabe 2005	14	7.3 (1.1)	13	6.4 (1.2)		4.0 %	0.90 [0.03, 1.77]
Zhang 2005	8	8.1 (0.8)	16	7.5 (0.6)		5.7 %	0.60 [-0.03, 1.23]
Subtotal (95% CI)	**2922**		**3154**			**80.7 %**	**0.56 [0.33, 0.79]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 38.70$, df = 13 (P = 0.00022); $I^2 = 66\%$							
Test for overall effect: Z = 4.74 (P < 0.00001)							
3 Third-generation SU							
Forst 2005	84	7.6 (1.3)	89	7.1 (1.6)		7.6 %	0.50 [0.07, 0.93]
Shihara 2011	83	-1.2 (1.9)	86	-0.7 (2.7)		5.1 %	-0.50 [-1.20, 0.20]
Tan 2004 (2)	123	0.6 (4.2)	121	-0.6 (4)		3.2 %	1.20 [0.17, 2.23]
Yamanouchi 2005	34	8.8 (1.8)	35	7.9 (2.3)		3.4 %	0.90 [-0.07, 1.87]



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Study or subgroup	Sulphonylurea N	Mean(SD)	Thiazolidenediones N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**324**		**331**			**19.3 %**	**0.46 [-0.22, 1.13]**
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 9.86$, df = 3 (P = 0.02); $I^2 = 70\%$							
Test for overall effect: Z = 1.33 (P = 0.18)							
Total (95% CI)	**3246**		**3485**			**100.0 %**	**0.53 [0.31, 0.75]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 52.46$, df = 17 (P = 0.00002); $I^2 = 68\%$							
Test for overall effect: Z = 4.72 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0.0\%$							

(1) Standard deviations read from graph

(2) Values are least-squares (LS). SD calculated from SE (LS)

Analysis 3.16. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 16 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 16 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Thiazolidenediones N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
ADOPT 2006	1310	0.07 (1.1)	1350	-0.4 (1.1)		6.9 %	0.47 [0.39, 0.55]
APPROACH 2010	321	-0.2 (0.9)	311	-0.3 (0.9)		6.5 %	0.10 [-0.04, 0.24]
Charbonnel 2005 (1)	626	7.3 (1.3)	624	7.2 (1)		6.6 %	0.10 [-0.03, 0.23]
Ebeling 2001	10	7.7 (0.6)	9	8 (1.5)		1.3 %	-0.30 [-1.35, 0.75]

(*Continued* . . .)

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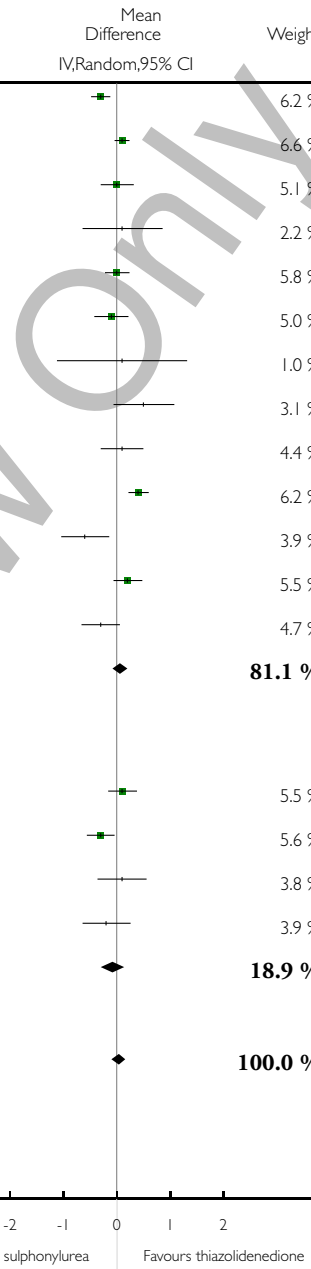
Study or subgroup	Sulphonylurea N	Mean(SD)	Thiazolidenediones N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hanefeld 2011	202	-0.7 (1)	384	-0.4 (1.2)		6.2 %	-0.30 [-0.48, -0.12]
Jain 2006 (2)	251	-2 (0.8)	251	-2.1 (0.8)		6.6 %	0.10 [-0.04, 0.24]
Lawrence 2004	20	6.6 (0.5)	20	6.6 (0.5)		5.1 %	0.0 [-0.31, 0.31]
Nakamura 2004	15	6.3 (1.1)	15	6.2 (1)		2.2 %	0.10 [-0.65, 0.85]
Nakamura 2006	18	-1.6 (0.4)	17	-1.6 (0.3)		5.8 %	0.0 [-0.23, 0.23]
Perriello 2007	135	7.9 (1.3)	140	8 (1.4)		5.0 %	-0.10 [-0.42, 0.22]
Sung 1999	12	8.3 (1.7)	10	8.2 (1.2)		1.0 %	0.10 [-1.12, 1.32]
Sutton 2002	68	8.6 (1.7)	61	8.1 (1.6)		3.1 %	0.50 [-0.07, 1.07]
Tan 2004a	96	-0.4 (1.3)	83	-0.5 (1.4)		4.4 %	0.10 [-0.30, 0.50]
Tan 2005 (3)	128	7.8 (0.8)	147	7.4 (0.8)		6.2 %	0.40 [0.21, 0.59]
Teramoto 2007	45	-1.4 (1.1)	46	-0.8 (1.1)		3.9 %	-0.60 [-1.05, -0.15]
Watanabe 2005	14	6.3 (0.4)	13	6.1 (0.3)		5.5 %	0.20 [-0.07, 0.47]
Zhang 2005	8	6.3 (0.3)	16	6.6 (0.6)		4.7 %	-0.30 [-0.66, 0.06]
Subtotal (95% CI)	**3279**		**3497**			**81.1 %**	**0.06 [-0.09, 0.20]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 108.70$, df = 16 (P<0.00001); $I^2 = 85\%$							
Test for overall effect: Z = 0.75 (P = 0.45)							
3 Third-generation SU							
Forst 2005	84	6.8 (0.9)	89	6.7 (0.9)		5.5 %	0.10 [-0.17, 0.37]
Shihara 2011 (4)	85	6.8 (0.7)	88	7.1 (1)		5.6 %	-0.30 [-0.56, -0.04]
Tan 2004 (5)	123	-0.7 (1.9)	121	-0.8 (1.8)		3.8 %	0.10 [-0.36, 0.56]
Yamanouchi 2005	34	7.7 (0.9)	35	7.9 (1)		3.9 %	-0.20 [-0.65, 0.25]
Subtotal (95% CI)	**326**		**333**			**18.9 %**	**-0.09 [-0.31, 0.14]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.37$, df = 3 (P = 0.15); $I^2 = 44\%$							
Test for overall effect: Z = 0.75 (P = 0.46)							
Total (95% CI)	**3605**		**3830**			**100.0 %**	**0.03 [-0.10, 0.16]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 125.31$, df = 20 (P<0.00001); $I^2 = 84\%$							
Test for overall effect: Z = 0.44 (P = 0.66)							
Test for subgroup differences: $Chi^2 = 1.07$, df = 1 (P = 0.30), $I^2 = 6\%$							



(1) Standard deviations read from graph

(2) Changes from baseline read from graph. LS mean and LS standard error. SD calculated from LS SE

(3) Change calculated from LS mean and SE read from graph

(4) Read from figure

(5) Values are least-squares (LS). SD calculated from SE (LS)

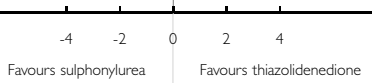
Analysis 3.17. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 17 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 17 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Thiazolidenediones N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Ebeling 2001	10	31 (5.1)	9	31.4 (4.5)		0.2 %	-0.40 [-4.72, 3.92]
Lawrence 2004	20	30.6 (8.8)	20	32.1 (8.2)		0.1 %	-1.50 [-6.77, 3.77]
Nakamura 2006	18	-0.4 (0.3)	17	0.6 (0.3)		93.8 %	-1.00 [-1.20, -0.80]
Watanabe 2005	14	24.1 (5.3)	13	24.5 (4.6)		0.3 %	-0.40 [-4.14, 3.34]
Subtotal (95% CI)	**62**		**59**			**94.4 %**	**-1.00 [-1.20, -0.80]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.21, df = 3 (P = 0.98); I^2 =0.0%							
Test for overall effect: Z = 9.87 (P < 0.00001)							
3 Third-generation SU							
Forst 2005	84	31.8 (4.1)	89	33.1 (5.1)		2.0 %	-1.30 [-2.68, 0.08]
Shihara 2011 (1)	83	24.8 (3.6)	86	24.9 (4.3)		2.6 %	-0.10 [-1.29, 1.09]
Yamanouchi 2005	34	25.4 (4)	35	26.7 (3.9)		1.1 %	-1.30 [-3.16, 0.56]
Subtotal (95% CI)	**201**		**210**			**5.6 %**	**-0.75 [-1.58, 0.08]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.09, df = 2 (P = 0.35); I^2 =4%							
Test for overall effect: Z = 1.77 (P = 0.076)							
Total (95% CI)	**263**		**269**			**100.0 %**	**-0.98 [-1.18, -0.79]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.64, df = 6 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 10.01 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.32, df = 1 (P = 0.57), I^2 =0.0%							



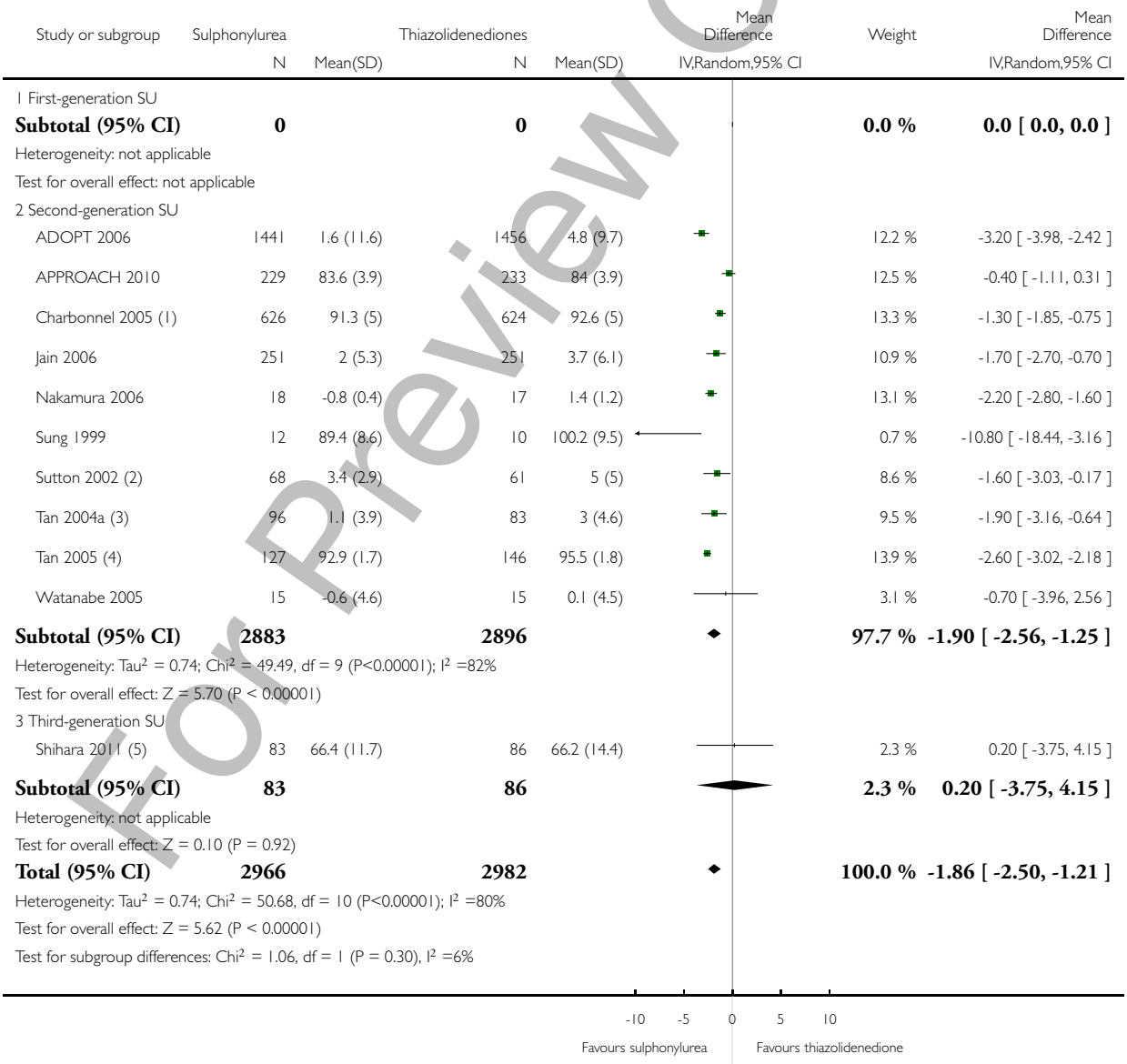
(1) Not reported how many participants were included in the analysis of weight. We assume the same number as for fasting blood glucose

Analysis 3.18. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 18 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 18 Change in weight from baseline (kg)



(1) Values read from graph.

(2) Not reported how many participants were included in the analysis of weight. We assume the same number as for HbA1c

(3) Values were expressed as least-square mean change with SE. SE converted to SD.

(4) Change calculated from LS mean and SE read from graph

(5) Not reported how many participants were included in the analysis of weight. We assume the same number as for fasting blood glucose

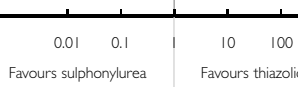
Analysis 3.19. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 19 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 19 Adverse events

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	1321/1447	1338/1458		0.99 [0.97, 1.02]
APPROACH 2010	237/339	233/333		1.00 [0.90, 1.10]
Charbonnel 2005	444/626	468/624		0.95 [0.88, 1.01]
Hanefeld 2011	144/207	294/391		0.93 [0.83, 1.03]
Jain 2006	209/251	205/251		1.02 [0.94, 1.11]
Nakamura 2006	6/18	8/17		0.71 [0.31, 1.62]
Perriello 2007	31/137	40/146		0.83 [0.55, 1.24]
Sung 1999	0/12	0/10		0.0 [0.0, 0.0]
Tan 2004a	91/109	70/91		1.09 [0.94, 1.25]
Zhang 2005	1/8	1/16		2.00 [0.14, 27.99]
Subtotal (95% CI)	**3154**	**3337**		**0.99 [0.97, 1.01]**
Total events: 2484 (Sulphonylurea), 2657 (Thiazolidenediones)				



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Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.16, df = 8 (P = 0.42); I^2 =2%				
Test for overall effect: Z = 0.90 (P = 0.37)				
3 Third-generation SU				
Shihara 2011	1/95	4/96		0.25 [0.03, 2.22]
Tan 2004	94/123	105/121		0.88 [0.78, 0.99]
Yamanouchi 2005	1/37	2/38		0.51 [0.05, 5.42]
Subtotal (95% CI)	**255**	**255**		**0.88 [0.78, 0.99]**
Total events: 96 (Sulphonylurea), 111 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.67, df = 2 (P = 0.43); I^2 =0.0%				
Test for overall effect: Z = 2.16 (P = 0.031)				
Total (95% CI)	**3409**	**3592**		**0.98 [0.94, 1.01]**
Total events: 2580 (Sulphonylurea), 2768 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.00; Chi^2 = 14.10, df = 11 (P = 0.23); I^2 =22%				
Test for overall effect: Z = 1.27 (P = 0.21)				
Test for subgroup differences: Chi^2 = 3.88, df = 1 (P = 0.05), I^2 =74%				

Analysis 3.20. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 20 Serious adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 20 Serious adverse events

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	308/1447	346/1458		0.90 [0.78, 1.03]
APPROACH 2010	71/339	71/333		0.98 [0.73, 1.32]
Hanefeld 2011	13/207	39/391		0.63 [0.34, 1.15]
Jain 2006	22/251	23/251		0.96 [0.55, 1.67]
Lawrence 2004	1/22	0/21		2.87 [0.12, 66.75]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	8/109	7/91		0.95 [0.36, 2.53]
Zhang 2005	0/8	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2401**	**2578**		**0.90 [0.80, 1.01]**
Total events: 423 (Sulphonylurea), 486 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.27$, df = 5 (P = 0.81); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.72 (P = 0.086)				
3 Third-generation SU				
Shihara 2011	0/95	0/96		0.0 [0.0, 0.0]
Tan 2004	5/123	8/121		0.61 [0.21, 1.83]
Yamanouchi 2005	0/95	0/96		0.0 [0.0, 0.0]
Subtotal (95% CI)	**313**	**313**		**0.61 [0.21, 1.83]**
Total events: 5 (Sulphonylurea), 8 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.88 (P = 0.38)				
Total (95% CI)	**2714**	**2891**		**0.90 [0.80, 1.01]**
Total events: 428 (Sulphonylurea), 494 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.74$, df = 6 (P = 0.84); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.80 (P = 0.072)				
Test for subgroup differences: $Chi^2 = 0.47$, df = 1 (P = 0.49), $I^2 = 0.0\%$				

Analysis 3.21. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 21 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 21 Drop-outs due to adverse events

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	215/1447	169/1458		1.28 [1.06, 1.55]
APPROACH 2010	14/339	16/333		0.86 [0.43, 1.73]
Charbonnel 2005	39/626	38/624		1.02 [0.66, 1.58]
Hanefeld 2011	13/207	21/391		1.17 [0.60, 2.29]
Jain 2006	25/251	14/251		1.79 [0.95, 3.35]
Lawrence 2004	2/22	1/21		1.91 [0.19, 19.52]
Nakamura 2004	0/15	0/15		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Perriello 2007	11/137	7/146		1.67 [0.67, 4.20]
Sutton 2002	4/99	8/104		0.53 [0.16, 1.69]
Tan 2004a	10/109	6/91		1.39 [0.53, 3.68]
Tan 2005	25/297	33/270		0.69 [0.42, 1.13]
Teramoto 2007	2/46	1/46		2.00 [0.19, 21.30]
Watanabe 2005	1/15	2/15		0.50 [0.05, 4.94]
Zhang 2005	0/8	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**3636**	**3797**		**1.15 [0.98, 1.36]**
Total events: 361 (Sulphonylurea), 316 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.60$, df = 11 (P = 0.39); $I^2 = 5\%$				
Test for overall effect: Z = 1.68 (P = 0.092)				
3 Third-generation SU				
Forst 2005	0/87	1/92		0.35 [0.01, 8.53]

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Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Tan 2004	3/123	5/121		0.59 [0.14, 2.42]
Subtotal (95% CI)	**210**	**213**		**0.54 [0.15, 1.97]**
Total events: 3 (Sulphonylurea), 6 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 1 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 0.93 (P = 0.35)				
Total (95% CI)	**3846**	**4010**		**1.16 [1.00, 1.34]**
Total events: 364 (Sulphonylurea), 322 (Thiazolidenediones)				
Heterogeneity: Tau^2 = 0.00; Chi^2 = 13.05, df = 13 (P = 0.44); I^2 =0%				
Test for overall effect: Z = 2.01 (P = 0.044)				
Test for subgroup differences: Chi^2 = 1.29, df = 1 (P = 0.26), I^2 =23%				

Analysis 3.22. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 22 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 22 Mild hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
ADOPT 2006	549/1447	141/1458		33.9 %	3.92 [3.31, 4.65]
APPROACH 2010	96/339	27/333		19.7 %	3.49 [2.34, 5.21]
Charbonnel 2005	63/626	22/624		16.3 %	2.85 [1.78, 4.58]
Hanefeld 2011	25/207	4/391		5.0 %	11.81 [4.16, 33.47]

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Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Jain 2006	61/251	11/251		11.5 %	5.55 [2.99, 10.29]
Nakamura 2006	6/18	1/17		1.5 %	5.67 [0.76, 42.32]
Sutton 2002	7/99	2/104		2.4 %	3.68 [0.78, 17.27]
Tan 2004a	32/109	4/91		5.3 %	6.68 [2.45, 18.18]
Subtotal (95% CI)	**3096**	**3269**		**95.6 %**	**4.05 [3.28, 5.00]**
Total events: 839 (Sulphonylurea), 212 (Thiazolidenediones)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.81$, df = 7 (P = 0.27); $I^2 = 21\%$					
Test for overall effect: Z = 12.96 (P < 0.00001)					
3 Third-generation SU					
Shihara 2011	7/95	5/96		4.4 %	1.41 [0.47, 4.30]
Subtotal (95% CI)	**95**	**96**		**4.4 %**	**1.41 [0.47, 4.30]**
Total events: 7 (Sulphonylurea), 5 (Thiazolidenediones)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**3191**	**3365**		**100.0 %**	**3.95 [3.08, 5.06]**
Total events: 846 (Sulphonylurea), 217 (Thiazolidenediones)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.05$, df = 8 (P = 0.15); $I^2 = 34\%$					
Test for overall effect: Z = 10.88 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 3.31$, df = 1 (P = 0.07), $I^2 = 70\%$					

Analysis 3.23. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 23 Moderate hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 23 Moderate hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 3.24. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 24 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 24 Severe hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	8/1447	1/1458		8.06 [1.01, 64.37]
APPROACH 2010	3/339	0/333		6.88 [0.36, 132.61]
Charbonnel 2005	1/626	0/624		2.99 [0.12, 73.27]
Hanefeld 2011	1/207	0/391		5.65 [0.23, 138.18]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	0/109	0/91		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2746**	**2914**		**6.11 [1.57, 23.79]**
Total events: 13 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 3 (P = 0.97); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.61 (P = 0.0090)				
3 Third-generation SU				
Forst 2005	0/87	0/92		0.0 [0.0, 0.0]
Shihara 2011	0/95	0/96		0.0 [0.0, 0.0]
Subtotal (95% CI)	**182**	**188**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**2928**	**3102**		**6.11 [1.57, 23.79]**
Total events: 13 (Sulphonylurea), 1 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 3 (P = 0.97); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.61 (P = 0.0090)				
Test for subgroup differences: Not applicable				

Analysis 3.25. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 25 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 25 Cancer

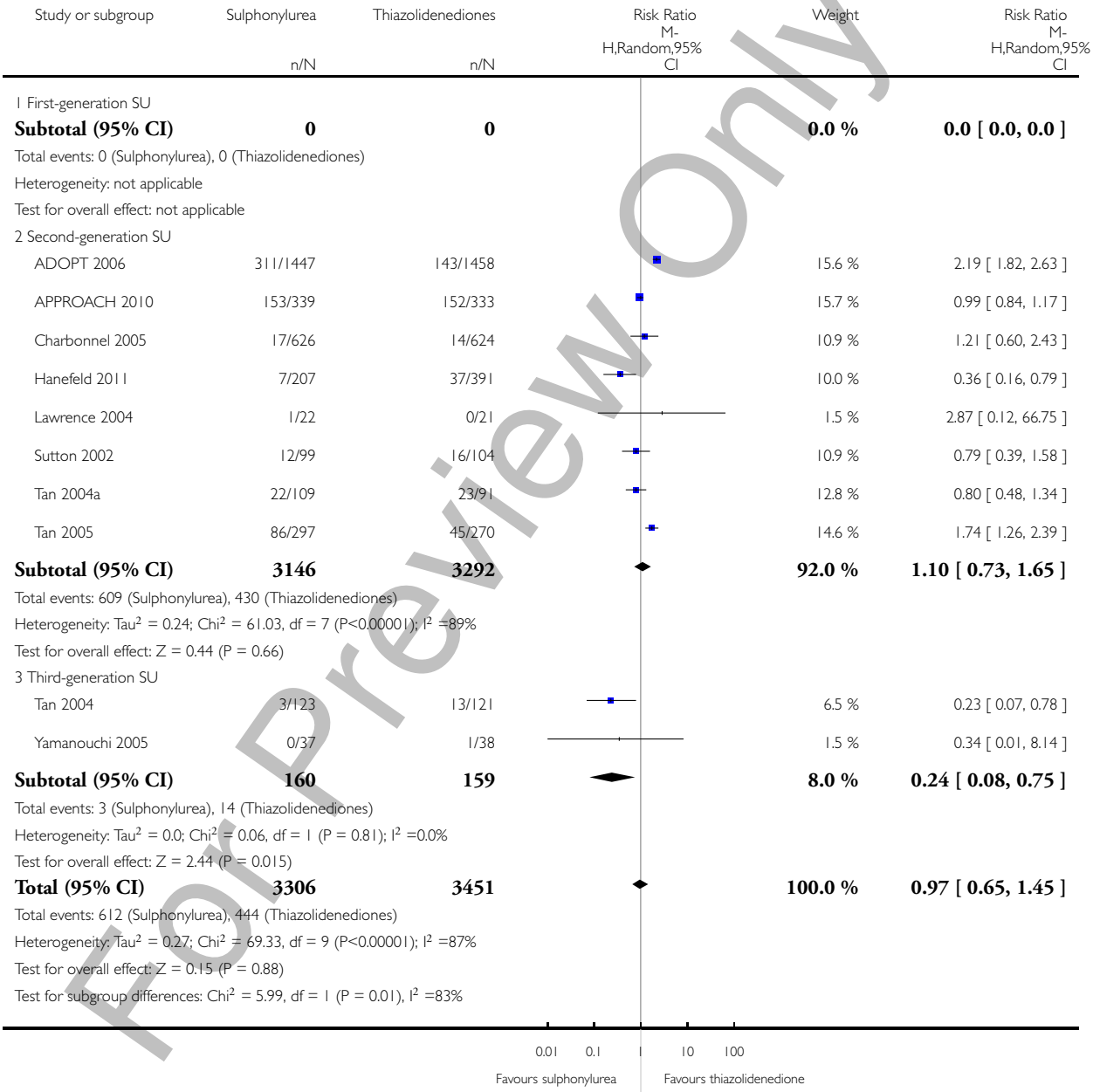
Study or subgroup	Sulphonylurea n/N	Thiazolidenediones n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
ADOPT 2006	55/1447	55/1458		1.01 [0.70, 1.45]
APPROACH 2010	2/339	3/333		0.65 [0.11, 3.89]
Hanefeld 2011	0/207	1/391		0.63 [0.03, 15.35]
Jain 2006	2/251	0/251		5.00 [0.24, 103.62]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Tan 2004a	1/109	0/91		2.51 [0.10, 60.86]
Subtotal (95% CI)	**2371**	**2541**		**1.02 [0.72, 1.45]**
Total events: 60 (Sulphonylurea), 59 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.70$, df = 4 (P = 0.79); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.10 (P = 0.92)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Thiazolidenediones)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**2371**	**2541**		**1.02 [0.72, 1.45]**
Total events: 60 (Sulphonylurea), 59 (Thiazolidenediones)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.70$, df = 4 (P = 0.79); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.10 (P = 0.92)				
Test for subgroup differences: Not applicable				

Analysis 3.26. Comparison 3 Sulphonylureas versus thiazolidinediones, Outcome 26 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 3 Sulphonylureas versus thiazolidinediones

Outcome: 26 Intervention failure

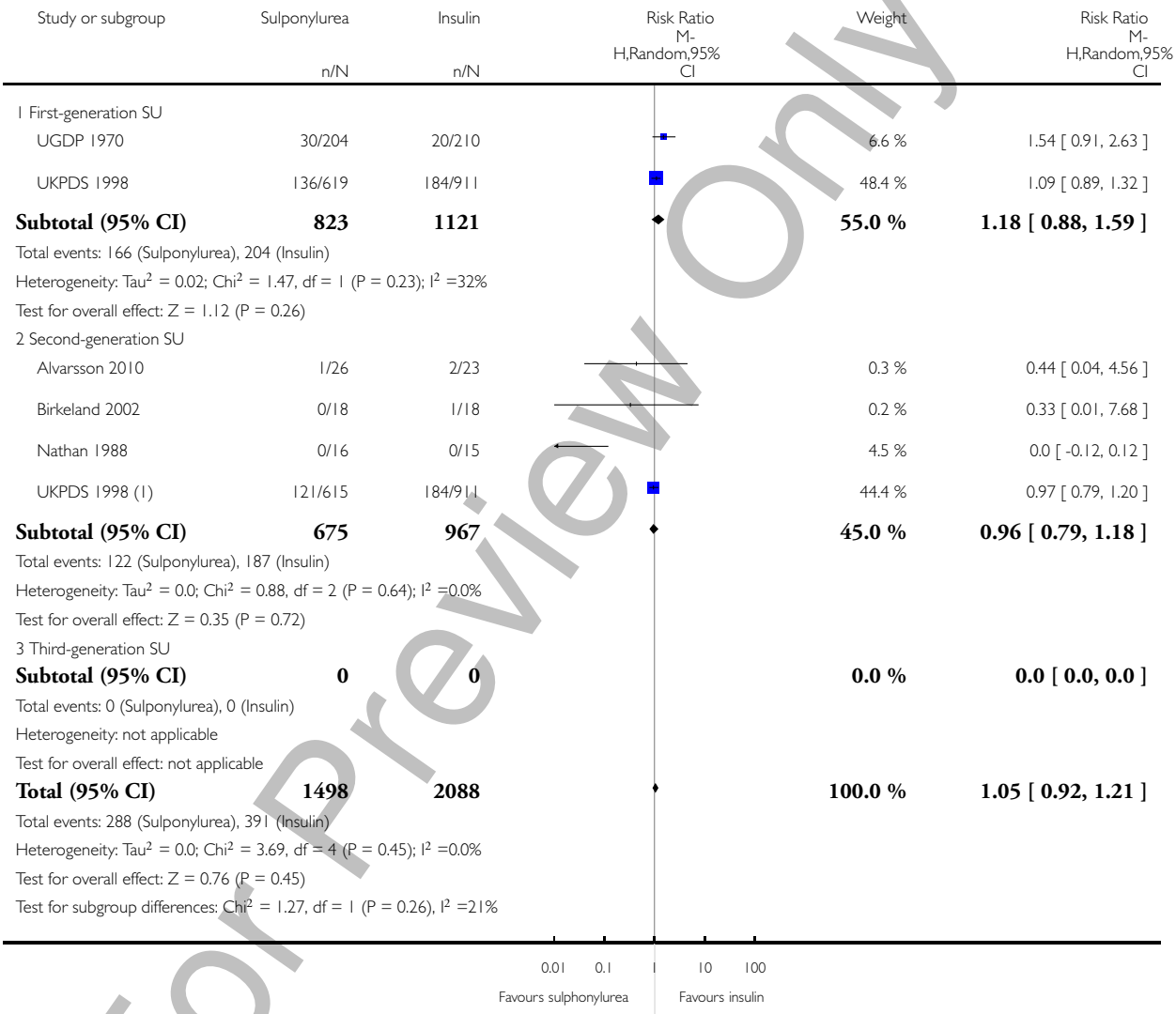


Analysis 4.1. Comparison 4 Sulphonylureas versus insulin, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 1 All-cause mortality



(1) Data are from Glucose Study 1 (UKPDS 33)

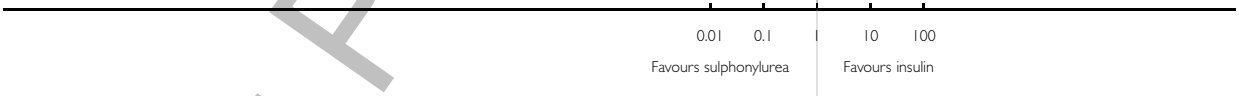
Analysis 4.2. Comparison 4 Sulphonylureas versus insulin, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	sulphonylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Alvarsson 2010	1/26	7/23		0.13 [0.02, 0.95]
Nathan 1988	0/16	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**42**	**38**		**0.13 [0.02, 0.95]**
Total events: 1 (sulphonylurea), 7 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.01 (P = 0.045)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**42**	**38**		**0.13 [0.02, 0.95]**
Total events: 1 (sulphonylurea), 7 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.01 (P = 0.045)				
Test for subgroup differences: Not applicable				



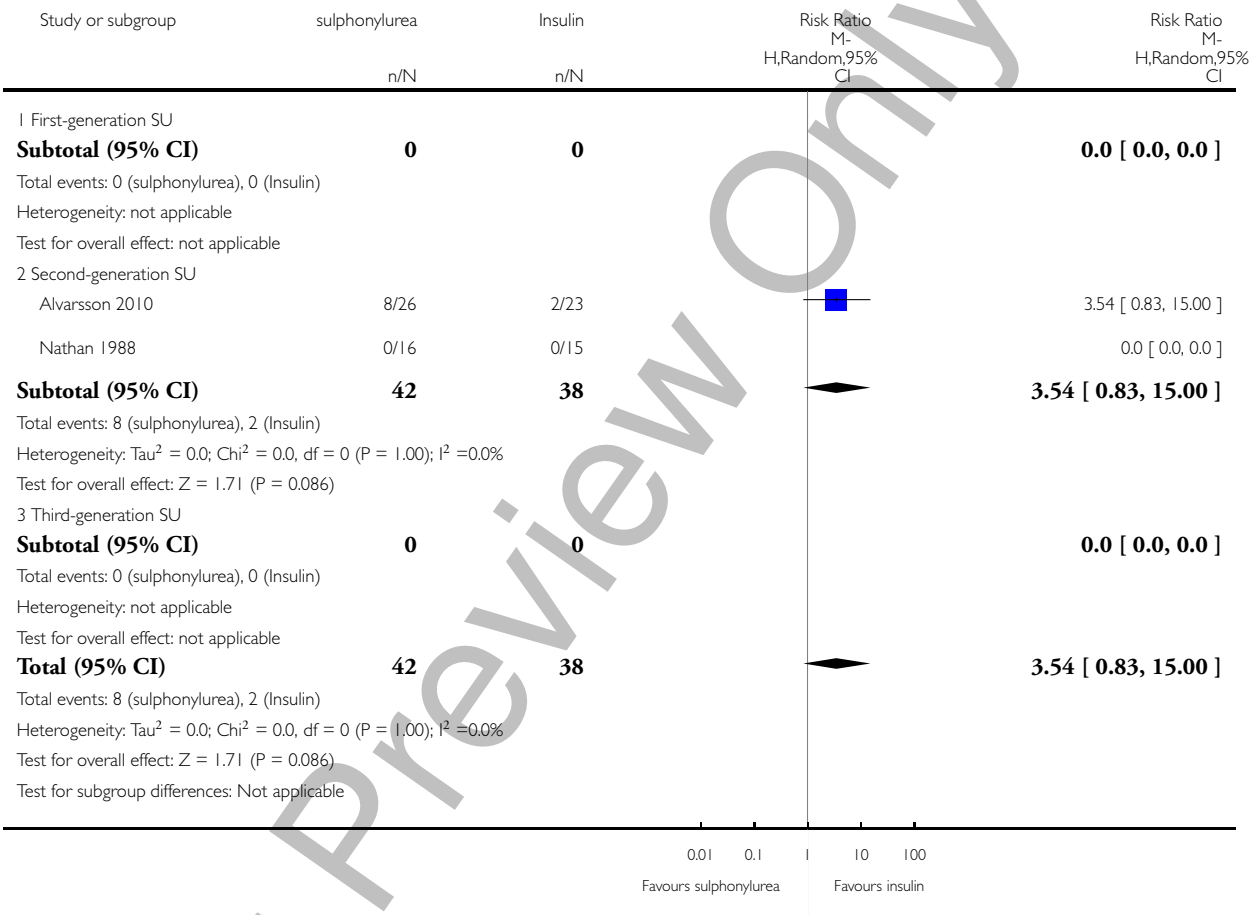
Analysis 4.3. Comparison 4 Sulphonylureas versus insulin, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 3 All-cause mortality; worst-best case scenario

Study or subgroup	sulphonylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Alvarsson 2010	8/26	2/23		3.54 [0.83, 15.00]
Nathan 1988	0/16	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**42**	**38**		**3.54 [0.83, 15.00]**
Total events: 8 (sulphonylurea), 2 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.71 (P = 0.086)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**42**	**38**		**3.54 [0.83, 15.00]**
Total events: 8 (sulphonylurea), 2 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.71 (P = 0.086)				
Test for subgroup differences: Not applicable				



Analysis 4.4. Comparison 4 Sulphonylureas versus insulin, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 4 Cardiovascular mortality

Study or subgroup	Sulponylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
UGDP 1970	26/204	13/210		2.06 [1.09, 3.89]
UKPDS 1998	71/619	104/911		1.00 [0.76, 1.33]
Subtotal (95% CI)	**823**	**1121**		**1.36 [0.68, 2.71]**
Total events: 97 (Sulponylurea), 117 (Insulin)				
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 4.07$, df = 1 (P = 0.04); $I^2 = 75\%$				
Test for overall effect: Z = 0.86 (P = 0.39)				
2 Second-generation SU				
Alvarsson 2010	0/26	1/23		0.30 [0.01, 6.94]
Birkeland 2002	0/18	1/18		0.33 [0.01, 7.68]
Nathan 1988	0/16	0/15		0.0 [0.0, 0.0]
UKPDS 1998 (1)	69/615	104/911		0.98 [0.74, 1.31]
Subtotal (95% CI)	**675**	**967**		**0.96 [0.73, 1.28]**
Total events: 69 (Sulponylurea), 106 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.00$, df = 2 (P = 0.61); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.25 (P = 0.80)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**1498**	**2088**		**1.09 [0.82, 1.44]**
Total events: 166 (Sulponylurea), 223 (Insulin)				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.72$, df = 4 (P = 0.22); $I^2 = 30\%$				
Test for overall effect: Z = 0.61 (P = 0.54)				
Test for subgroup differences: $Chi^2 = 0.79$, df = 1 (P = 0.37), $I^2 = 0.0\%$				

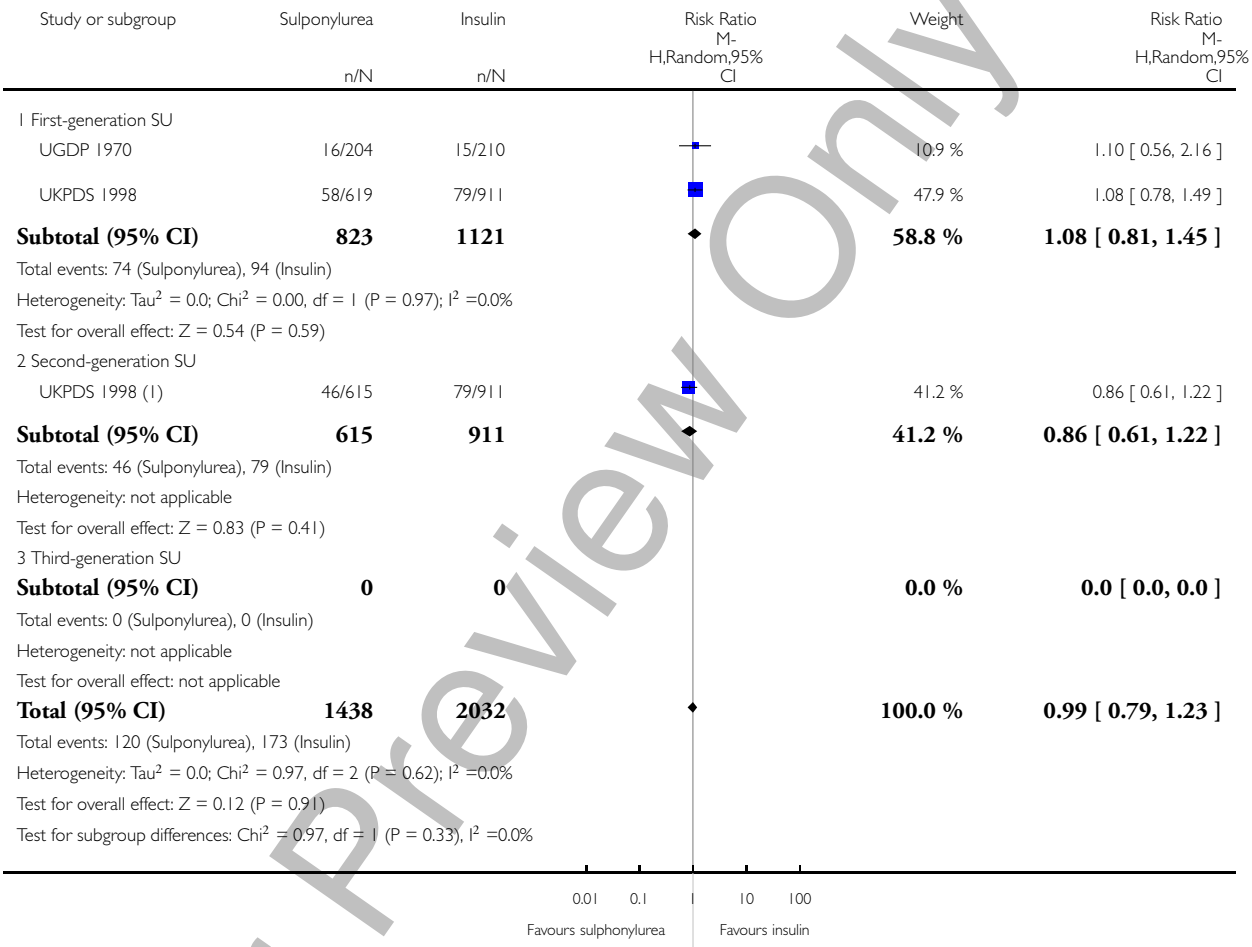
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.5. Comparison 4 Sulphonylureas versus insulin, Outcome 5 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 5 Non-fatal myocardial infarction



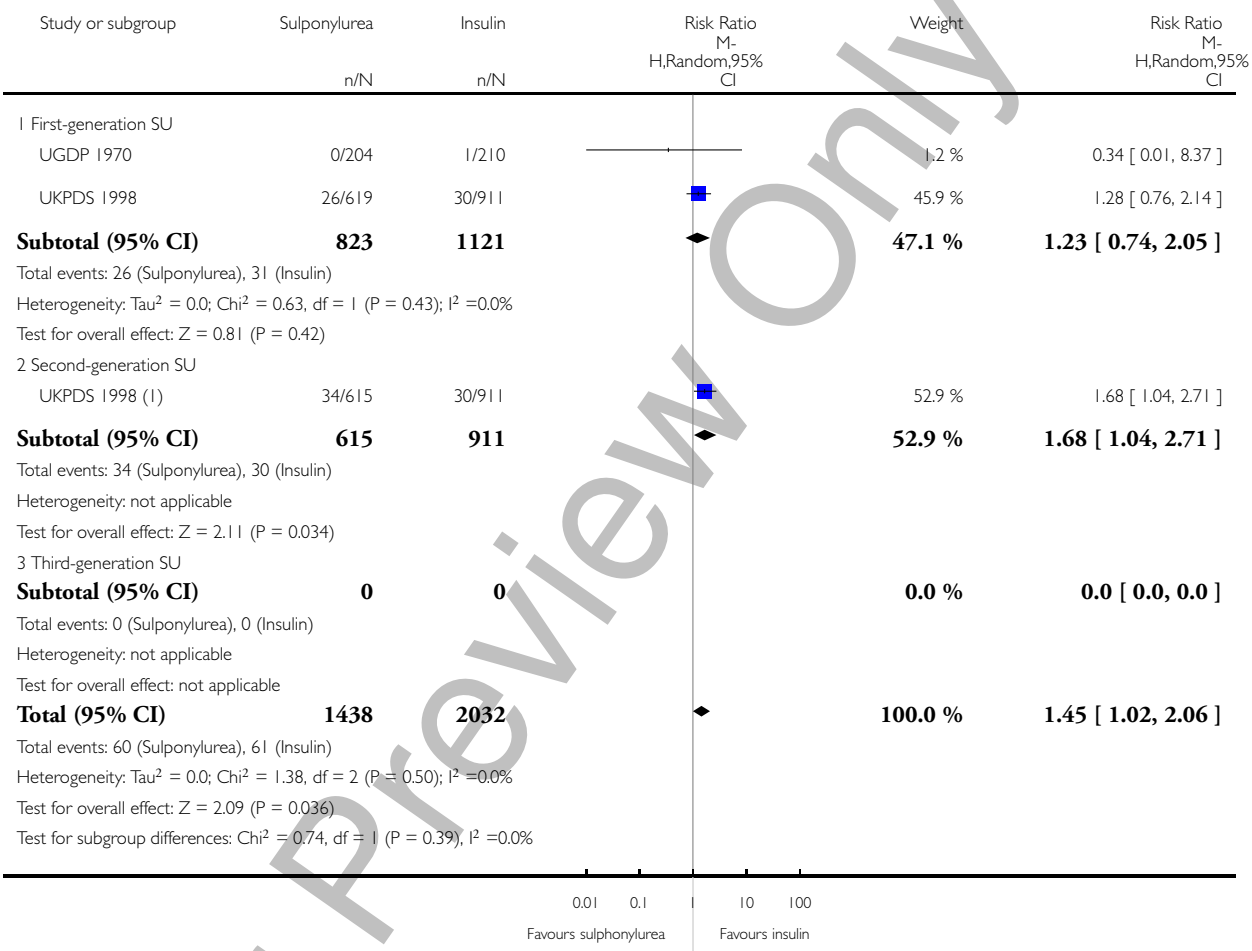
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.6. Comparison 4 Sulphonylureas versus insulin, Outcome 6 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 6 Non-fatal stroke



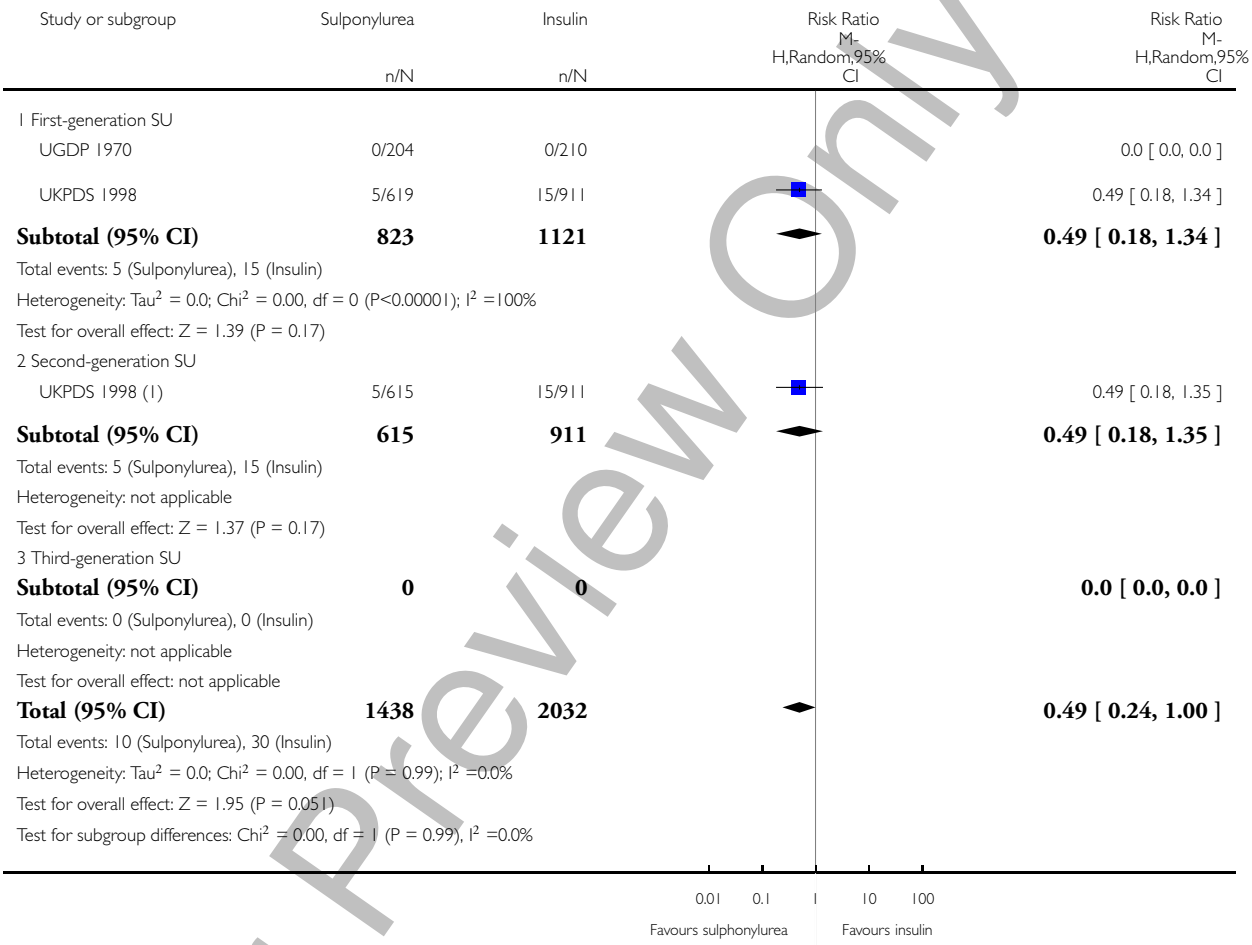
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.7. Comparison 4 Sulphonylureas versus insulin, Outcome 7 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 7 Amputation of lower extremity



(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.8. Comparison 4 Sulphonylureas versus insulin, Outcome 8 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 8 Microvascular outcomes

Study or subgroup	Sulponylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UKPDS 1998	68/619	77/911		52.8 %	1.30 [0.95, 1.77]
Subtotal (95% CI)	**619**	**911**		**52.8 %**	**1.30 [0.95, 1.77]**
Total events: 68 (Sulponylurea), 77 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.097)					
2 Second-generation SU					
UKPDS 1998 (1)	49/615	77/911		47.2 %	0.94 [0.67, 1.33]
Subtotal (95% CI)	**615**	**911**		**47.2 %**	**0.94 [0.67, 1.33]**
Total events: 49 (Sulponylurea), 77 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.74)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1234**	**1822**		**100.0 %**	**1.12 [0.82, 1.53]**
Total events: 117 (Sulponylurea), 154 (Insulin)					
Heterogeneity: Tau² = 0.02; Chi² = 1.85, df = 1 (P = 0.17); I² =46%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² =46%					

(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.9. Comparison 4 Sulphonylureas versus insulin, Outcome 9 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 9 Nephropathy

Study or subgroup	sulphonylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	5/204	0/210		100.0 %	11.32 [0.63, 203.45]
Subtotal (95% CI)	**204**	**210**		**100.0 %**	**11.32 [0.63, 203.45]**
Total events: 5 (sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.10)					
2 Second-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**204**	**210**		**100.0 %**	**11.32 [0.63, 203.45]**
Total events: 5 (sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.10)					
Test for subgroup differences: Not applicable					

Analysis 4.10. Comparison 4 Sulphonylureas versus insulin, Outcome 10 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 10 Retinopathy

Study or subgroup	Sulphonylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UGDP 1970	50/204	52/210		100.0 %	0.99 [0.71, 1.39]
Subtotal (95% CI)	**204**	**210**		**100.0 %**	**0.99 [0.71, 1.39]**
Total events: 50 (Sulphonylurea), 52 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 Second-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**204**	**210**		**100.0 %**	**0.99 [0.71, 1.39]**
Total events: 50 (Sulphonylurea), 52 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: Not applicable					

Analysis 4.11. Comparison 4 Sulphonylureas versus insulin, Outcome 11 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 11 Retinal photocoagulation

Study or subgroup	Sulponylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
UKPDS 1998	55/619	72/911		53.2 %	1.12 [0.80, 1.57]
Subtotal (95% CI)	**619**	**911**		**53.2 %**	**1.12 [0.80, 1.57]**
Total events: 55 (Sulponylurea), 72 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.49)					
2 Second-generation SU					
UKPDS 1998 (1)	45/615	72/911		46.8 %	0.93 [0.65, 1.32]
Subtotal (95% CI)	**615**	**911**		**46.8 %**	**0.93 [0.65, 1.32]**
Total events: 45 (Sulponylurea), 72 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1234**	**1822**		**100.0 %**	**1.03 [0.80, 1.31]**
Total events: 100 (Sulponylurea), 144 (Insulin)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.60, df = 1 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Chi^2 = 0.60, df = 1 (P = 0.44), I^2 =0.0%					

(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 4.12. Comparison 4 Sulphonylureas versus insulin, Outcome 12 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 12 Change in fasting blood glucose from baseline (mmol/L)

Study or subgroup	Sulphonylurea N	Mean(SD)	Insulin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
UKPDS 1998 (1)	446	7 (2.2)	676	7.4 (2.7)		34.0 %	-0.40 [-0.69, -0.11]
Subtotal (95% CI)	**446**		**676**			**34.0 %**	**-0.40 [-0.69, -0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.72 (P = 0.0065)							
2 Second-generation SU							
Alvarsson 2010 (2)	17	8.2 (1.6)	17	8.4 (2.4)		9.7 %	-0.20 [-1.57, 1.17]
Birkeland 2002	18	8.9 (3.8)	18	8 (2.9)		4.4 %	0.90 [-1.31, 3.11]
Hollander 1992	22	7.7 (1.4)	30	6.9 (1.6)		18.7 %	0.80 [-0.02, 1.62]
Nathan 1988	16	-4.4 (6.9)	15	-6.1 (4.5)		1.4 %	1.70 [-2.38, 5.78]
UKPDS 1998 (3)	472	7.6 (3.3)	676	7.4 (2.7)		31.9 %	0.20 [-0.16, 0.56]
Subtotal (95% CI)	**545**		**756**			**66.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.97, df = 4 (P = 0.56); I^2 =0.0%							
Test for overall effect: Z = 1.81 (P = 0.071)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**991**		**1432**			**100.0 %**	**0.12 [-0.37, 0.61]**
Heterogeneity: Tau^2 = 0.16; Chi^2 = 13.00, df = 5 (P = 0.02); I^2 =62%							
Test for overall effect: Z = 0.48 (P = 0.63)							
Test for subgroup differences: Chi^2 = 10.03, df = 1 (P = 0.00), I^2 =90%							

(1) Data after three years of follow-up

(2) Values read from graph after4 years of follow-up

(3) Data after three years of follow-up

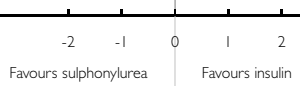
Analysis 4.13. Comparison 4 Sulphonylureas versus insulin, Outcome 13 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 13 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Insulin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
UKPDS 1998 (1)	446	6.8 (1.6)	676	7 (1.3)		35.1 %	-0.20 [-0.38, -0.02]
Subtotal (95% CI)	**446**		**676**			**35.1 %**	**-0.20 [-0.38, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.20 (P = 0.028)							
2 Second-generation SU							
Alvarsson 2010	18	-0.5 (1.4)	16	-0.9 (2)		1.0 %	0.40 [-0.77, 1.57]
Birkeland 2002	18	8.4 (1.2)	18	8.2 (1)		2.6 %	0.20 [-0.52, 0.92]
Forst 2003	68	7.6 (1.3)	75	7.4 (0.9)		9.5 %	0.20 [-0.17, 0.57]
Hollander 1992	22	6.5 (0.5)	30	6.6 (0.5)		16.5 %	-0.10 [-0.38, 0.18]
Nathan 1988	16	7.6 (1.7)	15	7.1 (1.1)		1.4 %	0.50 [-0.50, 1.50]
UKPDS 1998 (2)	472	6.9 (1.7)	676	7 (1.3)		33.8 %	-0.10 [-0.28, 0.08]
Subtotal (95% CI)	**614**		**830**			**64.9 %**	**-0.03 [-0.17, 0.10]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.28$, df = 5 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.45 (P = 0.65)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1060**		**1506**			**100.0 %**	**-0.09 [-0.20, 0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.46$, df = 6 (P = 0.37); $I^2 = 7\%$							
Test for overall effect: Z = 1.43 (P = 0.15)							
Test for subgroup differences: $Chi^2 = 2.18$, df = 1 (P = 0.14), $I^2 = 54\%$							



(1) Data after three years of follow-up

(2) Data after three years of follow-up

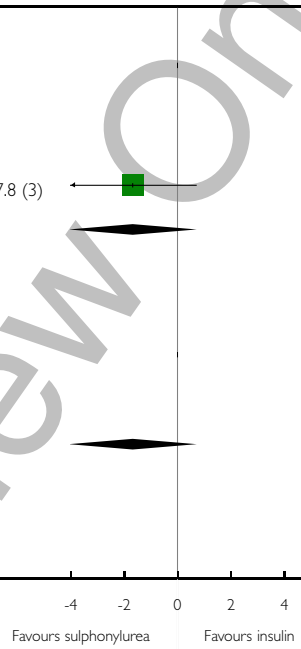
Analysis 4.14. Comparison 4 Sulphonylureas versus insulin, Outcome 14 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 14 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Insulin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Birkeland 2002	16	26.1 (4)	18	27.8 (3)		100.0 %	-1.70 [-4.10, 0.70]
Subtotal (95% CI)	**16**		**18**			**100.0 %**	**-1.70 [-4.10, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.39 (P = 0.17)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**16**		**18**			**100.0 %**	**-1.70 [-4.10, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.39 (P = 0.17)							
Test for subgroup differences: Not applicable							



Analysis 4.15. Comparison 4 Sulphonylureas versus insulin, Outcome 15 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 15 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Insulin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
UKPDS 1998 (1)	446	77.9 (15.1)	676	80.2 (15.3)		30.3 %	-2.30 [-4.11, -0.49]
Subtotal (95% CI)	**446**		**676**			**30.3 %**	**-2.30 [-4.11, -0.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.48 (P = 0.013)							
2 Second-generation SU							
Alvarsson 2010	18	1.5 (4.7)	16	3.1 (4.4)		19.6 %	-1.60 [-4.66, 1.46]
Birkeland 2002	18	78.2 (12.1)	18	82.4 (14.5)		4.0 %	-4.20 [-12.92, 4.52]
Forst 2003	68	84.4 (13.3)	75	86.5 (12.2)		13.2 %	-2.10 [-6.30, 2.10]
Nathan 1988	16	93.1 (15)	15	86 (16)		2.6 %	7.10 [-3.84, 18.04]
UKPDS 1998 (2)	472	81.1 (15.5)	676	80.2 (15.3)		30.3 %	0.90 [-0.91, 2.71]
Subtotal (95% CI)	**592**		**800**			**69.7 %**	**-0.37 [-2.39, 1.65]**
Heterogeneity: Tau^2 = 1.42; Chi^2 = 5.47, df = 4 (P = 0.24); I^2 =27%							
Test for overall effect: Z = 0.36 (P = 0.72)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1038**		**1476**			**100.0 %**	**-1.00 [-2.82, 0.83]**
Heterogeneity: Tau^2 = 2.02; Chi^2 = 9.19, df = 5 (P = 0.10); I^2 =46%							
Test for overall effect: Z = 1.07 (P = 0.29)							
Test for subgroup differences: Chi^2 = 1.95, df = 1 (P = 0.16), I^2 =49%							

(1) Data after three years of follow-up

(2) Data after three years of follow-up

Analysis 4.16. Comparison 4 Sulphonylureas versus insulin, Outcome 16 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 16 Adverse events

Study or subgroup	Sulponylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Forst 2003	25/68	26/75		100.0 %	1.06 [0.68, 1.65]
Subtotal (95% CI)	**68**	**75**		**100.0 %**	**1.06 [0.68, 1.65]**
Total events: 25 (Sulponylurea), 26 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**68**	**75**		**100.0 %**	**1.06 [0.68, 1.65]**
Total events: 25 (Sulponylurea), 26 (Insulin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
Test for subgroup differences: Not applicable					

Analysis 4.17. Comparison 4 Sulphonylureas versus insulin, Outcome 17 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 17 Drop-outs due to adverse events

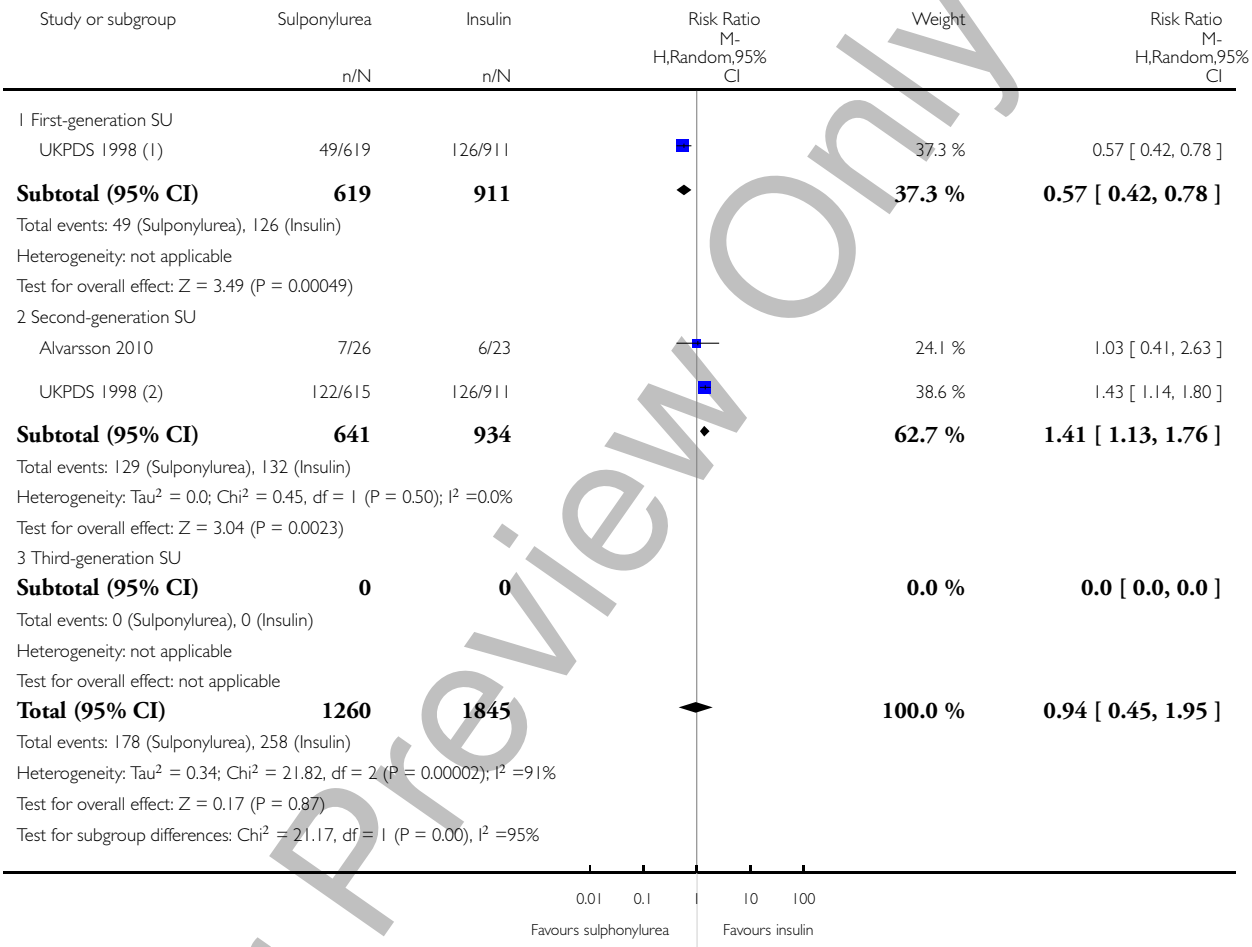
Study or subgroup	Sulponylurea n/N	Insulin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Alvarsson 2010	4/26	1/23		3.54 [0.43, 29.43]
Forst 2003	0/68	0/75		0.0 [0.0, 0.0]
Subtotal (95% CI)	**94**	**98**		**3.54 [0.43, 29.43]**
Total events: 4 (Sulponylurea), 1 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.17 (P = 0.24)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulponylurea), 0 (Insulin)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**94**	**98**		**3.54 [0.43, 29.43]**
Total events: 4 (Sulponylurea), 1 (Insulin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.17 (P = 0.24)				
Test for subgroup differences: Not applicable				

Analysis 4.18. Comparison 4 Sulphonylureas versus insulin, Outcome 18 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 18 Mild hypoglycaemia



(1) Data after one year of follow-up

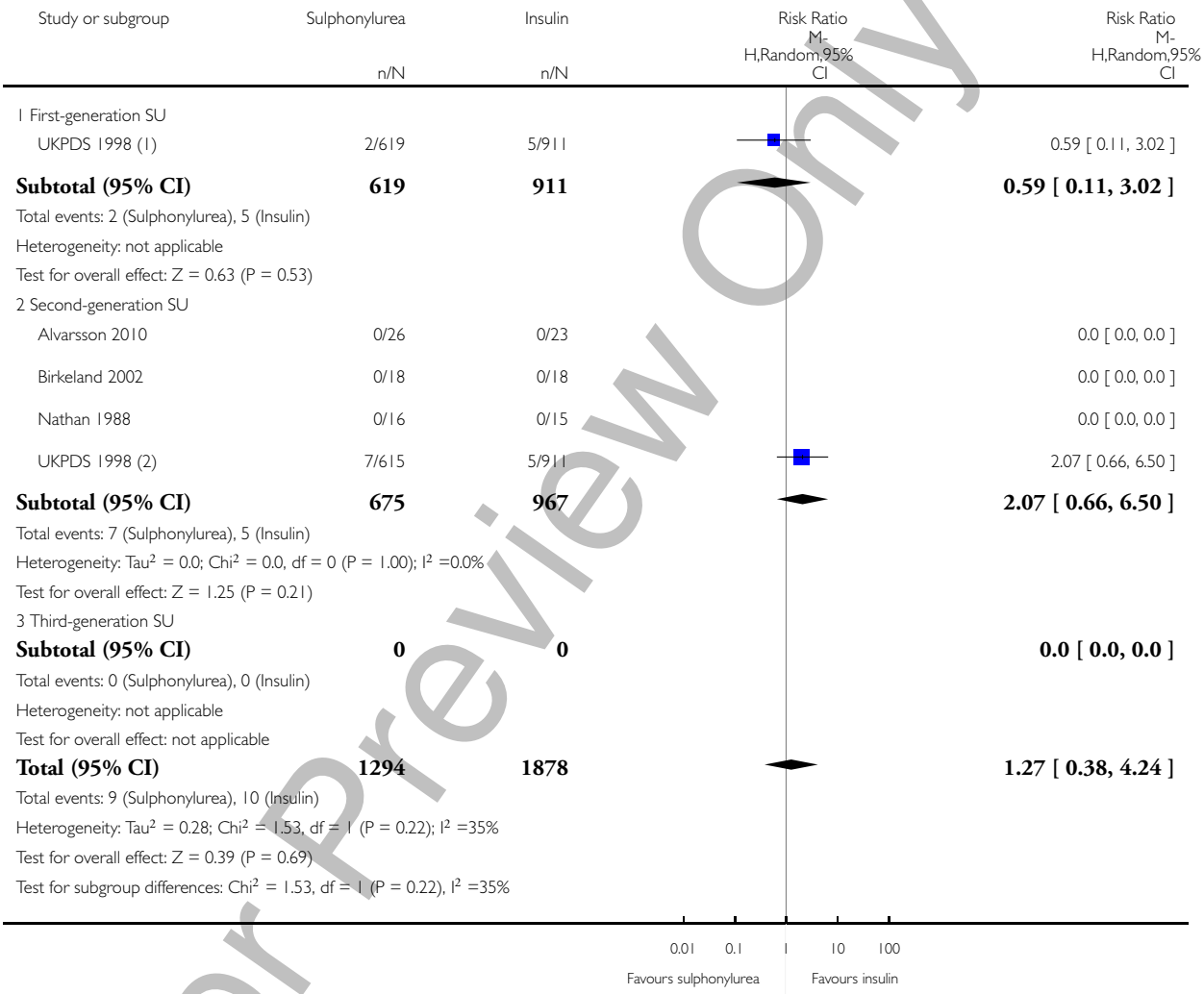
(2) Data after one year of follow-up

Analysis 4.19. Comparison 4 Sulphonylureas versus insulin, Outcome 19 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 19 Severe hypoglycaemia



(1) Data after one year of follow-up

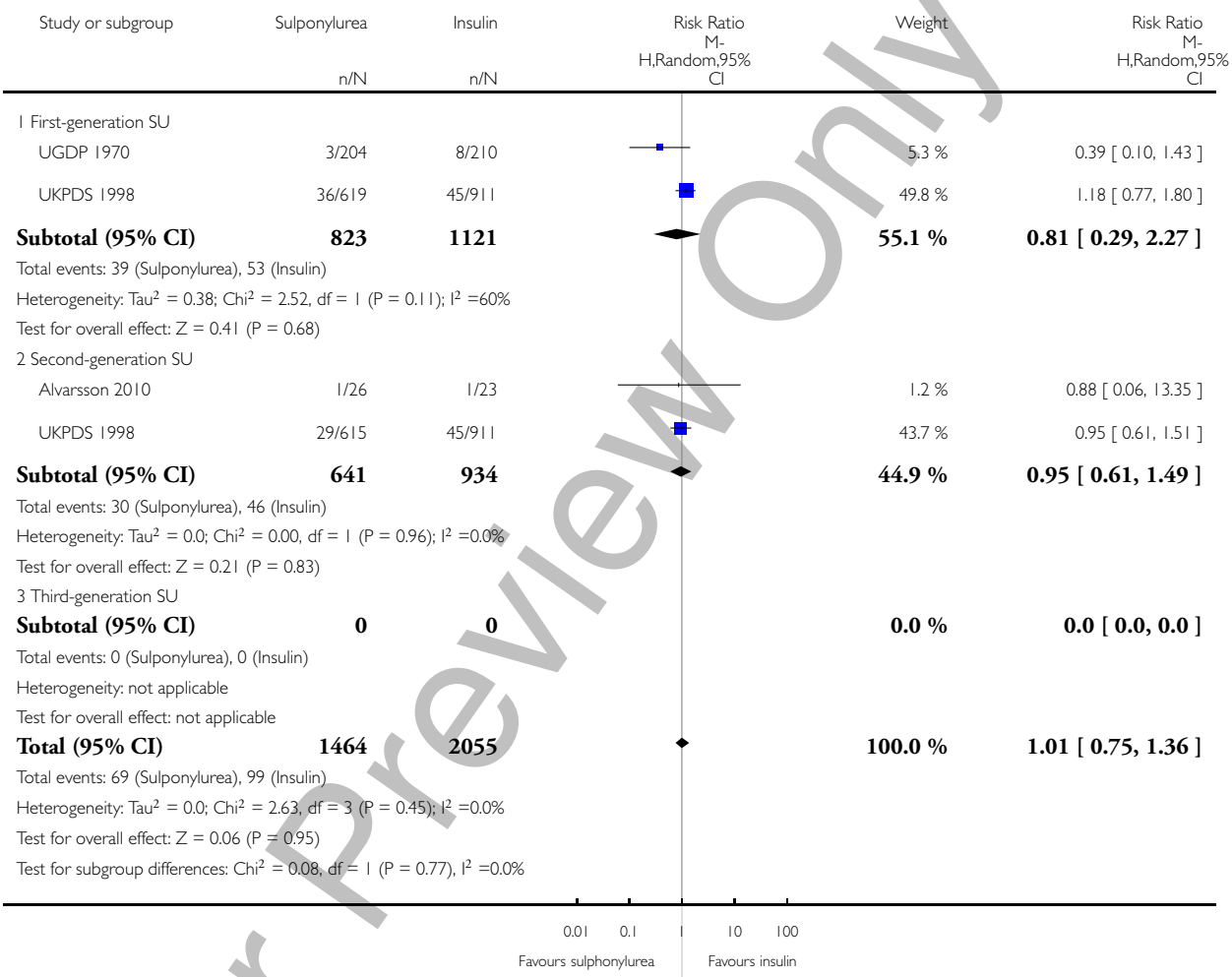
(2) Data after one year of follow-up

Analysis 4.20. Comparison 4 Sulphonylureas versus insulin, Outcome 20 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 20 Cancer

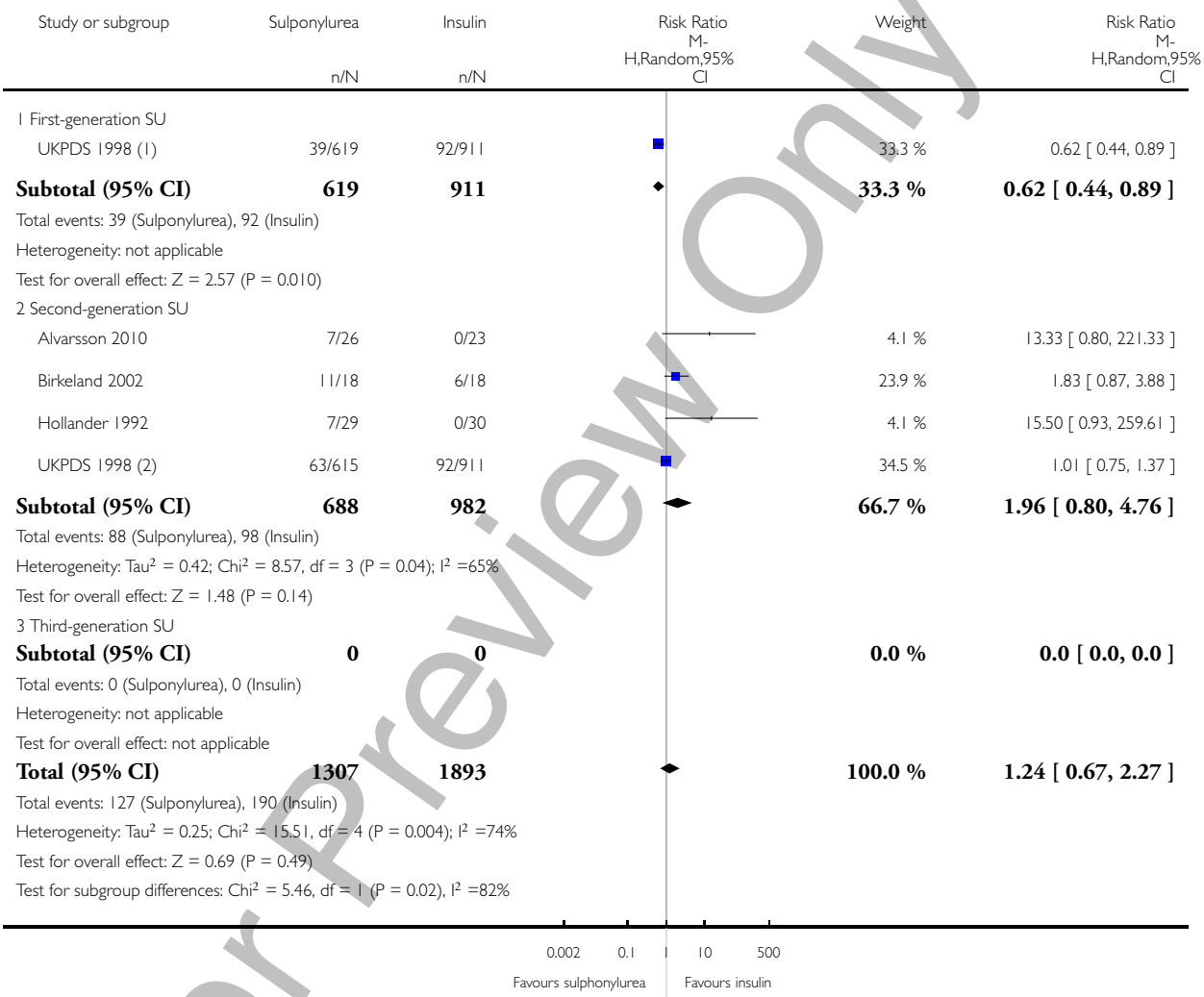


Analysis 4.21. Comparison 4 Sulphonylureas versus insulin, Outcome 21 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 4 Sulphonylureas versus insulin

Outcome: 21 Intervention failure



(1) Data after three years of follow-up

(2) Data after three years of follow-up

Analysis 5.1. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 1 All-cause mortality

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Coniff 1995	1/72	0/76		3.16 [0.13, 76.44]
van de Laar 2004	0/50	0/48		0.0 [0.0, 0.0]
Subtotal (95% CI)	**122**	**124**		**3.16 [0.13, 76.44]**
Total events: 1 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.71 (P = 0.48)				
2 Second-generation SU				
Hoffmann 1994	0/27	0/28		0.0 [0.0, 0.0]
Johnston 1997	2/104	2/206		1.98 [0.28, 13.86]
Kovacevic 1997	0/34	0/34		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**183**	**285**		**1.98 [0.28, 13.86]**
Total events: 2 (Sulphonylurea), 2 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 0 (P<0.00001); $I^2 = 100\%$				
Test for overall effect: Z = 0.69 (P = 0.49)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**305**	**409**		**2.25 [0.43, 11.84]**
Total events: 3 (Sulphonylurea), 2 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.96 (P = 0.34)				
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0.0\%$				

Analysis 5.2. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Hoffmann 1994	0/27	0/28		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.3. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 3 All-cause mortality; worst-best case scenario

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Hoffmann 1994	0/27	0/28		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.4. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 4 Cardiovascular mortality

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Coniff 1995	1/72	0/72		3.00 [0.12, 72.44]
van de Laar 2004	0/50	0/48		0.0 [0.0, 0.0]
Subtotal (95% CI)	**122**	**120**		**3.00 [0.12, 72.44]**
Total events: 1 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.68 (P = 0.50)				
2 Second-generation SU				
Hoffmann 1994	0/27	0/28		0.0 [0.0, 0.0]
Johnston 1997	1/102	1/206		2.02 [0.13, 31.96]
Kovacevic 1997	0/34	0/34		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**181**	**285**		**2.02 [0.13, 31.96]**
Total events: 1 (Sulphonylurea), 1 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.50 (P = 0.62)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**303**	**405**		**2.39 [0.30, 19.28]**
Total events: 2 (Sulphonylurea), 1 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.82 (P = 0.41)				
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.85), $I^2 = 0.0\%$				

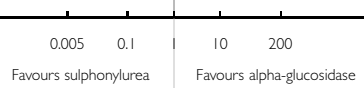
Analysis 5.5. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 5 Non-fatal macrovascular outcomes

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Johnston 1997	30/104	37/206		1.61 [1.06, 2.44]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**122**	**223**		**1.61 [1.06, 2.44]**
Total events: 30 (Sulphonylurea), 37 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.21 (P = 0.027)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**122**	**223**		**1.61 [1.06, 2.44]**
Total events: 30 (Sulphonylurea), 37 (Alpha-glucosidase inhibit)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.21 (P = 0.027)				
Test for subgroup differences: Not applicable				



Analysis 5.6. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 6 Non-fatal myocardial infarction

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
van de Laar 2004	1/50	1/48		0.96 [0.06, 14.92]
Subtotal (95% CI)	**50**	**48**		**0.96 [0.06, 14.92]**
Total events: 1 (Sulphonylurea), 1 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.03 (P = 0.98)				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**68**	**65**		**0.96 [0.06, 14.92]**
Total events: 1 (Sulphonylurea), 1 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.03 (P = 0.98)				
Test for subgroup differences: Not applicable				

Analysis 5.7. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 7 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 7 Non-fatal stroke

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.8. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 8 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 8 Amputation of lower extremity

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.9. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 9 Cardial revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 9 Cardial revascularisation

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%				

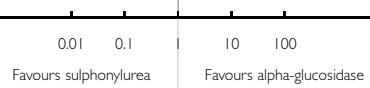
Analysis 5.10. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 10 Peripheral revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 10 Peripheral revascularisation

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				



Analysis 5.11. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 11 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 11 Microvascular outcomes

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%				

Analysis 5.12. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 12 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 12 Nephropathy

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.0, df = -1 (P = 0.0), I² =0.0%				

Analysis 5.13. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 13 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 13 Retinopathy

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.0, df = -1 (P = 0.0), I² =0.0%				

Analysis 5.14. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 14 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 14 Retinal photocoagulation

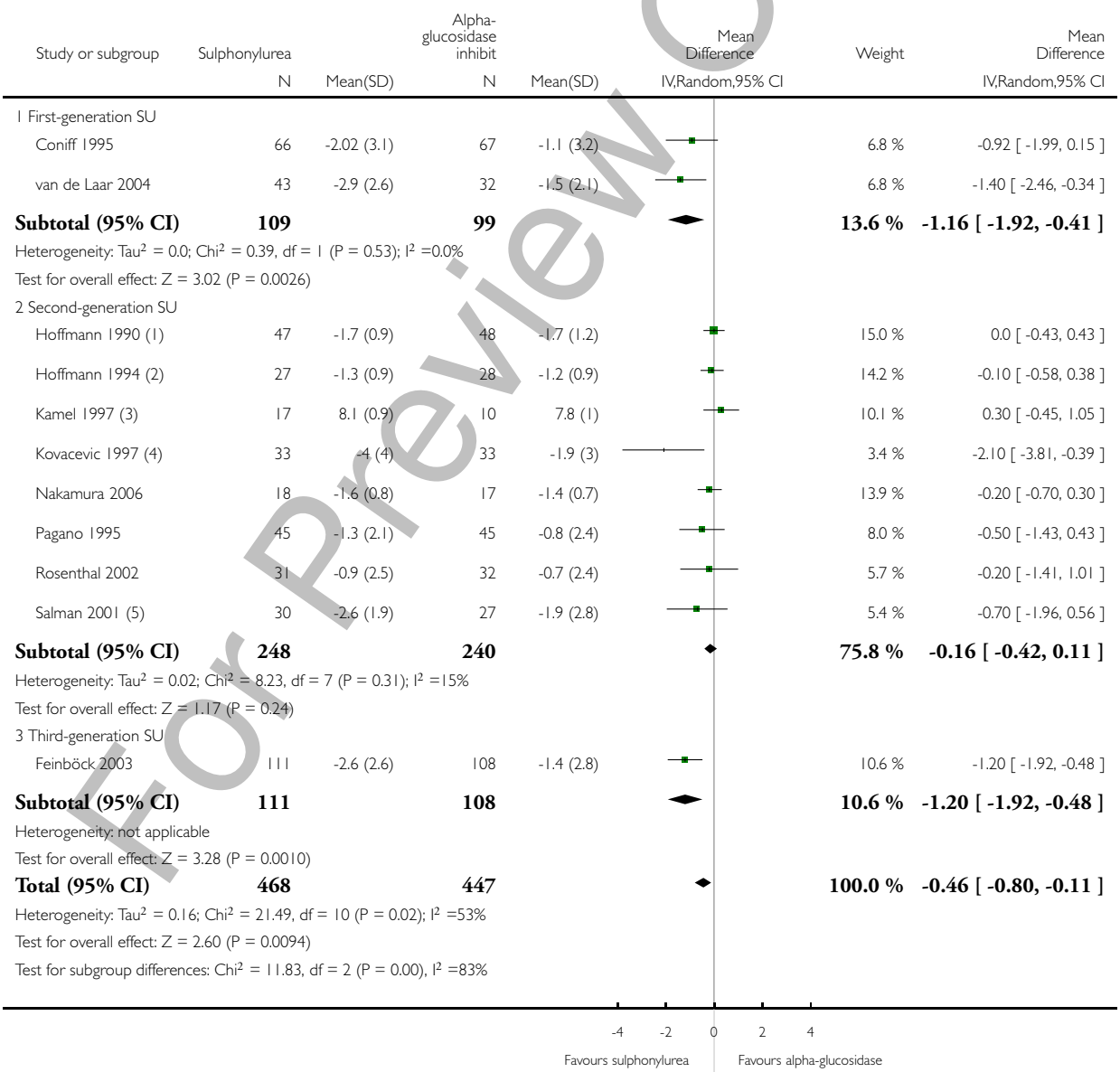
Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.15. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 15 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 15 Change in fasting blood glucose from baseline (mmol/L)



(1) Data from van de Laar

(2) Data from van de Laar

(3) Not described in abstract if the values are standard deviations or standard errors

(4) Data from van de Laar

(5) Data from van de Laar

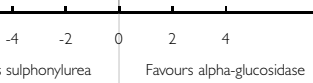
Analysis 5.16. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 16 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 16 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Alpha-glucosidase inhibit N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Coniff 1995 (1)	66	-0.9 (1.04)	67	-0.5 (1.05)		10.1 %	-0.40 [-0.76, -0.04]
van de Laar 2004	43	-1.8 (1.3)	32	-1.1 (1)		8.3 %	-0.70 [-1.22, -0.18]
Subtotal (95% CI)	**109**		**99**			**18.4 %**	**-0.50 [-0.79, -0.20]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.31 (P = 0.00094)							
2 Second-generation SU							
Hoffmann 1990 (2)	47	-1.9 (4)	48	-1.8 (4)		2.2 %	-0.10 [-1.71, 1.51]
Hoffmann 1994	27	-0.8 (0.4)	28	-1 (0.5)		11.2 %	0.20 [-0.04, 0.44]
Kamel 1997 (3)	17	7.3 (1.1)	10	7 (0.7)		6.8 %	0.30 [-0.38, 0.98]
Kanda 1998	9	9 (1.4)	10	7.5 (1.1)		3.7 %	1.50 [0.36, 2.64]
Kovacevic 1997	33	-1.6 (1.2)	33	-0.7 (0.9)		8.4 %	-0.90 [-1.41, -0.39]
Nakamura 2004	15	6.3 (1.1)	15	6.4 (1.2)		5.6 %	-0.10 [-0.92, 0.72]
Nakamura 2006	18	-1.6 (0.4)	17	-1.3 (0.3)		11.3 %	-0.30 [-0.53, -0.07]
Pagano 1995 (4)	45	-1.2 (1.3)	49	-0.8 (1.4)		8.1 %	-0.40 [-0.95, 0.15]
Rosenthal 2002	31	-0.2 (0.8)	32	-0.5 (0.4)		10.5 %	0.30 [-0.01, 0.61]



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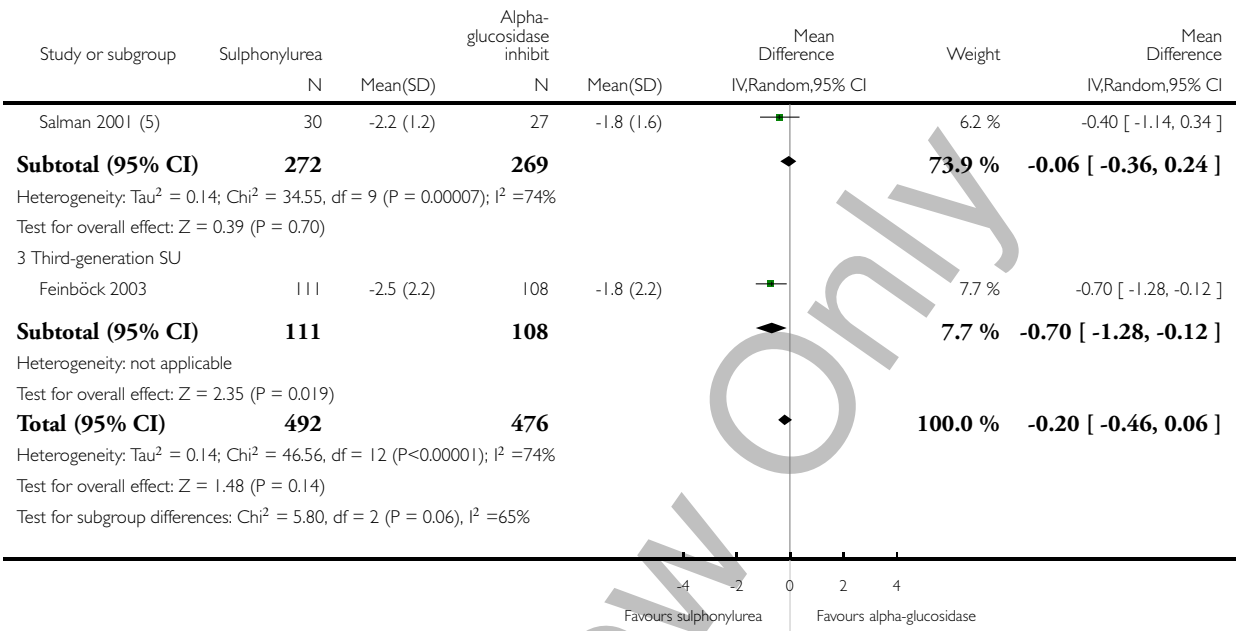
Study or subgroup	Sulphonylurea N	Mean(SD)	Alpha-glucosidase inhibit N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Salman 2001 (5)	30	-2.2 (1.2)	27	-1.8 (1.6)		6.2 %	-0.40 [-1.14, 0.34]
Subtotal (95% CI)	**272**		**269**			**73.9 %**	**-0.06 [-0.36, 0.24]**
Heterogeneity: Tau² = 0.14; Chi² = 34.55, df = 9 (P = 0.00007); I² =74%							
Test for overall effect: Z = 0.39 (P = 0.70)							
3 Third-generation SU							
Feinböck 2003	111	-2.5 (2.2)	108	-1.8 (2.2)		7.7 %	-0.70 [-1.28, -0.12]
Subtotal (95% CI)	**111**		**108**			**7.7 %**	**-0.70 [-1.28, -0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.35 (P = 0.019)							
Total (95% CI)	**492**		**476**			**100.0 %**	**-0.20 [-0.46, 0.06]**
Heterogeneity: Tau² = 0.14; Chi² = 46.56, df = 12 (P<0.00001); I² =74%							
Test for overall effect: Z = 1.48 (P = 0.14)							
Test for subgroup differences: Chi² = 5.80, df = 2 (P = 0.06), I² =65%							



(1) Values read from graph

(2) Data from van de Laar

(3) Not described in abstract if the values are standard deviations or standard errors

(4) Standard deviations calculated from standard errord

(5) Data from van de Laar

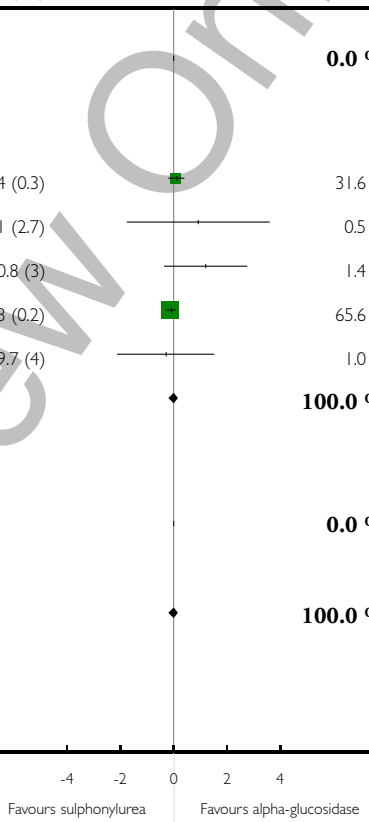
Analysis 5.17. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 17 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 17 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Alpha-glucosidase inhibit N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Hoffmann 1994 (1)	27	-0.3 (0.7)	28	-0.4 (0.3)		31.6 %	0.10 [-0.19, 0.39]
Kanda 1998	9	26 (3.2)	10	25.1 (2.7)		0.5 %	0.90 [-1.78, 3.58]
Kovacevic 1997 (2)	33	0.4 (3.4)	33	-0.8 (3)		1.4 %	1.20 [-0.35, 2.75]
Nakamura 2006	18	-0.4 (0.3)	17	-0.3 (0.2)		65.6 %	-0.10 [-0.27, 0.07]
Salman 2001	30	29.4 (2.8)	27	29.7 (4)		1.0 %	-0.30 [-2.11, 1.51]
Subtotal (95% CI)	**117**		**115**			**100.0 %**	**-0.02 [-0.20, 0.16]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.43, df = 4 (P = 0.35); I^2 =10%							
Test for overall effect: Z = 0.18 (P = 0.86)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**117**		**115**			**100.0 %**	**-0.02 [-0.20, 0.16]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.43, df = 4 (P = 0.35); I^2 =10%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Test for subgroup differences: Not applicable							



(1) Datafrom van de Laar

(2) Data from van de Laar

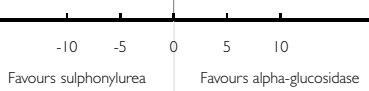
Analysis 5.18. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 18 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 18 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Alpha-glucosidase inhibit N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Coniff 1995 (1)	66	1.8 (2.5)	66	-1.4 (2.8)		20.4 %	3.20 [2.29, 4.11]
Subtotal (95% CI)	**66**		**66**			**20.4 %**	**3.20 [2.29, 4.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.93 (P < 0.00001)							
2 Second-generation SU							
Hoffmann 1990	47	71.8 (8.2)	48	72.3 (9)		9.6 %	-0.50 [-3.96, 2.96]
Nakamura 2006	18	-0.8 (0.4)	17	-0.6 (0.4)		22.0 %	-0.20 [-0.47, 0.07]
Pagano 1995	45	-1.3 (2.1)	45	-0.8 (2.4)		20.3 %	-0.50 [-1.43, 0.43]
Rosenthal 2002	31	83 (12.6)	32	82.2 (13.5)		4.0 %	0.80 [-5.65, 7.25]
Spengler 1992	29	0 (10)	26	-0.7 (11.8)		4.7 %	0.70 [-5.12, 6.52]
Subtotal (95% CI)	**170**		**168**			**60.5 %**	**-0.22 [-0.47, 0.03]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.59, df = 4 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 1.70 (P = 0.089)							
3 Third-generation SU							
Feinböck 2003	111	-0.4 (5.2)	108	-1.9 (3.9)		19.1 %	1.50 [0.28, 2.72]
Subtotal (95% CI)	**111**		**108**			**19.1 %**	**1.50 [0.28, 2.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.42 (P = 0.016)							
Total (95% CI)	**347**		**342**			**100.0 %**	**0.81 [-0.61, 2.23]**
Heterogeneity: Tau^2 = 2.36; Chi^2 = 56.81, df = 6 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 1.12 (P = 0.26)							
Test for subgroup differences: Chi^2 = 56.23, df = 2 (P = 0.00), I^2 =96%							



(1) Data read from graph

Analysis 5.19. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 19 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 19 Adverse events

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Coniff 1995	42/72	69/76		20.2 %	0.64 [0.52, 0.79]
van de Laar 2004	12/50	22/48		9.5 %	0.52 [0.29, 0.94]
Subtotal (95% CI)	**122**	**124**		**29.8 %**	**0.63 [0.52, 0.76]**
Total events: 54 (Sulphonylurea), 91 (Alpha-glucosidase inhibit)					
Heterogeneity: Tau² = 0.0; Chi² = 0.48, df = 1 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 4.66 (P < 0.00001)					
2 Second-generation SU					
Hoffmann 1990	3/47	14/48		3.3 %	0.22 [0.07, 0.71]
Kovacevic 1997	5/34	18/34		5.4 %	0.28 [0.12, 0.66]
Nakamura 2006	6/18	1/17		1.2 %	5.67 [0.76, 42.32]
Pagano 1995	10/47	10/49		6.4 %	1.04 [0.48, 2.27]
Rosenthal 2002	4/37	12/39		4.1 %	0.35 [0.12, 0.99]
Salman 2001 (1)	6/35	9/33		5.0 %	0.63 [0.25, 1.57]
Segal 1997	13/69	18/67		8.6 %	0.70 [0.37, 1.32]
Spengler 1992	23/36	23/36		15.6 %	1.00 [0.71, 1.42]
Subtotal (95% CI)	**323**	**323**		**49.7 %**	**0.64 [0.39, 1.03]**
Total events: 70 (Sulphonylurea), 105 (Alpha-glucosidase inhibit)					
Heterogeneity: Tau² = 0.28; Chi² = 19.70, df = 7 (P = 0.01); I² =64%					
Test for overall effect: Z = 1.83 (P = 0.067)					
3 Third-generation SU					
Feinböck 2003	58/111	88/108		20.5 %	0.64 [0.53, 0.78]
Subtotal (95% CI)	**111**	**108**		**20.5 %**	**0.64 [0.53, 0.78]**
Total events: 58 (Sulphonylurea), 88 (Alpha-glucosidase inhibit)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.37 (P = 0.000012)					
Total (95% CI)	**556**	**555**		**100.0 %**	**0.65 [0.51, 0.82]**
Total events: 182 (Sulphonylurea), 284 (Alpha-glucosidase inhibit)					
Heterogeneity: Tau² = 0.06; Chi² = 20.87, df = 10 (P = 0.02); I² =52%					
Test for overall effect: Z = 3.70 (P = 0.00022)					
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² =0.0%					

(1) Data from van de Laar

Analysis 5.20. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 20 Serious adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 20 Serious adverse events

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
van de Laar 2004	2/50	2/48		0.96 [0.14, 6.55]
Subtotal (95% CI)	**50**	**48**		**0.96 [0.14, 6.55]**
Total events: 2 (Sulphonylurea), 2 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.04 (P = 0.97)				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Pagano 1995	0/47	3/49		0.15 [0.01, 2.81]
Subtotal (95% CI)	**65**	**66**		**0.15 [0.01, 2.81]**
Total events: 0 (Sulphonylurea), 3 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.27 (P = 0.20)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**115**	**114**		**0.52 [0.09, 3.03]**
Total events: 2 (Sulphonylurea), 5 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.23; Chi^2 = 1.14, df = 1 (P = 0.29); I^2 =12%				
Test for overall effect: Z = 0.72 (P = 0.47)				
Test for subgroup differences: Chi^2 = 1.08, df = 1 (P = 0.30), I^2 =8%				

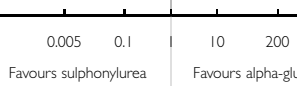
Analysis 5.21. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 21 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 21 Drop-outs due to adverse events

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Coniff 1995	3/72	7/76		0.45 [0.12, 1.68]
van de Laar 2004	3/50	15/48		0.19 [0.06, 0.62]
Subtotal (95% CI)	**122**	**124**		**0.28 [0.12, 0.67]**
Total events: 6 (Sulphonylurea), 22 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 0.91, df = 1 (P = 0.34); I² =0.0%				
Test for overall effect: Z = 2.84 (P = 0.0045)				
2 Second-generation SU				
Hoffmann 1994	0/27	0/28		0.0 [0.0, 0.0]
Johnston 1997	6/104	22/206		0.54 [0.23, 1.29]
Kovacevic 1997	0/34	0/34		0.0 [0.0, 0.0]
Nakamura 2004	0/15	0/15		0.0 [0.0, 0.0]
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Pagano 1995	0/47	1/49		0.35 [0.01, 8.32]
Salman 2001	0/35	3/33		0.13 [0.01, 2.52]
Segal 1997	2/69	3/67		0.65 [0.11, 3.75]
Spengler 1992	1/36	3/36		0.33 [0.04, 3.06]
Subtotal (95% CI)	**385**	**485**		**0.48 [0.24, 0.96]**
Total events: 9 (Sulphonylurea), 32 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 1.06, df = 4 (P = 0.90); I² =0.0%				
Test for overall effect: Z = 2.07 (P = 0.039)				
3 Third-generation SU				
Feinböck 2003	1/111	5/108		0.19 [0.02, 1.64]
Subtotal (95% CI)	**111**	**108**		**0.19 [0.02, 1.64]**
Total events: 1 (Sulphonylurea), 5 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.51 (P = 0.13)				
Total (95% CI)	**618**	**717**		**0.37 [0.22, 0.63]**



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Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 16 (Sulphonylurea), 59 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 3.24, df = 7 (P = 0.86); I² =0.0%				
Test for overall effect: Z = 3.65 (P = 0.00026)				
Test for subgroup differences: Chi² = 1.26, df = 2 (P = 0.53), I² =0.0%				

Analysis 5.22. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 22 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 22 Mild hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
van de Laar 2004	1/50	0/48		2.88 [0.12, 69.07]
Subtotal (95% CI)	**50**	**48**		**2.88 [0.12, 69.07]**
Total events: 1 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.65 (P = 0.51)				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Rosenthal 2002	0/37	0/39		0.0 [0.0, 0.0]
Segal 1997	6/69	0/67		12.63 [0.73, 219.86]
Spengler 1992	0/36	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**160**	**159**		**12.63 [0.73, 219.86]**

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Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 6 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.74 (P = 0.082)				
3 Third-generation SU				
Feinböck 2003	20/111	2/108		9.73 [2.33, 40.63]
Subtotal (95% CI)	**111**	**108**		**9.73 [2.33, 40.63]**
Total events: 20 (Sulphonylurea), 2 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 3.12 (P = 0.0018)				
Total (95% CI)	**321**	**315**		**8.59 [2.62, 28.12]**
Total events: 27 (Sulphonylurea), 2 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 0.56, df = 2 (P = 0.76); I² =0.0%				
Test for overall effect: Z = 3.55 (P = 0.00038)				
Test for subgroup differences: Chi² = 0.55, df = 2 (P = 0.76), I² =0.0%				

Analysis 5.23. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 23 Moderate hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 23 Moderate hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Rosenthal 2002	0/37	0/39		0.0 [0.0, 0.0]
Spengler 1992	0/36	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**91**	**92**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**91**	**92**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau² = ; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.0, df = 1 (P = 0.0), I² =0.0%				

Analysis 5.24. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 24 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 24 Severe hypoglycaemia

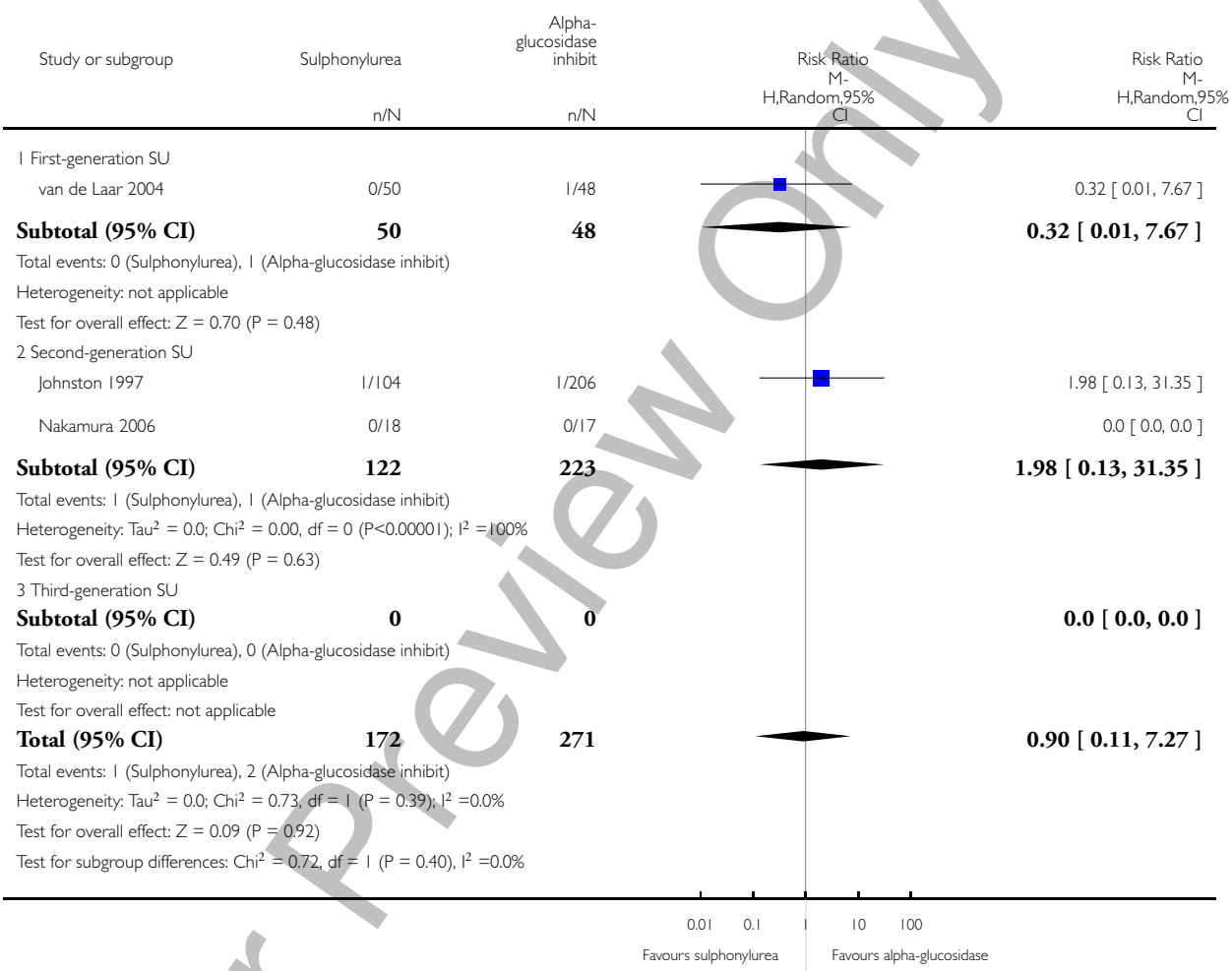
Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
van de Laar 2004	0/50	0/48		0.0 [0.0, 0.0]
Subtotal (95% CI)	**50**	**48**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Second-generation SU				
Nakamura 2006	0/18	0/17		0.0 [0.0, 0.0]
Rosenthal 2002	0/37	0/39		0.0 [0.0, 0.0]
Spengler 1992	0/36	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**91**	**92**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Feinböck 2003	0/111	0/108		0.0 [0.0, 0.0]
Subtotal (95% CI)	**111**	**108**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**252**	**248**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 5.25. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 25 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 25 Cancer



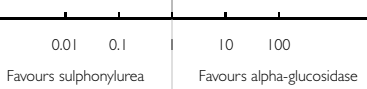
Analysis 5.26. Comparison 5 Sulphonylureas versus alpha-glucosidase inhibitors, Outcome 26 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 5 Sulphonylureas versus alpha-glucosidase inhibitors

Outcome: 26 Intervention failure

Study or subgroup	Sulphonylurea n/N	Alpha-glucosidase inhibit n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
van de Laar 2004	0/50	1/48		0.32 [0.01, 7.67]
Subtotal (95% CI)	**50**	**48**		**0.32 [0.01, 7.67]**
Total events: 0 (Sulphonylurea), 1 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.70 (P = 0.48)				
2 Second-generation SU				
Johnston 1997	2/104	17/206		0.23 [0.05, 0.99]
Salman 2001	0/35	0/33		0.0 [0.0, 0.0]
Segal 1997	0/69	1/67		0.32 [0.01, 7.81]
Subtotal (95% CI)	**208**	**306**		**0.25 [0.07, 0.92]**
Total events: 2 (Sulphonylurea), 18 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.85); I^2 =0.0%				
Test for overall effect: Z = 2.08 (P = 0.037)				
3 Third-generation SU				
Feinböck 2003	10/111	29/108		0.34 [0.17, 0.65]
Subtotal (95% CI)	**111**	**108**		**0.34 [0.17, 0.65]**
Total events: 10 (Sulphonylurea), 29 (Alpha-glucosidase inhibit)				
Heterogeneity: not applicable				
Test for overall effect: Z = 3.20 (P = 0.0014)				
Total (95% CI)	**369**	**462**		**0.32 [0.18, 0.57]**
Total events: 12 (Sulphonylurea), 48 (Alpha-glucosidase inhibit)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.21, df = 3 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 3.86 (P = 0.00011)				
Test for subgroup differences: Chi^2 = 0.17, df = 2 (P = 0.92), I^2 =0.0%				

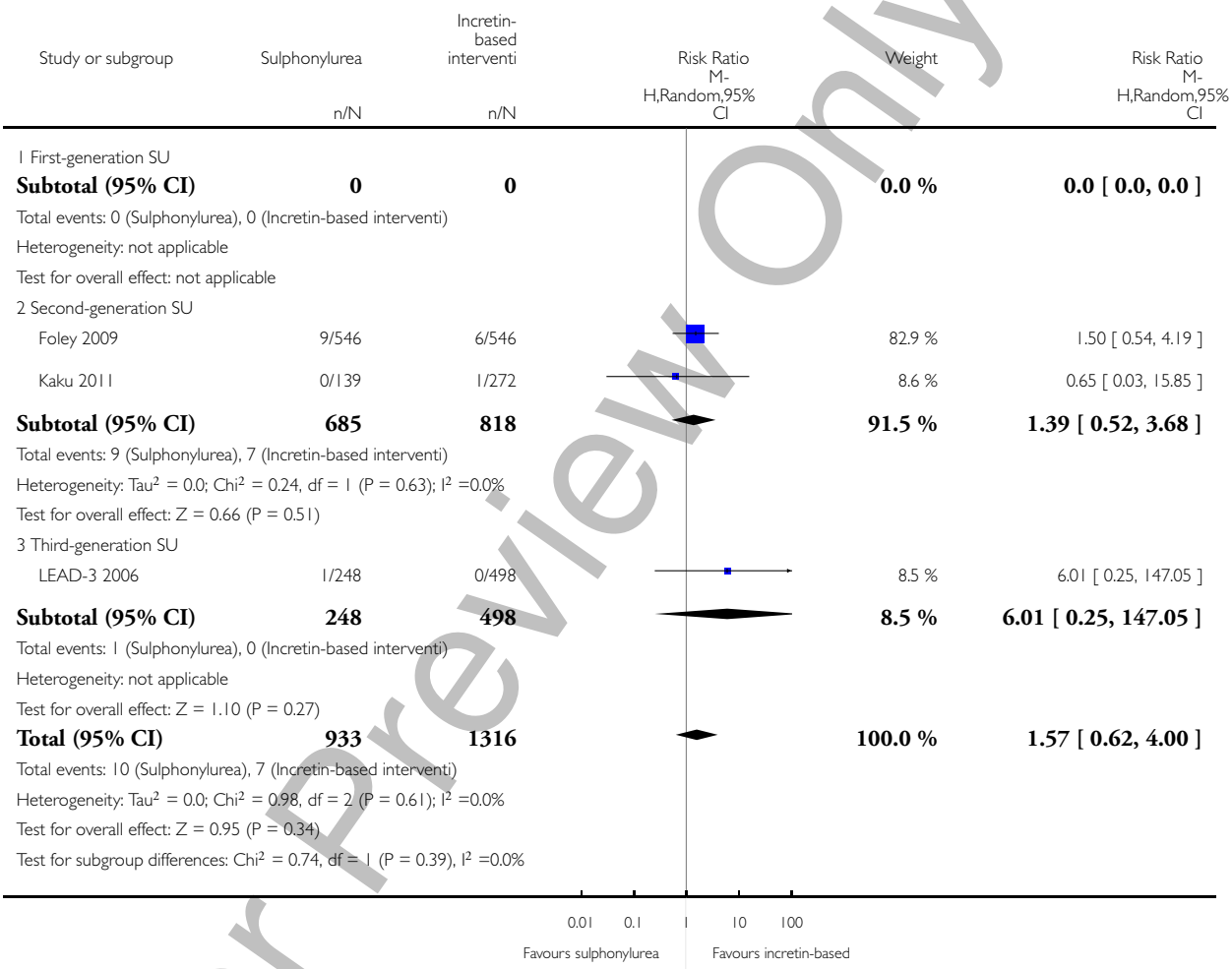


Analysis 6.1. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 1 All-cause mortality



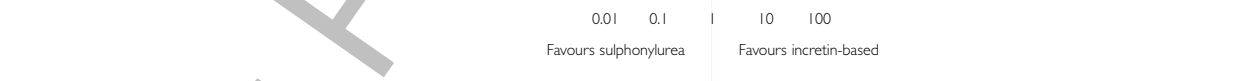
Analysis 6.2. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Foley 2009	9/546	23/546		100.0 %	0.39 [0.18, 0.84]
Subtotal (95% CI)	**546**	**546**		**100.0 %**	**0.39 [0.18, 0.84]**
Total events: 9 (Sulphonylurea), 23 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.42 (P = 0.016)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**546**	**546**		**100.0 %**	**0.39 [0.18, 0.84]**
Total events: 9 (Sulphonylurea), 23 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.42 (P = 0.016)					
Test for subgroup differences: Not applicable					



Analysis 6.3. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 3 All-cause mortality; worst-best case scenario

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Foley 2009	22/546	6/546		100.0 %	3.67 [1.50, 8.97]
Subtotal (95% CI)	**546**	**546**		**100.0 %**	**3.67 [1.50, 8.97]**
Total events: 22 (Sulphonylurea), 6 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.85 (P = 0.0044)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**546**	**546**		**100.0 %**	**3.67 [1.50, 8.97]**
Total events: 22 (Sulphonylurea), 6 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.85 (P = 0.0044)					
Test for subgroup differences: Not applicable					

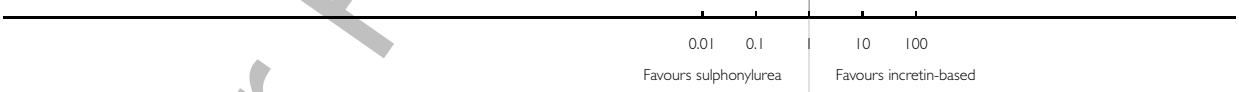
Analysis 6.4. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 4 Cardiovascular mortality

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
LEAD-3 2006	1/248	0/498		6.01 [0.25, 147.05]
Subtotal (95% CI)	**248**	**498**		**6.01 [0.25, 147.05]**
Total events: 1 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.10 (P = 0.27)				
Total (95% CI)	**387**	**770**		**6.01 [0.25, 147.05]**
Total events: 1 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.10 (P = 0.27)				
Test for subgroup differences: Not applicable				

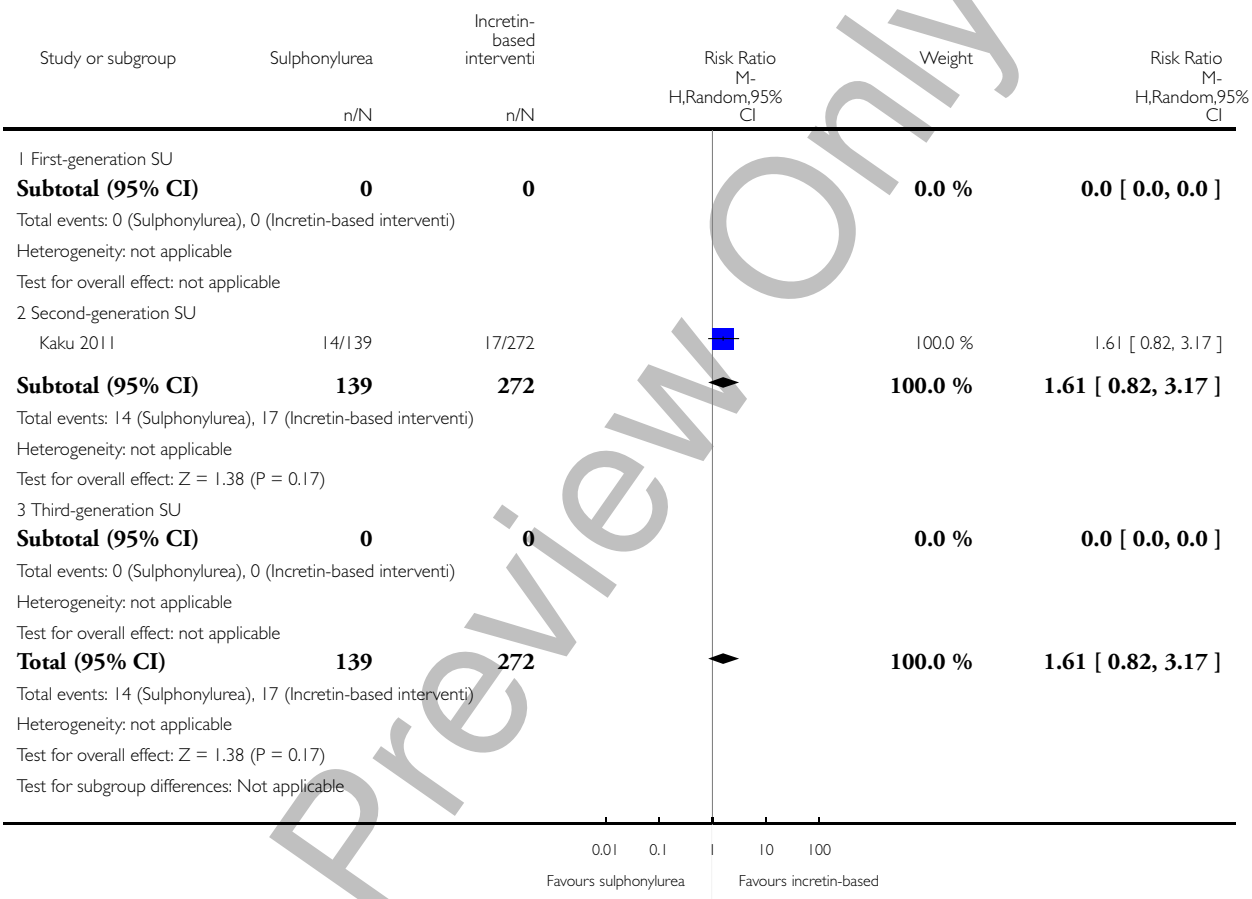


Analysis 6.5. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 5 Non-fatal macrovascular outcomes

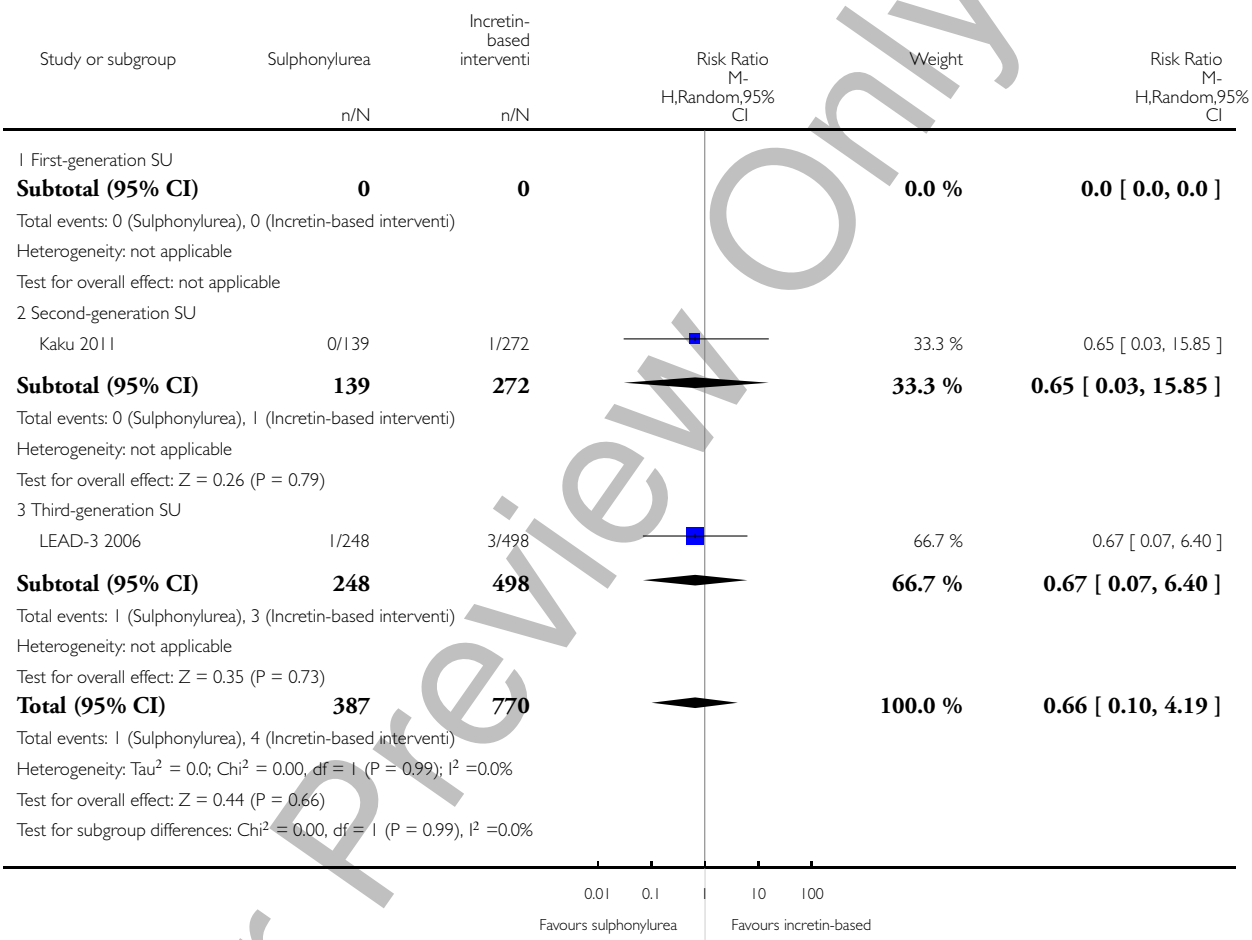


Analysis 6.6. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 6 Non-fatal myocardial infarction



Analysis 6.7. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 7 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 7 Non-fatal stroke

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Kaku 2011	2/139	1/272		100.0 %	3.91 [0.36, 42.79]
Subtotal (95% CI)	**139**	**272**		**100.0 %**	**3.91 [0.36, 42.79]**
Total events: 2 (Sulphonylurea), 1 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**139**	**272**		**100.0 %**	**3.91 [0.36, 42.79]**
Total events: 2 (Sulphonylurea), 1 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
Test for subgroup differences: Not applicable					

Analysis 6.8. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 8 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 8 Amputation of lower extremity

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 6.9. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 9 Cardial revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 9 Cardial revascularisation

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%				

Analysis 6.10. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 10 Peripheral revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 10 Peripheral revascularisation

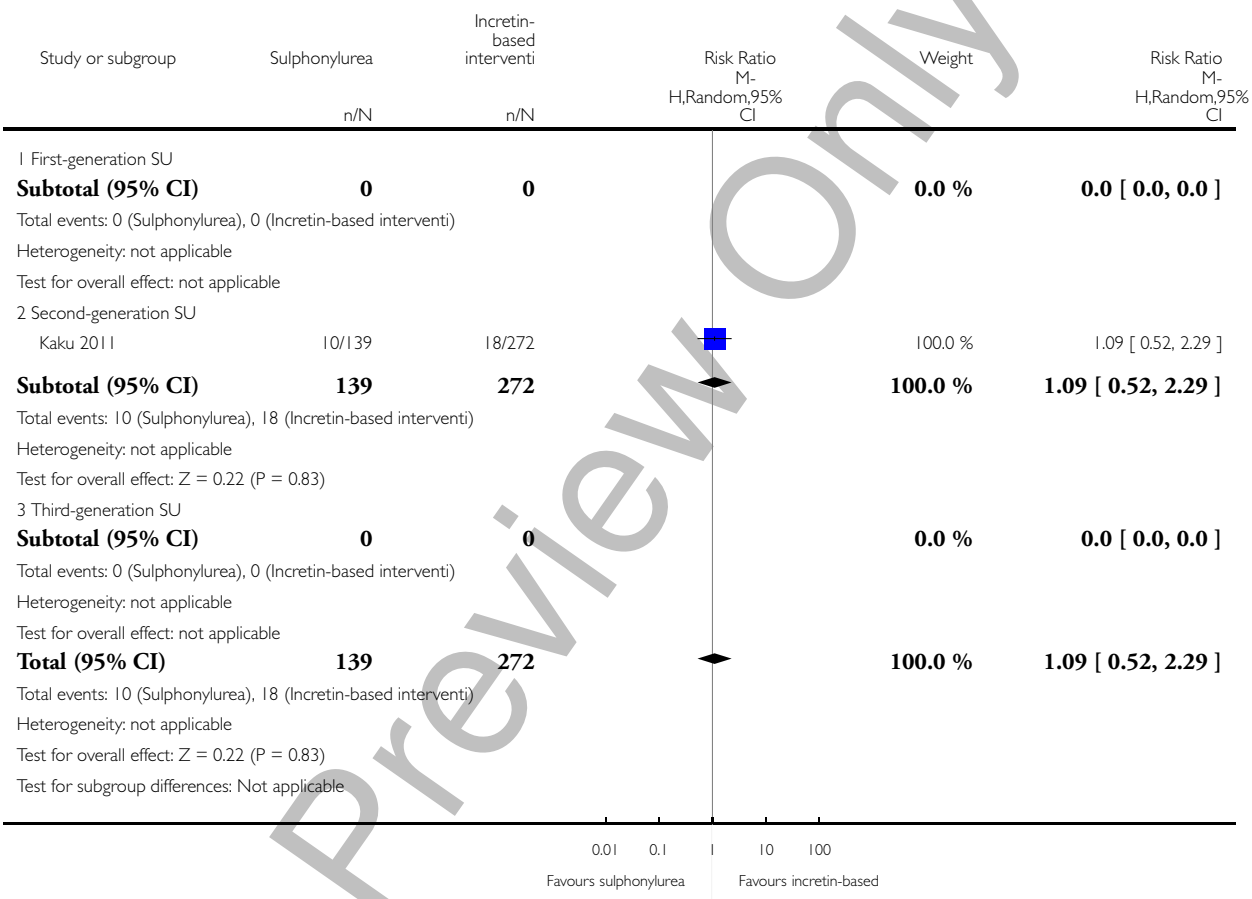
Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 6.11. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 11 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 11 Microvascular outcomes



Analysis 6.12. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 12 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 12 Nephropathy

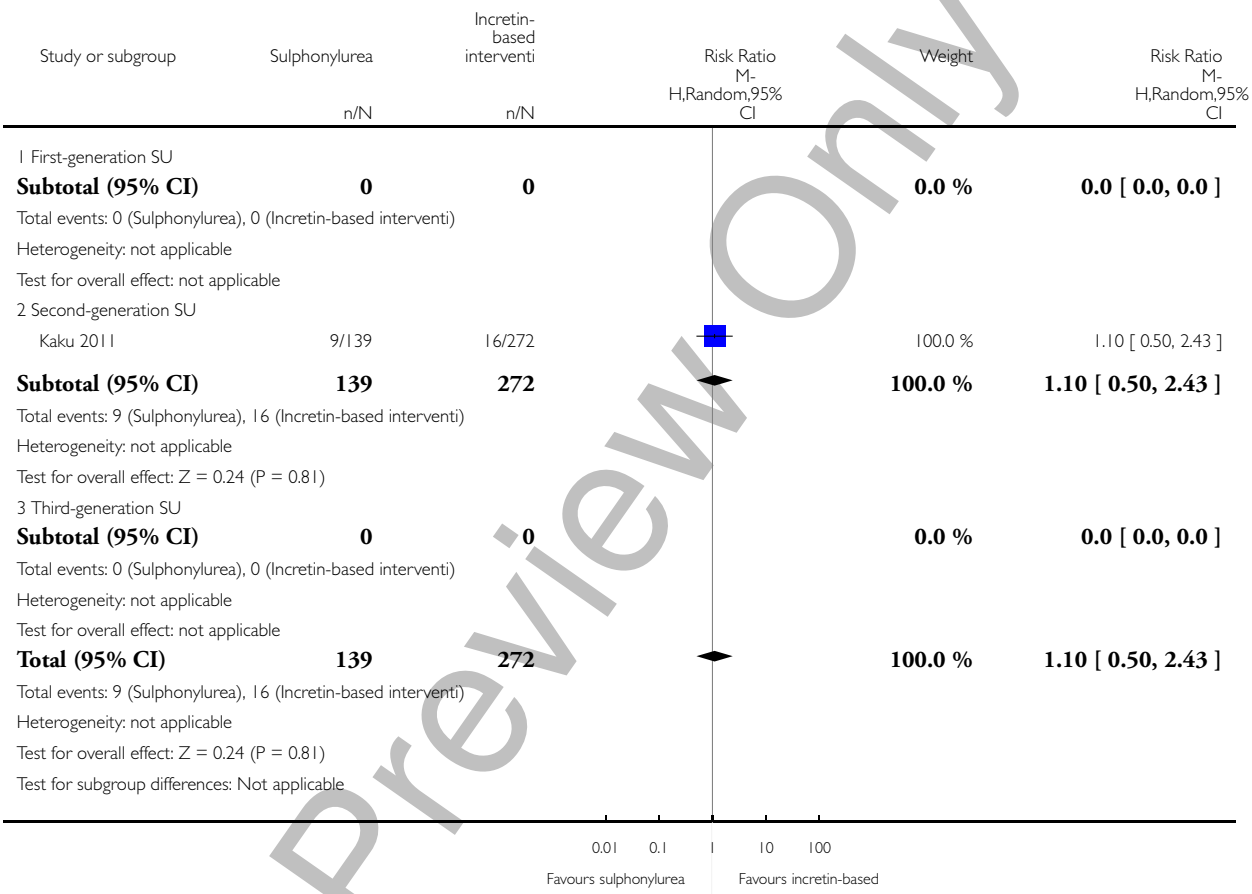
Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Kaku 2011	1/139	2/272		100.0 %	0.98 [0.09, 10.70]
Subtotal (95% CI)	**139**	**272**		**100.0 %**	**0.98 [0.09, 10.70]**
Total events: 1 (Sulphonylurea), 2 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**139**	**272**		**100.0 %**	**0.98 [0.09, 10.70]**
Total events: 1 (Sulphonylurea), 2 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
Test for subgroup differences: Not applicable					

Analysis 6.13. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 13 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 13 Retinopathy



Analysis 6.14. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 14 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 14 Retinal photocoagulation

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**139**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 6.15. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 15 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 15 Change in fasting blood glucose from baseline (mmol/L)

Study or subgroup	Sulphonylurea N	Mean(SD)	Incretin-based interventi N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Foley 2009 (1)	402	-0.7 (4)	409	-0.2 (4)		32.5 %	-0.50 [-1.05, 0.05]
Kaku 2011	130	-2.5 (2.4)	261	-3.2 (2.4)		33.3 %	0.70 [0.20, 1.20]
Subtotal (95% CI)	**532**		**670**			**65.8 %**	**0.11 [-1.07, 1.28]**
Heterogeneity: $Tau^2 = 0.65$; $Chi^2 = 9.91$, df = 1 (P = 0.002); $I^2 = 90\%$							
Test for overall effect: Z = 0.18 (P = 0.86)							
3 Third-generation SU							
LEAD-3 2006	248	-0.3 (3)	498	-1.1 (3)		34.2 %	0.80 [0.34, 1.26]
Subtotal (95% CI)	**248**		**498**			**34.2 %**	**0.80 [0.34, 1.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.43 (P = 0.00060)							
Total (95% CI)	**780**		**1168**			**100.0 %**	**0.34 [-0.44, 1.13]**
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 14.56$, df = 2 (P = 0.00069); $I^2 = 86\%$							
Test for overall effect: Z = 0.86 (P = 0.39)							
Test for subgroup differences: $Chi^2 = 1.17$, df = 1 (P = 0.28), $I^2 = 14\%$							

(1) Only the per-protocol population included in the analysis. Unclear how many it exactly is. Not stated in publication if it is SE or SD reported.

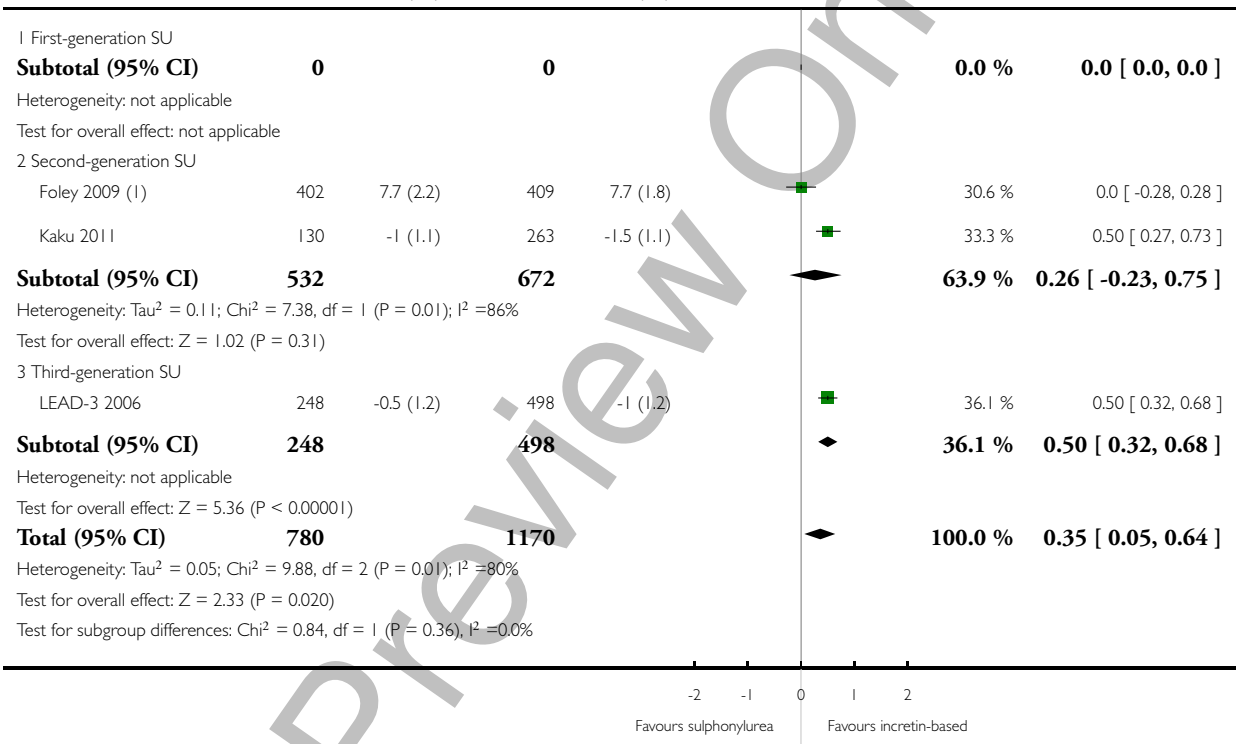
Analysis 6.16. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 16 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 16 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Incretin-based interventi N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Foley 2009 (1)	402	7.7 (2.2)	409	7.7 (1.8)		30.6 %	0.0 [-0.28, 0.28]
Kaku 2011	130	-1 (1.1)	263	-1.5 (1.1)		33.3 %	0.50 [0.27, 0.73]
Subtotal (95% CI)	**532**		**672**			**63.9 %**	**0.26 [-0.23, 0.75]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 7.38$, df = 1 (P = 0.01); $I^2 = 86\%$							
Test for overall effect: Z = 1.02 (P = 0.31)							
3 Third-generation SU							
LEAD-3 2006	248	-0.5 (1.2)	498	-1 (1.2)		36.1 %	0.50 [0.32, 0.68]
Subtotal (95% CI)	**248**		**498**			**36.1 %**	**0.50 [0.32, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.36 (P < 0.00001)							
Total (95% CI)	**780**		**1170**			**100.0 %**	**0.35 [0.05, 0.64]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.88$, df = 2 (P = 0.01); $I^2 = 80\%$							
Test for overall effect: Z = 2.33 (P = 0.020)							
Test for subgroup differences: $Chi^2 = 0.84$, df = 1 (P = 0.36), $I^2 = 0.0\%$							



(1) Only the per-protocol population included in the analysis. Unclear how many it exactly is. SE read from graph and converted to SD.

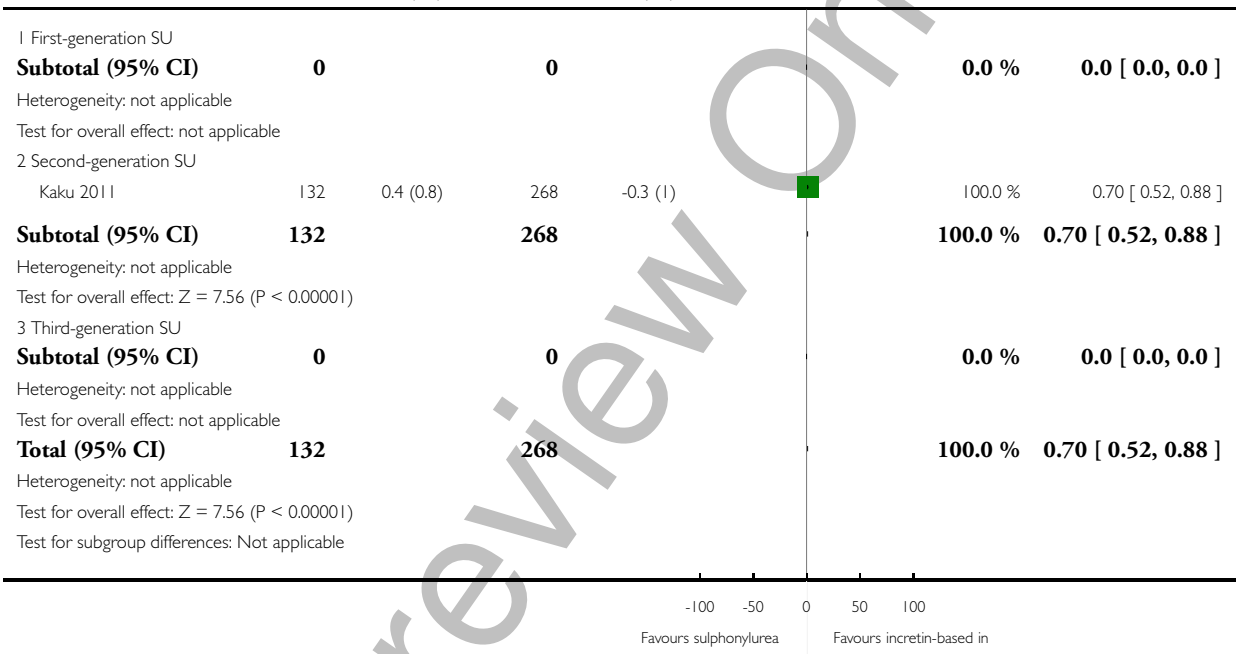
Analysis 6.17. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 17 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 17 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Incretin-based interventi N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Kaku 2011	132	0.4 (0.8)	268	-0.3 (1)		100.0 %	0.70 [0.52, 0.88]
Subtotal (95% CI)	**132**		**268**			**100.0 %**	**0.70 [0.52, 0.88]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.56 (P < 0.00001)							
3 Third-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**132**		**268**			**100.0 %**	**0.70 [0.52, 0.88]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.56 (P < 0.00001)							
Test for subgroup differences: Not applicable							



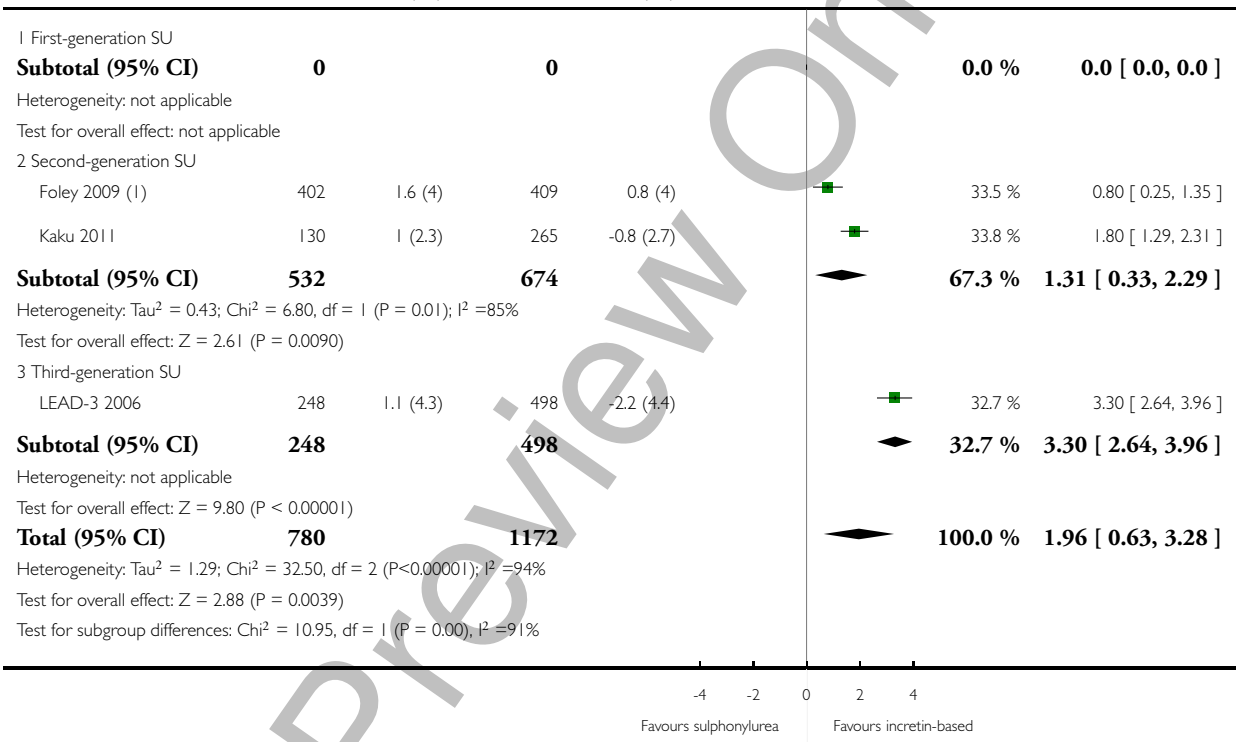
Analysis 6.18. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 18 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 18 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Incretin-based interventi N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Foley 2009 (1)	402	1.6 (4)	409	0.8 (4)		33.5 %	0.80 [0.25, 1.35]
Kaku 2011	130	1 (2.3)	265	-0.8 (2.7)		33.8 %	1.80 [1.29, 2.31]
Subtotal (95% CI)	**532**		**674**			**67.3 %**	**1.31 [0.33, 2.29]**
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 6.80$, df = 1 (P = 0.01); $I^2 = 85\%$							
Test for overall effect: Z = 2.61 (P = 0.0090)							
3 Third-generation SU							
LEAD-3 2006	248	1.1 (4.3)	498	-2.2 (4.4)		32.7 %	3.30 [2.64, 3.96]
Subtotal (95% CI)	**248**		**498**			**32.7 %**	**3.30 [2.64, 3.96]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.80 (P < 0.00001)							
Total (95% CI)	**780**		**1172**			**100.0 %**	**1.96 [0.63, 3.28]**
Heterogeneity: $Tau^2 = 1.29$; $Chi^2 = 32.50$, df = 2 (P<0.00001); $I^2 = 94\%$							
Test for overall effect: Z = 2.88 (P = 0.0039)							
Test for subgroup differences: $Chi^2 = 10.95$, df = 1 (P = 0.00), $I^2 = 91\%$							



(1) Only the per-protocol population included in the analysis. Unclear how many it exactly is. Not stated in publication if it is SE or SD reported.

Analysis 6.19. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 19 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 19 Adverse events

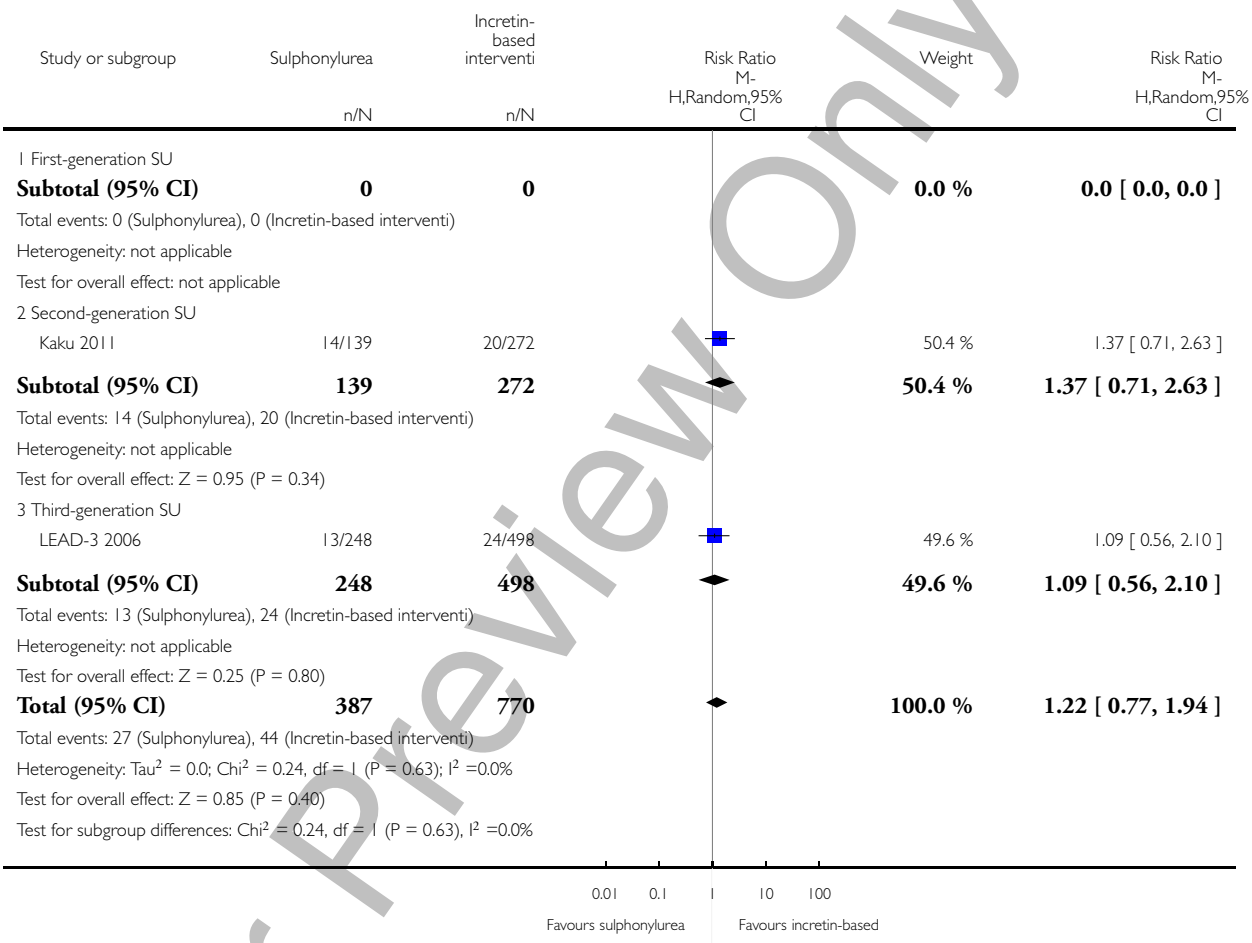
Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Kaku 2011	121/139	245/272		52.6 %	0.97 [0.90, 1.04]
Subtotal (95% CI)	**139**	**272**		**52.6 %**	**0.97 [0.90, 1.04]**
Total events: 121 (Sulphonylurea), 245 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					
3 Third-generation SU					
LEAD-3 2006	148/248	364/498		47.4 %	0.82 [0.73, 0.92]
Subtotal (95% CI)	**248**	**498**		**47.4 %**	**0.82 [0.73, 0.92]**
Total events: 148 (Sulphonylurea), 364 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.45 (P = 0.00057)					
Total (95% CI)	**387**	**770**		**100.0 %**	**0.89 [0.74, 1.08]**
Total events: 269 (Sulphonylurea), 609 (Incretin-based interventi)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.83, df = 1 (P = 0.01); I^2 =87%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Chi^2 = 5.76, df = 1 (P = 0.02), I^2 =83%					

Analysis 6.20. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 20 Serious adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 20 Serious adverse events



Analysis 6.21. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 21 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 21 Drop-outs due to adverse events

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Foley 2009	35/546	32/546		49.7 %	1.09 [0.69, 1.74]
Kaku 2011	8/139	20/272		17.0 %	0.78 [0.35, 1.73]
Subtotal (95% CI)	**685**	**818**		**66.7 %**	**1.00 [0.67, 1.50]**
Total events: 43 (Sulphonylurea), 52 (Incretin-based interventi)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 1 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.02 (P = 0.98)					
3 Third-generation SU					
LEAD-3 2006	15/248	43/498		33.3 %	0.70 [0.40, 1.24]
Subtotal (95% CI)	**248**	**498**		**33.3 %**	**0.70 [0.40, 1.24]**
Total events: 15 (Sulphonylurea), 43 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Total (95% CI)	**933**	**1316**		**100.0 %**	**0.89 [0.64, 1.24]**
Total events: 58 (Sulphonylurea), 95 (Incretin-based interventi)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.54$, df = 2 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: $Chi^2 = 1.03$, df = 1 (P = 0.31), $I^2 = 3\%$					

Analysis 6.22. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 22 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 22 Mild hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
Foley 2009	14/546	4/546		9.3 %	3.50 [1.16, 10.57]
Kaku 2011	55/139	66/272		47.8 %	1.63 [1.22, 2.19]
Subtotal (95% CI)	**685**	**818**		**57.1 %**	**1.99 [1.02, 3.87]**
Total events: 69 (Sulphonylurea), 70 (Incretin-based interventi)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 1.79$, df = 1 (P = 0.18); $I^2 = 44\%$					
Test for overall effect: Z = 2.01 (P = 0.044)					
3 Third-generation SU					
LEAD-3 2006	60/248	50/498		42.9 %	2.41 [1.71, 3.40]
Subtotal (95% CI)	**248**	**498**		**42.9 %**	**2.41 [1.71, 3.40]**
Total events: 60 (Sulphonylurea), 50 (Incretin-based interventi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.03 (P < 0.00001)					
Total (95% CI)	**933**	**1316**		**100.0 %**	**2.07 [1.44, 2.97]**
Total events: 129 (Sulphonylurea), 120 (Incretin-based interventi)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.05$, df = 2 (P = 0.13); $I^2 = 51\%$					
Test for overall effect: Z = 3.95 (P = 0.000079)					
Test for subgroup differences: $Chi^2 = 0.26$, df = 1 (P = 0.61), $I^2 = 0.0\%$					

Analysis 6.23. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 23 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 23 Severe hypoglycaemia

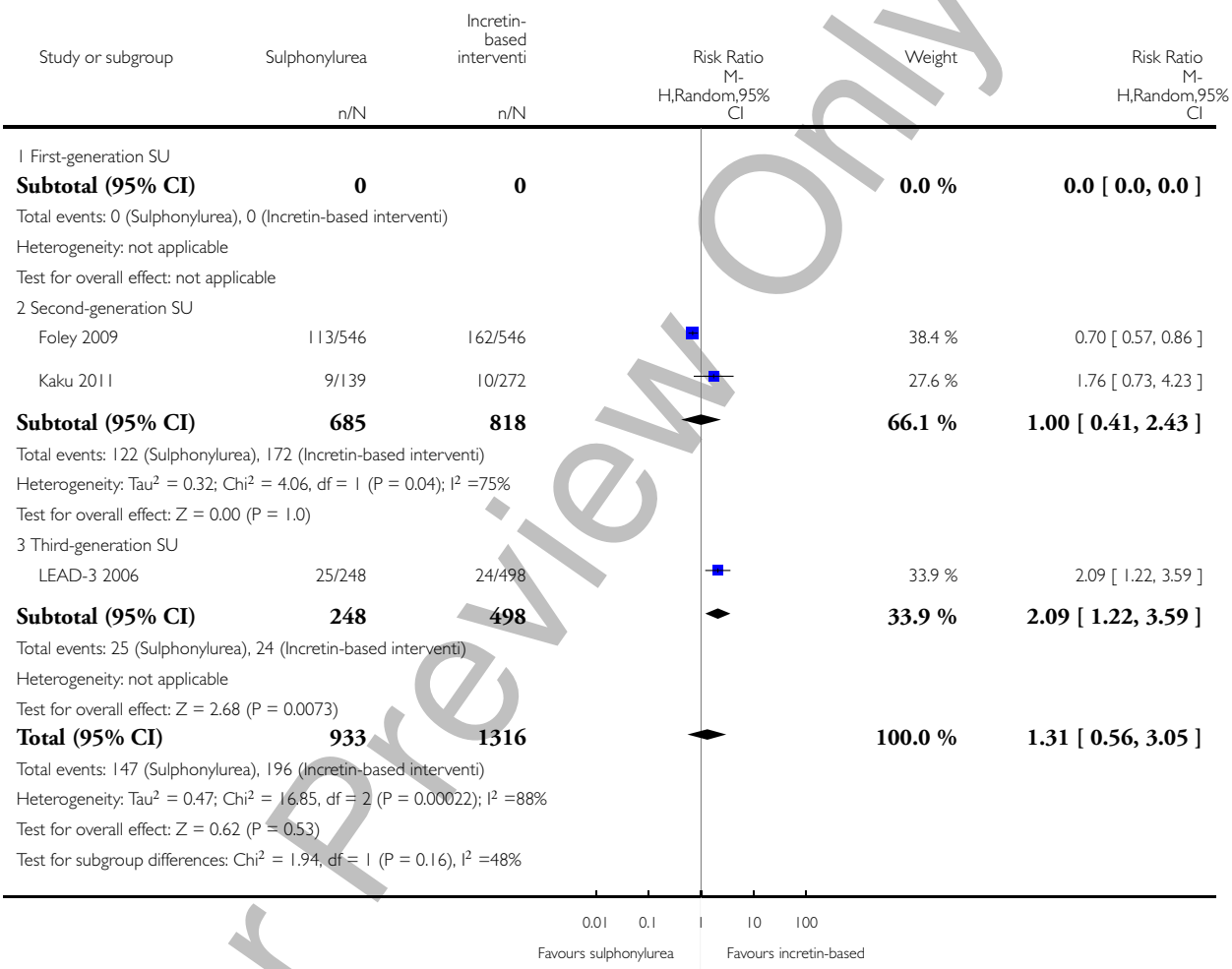
Study or subgroup	Sulphonylurea n/N	Incretin-based interventi n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Foley 2009	0/546	0/546		0.0 [0.0, 0.0]
Kaku 2011	0/139	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**685**	**818**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$				
Test for overall effect: $Z = 0.0$ ($P < 0.00001$)				
3 Third-generation SU				
LEAD-3 2006	0/248	0/498		0.0 [0.0, 0.0]
Subtotal (95% CI)	**248**	**498**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: not applicable				
Test for overall effect: $Z = 0.0$ ($P < 0.00001$)				
Total (95% CI)	**933**	**1316**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Incretin-based interventi)				
Heterogeneity: $Tau^2 =$; $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$				
Test for overall effect: $Z = 0.0$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 0.0$, df = -1 ($P = 0.0$), $I^2 = 0.0\%$				

Analysis 6.24. Comparison 6 Sulphonylureas versus incretin-based intervention, Outcome 24 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 6 Sulphonylureas versus incretin-based intervention

Outcome: 24 Intervention failure



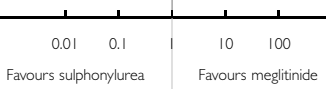
Analysis 7.1. Comparison 7 Sulphonylureas versus meglitinide, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 1 All-cause mortality

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
AGEE/DCD/046/UK	2/86	2/178		2.07 [0.30, 14.45]
AGEE/DCD/047/B/F/I	1/99	1/206		2.08 [0.13, 32.92]
Esposito 2004	0/87	0/88		0.0 [0.0, 0.0]
Madsbad 2001	1/81	0/175		6.44 [0.27, 156.37]
Marbury 1999	1/193	3/383		0.66 [0.07, 6.32]
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Wolffenbuttel 1999	0/140	2/288		0.41 [0.02, 8.48]
Subtotal (95% CI)	**704**	**1334**		**1.44 [0.47, 4.42]**
Total events: 5 (Sulphonylurea), 8 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.18$, df = 4 (P = 0.70); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.64 (P = 0.52)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**704**	**1334**		**1.44 [0.47, 4.42]**
Total events: 5 (Sulphonylurea), 8 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.18$, df = 4 (P = 0.70); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.64 (P = 0.52)				
Test for subgroup differences: Not applicable				



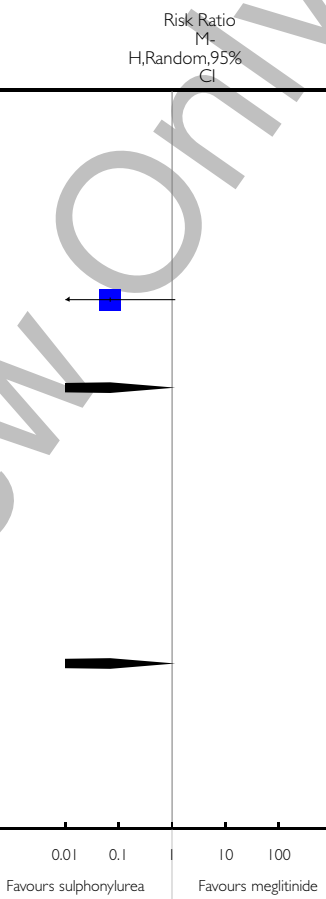
Analysis 7.2. Comparison 7 Sulphonylureas versus meglitinide, Outcome 2 All-cause mortality; best-worst case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 2 All-cause mortality; best-worst case scenario

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Esposito 2004	0/87	7/88		0.07 [0.00, 1.16]
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**105**	**104**		**0.07 [0.00, 1.16]**
Total events: 0 (Sulphonylurea), 7 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.86 (P = 0.063)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**105**	**104**		**0.07 [0.00, 1.16]**
Total events: 0 (Sulphonylurea), 7 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.86 (P = 0.063)				
Test for subgroup differences: Not applicable				

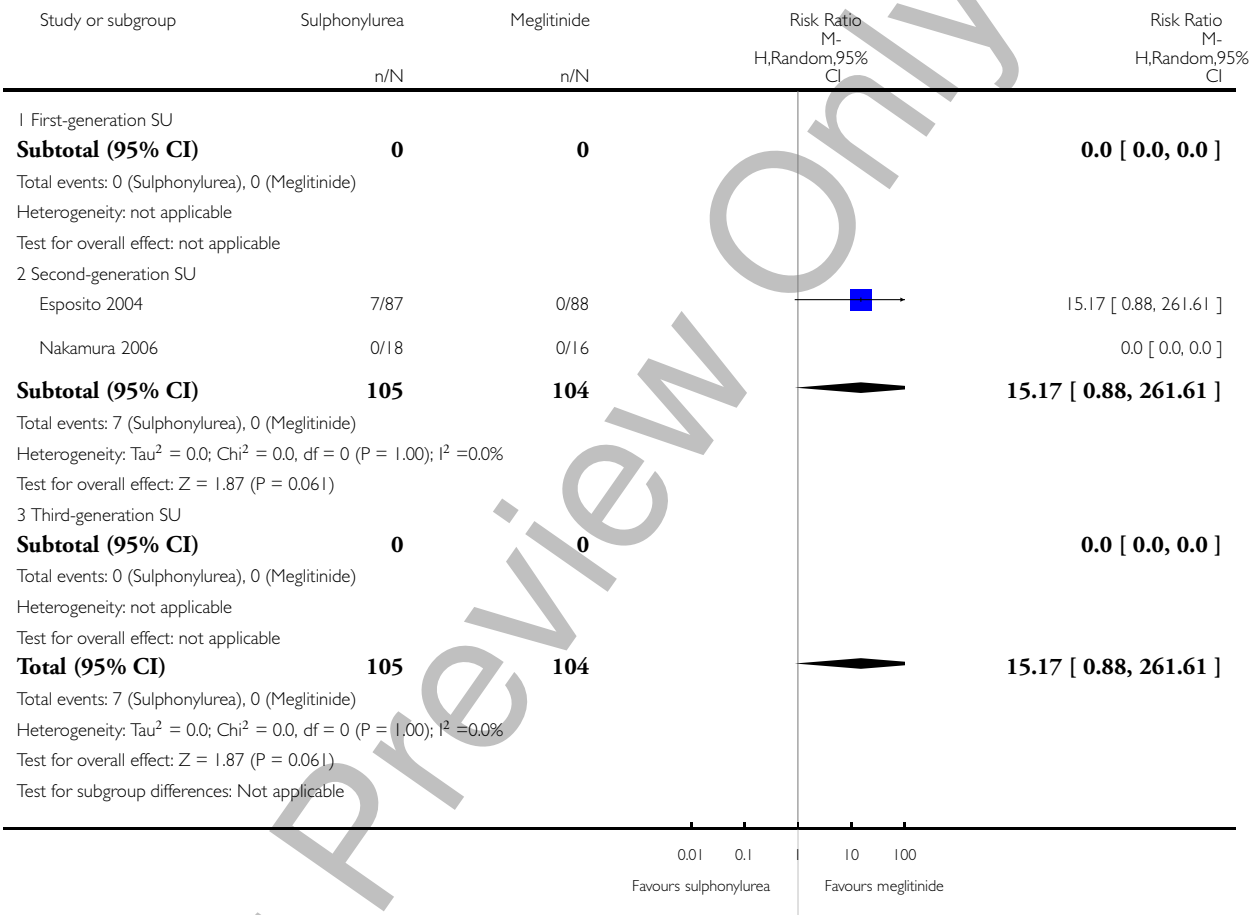


Analysis 7.3. Comparison 7 Sulphonylureas versus meglitinide, Outcome 3 All-cause mortality; worst-best case scenario.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 3 All-cause mortality; worst-best case scenario

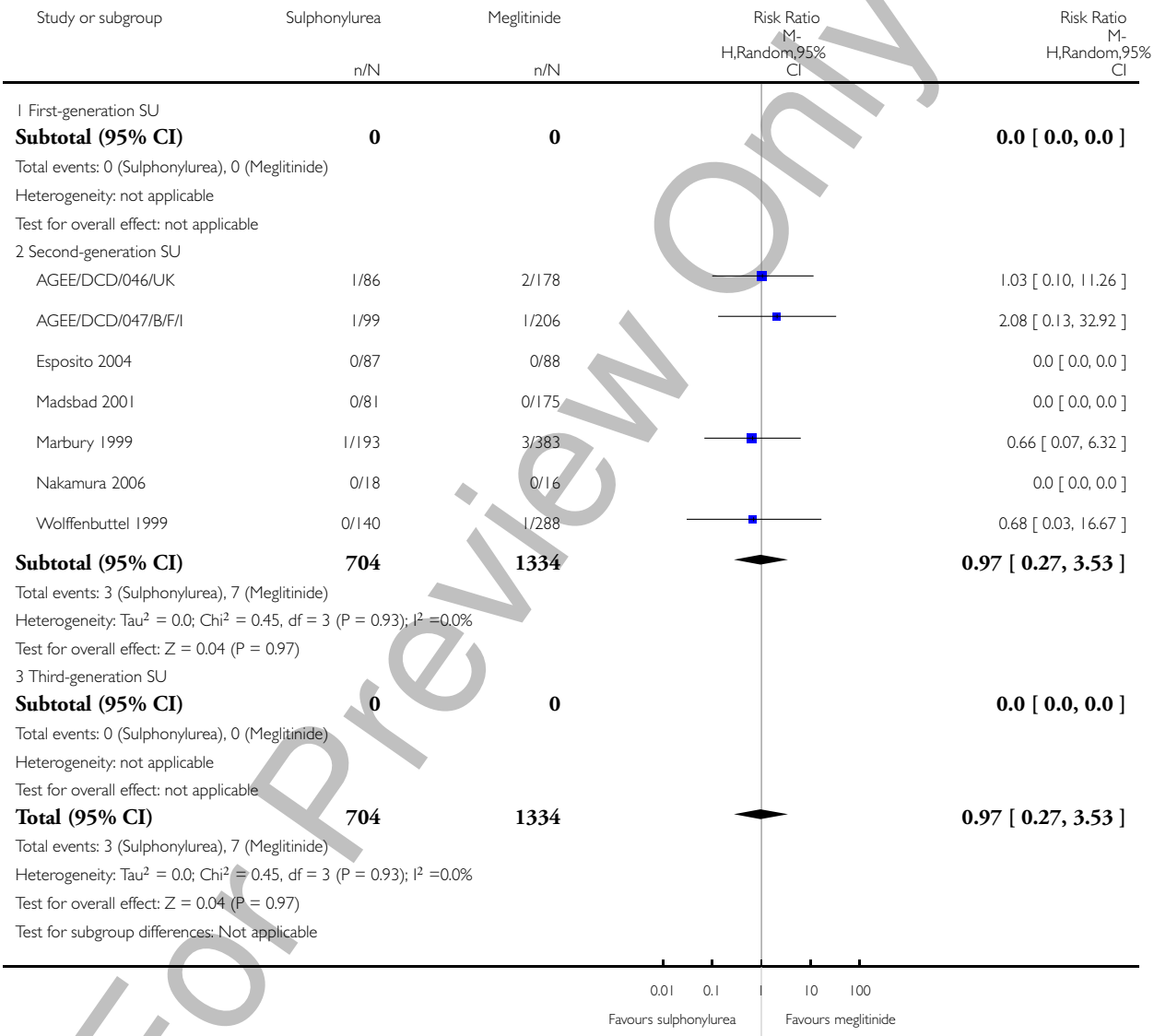


Analysis 7.4. Comparison 7 Sulphonylureas versus meglitinide, Outcome 4 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 4 Cardiovascular mortality

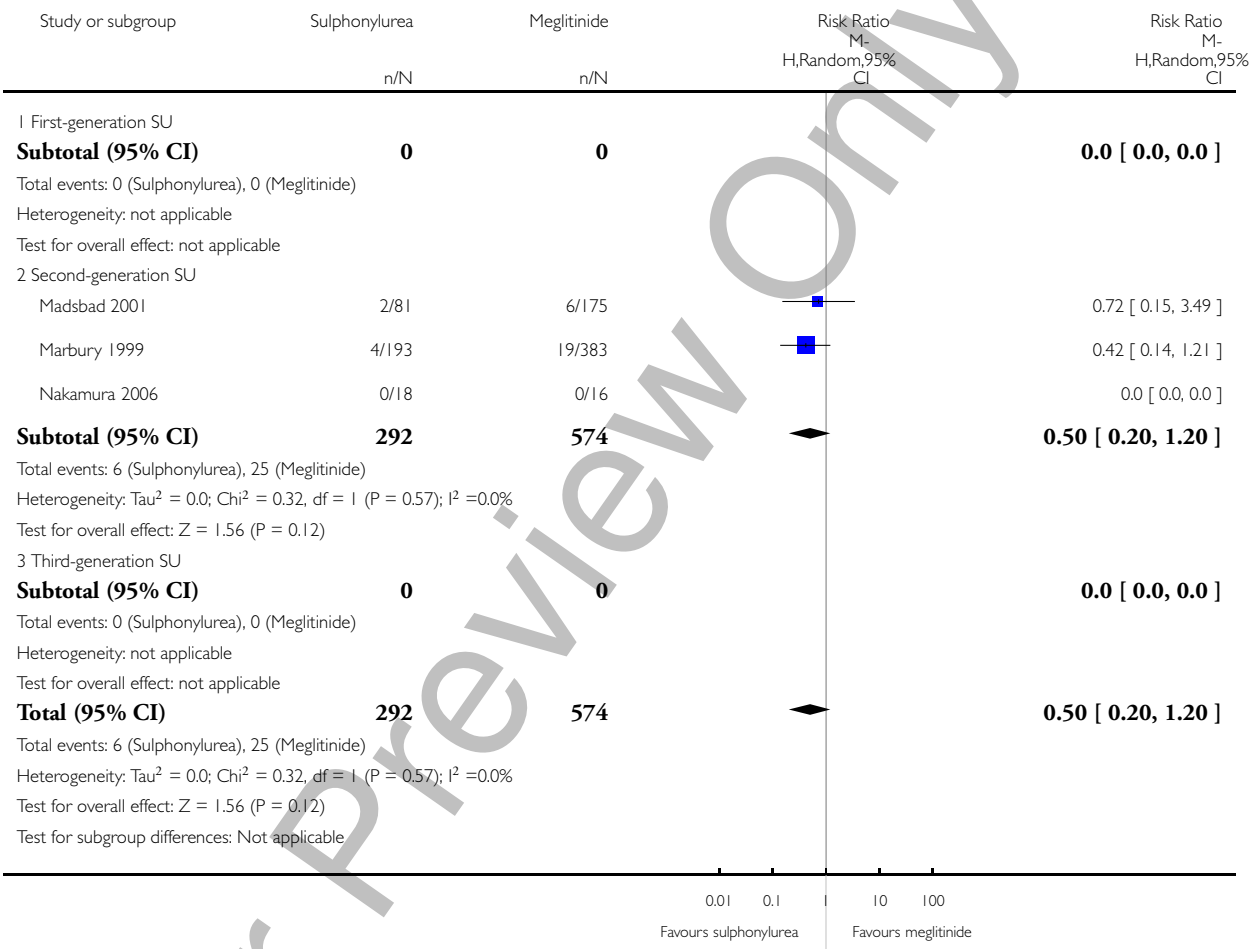


Analysis 7.5. Comparison 7 Sulphonylureas versus meglitinide, Outcome 5 Non-fatal macrovascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 5 Non-fatal macrovascular outcomes

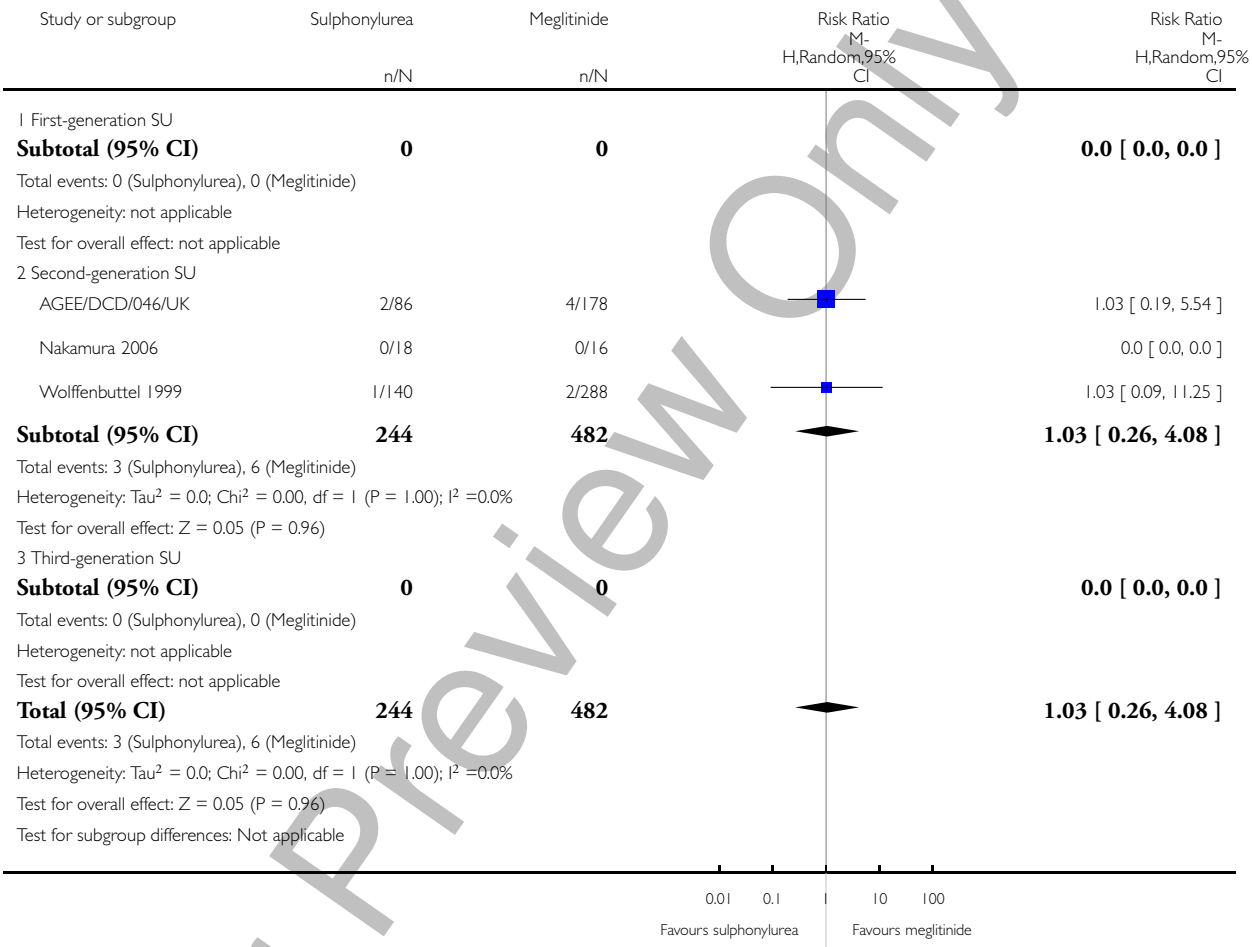


Analysis 7.6. Comparison 7 Sulphonylureas versus meglitinide, Outcome 6 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 6 Non-fatal myocardial infarction



Analysis 7.7. Comparison 7 Sulphonylureas versus meglitinide, Outcome 7 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 7 Non-fatal stroke

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.8. Comparison 7 Sulphonylureas versus meglitinide, Outcome 8 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 8 Amputation of lower extremity

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.9. Comparison 7 Sulphonylureas versus meglitinide, Outcome 9 Cardial revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 9 Cardial revascularisation

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.10. Comparison 7 Sulphonylureas versus meglitinide, Outcome 10 Peripheral revascularisation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 10 Peripheral revascularisation

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.11. Comparison 7 Sulphonylureas versus meglitinide, Outcome 11 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 11 Microvascular outcomes

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.12. Comparison 7 Sulphonylureas versus meglitinide, Outcome 12 Nephropathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 12 Nephropathy

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.13. Comparison 7 Sulphonylureas versus meglitinide, Outcome 13 Retinopathy.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 13 Retinopathy

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.14. Comparison 7 Sulphonylureas versus meglitinide, Outcome 14 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 14 Retinal photocoagulation

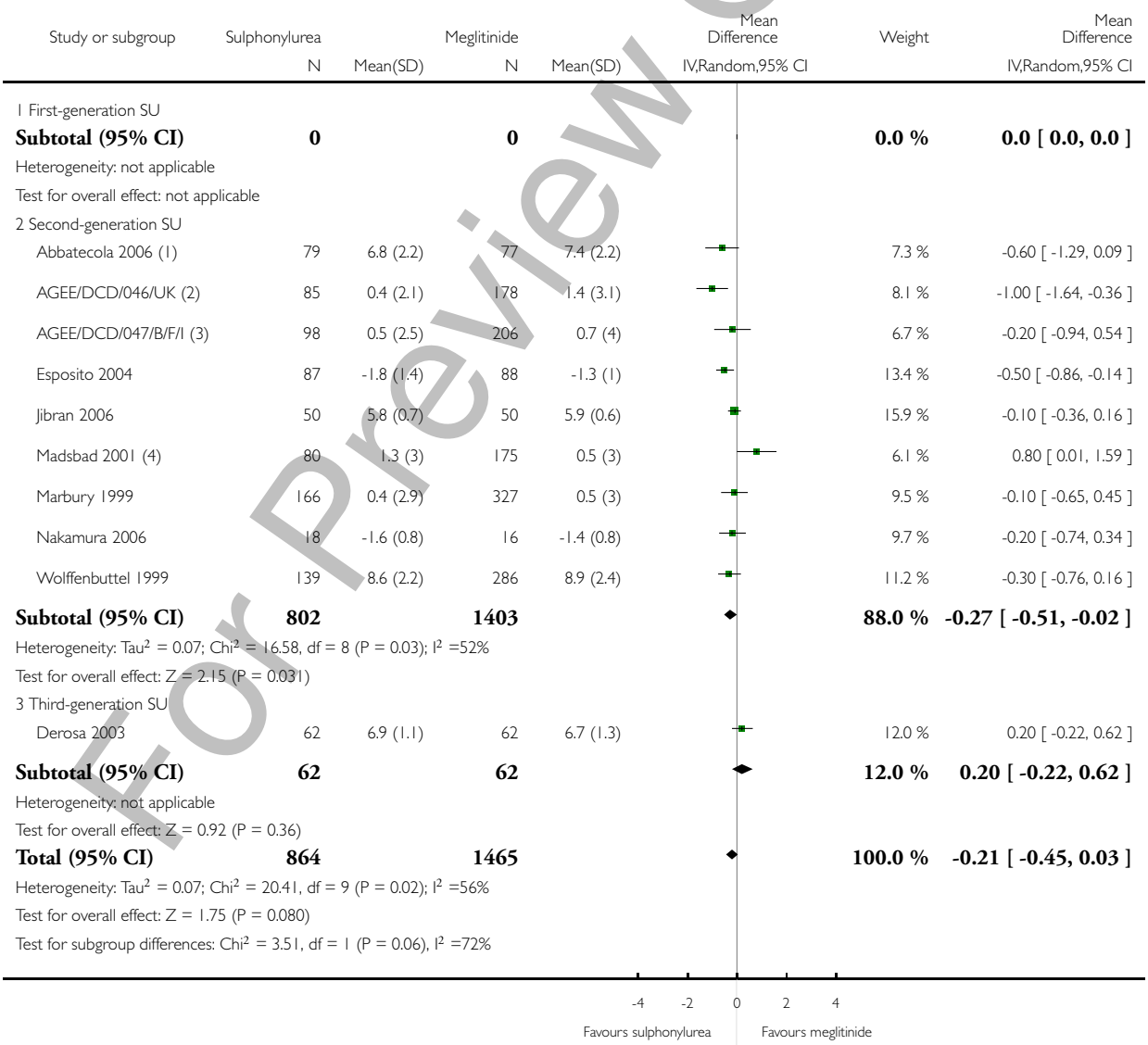
Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.15. Comparison 7 Sulphonylureas versus meglitinide, Outcome 15 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 15 Change in fasting blood glucose from baseline (mmol/L)



(1) SE read from graph. SE converted to SD

(2) SD calculated from 95% confidence interval

(3) SD calculated from 95% confidence interval

(4) SD calculated from 95% confidence interval

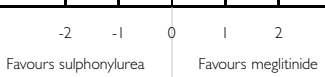
Analysis 7.16. Comparison 7 Sulphonylureas versus meglitinide, Outcome 16 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 16 Change in HbA1c from baseline (%)

Study or subgroup	Sulphonylurea N	Mean(SD)	Meglitinide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Abbatecola 2006 (1)	79	6.7 (1.7)	77	6.5 (1)		6.8 %	0.20 [-0.24, 0.64]
AGEE/DCD/046/UK (2)	85	0.6 (1.5)	178	0.6 (1.4)		8.2 %	0.0 [-0.38, 0.38]
AGEE/DCD/047/B/F/I (3)	98	0.6 (1.5)	206	0.7 (1.5)		8.7 %	-0.10 [-0.46, 0.26]
Esposito 2004	87	-0.8 (0.5)	88	-0.9 (0.5)		17.8 %	0.10 [-0.05, 0.25]
Jibran 2006	50	9.4 (1.5)	50	8.8 (1.7)		3.9 %	0.60 [-0.03, 1.23]
Madsbad 2001 (4)	80	0.8 (1.5)	175	0.2 (1.4)		8.0 %	0.60 [0.21, 0.99]
Marbury 1999	171	0.1 (1.4)	338	0.08 (1.3)		12.7 %	0.02 [-0.23, 0.27]
Nakamura 2006	18	-1.6 (0.4)	16	-1.4 (0.4)		12.0 %	-0.20 [-0.47, 0.07]
Wolffenbuttel 1999 (5)	139	0.5 (1.4)	286	0.6 (1.5)		11.1 %	-0.10 [-0.39, 0.19]
Subtotal (95% CI)	**807**		**1414**			**89.2 %**	**0.07 [-0.08, 0.22]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.62$, df = 8 (P = 0.03); $I^2 = 52\%$							
Test for overall effect: Z = 0.92 (P = 0.36)							
3 Third-generation SU							
Derosa 2003	62	6.7 (0.9)	62	6.8 (0.8)		10.8 %	-0.10 [-0.40, 0.20]
Subtotal (95% CI)	**62**		**62**			**10.8 %**	**-0.10 [-0.40, 0.20]**



(*Continued . . .*)

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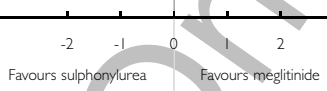
Study or subgroup	Sulphonylurea N	Mean(SD)	Meglitinide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: not applicable							
Test for overall effect: Z = 0.65 (P = 0.51)							
Total (95% CI)	**869**		**1476**			**100.0 %**	**0.05 [-0.09, 0.19]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 17.59, df = 9 (P = 0.04); I^2 =49%							
Test for overall effect: Z = 0.72 (P = 0.47)							
Test for subgroup differences: Chi^2 = 1.00, df = 1 (P = 0.32), I^2 =0.0%							



(1) SE read from graph. SE converted to SD

(2) SD calculated from 95% confidence interval

(3) SD calculated from 95% confidence interval

(4) SD calculated from 95% confidence interval

(5) SD calculated from 95% confidence interval.

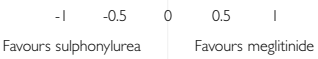
Analysis 7.17. Comparison 7 Sulphonylureas versus meglitinide, Outcome 17 Change in BMI from baseline (kg/m^2).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 17 Change in BMI from baseline (kg/m^2)

Study or subgroup	Sulphonylurea N	Mean(SD)	Meglitinide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Esposito 2004	87	0.4 (0.4)	88	0.3 (0.4)		42.3 %	0.10 [-0.02, 0.22]
Nakamura 2006	18	-0.4 (0.3)	16	-0.3 (0.1)		39.0 %	-0.10 [-0.25, 0.05]
Subtotal (95% CI)	**105**		**104**			**81.3 %**	**0.00 [-0.19, 0.20]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.31, df = 1 (P = 0.04); I^2 =77%							
Test for overall effect: Z = 0.05 (P = 0.96)							
3 Third-generation SU							
Derosa 2003	62	25.9 (1.2)	62	26.2 (0.8)		18.7 %	-0.30 [-0.66, 0.06]
Subtotal (95% CI)	**62**		**62**			**18.7 %**	**-0.30 [-0.66, 0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							
Total (95% CI)	**167**		**166**			**100.0 %**	**-0.05 [-0.25, 0.14]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.19, df = 2 (P = 0.03); I^2 =72%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Test for subgroup differences: Chi^2 = 2.14, df = 1 (P = 0.14), I^2 =53%							



Analysis 7.18. Comparison 7 Sulphonylureas versus meglitinide, Outcome 18 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 18 Change in weight from baseline (kg)

Study or subgroup	Sulphonylurea N	Mean(SD)	Meglitinide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 First-generation SU							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Second-generation SU							
Jibran 2006	50	71.7 (15.2)	50	66.8 (8.8)		0.9 %	4.90 [0.03, 9.77]
Marbury 1999 (1)	166	0.05 (4)	327	-0.2 (4.9)		23.2 %	0.25 [-0.56, 1.06]
Nakamura 2006	18	-0.8 (0.4)	16	-0.7 (0.4)		67.4 %	-0.10 [-0.37, 0.17]
Wolffenbuttel 1999	139	82 (11.9)	286	81.5 (13.5)		3.1 %	0.50 [-2.02, 3.02]
Subtotal (95% CI)	**373**		**679**			**94.5 %**	**0.13 [-0.50, 0.76]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 4.82$, df = 3 (P = 0.19); $I^2 = 38\%$							
Test for overall effect: Z = 0.40 (P = 0.69)							
3 Third-generation SU							
Derosa 2003	62	76.6 (5.3)	62	76.5 (5.3)		5.5 %	0.10 [-1.77, 1.97]
Subtotal (95% CI)	**62**		**62**			**5.5 %**	**0.10 [-1.77, 1.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.11 (P = 0.92)							
Total (95% CI)	**435**		**741**			**100.0 %**	**0.05 [-0.40, 0.51]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 4.84$, df = 4 (P = 0.30); $I^2 = 17\%$							
Test for overall effect: Z = 0.23 (P = 0.82)							
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.98), $I^2 = 0.0\%$							

(1) SE read from graph. SE converted to SD.

Analysis 7.19. Comparison 7 Sulphonylureas versus meglitinide, Outcome 19 Adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 19 Adverse events

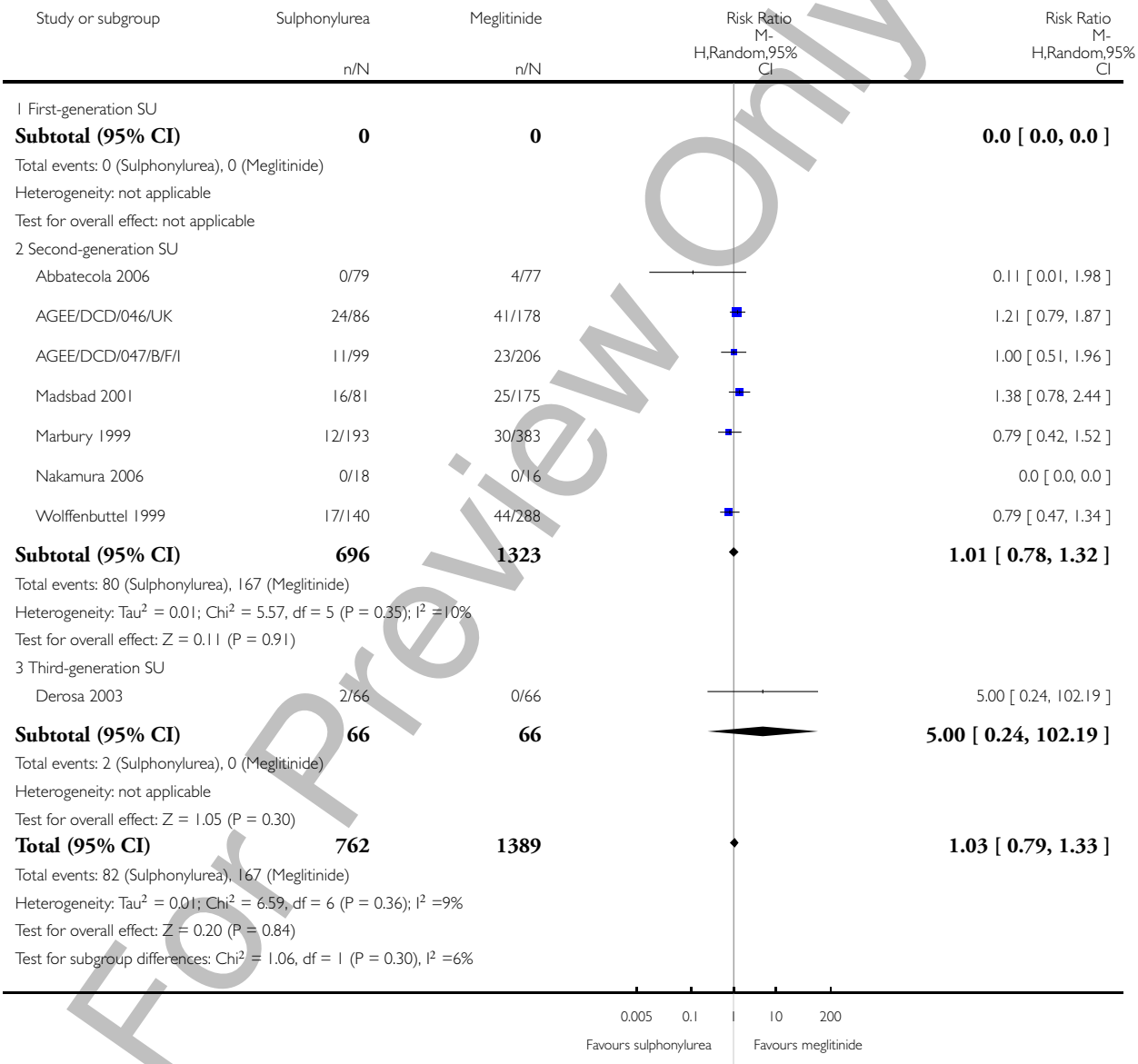
Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
AGEE/DCD/046/UK	79/86	162/178		46.0 %	1.01 [0.93, 1.09]
AGEE/DCD/047/B/F/I	66/99	145/206		10.3 %	0.95 [0.80, 1.12]
Madsbad 2001	66/81	138/175		16.8 %	1.03 [0.91, 1.18]
Marbury 1999	55/193	116/383		3.8 %	0.94 [0.72, 1.23]
Wolffenbuttel 1999	108/140	222/288		23.1 %	1.00 [0.90, 1.12]
Subtotal (95% CI)	**599**	**1230**		**100.0 %**	**1.00 [0.95, 1.06]**
Total events: 374 (Sulphonylurea), 783 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.08 (P = 0.94)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**599**	**1230**		**100.0 %**	**1.00 [0.95, 1.06]**
Total events: 374 (Sulphonylurea), 783 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.08 (P = 0.94)					
Test for subgroup differences: Not applicable					

Analysis 7.20. Comparison 7 Sulphonylureas versus meglitinide, Outcome 20 Drop-outs due to adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 20 Drop-outs due to adverse events



Analysis 7.21. Comparison 7 Sulphonylureas versus meglitinide, Outcome 21 Serious adverse events.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 21 Serious adverse events

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
AGEE/DCD/046/UK	10/86	14/178		14.8 %	1.48 [0.68, 3.19]
AGEE/DCD/047/B/F/I	9/99	23/206		16.2 %	0.81 [0.39, 1.69]
Madsbad 2001	13/81	23/175		21.2 %	1.22 [0.65, 2.29]
Marbury 1999	12/193	39/383		21.4 %	0.61 [0.33, 1.14]
Wolffenbuttel 1999	18/140	30/288		26.4 %	1.23 [0.71, 2.14]
Subtotal (95% CI)	**599**	**1230**		**100.0 %**	**1.02 [0.74, 1.39]**
Total events: 62 (Sulphonylurea), 129 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.67$, df = 4 (P = 0.32); $I^2 = 14\%$					
Test for overall effect: Z = 0.11 (P = 0.91)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**599**	**1230**		**100.0 %**	**1.02 [0.74, 1.39]**
Total events: 62 (Sulphonylurea), 129 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.67$, df = 4 (P = 0.32); $I^2 = 14\%$					
Test for overall effect: Z = 0.11 (P = 0.91)					
Test for subgroup differences: Not applicable					

Analysis 7.22. Comparison 7 Sulphonylureas versus meglitinide, Outcome 22 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 22 Mild hypoglycaemia

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
AGEE/DCD/046/UK	19/86	25/178		16.5 %	1.57 [0.92, 2.69]
AGEE/DCD/047/B/F/I	15/99	30/206		14.6 %	1.04 [0.59, 1.84]
Madsbad 2001	15/81	27/175		14.5 %	1.20 [0.68, 2.13]
Marbury 1999	36/193	58/383		33.3 %	1.23 [0.84, 1.80]
Nakamura 2006	6/18	1/16		1.2 %	5.33 [0.72, 39.69]
Wolffenbuttel 1999	20/140	44/288		20.0 %	0.94 [0.57, 1.52]
Subtotal (95% CI)	**617**	**1246**		**100.0 %**	**1.20 [0.96, 1.49]**
Total events: 111 (Sulphonylurea), 185 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.36$, df = 5 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.64 (P = 0.10)					
3 Third-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**617**	**1246**		**100.0 %**	**1.20 [0.96, 1.49]**
Total events: 111 (Sulphonylurea), 185 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.36$, df = 5 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.64 (P = 0.10)					
Test for subgroup differences: Not applicable					

Analysis 7.23. Comparison 7 Sulphonylureas versus meglitinide, Outcome 23 Moderate hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 23 Moderate hypoglycaemia

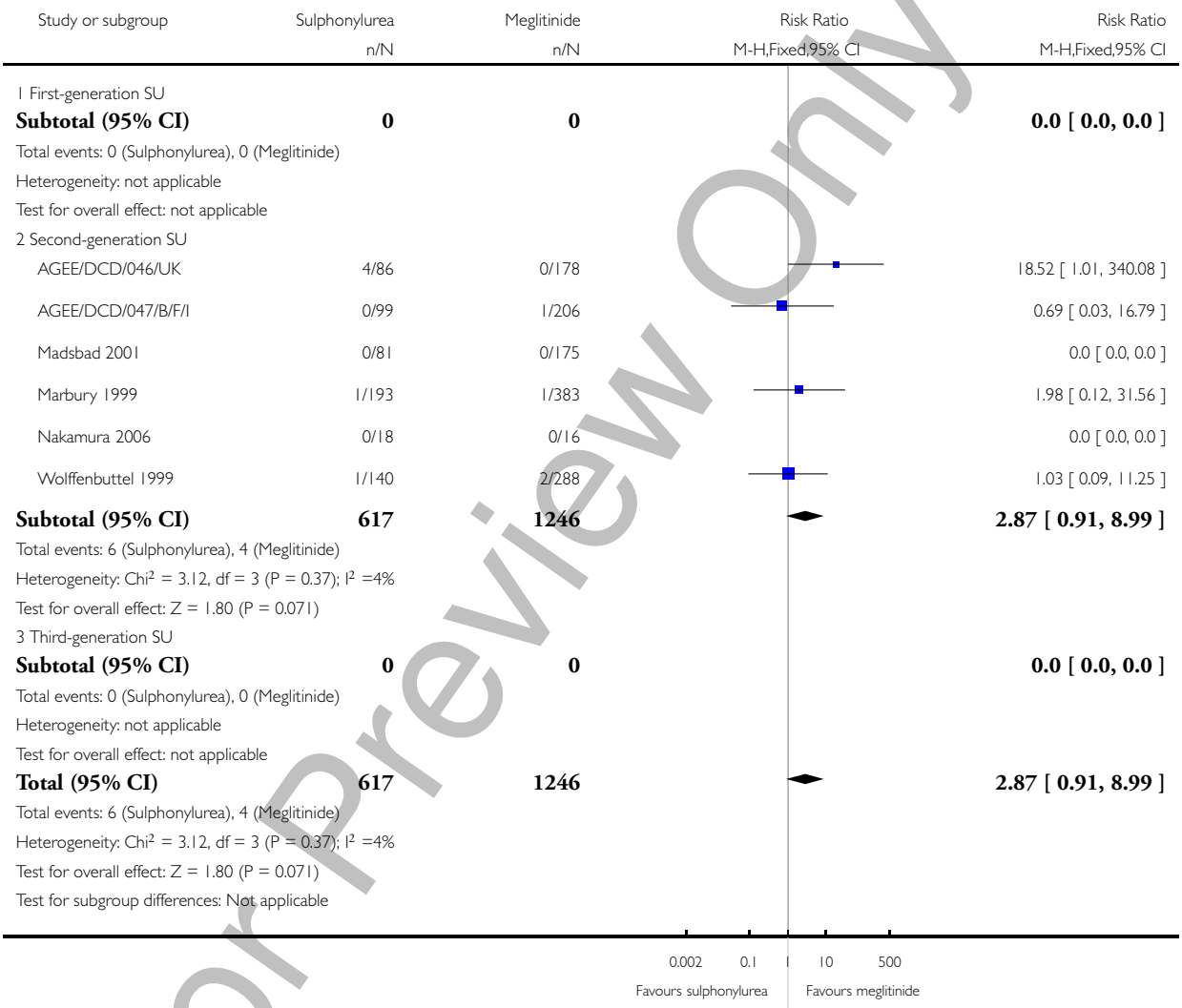
Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**18**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 7.24. Comparison 7 Sulphonylureas versus meglitinide, Outcome 24 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 24 Severe hypoglycaemia



Analysis 7.25. Comparison 7 Sulphonylureas versus meglitinide, Outcome 25 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 25 Cancer

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 First-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Second-generation SU				
Madsbad 2001	1/81	0/175		6.44 [0.27, 156.37]
Nakamura 2006	0/18	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**99**	**191**		**6.44 [0.27, 156.37]**
Total events: 1 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.14 (P = 0.25)				
3 Third-generation SU				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**99**	**191**		**6.44 [0.27, 156.37]**
Total events: 1 (Sulphonylurea), 0 (Meglitinide)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.14 (P = 0.25)				
Test for subgroup differences: Not applicable				

Analysis 7.26. Comparison 7 Sulphonylureas versus meglitinide, Outcome 26 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 7 Sulphonylureas versus meglitinide

Outcome: 26 Intervention failure

Study or subgroup	Sulphonylurea n/N	Meglitinide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 First-generation SU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sulphonylurea), 0 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Second-generation SU					
AGEE/DCD/046/UK	2/86	14/178		5.3 %	0.30 [0.07, 1.27]
Madsbad 2001	2/81	3/175		3.6 %	1.44 [0.25, 8.45]
Marbury 1999	33/193	64/383		77.5 %	1.02 [0.70, 1.50]
Wolffenbuttel 1999	5/140	9/288		9.8 %	1.14 [0.39, 3.35]
Subtotal (95% CI)	**500**	**1024**		**96.3 %**	**0.98 [0.69, 1.38]**
Total events: 42 (Sulphonylurea), 90 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.96$, df = 3 (P = 0.40); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.12 (P = 0.90)					
3 Third-generation SU					
Derosa 2003	2/66	3/66		3.7 %	0.67 [0.12, 3.86]
Subtotal (95% CI)	**66**	**66**		**3.7 %**	**0.67 [0.12, 3.86]**
Total events: 2 (Sulphonylurea), 3 (Meglitinide)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
Total (95% CI)	**566**	**1090**		**100.0 %**	**0.96 [0.69, 1.35]**
Total events: 44 (Sulphonylurea), 93 (Meglitinide)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.14$, df = 4 (P = 0.53); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.21 (P = 0.84)					
Test for subgroup differences: $Chi^2 = 0.18$, df = 1 (P = 0.67), $I^2 = 0.0\%$					

Analysis 8.1. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 1 All-cause mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 1 All-cause mortality

Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
UKPDS 1998 (1)	121/615	136/619		100.0 %	0.90 [0.72, 1.11]
Total (95% CI)	**615**	**619**		**100.0 %**	**0.90 [0.72, 1.11]**

Total events: 121 (Second-gen SU), 136 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable

(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.2. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 2 Cardiovascular mortality.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 2 Cardiovascular mortality

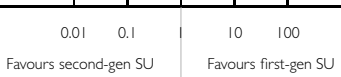
Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
UKPDS 1998 (1)	69/615	71/619		100.0 %	0.98 [0.72, 1.34]
Total (95% CI)	**615**	**619**		**100.0 %**	**0.98 [0.72, 1.34]**

Total events: 69 (Second-gen SU), 71 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.3. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 3 Non-fatal myocardial infarction.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 3 Non-fatal myocardial infarction

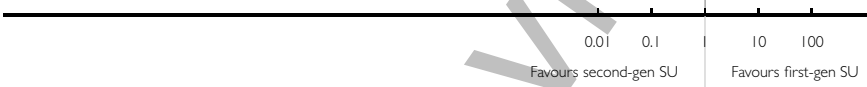
Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
UKPDS 1998 (1)	46/615	58/619		100.0 %	0.80 [0.55, 1.16]
Total (95% CI)	**615**	**619**		**100.0 %**	**0.80 [0.55, 1.16]**

Total events: 46 (Second-gen SU), 58 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



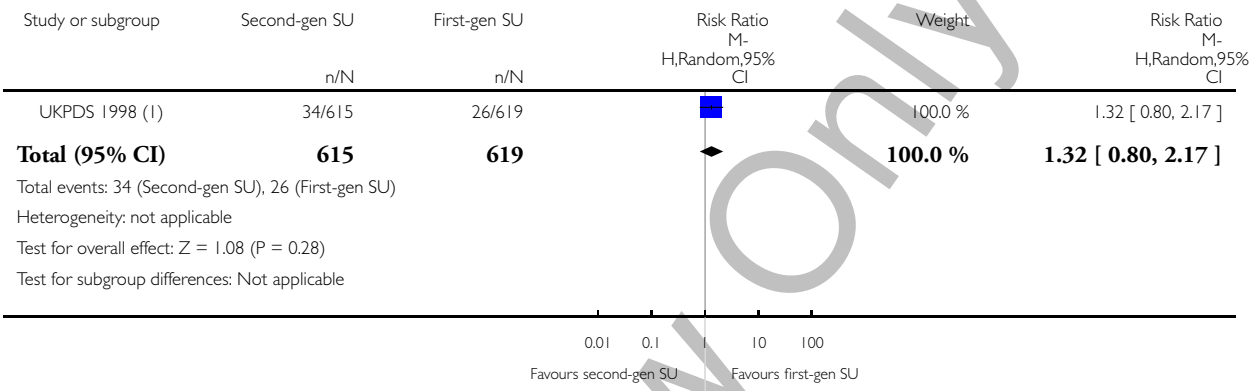
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.4. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 4 Non-fatal stroke.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 4 Non-fatal stroke



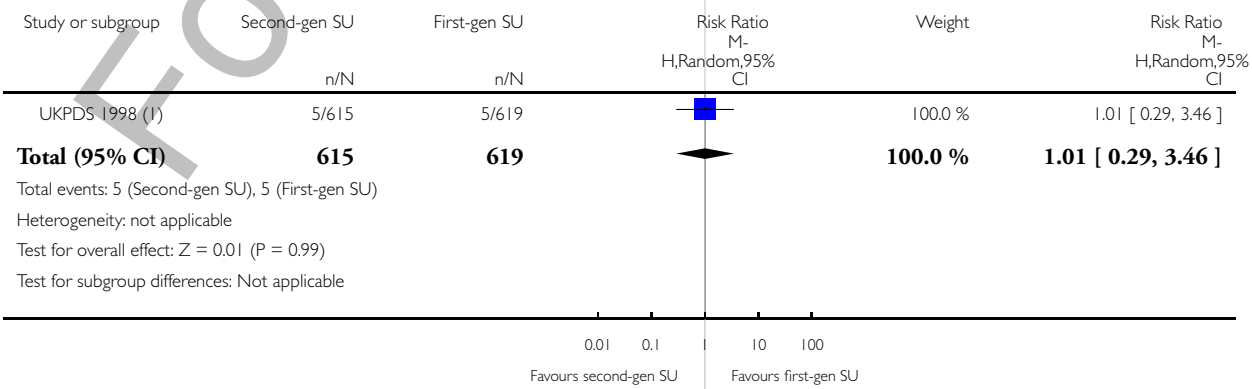
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.5. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 5 Amputation of lower extremity.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 5 Amputation of lower extremity



(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.6. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 6 Microvascular outcomes.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 6 Microvascular outcomes

Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
UKPDS 1998 (1)	49/615	68/619		100.0 %	0.70 [0.48, 1.03]
Total (95% CI)	**615**	**619**		**100.0 %**	**0.70 [0.48, 1.03]**

Total events: 49 (Second-gen SU), 68 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 1.80 (P = 0.071)

Test for subgroup differences: Not applicable

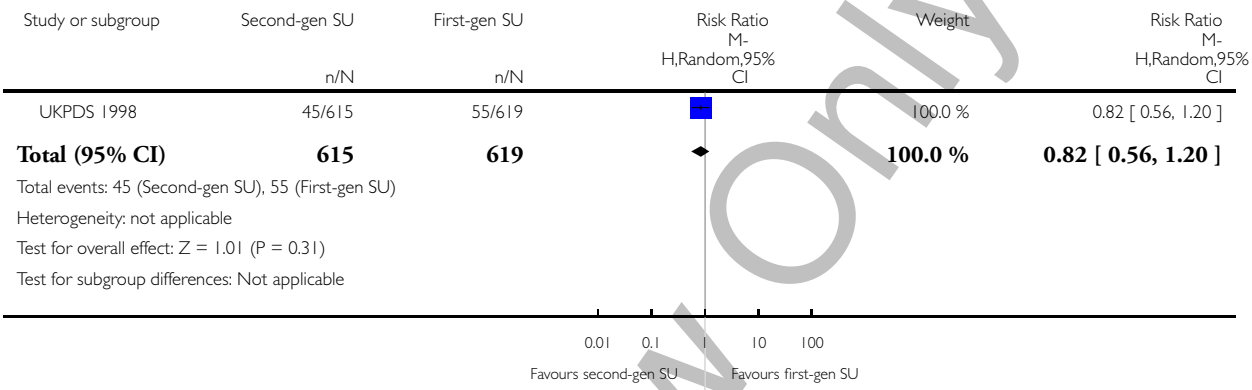
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.7. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 7 Retinal photocoagulation.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 7 Retinal photocoagulation

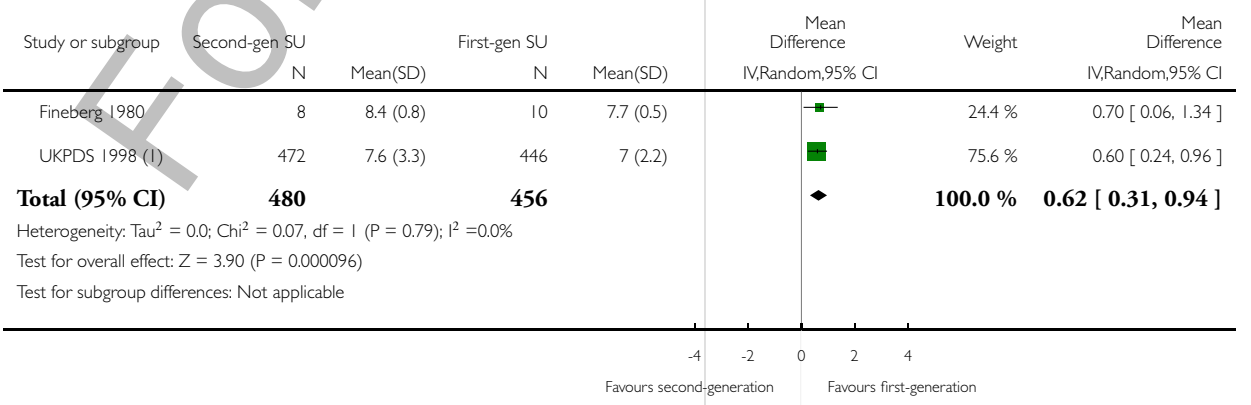


Analysis 8.8. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 8 Change in fasting blood glucose from baseline (mmol/L).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 8 Change in fasting blood glucose from baseline (mmol/L)



(1) Data after three years of follow-up

Analysis 8.9. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 9 Change in HbA1c from baseline (%).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

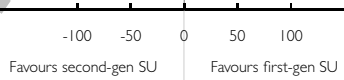
Outcome: 9 Change in HbA1c from baseline (%)

Study or subgroup	Second-gen SU N	Mean(SD)	First-gen SU N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Harrower 1985	78	-2.3 (2)	18	0.7 (0.7)		49.7 %	-3.00 [-3.55, -2.45]
UKPDS 1998 (1)	472	6.9 (1.7)	446	6.8 (1.6)		50.3 %	0.10 [-0.11, 0.31]
Total (95% CI)	**550**		**464**			**100.0 %**	**-1.44 [-4.48, 1.60]**

Heterogeneity: $Tau^2 = 4.76$; $Chi^2 = 106.34$, df = 1 (P<0.00001); $I^2 = 99\%$

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable



(1) Data after three years of follow-up

Analysis 8.10. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 10 Change in weight from baseline (kg).

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 10 Change in weight from baseline (kg)

Study or subgroup	Second-gen SU N	Mean(SD)	First-gen SU N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Harrower 1985	78	0.8 (1.2)	18	0.1 (2.1)		56.1 %	0.70 [-0.31, 1.71]
UKPDS 1998 (1)	472	81.1 (15.5)	446	77.9 (15.1)		43.9 %	3.20 [1.22, 5.18]
Total (95% CI)	**550**		**464**			**100.0 %**	**1.80 [-0.63, 4.23]**

Heterogeneity: Tau² = 2.48; Chi² = 4.87, df = 1 (P = 0.03); I² =79%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

(1) Data after three years of follow-up

Analysis 8.11. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 11 Mild hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 11 Mild hypoglycaemia

Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
UKPDS 1998 (1)	122/615	49/619		100.0 %	2.51 [1.83, 3.42]
Total (95% CI)	**615**	**619**		**100.0 %**	**2.51 [1.83, 3.42]**

Total events: 122 (Second-gen SU), 49 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 5.77 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Data after one year of follow-up

Analysis 8.12. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 12 Severe hypoglycaemia.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 12 Severe hypoglycaemia

Study or subgroup	Second-gen SU n/N	First-gen SU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
UKPDS 1998 (1)	7/615	2/619		100.0 %	3.52 [0.73, 16.89]
Total (95% CI)	**615**	**619**		**100.0 %**	**3.52 [0.73, 16.89]**

Total events: 7 (Second-gen SU), 2 (First-gen SU)

Heterogeneity: not applicable

Test for overall effect: Z = 1.57 (P = 0.12)

Test for subgroup differences: Not applicable

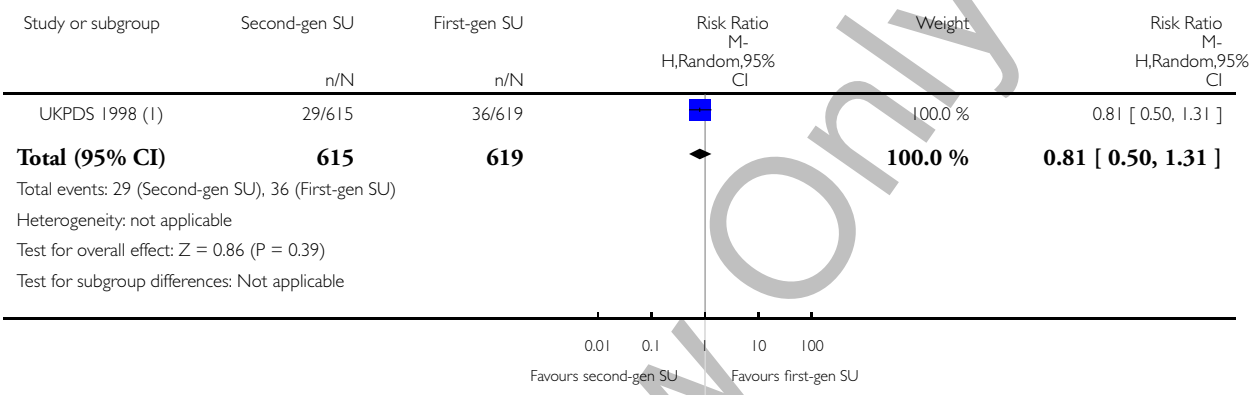
(1) Data after one year of follow-up

Analysis 8.13. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 13 Cancer.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 13 Cancer



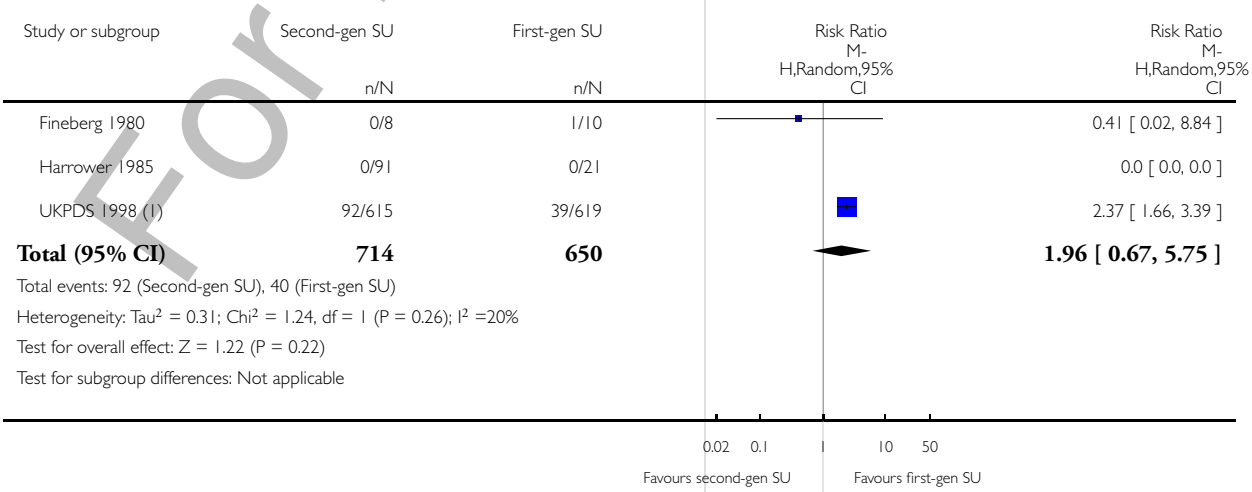
(1) Data are from Glucose Study 1 (UKPDS 33)

Analysis 8.14. Comparison 8 Second-generation sulphonylureas versus first-generation sulphonylureas, Outcome 14 Intervention failure.

Review: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Comparison: 8 Second-generation sulphonylureas versus first-generation sulphonylureas

Outcome: 14 Intervention failure



(1) After 3 years of follow-up

ADDITIONAL TABLES

Table 1. Overview of study populations

Characteristic Study ID	Intervention (s) and control(s)	[N] screened	[N] randomised	[N] safety	[N] lost to follow-up (mortality)	[N] finishing study	[%] of randomised participants finishing study
Abbatecola 2006	I1: glibenclamide C1: repaglinide	-	I1: 79 C1: 77 T: 156	I1: 73 C1: 74 T: 147	-	I1: 63 C1: 65 T: 128	I1: 80 C1: 84 T: 82
ADOPT 2006	I1: glibenclamide C1: rosiglitazone C2: metformin	6676	I1: 1447 C1: 1458 C2: 1455 T: 4360	I1: 1441 C1: 1456 C2: 1455 T: 4351	-	I1: 807 C1: 917 C2: 903 T: 2627	I1: 56 C1: 63 C2: 62 T: 60
AGEE/DCD/046/UK	I1: glibenclamide C1: repaglinide	313	I1: 86 C1: 178 T: 264	I1: 85 C1: 178 T: 264	-	I1: 57 C1: 111 T: 168	I1:66 C1: 62 T: 64
AGEE/DCD/047/B/F/I	I1: gliclazide C1: repaglinide	337	I1: 99 C1: 206 T: 305	I1: 99 C1: 206 T: 305	-	I1: 68 C1: 138 T: 206	I1: 69 C1: 67 T: 68
Alvarsson 2010	I1: glibenclamide C1: insulin	56	I1: 26 C1: 23 T: 49	-	I1: 7 C1: 5 T: 12	I1: 18 C1: 16 T: 34	I1: 69 C1: 70 T: 70
APPROACH 2010[a]	I1: glipizide C1: rosiglitazone	1147	I1: 339 C1: 333 T: 672	I1: 337 C1: 331 T: 668	I1: 22 C1: 17 T: 39	I1: 264 C1: 259 T: 523	I1: 78 C1: 78 T: 78
Birkeland 1994	I1: glibenclamide I2: glipizide C1: placebo	-	I1: 15 I2: 15 C1: 16 T: 46	-	I1: 0 I2: 0 C1: 0 T: 0	I1: 15 I2: 13 C1: 12 T: 40	I1: 100 I2: 87 C1: 75 T: 87
Birkeland 2002	I1: glibenclamide	54	I1: 18 C1: 18	-	-	-	N/A

Table 1. Overview of study populations (*Continued*)

	C1: insulin		T: 36				
Campbell 1994	I1: glipizide C1: metformin	50 (?)	I1: 24 C1: 24 T: 48	I1: 24 C1: 24 T: 48	I1: 0 C1: 0 T: 0	I1: 24 C1: 24 T: 48	I1: 100 C1: 100 T: 100
Charbonnel 2005[b]	I1: gliclazide C1: pioglitazone	2412	I1: 626 C1: 624 T: 1270	-	I1: 4 C1: 4 T: 8	I1: 525 C1: 530 T: 1055	I1: - C1: - T: 83
Collier 1989	I1: gliclazide C1: metformin	-	I1: 12 C1: 12 T: 24	I1: 12 C1: 12 T: 24	-	I1: 12 C1: 12 T: 24	I1: 100 C1: 100 T: 100
Coniff 1995	I1: tolbutamide C1: acarbose C2: placebo	-	I1: 72 C1: 76 C2: 72 T: 220	I1: 71 C1: 74 C2: 72 T: 217	-	-	N/A
Dalzell 1986	I1: tolbutamide C1: metformin	-	I1: 15 C1: 18 T: 33	-	-	-	N/A
DeFronzo 2005	I1: glibenclamide C1: metformin	788	I1: 209 C1: 210 T: 419	-	-	I1: 174 C1: 157 T: 331	I1: 83 C1: 75 T: 79
Deng 2003	I1: glibenclamide C1: Xiaoyaosan	160	I1: 80 C1: 80 T: 160	-	-	-	N/A
Derosa 2003	I1: glimepiride C1: repaglinide	-	I1: 66 C1: 66 T: 132	I1: 66 C1: 66 T: 132	I1: 4 C1: 4 T: 8	I1: 62 C1: 62 T: 124	I1: 94 C1: 94 T: 94
Derosa 2004	I1: glimepiride C1: metformin	-	I1: 81 C1: 83 T: 164	I1: 81 C1: 83 T: 164	-	I1: 73 C1: 75 T: 148	I1:90 C1: 90 T: 90
Diehl 1985	I1: chlorpropamide C1: insulin	137	I1: 40 C1: 37 T: 77	-	-	I1: 30 C1: 28 T: 58	I1: 75 C1: 77 T: 75

Table 1. Overview of study populations (*Continued*)

Ebeling 2001	I1: glibenclamide C1: pioglitazone C2: placebo	-	I1: 10 C1: 9 C2: 10 T: 29	-	-	-	N/A
Esposito 2004	I1: glibenclamide C1: repaglinide	210	I1: 87 C1: 88 T: 175	I1: 87 C1: 88 T: 175	I1: 7 C1: 7 T: 14	I1: 80 C1: 81 T: 161	I1: 92 C1: 92 T: 92
Feinböck 2003	I1: glibenclamide C1: acarbose	-	I1: 111 C1: 108 T: 219	I1: 93 C1: 59 T: 152	-	I1: 93 C1: 59 T: 152	I1: 84 C1: 55 T: 69
Fineberg 1980[c]	I1: glipizide C1: tolbutamide	-	I1: - C1: - T: 29	-	-	I1: 8 C1: 10 T: 18	I1: - C1: - T: 62
Foley 2009	I1: gliclazide C1: vildagliptin	-	I1: 546 C1: 546 T: 1092	I1: 402 C1: 409 T: 811	I1: 13 C1: 17 T: 30	I1: 402 C1: 409 T: 811	I1:74 C1: 75 T: 74
Forst 2003	I1: glibenclamide C1: insulin	200	I1: 68 C1: 75 T: 143	I1: 68 C1: 75 T: 143	I1: 0 C1: 0 T: 0	I1: 68 C1: 75 T: 143	I1: 100 C1: 100 T: 100
Forst 2005	I1: glimepiride C1: pioglitazone	192	I1: 87 C1: 92 T: 179	I1: 84 C1: 89 T: 173	I1: 3 C1: 3 T: 6	I1: 84 C1: 89 T: 173	I1:97 C1: 97 T: 97
Hanefeld 2005	I1: glibenclamide C1: rosiglitazone 2 mg C2: rosiglitazone 4 mg	-	I1: 207 C1: 200 C2: 191 T: 598	-	I1: 0 C1: 0 C2: 0 T: 0	I1: 173 C1: 153 C2: 158 T: 484	I1: 84 C1: 77 C2: 83 T: 81
Harrower 1985	I1: glipizide I2: gliquidone I3: gliclazide I4: glibenclamide C1: chlorpropamide	-	I1: 24 I2: 22 I3: 22 I4: 23 C1: 21 T: 112	-	I1: 4 I2: 3 I3: 2 I4: 4 C1: 3 T: 16	I1: 20 I2: 19 I3: 20 I4: 19 C1: 18 T: 96	I1: 83 I2: 86 I3: 91 I4: 83 C1: 86 T: 86

Table 1. Overview of study populations (*Continued*)

Hermann 1991[d]	I1: glibenclamide C1: metformin	-	I1: - C1: - T: 25	I1: 10 C1: 12 T: 22	-	I1: 10 C1: 12 T: 22	N/A
Hermann 1991a	I1: glibenclamide C1: metformin	-	I1: 34 C1: 38 T: 72	-	I1: 0 C1: 0 T: 0	I1: 28 C1: 28 T: 56	I1: 82 C1: 74 T: 78
Hoffmann 1990	I1: glibenclamide C1: acarbose	-	I1: 47 C1: 48 T: 95	-	-	-	N/A
Hoffmann 1994	I1: glibenclamide C1: placebo C2: acarbose	96	I1: 27 C1: 30 C2: 28 T: 85	-	I1: 0 C1: 0 T: 0	I1: 27 C1: 30 C2: 28 T: 85	I1: 100 C1: 100 C2: 100
Hollander 1992	I1: glibenclamide C1: insulin	-	I1: 29 C1: 30 T: 59	-	-	-	N/A
Jain 2006	I1: glibenclamide C1: pioglitazone	-	I1: 251 C1: 251 T: 502	-	I1: 21 C1: 22 T: 43	I1: 128 C1: 134 T: 262	I1: 50 C1: 53 T: 52
Jibran 2006	I1: glibenclamide C1: repaglinide	-	I1: 50 C1: 50 T: 100	-	-	-	N/A
Johnston 1997	I1: glibenclamide C1: placebo C2: miglitol 25 mg C3: miglitol 50 mg	-	I1: 104 C1: 101 C2: 104 C3: 102 T: 411	-	-	-	N/A
Kaku 2011	I1: glibenclamide C1: liraglutide	464	I1: 139 C1: 272 T: 411	I1: 132 C1: 268 T: 400	-	I1: 110 C1: 225 T: 335	I1: 79 C1: 83 T: 82
Kamel 1997	I1: gliclazide I2: glibenclamide C1: acarbose	-	I1: 9 I2: 8 C1: 10 C2: 6	-	-	-	N/A

Table 1. Overview of study populations (*Continued*)

	C2: metformin C3: placebo		C3: 10 T: 43				
Kanda 1998	I1: gliclazide C1: acarbose	25	I1: 9 C1: 10 T: 19	-	-	I1: 9 C1: 10 T: 19	I1: 100 C1: 100 T: 100
Kovacevic 1997	I1: glibenclamide C1: acarbose C2: placebo	-	I1: 34 C1: 34 C2: 34 T: 102	I1: 33 C1: 33 C2: 31 T: 97	-	I1: 33 C1: 33 C2: 31 T: 97	I1: 97 C1: 97 C2: 91 T: 95
Lawrence 2004	I1: gliclazide C1: metformin C2: pioglitazone	67	I1: 22 C1: 21 C2: 21 T: 64	-	I1: 0 C1: 0 C2: 0 T: 0	I1: 20 C1: 20 C2: 20 T: 60	I1: 91 C1: 95 C2: 95 T: 94
LEAD-3 2006[e]	I1: glimepiride C1: liraglutide 1.2 mg C2: liraglutide 1.8 mg	-	I1: 248 C1: 251 C2: 247 T: 746	I1: 248 C1: 251 C2: 246 T: 745	-	I1: 152 C1: 162 C2: 173 T: 487	I1: 61 C1: 65 C2: 70 T: 65
Madsbad 2001	I1: glipizide C1: repaglinide	320	I1: 81 C1: 175 T: 256	I1: 81 C1: 175 T: 256	-	I1: 58 C1: 140 T: 198	I1: 72 C1: 80 T: 77
Marbury 1999	I1: glibenclamide C1: repaglinide	-	I1: 193 C1: 383 T: 576	I1: 193 C1: 383 T: 576	-	I1: 115 C1: 216 T: 331	I1: 60 C1: 56 T: 57
Memisogullari 2009	I1: gliclazide C1: nothing	-	I1: 26 C1: 30 T: 56	-	I1:0 C1: 0 T: 0	-	N/A
Nakamura 2004	I1: glibenclamide C1: pioglitazone C2: voglibose	-	I1: 15 C1: 15 C2: 15 T: 45	I1: 15 C1: 15 C2: 15 T: 45	I1: 0 C1: 0 C2: 0 T: 0	I1: 15 C1: 15 C2: 15 T: 45	I1: 100 C1: 100 C2: 100 T: 100
Nakamura 2006	I1: glibenclamide C1: pioglitazone	78	I1: 18 C1: 17 C2: 17 C3: 16	I1: 18 C1: 17 C2: 17 C3: 16	I1: 0 C1: 0 C2: 0 C3: 0	I1: 18 C1: 17 C2: 17 C3: 16	I1: 100 C1: 100 C2: 100 C3: 100

Table 1. Overview of study populations (*Continued*)

	C2: voglibose C3: nateglinide		T: 68	T: 68	T: 0	T: 68	T: 100
Nathan 1988	I1: glibenclamide C1: insulin	-	I1: 16 C1: 15 T: 31	I1: 16 C1: 15 T: 31	I1: 0 C1: 0 T: 0	I1: 16 C1: 15 T: 31	I1: 100 C1: 100 T: 100
Pagano 1995 [f]	I1: glibenclamide C1: miglitol	-	I1: 47 C1: 50 T: 100	I1: - C1: - T: 99	I1: - C1: - T: 3	I1: 47 C1: 49 T: 96	I1: - C1: - T: 96
Perriello 2007	I1: gliclazide C1: pioglitazone	-	I1: 137 C1: 146 T: 283	-	-	I1: 135 C1: 140 T: 275	I1: 99 C1: 96 T: 97
Rosenthal 2002	I1: glibenclamide C1: acarbose	-	I1: 37 C1: 39 T: 76	I1: 31 C1: 32 T: 63	-	I1: 31 C1: 32 T: 63	I1: 84 C1: 82 T: 83
Salman 2001	I1: gliclazide C1: acarbose	-	I1: 35 C1: 33 T: 68	I1: 30 C1: 27 T: 57	-	I1: 30 C1: 27 T: 57	I1: 86 C1: 82 T: 84
Segal 1997	I1: glibenclamide C1: miglitol C2: placebo	-	I1: 69 C1: 67 C2: 65 T: 201	I1: 69 C1: 67 C2: 65 T: 201	I1: 11 C1: 12 C2: 6 T: 29	I1: 50 C1: 49 C2: 58 T: 157	I1: 72 C1: 73 C2: 89 T: 78
Shihara 2011	I1: glimepiride C1: pioglitazone	238	I1: 95 C1: 96 T: 191	I1: 86 C1: 91 T: 177	-	I1: 86 C1: 91 T: 177	I1: 91 C1: 95 T: 93
Spengler 1992 [g]	I1: glibenclamide C1: acarbose	-	I1: 36 C1: 36 T: 72	-	-	I1: 29 C1: 26 T: 55	I1: 81 C1: 72 T: 76
Sung 1999	I1: glibenclamide C1: troglitazone	-	I1: 12 C1: 10 T: 22	-	-	-	N/A
Sutton 2002 [h]	I1: glibenclamide C1: rosiglitazone	351	I1: 99 C1: 104 T: 203	I1: 99 C1: 104 T: 203	I1: 3 C1: 2 T: 5	I1: 65 C1: 64 T: 129	I1: 66 C1: 62 T: 64

Table 1. Overview of study populations (*Continued*)

Tan 2004	I1: glimepiride C1: pioglitazone	584	I1: 123 C1: 121 T: 244	I1: 92 C1: 100 T: 192	I1: 11 C1: 6 T: 17	I1: 89 C1: 87 T: 176	I1: 72 C1: 72 T: 72
Tan 2004a	I1: glimepiride C1: pioglitazone	-	I1: 109 C1: 91 T: 200	I1: 109 C1: 91 T: 200	-	I1: 68 C1: 55 T: 123	I1: 62 C1: 60 T: 62
Tan 2005[i]	I1: gliclazide C1: pioglitazone	2412	I1: 297 C1: 270 T: 567	-	I1: 4 C1: 2 T: 6	I1: 127 C1: 147 T: 274	I1: 43 C1: 54 T: 48
Tang 2004	I1: glimepiride C1: metformin	-	I1: 33 C1: 29 T: 62	-	-	-	N/A
Teramoto 2007	I1: glibenclamide C1: pioglitazone	126	I1: 46 C1: 46 T: 92	I1: 41 C1: 39 T: 80	-	I1: 41 C1: 39 T: 80	I1: 89 C1: 85 T: 86
Tessier 1999	I1: gliclazide C1: metformin	-	I1: 19 C1: 20 T: 39	-	I1: 1 C1: 2 T: 3	I1: 18 C1: 18 T:36	I1: 94.7 C1: 90 T: 92.3
Tosi 2003	I1: glibenclamide C1: metformin	-	I1: 22 C1: 22 T: 44	-	-	I1: 20 C1: 19 T: 39	I1: 91 C1: 86 T: 89
UGDP 1970	I1: tolbutamide C1: placebo C1: insulin	-	I1: 204 C1: 205 C2: 210 T: 619	I1: 75% on tolbutamide C1: 75% on placebo C2: - T: -	-	-	N/A
UKPDS 1998[j]	Study 1: I1: chlorpropamide I2: glibenclamide I3: glipizide C1: insulin	7616	I1: 788 I2: 615 I3: 170 C1: 1156 T: 2729	-	-	-	N/A

Table 1. Overview of study populations (*Continued*)

UKPDS 34 1998	I1: chlorpropamide I2: glibenclamide C1: metformin C2: insulin	4209	I1: 265 I2: 277 C1: 342 C2: 409 T: 1293	-	I1: - I2: - C1: - C2: - T: 13	-	N/A
van de Laar 2004	I1: tolbutamide C1: acarbose	144	I1: 50 C1: 48 T: 98	I1: 48 C1: 48 T: 96	I1: 5 C1: 16 T: 21	I1: 43 C1: 32 T: 75	I1: 86 C1: 67 T: 77
Watanabe 2005	I1: glibenclamide C1: pioglitazone	-	I1: 15 C1: 15 T: 30	I1: 14 C1: 13 T: 27	I1: 1 C1: 2 T: 3	I1: 14 C1: 13 T: 27	I1: 93 C1: 87 T: 90
Wolffenbuttel 1989	I1: tolbutamide C1: insulin	-	I1: 6 C1: 7 T: 13	-	-	-	N/A
Wolffenbuttel 1999	I1: glibenclamide C1: repaglinide	491	I1: 140 C1: 288 T: 428	I1: 139 C1: 286 T: 425	-	I1: 109 C1: 211 T: 320	I1: 78 C1: 74 T: 75
Yamanouchi 2005	I1: glimepiride C1: pioglitazone C2: metformin	-	I1: 37 C1: 38 C2: 39 T: 114	-	I1: 3 C1: 0 C2: 1 T: 4	I1: 34 C1: 35 C2: 37 T: 106	I1: 92 C1: 92 C2: 95 T: 93
Zhang 2005	I1: glipizide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	45	I1: 8 C1: 8 C2: 8 T: 24	I1: 8 C1: 8 C2: 8 T: 24	I1: 0 C1: 0 C2: 0 T: 0	I1: 8 C1: 8 C2: 8 T: 24	I1: 100 C1: 100 C2: 100 T: 100
Total [k]	***I: any sulphonylurea C: any comparator***		***I: 9707 C: 12,805 T:22,589***			***I: 4901 C: 6888 T:11,789***	

"-" denotes not reported

[a] The number of participants finishing the trial is taken from clinicaltrials.gov and is the number of individuals who completed the trial as defined by investigator.

[b] Twenty of the randomised participants are not included in the analysis. It is unknown to which group they belong. Therefore the total number of randomised participants does not equal the sum of the number of randomised patients in each intervention group.

[c] The number of randomised participants to each comparator group is not reported. Only the 18 participants finishing the trial are described in the publication.
[d] It is reported that 25 participants were randomised, but only the 22 participants who completed the trial are presented.
[e] Data after 52 weeks of double-blind intervention. From the double-blind intervention period to the open-label extension of 91 weeks 84 participants discontinued in the glimepiride group, 70 in the liraglutide 1.2 mg group and 71 in the liraglutide 1.8 mg group.
[f] It is not described in the publication to which group the three patients who were lost to follow-up belonged. However, it is stated in the publication that 100 participants were randomised.
[g] A total of 72 participants underwent randomisation, but only 55 participants are included in the analyses of the trial. Eleven participants were excluded because they had received sulphonylurea previously, but the authors did not report to which group they initially were randomised.
[h] In the publication there is a discrepancy in the number of participants finishing the study.
[i] The number of patients screened is the number screened to the initial 52 weeks (Charbonnel 2005).
[j] The numbers for chlorpropamide and insulin interventions are the number of participants randomised to 'Glucose Study 1' plus the number of participants randomised to 'Glucose Study 2'. Lost to follow-up mortality is not explicitly explained for each antidiabetic intervention group. For 'Glucose Study 1' vital status was unknown for 57 participants in the intensive intervention group (chlorpropamide/glibenclamide/insulin).
[k] The number of total is not the same as the number of I and C together, as some of the trials only reported the total number of participants randomised (Fineberg 1980; Hermann 1991; Pagano 1995). Several trials did not report the number of participants finishing study.
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; C: control; I: intervention; LEAD-3: Liraglutide Effect and Action in Diabetes-3; N/A: not acknowledged; T: total; UKPDS: United Kingdom Prospective Diabetes Study

APPENDICES

Appendix 1. Search strategies

Search terms and databases
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (MEDLINE medical index term); exp = exploded MeSH; the dollar sign ($) or asterisk (*) stand for any character(s); the question mark (?) = to substitute for one or no characters; ab = abstract; adj = adjacent; ot = original title; pt = publication type; rn = Registry number or Enzyme Commission number; sh = MeSH; ti = title; tw = text word
The Cochrane Library
#1 MeSH descriptor Diabetes mellitus, type 2 explode all trees #2 MeSH descriptor Insulin resistance explode all trees #3 ((impaired in All Text and glucose in All Text and toleranc* in All Text) or (glucose in All Text and intoleranc* in All Text) or (insulin* in All Text and resistanc* in All Text)) #4 (obes* in All Text near/6 diabet* in All Text) #5 (MODY in All Text or NIDDM in All Text or TDM2 in All Text) #6 ((non in All Text and insulin* in All Text and depend* in All Text) or (noninsulin* in All Text and depend* in All Text) or (non in All Text and insulindepend* in All Text) or noninsulindepend* in All Text)

(*Continued*)

#7 (typ* in All Text and (2 in All Text near/6 diabet* in All Text))
#8 (typ* in All Text and (II in All Text near/6 diabet* in All Text))
#9 (non in All Text and (keto* in All Text near/6 diabet* in All Text))
#10 (nonketo* in All Text near/6 diabet* in All Text)
#11 (adult* in All Text near/6 diabet* in All Text)
#12 (matur* in All Text near/6 diabet* in All Text)
#13 (late in All Text near/6 diabet* in All Text)
#14 (slow in All Text near/6 diabet* in All Text)
#15 (stabl* in All Text near/6 diabet* in All Text)
#16 (insulin* in All Text and (defic* in All Text near/6 diabet* in All Text))
#17 (plurimetabolic in All Text and syndrom* in All Text)
#18 (pluri in All Text and metabolic in All Text and syndrom* in All Text)
#19 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#20 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#21 (#19 or #20)
#22 MeSH descriptor Diabetes insipidus explode all trees
#23 (diabet* in All Text and insipidus in All Text)
#24 (#22 or #23)
#25 (#21 and not #24)
#26 MeSH descriptor Sulfonylurea compounds explode all trees
#27 (insulin? in All Text and secretagog* in All Text)
#28 (acetohexamid* in All Text or carbutamid* in All Text or chlorpropamid* in All Text or tolbutamid* in All Text or tolazamid* in All Text)
#29 (glipizid* in All Text or gliclazid* in All Text or glibenclamid* in All Text or glyburid* in All Text or gliquidon* in All Text or glyclopyramid* in All Text)
#30 glimepirid* in All Text
#31 (meglitinid* in All Text or repaglinid* in All Text or nateglinid* in All Text)
#32 (sulfonylurea* in All Text or sulphonylurea* in All Text)
#33 (glibenese* in All Text or minidiab* in All Text or glucotrol* in All Text or daonil* in All Text or euglucon* in All Text or glynase* in All Text)
#34 (#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
#35 (#25 and #34)

MEDLINE

1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. exp Glucose Intolerance/
4. (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).tw,ot.
5. (obes$ adj3 diabet$).tw,ot.
6. (MODY or NIDDM or T2DM).tw,ot.
7. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,ot.
8. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet$).tw,ot.
9. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
10. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).tw,ot.
11. or/1-10
12. exp Diabetes Insipidus/
13. diabet$ insipidus.tw,ot.
14. 12 or 13
15. 11 not 14

(*Continued*)

16. exp Sulfonylurea Compounds/
17. exp Glyburide/
18. insulin? secretagog$.tw,ot.
19. (acetohexamid$ or Carbutamid$ or Chlorpropamid$ or Tolbutamid$ or Tolazamid$).tw,ot.
20. (Glipizid$ or Gliclazid$ or Glibenclamid$ or glyburid$ or Gliquidon$ or Glyclopyramid$).tw,ot.
21. glimepirid$.tw,ot.
22. (meglitinid$ or repaglinid$ or nateglinid$).tw,ot.
23. (sulfonylurea$ or sulphonylurea$).tw,ot.
24. (glibenese$ or minidiab$ or Glucotrol$ or daonil$ or euglucon$ or Glynase$).tw,ot.
25. or/16-24
26. 15 and 25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomi?ed.ab.
30. placebo.ab.
31. clinical trials as topic.sh.
32. randomly.ab.
33. trial.ti.
34. or/27-33
35. Meta-analysis.pt.
36. exp Technology Assessment, Biomedical/
37. exp Meta-analysis/
38. exp Meta-analysis as topic/
39. hta.tw,ot.
40. (health technology adj6 assessment$).tw,ot.
41. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
42. ((review$ 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.
43. or/35-42
44. (comment or editorial or historical-article).pt.
45. 43 not 44
46. 34 or 45
47. 26 and 46
48. (animals not (animals and humans)).sh.
49. 47 not 48

EMBASE

1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. (MODY or NIDDM or T2D or T2DM).tw,ot.
4. ((typ? 2 or typ? II or typ?II or typ?2) adj3 diabet*).tw,ot.
5. (obes* adj3 diabet*).tw,ot.
6. (non insulin* depend* or non insulin?depend* or noninsulin* depend* or noninsulin?depend*).tw,ot.
7. ((keto?resist* or non?keto*) adj3 diabet*).tw,ot.
8. ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw,ot.
9. (insulin* defic* adj3 relativ*).tw,ot.
10. insulin* resistanc*.tw,ot.
11. or/1-10
12. exp Diabetes Insipidus/

(*Continued*)

13. diabet* insipidus.tw,ot.
14. 12 or 13
15. 11 not 14
16. exp sulfonylurea derivative/
17. insulin? secretagog*.tw,ot.
18. exp acetohexamide/
19. exp carbutamide/
20. exp chlorpropamide/
21. exp tolbutamide/
22. exp tolazamide/
23. (acetohexamid* or carbutamid* or chlorpropamid* or tolbutamid* or tolazamid*).tw,ot.
24. exp glipizide plus metformin/ or exp glipizide/ or exp glibenclamide/
25. exp gliclazide/
26. exp gliquidone/
27. (glipizid* or gliclazid* or glibenclamid* or glyburid* or gliquidon* or glyclopyramid*).tw,ot.
28. exp glimepiride/
29. glimepirid*.tw,ot.
30. exp meglitinide/
31. exp repaglinide/
32. exp nateglinide/
33. (meglitinid* or repaglinid* or nateglinid*).tw,ot.
34. (sulfonylurea* or sulphonylurea*).tw,ot.
35. (glibenese* or minidiab* or glucotrol* or daonil* or euglucon* or glynase*).tw,ot.
36. or/16-35
37. 15 and 36
38. exp Randomized Controlled Trial/
39. exp Controlled Clinical Trial/
40. exp Clinical Trial/
41. exp Comparative Study/
42. exp Drug comparison/
43. exp Randomization/
44. exp Crossover procedure/
45. exp Double blind procedure/
46. exp Single blind procedure/
47. exp Placebo/
48. exp Prospective Study/
49. ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
50. (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
51. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
52. (cross over or crossover).ab,ti.
53. or/38-52
54. exp meta analysis/
55. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
56. ((review$ 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$)).ab,ti,ot.
57. exp Literature/
58. exp Biomedical Technology Assessment/
59. hta.tw,ot.
60. (health technology adj6 assessment$).tw,ot.

(*Continued*)

61. or/54-60
62. 53 or 61
63. 37 and 62
64. (comment or editorial or historical-article).pt.
65. 63 not 64

LILACS

(sulfonylurea OR sulphonylurea) [Words] and diabetes [Words] and not insipidus [Words]

Science Citation Index Expanded

1 TS=((impaired glucose toleranc*) or (glucose intoleranc*) or (insulin* resistanc*))
2 TS=(obes* SAME diabet*)
3 TS=(mody OR NIDDM OR TDM2)
4 TS=((non insulin* depend*) or (noninsulin* depend*) or (non insulindepend*) or (noninsulindepend*))
5 TS=(typ* AND (2 SAME diabet*))
6 TS=(typ* AND (II SAME diabet*))
7 TS=(non AND (keto* SAME diabet*))
8 TS=(nonketo* SAME diabet*)
9 TS=(adult* SAME diabet*)
10 TS=(matur* SAME diabet*)
11 TS=(late SAME diabet*)
12 TS=(slow SAME diabet*)
13 TS=(stabl* SAME diabet*)
14 TS=(insulin and (defic* SAME diabet*))
15 TS=(plurimetabolic syndrom*)
16 TS=(pluri metabolic syndrom*)
17 #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
18 TS=(diabet* insipidus)
19 #17 NOT #18
20 TS=(insulin* secretagog*)
21 TS=(acetohexamid* or carbutamid* or chlorpropamid* or tolbutamid* or tolazamid*)
22 TS=(glipizid* or gliclazid* or glibenclamid* or glyburid* or gliquidon* or glyclopyramid*)
23 TS=(glimepirid*)
24 TS=(sulfonylurea* or sulphonylurea*)
25 TS=(glibenese* or minidiab* or glucotrol* or daonil* or euglucon* or glynase*)
26 #25 OR #24 OR #23 OR #22 OR #21 OR #20
27 #26 AND #19
28 TS=(((random* OR controlled OR clinical) AND trial*) OR placebo* OR meta-analysis)
29 #28 AND #27

CINAHL (Ovid SP)

S1 (MM "Diabetes Mellitus, Non-Insulin-Dependent")
S2 (MM "Insulin Resistance")
S3 (MM "Glucose Intolerance")
S4 (impaired glucos* toleranc* or glucos* intoleranc* or insulin resistan*) or TI (impaired glucos* toleranc* or glucos* intoleranc* or insulin resistan*)
S5 TX obes* N3 diabet* or TI obes* N3 diabet*

(*Continued*)

S6 TX (MODY or NIDDM or T2DM) or TI (MODY or NIDDM or T2DM)
S7 TX (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*) or TI (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*)
S8 TX ((typ? 2 or typ? II or typ?2 or typ?II) AND diabet*) or TI ((typ? 2 or typ? II or typ?2 or typ?II) AND diabet*)
S9 TX ((keto?resist* or non?keto*) AND diabet*) and TI ((keto?resist* or non?keto*) AND diabet*)
S10 TX ((late or adult* or matur* or slow or stabl*) AND onset AND diabet*) or TI ((late or adult* or matur* or slow or stabl*) AND onset AND diabet*)
S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S12 (MM "Diabetes Insipidus")
S13 TX diabet* insipidus or TI diabet* insipidus
S14 S12 or S13
S15 S11 NOT S14
S16 (MM "Sulfonylurea Compounds")
S17 (MM "Glyburide")
S18 TX insulin* secretagog* or TI insulin* secretagog*
S19 TX (acetohexamid* or Carbutamid* or Chlorpropamid* or Tolbutamid* or Tolazamid*) or TI (acetohexamid* or Carbutamid* or Chlorpropamid* or Tolbutamid* or Tolazamid*)
S20 TX (Glipizid* or Gliclazid* or Glibenclamid* or glyburid* or Gliquidon* or Glyclopyramid*) and TI (Glipizid* or Gliclazid* or Glibenclamid* or glyburid* or Gliquidon* or Glyclopyramid*)
S21 TX glimepirid* or TI glimepirid*
S22 TX (meglitinid* or repaglinid* or nateglinid*) or TI (meglitinid* or repaglinid* or nateglinid*)
S23 TX (sulfonylurea* or sulphonylurea*) or TI (sulfonylurea* or sulphonylurea*)
S24 TX (glibenese* or minidiab* or Glucotrol* or daonil* or euglucon* or glynase*) or TI (glibenese* or minidiab* or Glucotrol* or daonil* or euglucon* or glynase*)
S25 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
S26 S15 and S25
S27 TX (random* OR blind* OR placebo* OR group*) or TI (random* OR blind* OR placebo* OR group*)
S28 S26 and S27

Appendix 2. Description of interventions

Characteristic Study ID	Intervention(s) [route, frequency, total dose/day]	Control(s) [route, frequency, total dose/day]
Abbatecola 2006	I1: glibenclamide, po., initially 2.5 mg twice a day, given up to 30 minutes before daily meals Diet (individualised in beginning of trial) and exercise was kept constant during trial	C1: repaglinide, po., initially 1 mg twice a day, given up to 30 minutes before daily meals Diet (individualised in beginning of trial) and exercise was kept constant during trial
ADOPT 2006	I1: glibenclamide, po., initial 2.5 mg, then up to 15 mg /day given as 7.5 mg twice daily	C1: rosiglitazone, po., initial 4 mg, then 8 mg (4 mg twice a day) C2: metformin, po., initial 500 mg, then up to 2 g (1 g twice a day)

(*Continued*)

AGEE/DCD/046/UK	I1: glibenclamide, po., initial dose of 2.5 mg or 5 mg in the morning. Dosage was titrated in a step-wise fashion of a maximum of 4 steps in order to optimise glycaemic control. Maximum dose 15 mg daily. Placebo tablets were given	C1: repaglinide, po., initial dose 0.5 mg or 1 mg 3 times a day. Dosage was titrated in a step-wise fashion of a maximum of 4 steps in order to optimise glycaemic control. Maximum dose 4 mg 3 times a day
AGEE/DCD/047/B/F/I	I1: gliclazide, po., initially 80 mg (40 mg in the morning, 40 mg in the evening). Previously sulphonylurea treated patients with FBG > 9 mmol/L started on 80 or 160 mg daily (80 + 0 + 80 mg) . Dosage was titrated in a step-wise fashion of a maximum of 4 steps in order to optimise glycaemic control. Max 240 mg (80 x 3 daily) Placebo tablets were given	C1: repaglinide, po., initial dose 0.5 mg three times. Patients on previously sulphonylurea initiated with 0.5 mg or 1 mg 3 times a day. Dosage was titrated in a step-wise fashion of a maximum of 4 steps in order to optimise glycaemic control. Maximum dose 4 mg 3 times a day
Alvarsson 2010	I1: glibenclamide, po., initiated with 1.75 mg once daily. Steps of 1.75 to 3.5 mg to keep HbA1c levels within target level	C1: insulin, injection, administered twice daily as premixed insulin Initial dose was 0.25 U/kg/24 h Two-thirds of the daily dose was given before breakfast and one-third before supper The insulin doses were adjusted as follows: (i) increase of total dose by 10% if mean 24 h capillary blood glucose was above 12 mmol/L, (ii) decrease of total dose by 10% if mean capillary blood
APPROACH 2010	I1: glipizide, po., starting daily doses 5 mg. Up titrated to target and as tolerated to a maximal total daily dose of 15 mg by 12 weeks. If > 1 titration was required, 2 pills per day were given	C1: rosiglitazone, po., starting daily doses 4 mg. Up titrated to target as tolerated to a maximal total daily dose of 8 mg by 12 weeks. If > 1 titration was required, 2 pills per day were given Placebo was also given when up titrated in order to keep the participants and personal blinded
Birkeland 1994	I1: glibenclamide, po. One tablet (1.75 mg) in the morning, dose adjusted weekly by adding 1 tablet at the time. Max 6 tablets a day (4 before breakfast, 2 before dinner). Diet I2: glipizide, po. One tablet (2.5 mg/day), adjusted weekly by adding 1 tablet at the time to achieved target. Max dose was 6 tablets/day (4 before breakfast + 2 before dinner). Diet	C1: placebo tablets, po. One tablet placebo in the morning, dose adjusted weekly by adding 1 tablet at the time. Max 6 tablets a day (4 before breakfast, 2 before dinner). Diet
Birkeland 2002	I1: glibenclamide, po. Maximal dose was 10.5 mg/day (7 mg before breakfast, 3.5 mg before dinner)	C1: intermediate insulin, 8 U at 8.00 and 22.00. Adjusted to achieve glycaemic target
Campbell 1994	I1: glipizide, po., initiated at 5 mg once daily to a maximum divided daily dose of 15 mg	C1: metformin, po., initial 500 mg metformin/day, increased with 500 mg at each visit (every second week) to a maximum at 3 g

(*Continued*)

Charbonnel 2005	I1: gliclazide, po., starting dose was 80 mg daily for 4 weeks (weeks 0 to 4), 160 mg daily for the next 4 weeks (weeks 4 to 8), 240 mg daily for weeks 8 to 12, and 320 mg daily for the final 4 weeks (weeks 12 to 16) on the basis of tolerability. The dose of study drug was increased at each time point during titration unless the patient had not tolerated the previous dose or the investigator considered the patient at risk of experiencing hypoglycaemia or other tolerability issues should the dose of study drug be further increased. Diet	C1: pioglitazone, po., starting daily dose was 15 mg for 4 weeks (weeks 0 to 4), increased to 30 mg daily for the next 4 weeks (weeks 4 to 8), and, finally, to 45 mg daily for the subsequent 8 weeks (weeks 8 to 16) on the basis of tolerability. The dose of study drug was increased at each time point during titration unless the patient had not tolerated the previous dose or the investigator considered the patient at risk of experiencing hypoglycaemia or other tolerability issues should the dose of study drug be further increased. Diet
Collier 1989	I1: gliclazide, po., doses from 80 to 240 mg/day. Diet	C1: metformin, po., doses from 1.5 to 3.0 g/day. Diet
Coniff 1995	I1: tolbutamide, po., initial 250 mg, up titrated in increments of 150 mg 3 times a day if 1-hour postprandial plasma glucose level was >= 200 mg/dl following 6, 12 or 18 weeks of treatment. The dosage of tolbutamide could be reduced at any time if intolerable adverse events such as hypoglycaemia occurred. Diet	C1: acarbose, po., 200 mg 3 times a day with meals. Diet C2: placebo, po. Diet
Dalzell 1986	I1: tolbutamide, po., 1.5 g/day. Diet	C1: metformin, po., 1.5 g/day. Diet
DeFronzo 2005	I1: glibenclamide, po., initially 5 mg twice daily for the first week and then 10 mg twice daily plus metformin placebo. Diet	C1: metformin, po., initially one 500 mg tablet of metformin. After 1 week the metformin dose was increased to 1000 mg per day by adding a 500 mg tablet to the breakfast meal. After 2 weeks the metformin dose was increased to 1500 mg per day by adding a 500 mg tablet to be taken at lunch. After 3 weeks the dose was increased to 2000 mg per day by adding a second 500 mg tablet to be taken with the evening meal, and after 4 weeks the daily dose was increased to 2500 mg by adding a second 500 mg tablet to the breakfast dose. Glibenclamide placebo
Deng 2003	I1: glibenclamide. 2.5 mg a day	C1: xiaoyaosan (mixture of 12 herbs). One dose per day, taken 2 hours after dinner
Derosa 2003	I1: glimepiride, po., initial dose of 1 mg/day, which was up titrated. Diet	C1: repaglinide, po., initial dose of 1 mg, which was up titrated. Diet
Derosa 2004	I1: glimepiride, po., initial dose of 1 mg/day, which was up titrated to a maximum of 2 mg twice a day (total dose 4 mg). Diet	C1: metformin, po., initial dose 1000 mg/day, up titrated to a maximum dose of 1000 mg 3 times a day (total dose 3000 mg/day). Diet
Diehl 1985	I1: chlorpropamide	C1: insulin

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Ebeling 2001	I1: glibenclamide, po., 2.5 mg once daily. If the reduction of HbA1c at week 9 was not greater than or equal to 0.3%, the antidiabetic medication was doubled	C1: pioglitazone, po., 30 mg once daily. If the reduction of HbA1c at week 9 was not greater than or equal to 0.3% the dose was increased to 45 mg
Esposito 2004	I1: glibenclamide, po. Daily doses were 5, 10, 15 and 20 mg equally divided before breakfast and dinner. Diet	C1: repaglinide, po., daily doses were 1.5, 3, 6 and 12 mg all in 3 identical doses taken before meals. Diet
Feinböck 2003	I1: glimepiride, po., initial 1 mg/day as a single morning dose, increased to 2, 3, 4 or 6 mg/day	C1: acarbose, po., initial 50 mg 3 times a day, increased to 100, 150 or 200 mg 3 times daily
Fineberg 1980	I1: glipizide, po., 5 or 10 mg tablets. Dose was given twice a day. Maximum dose 40 mg	C1: tolbutamide, po., 500 mg tablets. Administered in divided doses. Maximum dose 3 g
Foley 2009	I1: gliclazide, po., initial dose of 80 mg, which was up titrated to a maximum daily dose of 320 mg	C1: vildagliptin, po., initial dose of 50 mg twice a day, no dose adjustments
Forst 2003	I1: glibenclamide, po., 3.5 to 10.5 mg/day	C1: insulin lispro, sc., 4 to 8 units before meals (usually 3 times a day)
Forst 2005	I1: glimepiride, po., individual dose of 1 to 6 mg	C1: pioglitazone, po., 45 mg in the morning
Hanefeld 2005	I: glibenclamide, po., was up titrated during the first 12 weeks to optimal effect, where after the dose remained constant. Placebo	C1: rosiglitazone po., 2 mg twice a day. Placebo C2: rosiglitazone po., 4 mg twice a day
Harrower 1985	I1: glipizide, po., mean dose 9 mg I2: gliquidone, po., mean dose 70 mg I3: gliclazide, po., mean dose 118 mg I4: glibenclamide, po., mean dose 7.5 mg	C1: chlorpropamide, po., 250 mg
Hermann 1991	I1: glibenclamide, po., 1.75 to 10.5 mg daily. Diet	C1: metformin, po., 0.5 to 3 g. Diet
Hermann 1991a	I1: glibenclamide, po., initial 3.5 mg. Up to 14. 0 mg. Tablets given shortly before breakfast and if daily dosis more than 7 mg then divided between breakfast and evening meal. Placebo metformin. Diet	C1: metformin, po., initial 1 g. 1.0 to 3.0 g in 2 doses a day - shortly before breakfast and evening meal. Placebo glibenclamide. Diet
Hoffmann 1990	I1: glibenclamide, po., once or a day. Daily dose from 3.5 to 10.5 mg. Diet	C1: acarbose, po., initial dosis 3 x 50 mg/day. Thereafter 3 x 100 mg/day. Taken with meals. Diet
Hoffmann 1994	I1: glibenclamide, po., adjusted individually to adjust hypoglycaemia: 1 to 3 tablets of 3.5 mg daily mode 1-0-0 to 2-0-1. Diet	C1: placebo, po., 1 placebo tablet 3 times a day. Diet C2: acarbose, po., 100 mg acarbose 3 times a day. Diet

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Hollander 1992	I1: glibenclamide, po	C1: insulin
Jain 2006	I1: glibenclamide, po., 5 mg/day, could be increased every 4 weeks in increments of 5 mg/day to a maximum of 15 mg/day	C1: pioglitazone, po., 15 mg/day, could be increased every 4 weeks in increments of 15 mg/day to a maximum of 45 mg/day
Jibran 2006	I1: glibenclamide, po., initiated at 5 mg/day and titrated to a maximum of 15 mg/day. Diet	C1: repaglinide, po., initiated with 0.5 mg 3 times a day at any time from 30 minutes to immediately before meals, titrated to a maximum of 2 mg 3 times a day based on glucose levels. Diet
Johnston 1997	I1: glibenclamide, po., initially 1.25 mg/day in the morning and could be increased to 6 additional dose levels (2.5, 5, 7.5, 10, 15 and 20 mg/day). Dose increases could only occur by one increment at a time. In general, doses were increased as long as FPG levels were greater than 140 mg/dL, and decreased if the FPG and/or home glucose monitoring data suggested a risk of hypoglycaemia. Diet	C1: placebo tablets, po. Diet C2: miglitol, po., 25 mg with the first bite of each main meal and could not change their miglitol dose for the duration of double-blind treatment. Diet C3: miglitol, po., 50 mg with the first bite of each main meal and could not change their miglitol dose for the duration of double-blind treatment. Treated with miglitol 25 mg the first 2 weeks. Diet
Kaku 2011	I1: glibenclamide, po., 1.25 to 2.5 mg/day. Initially, the patients entered a 2-week dose escalation period. Tablet taken before or after breakfast, if 2.5 (2 tablets) in the morning, or 1 in the morning and 1 in the evening. Placebo liraglutide injections during the double-blind intervention period. Adhere to previous diet and exercise, if any	C1: liraglutide, sc., initially the patients were entered into a 2-week dose escalation period (in 0. 3 mg increments), followed by a 50-week maintenance period during which they received liraglutide 0.9 mg/day given subcutaneously (in the morning or evening). Placebo glibenclamide tablets, po., during the double-blind intervention period. Adhere to previous diet and exercise, if any
Kamel 1997	I1: gliclazide, po I2: glibenclamide, po	C1: acarbose, po C2: metformin, po C3: placebo, po
Kanda 1998	I1: gliclazide, po., 40 mg/day	C1: acarbose, po., 300 mg/day
Kovacevic 1997	I1: glibenclamide, po., according to blood glucose (1 to 3 x 3.5 mg/day before breakfast and dinner). Diet	C1: acarbose, po., 3 x 100 mg/day, before main meals). Diet C2: placebo, po., 2 x 1 tablet a day before meals. Diet
Lawrence 2004	I1: gliclazide, po., 80 mg once daily, up titrated up to 160 mg once daily depending on FBG	C1: metformin, po., initial 500 mg twice a day, up titrated up to 1 g three times a day depending on FBG C2: pioglitazone, po., 30 mg once daily, up titrated to 45 mg once daily depending on FBG

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LEAD-3 2006	I1: glimepiride, capsule, po., 8 mg once daily in the morning before or with the first meal of the day. Liraglutide placebo, sc., once daily	C1: liraglutide, sc., 1.2 mg was injected once daily at any time of day in the upper arm, abdomen or thigh with a prefilled pen injection device. Participants were encouraged to inject liraglutide at the same time each day. Placebo glimepiride, po., once daily C2: liraglutide, sc., 1.8 mg was injected once daily at any time of day in the upper arm, abdomen or thigh with a prefilled pen injection device. Participants were encouraged to inject liraglutide at the same time each day. Placebo glimepiride, po., once daily
Madsbad 2001	I1: glipizide, po., 4 dose levels: 1) 5 mg before breakfast; 2) 7.5 mg before breakfast; 3) 10 mg before breakfast; 4) 10 mg before breakfast plus 5 mg before dinner. Patients also received placebo at lunch and dinner	C1: repaglinide, po., 4 dose levels: 1) 0.5 mg with meals; 2) 1.0 mg with meals; 3) 2.0 mg with meals; 4) 4.0 mg with meals. In all cases, medication was taken 30 min before meals. Patients with FBG > 9.0 mmol/L on their previous antidiabetic drug started at dose level 2. Otherwise all patients started at dose level 1
Marbury 1999	I1: glibenclamide, po., once daily before breakfast, with 2 identical placebo tablets before lunch and before dinner. Administered in accordance with the dosing recommendations in effect at the time the trial was conducted. The dose was increased as necessary to 5, 10 or 15 mg daily (administered as 10 mg before breakfast and 5 mg before dinner). Patients with an FPG > 160 mg/dl who had previously taken oral antidiabetic intervention could begin at a higher dose	C1: repaglinide, po., initiated at 0.5 mg preprandially (with 3 daily meals) and adjusted in increments of 1, 2 or 4 mg. Patients with an FPG > 160 mg/dl who had previously taken oral antidiabetic intervention could begin at a higher dose
Memisogullari 2009	I1: gliclazide, po., 80 mg/day. Diet	C1: no comparator. Diet
Nakamura 2004	I1: glibenclamide, po., 5 mg/day	C1: pioglitazone, po., 15 mg/day C2: voglibose, po., 0.6 mg/day
Nakamura 2006	I1: glibenclamide, po., 2.5 mg twice a day before meals	C1: pioglitazone, po., 15 mg once a day before breakfast C2: voglibose, po., 0.6 mg/day 3 times a day before meals C3: nateglinide, po., 270 mg 3 times a day before meals
Nathan 1988	I1: glibenclamide, po., initial 2.5 mg /day, adjusted weekly, max 10 mg twice a day Placebo insulin. Diet	C1: insulin (neutral protamine Hagedorn), initial 15 U/day, adjusted according to nurse or physician Maximum increment was doubling of previous dose, adjusted weekly. Placebo glibenclamide. Diet

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Pagano 1995	I1: glibenclamide, po., initially 2.5 mg twice a day in 6 weeks. After this the dose was increased to 5 mg twice daily. Taken before meals. Placebo tablets before breakfast. Diet	C1: miglitol, po., 50 mg 3 times a day for 6 weeks, thereafter 100 mg three times a day Taken before meals. Diet
Perriello 2007	I1: gliclazide, po., 80 to 320 mg/day. With higher dosis 80 or 160 mg were given twice daily	C1: pioglitazone, po., 30 to 45 mg/day. Patients receiving maximum dose, received 45 mg in the morning and placebo in the evening
Rosenthal 2002	I1: glibenclamide, po., titrated from 1.75 mg/day once daily to a maximum of 10.5 mg/day (mean dose 5.1 mg/day)	C1: acarbose, po., 50 mg 3 times a day titrated up to 100 mg 3 times a day
Salman 2001	I1: gliclazide, po., initial dose of 40 mg twice daily until week 4. After this the dosage was increased up to 80 mg twice daily, depending on the patient's degree of metabolic control	C1: acarbose, po., adjusted from 50 mg once daily up to 100 mg twice daily during the first weeks of active treatment. After 4 weeks, all patients received acarbose 100 mg 3 times daily until the end of the trial. Patients who exhibited gastrointestinal intolerance were returned to the previously tolerable dosage level, and then after 4 weeks the dose was again increased gradually
Segal 1997	I1: glibenclamide, po., 3.5 mg daily. Protocol allowed doubling of dose after 4 weeks, if hyperglycaemia persisted	C1: miglitol, po., 50 mg 3 times a day in the first 4 weeks followed by 100 mg 3 times a day C2: placebo, po., daily
Shihara 2011	I1: glimepiride, po., HbA1c $\geqq$ 6.4% to < 7.4 % 0. 5 mg/day; HbA1c >= 7.4% to < 10.4 % 1 mg/day Maximum dose 6 mg/day. Diet and exercise unchanged from baseline	C1: pioglitazone, po., initial 15 mg/day, could be increased to 45 mg (men) and 30 mg (women) Diet and exercise unchanged from baseline
Spengler 1992	I1: glibenclamide, po., tablets of 3.5 mg. Dosis ranged from1-3 x 1 tablet per day, according to metabolic control. Diet	C1: acarbose, po., 3 x 50 mg for 2 weeks and 3 x 100 mg per day from third week. Diet
Sung 1999	I1: glibenclamide, po., 20 mg/day. Diet and exercise prescription was not changed	C1: troglitazone, po., 400 mg/day. Diet and exercise prescription was not changed
Sutton 2002	I1: glibenclamide, po., once or twice a day. Initial dose not described. Daily dose not exceed 20 mg/day	C1: rosiglitazone, po., 4 mg, twice a day
Tan 2004	I1: glimepiride, po., 2 mg a day. Dose adjustments made with 4 weeks interval 2 mg increments to a maximum of 8 mg a day	C1: pioglitazone, po., the initial dosis was 15 mg a day. Doses were adjusted in 15 mg increments to a maximum of 45 mg a day

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Tan 2004a	I1: glibenclamide, po., initial dosis was 1.75 mg. Adjusted according to titration gold. The dose was increased to 3.5 mg at week 4, to 7.0 mg at week 8 and to 10.5 mg at week 12. Diet	C1: pioglitazone, po., initial dosis was 30 mg. Adjusted according to titration gold. The dose was increased to 45 mg at week 4. Diet
Tan 2005	I1: gliclazide, po., up to 320 mg daily on the basis of tolerability	C1: pioglitazone, po., up to 45 mg daily on the basis of tolerability
Tang 2004	I1: glimepiride, po., 1 to 2 mg/day	C1: metformin, po., 750 to 1500 mg/day
Teramoto 2007	I1: glibenclamide, po., 1.25 mg/day for 1 to 8 weeks, if FPG $\geqq$ 126 mg/dl, the dose was increased to 2.5 mg/day	C1: pioglitazone, po., 15 mg once a day for 1 to 8 weeks, if FPG $\geqq$ 126 mg/dl, the dose was increased to 30 mg/day
Tessier 1999	I1: gliclazide, po., titrated to glycaemic target. Gliclazide was increased with the intervals: 80, 160, 240 and 320 mg/d divided into 2 doses with breakfast and supper	C1: metformin, po., titrated to glycaemic target. Metformin dosage was 750, 1500 and 2250 mg (divided into 3 doses) one with each meal
Tosi 2003	I1: glibenclamide, po. The starting dose was 1 tablet before lunch, consisting of glibenclamide 5 mg The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets 3 times daily (before breakfast, before lunch and before dinner) For the group treated with glibenclamide alone, the last 2 steps were 1 tablet of active drug + 1 tablet of placebo	C1: metformin, po. The starting dose was 1 tablet before lunch, consisting of metformin 500 mg. The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets 3 times daily (before breakfast, before lunch and before dinner). Therefore scheduled dose steps were 500, 1.000, 2.000, 3.000 mg/d for metformin. Diet
UGDP 1970	I1: tolbutamide, po., 1.5 g per day (1 g before breakfast, 0.5 g before evening meal). Diet	C1: placebo tablets, po., given twice a day (before breakfast and before evening meal). Diet C2: insulin (lente), injection, 10, 12, 14 or 16 units per day depending on the patient's body surface. Diet
UKPDS 1998	I1: chlorpropamide, po., 100 to 500 mg. Diet I2: glibenclamide, po., 2.5 to 20 mg. Diet I3: glipizide, po., 2.5 to 40 mg. Diet	C1: insulin, initial once daily ultralente insulin or isophane insulin. If the daily dose was more than 14 units (U) or pre-meal or bed-time home blood glucose measurements were more than 7 mmol/L, a short-acting insulin, usually soluble (regular) insulin was added, i.e., basal/bolus regimen. Diet
UKPDS 34 1998	I1: chlorpropamide, po., 100 to 500 mg. Diet I2: glibenclamide, po., 2.5 to 20 mg. Diet	C1: metformin, po., 850 mg tablet per day, then 850 mg twice daily, and then 1700 mg in the morning and 850 mg with the evening meal (maximum dose = 2550 mg). If on any dose, symptoms of diarrhoea

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		or nausea occurred, patients reduced the dose to that which previously did not cause symptoms. Diet C2: insulin, initial once daily ultralente insulin or isophane insulin. If the daily dose was more than 14 units (U) or pre-meal or bed-time home blood glucose measurements were more than 7 mmol/L, a short-acting insulin, usually soluble (regular) insulin was added, i.e. basal/bolus regimen. Diet
van de Laar 2004	I1: tolbutamide, po., up titrated to receive glycaemic target (milligrams, morning-afternoon-evening): 500-0-0, 500-0-500, 500-500-500 and 1000-500-500, respectively. Otherwise medication dosage was continued to the end of the trial. Diet	C1: acarbose, po., dosis was increased to receive glycaemic target (milligrams, morning- afternoon-evening): 50-0-0, 50-0-50, 50-50-50 and 100-100-100, respectively. Otherwise medication dosage was continued to the end of the trial. Diet
Watanabe 2005	I1: glibenclamide, po., regulation within the range of 1.25 to 2.5 mg/day	C1: pioglitazone, po.,15 mg/day
Wolffenbuttel 1989	I1: tolbutamide, po., given in two doses of 500 to 1000 mg. When adequate control could not be achieved with this drug glibenclamide was given in 2 doses of 2.5 to 10 mg	C1: insulin, 2 daily injections of intermediate-acting insulin (before breakfast and before dinner), supplemented with short-acting insulin, when postprandial glucose levels exceeded 11 mmol/L
Wolffenbuttel 1999	I1: glibenclamide (micronised formulation), po., 1.75 mg before breakfast (step 1); 3.5 mg before breakfast (step 2); 7.0 mg (step 3) before breakfast; 7 mg before breakfast + 3.5 mg before dinner (step 4) Drug-naive patients started at step 1, previously sulphonylurea-treated patients started on step 1 or 2. Patients on maximal dosages of sulphonylurea started on step 2 or 3 Patients also received placebo	C1: repaglinide, po., 1.5 mg (step 1), 3.0 mg (step 2), 6.0 mg (step 3), and 12.0 mg (step 4) daily, all in three identical dosages (0.5-4.0 mg) taken in encapsulated tablets just before meals. Drug naive patients started on step 1, where as patients previously on sulphonylureas could start on step 1 or step 2. Patients on maximal dosages of sulphonylureas with fasting blood glucose > 10 mmol/L started on dosage level 2 or 3
Yamanouchi 2005	I1: glimepiride, po., 1.0 to 2.0 mg/day. Dietary regimens remained unchanged	C1: pioglitazone, po., 30 to 45 mg/day. Dietary regimens remained unchanged C2: metformin, po., tablet a 250 mg, 750 mg/day. Dietary regimens remained unchanged
Zhang 2005	I1: glipizide, po., 5 mg, 3 times a day	C1: rosiglitazone, po., 4 mg/day once a day C2: rosiglitazone, po., 8 mg, once a day

Footnotes
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; C: control; FBG: fasting blood glucose; FPG: fasting plasma glucose; I: intervention; LEAD-3: Liraglutide Effect and Action in Diabetes-3; po.: per oral; sc.: subcutaneous; UKPDS: United Kingdom Prospective Diabetes Study; U: units

Appendix 3. Baseline characteristics (I)

Characteristic Study ID	Intervention(s) and control(s)	Duration of intervention (follow-up)	Country (Setting)	Participants [N]	Sex [female/male]	Age [mean years (SD)]	HbA1c [mean % (SD)]	Fasting plasma glucose [mean mmol/L (SD)]	BMI [mean kg/m^2(SD)]
Abbatecola 2006	I1: glibenclamide C1: repaglinide	12 mo + 3 wk (12 mo + 3 wk)	Italy (outpatients)	156	I1: 41/38 C1: 39/38	I1: 74.3 (2.3) C1: 74.5 (2.5)	I1: 7.2 (0.7) C1: 7.3 (0.8)	I1: 9.0 (0.3) C1: 8.9 (0.4)	I1: 26.7 (0.4) C1: 27.1 (0.2)
ADOPT 2006[a,b]	I1: glibenclamide C1: rosiglitazone C2: metformin	4 yr (4 yr)	North America, Canada, Europe (outpatients)	4360	I1: 605/836 C1: 645/811 C2: 590/864	I1: 56.4 (10.2) C1: 56.3 (10.0) C2: 57.9 (9.9)	I1: 7.4 (0.9) C1: 7.4 (0.9) C2: 7.4 (0.9)	I1: 8.5 (1.5) C1: 8.4 (1.4) C2: 8.4 (1.4)	I1: 32.3 (6.3) C1: 32.2 (6.7) C2: 32.1 (6.1)
AGEE/DCD/046/UK[a]	I1: glibenclamide C1: repaglinide	12 mo + 6 to 8 wk (12 mo + 6 to 8 wk+ 3 mo)	United Kingdom (outpatients)	264	I1: 19/66 C1: 69/109	I1: 60.6 (8.3) C1: 62.3 (7.6)	I1: 7.5 (1.6) C1: 7.4 (1.5)	I1: 11.2 (3.4) C1: 10.8 (3.5)	I1: 28.4 (3.3) C1: 27.8 (3.5)
AGEE/DCD/047/B/F/I	I1: gliclazide C1: repaglinide	12 mo + 6 to 8 wk (12 mo + 6 to 8 wk)	Belgium, France, Italy (outpatients)	305	I1: 34/65 C1: 70/136	I1: 58.7 (8.0) C1: 58.3 (8.1)	I1: 7.1 (1.3) C1: 7.3 (1.4)	I1: 11.2 (3.3) C1: 11.3 (3.4)	I1: 27.6 (4.0) C1: 27.7 (3.4)
Alvarsson 2010[c]	I1: glibenclamide C1: insulin	6 yr (6yr)	Sweden (outpatients)	49	I1: 4/14 C1: 6/10	I1: 55.9 (7.2) C1: 51.7 (7.6)	I1: 6.8 (0.85) C1: 7.1 (1.6)	I1: 9.8 (2.2) C1: 10.6 (2.4)	I1: 28.5 (3.0) C1: 26.5 (3.6)
APPROACH 2010[d]	I1: glipizide C1: rosiglitazone	18.6 mo (18.6 mo)	Asia, Europe, North America, South America (outpatients)	672	I1: 116/233 C1: 100/233	I1: 60.2 (9.0) C1: 61.8 (8.4)	I1: 7.2 (0.9) C1: 7.1 (0.8)	I1: 8.1 (2.3) C1: 8.3 (2.6)	I1: 29.8 (5.3) C1:29.3 (5.5)

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Birkeland 1994[e]	I1: glibenclamide I2: glipizide C1: placebo	15 mo (15 mo)	Norway (outpatients)	46	All patients: 24/22	All patients: 59 (7)	I1: 9.5 (2.4) I2: 10.1 (2.7) C1: 9.0 (2.0)	I1: 9.5 (2.4) I2: 10.1 (2.7) C1: 9.0 (2.4)	All patients: 26.4 (3.9)
Birkeland 2002	I1: glibenclamide C1: insulin	42 mo (42 mo)	Norway (outpatients)	36	All patients: 14/22	All patients: 59.2 (6.1)	I1: 8.5 (1.4) C1: 9.1 (1.4)	I1: 11.4 (2.3) C1: 11.6 (3.2)	I1: 26.2 (3.8) C1: 26.4 (3.1)
Campbell 1994	I1: glipizide C1: metformin	12 mo (12 mo)	UK (outpatients)	48	I1: 16/8 C1: 16/8	I1: 57 (9) C1: 57 (10)	I1: 11.8 (2.1) C1: 11.5 (1.9)	I1: 12.2 (3.3) C1: 11.2 (2.8)	I1: 31.2 (6.6) C1: 29.6 (5.6)
Charbonnel 2005[f]	I1: gliclazide C1: pioglitazone	52 wk (52 wk)	Europe, Australia, Canada, South Africa, Israel (outpatients)	1270	I1: 240/386 C1: 241/383	I1: 56 (9.6) C1: 56 (9.5)	I1: 8.7 (1.1) C1: 8.7 (1.0)	I1: 11.1 (2.9) C1: 11.1 (2.8)	I1: 30.6 (5.1) C1: 31.7 (6.0)
Collier 1989	I1: gliclazide C1: metformin	6 mo (6 mo)	- (outpatients)	24	I1: 6/6 C1: 6/6	I1: 55.5 (5.1) C1: 53.1 (5.1)	I1: 11.7 (1.5) C1: 12.1 (2.4)	I1: 12.2 (2.4) C1: 11.8 (3.1)	I1: 23.1 (1.3) C1: 24.3 (1.4)
Coniff 1995[b]	I1: tolbutamide C1: acarbose C2: placebo	24 wk (30 wk)	USA (outpatients)	220	I1: 29/37 C1: 41/26 C2: 30/32	I1: 55.4 C1: 56.2 C2: 56.3	I1: 7 C1: 6.9 C2: 7.1	I1: 12 C1: 12.2 C2: 12.6	I1: 29.5 C1: 29.7 C2: 29.9
Dalzell 1986[g]	I1: tolbutamide C1: metformin	1 yr (1 yr)	Ireland (outpatients)	33	-	I1: 54.1 (1.1) C1: 52.5 (1.9)	-	I1: 16.4 (0.8) C1: 15.7 (0.9)	-
DeFronzo 2005[b,h]	I1: glibenclamide C1: metformin	29 wk (29 wk)	USA (outpatients)	419	I1: 106/103 C1: 114/96	I1: 56 (14.5) C1: 55 (14.5)	I1: 8.5 (1.4) C1: 8.9 (1.4)	I1: 13.7 (2.4) C1: 14.1 (3.2)	I1: 29.1 (4.3) C1: 29.0 (4.3)

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Deng 2003	I1: glibenclamide C1: xiaoyaosan	6 mo (6 mo)	China (-)	160	-	-	I1: 9.0 (1.7) C1: 9.0 (1.6)	I1: 10.3 (1.0) C1: 10.4 (1.0)	-
Derosa 2003[b]	I1: glimepiride C1: repaglinide	14 mo (14 mo)	Italy (outpatients)	132	I1: 32/30 C1: 31/31	I1: 54 (10) C1: 56 (9)	I1: 7.8 (1.2) C1: 8.0 (1.1)	I1: 9.1 (1.0) C1: 8.8 (1.2)	I1: 26.4 (1.0) C1: 26.1 (1.2)
Derosa 2004[b]	I1: glimepiride C1: metformin	14 months	Italy (outpatients)	164	I1: 38/43 C1: 42/41	I1: 56 (10) C1: 58 (9)	I1: 8.5 (1.2) C: 8.4 (1)	I1: 9.2 (1.1) C1: 9.6 (0.8)	I1: 27.6 (1.2) C1: 28.1 (1.5)
Diehl 1985[b]	I1: chlorpropamide C1: insulin	24 wk (24 wk)	USA (outpatients)	77	I1: 29/11 C1: 26/11	I1: 50.6 (9.5) C1: 51.2 (9.3)	-	I1: 13.1 (4.5) C1: 13.5 (4.1)	-
Ebeling 2001[i]	I1: glibenclamide C1: pioglitazone C2: placebo	6 mo (6 mo)	Finland (outpatients)	29	All patients: 8/21	All patients: 55.2 (9.7)	I1: 8.9 (0.9) C1: 9.1 (0.9) C2: 8.6 (0.6)	I1: 11.6 (1.6) C1: 10.9 (1.8) C2: 11.3 (1.6)	I1: 30.2 (5.4) C1: 30.5 (3.9) C2: 31.9 (4.7)
Esposito 2004[b]	I1: glibenclamide C1: repaglinide	12 mo + 6 to 8 wk (12 mo + 6 to 8 wk)	Italy (outpatients)	175	I1: 41/46 C1: 41/47	I1: 51.3 (5.9) C1: 52 (6.4)	I1: 7.4 (1.1) C1: 7.5 (1.1)	I1: 9.1 (1.7) C1: 8.8 (1.8)	I1: 28.3 (4.1) C1: 28.5 (4.3)
Feinböck 2003	I1: glibenclamide C1: acarbose	26 wk (26 wk)	Austria (outpatients)	219	I1: 38/73 C1: 45/63	I1: 57.7 (10.2) C1: 57.1 (10.7)	I1: 9.1 (1.9) C1: 9.4 (2.0)	I1: 10.3 (2.8) C1: 10.9 (3.0)	I1: 29.2 (3.6) C1: 29.1 (3.4)
Fineberg 1980[b,j]	I1: glipizide C1: tolbutamide	6 mo (6 mo)	USA (outpatients)	18	I1:2/6 C1: 2/8	I1: 61 (11.3) C1: 64 (9.5)	-	I1: 10.6 (1.1) C1: 9.6 (1.4)	-
Foley 2009	I1: gliclazide C1: vildagliptin	104 wk (104 wk)	Europe, Latin America, South Africa (outpa-	1092	I1: 258/288 C1: 225/321	I1: 54.3 (10.4) C1: 55.2 (10.6)	I1: 8.7 (1.1) C1: 8.6 (1.0)	I1: 10.8 (2.9) C1: 10.8 (2.9)	I1: 30.8 (5.5) C1: 30.6 (5.0)

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			tients)						
Forst 2003	I1: glibenclamide C1: insulin lispro	24 wk (24 wk)	Sweden, Germany, Switzerland (outpatients)	143	I1: 29/39 C1: 24/51	I1: 56.6 (8.6) C1: 58.7 (7.3)	I1: 7.7 (1.2) C1: 7.5 (1.0)	-	I1: 28.7 (3.9) C1: 29.7 (3.6)
Forst 2005[k]	I1: glimepiride C1: pioglitazone	24 wk (24 wk)	Germany (outpatients)	179	I1: 32/52 C1: 34/55	I1: 63.0 (7.4) C1: 62.2 (8.4)	I1: 7.4 (0.9) C1: 7.5 (0.9)	-	I1: 31.8 (4.3) C1: 31.7 (5.0)
Hanefeld 2005 2011[b,l]	I1: glibenclamide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	52 wk (52 wk)	France, Germany, Italy, UK, Belgium, Sweden, Ireland, Netherlands (outpatients)	598	I1: 60/143 C1: 62/133 C2: 80/109	I1: 60.1 (8.3) C1: 60.4 (8.2) C2: 60.6 (9.2)	I1: 8.2 (1.3) C1: 8.1 (1.3) C2: 8.2 (1.4)	I1: 10.6 (2.8) C1: 10.6 (3.1) C2: 10.9 (2.9)	I1: 28.7 (3.9) C1: 28.7 (3.7) C2: 28.8 (3.7)
Harrower 1985[m]	I1: glipizide I2: gliquidone I3: gliclazide I4: glibenclamide C1: chlorpropamide	12 mo (12 mo)	Scotland (outpatients)	112	-	I1: 62 (8.8) I2: 63.5 (12.7) I3: 60.0 (10.3) I4: 60.0 (9.6) C1: 60.5 (9.2)	I1: 10 (2) I2: 14 (3) I3: 13 (5) I4: 11 (6) C1: 11 (6)	-	-
Hermann 1991[n]	I1: glibenclamide C1: metformin	6 mo (6 mo)	Sweden (outpatients)	25	All patients: 7/18	All patients: 58.9 (8.8)	I1: 8.1 (1.0) C1: 7.9 (1.6)	I1: 7.4 (1.3) C1: 6.9 (2.0)	All patients: 26.2 (3.8)
Hermann 1991a[o]	I1: glibenclamide C1: metformin	6 mo + 2 to 12 wk (6 mo + 2 to 12 wk)	Sweden (outpatients)	72	All patients: 45/79	All patients: 59.4 (8.8)	I1: 6.7 (1.7) C1: 6.9 (1.8)	I1: 8.6 (2.3) C1: 9.3 (2.5)	All patients: 28.3 (4.6)
Hoffmann 1990[f,p]	I1: glibenclamide C1: acar-	24 wk (24 wk)	Germany (outpatients)	95	All patients: 56/39	All patients: 62 (6)	I1: 10.8 (1.4) C1: 10.7	I1: 9.2 (0.7) C1: 8.9 (1.	-

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	bose						(0.2)	0)	
Hoffmann 1994[q]	I1: glibenclamide C1: placebo C2: acarbose	24 wk (24 wk)	Germany (outpatients)	85	I1: 14/13 C1: 18/12 C2: 15/13	I1: 59.5 (5.7) C1: 56.9 (6.7) C2: 58.8 (6.9)	I1: 8.3 (0.4) C1: 9.0 (1.1) C2: 8.3 (0.4)	I1: 9.0 (1.1) C1: 9.0 (1.1) C2: 9.0 (1.1)	I1: 26.5 (2.1) C1: 26.8 (1.5) C2: 26.5 (1.6)
Hollander 1992	I1: glibenclamide C1: insulin	44 wk (44 wk)	- (-)	59	-	-	All patients: 8.8 (3)	All patients: 13.4 (0.8)	-
Jain 2006[b]	I1: glibenclamide C1: pioglitazone	56 wk (56 wk)	USA, Puerto Rico (outpatients)	502	I1: 110/141 C1: 118/133	I1: 52.1 (12.4) C1: 52.1 (11.3)	I1: 9.2 (1.2) C1: 9.2 (1.2)	I1: 10.2 (3.0) C1: 10.5 (2.9)	I1: 32.8 (5.7) C1: 32.5 (5.8)
Jibran 2006[b]	I1: glibenclamide C1: repaglinide	12 mo (12 mo)	Pakistan (outpatients)	100	I1: 40/10 C1: 34/16	I1: 45.8 (8.8) C1: 46.6 (10.5)	I1: 10.2 (1.6) C1: 9.9 (1.6)	I1: 7.8 (3.1) C1: 9.5 (2.9)	I1: 30.4 (5.6) C1: 27.1 (3.5)
Johnston 1997[r]	I1: glibenclamide C1: placebo C2: miglitol 25 mg C3: miglitol 50 mg	56 wk (56 wk)	USA (outpatients)	411	I1: 33/59 C1: 26/66 C2: 24/61 C3: 26/66	I1: 67.7 (6.1) C1: 68.5 (6.0) C2: 67.2 (6.1) C3: 67.8 (7.1)	I1: 8.4 (1.0) C1: 8.4 (1.0) C2: 8.3 (1.0) C3: 8.4 (1.0)	I1: 10.8 (2.3) C1: 10.8 (2.5) C2: 10.9 (2.5) C3: 11.0 (1.1)	I1: 29.3 (6.1) C1: 30.4 (6.0) C2: 29.7 (6.1) C3: 29.4 (6.1)
Kaku 2011[b,s]	I1: glibenclamide C1: liraglutide	52 wk (52 wk)	Japan (outpatients)	411	I1: 46/86 C1: 85/183	I1: 58.5 (10.4) C1: 58.2 (10.4)	I1: 9.2 (1.0) C1: 9.3 (1.1)	I1: 11.2 (2.7) C1: 11.3 (2.8)	I1: 24.6 (3.8) C1: 24.9 (3.7)
Kamel 1997	I1: gliclazide I2: glibenclamide C1: acarbose C2: metformin C3: placebo	24 wk (24 wk)	Turkey (-)	43	-	-	I1: 8.4 (1.1) I2: 8.4 (1.1) C1: 8.5 (0.8) C2: 8.4 (0.7) C3: 8.1 (0.5)	I1: 10.3 (2) I2: 10.4 (1.8) C1: 9.6 (1.4) C2: 10.8 (1.2) C3: 9.3 (0.8)	-

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Kanda 1998[b]	I1: gliclazide C1: acarbose	12 mo (12 mo)	Japan (-)	19	I1: 5/4 C1: 5/5	I1: 40.5 (11.3) C1: 40.1 (9.8)	I1: 8.7 (1.3) C1: 8.6 (1.1)	I1: 10 (2.5) C1: 8.7 (2.4)	I1: 25.7 (3.1) C1: 25.4 (2.6)
Kovacevic 1997	I1: glibenclamide C1: acarbose C2: placebo	24 wk (24 wk)	Croatia (outpatients)	102	All patients: 55/47	All patients: 57.5 (8.1)	I1: 9.0 (1.0) C1: 8.3 (0.7) C2: 8.3 (1.1)	I1: 13.9 (4.2) C1: 11.7 (3.11) C2: 11.9 (3.3)	All patients: 28.7 (2.8)
Lawrence 2004[t]	I1: gliclazide C1: metformin C2: pioglitazone	24 wk (24 wk)	UK (outpatients)	64	I1: 7/13 C1: 8/12 C2: 6/14	I1: 63.5 (11.4) C1: 59.5 (9.3) C2: 60.4 (7.5)	I1: 7.9 (0.9) C1: 8.0 (0.9) C2: 7.4 (0.9)	I1: 10.1 (2.1) C1: 9.8 (2.3) C2: 9.5 (2.1)	I1: 28.7 (28.3 to 34.4) C1: 29.2 (28.1 to 31.6) C2: 30.6 (29.4 to 35.2)
LEAD-3 2006[u]	I1: glimepiride C1: liraglutide 1.2 mg C2: liraglutide 1.8 mg	195 wk (195 wk)	USA, Mexico (outpatients)	746	I1: 115/133 C1: 134/117 C2: 126/121	I1: 53.4 (10.9) C1: 53.7 (11.0) C2: 52.0 (10.8)	I1: 8.4 (1.2) C1: 8.3 (1.0) C2: 8.3 (1.1)	I1: 9.5 (2.6) C1: 9.3 (2.6) C2: 9.5 (2.6)	I1: 33.2 (5.6) C1: 33.2 (5.6) C2: 32.8 (6.3)
Madsbad 2001	I1: glipizide C1: repaglinide	12 mo + 6 to 8 wk (12 mo + 6 to 8 wk)	Denmark, Norway, Finland, Sweden (outpatients)	256	I1: 29/52 C1: 68/107	I1: 62.0 (8.8) C1: 60.2 (8.1)	I1: 7.2 (1.4) C1: 7.3 (1.2)	I1: 10.8 (2.7) C1: 11.0 (3.0)	I1: 28 (3.5) C1: 28 (3.6)
Marbury 1999[b,v]	I1: glibenclamide C1: repaglinide	12 mo (12 mo + 3 mo)	USA, Canada (outpatients)	576	I1: 62/120 C1: 120/242	I1: 58.7 (9.0) C1: 58.3 (9.4)	I1: 8.9 (1.6) C1: 8.7 (1.7)	I1: 11.4 (3.3) C1: 11.2 (3.4)	I1: 29.1 (3.7) C1: 29.4 (3.7)
Memisogull 2009	I1: gliclazide C1: nothing	6 mo (6 mo)	Turkey (outpatients)	56	All patients: 27/29	I1: 45.2 (10.6) C1: 46.8 (9.1)	-	-	-

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Nakamura 2004	I1: glibenclamide C1: pioglitazone C2: voglibose	12 mo (12 mo)	Japan (outpatients)	45	I1: 7/8 C1: 6/9 C2: 7/8	I1: 55.0 (11.5) C1: 56.5 (12.0) C2: 55.0 (11.0)	I1: 7.8 (1.4) C1: 7.9 (1.3) C2: 8.1 (1.6)	-	-
Nakamura 2006	I1: glibenclamide C1: pioglitazone C2: voglibose C3: nateglinide	12 mo (12 mo)	Japan (outpatients)	68	I1: 8/10 C1: 8/9 C2: 7/10 C3: 7/9	I1: 53.5 (12.0) C1: 56.0 (12.8) C2: 55.0 (12.8) C3: 53.5 (12.2)	I1: 7.8 (1.3) C1: 8.0 (1.4) C2: 7.6 (1.3) C3: 7.7 (1.4)	-	-
Nathan 1988	I1: glibenclamide C1: insulin	9 mo (9 mo)	USA (outpatients)	31	I1: 7/9 C1: 7/8	I1: 50.3 (5.9) C1: 53.5 (7.1)	I1: 10.5 (2.4) C1: 10.3 (1.5)	I1: 13.9 (5.4) C1: 10.3 (1.5)	I1: 30.2 (5.7) C1: 28.6 (5.1)
Pagano 1995[w]	I1: glibenclamide C1: miglitol	6 mo (6 mo)	Italy (outpatients)	100	I1: 23/24 C1: 16/33	I1: 59 (1.1) C1: 57 (1.2)	I1: 7.8 (0.7) C1: 8.2 (1.4)	I1: 9.1 (1.4) C1: 8.9 (1.4)	I1: 26.7 (2.7) C1: 26.4 (2.8)
Perriello 2007	I1: gliclazide C1: pioglitazone	1 yr (1 yr)	Italy (outpatients)	283	I1: 49/88 C1: 49/97	I1: 59 (7) C1: 58 (8)	I1: 8.7 (0.9) C1: 8.8 (0.9)	I1: 10.4 (2.1) C1: 10.9 (2.1)	I1: 28.8 (2.8) C1: 29.2 (3.1)
Rosenthal 2002[b]	I1: glibenclamide C1: acarbose	6 mo (6 mo)	USA (outpatients)	76	-	I1: 57.7 (10.5) C1: 57.4 (8.6)	I1: 7.2 (1.7) C1: 7.0 (1.4)	I1: 8.6 (2.6) C1: 7.6 (2.4)	I1: 28.8 (4.3) C1: 29.1 (4.3)
Salman 2001[x]	I1: gliclazide C1: acarbose	24 wk (24 wk)	Turkey (outpatients)	68	I1: 14/16 C1: 10/17	I1: 56.1 (8.7) C1: 52.6 (9.1)	I1: 8.7 (0.6) C1: 8.9 (0.7)	I1: 9.7 (2.0) C1: 9.9 (2.4)	I1: 29.2 (2.8) C1: 30.2 (3.8)
Segal 1997[b,y]	I1: glibenclamide C1: miglitol C2: placebo	24 wk (24 wk)	Austria, Germany, Israel, Czech Republic (outpatients)	201	I1: 14/23 C1: 18/22 C2: 18/24	I1: 56 C1: 61 C2: 59	I1: 8.0 C1: 8.0 C2: 8.3	I1: 9.6 C1: 9.4 C2: 9.6	I1: 29.2 C1: 28.6 C2: 29.1

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Shihara 2011[b]	I1: glimepiride C2: pioglitazone	6 mo (6 mo)	Japan (outpatients)	191	I1: 33/62 C1: 31/65	I1: 57.7 (10.4) C1: 56.8 (10.3)	I1: 7.8 (0.9) C1: 7.8 (0.9)	I1: 8.0 (2.2) C1: 8.1 (2.5)	I1: 24.6 (3.8) C1: 24.5 (4.3)
Spengler 1992[z]	I1: glibenclamide C1: acarbose	24 wk (24 wk)	Germany (outpatients)	72	I1: 18/11 C1: 15/11	I1: 60 (7) C1: 59 (5)	I1: 11.0 (9.6 to 12.5) C1: 10.8 (9.6 to 12.3)	I1: 8.6 (7.5 to 10.5) C1: 8.6 (7.5 to 9.9)	-
Sung 1999[aa]	I1: glibenclamide C1: troglitazone	6 mo (6 mo)	USA (outpatients)	22	All patients: 7/15	All patients: 52 (12)	I1: 8.7 (1.2) C1: 8.3 (0.8)	I1: 10.7 (2.0) C1: 10.1 (1.5)	All patients: 35 (5)
Sutton 2002[b]	I1: glibenclamide C1: rosiglitazone	52 wk (52 wk)	USA (outpatients)	203	I1: 29/70 C1: 26/78	I1: 56.1 (8.9) C1: 55.1 (9.0)	I1: 9.5 (1.6) C1: 9.1 (1.7)	I1: 13.6 C1: 13.1	-
Tan 2004	I1: glimepiride C1: pioglitazone	52 wk (52 wk)	Mexico (outpatients)	244	I1: 58/65 C1: 67/54	I1: 55.7 (9.3) C1: 55.1 (8.0)	I1: 8.5 (1.0) C1: 8.5 (0.9)	I1: 9.1 (2.7) C1: 9.1 (2.5)	I1: 28.8 (3.2) C1: 29.3 (3.3)
Tan 2004a	I1: glibenclamide C1: pioglitazone	52 wk (52 wk)	Denmark, Norway, Sweden, Finland (outpatients)	200	I1: 29/80 C1: 35/56	I1: 57.9 (9.2) C1: 60.0 (8.5)	I1: 8.5 (0.8) C1: 8.4 (0.7)	I1: 10.7 (2.0) C1: 10.6 (2.4)	I1: 29.6 (4.8) C1: 30.2 (5.6)
Tan 2005[ab]	I1: gliclazide C1: pioglitazone	52 wk (52 wk)	Australia, Canada, Finland, Poland, the Slovak Republic, UK, South Africa (outpatients)	567	I1: 115/182 C1: 99/171	I1: 56 (9.9) C1: 57 (9.8)	I1: 8.8 (0.3) C1: 8.6 (0.2)	I1: 11.3 (1.7) C1: 10.9 (1.5)	I1: 31 (5.6) C1: 32 (6.4)
Tang 2004	I1: glimepiride C1: metformin	6 mo (6 mo)	China (-)	62	I1: 12/21 C1: 11/18	I1: 56.4 (8.8) C1: 53.8 (9.7)	I1: 6.8 (1.6) C1: 7.2 (1.4)	I1: 7.0 (2.5) C1: 7.5 (1.7)	I1: 23.3 (1.7) C1: 24.6 (2.2)

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Teramoto 2007[f]	I1: glibenclamide C1: pioglitazone	24 wk (24 wk)	Japan (outpatients)	92	I1: 11/35 C1: 13/33	I1: 56.4 (10.5) C1: 57.0 (10.7)	I1: 8.4 (1.3) C1: 8.0 (1.3)	I1: 10.7 (2.8) C1: 10.5 (4.2)	I1: 25.2 (4.8) C1: 24.7 (3.4)
Tessier 1999[ac]	I1: gliclazide C1: metformin	24 wk (24 wk)	Canada (outpatients)	39	I1: 8/10 C1: 3/15	I1: 59.3 (7.3) C1: 59.1 (7.1)	I1: 7.8 (1.8) C1: 7.1 (1.7)	I1: 11.3 (3.1) C1:9.1 (3.5)	I1: 28.6 (4.0) C1: 29.3 (3.0)
Tosi 2003	I1: glibenclamide C1: metformin	6 mo (6 mo)	Italy (outpatients)	44	I1: 6/16 C1: 6/16	I1: 57.9 (7.5) C1: 58.2 (7.3)	I1: 7.9 (1.0) C1: 7.7 (0.9)	I1: 13.4 (3.4) C1: 12.8 (4.0)	I1: 26.3 (2.3) C1: 26.4 (2.7)
UGDP 1970[ad]	I1:tolbutamide C1: placebo C2: insulin	4.75 yr (4.75 yr)	USA (outpatients)	619	I1: 141/63 C1:142/63 C2: 153/57	All patients: 52.7 (11.2)	-	I1: 7.8- C1: 8.0 C2: 7.9	-
UKPDS 1998[ae]	I1: chlorpropamide I2: glibenclamide I3: glipizide C1: insulin	10.0 yr (10.0 yr)	UK (outpatients)	2729	I1: 334/454 I2: 234/381 I3: 63/107 C1: 444/803	I1: 53.4 (9.2) I2: 54 (8) I3: 52 (10) C1: 53.6 (9.8)	I1: 6.4 (1.5) I2: 6.3 (1.3) I3: 6.9 (1.3) C1: 6.3 (2.1)	I1: 8.8 (2.0) I2: 8.0 (1.8) I3: 8.1 (2.0) C1: 8.1 (2.1)	I1: 27.3 (4.9) I2: 27.4 (4.9) I3: 28.5 (5.5) C1: 27.5 (5.3)
UKPDS 34 1998[af]	I1: chlorpropamide I2: glibenclamide C1: metformin C2: insulin	10.7 yr (10.7 yr)	UK (outpatients)	1293	I1: 146/119 I2: 150/127 C1: 185/157 C2: 217/192	I1: 53 (9) I2: 53 (9) C1: 53 (8) C2: 53 (8)	I1: 7.2 (1.8) I2: 7.2 (1.5) C1: 7.3 (1.5) C2: 7.2 (1.5)	I1: 8.0 (7.2 to 9.6) I2: 8.2 (7.3 to 9.6) C1: 8.1 (7.2 to 9.8) C2: 7.2 (1.5)	I1: 31.2 (4.5) I2: 31.5 (4.4) C1: 31.6 (4.2) C2: 31.0 (4.2)
van de Laar 2004[ag]	I1: tolbutamide C1: acarbose	30 wk (30 wk)	The Netherlands (outpatients, general practice)	96	I1: 23/25 C1: 23/25	I1: 57.8 (7.3) C1: 59.3 (7.5)	I1: 8.1 (1.6) C1: 8.1 (1.8)	I1: 9.2 (1.8) C1: 9.1 (2.2)	I1: 28.8 (5.5) C1: 29.1 (4.6)

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Watanabe 2005[b,ah]	I1: glibenclamide C1: pioglitazone	6 mo (6 mo)	Japan (outpatients)	30	I1: 2/12 C1: 2/11	I1: 65.1 (8.1) C1: 62.9 (10.3)	I1: 7.2 (0.5) C1: 6.9 (0.2)	I1: 8.2 (1.7) C1: 7.4 (1.4)	I1: 24.7 (3.7) C1: 24.4 (4.4)
Wolffenbuttel 1989	I1: tolbutamide C1: insulin	6 mo (6 mo)	The Netherlands (outpatients)	13	All patients: 7/6	All patients: 61 (3)	All patients: 13.0 (1.7)	All patients: 13.4 (2.7)	All patients: 24.1 (0.6)
Wolffenbuttel 1999[a,ai]	I1: glibenclamide C1: repaglinide	12 mo + 6 to 8 wk (12 mo + 6 to 8 wk)	The Netherlands, Germany, Austria (outpatients)	425	I1: 44/95 C1: 109/177	I1: 61 (9) C1: 61 (9)	I1: 7.0 (1.2) C1: 7.1 (1.4)	I1: 10.7 (3.0) C1: 10.9 (3.1)	I1: 28.0 (3.4) C1: 28.4 (3.6)
Yamanouchi 2005	I1: glimepiride C1: pioglitazone C2: metformin	12 mo (12 mo)	Japan (outpatients)	114	I1: 18/19 C1: 20/18 C2: 19/20	I1: 55.6 (9.3) C1: 55.2 (9.2) C2: 54.7 (9.8)	I1: 9.8 (0.7) C1: 10.2 (0.8) C2: 9.9 (0.7)	I1: 12.1 (1.6) C1: 12.0 (1.9) C2: 11.8 (1.7)	I1: 25.6 (3.5) C1: 25.8 (4.2) C2: 26.2 (3.8)
Zhang 2005	I1: glipizide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	6 mo (6 mo)	China (outpatients)	24	I1: 0/8 C1: 0/8 C2: 0/8	I1: 69 (3) C1: 70 (2) C2: 69 (3)	I1: 7.9 (0.5) C1: 8.0 (0.3) C2: 8.1 (0.4)	I1: 9.6 (0.7) C1: 9.8 (0.3) C2: 9.5 (0.8)	-

Footnotes
"-" denotes not reported
[a] Baseline characteristics only reported for the participants who received a dose of the study drug
[b] Fasting plasma glucose values are converted from mg/dl to mmol/L
[c] Baseline characteristics are from the participants who completed the trial. All SDs are calculated from SE
[d] Fasting plasma glucose values are converted from mg/dl to mmol/L. Values of fasting plasma glucose are medians
[e] HbA1c is read from graph.
[f] Baseline characteristics are not reported for all 1270 participants randomised, but only for the 1250 participants, who are reported in the publication
[g] Not described in abstract whether the values are SEs or SDs.
[h] All SDs are calculated from SEs.
[i] All SDs are calculated from SEs.
[j] Baseline variables only available for the 18 participants who completed the trial. All SDs are calculated from SE
[k] Baseline characteristics only available for the 173 participants who completed the trial

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[l] The baseline values are only reported for the participants with at least one on-therapy data value for an efficacy parameter
[m] SDs for age and duration of disease are calculated from SE.
[n] Only baseline characteristics on the 22 participants who completed the trial
[o] SDs for HbA1c and fasting blood glucose are calculated from SEs
[p] All SDs are calculated from SEs.
[q] Fasting blood glucose is reported as geometric least square mean. HbA1c is reported as least square mean
[r] Baseline characteristics only reported for participants with data for efficacy (I: 92; C1: 92; C2: 95; C3: 85). Data are presented as least square mean. All SDs are converted from least square SEs
[s] Baseline characteristics only reported for the participants receiving the study drug (I: 132, C: 268)
[t] Baseline variables only reported for the participants completing the trial (20 in each intervention group). Median (interquartile range) for BMI
[u] Baseline characteristics for the 745 participants who received at least one dose of study medication (one on liraglutide 1.8 mg did never receive a dose). Reported that 38% in the glimepiride group, 32% in the liraglutide 1.2 mg group, and 35% in the liraglutide 1.8 mg group had Hispanic ethnicity
[v] Only baseline characteristics on the patients actually treated
[w] Baseline characteristics only available for the 96 participants who completed the trial. All SDs are calculated from SEs
[x] The baseline characteristics are only reported for the 57 patients who completed the trial
[y] Baseline characteristics only available for per protocol population
[z] Baseline characteristics only available for the 55 participants who completed the trial. Intervals in parentheses are ranges
[aa] The value reported for fasting blood glucose is glucose without further specification
[ab] The baseline characteristics are reported for the 567 participants after completing one year of intervention (Charbonnel 2005). The values for HbA1c and fasting blood glucose are read from graph as least square means and SE. SE is converted to SD
[ac] Only baseline characteristics on the participants who completed the trial (36 out of 39)
[ad] When reported number is for all groups, then it is also including the two intervention groups that are not included in the meta-analysis. Fasting blood glucose is converted from mg/dl to mmol/L
[ae] The baseline characteristics for 'Glucose Study 1' and 'Glucose Study 2' are combined for all variables except lipids. The number of females and males for insulin in 'Glucose Study 1' gives 1002, even though only 911 were randomised to insulin. Interquartile ranges were converted to SD for 'Glucose Study 2' for HbA1c. Interquartile ranges were converted to SD for 'Glucose Study 1' and 'Glucose Study 2' for FPG
[af] Fasting blood glucose values are medians and interquartile ranges
[ag] Two of the participants randomised to tolbutamide never received the drug. Baseline characteristics for tolbutamide only for the 48 participants who received the drug
[ah] Baseline characteristics only available for the 27 participants who completed the trial
[ai] Fasting blood glucose levels are reported as median and ranges
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; BMI: body mass index; C: control; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; I: intervention; mo: month(s); UKPDS: United Kingdom Prospective Diabetes Study; wk: week(s); yr: year(s)

Appendix 4. Baseline characteristics (II)

Characteristic Study ID	Intervention(s) and control(s)	Weight [mean kg (SD)]	Duration of disease [mean years (SD)]	Ethnic groups [% Caucasian/ Asian/ Hispanic/ Black/ Other]	Systolic/diastolic blood pressure [mean mm Hg (SD)]
Abbatecola 2006	I1: glibenclamide C1: repaglinide	I1: NR C1: NR	I1: 1.1 (0.4) C1: 1.3 (0.6)	-	-
ADOPT 2006[a]	I1: glibenclamide C1: rosiglitazone C2: metformin	I1: 92.0 (20.0) C1: 91.5 (19.7) C2: 91.6 (18.7)	Expressed in publication as: < 1 year; 1 to 2 years; and > 2 years. Participants had to be diagnosed with type 2 diabetes mellitus within 3 years from trial screening	I1: 89/2/4/4/0.3 C1: 87/3/5/4/1 C2: 89/2/4/4/1	I1: 133 (15)/79 (9) C1: 133 (16)/80 (9) C2: 133 (15)/80 (9)
AGEE/DCD/046/ UK[a]	I1: glibenclamide C1: repaglinide	I1: 82.1 (10.6) C1: 78.8 (11.5)	-	-	-
AGEE/DCD/047/ B/F/I	I1: gliclazide C1: repaglinide	I1: 77.4 (13) C1: 76.9 (11)	-	-	-
Alvarsson 2010[b]	I1: glibenclamide C1: insulin	I1: 86.4 (11.5) C1: 80.3 (9.6)	All newly diagnosed	-	I1: 141.0 (12.7)/86 (4.2) C1: 146.0 (32)/83. 0 (8.0)
APPROACH 2010 [c]	I1: glipizide C1: rosiglitazone	I1: 83.8 (18.5) C1: 82.0 (19.1)	I1: 4.6 (1.7 to 8.9) C1: 5.0 (2.2 to 7.9)	I1: 75/21/-/2/2 C1: 72/25/-/1/2	I1: 131 (15)/76 (10) C1: 128 (16)/75 (10)
Birkeland 1994	I1: glibenclamide I2: glipizide C1: placebo	-	All patients: 3.5 (3. 1)	-	-
Birkeland 2002	I1: glibenclamide C1: insulin	I1: 76.8 (13.0) C1: 75.3 (13.2)	All patients: 7.6 (2. 8)	I1: 100/0/0/0/0 C1: 100/0/0/0/0	All patients: 147 (4) /92 (2)
Campbell 1994	I1: glipizide C1: metformin	I1: 82.2 (16.8) C1: 78.2 (15.7)	I1: 2.8 (3.9) C1: 2.3 (3.2)	-	-
Charbonnel 2005[d]	I1: gliclazide C1: pioglitazone	I1: 88.1 (16.9) C1: 90.7 (18.6)	I1: 3.0 (3.8) C1: 2.8 (3.8)	-	-
Collier 1989	I1: gliclazide C1: metformin	-	All newly diagnosed	-	-

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Coniff 1995[e]	I1: tolbutamide C1: acarbose C2: placebo	I1: 84.4 C1: 81.6 C2: 85.8	I1: 5.6 C1: 5.1 C2: 5.5	I1: 44/-/27/26/2 C1: 51/-/24/22/3 C2: 45/-/27/27/0	-
Dalzell 1986[f]	I1: tolbutamide C1: metformin	-	-	-	-
DeFronzo 2005[g]	I1: glibenclamide C1: metformin	I1: 92.6 (14.5) C1: 92.6 (14.5)	I1: 8.7 (5.8) C1: 8.4 (5.8)	-	-
Deng 2003	I1: glibenclamide C1: xiaoyaosan-	-	-	I1: 0/100/0/0/0 C1: 0/100/0/0/0	-
Derosa 2003[h]	I1: glimepiride C1: repaglinide	I1: 77.1 (5.9) C1: 76.4 (5.2)	-	-	I1: 128 (5)/85 (3) C1: 129 (4)/85 (4)
Derosa 2004	I1: glimepiride C1: metformin	-	NR, but all participants had to be diagnosed within 6 months from entry to the trial	-	I1: 128 (5)/ 85 (4) C1: 129 (5)/ 86 (3)
Diehl 1985	I1: chlorpropamide C1: insulin	-	Mostly newly diagnosed	I1: 95 Mexican-American C1: 91.9 Mexican-American	-
Ebeling 2001[i]	I1: glibenclamide C1: pioglitazone C2: placebo	-	All patients: 5.9 (1.3)	-	-
Esposito 2004[j]	I1: glibenclamide C1: repaglinide	-	-	-	I1: 143 (16)/86 (9) C1: 142 (17)/87 (9)
Feinböck 2003	I1: glibenclamide C1: acarbose	I1: 85.0 (12.8) C1: 83.0 (12.5)	I1: 3.0 (3.6) C1: 3.6 (4.8)	I1: 99/1/0/0/0 C1: 99/1/0/0/0	-
Fineberg 1980[k]	I1: glipizide C1: tolbutamide	-	I1: 5 (2.8) C1: 9 (6.3)	-	-
Foley 2009	I1: gliclazide C1: vildagliptin	I1: 84.3 (17.6) C1: 84.2 (16.3)	I1: 1.9 (3.1) C1: 2.4 (4.3)	I1: 73/-/15/-/12 C1: 74/-/15/-/20	-
Forst 2003	I1: glibenclamide C1: insulin lispro	I1: 84.1 (13.7) C1: 87.2 (12.3)	I1: 4.3 (3.4) C1: 4.4 (2.9)	I1: 99/0/0/1/0 C1: 99/1/0/0/0	-
Forst 2005[l]	I1: glimepiride C1: pioglitazone	-	I1: 6.9 (6.5) C1: 7.4 (7.9)	-	I1: 148 (20)/85 (10) C1: 149 (21)/87

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					(12)
Hanefeld 2005[m]	I1: glibenclamide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	-	I1: 6.4 (6.9) C1: 5.9 (6.0) C2: 6.0 (7.0)	I1: 100/-/-/-/- C1: 99/-/-/-/- C2: 97/-/-/-/-	-
Harrower 1985[n]	I1: glipizide I2: gliquidone I3: gliclazide I4: glibenclamide C1: chlorpropamide	I1: 64 (15) I2: 63 (7) I3: 65 (13) I4: 57 (26) C1: 60 (11)	I1: 2.6 (2.4) I2: 5.0 (5.6) I3: 3.5 (3.8) I4: 3.5 (3.4) C1: 4.2 (4.1)	-	-
Hermann 1991[o]	I1: glibenclamide C1: metformin	I1: 73.9 (9.6) C1: 79.1 (9.2)	All patients: 7.6 (1/3 to 24)	-	-
Hermann 1991a[p]	I1: glibenclamide C1: metformin	I1: 82.6 (15.7) C1: 78.6 (17.9)	All patients: 3.6 (0 to 38)	I1: 100/0/0/0/0 C1: 100/0/0/0/0	I1: 141 (17.5)/84 (5.8) C1: 140 (24.7)/85 (12.3)
Hoffmann 1990[q]	I1: glibenclamide C1: acarbose	I1: 72.8 (8.2) C1: 73.4 (8.3)	-	-	I1: 141 (12)/78 (10) C1: 145 (10)/81 (9)
Hoffmann 1994	I1: glibenclamide C1: placebo C2: acarbose	-	I1: 1.5 (1.1) C1: 1.0 (0.9) C2: 1.1 (0.9)	-	-
Hollander 1992	I1: glibenclamide C1: insulin	-	-	-	-
Jain 2006	I1: glibenclamide C1: pioglitazone	I1: 94.3 (20.0) C1: 93.9 (19.7)	I1: 0.8 (1.3) C1: 0.8 (1.2)	I1: 66/0/20/14/1 C1: 61/2/21/16/1	-
Jibran 2006	I1: glibenclamide C1: repaglinide	I1: 72.7 (17.4) C1: 65.8 (9.4)	-	-	-
Johnston 1997[r]	I1: glibenclamide C1: placebo C2: miglitol 25 mg C3: miglitol 50 mg	-	I1: 7.2 (8.2) C1: 7.0 (8.0) C2: 7.5 (8.2) C3: 6.8 (8.1)	I1: 90/-/7/2/1 C1: 89/-/5/2/3 C2: 86/-/12/2/0 C3: 78/-/13/7/3	-
Kaku 2011[s]	I1: glibenclamide C1: liraglutide	I1: 65.4 (12.9) C1: 66.2 (12.6)	I1: 8.5 (6.5) C1: 8.1 (6.7)	I1: 0/100/0/0/0 C1: 0/100/0/0/0	I1: 132 (17)/78 (11) C1: 131 (16)

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Kamel 1997	I1: gliclazide I2: glibenclamide C1: acarbose C2: metformin C3: placebo	-	-	-	-
Kanda 1998[t]	I1: gliclazide C1: acarbose	-	I1: 3.2 (5.2) C1: 3.0 (5.3)	I1: 0/100/0/0/0 C1: 0/100/0/0/0	-
Kovacevic 1997	I1: glibenclamide C1: acarbose C2: placebo	-	All patients: 4.5 years	-	-
Lawrence 2004[u]	I1: gliclazide C1: metformin C2: pioglitazone	-	-	-	-
LEAD-3 2006[v]	I1: glimepiride C1: liraglutide 1.2 mg C2: liraglutide 1.8 mg	I1: 93.4 (19.2) C1: 92.5 (19.2) C2: 92.8 (20.7)	I1: 5.6 (5.1) C1: 5.2 (5.5) C2: 5.3 (5.1)	I1: 77/4/-/12/7 C1: 80/2/-/14/5 C2: 75/5/-/12/8	I1: 130 (16)/80 (9) C1: 128 (14)/79 (8) C2: 128 (14)/79 (8)
Madsbad 2001	I1: glipizide C1: repaglinide	I1: 83.6 (14.5) C1: 82.9 (13.4)	I1: 7.0 (4.9) C1: 8.1 (6.0)	-	-
Marbury 1999[w]	I1: glibenclamide C1: repaglinide	-	I1: 8.3 (6.8) C1: 7.2 (6.2)	I1: 79/-/-/9/12 C1: 77/-/-/9/14	-
Memisogullari 2009	I1: gliclazide C1: nothing	-	-	-	-
Nakamura 2004	I1: glibenclamide C1: pioglitazone C2: voglibose	-	I1: 17.0 (4.8) C1: 17.5 (4.5) C2: 16.8 (5.0)	-	I1: 120 (13)/78 (5) C1: 124 (12)/74 (8) C2: 122 (12)/76 (6)
Nakamura 2006	I1: glibenclamide C1: pioglitazone C2: voglibose C3: nateglinide	-	I1: 16.5 (5.5) C1: 16.0 (5.0) C2: 16.2 (5.5) C3: 16.6 (5.8)	-	I1: 122 (8)/72 (6) C1: 120 (10)/74 (6) C2: 118 (10)/76 (4) C3: 122 (12)/78 (8)
Nathan 1988	I1: glibenclamide C1: insulin	I1: 89.3 (15) C1: 80.6 (14)	I1: 5.9 (10.8) C1: 3.7 (3.9)	-	-
Pagano 1995[x]	I1: glibenclamide C1: miglitol	I1: 71.6 (10.3) C1: 72.5 (11.2)	I1: 7 (5.5) C1: 5 (4.2)	-	-

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Perriello 2007	I1: gliclazide C1: pioglitazone	I1: 78.8 (10.7) C1: 81.1 (12)	I1: 8.5 (4.1) C1: 9.8 (5.4)	-	-
Rosenthal 2002[y]	I1: glibenclamide C1: acarbose	I1: 82.8 (13.8) C1: 84.7 (15.1)	I1: 8.6 (2.6) C1: 7.6 (2.4)	-	I1: 139 (14)/86 (6.) C1: 135 (12)
Salman 2001[z]	I1: gliclazide C1: acarbose	-	I1: 4.7 (5.6) C1: 4.2 (3.4)	-	I1: 141 (23)/84 (12) C1: 144 (24)/86 (12)
Segal 1997[a]	I1: glibenclamide C1: miglitol C2: placebo	-	-	-	-
Shihara 2011[ab]	I1: glimepiride C2: pioglitazone	I1: 65.6 (12.5) C1: 65.5 (14.6)	I1: 6.0 (8.2) C1: 4.1 (4.3)	-	-
Spengler 1992[ac]	I1: glibenclamide C1: acarbose	I1: 73 (10) C1: 76 (10)	I1: 0.7 C1: 1.0	-	-
Sung 1999[ad]	I1: glibenclamide C1: troglitazone	I1: 90.2 (9.1) C1: 100.2 (8.2)	-	-	I1: 133 (10)/74 (9) C1: 133 (10)/75 (8)
Sutton 2002	I1: glibenclamide C1: rosiglitazone	I1: 85.1 (13.6) C1: 86.2 (15.6)	I1: 6.2 (6.3) C1: 5.3 (6.2)	I1: 76/-/-/3/21 C1: 73/-/-/5/22	I1: 130 (14)/76 (8) C1: 131 (12)/78 (8)
Tan 2004	I1: glimepiride C1: pioglitazone	I1: 74.5 (10.8) C1: 74.2 (10.5)	I1: 6.8 (6.9) C1: 6.5 (6.6)	I1: 1/0/99/0 C1: 0/0/100/0	I1: 127 (18)/80 (10) C1: 128 (15)/82 (10)
Tan 2004a	I1: glibenclamide C1: pioglitazone	I1: 89.0 (16.0) C1: 88.4 (17.5)	I1: 5.2 (4.7) C1: 4.8 (4.7)	I1: 100/0/0/0/0 C1: 99/0/0/0/1	I1: 143 (16)/86 (9) C1: 145 (20)/87 (10)
Tan 2005[ae]	I1: gliclazide C1: pioglitazone	I1: 89.2 (18.2) C1: 91.7 (19.9)	I1: 2.9 (3.8) C1: 2.7 (3.5)	I1: 93/-/-/-/7 C1: 94/-/-/-/6	-
Tang 2004	I1: glimepiride C1: metformin	-	-	-	-
Teramoto 2007	I1: glibenclamide C1: pioglitazone	I1: 67.7 (14.5) C1: 57.0 (10.7)	-	I1:0/100/0/0/0 C1: 0/100/0/0/0	-
Tessier 1999[af]	I1: gliclazide C1: metformin	I1: 81.9 (16.3) C1: 84.9 (11.1)	I1: 4.7 (6.1) C1: 5.4 (6.5)	-	-
Tosi 2003	I1: glibenclamide C1: metformin	I1: 71.4 (8.8) C1: 74.9 (10.6)	I1: 9.9 (6.6) C1: 11.2 (9.6)	I1: 100/0/0/0/0 C1: 100/0/0/0/0	I1: 130 (15)/83 (10) C1: 141 (15)/87 (7)

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UGDP 1970[ag]	I1:tolbutamide C1: placebo C2: insulin	I1: 77.1 C1: 79.4 C2: 78.5	All newly diagnosed	All patients: 53/-/-/-/-	I1: 143/86 C1: 145/84 C2: 145/86
UKPDS 1998[ah]	I1: chlorpropamide I2: glibenclamide I3: glipizide C1: insulin	I1: 76.0 (15.5) I2: 77 (14) I3: 80.7 (16.8) C1: 77.2 (15.1)	All newly diagnosed	I1: 79/11/10/0 I2: 84/8/7/1 I3: 77/18/5/0 C1: 82/10/8/1	I1: 135 (19)/83 (10) I2: 136 (19)/83 (10) I3: 131 (19)/80 (10) C1: 136 (21)/83 (11)
UKPDS 34 1998	I1: chlorpropamide I2: glibenclamide C1: metformin C2: insulin	I1: 85 (15) I2: 86 (14) C1: 87 (17) C2: 85 (14)	All newly diagnosed	I1: 86/4/8/0 I2: 87/4/8/1 C1: 85/4/10/1 C2: 88/4/8/0	I1: 141 (18)/86 (9) I2: 139 (19)/85 (9) C1: 140 (18)/85 (9) C2: 139 (19)/85 (10)
van de Laar 2004[ai]	I1: tolbutamide C1: acarbose	I1: 79.7 (15.4) C1: 81.0 (13.2)	-	I1: 94/4/0/0/2 C1: 98/2/0/0/0	I1: 139 (24)/83 (11) C1: 139 (19)/83 (9)
Watanabe 2005[aj]	I1: glibenclamide C1: pioglitazone	-	-	-	I1: 119 (30)/85 (8) C1: 130 (12)/82 (9)
Wolffenbuttel 1989[ak]	I1: tolbutamide C1: insulin	-	All patients: 5 (1 to 22)	-	-
Wolffenbuttel 1999	I1: glibenclamide C1: repaglinide	I1: 81.3 (12.2) C1: 81.5 (13.4)	I1: 6 (0.5 to 28) C1: 6 (0.5 to 35)	-	I1: 146/83 C1: 147/86
Yamanouchi 2005	I1: glimepiride C1: pioglitazone C2: metformin	-	I1: 3.3 (2.6) C1: 3.2 (2.1) C2: 3.0 (2.5)	-	I1: 141 (21)/85 (8) C1: 143 (17)/85 (10) C2: 143 (19)/86 (10)
Zhang 2005	I1: glipizide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	I1: 24.1 (0.6) C1: 23.9 (0.5) C2: 24.3 (0.6)	All newly diagnosed	-	I1: 138 (2)/70 (2) C1: 134 (5)/82 (4) C2: 139 (4)/80 (3)

Footnotes
"-" denotes not reported
[a] Baseline characteristics only reported for the participants who received a dose of the study drug
[b] Baseline characteristics are from the participants who completed the trial. All SDs are calculated from SE
[c] Fasting plasma glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L. Values of fasting plasma glucose and triglycerides are medians. SDs for triglycerides are calculated from interquartile ranges
[d] Baseline characteristics are not reported for all 1270 participants randomised, but only for the 1250 participants, who are reported in the publication. SDs for all cholesterol values are read from graph
[e] Fasting plasma glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L

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[f] Not described in abstract whether the values are SEs or SDs.
[g] All SDs are calculated from SEs.
[h] Fasting plasma glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[i] All SDs are calculated from SEs.
[j] Fasting plasma glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[k] Baseline variables only available for the 18 participants who completed the trial. All SDs are calculated from SE. Fasting plasma glucose is converted from mg/dl to mmol/L
[l] Baseline characteristics only available for the 173 participants who completed the trial. Cholesterol and triglycerides are converted from mg/dl to mmol/L
[m] The baseline values are only reported for the participants with at least one on-therapy data value for an efficacy parameter. Fasting blood glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[n] SDs for age and duration of disease are calculated from SEs.
[o] Only baseline characteristics on the 22 participants who completed the trial. Duration of disease is mean (range)
[p] SDs for blood pressure are calculated from SEs.
[q] All SDs are calculated from SEs. Fasting plasma glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[r] Baseline characteristics only reported for participants with data for efficacy (I: 92; C1: 92; C2: 95; C3: 85). Data are presented as least square mean. All SDs are converted from least square SEs. FPG is converted from mg/dl to mmol/L
[s] Baseline characteristics only reported for the participants receiving the study drug (I: 132, C: 268). Fasting blood glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[t] Fasting blood glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[u] Baseline variables only reported for the participants completing the trial (20 in each intervention group)
[v] Baseline characteristics for the 745 participants who received at least one dose of study medication (one on liraglutide 1.8 mg did never receive a dose). Reported that 38% in the glimepiride group, 32% in the liraglutide 1.2 mg group, and 35% in the liraglutide 1.8 mg group had Hispanic ethnicity
[w] Only baseline characteristics on the patients actually treated. Fasting plasma glucose is converted from mg/dl to mmol/L
[x] Baseline characteristics only available for the 96 participants who completed the trial. All SDs are calculated from SEs
[y] Fasting plasma glucose, cholesterol and lipid values are converted from mg/dl to mmol/L
[z] The baseline characteristics are only reported for the 57 patients who completed the trial
[aa] Fasting plasma glucose values are converted from mg/dl to mmol/L. Baseline characteristics only available for per protocol population
[ab] Fasting plasma glucose, cholesterol and lipids are converted from mg/dl to mmol/L
[ac] Baseline characteristics only available for the 55 participants who completed the trial. Intervals in parentheses are ranges
[ad] Weight is converted from lbs to kg.
[ae] The baseline characteristics are reported for the 567 participants after completing one year of intervention (Charbonnel 2005). The values for HbA1c and fasting blood glucose are read from graph as least square means and SE. SE is converted to SD
[af] Only baseline characteristics on the participants who completed the trial (36 out of 39)
[ag] When reported number is for all groups, then it is also including the two intervention groups that are not included in the meta-analysis. Fasting blood glucose is converted from mg/dl to mmol/L
[ah] The baseline characteristics for 'Glucose Study 1' and 'Glucose Study 2' are combined for all variables except lipids. The number of females and males for insulin in 'Glucose Study 1' gives 1002, even though only 911 were randomised to insulin. Interquartile ranges were converted to SD for 'Glucose Study 2' for HbA1c. Interquartile ranges were converted to SD for 'Glucose Study 1' and 'Glucose Study 2' for FPG. Data on weight were converted from lbs to kg for the data from 'Glucose Study 2'
[ai] Two of the participants randomised to tolbutamide never received the drug. Baseline characteristics for tolbutamide only for the 48 participants who received the drug
[aj] Baseline characteristics only available for the 27 participants who completed the trial. Fasting blood glucose, cholesterol and triglyceride values are converted from mg/dl to mmol/L
[ak] The number in parentheses for duration of diabetes is range.
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; C: control; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; I: intervention; LEAD-3: Liraglutide Effect and Action in Diabetes-3; UKPDS: United Kingdom Prospective

Appendix 5. Baseline characteristics (III)

Characteristic Study ID	Intervention(s) and control(s)	Total cholesterol [mean mmol/L (SD)]	LDL-cholesterol [mean mmol/L (SD)]	HDL-cholesterol [mean mmol/L (SD)]	Triglycerides [mean mmol/L (SD)]
Abbatecola 2006	I1: glibenclamide C1: repaglinide	I1: 5.1 (0.3) C1: 5.0 (0.4)	I1: 3.1 (0.4) C1: 3.2 (0.5)	I1: 1.3 (0.08) C1: 1.3 (0.07)	I1: 2.0 (0.2) C1: 2.0 (0.2)
ADOPT 2006[a,b]	I1: glibenclamide C1: rosiglitazone C2: metformin	I1: 5.2 (1.0) C1: 5.3 (1.0) C2: 5.2 (1.0)	I1: 3.1 (0.9) C1: 3.1 (0.9) C2: 3.1 (0.9)	I1: 1.2 (0.4) C1: 1.2 (0.3) C2: 1.2 (0.3)	I1: 1.8 (0.9) C1: 1.8 (0.9) C2: 1.9 (0.9)
AGEE/DCD/046/ UK	I1: glibenclamide C1: repaglinide	-	-	-	-
AGEE/DCD/047/ B/F/I	I1: gliclazide C1: repaglinide	-	-	-	-
Alvarsson 2010[c]	I1: glibenclamide C1: insulin	I1: 5.5 (0.8) C1: 5.4 (0.8)	I1: 3.4 (0.8) C1: 3.4 (0.8)	I1: 1.1 (0.4) C1: 1.1 (0.4)	I1: 2.3 (1.3) C1: 1.9 (0.8)
APPROACH 2010[d]	I1: glipizide C1: rosiglitazone	I1: 4.4 (1.04) C1: 4.4 (1.07)	I1: 2.3 (0.9) C1: 2.3 (0.9)	I1: 1.1 (0.3) C1: 1.1 (0.3)	I1: 4.1 (0.7) C1: 1.8 (0.7)
Birkeland 1994	I1: glibenclamide I2: glipizide C1: placebo	-	-	-	-
Birkeland 2002	I1: glibenclamide C1: insulin	I1: 6.4 (1.1) C1: 6.8 (0.4)	-	I1: 1.3 (0.4) C1: 1.4 (0.3)	I1: 1.8 (1.0) C1: 1.8 (1.0)
Campbell 1994	I1: glipizide C1: metformin	I1: 6.4 (1.4) C1: 6.5 (1.3)	-	I1: 0.9 (0.2) C1: 0.9 (0.3)	I1: 2.1 (0.7) C1: 2.2 (0.7)
Charbonnel 2005[e]	I1: gliclazide C1: pioglitazone	I1: 5.7 (1.0) C1: 5.7 (1.2)	I1: 3.5 (0.8) C1: 3.5 (0.6)	I1: 1.0 (0.2) C1: 1.0 (0.2)	I1: 2.8 (3.2) C1: 2.6 (2.8)
Collier 1989	I1: gliclazide C1: metformin	I1: 7.0 (0.7) C1: 6.5 (0.9)	-	-	I1: 1.9 (0.6) C1: 1.6 (0.5)

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Coniff 1995[a]	I1: tolbutamide C1: acarbose C2: placebo	I1: 5.6 C1: 5.9 C2: 5.9	I1: 3.9 C1: 3.9 C2: 4.0	I1: 1.0 C1: 1.0 C2: 1.1	I1: 2.2 C1: 2.8 C2: 2.7
Dalzell 1986[f]	I1: tolbutamide C1: metformin	-	-	-	-
DeFronzo 2005[a,g]	I1: glibenclamide C1: metformin	I1: 5.5 (1.1) C1: 5.4 (1.1)	I1: 3.5 (1.1) C1: 3.4 (1.1)	I1: 0.9 (1.1) C1: 0.9 (1.1)	I1: 2.4 (1.3) C1: 2.6 (2.0)
Deng 2003	I1: glibenclamide C1: xiaoyaosan-	-	-	-	-
Derosa 2003[a]	I1: glimepiride C1: repaglinide	I1: 5.6 (1.1) C1: 5.5 (1.0)	I1: 3.6 (0.6) C1: 3.6 (0.6)	I1: 1.1 (0.1) C1: 1.1 (0.2)	I1: 1.9 (0.4) C1: 1.7 (0.4)
Derosa 2004[a]	I1: glimepiride C1: metformin	I1: 5.3 (1.02) C1: 5.7 (1.2)	I1: 3.5 (0.5) C1: 3.7 (0.5)	I1: 1.08 (0.1) C1: 1.1 (0.1)	I1: 1.8 (0.2) C1: 2.03 (0.3)
Diehl 1985	I1: chlorpropamide C1: insulin	-	-	-	-
Ebeling 2001[h]	I1: glibenclamide C1: pioglitazone C2: placebo	I1: 5.4 (0.6) C1: 5.2 (0.7) C2: 5.2 (0.9)	-	I1: 1.2 (0.2) C1: 1.2 (0.2) C2: 1.2 (0.3)	I1: 2.1 (0.4) C1: 2.3 (1.4) C2: 2.2 (1.1)
Esposito 2004[a]	I1: glibenclamide C1: repaglinide	I1: 5.2 (0.9) C1: 5.1 (0.9)	-	I1: 1.1 (0.3) C1: 1.1 (0.3)	I1: 1.8 (0.8) C1: 1.8 (0.8)
Feinböck 2003	I1: glibenclamide C1: acarbose	-	-	-	-
Fineberg 1980	I1: glipizide C1: tolbutamide	-	-	-	-
Foley 2009	I1: gliclazide C1: vildagliptin	-	-	-	-
Forst 2003	I1: glibenclamide C1: insulin lispro	-	-	-	-
Forst 2005[a,i]	I1: glimepiride C1: pioglitazone	I1: 5.8 (1.0) C1: 5.8 (1.1)	I1: 3.5 (0.6) C1: 3.5 (0.8)	I1: 1.2 (0.4) C1: 1.2 (0.3)	I1: 2.3 (1.2) C1: 2.1 (1.2)
Hanefeld 2005[a,j]	I1: glibenclamide C1: rosiglitazone 4 mg C2: rosiglitazone 8	I1: 5.6 I2: 5.6 I3: 5.7	I1: 3.6 (0.9) I2: 3.7 (0.9) I3: 3.6 (0.9)	I1: 1.1 I2: 1.2 I3: 1.2	I1: 2.0 (1.3) I2: 2.2 (4.3) I3: 1.9 (1.4)

(*Continued*)

	mg				
Harrower 1985	I1: glipizide I2: gliquidone I3: gliclazide I4: glibenclamide C1: chlorpropamide	-	-	-	-
Hermann 1991[k]	I1: glibenclamide C1: metformin	I1: 6.2 (1.2) C1: 5.8 (1.3)	I1: 4.4 (1.3) C1: 4.1 (1.1)	I1: 1.1 (0.3) C1: 1.0 (0.2)	I1: 1.5 (0.8) C1: 1.6 (0.8)
Hermann 1991a[l]	I1: glibenclamide C1: metformin	I1: 5.7 (1.0) C1: 5.4 (1.5)	I1: 3.9 (8) C1: 3.7 (1.5)	I1: 0.9 (0.3) C1: 0.8 (0.4)	I1: 2.0 (2.2) C1: 2.0 (1.3)
Hoffmann 1990[a,m]	I1: glibenclamide C1: acarbose	I1: 5.8 (0.8) C1: 5.9 (0.9)	I1: 4.3 (1.7) C1: 4.0 (1.6)	I1: 1.2 (0.2) C1: 1.2 (0.2)	I1: 2.2 (1.0) C1: 1.9 (0.4)
Hoffmann 1994	I1: glibenclamide C1: placebo C2: acarbose	I1: 5.6 (1.2) C1: 5.7 (1.2) C2: 5.7 (1.0)	-	I1: 1.6 (0.7) C1: 1.4 (0.4) C2: 1.4 (0.4)	I1: 2.0 (1.3) C1: 1.7 (0.8) C2: 1.9 (1.1)
Hollander 1992	I1: glibenclamide C1: insulin	-	-	-	-
Jain 2006	I1: glibenclamide C1: pioglitazone	-	-	-	-
Jibran 2006	I1: glibenclamide C1: repaglinide	-	-	-	-
Johnston 1997[n]	I1: glibenclamide C1: placebo C2: miglitol 25 mg C3: miglitol 50 mg	-	-	-	-
Kaku 2011[a,o]	I1: glibenclamide C1: liraglutide	I1: 5.3 (0.9) C1: 5.2 (0.8)	I1: 3.2 (0.8) C1: 3.1 (0.7)	I1: 1.6 (0.5) C1: 1.5 (0.4)	I1: 1.5 (1.0) C1: 1.5 (1.2)
Kamel 1997	I1: gliclazide I2: glibenclamide C1: acarbose C2: metformin C3: placebo	-	-	-	-
Kanda 1998[a]	I1: gliclazide C1: acarbose	I1: 5.7 (1.1) C1: 5.3 (1.0)	-	I1: 1.1 (0.3) C1: 1.2 (0.4)	I1: 1.4 (1.3) C1: 1.3 (0.9)

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Kovacevic 1997	I1: glibenclamide C1: acarbose C2: placebo	-	-	-	-
Lawrence 2004[p]	I1: gliclazide C1: metformin C2: pioglitazone	I1: 5.4 (0.8) C1: 5.6 (0.7) C2: 5.4 (0.8)	I1: 5.0 (1.6) C1: 5.1 (1.1) C2: 5.0 (1.1)	I1: 1.3 (0.3) C1: 1.3 (0.2) C2: 1.3 (0.3)	I1: 1.8 (1.1) C1: 2.3 (1.2) C2: 2.3 (1.7)
LEAD-3 2006[q]	I1: glimepiride C1: liraglutide 1.2 mg C2: liraglutide 1.8 mg	-	-	-	-
Madsbad 2001	I1: glipizide C1: repaglinide	-	-	-	-
Marbury 1999[r]	I1: glibenclamide C1: repaglinide	-	-	-	-
Memisogullari 2009	I1: gliclazide C1: nothing	-	-	-	-
Nakamura 2004	I1: glibenclamide C1: pioglitazone C2: voglibose	-	-	-	-
Nakamura 2006[a]	I1: glibenclamide C1: pioglitazone C2: voglibose C3: nateglinide	I1: 5.3 (0.9) C1: 5.4 (1.0) C2: 5.3 (0.8) C3: 5.4 (1.0)	-	I1: 0.9 (0.2) C1: 0.8 (0.3) C2: 0.9 (0.2) C3: 0.9 (0.2)	I1: 1.6 (0.4) C1: 1.7 (1.1) C2: 1.6 (0.4) C3: 1.6 (0.4)
Nathan 1988	I1: glibenclamide C1: insulin	I1: 6.0 (1.5) C1: 6.0 (1.0)	-	I1: 1.13 (0.4) C1: 1.17 (0.4)	I1: 1.9 (0.6) C1: 1.9 (1.2)
Pagano 1995[s]	I1: glibenclamide C1: miglitol	I1: 5.9 (1.4) C1: 5.6 (0.7)	-	I1: 1.2 (0.3) C1: 1.2 (0.4)	I1: 1.8 (0.7) C1: 1.8 (0.7)
Perriello 2007	I1: gliclazide C1: pioglitazone	-	-	-	-
Rosenthal 2002[a]	I1: glibenclamide C1: acarbose	I1: 5.7 (1.0) C1: 5.9 (1.2)	-	I1: 1.2 (0.3) C1: 1.2 (0.4)	I1: 2.0 (1.4) C1: 2.2 (1.2)
Salman 2001[t]	I1: gliclazide C1: acarbose	I1: 5.9 (1.1) C1: 5.7 (1.2)	I1: 3.8 (0.9) C1: 3.7 (1.2)	I1: 1.1 (0.2) C1: 1.1 (0.3)	I1: 2.3 (1.1) C1: 2.3 (1.7)

(*Continued*)

Segal 1997[u]	I1: glibenclamide C1: miglitol C2: placebo	-	-	-	-
Shihara 2011[a]	I1: glimepiride C2: pioglitazone	I1: 5.3 (2.2) C1: 5.3 (1.0)	I1: 3.2 (0.9) C1: 3.2 (0.8)	I1: 1.5 (0.6) C1: 1.4 (0.4)	I1: 1.5 (0.8) C1: 1.8 (1.3)
Spengler 1992[v]	I1: glibenclamide C1: acarbose	I1: 6.0 (4.9 to 7.4) C1: 5.8 (5.1 to 6.7)	-	-	I1: 2.19 (1.5 to 3.1) C1: 1.95 (1.5 to 2. 3)
Sung 1999	I1: glibenclamide C1: troglitazone	-	-	-	-
Sutton 2002[a]	I1: glibenclamide C1: rosiglitazone	-	I1: 3.5 C1: 3.6	-	I1: 2.1 C1: 2.5
Tan 2004	I1: glimepiride C1: pioglitazone	-	-	-	-
Tan 2004a	I1: glibenclamide C1: pioglitazone	I1: 5.6 C1: 5.7	I1: 3.5 C1: 3.6	I1: 1.1 C1: 1.2	I1: 2.3 C1: 2.1
Tan 2005[w]	I1: gliclazide C1: pioglitazone	-	-	-	-
Tang 2004	I1: glimepiride C1: metformin	I1: 5.1 (0.9) C1: 5.1 (0.8)	I1: 2.9 (0.7) C1: 2.9 (0.6)	I1: 1.4 (0.3) C1: 1.3 (0.3)	I1: 1.5 (0.9) C1: 1.7 (0.9)
Teramoto 2007[a]	I1: glibenclamide C1: pioglitazone	-	I1: 3.7 (0.8) C1: 3.7 (0.5)	I1: 1.2 (0.2) C1: 1.3 (0.3)	I1: 2.3 (1.1) C1: 2.7 (1.6)
Tessier 1999[x]	I1: gliclazide C1: metformin	I1: 4.8 (0.8) C1: 5.4 (1.2)	I1: 2.8 (0.7) C1: 3.1 (0.9)	I1: 1.3 (0.7) C1: 1.0 (0.3)	I1: 1.9 (0.9) C1: 3.7 (5.8)
Tosi 2003	I1: glibenclamide C1: metformin	I1: 5.7 (0.9) C1: 5.6 (1.3)	I1: 3.5 (1.0) C1: 3.3 (1.2)	I1: 1.3 (0.3) C1: 1.2 (0.3)	I1: 2.0 (1.2) C1: 2.6 (2.3)
UGDP 1970[y]	I1:tolbutamide C1: placebo C2: insulin	-	-	-	-
UKPDS 1998[z]	I1: chlorpropamide I2: glibenclamide I3: glipizide C1: insulin	I1: 5.5 (1.5) I2: 5.5 (1.1) I3: - C1: 5.4 (1.1)	I1: 3.5 (1.1) I2: 3.5 (1.0) I3: - C1: 3.5 (1.0)	I1: 1.1 (0.3) I2: 1.1 (0.3) I3: - C1: 1.1 (0.3)	I1: 2.6 (4.9) I2: 2.4 (4.4) I3: - C1: 2.5 (4.7)

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UKPDS 34 1998[aa]	I1: chlorpropamide I2: glibenclamide C1: metformin C2: insulin	I1: 5.6 (1.2) I2: 5.6 (1.2) C1: 5.6 (1.3) C2: 5.6 (1.1)	I1: 3.6 (1.1) I2: 3.6 (1.07) C1: 3.7 (1.2) C2: 3.7 (0.2)	I1: 1.05 (0.2) I2: 1.07 (0.3) C1: 1.06 (0.2) C2: 1.05 (0.2)	I1: 2.9 (1.01 to 7.86) I2: 2.7 (0.99 to 7.10) C1: 2.8 (1.01 to 7.74) C2: 2.9 (1.02 to 8.19)
van de Laar 2004[ab]	I1: tolbutamide C1: acarbose	I1: 5.9 (1.1) C1: 5.8 (1.0)	I1: 3.7 (0.9) C1: 3.7 (0.8)	I1: 1.1 (0.3) C1: 1.0 (0.2)	I1: 2.6 (2.2) C1: 2.4 (2.0)
Watanabe 2005[a,ac]	I1: glibenclamide C1: pioglitazone	I1: 5.0 (0.8) C1: 5.0 (1.1)	I1: 2.8 (0.5) C1: 2.6 (0.7)	I1: 1.7 (1.2) C1: 1.4 (0.5)	I1: 1.4 (0.6) C1: 1.6 (0.9)
Wolffenbuttel 1989	I1: tolbutamide C1: insulin	-	All patients: 3.7 (0.8)	All patients: 0.9 (0.2)	All patients: 2.4 (1.0)
Wolffenbuttel 1999[ad]	I1: glibenclamide C1: repaglinide	I1: 6.1 (1.1) C1: 6.0 (1.2)	-	I1: 1.2 (0.3) C1: 1.2 (0.4)	I1: 1.84 (0.68 to 31.9) C1: 1.92 (0.36 to 27.7)
Yamanouchi 2005	I1: glimepiride C1: pioglitazone C2: metformin	I1: 5.9 (0.5) C1: 5.8 (0.6) C2: 5.7 (0.4)	-	I1: 1.4 (0.1) C1: 1.4 (0.1) C2: 1.3 (0.09)	I1: 2.6 (1.4) C1: 2.5 (1.3) C2: 2.3 (1.1)
Zhang 2005	I1: glipizide C1: rosiglitazone 4 mg C2: rosiglitazone 8 mg	I1: 5.5 (0.2) C1: 5.5 (0.2) C2: 5.5 (0.1)	I1: 3.2 (0.2) C1: 3.3 (0.08) C2: 3.3 (0.2)	I1: 1.2 (0.2) C1: 1.2 (0.09) C2: 1.2 (0.6)	I1: 2.02 (0.8) C1: 2.01 (0.8) C2: 2.1 (0.6)

Footnotes
"-" denotes not reported
[a] Cholesterol and triglyceride values are converted from mg/dl to mmol/L
[b] Baseline characteristics only reported for the participants who received a dose of the study drug (glibenclamide: 1441; rosiglitazone: 1456; metformin: 1454). Values of cholesterol and triglycerides are medians and SDs are calculated from interquartile ranges
[c] Baseline characteristics are from the participants who completed the trial. All SDs are calculated from SE
[d] Values of fasting plasma triglycerides are medians. SDs for triglycerides are calculated from interquartile ranges
[e] Baseline characteristics are not reported for all 1270 participants randomised, but only for the 1250 participants, who are reported in the publication. SDs for all cholesterol values are read from graph
[f] Not described in abstract whether the values are SEs or SDs.
[g] All SDs are calculated from SEs.
[h] All SDs are calculated from SEs.
[i] Baseline characteristics only available for the 173 participants who completed the trial
[j] The baseline values are only reported for the participants with at least one on-therapy data value for an efficacy parameter
[k] Only baseline characteristics on the 22 participants who completed the trial
[l] SDs for cholesterol and lipids are calculated from SEs.

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[m] All SDs are calculated from SEs.
[n] Baseline characteristics only reported for participants with data for efficacy (I: 92; C1: 92; C2: 95; C3: 85). Data are presented as least square mean. All SDs are converted from least square SEs
[o] Baseline characteristics only reported for the participants receiving the study drug (I: 132, C: 268)
[p] Baseline variables only reported for the participants completing the trial (20 in each intervention group). LDL-cholesterol is converted from mg/dl to mmol/L
[q] Baseline characteristics for the 745 participants who received at least one dose of study medication (one on liraglutide 1.8 mg did never receive a dose). Reported that 38% in the glimepiride group, 32% in the liraglutide 1.2 mg group, and 35% in the liraglutide 1.8 mg group had Hispanic ethnicity
[r] Only baseline characteristics on the patients actually treated
[s] Baseline characteristics only available for the 96 participants who completed the trial. All SDs are calculated from SEs
[t] The baseline characteristics are only reported for the 57 patients who completed the trial
[u] Baseline characteristics only available for per protocol population
[v] Baseline characteristics only available for the 55 participants who completed the trial. Intervals in parentheses are ranges
[w] The baseline characteristics are reported for the 567 participants after completing one year of intervention (Charbonnel 2005). The values for HbA1c and fasting blood glucose are read from graph as least square means and SE. SE is converted to SD
[x] Only baseline characteristics on the participants who completed the trial (36 out of 39)
[y] When reported number is for all groups, then it is also including the two intervention groups that are not included in the meta-analysis
[z] The baseline characteristics for 'Glucose Study 1' and 'Glucose Study 2' are combined for all variables except lipids. The number of females and males for insulin in 'Glucose Study 1' gives 1002, even though only 911 were randomised to insulin. Interquartile ranges were converted to SD for 'Glucose Study 2' for HbA1c. Interquartile ranges were converted to SD for 'Glucose Study 1' and 'Glucose Study 2' for FPG. Data on weight were converted from lbs to kg for the data from 'Glucose Study 2'
[aa] Values for triglycerides are geometric means (1SD) according to publication
[ab] Two of the participants randomised to tolbutamide never received the drug. Baseline characteristics for tolbutamide only for the 48 participants who received the drug
[ac] Baseline characteristics only available for the 27 participants who completed the trial
[ad] Triglycerides are reported as median and ranges.
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; C: control; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; I: intervention; LEAD-3: Liraglutide Effect and Action in Diabetes-3; UKPDS: United Kingdom Prospective Diabetes Study

Appendix 6. Matrix of study endpoints

Characteristic Study ID	Primary[a] endpoint(s)	Secondary[b] endpoint(s)	Other[c] endpoint(s)
Abbatecola 2006	HbA1c, coefficient of variation FPG, coefficient of variation postprandial glucose, cognition composite score	Cognitive measures: Mini-Mental State Examination: trail A and B, digit span back- and forward verbal fluence	Adverse events, hypoglycaemic episodes, homeostasis model of assessment - insulin resistance, blood pressure, biochemical variables, carotid ultrasound and depression (depression scale)

(*Continued*)

ADOPT 2006	Time to monotherapy failure	Glycaemic control, islet ß-cell function, insulin sensitivity. Maintenance/restoration of beta-cell function: homoeostasis model assessment insulin sensitivity, progression of microalbuminuria, fibrinolytic markers	Cardiovascular risk factors, renal function, health status, quality of life and safety parameters
AGEE/DCD/046/UK	Change from baseline in HbA1c and fasting blood glucose	Change in triglycerides, total cholesterol, HDL cholesterol from baseline	Beta-cell status, safety profile, hypoglycaemic episodes and low blood glucose measurements (< 4 mmol/L)
AGEE/DCD/047/B/F/I	Change from baseline in HbA1c and fasting blood glucose	Change in triglycerides, total cholesterol, HDL cholesterol from baseline	Beta-cell status, safety profile, hypoglycaemic episodes and low blood glucose measurements (< 4 mmol/L)
Alvarsson 2010	-	-	Retinopathy, quality of life, beta-cell function and biochemical variables
APPROACH 2010	Percent atheroma volume	Intravascular ultrasound efficacy parameters (include change in normalised total atheroma volume and change in atheroma volume within the most diseased 10 mm subsegment; vessel volume, change in biochemical variables	Major adverse cardiovascular events (cardiovascular and non-cardiovascular death, non-fatal myocardial infarction and stroke, coronary revascularisation and hospitalisation for recurrent myocardial ischaemia) and new or worsening heart failure are prospectively adjudicated by an independent endpoint committee blinded to treatment assignment, laboratory parameters
Birkeland 1994	Glycaemic control and insulin secretion	-	Biochemical variables
Birkeland 2002	Retinopathy	Nephropathy, macrovascular disease	Metabolic profile
Campbell 1994	-	-	Glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion
Charbonnel 2005	HbA1c	FPG, insulin, and lipids	-

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Collier 1989	-	-	Platelet density profiles, intraplatelet nucleotides, intraplatelet nucleotides, intraplatelet β-thromboglobulin, plasma β-triglycerides levels, intraplatelet cyclic AMP levels, platelet release reaction, platelet thromboxane B2 production and plasma fibrinogen levels
Coniff 1995	HbA1c	Full-meal test tolerance, adverse events (including hypoglycaemia), blood lipids, change in HbA1c from each scheduled visit	-
Dalzell 1986	Plasma glucose and fasting lipids	-	Dietary adherence
DeFronzo 2005	-	-	Plasma glucose (while the patients were fasting and after the oral administration of glucose), lactate, lipids, insulin and glycosylated haemoglobin
Deng 2003	Fasting blood glucose, 2-hour postprandial blood glucose, and HbA1c	-	-
Derosa 2003	Glycaemic control	-	Lipoprotein (a), plasminogen activator inhibitor-1, homocysteine, biochemical variables, blood pressure
Derosa 2004	Extraglycaemic parameters, specifically those associated with cardiovascular risk	Efficacy on glycaemic control	-
Diehl 1985	Compliance	-	-
Ebeling 2001	Relation between inflammatory factors and activation of the complement	Influence of improvement of glycaemic control by pioglitazone or glibenclamide and the concentrations of acute phase serum proteins	Metabolic control and changes in complement activation. Biochemical variables
Esposito 2004	Carotis intima media thickness	-	Biochemical variables, markers of systemic vascular inflammation

(*Continued*)

Feinböck 2003	Number of responders in each intervention group	Change in HbA1c, weight and postprandial blood glucose and C-peptide levels from baseline	Standard biochemical variables, glycaemic response to breakfast, HbA1c and C-peptide
Fineberg 1980	-	-	Fasting and 2-our postprandial serum glucose levels, insulin secretion and dynamics and glucose disappearance rates
Foley 2009	Change in HbA1c from baseline	In main publication: body weight, FPG, fasting plasma lipids, fasting proinsulin, fasting insulin, fasting proinsulin/insulin ratio, and homeostasis model assessment of insulin resistance. From clinicaltrials.gov: adverse events; fasting plasma glucose; patients with HbA1c < 7%;with reduction in HbA1c >/= 0.7%; with reduction in HbA1c >/= 0.5% after 104 weeks	Adverse events
Forst 2003	Postprandial blood glucose excursion	-	Glycaemic control, biochemical variables, safety data
Forst 2005	Heat-stimulated microvascular blood flow	Biochemical variables (metabolic control and insulin sensitivity)	Carotis intima-media thickness
GSK 2005	HbA1c	HbA1c, FPG, fructosamine, C-peptide, insulin, pro-insulin, 32-33 split pro-insulin, urinary albumin, albumin excretion rate, and serum lipids. Proportion of patients that responded to treatment, i.e. HbA1c >= 0.7% and FPG >= 30 mg/dL decrease from baseline Proportions of patients who achieve $\leq$ 140 mg/dL	-
Harrower 1985	-	-	Diabetic control, biochemical variables
Hermann 1991	Glycaemic control	-	Fasting concentrations of lipids and C-peptide concentration
Hermann 1991a	Benefits in terms of efficacy and safety	Responders, additive effect of metformin and glibenclamide	Lipids, insulin

(*Continued*)

Hoffmann 1990	HbA1c	Fasting blood glucose, post-prandial blood glucose, renal glucose excretion, subjective compatibility	Resting ECG, 24-hour urine ketones, biochemical variables in blood, eye background
Hoffmann 1994	Postprandial insulin increase	HbA1c, BG, insulin, and urinary glucose	ND
Hollander 1992	ND	ND	HbA1c, FBG and stimulated C-peptide
Jain 2006	HbA1c	ND	Adverse events and biochemical variables
Jibran 2006	-	-	FBG, 2-hour postprandial glucose, HbA1c, weight, adverse events and biochemical variables
Johnston 1997	HbA1c	FPG, serum insulin, lipids, urinary albumin and glucose excretion	Treatment failures and treatment responders
Kaku 2011	HbA1c	FPG, PPG, 7-point plasma glucose profile, body weight, waist circumference, indicators of beta-cell function, cardiovascular biomarkers, lipid profile, funduscopy, hypoglycaemic episodes (defined as major, hypoglycaemia requiring third-party assistance; minor, self treated hypoglycaemia; and symptoms only), adverse events	Liraglutide antibodies
Kamel 1997	-	-	FPG, HbA1c, postprandial serum insulin level, fasting serum-insulin levels and C-peptide
Kanda 1998	Waist circumference, visceral and subcutaneous fat	-	-
Kovacevic 1997	HbA1c, relative postprandial serum insulin increase	Blood glucose (fasting, 1-hour postprandial), fasting serum insulin, 1-hour postprandial serum insulin and urine glucose	Biochemical parameters
Lawrence 2004	-	-	Lipids and biochemical variables

(*Continued*)

LEAD-3 2006	HbA1c	Body weight, FPG, self measured 8-point plasma-glucose profiles, blood pressure, ß-cell function (proinsulin to insulin ratio and 2 models of B-cell function: homoeostasis model assessment-B and homoeostasis model assessment-insulin resistance), fasting glucagon and patients' reported assessment of quality of life	-
Madsbad 2001	Change in HbA1c and fasting blood glucose	FBG, fasting C-peptide, insulin, triglycerides, total cholesterol and HDL-cholesterol	Safety endpoints
Marbury 1999	Change in HbA1c and FPG	Beta-cell function	Lipid metabolism, changes in body weight, and safety profiles, including hypoglycaemic events
Memisogullari 2009	Not clearly defined	Not clearly defined	Glycaemic control, markers of inflammation
Nakamura 2004	Not explicitly described, whether the outcomes assessed are primary or secondary: urinary albumin excretion, intima-media thickness, pulse wave velocity, HbA1c	-	-
Nakamura 2006	End-stage renal disease	Doubling of serum creatinine	Glucose, HbA1c, creatinine, urea nitrogen, total cholesterol, HDL-cholesterol and triglyceride, urinary albumin excretion
Nathan 1988	Efficacy and complications	-	Lipid status, weight
Pagano 1995	HbA1c	-	Meal-stimulated serum insulin and C-peptide, FBG, postprandial glucose, total and HDL cholesterol, triglycerides, side effects and compliance
Perriello 2007	Improvement of HbA1clevels expressed as per cent of participants reaching an HbA1c < 7.5% at the end (12 months) of treatment or at the last available post-treatment visit	Changes in HbA1c, FBG, insulin, and homeostasis model assessment of insulin resistance and self-monitoring blood glucose, changes in plasminogen activator inhibitor-1, antithrombin-III, von Willebrand factor,	-

(*Continued*)

		and platelets	
Rosenthal 2002	Blood pressure and serum insulin	Biochemical variables	-
Salman 2001	Fasting and postprandial plasma insulin, C-peptide, glucose levels and HbA1C	Lipid profiles	Biochemical tests for evaluation of drug safety
Segal 1997	Difference between the least-squared means of HbA1c at the endpoint in the miglitol and glibenclamide groups versus placebo	Glucose, insulin, triglycerides, blood chemistry and haematology	-
Shihara 2011	Percentage of patients with HbA1c < 6.9 at the end of study	Change in HbA1c at 6 months compared with baseline, fasting plasma glucose, insulin. Lipids and BNP, body weight, and BMI. Safety of study medication	Compliance
Spengler 1992	-	-	FBG and glucose 1 hour after breakfast, HbA1c, triglycerides, cholesterol, body weight, blood pressure, subjective symptoms, biochemical variables
Sung 1999	-	-	Haemodynamic mechanism of blood pressure lowering, glucose, insulin, C-peptide, and HbA1c. Resting and stress blood pressure, stroke volume and cardiac output
Sutton 2002	Change from baseline in left ventricular mass index at weeks 28 and 52	-	Change from baseline in left ventricular end-diastolic volume, ejection fraction, blood pressure, heart rate, arterial pressure, pulse, glycaemic control, serum lipids at weeks 28 and 52
Tan 2004	Glycaemic control and insulin sensitivity	-	Safety assessment
Tan 2004a	Insulin sensitivity	Glycaemic control, serum lipids, albumin:creatinine ratios	Safety
Tan 2005	Time to intervention failure	-	HbA1c, FPG, fasting serum insulin and homeostasis model assessment for insulin sensitivity and for ß-cell activity

(*Continued*)

Tang 2004	-	-	Free fatty acids level, body weight index, blood glucose and insulin resistance
Teramoto 2007	Change from the baseline of lipid parameters (triglycerides and HDL-cholesterol)	Secondary endpoints were changes from the baseline of LDL-cholesterol particle size and the ratio of visceral to subcutaneous fat volumes	Glycaemic control, fasting serum insulin
Tessier 1999	-	-	Efficacy, lipid peroxidation and side effects
Tosi 2003	Efficacy (HbA1c, fasting glucose) and tolerability (side effects)	HbA1c < 6.0%; fasting glucose < 140 mg/dl	Insulin resistance HOMA index, beta-cell function HOMA index, BMI, lipid profile, predictors of HbA1c change
UGDP 1970	Evaluation of the efficacy of various hypoglycaemic treatments in the prevention of vascular complications in patients with mild diabetes. Study of the natural history of a group of patients with maturity onset, non-insulin dependent diabetes. Development of methods applicable to co-operative clinical trials	-	-
UKPDS 1998	Time to the first occurrence of: 1) any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction); 2) diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia and sudden death); 3) all-cause mortality. These aggregates were used to assess the difference between conventional and intensive treatment	Single outcomes	Surrogate clinical endpoints; neuropathy; retinopathy; hyperglycaemia; quality of life, cost-benefit analyses

(*Continued*)

UKPDS 34 1998	Time to the first occurrence of: 1) any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction); 2) diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia and sudden death); 3) all-cause mortality. These aggregates were used to assess the difference between conventional and intensive treatment	Single outcomes	Surrogate clinical endpoints; neuropathy; retinopathy; hyperglycaemia; quality of life, cost-benefit analyses
van de Laar 2004	HbA1c	Fasting and post-load blood glucose and insulin levels, lipids, diabetes status, and frequency and severity adverse events	-
Watanabe 2005	Change in pulse-wave velocity	-	BMI, blood pressure, brachial-ankle pulse-wave velocity, FPG, HbA1c, fasting immunoreactive in- sulin, homeostasis model insulin resistance index, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
Wolffenbuttel 1989	-	-	Glycaemic control, beta-cell function and lipids
Wolffenbuttel 1999	HbA1c and fasting plasma glucose	Fasting insulin and lipid levels and 4-point blood glucose profiles	Hypoglycaemia, adverse events
Yamanouchi 2005	HbA1c	-	Biochemical variables
Zhang 2005	Blood biochemistry and metabolism, high-sensitivity C-reactive protein, fibrinogen and carotis intima-media thickness of patients before the	Adverse events	-

(*Continued*)

	treatment and 3 and 6 months after the treatment		

Footnotes
"-" denotes not reported
[a,b] As stated in the publication
[c] Not stated as primary or secondary endpoint(s) in the publication
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; BG: blood glucose; BMI; body mass index; C: control; ECG: electrocardiogram; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; HOMA: homeostatic model assessment; I: intervention; LDL: low-density lipoprotein; ND: not defined; UKPDS: United Kingdom Prospective Diabetes Study

Appendix 7. Definitions of outcomes in trials or as reported (I)

Characteristic Study ID	Cardiovascular mortality	Cancer	Non-fatal macrovascular outcomes	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity	Peripheral revascularisation	Coronary revascularisation
Abbatecola 2006	ND	ND	ND	ND	ND	ND	ND	ND
ADOPT 2006	All cardiovascular deaths	Serious adverse event malignancies excluding skin cancer	Major adverse cardiovascular events (fatal and non-fatal myocardial infarction, congestive heart failure and stroke)	Non-fatal myocardial infarction	Only total stroke reported Unknown whether it is fatal or non-fatal	ND	Peripheral vascular disease	ND
AGEE/ DCD/046/ UK	Death due to myocardial infarction	ND	ND	Myocardial infarction	ND	ND	ND	ND
AGEE/ DCD/047/ B/F/I	One patient had myocardial infarction and one had sudden cardiac	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

	arrest							
Alvarsson 2010	Death following coronary bypass surgery	Death due to liver and gastric carcinoma	ND	ND	ND	ND	ND	ND
APPROACH 2010	Cardiovascular death	Death due to cancer	Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or hospitalisation for myocardial ischaemia	Non-fatal myocardial infarction	Non-fatal stroke	Amputation	Revascularisation	Coronary revascularisation
Birkeland 1994	ND	ND	ND	ND	ND	ND	ND	ND
Birkeland 2002	One patient died due to myocardial infarction	ND	ND	ND	ND	ND	ND	ND
Campbell 1994	ND	ND	ND	ND	ND	ND	ND	ND
Charbonnel 2005	ND	ND	ND	ND	ND	ND	ND	ND
Collier 1989	ND	ND	ND	ND	ND	ND	ND	ND
Coniff 1995	Cardiac arrest	ND	ND	ND	ND	ND	ND	ND
Dalzell 1986	ND	ND	ND	ND	ND	ND	ND	ND
DeFronzo 2005	Death, possible due to myocardial infarction	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

Deng 2003	ND	ND	ND	ND	ND	ND	ND	ND
Derosa 2003	ND	ND	ND	ND	ND	ND	ND	ND
Derosa 2004	ND	ND	ND	ND	ND	ND	ND	ND
Diehl 1985	ND	ND	ND	ND	ND	ND	ND	ND
Ebeling 2001	ND	ND	ND	ND	ND	ND	ND	ND
Esposito 2004	ND	ND	ND	ND	ND	ND	ND	ND
Feinböck 2003	ND	ND	ND	ND	ND	ND	ND	ND
Fineberg 1980	ND	ND	ND	ND	ND	ND	ND	ND
Foley 2009	ND	ND	ND	ND	ND	ND	ND	ND
Forst 2003	ND	ND	ND	ND	ND	ND	ND	ND
Forst 2005	ND	ND	ND	ND	ND	ND	ND	ND
Hanefeld 2005	ND	Carcinoma	ND	Non-fatal myocardial infarction	ND	ND	ND	ND
Harrower 1985	ND	ND	ND	ND	ND	ND	ND	ND
Hermann 1991	ND	ND	ND	ND	ND	ND	ND	ND
Hermann 1991a	One patient had a sudden death	ND	Cardiovascular adverse events	Non-fatal myocardial infarction	ND	ND	ND	ND
Hoffmann 1990	ND	ND	ND	ND	ND	ND	ND	ND
Hoffmann 1994	ND	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

Hollander 1992	ND	ND	ND	ND	ND	ND	ND	ND
Jain 2006	Death due to coronary disease	Colon cancer stage 4	Cardiovascular events	Myocardial infarction	ND	ND	ND	ND
Jibran 2006	ND	ND	ND	ND	ND	ND	ND	ND
Johnston 1997	Death due to cerebrovascular accident	Death due to cancer	Total cardiovascular events	ND	Cerebrovascular event	ND	ND	ND
Kaku 2011	Cardiovascular death	Incidence of single cancer type listed, but not total participants having any cancer	Cardiac disorder	Acute myocardial infarction	Cerebral infarction	Amputation of lower extremity	Peripheral revascularisation	Coronary revascularisation
Kamel 1997	ND	ND	ND	ND	ND	ND	ND	ND
Kanda 1998	ND	ND	ND	ND	ND	ND	ND	ND
Kovacevic 1997	ND	ND	ND	ND	ND	ND	ND	ND
Lawrence 2004	Death due to myocardial infarction	ND	ND	Non-fatal myocardial infarction	ND	ND	ND	ND
LEAD-3 2006	ND	Incidence of single cancer type listed, but not total participants having any cancer	ND	Myocardial infarction (we assume non-fatal as no deaths due to cardiovascular disease is reported)	ND	ND	ND	ND

(*Continued*)

Madsbad 2001	ND	Death due to malign neoplasm	Vascular extracardiac disorders	Myocardial infarction	Cerebrovascular event	ND	ND	ND
Marbury 1999	Intracerebral haemorrhage, postoperative complications after a femoral to peroneal bypass, cardiovascular disease, and cardiovascular disorder	ND	Adverse cardiovascular events	ND	ND	ND	ND	ND
Memisogulla 2009	ND	ND	ND	ND	ND	ND	ND	ND
Nakamura 2004	ND	ND	ND	ND	ND	ND	ND	ND
Nakamura 2006	ND	ND	ND	ND	ND	ND	ND	ND
Nathan 1988	ND	ND	ND	ND	ND	ND	ND	ND
Pagano 1995	ND	ND	ND	ND	ND	ND	ND	ND
Perriello 2007	ND	ND	Cardiovascular events	ND	ND	ND	ND	ND
Rosenthal 2002	ND	ND	ND	ND	ND	ND	ND	ND
Salman 2001	ND	ND	ND	ND	ND	ND	ND	ND
Segal 1997	ND	ND	ND	ND	ND	ND	ND	ND
Shihara 2011	ND	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

Spengler 1992	ND	ND	ND	ND	ND	ND	ND	ND
Sung 1999	ND	ND	ND	ND	ND	ND	ND	ND
Sutton 2002	ND	ND	Incidence of cardiac-related adverse events	ND	ND	ND	ND	ND
Tan 2004	ND	ND	ND	ND	ND	ND	ND	ND
Tan 2004a	ND	History of cancer	ND	Non-fatal myocardial infarction	ND	ND	ND	ND
Tan 2005	ND	ND	ND	ND	ND	ND	ND	ND
Tang 2004	ND	ND	ND	ND	ND	ND	ND	ND
Teramoto 2007	ND	ND	ND	ND	ND	ND	ND	ND
Tessier 1999	ND	ND	ND	ND	ND	ND	ND	ND
Tosi 2003	ND	ND	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"
UGDP 1970	A sudden death was defined as a death occurring within 3 hours of the onset of symptoms in an otherwise clinically stable patient and in a manner consistent with	Any cancer	ND	Patients hospitalised with a diagnosis of non-fatal myocardial infarction or changes from a less severe finding for Q/QS and T patterns on the baseline	Stroke	Amputation of all or part of either lower limb	ND	ND

(*Continued*)

	a cardiovascular event. A death was considered to be due to a myocardial infarction if this diagnosis was made from ECG changes and changes in serum enzymes observed during the terminal course of illness, or if the events leading to death were clinically compatible with the diagnosis and autopsy findings provided evidence that a myocardial infarction was the principal cause of death. The category, other heart disease, included deaths due to congestive heart failure, valvular heart disease,			ECG to a more severe finding for these abnormalities on a follow-up ECG				

(*Continued*)

	atherosclerotic heart disease, and hypertensive heart disease. Deaths due to cerebral vascular disease, pulmonary embolism and peripheral vascular disease were classified in the category extracardiac vascular disease							
UKPDS 1998	Death due to cardiovascular disease is calculated by adding: fatal myocardial infarction, sudden death and fatal stroke, death from peripheral vascular disease	Death from cancer	Not reported separately in trial	WHO clinical criteria with associated ECG/ enzyme changes or new pathological Q wave (ICD 9 Code 410)	Major stroke- stroke with symptoms that persisted for more than 1 month (ICD 430 to 434.9 and 436)	Major limb complications - requiring amputation of digit or limb for any reason (ICD codes 5.845 to 5. 848)	ND	ND
UKPDS 34 1998	ND	ND	ND	WHO clinical criteria with associated ECG/ enzyme changes or new pathological Q wave (ICD 9 Code 410)	Major stroke - stroke with symptoms that persisted for more than one month (ICD 430 to 434.9 and 436)	Major limb complications- requiring amputation of digit or limb for any reason (ICD codes 5.845 to 5. 848)	ND	ND

(*Continued*)

van de Laar 2004	ND	Breast carcinoma	ND	Myocardial infarction	ND	ND	ND	ND
Watanabe 2005	ND	ND	ND	ND	ND	ND	ND	ND
Wolffenbuttel 1989	ND	ND	ND	ND	ND	ND	ND	ND
Wolffenbuttel 1999	Death due to myocardial infarction	ND	ND	Myocardial infarctions	ND	ND	ND	ND
Yamanouchi 2005	ND	ND	Adverse cardiac events	ND	ND	ND	ND	ND
Zhang 2005	ND	ND	ND	ND	ND	ND	ND	ND

Footnotes
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; ND: not defined; LEAD-3: Liraglutide Effect and Action in Diabetes-3; UKPDS: United Kingdom Prospective Diabetes Study

Appendix 8. Definitions of outcomes in trials or as reported (II)

Characteristic Study ID	Composite microvascular outcomes	End-stage renal disease	Nephropathy	Retinopathy	Retinal photocoagulation	Blindness	Mild hypoglycaemia	Moderate hypoglycaemia
Abbatecola 2006	ND	ND	ND	ND	ND	ND	ND	ND
ADOPT 2006	ND	ND	ND	ND	ND	ND	Hypoglycaemia requiring minor intervention	Hypoglycaemia requiring minor intervention
AGEE/DCD/046/UK	ND	ND	ND	ND	ND	ND	Mild/moderate hypoglycaemic reactions	ND

(*Continued*)

AGEE/ DCD/047/ B/F/I	ND	ND	ND	ND	ND	ND	Mild/moderate hypoglycaemic reactions	ND
Alvarsson 2010	ND	ND	ND	ND	ND	ND	Minor symptoms related to hypoglycaemia	ND
APPROACH 2010	ND	ND	Diabetic nephropathy	Diabetic retinopathy or proliferative retinopathy	ND	ND	Hypoglycaemia. We judged it must be the number reported, not requiring external assistance	ND
Birkeland 1994	ND	ND	ND	ND	ND	ND	ND	ND
Birkeland 2002	ND	ND	ND	ND	ND	ND	Hypoglycaemia reported after 1 year, none serious	ND
Campbell 1994	ND	ND	ND	ND	ND	ND	ND	ND
Charbonnel 2005	ND	ND	ND	ND	ND	ND	Hypoglycaemia (not requiring hospitalisation)	ND
Collier 1989	ND	ND	ND	ND	ND	ND	Mild hypoglycaemic episodes	ND
Coniff 1995	ND	ND	ND	ND	ND	ND	ND	ND
Dalzell 1986	ND	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

DeFronzo 2005	ND	ND	ND	ND	ND	ND	ND	ND
Deng 2003	ND	ND	ND	ND	ND	ND	ND	ND
Derosa 2003	ND	ND	ND	ND	ND	ND	Hypoglycaemic episodes were almost always mild	ND
Derosa 2004	ND	ND	ND	ND	ND	ND	Mild hypoglycaemia	ND
Diehl 1985	ND	ND	ND	ND	ND	ND	ND	ND
Ebeling 2001	ND	ND	ND	ND	ND	ND	ND	ND
Esposito 2004	ND	ND	ND	ND	ND	ND	ND	ND
Feinböck 2003	ND	ND	ND	ND	ND	ND	Mild and moderate hypoglycaemia	ND
Fineberg 1980	ND	ND	ND	ND	ND	ND	ND	ND
Foley 2009	ND	ND	ND	ND	ND	ND	Defined as symptoms suggestive of low blood glucose confirmed by self monitored blood glucose (SMBG) measurement of < 3.1 mmol/L plasma glucose equivalent not requiring the assistance of another party	ND

(*Continued*)

Forst 2003	ND	ND	ND	ND	ND	ND	ND	ND
Forst 2005	ND	ND	ND	ND	ND	ND	ND	ND
Hanefeld 2005	ND	ND	ND	ND	ND	ND	Hypoglycaemia reported as adverse events	ND
Harrower 1985	ND	ND	ND	ND	ND	ND	ND	ND
Hermann 1991	ND	ND	ND	ND	ND	ND	ND	ND
Hermann 1991a	ND	ND	ND	ND	ND	ND	Hypoglycaemia, including tremor. No one had severe hypoglycaemia	ND
Hoffmann 1990	ND	ND	ND	ND	ND	ND	ND	ND
Hoffmann 1994	ND	ND	ND	ND	ND	ND	ND	ND
Hollander 1992	ND	ND	ND	ND	ND	ND	ND	ND
Jain 2006	ND	ND	ND	ND	ND	ND	Hypoglycaemia, not otherwise specified, but registered as adverse event, and not as a serious adverse event	ND
Jibran 2006	ND	ND	ND	ND	ND	ND	ND	ND
Johnston 1997	ND	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

Kaku 2011	Microvascular complications (total)	End-stage renal disease	Diabetic nephropathy	Diabetic retinopathy	Retinal photocoagulation	Blindness	Minor, self treated hypoglycaemia and symptoms only	ND
Kamel 1997	ND	ND	ND	ND	ND	ND	ND	ND
Kanda 1998	ND	ND	ND	ND	ND	ND	ND	ND
Kovacevic 1997	ND	ND	ND	ND	ND	ND	ND	ND
Lawrence 2004	ND	ND	ND	ND	ND	ND	ND	ND
LEAD-3 2006	ND	ND	ND	ND	ND	ND	Self treated plasma glucose < 3.1 mM (reported after 2 years of follow-up)	ND
Madsbad 2001	ND	ND	ND	ND	ND	ND	Minor hypoglycaemic event	ND
Marbury 1999	ND	ND	ND	ND	ND	ND	Mild-to-moderate hypoglycaemic events were defined as symptoms of sweating, strong hunger, dizziness, tremors, and/or a blood glucose level < 45 mg/dl	Mild-to-moderate hypoglycaemic events were defined as symptoms of sweating, strong hunger, dizziness, tremors, and/or a blood glucose level < 45 mg/dl

(*Continued*)

Memisogulla 2009	ND	ND	ND	ND	ND	ND	ND	ND
Nakamura 2004	ND	ND	ND	ND	ND	ND	ND	ND
Nakamura 2006	ND	ND	ND	ND	ND	ND	ND	ND
Nathan 1988	ND	ND	ND	ND	ND	ND	ND	ND
Pagano 1995	ND		ND	ND	ND	ND	ND	ND
Perriello 2007	ND	ND	ND	ND	ND	ND	ND	ND
Rosenthal 2002	ND	ND	ND	ND	ND	ND	Hypoglycaemia	ND
Salman 2001	ND	ND	ND	ND	ND	ND	Mild to moderate hypoglycaemia	ND
Segal 1997	ND	ND	ND	ND	ND	ND	Tremor, possibly due to hypoglycaemia	ND
Shihara 2011	ND	ND	ND	ND	ND	ND	Blood glucose concentration < 60 mg/dl, asymptomatic hypoglycaemia	ND
Spengler 1992	ND	ND	ND	ND	ND	ND	No hypoglycaemic events were seen during treatment	No hypoglycaemic events were seen during treatment
Sung 1999	ND	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

Sutton 2002	ND	ND	ND	ND	ND	ND	Signs and symptoms of hypoglycaemia	ND
Tan 2004	ND	ND	ND	ND	ND	ND	ND	ND
Tan 2004a	Microvascular complications Both reported incidences in trial were neuropathy	ND	ND	ND	ND	ND	Hypoglycaemia with symptoms or with blood glucose level < 2.8 mmol/L	ND
Tan 2005	ND	ND	ND	ND	ND	ND	ND	ND
Tang 2004	ND	ND	ND	ND	ND	ND	ND	ND
Teramoto 2007	ND	ND	ND	ND	ND	ND	ND	ND
Tessier 1999	ND	ND	ND	ND	ND	ND	ND	ND
Tosi 2003	Microvascular complications	End-stage renal disease	Normoalbuminuria to microalbuminuria	ND	Retinal photocoagulation	Blindness	Mild symptoms, suggestive of hypoglycaemia	Moderate episodes of hypoglycaemia
UGDP 1970	ND	ND	Urine protein >= 1 g/L	Readings of right central fundus photographs for one or more of the following abnormalities: retinal haemorrhages and microaneurysms, preretinal and vitreous haemorrhages, ve-	ND	ND	ND	ND

(*Continued*)

				nous pathology, arterial pathology, or proliferative changes and neovascularisation				
UKPDS 1998	Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure)	Renal failure dialysis and/or plasma creatinine > 250 mmol/L not ascribable to any acute intercurrent illness	Urine albumin was assessed in mg/L with no adjustment for urine creatinine concentration Data for albuminuria at the triennial visit were the median of that year and the years before and after	Retinopathy was defined as one microaneurysm or more in one eye or worse retinopathy, and progression of retinopathy as a 2-step change in grade	ICD 8.662	ND	Hypoglycaemic episodes were defined as minor if the patient was able to treat the symptoms unaided	ND
UKPDS 34 1998	Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure)	Renal failure dialysis and/or plasma creatinine > 250 mmol/L not ascribable to any acute intercurrent illness	Urine albumin was assessed in mg/L with no adjustment for urine creatinine concentration Data for albuminuria at the triennial visit were the median of that year and the years before and after	Retinopathy was defined as one microaneurysm or more in one eye or worse retinopathy, and progression of retinopathy as a 2-step change in grade	ICD 8.662	ND	Hypoglycaemic episodes were defined as minor if the patient was able to treat the symptoms unaided	ND

(*Continued*)

van de Laar 2004	ND	ND	ND	ND	ND	ND	Hypoglycaemia, not serious	ND
Watanabe 2005	ND	ND	ND	ND	ND	ND	ND	ND
Wolffenbuttel 1989	ND	ND	ND	ND	ND	ND	ND	ND
Wolffenbuttel 1999	ND	ND	ND	ND	ND	ND	Mild and moderate symptoms were those that could be treated/corrected by the patient without the assistance of other individuals	ND
Yamanouchi 2005	ND	ND	ND	ND	ND	ND	ND	ND
Zhang 2005	ND	ND	ND	ND	ND	ND	ND	ND

Footnotes
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; ND: not defined; UKPDS: United Kingdom Prospective Diabetes Study

Appendix 9. Definitions of outcomes in trials or as reported (III)

Characteristic Study ID	Severe hypoglycaemia	Nocturnal hypoglycaemia	Adverse events	Serious adverse events	Drop-outs due to adverse events	Hospitalisation	Out-patient treatment
Abbatecola 2006	Major hypoglycaemic events were considered events hav-	ND	ND	ND	Did not complete trial due to one or more major hypogly-	ND	ND

(*Continued*)

	ing severe central nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat him/herself, blood glucose level readings were < 3 mmol/L or reversal of symptoms by food intake				caemic events		
ADOPT 2006	Hypoglycaemia requiring medical intervention	ND	Adverse events	Event that was fatal, life-threatening, or disabling, resulted in hospitalisation or prolonged hospital stay, was associated with congenital abnormality, cancer or a drug overdose (intentional or accidental), or was suggested by the investigator as serious or suggested any substantial hazard, contraindication, side effect or precaution	Drop-outs due to adverse events	Hospitalisation for any cause	ND
AGEE/DCD/046/UK	Severe hypoglycaemic reactions	ND	Adverse events	Serious adverse events	Withdrawals due to adverse events	ND	ND

(*Continued*)

AGEE/DCD/047/B/F/I	Severe glycaemic reactions	ND	Adverse events	Serious adverse events	Withdrawals due to adverse events	ND	ND
Alvarsson 2010	Major hypoglycaemic event	ND	ND	ND	ND	ND	ND
APPROACH 2010	Requiring external assistance	ND	Adverse events	Serious adverse events	Drop-out due to adverse events	ND	ND
Birkeland 1994	Serious hypoglycaemic episodes	ND	ND	ND	Withdrawal due to hypo- and hyperglycaemia	ND	ND
Birkeland 2002	Serious hypoglycaemic episodes	ND	ND	ND	ND	ND	ND
Campbell 1994	ND	ND	ND	ND	ND	ND	ND
Charbonnel 2005	Hypoglycaemia requiring hospitalisation	ND	Adverse events	ND	Drop-outs due to adverse events	ND	ND
Collier 1989	ND	ND	ND	ND	ND	ND	ND
Coniff 1995	ND	ND	Adverse events	ND	Withdrawn due to adverse events	ND	ND
Dalzell 1986	ND	ND	ND	ND	ND	ND	ND
DeFronzo 2005	ND	ND	ND	ND	Withdrawal due to adverse effects	ND	ND
Deng 2003	ND	ND	ND	ND	ND	ND	ND
Derosa 2003	ND	ND	ND	ND	Drop-out due to transient side effects	ND	ND
Derosa 2004	Severe hypoglycaemia	ND	ND	Serious adverse events	Withdrawal due to	ND	ND

(*Continued*)

					persistent side effects		
Diehl 1985	ND	ND	ND	ND	ND	ND	ND
Ebeling 2001	ND	ND	ND	ND	ND	ND	ND
Esposito 2004	ND	ND	ND	ND	With-drawal due to severe illness	ND	ND
Feinböck 2003	Hypoglycaemia requiring hospitalisation or external help	ND	Adverse events	ND	Excluded owing adverse events	ND	ND
Fineberg 1980	ND	ND	ND	ND	ND	ND	ND
Foley 2009	Requiring the assistance of another party	ND	ND	ND	Drop-outs due to adverse events	ND	ND
Forst 2003	ND	ND	Adverse events	ND	ND	ND	ND
Forst 2005	ND	ND	ND	ND	Withdrawal due to an adverse event	ND	ND
Hanefeld 2005	Hypoglycaemia reported as a serious adverse event	ND	Adverse events	Serious adverse events	Withdrawn due to adverse events	ND	ND
Harrower 1985	ND	ND	ND	ND	ND	ND	ND
Hermann 1991	ND	ND	ND	Serious adverse events	ND	ND	ND
Hermann 1991a	Serious, long-lasting hypoglycaemia	ND	Adverse events	ND	Withdrawn due to adverse events	ND	ND
Hoffmann 1990	ND	ND	Adverse events	ND	ND	ND	ND

(*Continued*)

Hoffmann 1994	ND	ND	ND	ND	ND	ND	ND
Hollander 1992	ND	ND	ND	ND	ND	ND	ND
Jain 2006	ND	ND	Any untoward medical event concurrent with the use of the study drugs	Serious adverse events	Withdrawal due to an adverse event	ND	ND
Jibran 2006	ND	ND	ND	ND	ND	ND	ND
Johnston 1997	ND	ND	ND	ND	ND	ND	ND
Kaku 2011	Hypoglycaemia requiring third-party assistance	Nocturnal hypoglycaemia	Adverse events	Serious adverse events	Drop-outs due to adverse events	ND	ND
Kamel 1997	ND	ND	ND	ND	ND	ND	ND
Kanda 1998	ND	ND	ND	ND	ND	ND	ND
Kovacevic 1997	ND	ND	Adverse side effects	ND	Drop-out due to gastrointestinal side effects and cancer	ND	ND
Lawrence 2004	ND	ND	ND	ND	ND	ND	ND
LEAD-3 2006	One incidence after insulin infusion (part of a substudy procedure)	ND	Treatment-emergent adverse events over 2 years	Serious adverse events	Not completed trial due to adverse events	ND	ND
Madsbad 2001	Hypoglycaemia requiring third party assistance	ND	Adverse events	Serious adverse events	Drop-outs due to adverse events	ND	ND

(*Continued*)

Marbury 1999	Severe hypoglycaemia was characterised as severely impaired consciousness requiring assistance from a third party, medical care or hospitalisation	ND	Adverse events possible or probably related to the study drug	Serious adverse events	Not completing the trial due to adverse events	ND	ND
Memisogullari 2009	ND	ND	ND	ND	ND	ND	ND
Nakamura 2004	ND	ND	ND	ND	There were no drop-outs during the trial	ND	ND
Nakamura 2006	ND	ND	ND	ND	There were no drop-outs during the trial	ND	ND
Nathan 1988	Seizure,coma, treatment with intravenous dextrose or glucagon	ND	ND	ND	ND	ND	ND
Pagano 1995	ND	ND	Side effects	Severe side effects	Severe side effect leading to discontinuation of therapy	ND	ND
Perriello 2007	ND	ND	Mild adverse events	ND	Discontinuation due to adverse events	ND	ND
Rosenthal 2002	ND	ND	Adverse events possibly related	ND	ND	ND	ND

(*Continued*)

			to treatment				
Salman 2001	ND	ND	ND	ND	All events that led to discontinuation were gastrointestinal	ND	ND
Segal 1997	ND	ND	Adverse events	ND	ND	ND	ND
Shihara 2011	Severe hypoglycaemia	ND	Adverse events possibly related to treatment	Serious adverse events	ND	ND	ND
Spengler 1992	No hypoglycaemic events were seen during treatment	No hypoglycaemic events were seen during treatment	ND	ND	Drop-out due to gastrointestinal symptoms and hospitalisation	ND	ND
Sung 1999	ND	ND	Adverse events	ND	ND	ND	ND
Sutton 2002	ND	ND	ND	ND	ND	ND	ND
Tan 2004	ND	ND	ND	ND	ND	ND	ND
Tan 2004a	No severe hypoglycaemic events were reported in the trial	ND	Adverse events	Serious adverse events	Drop-outs due to adverse events	ND	ND
Tan 2005	ND	ND	ND	ND	Drop-outs due to adverse events	ND	ND
Tang 2004	ND	ND	ND	ND	ND	ND	ND
Teramoto 2007	ND	ND	ND	ND	ND	ND	ND
Tessier 1999	ND	ND	ND	ND	ND	ND	ND
Tosi 2003	Severe episodes of hypoglycaemia	Nocturnal episodes	Adverse events	Serious adverse events	Drop-outs due to adverse events	Hospitalisation	Out-patient treatment
UGDP 1970	ND	ND	ND	ND	ND	ND	ND

(*Continued*)

UKPDS 1998	Major if third party help or medical intervention was necessary	ND	ND	ND	ND	ND	ND
UKPDS 34 1998	Major if third party help or medical intervention was necessary	ND	ND	ND	ND	ND	ND
van de Laar 2004	ND	ND	Adverse events	Specified for each patient	Drop-outs due to adverse events	ND	ND
Watanabe 2005	ND	ND	ND	ND	Drop-outs due to adverse events	ND	ND
Wolffenbuttel 1989	ND	ND	ND	ND	ND	ND	ND
Wolffenbuttel 1999	Severe hypoglycaemias were those that could be resolved only with the assistance of another individual	ND	Adverse events	Serious adverse events	Withdrawals due to adverse events	ND	ND
Yamanouchi 2005	ND	ND	ND	ND	Discontinuation of treatment due to oedema	ND	ND
Zhang 2005	ND	ND	ND	ND	ND	ND	ND

Footnotes
ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History; LEAD-3: Liraglutide Effect and Action in Diabetes-3; ND: not defined; UKPDS: United Kingdom Prospective Diabetes Study

Appendix 10. Overview of intervention effects (I)

Outcome Comparison	All-cause mortality	Cardiovascular mortality	Composite non-fatal macrovascular outcomes	Non-fatal myocardial infarction	Non-fatal stroke	Amputation	Cardial revascularisation	Peripheral revascularisation	Composite microvascular outcomes
First-generation SU versus placebo	NS	Favours placebo (TSA-)	-	-	-	-	-	-	-
First-generation SU versus diet	-	-	-	-	-	-	-	-	-
First-generation SU versus metformin	-	-	-	-	-	-	-	-	-
First-generation SU versus thiazolidinediones	-	-	-	-	-	-	-	-	-
First-generation SU versus insulin	NS	NS	-	NS	NS	-	-	-	-
First-generation SU versus alpha-glucosidase inhibitors	-	-	-	-	-	-	-	-	-
Second-generation SU versus placebo	-	-	-	-	-	-	-	-	-

(*Continued*)

Second-generation SU versus diet	-	-	-	-	-	-	-	-	-
Second-generation SU versus metformin	NS	NS	Favours SU (TSA-)	NS	-	-	-	-	-
Second-generation SU versus thiazolidinediones	NS	NS	NS	NS	-	-	-	-	-
Second-generation SU versus insulin	NS	NS	-	-	-	-	-	-	-
Second-generation SU versus alpha-glucosidase inhibitors	-	-	-	-	-	-	-	-	-
Second-generation SU versus incretin	NS	-	-	-	-	-	-	-	-
Second-generation SU versus meglitinide	NS	NS	NS	NS	-	-	-	-	-
Third-generation SU versus	-	-	-	-	-	-	-	-	-

(*Continued*)

metformin									
Third-generation SU versus thiazolidinediones	-	-	-	-	-	-	-	-	-
Third-generation SU versus alpha-glucosidase inhibitor	-	-	-	-	-	-	-	-	-
Third-generation SU versus incretin	-	-	-	-	-	-	-	-	-
Third-generation SU versus meglitinide	-	-	-	-	-	-	-	-	-
Second-generation SU versus first-generation SU	-	-	-	-	-	-	-	-	-

Footnotes
"-" denotes meta-analysis could not be performed
NS: non-significant in random-effects model; SU: sulphonylurea; TSA- : the significance of the effect estimate does not hold the trial sequential analysis (more trials needed before firm evidence is established); TSA+: the significance of the effect estimate is confirmed in the trials sequential analysis (firm evidence established)

Appendix 11. Overview of intervention effects (II)

Outcome Comparison	Nephropathy	Retinopathy	Cancer	Fasting blood glucose	HbA1c	Body mass index	Weight	Adverse events
First-generation SU versus placebo	-	-	-	-	-	-	-	-
First-generation SU versus diet	-	-	-	-	-	-	-	-
First-generation SU versus metformin	-	-	-	NS	-	-	-	-
First-generation SU versus thiazolidinediones	-	-	-	-	-	-	-	-
First-generation SU versus insulin	-	-	-	-	-	-	-	-
First-generation SU versus alpha-glucosidase inhibitors	-	-	-	Favour SU (TSA+)	Favour SU (TSA+)	-	-	Favour SU (TSA-)
Second-generation SU versus placebo	-	-	-	Favour SU (TSA+)	Favour SU (TSA+)	NS	-	NS
Second-generation SU versus diet	-	-	-	-	-	-	-	-
Second-generation SU	-	-	-	Favour met (TSA-)	NS	NS	Favour met (TSA+)	NS

(*Continued*)

versus metformin								
Second-generation SU versus thiazolidinediones	-	-	NS	Favour thiaz (TSA+)	NS	Favour SU (TSA-)	Favour SU (TSA+)	NS
Second-generation SU versus insulin	-	-	NS	NS	NS	-	NS	-
Second-generation SU versus alpha-glucosidase inhibitors	-	-	-	NS	NS	NS	NS	NS
Second-generation SU versus incretin	-	-	-	NS	NS	-	Favour incretin (TSA-)	-
Second-generation SU versus meglitinide	-	-	-	Favour SU (TSA-)	NS	NS	NS	NS
Third-generation SU versus metformin	-	-	-	NS	NS	NS	-	-
Third-generation SU versus thiazolidinediones	-	-	-	NS	NS	NS	-	Favour SU (TSA-)
Third-generation SU versus alpha-glucosidase inhibitor	-	-	-	-	-	-	-	-

(*Continued*)

Third-generation SU versus incretin	-	-	-	-	-	-	-	-
Third-generation SU versus meglitinide	-	-	-	-	-	-	-	-
Second-generation SU versus first-generation SU	-	-	-	Favour first-gen (TSA+)	NS	-	NS	-

Footnotes
"-" denotes meta-analysis could not be performed
HbA1c: glycosylated haemoglobin A1c; met: metformin; NS: non-significant in random-effects model; SU: sulphonylurea; TSA- : the significance of the effect estimate does not hold the trial sequential analysis (more trials needed before firm evidence is established) ; TSA+: the significance of the effect estimate is confirmed in the trials sequential analysis (firm evidence established)

Appendix 12. Overview of intervention effects (III)

Outcome Comparison	Serious adverse events	Drop-outs due to adverse events	Mild hypoglycaemia	Moderate hypoglycaemia	Severe hypoglycaemia	Intervention failure	Cost of intervention	Quality of life
First-generation SU versus placebo	-	-	-	-	-	-	-	-
First-generation SU versus diet	-	-	-	-	-	-	-	-
First-generation SU versus metformin	-	-	-	-	-	-	-	-
First-generation SU versus thia-	-	-	-	-	-	-	-	-

(*Continued*)

zolidinediones								
First-generation SU versus insulin	-	-	-	-	-	-	-	-
First-generation SU versus alpha-glucosidase inhibitors	-	Favour SU (TSA-)	-	-	-	-	-	-
Second-generation SU versus placebo	-	NS	-	-	-	Favour SU (TSA-)	-	-
Second-generation SU versus diet	-	-	-	-	-	-	-	-
Second-generation SU versus metformin	NS	NS	Favour met (TSA-)	-	Favour met (TSA-)	NS	-	-
Second-generation SU versus thiazolidinediones	NS	NS	Favour thiaz (TSA+)	-	Favour thiaz (TSA-)	NS	-	-
Second-generation SU versus insulin	-	-	Favour insulin (TSA-)	-	-	NS	-	-
Second-generation SU versus alpha-glucosidase inhibitors	-	Favour SU (TSA-)	-	-	-	Favour SU (TSA-)	-	-

(*Continued*)

Second-generation SU versus incretin	-	NS	Favour incretin (TSA-)	-	-	NS	-	-
Second-generation SU versus meglitinide	NS	NS	NS	-	NS	NS	-	-
Third-generation SU versus metformin	-	-	-	-	-	NS	-	-
Third-generation SU versus thiazolidinediones	-	NS	-	-	-	Favour SU (TSA-)	-	-
Third-generation SU versus alpha-glucosidase inhibitor	-	-	-	-	-	-	-	-
Third-generation SU versus incretin	-	-	-	-	-	-	-	-
Third-generation SU versus meglitinide	-	-	-	-	-	-	-	-
Second-generation SU versus first-generation SU	-	-	-	-	-	-	-	-

Footnotes

"-" denotes meta-analysis could not be performed

First-gen: first-generation; NS: non-significant in random-effects model; SU: sulphonylurea; thiaz: thiazolidinediones; TSA- : a 10% relative risk reduction or relative risk increase (binary outcomes) or the magnitude of the effect estimate (continuous outcomes) does

(*Continued*)

not hold the trial sequential analysis (more trials needed before firm evidence is established); TSA+: a 10% relative risk reduction or relative risk increase (binary outcomes) or the magnitude of the effect estimate (continuous outcomes) is confirmed in the trials sequential analysis (firm evidence established)

CONTRIBUTIONS OF AUTHORS

Bianca Hemmingsen: development of protocol, undertaking of searches, selection of trials, data extraction, bias risk assessment of trials, data analysis, contact person, development of review.

Jeppe Schroll: selection of trials, data extraction, bias risk assessment of trials, data analysis, development of review.

Søren S. Lund: development of protocol, development of review.

Jørn Wetterslev: development of protocol, advised on statistical methods to be used, data analysis, development of review.

Christian Gluud: development of protocol, development of review.

Allan Vaag: development of protocol, development of review.

David Sonne: selection of trials, data extraction, bias risk assessment of trials, development of review.

Lars H. Lundstrøm: development of protocol, selection of trials, data extraction, bias risk assessment of trials, development of review.

Thomas Almdal: development of protocol, selection of trials, data extraction, bias risk assessment of trials, development of review.

DECLARATIONS OF INTEREST

Søren Søgaard Lund, Allan Vaag and Thomas Almdal have reported equity in Novo Nordisk A/S. Søren Søgaard Lund and Allan Vaag received fees from Novo Nordisk A/S for speaking. Thomas Almdal was employed at Steno Diabetes Center, Gentofte, Denmark during the development of the protocol and the review. Steno Diabetes Center is an academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation. Søren Søgaard Lund and Allan Vaag were employed at Steno Diabetes Center when the protocol was published and the work on the review was initiated. Søren Søgaard Lund is now employed with Boehringer Ingelheim, Ingelheim, Germany and Allan Vaag at Rigshospitalet, Copenhagen, Denmark.

SOURCES OF SUPPORT

Internal sources

- Copenhagen Trial Unit, Rigshospitalet, Denmark.
- Cochrane Metabolic and Endocrine Disorders Group, Germany.

External sources

- The Copenhagen Insulin and Metformin Therapy Group, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

David Peick Sonne and Jeppe Schroll joined as authors after publication of the protocol. Christina Hemmingsen withdrew as an author after publication of the protocol.

The title of the review is different from the protocol as we only were allowed by the Cochrane Metabolic and Endocrine Disorders Group to focus on the sulphonylureas.

After advice from the Cochrane Metabolic and Endocrine Disorder Group, we changed the inclusion criteria for trials to a duration of 24 weeks or more and avoided combination therapies.

It was not predefined to search the Food and Drug Administration web site.

We have renamed the macrovascular complications as non-fatal macrovascular outcomes, as it was more in line with the definition in the protocol. The microvascular complication outcome was renamed as microvascular outcome.

We originally planned to assess baseline imbalance and early stopping as bias components, but did not do this, based on decisions taken at the Cochrane Colloquium 2010.

When no differences in mean and standard deviations for the continuous outcomes were reported in trials, we used the end of follow-up values, if available.

We originally planned only to report the results of the fixed-effect model in case of discrepancy between the two models. On request from the Cochrane Metabolic and Endocrine Disorder Group we reported both results, if heterogeneity was present.

The comparison of all sulphonylureas versus each comparator was made post hoc due to little power for each sulphonylurea generation.

Appendix 5 of the protocol (adverse events) was deleted as this would have given rise to double entry of data.

We did not search for ongoing trials.

We performed best-worst case scenario and worst-best case scenario for the primary outcomes.

The assessment of change in weight from baseline was not described in the protocol.

Trial sequential analysis was performed for all trials, and not only trials with low risk of bias due to limited data.

Second-generation sulphonylurea monotherapy versus metformin in patients with type 2 diabetes: a systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

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Abstract

Objectives To compare the benefits and harms of second-generation sulphonylurea monotherapy versus metformin in randomised clinical trials of patients with type 2 diabetes.

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

Data sources The Cochrane Library, Medline, Embase, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature, and Cumulative Index to Nursing and Allied Health Literature until August 2011. We also searched abstracts from major diabetes congresses, reference lists of included trials, (systematic) reviews, meta-analyses, health technology assessment reports, contacted trial authors, pharmaceutical companies, and the US Food and Drug Administration homepage.

Criteria for trial selection Randomised clinical trials comparing second-generation sulphonylurea monotherapy versus metformin in patients with type 2 diabetes, older than 18 years, and with an intervention period of at least 24 weeks. We included trials irrespective of language, publication status, antidiabetic interventions used before randomisation, and predefined outcomes.

Review methods Two authors independently assessed trials for inclusion and extracted data related to interventions, outcomes, and risk of bias. The risk of random errors was assessed by trial sequential analysis.

Results We included 11 trials with 4258 participants. All trials were judged as high risk of bias. Data on patient important outcomes were sparse. Second-generation sulphonylurea versus metformin did not significantly affect all cause mortality (relative risk 0.98, 95% confidence interval 0.61 to 1.58) or cardiovascular mortality (1.47, 0.54 to 4.01). Sulphonylurea compared with metformin significantly decreased the risk of non-fatal macrovascular outcomes (0.67, 0.48 to 0.93; P=0.02). However, the definition varied among trials and trial sequential analyses showed that more trials are needed before reliable conclusions can be drawn regarding the above outcomes. No statistical significance between the interventions was found in random-effects model for change in HbA1c. Second-generation sulphonylurea resulted in higher fasting blood glucose and weight gain compared with metformin. However, only the achieved changes in weight gain were confirmed in the trial sequential analysis. Second-generation sulfonylurea significantly increased mild hypoglycaemia (2.95, 2.13 to 4.07; P<0.00001) and severe hypoglycaemia (5.64, 1.22 to 26.00; P=0.03).

Conclusions Despite fasting blood glucose and higher risk of hypoglycaemia, there is no evidence that second-generation sulphonylurea compared with metformin increases all cause or cardiovascular mortality in patients with type 2 diabetes. In general the amount of data is far too small and inconsistent to provide firm evidence concerning patient relevant outcomes in relation to benefits and harms of second-generation sulphonylurea monotherapy versus metformin.

Introduction

The American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for treatment of type 2 diabetes recommend initiation of metformin at diagnosis, or soon after, along with lifestyle interventions.[1] In cases where metformin cannot be used another oral antidiabetic agent might be prescribed, e.g., a sulphonylurea agent. The rationale for recommending metformin as first drug of choice in patients with type 2 diabetes is based on its perceived beneficial effect on conventional surrogate outcomes, including weight, tolerability, and costs,[1] on the United Kingdom Prospective Diabetes Study (UKPDS) 34 trial outcomes in a selected small subgroup of obese patients,[2] and finally on observational studies.[3-5] However, given the fear of lactate acidosis use of metformin has traditionally been avoided in patients with important co-morbidities including renal complications, cardiac congestion, pulmonary diseases, or advanced age.[6]

The sulphonylureas are divided into different classes. The first-generation sulphonylureas (carbutamide, tolbutamide, acetohexamide, tolazomide, and chlorpropamide) were introduced in diabetes treatment in the 1950s.[1;7-9] The second-generation sulphonylureas (e.g., glibenclamide, glipizide, glibornuride, and gliclazide) and the third-generation sulphonylureas (glimepiride, gliclazide modified release (MR), and glipizide gastrointestinal therapeutic system (GITS)) sulphonylureas) have almost completely replaced the first-generation sulphonylureas. The second and third generation sulphonylureas are preferred because of their perceived greater potency and perceived better safety profiles.[1;7-9] The sulphonylureas increase insulin secretion by closing of adenosine triphosphate-sensitive K^+ channels (K_{ATP}) in the plasma membrane on the pancreatic β-cells. This depolarises the cell resulting in increased influx of calcium which triggers preformed insulin-containing granula in the cytoplasma to fuse with the plasma membrane and ultimately release insulin to the extracellular space. The differences in the pharmacokinetic profiles of the insulin secretagogues are primarily explained by different binding affinities to the K_{ATP} channels on the β-cells.[10]

The purpose of this systematic review was to assess whether the use of second-generation sulphonylurea agents are associated with a different risk of benefits and harms in patient important outcomes compared with metformin in patients with type 2 diabetes.

Methods

This review follows the recommendations of the Cochrane Collaboration.[11] It is based on our published Cochrane protocol.[12] We included randomised clinical trials comparing sulphonylurea monotherapy versus other antidiabetic interventions or placebo.[12;13] Trials were analysed according to the generation of sulphonylureas applied. In this paper we only report the data from the comparison of second-generation sulphonylurea with metformin because it is the comparison with the, at present, greatest clinical relevance. The Cochrane version reports all comparisons.[13]

Search strategy

We searched the Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL in August 2011 for randomised clinical trials of sulphonylurea monotherapy versus other antidiabetic intervention or placebo in patients with type 2 diabetes. Web appendix 1 describes the search terms and strategies for each database. We also searched abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes congresses. We searched reference lists of included trials and (systematic) reviews, meta-analyses, health technology assessment reports, and the US Food and Drug Administration Homepage.
We contacted authors for information about additional trials.

Trial selection

To determine which references to assess further, two authors (BH and LL, TA, or JS) independently screened the abstracts, titles, or both. All potentially relevant references were obtained as full text. Any disagreements were resolved by discussion, or if required by a third party (JW or CG).

A trial was considered eligible if it was a randomised clinical trial (cross over or parallel) evaluating adult patients with type 2 diabetes; had a duration of intervention of 24 weeks or more; and compared allocation to sulphonylurea monotherapy versus metformin.[12;13] We included trials irrespective of outcomes reported, language, or whether escape medicine was allowed if monotherapy failed.[12;13]

Data extraction and bias assessment

Two authors (BH and LL, TA, JS, or DS) independently extracted information from each included trial using standard data extraction forms and assessed the risk of bias as advised in the Cochrane Handbook of Systematic Reviews of Interventions.[11]

We assessed the following risk of bias domains: sequence generation, concealment of allocation, blinding of participants and investigators, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, academic bias and sponsor bias. We classified each domain as low, uncertain, or high risk of bias.[12;13] Web appendix 2 gives details. Discrepancies between authors' assessments were resolved by involvement of a third author (CG, AV, SL, or JW).

We extracted baseline characteristics (such as age, duration of disease, and HbA1c) and outcomes from the included trials. Our predefined outcomes were all cause mortality, cardiovascular mortality, non-fatal macrovascular outcomes as a composite outcome, non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity, peripheral revascularisation, microvascular outcomes as a composite outcome, nephropathy, retinal photocoagulation, adverse events, serious adverse events, drop-outs due to adverse events, mild hypoglycaemia, severe hypoglycaemia, cancer, intervention failure, change in fasting blood glucose from baseline, change in HbA1c from baseline, change in body mass index from baseline, change in weight from baseline, quality of life, and costs of intervention.[12;13] We sought any relevant missing information from the original author(s) of the randomised trial. When we identified more than one publication of an original trial, we assessed these together to maximise data collection. In case of substantial disagreements between older and newer publications, we contacted the authors.[12;13]

Statistical analysis

We used Review Manager version 5.1.7 for statistical analysis.[14] The medians reported in the included trials were assumed to be close to the arithmetic mean. Reported standard errors and confidence intervals were converted into standard deviations. We used both a random effects model and a fixed effect model.[15;16] In case difference in the statistical significance of the effect estimate between the two models, we reported both results; otherwise, we reported the random effects model.[12;13]

We examined heterogeneity with the I^2 statistic.[11] $I^2 \geq 50\%$ indicated substantial heterogeneity.[11]

Trial sequential analysis

The trial sequential analysis of a meta-analysis is similar to interim analyses in a single trial, where alpha and beta spending 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.[17-20] 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 of boundaries can be applied to a meta-analysis.[17-21] Cumulative meta-analyses of trials are at risk of producing random errors because of sparse data and repetitive testing when the required information size (analogous to the sample size of an optimally powered clinical trial) has not been met. Trial sequential analysis depends on the quantification of the required information size (the meta-analysis sample size). 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. We calculated the diversity (D^2) adjusted required information size.[20] We did the trial sequential analyses with an intention to maintain an overall 5% risk of a type I error and 20% risk of a type II error for the primary outcomes and the secondary outcomes showing statistical significance in both random effects model and fixed effect model. On the basis of pre-determined criteria,[12] we calculated the required information size for the binary outcomes to detect or reject an intervention effect of a 10% relative risk reduction between the second-generation sulphonylurea and the comparator. For the continuous outcomes the trial sequential analysis estimated the required information size to detect or reject the observed differences between the interventions. We used software Trial Sequential Analysis, version 0.9.[22]

Results

Results of the search and trial, participant, and intervention characteristics

We identified 11,048 references through electronic and hand searches (fig 1). After excluding duplicate reports, we screened 7409 references. The excluded trials are listed in web appendix. Twenty-two publications describing 11 randomised clinical trials met our inclusion criteria for the comparison of second-generation sulphonylurea versus metformin.[2;23-43]

All the trials for this comparison were published in English. The trials included 4258 participants of whom 2093 were randomised to second-generation sulphonylurea and 2162 were randomised to metformin monotherapy. However, one trial did not describe which intervention group three of the participants were randomised to.[33] Table 1 shows characteristics of the eleven included trials, table 2 shows characteristics of the interventions, and table 3 shows baseline characteristics. The number of randomised participants ranged from 23 to 2902.[23-30;38] The duration of intervention varied from 24 weeks to 10.7 years. Six of the trials applied glibenclamide as the second-generation sulphonylurea.[2;23-29;32-38;41;42] Four trials applied gliclazide.[31;38-40] One trial applied glipizide.[30]

The United Kingdom Prospective Diabetes Study (UKPDS) 34 trial included overweight/obese participants with type 2 diabetes comparing intensive glycaemic control with metformin versus intensive glycaemic control with other antidiabetic interventions (chlorpropamide, glibenclamide, or insulin).[2;42;43] In this part of the trial, the vascular outcomes and mortality were only reported as metformin versus a combined group of the other interventions at the end of follow-up – not versus individual groups allocated to sulphonylurea or insulin.[2]

Two of the trials had a cross over design.[33;41] The remaining nine trials had a parallel design. Six of the trials were open labelled,[2;30;31;33;39;40;42] and five trials were blinding investigators and participants.[23-29;32;34-38;41] One trial did not describe the blinding of participants and investigators, but as one of the intervention arms involved a placebo group, we assumed this trial was designed to blind the investigators and participants.[38]

Bias risk assessment

All the trials were judged as high risk of bias on at least one bias domain (table 4). We divided the trials into those with a lower risk of bias and those with a high risk of bias based on the assessment of sequence generation, concealment of allocation, and blinding according to the Cochrane Handbook risk of bias tool.[11] For detailed description see Web appendix 2. When we judged all three domains to be adequately assessed, we designated the trial as having a lower risk of bias. Table 4 reports the bias risk assessments of the included trials. Only three of the trials were considered to have lower risk of bias.[23-29;34-37;41]

Clinical outcomes

All cause mortality

The effect estimate of all cause mortality was dominated by the A Diabetes Outcome Progression Trial (ADOPT) trial, which contributed with 62 out of 65 fatal events.[23-29] All cause mortality was not significantly influenced by the interventions (relative risk 0.98, 95% confidence interval 0.61 to 1.58; 6 trials, 3528 participants; I^2=0%, P=0.68; fig 2). Trial sequential analysis showed that only 2.3% of the required information size was accrued to detect or reject a 10% relative risk reduction.

Sensitivity analysis excluding the trial with the longest duration[23-29] and excluding the trials without describing how the diagnosis of type 2 diabetes was established did not change the statistical significance of the effect estimate. Sensitivity analyses according to the language of publication, funding source, or publication status could not be performed. Subgroup analyses were not conducted, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

Cardiovascular mortality

Cardiovascular mortality of second-generation sulphonylurea was not significantly increased compared with metformin (relative risk 1.47, 95% confidence interval 0.54 to 4.01; 6 trials, 3528 participants; I^2=0%, P=0.52; fig 2). The total number of deaths due to cardiovascular disease was 15 of which 12 were reported in the ADOPT trial.[23-29] Trial sequential analysis showed that only 2.7% of the required information size to detect or reject a 10% relative risk reduction was accrued.

Sensitivity analysis excluding the trial with the longest duration[23-29] and excluding the trials without describing how the diagnosis of type 2 diabetes was established did not change the statistical significance of the effect estimate. Sensitivity analyses according to the language of publication, funding source, or publication status could not be performed. Subgroup analyses were not conducted, as none of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

Non-fatal macrovascular outcomes

Non-fatal macrovascular outcomes as a composite outcome were not reported fully concordant with our predefined assessment of this outcome (for macrovascular definitions in trials, see web

appendix 4). The ADOPT trial and Hermann et al trial defined their outcome in a manner, which may have included cardiac outcomes of a non-atherosclerotic origin.[23-29;34-37] Tosi et al reported that no cardiovascular events were observed during the trial.[41] The ADOPT trial included fatal myocardial infarctions in their composite cardiovascular outcome. Also, the non-fatal macrovascular outcomes in the ADOPT trial included congestive heart failure (9 participants in the glibenclamide group versus 19 in the metformin group), which might not have an atherosclerotic origin. Owing to the definition of 'cardiovascular disease' in the ADOPT trial it is not possible to exclude the events of congestive heart failure. We pooled the non-fatal macrovascular outcomes and found a statistical significant reduction in favour of second-generation sulphonylureas (relative risk 0.67, 95% confidence interval 0.48 to 0.93; P=0.02; 3 trials, 3018 participants; I^2=0%, P=0.53; fig 2). Trial sequential analysis showed that only 5% of the required information size to detect or reject a 10% relative risk reduction was accrued and the trial sequential monitoring boundary was not crossed, meaning that firm evidence could not be established.

Thirty-nine non-fatal myocardial infarctions were reported, of which 36 originated from the ADOPT trial.[23-29] The effect estimate of non-fatal myocardial infarctions did not show statistical significant differences (relative risk 1.02, 95% confidence interval 0.37 to 2.85; 4 trials, 3061 participants; I^2=15%, P=0.31; fig 2). For the single components of the composite non-fatal macrovascular outcomes no meta-analysis could be conducted due to lack of data.

Microvascular outcomes

Meta-analysis of microvascular outcomes could not be performed due to lack of data.

Hypoglycaemia

Mild hypoglycaemia was significantly increased with sulfonylurea (relative risk 2.95, 95% confidence interval 2.13 to 4.07; P<0.00001; 5 trials, 4056 participants; I^2 =29%, P=0.23; fig 3). D^2 was 79%. Trial sequential analysis showed that 2.9% of the required information size to detect or reject a 10% relative risk increase was accrued. Due to the reporting in the trials, meta-analysis of moderate hypoglycaemia could not be performed. Severe hypoglycaemia showed significance for a lower risk with metformin (5.64, 1.22 to 26.00; P=0.03; 4 trials, 3637 participants; I^2=0%, P=0.62; fig 3). Trial sequential analysis showed that 0.1% of the required information size to detect or reject a 10% relative risk increase was accrued. Unfortunately did the UKPDS 34 publication not report

number of participants with hypoglycaemia in each of the intervention arms at the end-of follow-up.[2;42;43] The data are therefore taken after one year of follow-up. Due to a relatively large number of participants lost to follow-up for the hypoglycaemia data in the UKPDS trial, available case analysis was also performed with the UKPDS trial data, which did not change the statistical significance of mild or severe hypoglycaemia. Reporting of hypoglycaemia in trials is listed in web appendix 5.

Adverse events

The effect estimate for adverse events was not significantly influenced by the interventions (relative risk 0.99, 95% confidence interval 0.97 to 1.01; 4 trials, 3042 participants; I^2=0%, P=0.71; fig 3). The effect-estimate of serious adverse events did not show any significance (0.94, 0.82 to 1.07; 4 trials, 3042 participants; I^2=0%; P=0.99; fig 3). Six-hundred and forty-one participants reported a serious adverse event, of which 639 were from the ADOPT trial.[23-29] Drop-outs due to adverse events were not significantly influenced by the interventions, but showed a tendency of favouring metformin (1.19, 0.99 to 1.42; 7 trials, 3567 participants; I^2=0%, P=0.54; fig 3). Reporting of adverse events in trials is listed in web appendix 5.

Cancer

Only the ADOPT trial provided data on cancer (55 patients out of 1447 in the sulphonylurea arm; 50 patient out of 1455 in the metformin arm).[23-29] Meta-analysis could not be performed due to lack of data.

Intervention failure

Intervention failure to monotherapy was not significantly influenced by the interventions in the random effects model (relative risk 0.97, 95% confidence interval 0.60 to 1.57; 7 trials, 4143 participants; fig 3), but showed significance in the fixed effect model favouring metformin (1.35, 1.17 to 1.55; P < 0.0001; I^2=69%, P=0.006).

Glycaemic control

The change in HbA1c from baseline was not significantly different between second-generation sulphonylurea and metformin in random effects model (mean difference 0.17%, -0.09 to 0.44; 10

trials, 3351 participants; fig 4), but showed statistical significance in favour of metformin in the fixed effect model (mean difference 0.25%, 95% confidence interval 0.18 to 0.33; P<0.00001; I^2=72%, P=0.0002). The change in fasting blood glucose from baseline was significantly larger with metformin compared with second-generation sulphonylurea (mean difference 0.43 mmol/L, 95% confidence interval 0.10 to 0.75; P=0.009; 11 trials, 3891 participants; I^2=44%, P=0.06; fig 4). Trial sequential analysis showed that firm evidence for the achieved changes was not established (fig 5). One trial included in the analyses of fasting blood glucose and HbA1c change from baseline allowed the addition of escape medicine when monotherapy failed, but we included only data on the participants who remained on monotherapy.[34-37] The UKPDS 34 trial also allowed addition of escape medicine in case of monotherapy failure.[2] The data for the UKPDS 34 trial was after 3 years of follow-up.[2] Exclusion of this trial from the analysis did not change the significance of the effect estimate for fasting blood glucose.

Weight

The change in weight from baseline was significantly changed in favour of metformin (mean difference 3.77 kg, 95% confidence interval 3.06 to 4.47; P < 0.00001; 7 trials, 3497 participants; I^2=39%, P=0.13; fig 4). Trial sequential analysis showed firm evidence for the achieved differences of weight disregarding of risk of bias (fig 5). Change in body mass index from baseline did not show statistical significance in random effects model (mean difference 0.25 kg/m^2, 95% confidence interval -1.21 to 1.70; 3 trials, 103 participants; I^2=71%, P=0.03; fig 4), but showed statistical significance in fixed effect model (mean difference 0.54 kg/m^2, 95% confidence interval 0.06 to 1.03; P=0.03). However, only one of the trials included in the meta-analysis of changes in body mass index from baseline reported the actual change of the mean and standard deviation in each of the intervention groups.[41] For the remaining two trials the end of follow-up values were used.[31;39] Both of these trials had relatively small sample size. The sulphonylurea group had lower body mass index compared with the metformin group at baseline and at the end of follow-up in both trials.[31;39]

Discussion

Based on our published protocol, we identified and meta-analysed eleven randomised clinical trials comparing the effects of second-generation sulphonylurea monotherapy with metformin in patients with type 2 diabetes.[12] No difference was found between second-generation sulphonylurea versus metformin monotherapy in terms of their potential effect on all cause or cardiovascular mortality. In contrast, a potential benefit of second-generation sulphonylurea over metformin was observed on

non-fatal macrovascular outcomes. This benefit should be interpreted with caution. The definition of the composite cardiovascular outcome for the two trials contributing with data to this meta-analysis rendered it impossible to include, exclusively, the number of events with atherosclerotic origin.[23-29;34-37] However, we cannot rule out the clinical relevance of the events which were reported in the trials whether of atherosclerotic origin or not, which favours inclusion of all reported events as we did in the present meta-analysis. In addition, trial sequential analysis demonstrated that the amount of evidence was insufficient to draw firm conclusions for mortality or any of the vascular outcomes. All trials had high risk of bias in one or more bias domains, and only three trials were considered to have lower risk of bias.[23-29;34-37;41] Meta-analyses of patient important outcomes were based on very sparse data and did, except for non-fatal macrovascular outcomes and severe hypoglycaemia, not show any significance of the effect estimates.

Metformin monotherapy seems to be associated with lower risk of hypoglycaemia, more pronounced reduction in fasting blood glucose and weight compared with second-generation sulphonylurea. However, only the changes in weight could be confirmed in the trial sequential analysis and thus constitutes the only firm evidence obtained from randomised clinical trials disregarding risk of bias to support the choice of metformin over a second-generation sulphonylurea as monotherapy. The change in BMI from baseline did not show statistical significance for the comparison of second-generation sulphonylurea with metformin. We would have expected that change in BMI from baseline was in favour of metformin. The reason for lack of statistical significance is probably the few number of trials contributing with data.[31;39;41] Besides, despite of a difference in BMI, two of these trials reported no change from baseline in BMI.[31;39] Both of these trials had a small sample size and a higher BMI at baseline in the metformin group. This may explain the lack of statistical significance in this analysis.

Regardless, the significant dissociation between non-fatal macrovascular outcome data and two of the conventional surrogate outcomes in type 2 diabetes, namely fasting blood glucose and weight, adds further concern to the use of these surrogate markers in the registration and treatment choices of glucose lowering drugs in patients with type 2 diabetes.

Strengths and limitations

Our systematic review has several strengths. It is based on a published protocol, a comprehensive search strategy and rigid inclusion criteria for the randomised trials.[12] Two authors independently selected trials and extracted data. We contacted corresponding authors of all trials to clarify methodological details and outcomes. We evaluated the strength of the available evidence by assessing the risks of bias[44-46] and by using trial sequential analyses to control the risks of random errors.[17;19;47;48]

The weaknesses of our analyses and conclusions mirror the weaknesses of the included trials. Most importantly, only three of the eleven included trials were classified as lower risk of bias according to randomisation, allocation, and blinding. All of the included trials were judged as high risk of bias in one or more bias domains. We did not have access to data at the patient level and could therefore not perform analyses taking time on treatment into account. Because we could not include mortality or vascular event data from the UKPDS,[2] the present review consists exclusively of trials which did not predefine mortality or vascular events as their primary outcome – i.e., events were reported as adverse events. This might have lead to bias arising from trial design features such as lack of adjudication of events.

The participants of the included trials represented a diverse sample of the population with type 2 diabetes. The results of our review should therefore be interpreted with caution. The inclusion criteria varied among the trials, but nearly all trials excluded participants with existing co-morbidities, especially renal or hepatic disease. However, the diversity of patient characteristics is typical in real life, which may justify the clinical relevance of our results.

Relation to other studies and reviews

A Cochrane review compared the effect of metformin monotherapy with other antidiabetic interventions.[49] However, this Cochrane review only included six randomised trials with a duration of the intervention of 24 weeks or more comparing second-generation sulphonylurea with metformin monotherapy.[2;30-32;34-37;40;42] Unlike our present review of sulphonylurea versus metformin monotherapy, the Cochrane review of metformin monotherapy could include mortality and vascular outcomes from United Kingdom Prospective Diabetes Study (UKPDS) – however, like our review, not for metformin versus sulphonylurea.[49] The Cochrane review of metformin monotherapy made a pooled analysis of non-UKPDS trials having various comparators, which

showed no significant difference for mortality or vascular outcomes.[49] The conclusion from that Cochrane review was that metformin might be beneficial regarding cardiovascular outcomes in overweight/obese patients with type 2 diabetes.[49] For the comparison second-generation sulphonylurea versus metformin we found a minor (0.43 mmol/L), but statistical significant change in fasting blood glucose from baseline and lower risk of mild as well as severe hypoglycaemia in favour of metformin. The Cochrane review of metformin monotherapy also found less hypoglycaemia with metformin compared with sulphonylurea and improved glycaemic control in terms of fasting blood glucose and HbA1c.[49] However, we did only find statistical significance for a lower HbA1c in favour of metformin in the fixed effect model.

Several observational studies have indicated an increased mortality and risk of cardiovascular disease with sulphonylurea monotherapy compared with metformin monotherapy.[3-5] Our data, based on randomised clinical trials, did not find increased mortality with second-generation sulphonylurea monotherapy compared with metformin monotherapy. Contrary, although very heterogeneously reported, the composite non-fatal macrovascular outcome showed statistical significance in favour of sulphonylurea. For both outcomes, we cannot exclude the risk of random errors and more randomised clinical trials are needed. An observational study has indicated that second-generation sulphonylureas may be associated with different risks of macrovascular disease with gliclazide, putatively, exhibiting greatest beneficial outcome profiles.[4] In the current analysis, we were unable to differentiate effects between different types of second-generation sulphonylureas due to the insufficient number of trials.

Unfortunately, we were not able to include patient important data to the longest follow-up from the UKPDS trial.[2] The importance of the UKDPS trial is based on the length of the intervention, around 10 years. According to the design article, the researchers planned to compare the subgroup of overweight/obese participants randomised to either sulphonylurea versus metformin monotherapy.[42] However, to our knowledge, these data have never been reported separately. Instead, the participants randomised to sulphonylurea and insulin are reported together, which preclude direct comparison of sulphonylurea versus metformin.[2;42] The largest trial, reporting patient important outcomes for second-generation sulphonylurea monotherapy compared with metformin, is the ADOPT trial.[23-29] This trial showed statically significant benefit in terms of time to treatment failure (the primary outcome) and HbA_{1c} for metformin versus glibenclamide after

about four years of follow-up. Contrary, a numerical lower number of cardiovascular events appeared with sulphonylurea versus metformin. However, like the UKPDS trial, the ADOPT trial has never published statistical tests of the cardiovascular events comparing the sulphonylurea and metformin groups. As yet, this is only available from meta-analyses, like the present. A later re-analysis of the ADOPT taking into account the differences in time on treatment between interventions did not bring clarity about the presence of any statistically significant differences in cardiovascular risk between the metformin and glibenclamide groups.[26]

In our Cochrane review we also compared first-generation sulphonylurea versus metformin.[13] However, no meta-analyses could be performed for any of the patient important outcomes due to lack of data.[13] For the comparison of third-generation sulphonylurea versus metformin, only three trials could be included in the systematic review.[50-52] Likewise, no meta-analyses could be performed on patient important outcomes due to lack of data.[13]

A recent radnomised trial by Hong et al in about 300 Chinese patients with type 2 diabetes and existing coronary artery disease indicated a significant benefit in favour of metformin compared with glipizide for the primary composite cardiovascular outcome for about 3 years.[53] Notably, the primary outcome was not reported after 3 years, but after a median follow up of about 5 years – i.e., about two years after the trial medication was stopped. This trial was published after the database search of our present systematic review was finalised and has therefore not been included. Implementing the patient important data from Hong et al into our meta-analyses did not change the significance of the effect estimates for the primary outcomes as well as non-fatal myocardial infarction. However, the composite outcome of non-fatal macrovascular complications did no longer reach statistical significance (relative risk 0.86, 95% confidence interval 0.49 to 1.50 with second-generation sulphonylurea versus metformin). The discrepancy of the result of this relatively small trial and our current meta-analysis comprising substantially more number of patients underscores the need for further adequately bias controlled trials, and, in particular, in broader populations, to clarify the benefits and harms of metformin and sulphonylurea in patients with type 2 diabetes.

Clinical implementations

Treatment recommendations from international medical societies do not recommend sulphonylurea as first-line antidiabetic drug.[1] The most widespread guidelines recommend metformin as first-line therapy.[1;54] This recommendation is likely to be highly influenced by the results from the subgroup of overweight/obese participants in the UKPDS trial, a trial of limited size and possible bias in the reporting of the comparison of second-generation sulphonylurea with metformin (because UKPDS apparently did not adhere to the predefined statistical analysis plan from the design article). Additional factors such as price, a likely beneficial effect on weight as well as a number of potentially biased retrospective analyses, has all together made sulphonylurea as monotherapy less used.[2;42;55] Sulphonylurea is now largely prescribed as a part of a combination regime.[55] The use of sulphonylureas has to a quite extensive extent been replaced with the novel, and with respect to hard outcome variables, as yet, unproven but more expensive dipeptidyl peptidase IV-inhibitors.[55] On the basis of the present results, we strongly recommend that future glucose lowering interventions in type 2 diabetes should be based on evidence from high quality randomised long term trials with patient important outcomes.

Differences between planned protocol and review

David Peick Sonne and Jeppe Schroll joined as authors after publication of the protocol. Christina Hemmingsen withdrew as an author after publication of the protocol. The title of the review is different from the protocol as we only were allowed from the Cochrane Metabolic and Endocrine Disorders Group to focus on the sulphonylureas. After advice from the Cochrane Metabolic and Endocrine Disorder Group, we changed the inclusion of trials to have a duration of 24 weeks or more and avoided combination therapies. It was not predefined to search the US Food and Drug Administration Homepage. We originally planned to assess baseline imbalance and early stopping as bias components, but did not do this, based on decisions taken at the Cochrane Colloquium 2010. We did not search for ongoing trials. The assessment of change in weight from baseline was not described in the protocol. When no differences in mean and standard deviations for the continuous outcomes were reported in trials, we used the end of follow-up values, if available.

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This review is also published as a Cochrane review in the Cochrane Database of Systematic Reviews XXX, Issue XXX. Cochrane reviews are regularly updated as new evidence emerges and in response to comments and criticism, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Contributors

BH developed the protocol and was responsible for the searches, selected trials, extracted data, assessed the risk of bias, conducted the analysis, and contacted authors. JBS selected trials, extracted data, assessed the risk of bias, and advised on interpretation of the data. SSL developed the protocol and advised on interpretation of the data. JW developed the protocol, advised on statistical methods, data analyses, and advised on interpretation of the data. CG developed the protocol, advised on statistical methods and interpretation of data. AV developed the protocol and advised on interpretation of the data. DPS extracted data, assessed the risk of bias, and advised on interpretation of the data. LHL developed the protocol, selected trials, extracted data, and assessed the risk of bias. TA selected trials, extracted data, assessed the risk of bias, and advised on interpretation of the data. All authors read and approved the final manuscript, and were involved in the development of the final review. BH and TA are the guarantors.

Competing interest

All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that SSL, AV, and TA have reported equity in Novo Nordisk A/S. SSL and AV received fees from Novo Nordisk A/S for speaking. TA was employed at Steno Diabetes Center, Gentofte, Denmark during development of the protocol and the review. Steno Diabetes Center is owned by Novo Nordisk A/S. SSL and AV were employed at Steno Diabetes Center when the protocol was published and the work on the review was initiated. SSL is now employed with Boehringer Ingelheim, Ingelheim, Germany and AV at Rigshospitalet, Copenhagen, Denmark.

Ethical approval

Not needed.

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Copenhagen Trial Unit.

Data sharing

No additional data available.

What is already known on this topic

- Current guidelines for type 2 diabetes recommend metformin monotherapy as first line antidiabetic intervention
- Prescription of second-generation sulphonylurea monotherapy as first line antidiabetic intervention is sparse
- Observational studies indicate an increased mortality and cardiovascular risk with monotherapy of second-generation sulphonylurea compared to metformin

What this study adds

- We observed no difference of second-generation sulphonylurea versus metformin on all cause mortality and cardiovascular mortality. Firm evidence could not be established, because data on patient-important outcomes were sparse
- Second-generation sulphonylurea may reduce the risk of non-fatal macrovascular events compared with metformin
- Metformin seems to be associated with a larger reduction in fasting blood glucose and weight as well as lower risk of hypoglycaemia compared with second-generation sulphonylurea monotherapy

Table 1. Characteristics of the included trials

Trial	Location	Design	No of participants sulphonylurea/metformin (total) participants	Duration of intervention
ADOPT 2006[23-29]	North America, Europe, and Canada	Parallel Blinding investigators and participants	1447/1455 (2902)	4 years
Campbell et al 1994[30]	United Kingdom	Parallel Open label	24/24 (48)	1 year
Collier et al 1989[31]	NR	Parallel Open label	12/12 (24)	6 months
DeFronzo et al 1995[32]	United States of America	Parallel Blinding investigators and participants	209/210 (419)	29 weeks
Hermann et al 1991[33#]	Sweden	Cross over Open label	10/12 (25)	6 months
Hermann et al 1991a[34-37]	Sweden	Parallel Blinding investigators and participants	34/38 (72)	6 months+ 2-12 weeks
Kamel et al 1997[38]*	Turkey	Parallel Blinding investigators and participants	17/6 (23)	24 weeks
Lawrence et al 2004[39]	United Kingdom	Parallel Open label	22/21 (43)	24 weeks
Tessier et al 1999[40%]	Canada	Parallel Open label	19/20 (39)	24 weeks
Tosi et al 2003[41]	Italy	Cross over Blinding investigators and participants	22/22 (44)	6 months
UKPDS 34 1998[2;42;43]	United Kingdom	Parallel Open label	277/342 (619)	10.7 years

ADOPT=A Diabetes Outcome Progression Trial; NR=not reported; UKPDS=United Kingdom Prospective Diabetes Study

[#]Number of participants randomised to each intervention arm not reported. Only the participants who finished the trial

*The 17 participants in the sulphonylurea arm is addition of the gliclazide arm (9 participants) and the glibenclamide arm (8 participants)

%: Only baseline characteristics on the participants who completed the trial (36 out of 39)

Table 2. Characteristics of the intervention

Trial	Sulphonylurea intervention	Metformin intervention	Plan in case of monotherapy failure	Intervention arm in study, not included in this analysis
ADOPT 2006[23-29]	Glibenclamide, po., initial 2.5 mg, then up to 15 mg /day given as 7.5 mg twice daily	Metformin, po., initial 500 mg, then up to 2 gm (1 gram twice a day)	Escape medicine not allowed, participants excluded	Rosiglitazone
Campbell et al 1994[30]	Glipizide, po., initiated at 5 mg once daily to a maximum divided daily dose of 15 mg	Metformin, po., initial 500 mg, increased with 500 mg at each visit (every second week) to a maximum at 3 gram	NR	
Collier et al 1989[31]	Gliclazide, po., doses from 80-240 mg/day	Metformin, po., doses from 1.5-3.0 gram/day	NR	Healthy controls
DeFronzo et al 1995[32]	Glibenclamide, po., initially 5 mg twice daily for the first week and then 10 mg twice daily plus metformin placebo	Metformin, po., initially one 500 mg tablet of metformin. After one week the metformin dose was increased to 1000 mg per day by adding a 500 mg tablet to the breakfast meal. After two weeks the metformin dose was increased to 1500 mg per day by adding a 500 mg tablet to be taken at lunch. After three weeks the	Escape medicine not allowed, participants excluded	Combination of metformin plus glibenclamide

		dose was increased to 2000 mg per day by adding a second 500 mg tablet to be taken with the evening meal, and after four weeks the daily dose was increased to 2500 mg by adding a second 500 mg tablet to the breakfast dose. Glibenclamide placebo		
Hermann et al 1991[33]	Glibenclamide, po., 1.75-10.5 mg daily	Metformin, po., 0.5-3 gram	NR	
Hermann et al 1991a[34-37]	Glibenclamide, po., initial 3.5 mg. Up to 14.0 mg. Tablets given shortly before breakfast and if daily dosis exceeded 7 mg then divided between breakfast and evening meal Placebo metformin	Metformin, po., initial 1 gram. 1.0-3.0 gram in two doses a day – shortly before breakfast and evening meal. Placebo glibenclamide	Escape medicine allowed	Combination of metformin plus glibenclamide
Kamel et al 1997[38]	Gliclazide and Glibenclamide	Metformin	NR	Acarbose and placebo
Lawrence et al 2004[39]	Gliclazide, po., 80 mg once daily, uptitrated up to 160 mg once daily depending on fasting blood glucose	Metformin, po., initial 500 mg twice a day, uptitrated up to 1 gram three times a day depending on fasting blood glucose	Escape medicine not allowed, participants excluded	Pioglitazone

Tessier et al 1999[40]	Gliclazide, po., titrated to glycaemic target. Gliclazide was increased with the intervals: 80, 160, 240, and 320 mg/d divided into two doses with breakfast and evening meal	Metformin, po., titrated to glycaemic target. Metformin dosage was 750, 1500 and 2250 mg (divided into three doses) one with each meal	NR	
Tosi et al 2003[41]	Glibenclamide, po., starting dose was 1 tablet before lunch, consisting of glibenclamide 5 mg. The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets three times daily (before breakfast, before lunch, and before dinner). For the group treated with glibenclamide alone, the last 2 steps were 1 tablet of active drug +1 tablet of placebo	Metformin, po., starting dose was 1 tablet before lunch, consisting of metformin 500 mg. The subsequent steps were 1 tablet twice daily (before breakfast and before dinner), 2 tablets twice daily (before breakfast and before dinner), and 2 tablets three times daily (before breakfast, before lunch, and before dinner). Therefore scheduled dose steps were 0.5, 1, 2, 3 gram/d for metformin	Escape medicine not allowed, participants excluded	Combination of metformin plus glibenclamide
UKPDS 34 1998[2;42;43]	Glibenclamide, po., 2.5–20 mg	Metformin, po., 850 mg tablet per day, then 850 mg	Escape medicine allowed	Chlorpropamide and insulin

		twice daily, and then 1700 mg in the morning and 850 mg with the evening meal (maximum dose=2550 mg). If on any dose, symptoms of diarrhoea or nausea occurred, patients reduced the dose to that which previously did not cause symptoms		

ADOPT=A Diabetes Outcome Progression Trial; mg=milligram; NR=not reported; po.= peroral; UKPDS=United Kingdom Prospective Diabetes Study

Table 3. Baseline characteristics

Trial	Duration of type 2 diabetes (years)	Age (years)	HbA1c (%)	Body mass index (kg/m^2)
ADOPT 2006[23-29#]	Expressed in publication as: <1 year; 1-2 years; and >2 years. Participants had to be diagnosed with type 2 diabetes within 3 years from screening to trial	56.4 (10.2)/ 57.9 (9.9)	7.4 (0.9)/ 7.4 (0.9)	32.3 (6.3)/ 32.1 (6.1)
Campbell et al 1994[30]	2.8 (3.9)/ 2.3 (3.2)	57 (9)/ 57 (10)	11.8 (2.1)/ 11.5 (1.9)	31.2 (6.6)/ 29.6 (5.6)
Collier et al 1989[31]	All newly diagnosed	55.5 (5.1)/ 53.1 (5.1)	11.7 (1.5)/ 12.1 (2.4)	23.1 (1.3)/ 24.3 (1.4)
DeFronzo et al 1995[32]¤	8.7 (5.8)/ 8.4 (5.8)	56 (14.5)/ 55 (14.5)	8.5 (1.4)/ 8.9 (1.4)	29.1 (4.3)/ 29.0 (4.3)
Hermann et al 1991[33&]	All patients: 7.6 (1/3-24)	All patients: 58.9 (8.8)	8.1 (1.0)/ 7.9 (1.6)	All patients: 26.2 (3.8)
Hermann et al 1991a[34-37?]	All patients: 3.6 (0-38)	All patients: 59.4 (8.8)	6.7 (1.7)/ 6.9 (1.8)	All patients: 28.3 (4.6)
Kamel et al 1997[38]	NR	NR	Gliclazide: 8.4 (1.1); glibenclamide: 8.4 (1.1); metformin: 8.4 (0.5)	NR
Lawrence et al 2004[39!]	NR	63.5 (11.4)/ 59.5 (9.3)	7.9 (0.9)/ 8.0 (0.9)	28.7 (28.3-34.4)/ 29.2 (28.1-31.6)
Tessier et al 1999[40%]	4.7 (6.1)/ 5.4 (6.5)	59.3 (7.3)/ 59.1 (7.1)	7.8 (1.8)/ 7.1 (1.7)	28.6 (4.0)/ 29.3 (3.0)
Tosi et al 2003[41]	9.9 (6.6)	57.9 (7.5)/ 58.2 (7.3)	7.9 (1.0)/ 7.7 (0.9)	26.3 (2.3)/ 26.4 (2.7)
UKPDS 34 1998[2;42;43]	All newly diagnosed	53 (9)/ 53 (8)	7.2 (1.5)/ 7.3 (1.5)	31.5 (4.4)/ 31.6 (4.2)

ADOPT=A Diabetes Outcome Progression Trial; NR=not reported; T2DM=type 2 diabetes mellitus; UKPDS=United Kingdom Prospective Diabetes Study

#: Baseline characteristics only reported for the participants who received a dose of the study drug (glibenclamide: 1441; rosiglitazone: 1456; metformin: 1454)

¤: All standard deviations are calculated from standard errors. Fasting plasma glucose values are converted from mg/dl to mmol/L

&: Only baseline characteristics on the 22 participants who completed the trial. Duration of disease is mean (range)

?: Standard deviations for HbA1c are calculated from standard errors
!: Baseline variables only reported for the participants completing the trial (20 in each intervention arm). Median (interquartile range) for body mass index
%: Only baseline characteristics on the participants who completed the trial (36 out of 39)

Table 4. Risk of bias in the included trials

Trial	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Academic bias	Sponsor bias
ADOPT 2006[23-29]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Campbell et al 1994[30]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear
Collier et al 1989[31]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
DeFronzo et al 1995[32]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Inadequate
Hermann et al 1991[33]	Adequate	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
Hermann et al 1991a[34-37]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Inadequate
Kamel et al 1997[38]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear
Lawrence et al 2004[39]	Unclear	Unclear	Inadequate	Adequate	Adequate	Unclear	Adequate	Inadequate
Tessier et al 1999[40]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate
Tosi et al 2003[41]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate	Inadequate
UKPDS 34 1998[2;42;43]	Adequate	Adequate	Inadequate	Adequate	Unclear	Inadequate	Adequate	Inadequate

ADOPT=A Diabetes Outcome Progression Trial; UKPDS=United Kingdom Prospective Diabetes Study

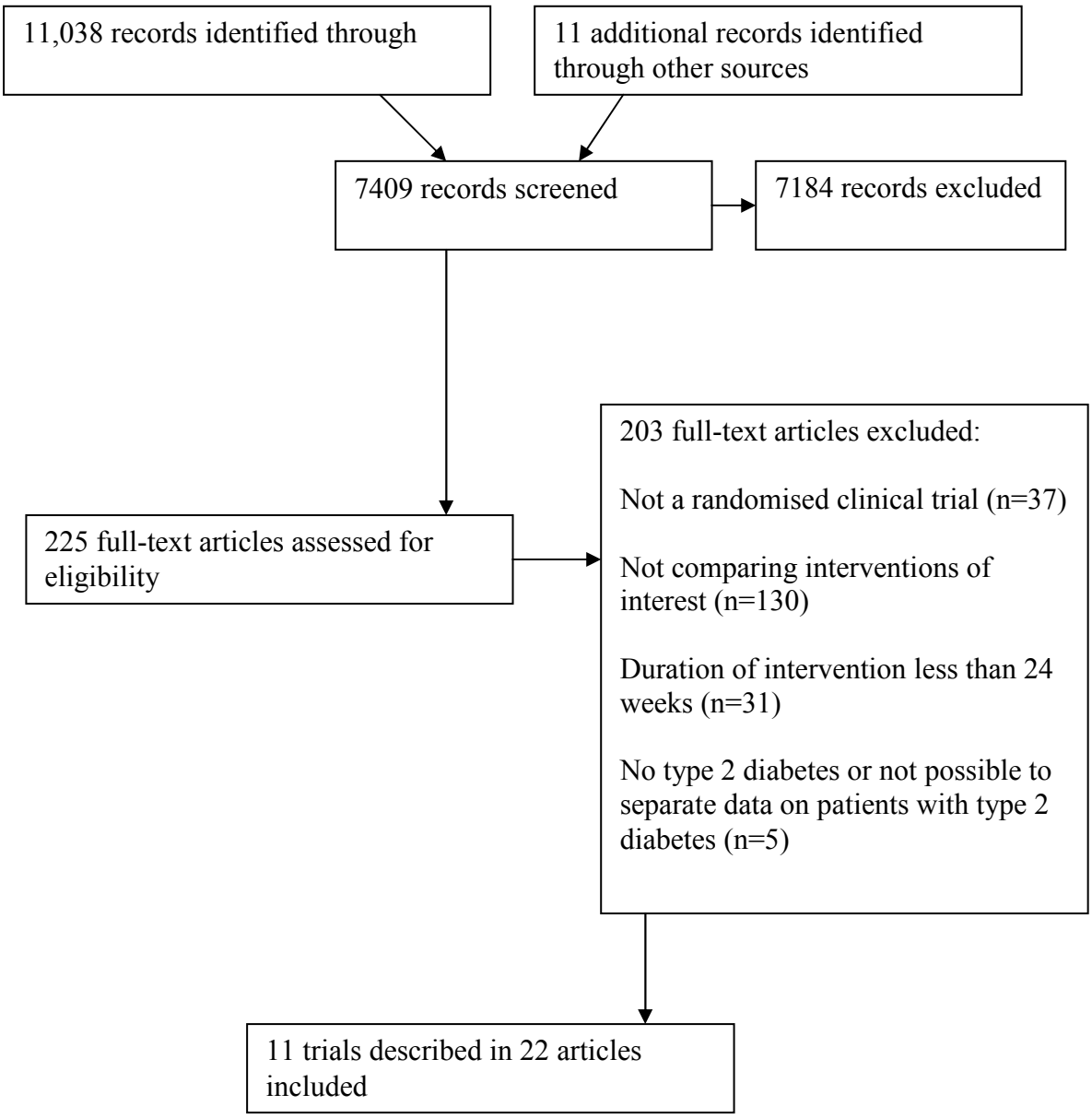


Fig 1 Flow diagram of identification of randomised trials for inclusion

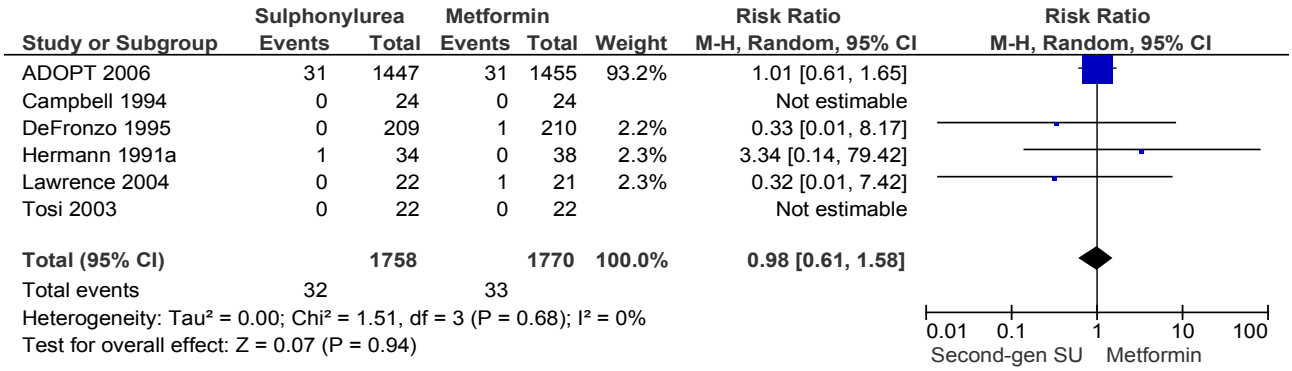


Fig 2a. Forest plot for all-cause mortality

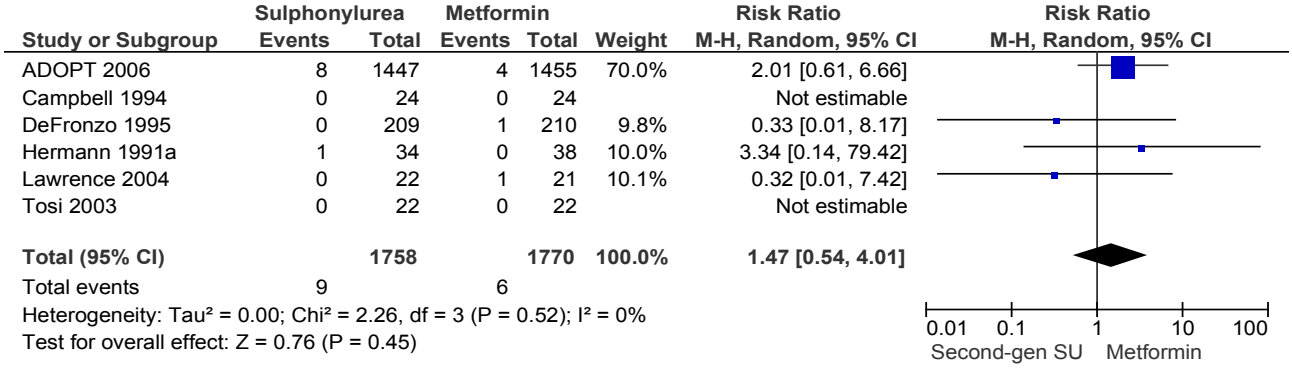


Fig 2b. Forest plot for cardiovascular mortality

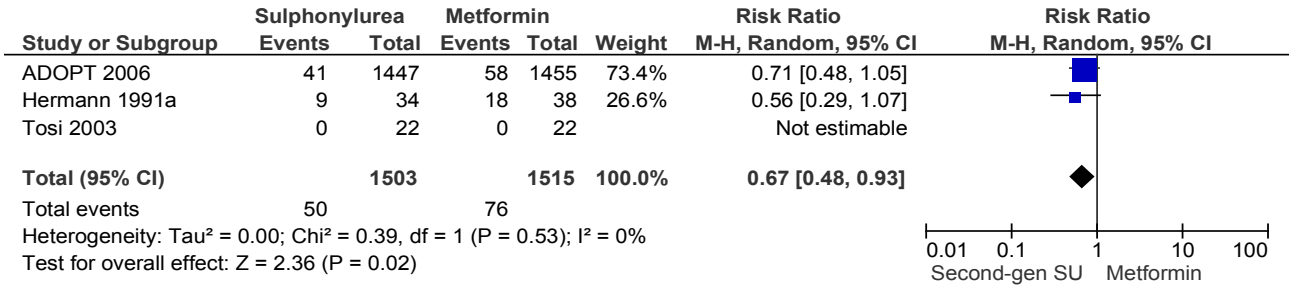


Fig 2c. Forest plot for non-fatal macrovascular outcomes

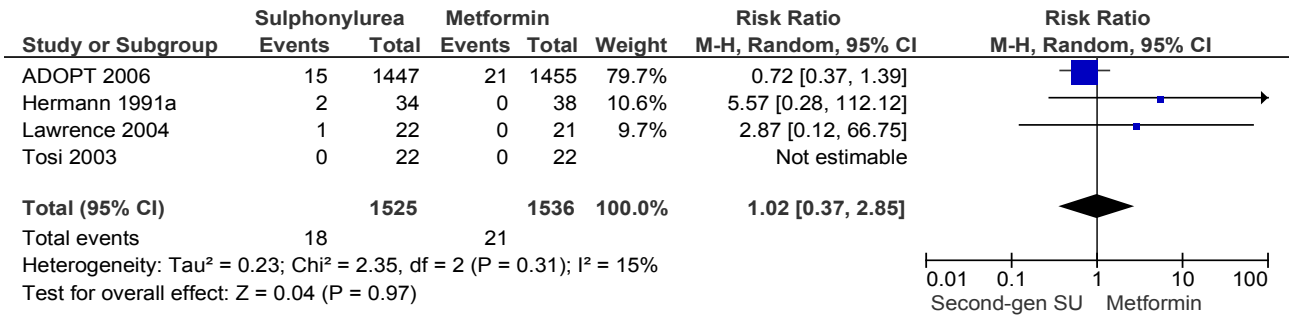


Fig 2d. Forest plot for non-fatal myocardial infarction

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	549	1447	167	1455	56.4%	3.31 [2.82, 3.87]
DeFronzo 1995	6	209	4	210	6.0%	1.51 [0.43, 5.26]
Hermann 1991a	12	34	8	38	14.0%	1.68 [0.78, 3.61]
Tosi 2003	1	22	1	22	1.4%	1.00 [0.07, 15.00]
UKPDS 34 1998	49	277	15	342	22.2%	4.03 [2.31, 7.03]
Total (95% CI)		**1989**		**2067**	**100.0%**	**2.95 [2.13, 4.07]**
Total events	617		195			

Heterogeneity: Tau² = 0.04; Chi² = 5.67, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 6.56 (P < 0.00001)

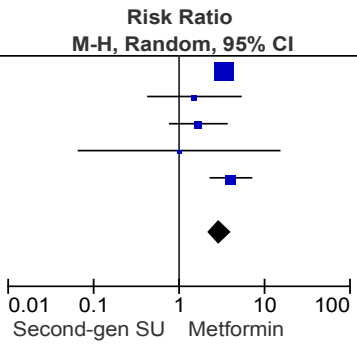


Fig 3a. Forest plot for mild hypoglycaemia

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	8	1447	1	1455	54.1%	8.04 [1.01, 64.23]
Hermann 1991a	0	34	0	38		Not estimable
Tosi 2003	0	22	0	22		Not estimable
UKPDS 34 1998	3	277	1	342	45.9%	3.70 [0.39, 35.41]
Total (95% CI)		**1780**		**1857**	**100.0%**	**5.64 [1.22, 26.00]**
Total events	11		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)

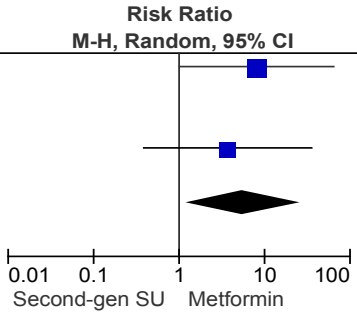


Fig 3b. Forest plot for severe hypoglycaemia

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	1321	1447	1341	1455	99.1%	0.99 [0.97, 1.01]
Collier 1989	2	12	4	12	0.0%	0.50 [0.11, 2.23]
Hermann 1991a	26	34	32	38	0.9%	0.91 [0.72, 1.14]
Tosi 2003	3	22	3	22	0.0%	1.00 [0.23, 4.42]
Total (95% CI)		**1515**		**1527**	**100.0%**	**0.99 [0.97, 1.01]**
Total events	1352		1380			

Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

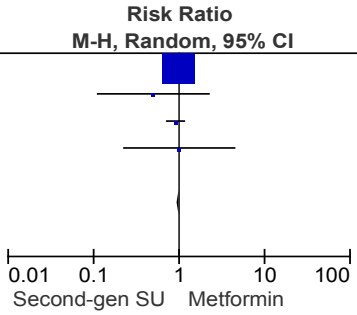


Fig 3c. Forest plot for adverse events

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	308	1447	331	1455	99.7%	0.94 [0.82, 1.07]
Hermann 1991	0	10	0	12		Not estimable
Lawrence 2004	1	22	1	21	0.3%	0.95 [0.06, 14.30]
Tosi 2003	0	22	0	22		Not estimable
Total (95% CI)		**1501**		**1510**	**100.0%**	**0.94 [0.82, 1.07]**
Total events	309		332			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)

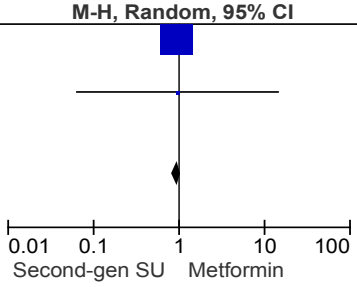


Fig 3d. Forest plot for serious adverse events

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	215	1447	178	1455	94.3%	1.21 [1.01, 1.46]
Campbell 1994	0	24	0	24		Not estimable
DeFronzo 1995	5	209	5	210	2.1%	1.00 [0.30, 3.42]
Hermann 1991a	3	34	9	38	2.2%	0.37 [0.11, 1.26]
Lawrence 2004	2	22	1	21	0.6%	1.91 [0.19, 19.52]
Tessier 1999	1	19	1	20	0.4%	1.05 [0.07, 15.66]
Tosi 2003	1	22	0	22	0.3%	3.00 [0.13, 69.87]
Total (95% CI)		**1777**		**1790**	**100.0%**	**1.19 [0.99, 1.42]**
Total events	227		194			

Heterogeneity: Tau² = 0.00; Chi² = 4.09, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)

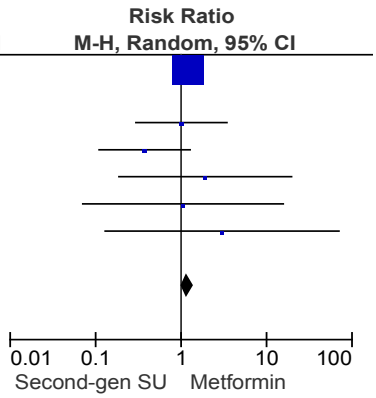


Fig 3e. Forest plot for drop-outs due to adverse events

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	311	1447	207	1455	32.1%	1.51 [1.29, 1.77]
Campbell 1994	0	24	0	24		Not estimable
DeFronzo 1995	6	209	21	210	15.7%	0.29 [0.12, 0.70]
Hermann 1991a	13	34	13	34	21.9%	1.00 [0.55, 1.83]
Lawrence 2004	1	22	0	21	2.2%	2.87 [0.12, 66.75]
Tosi 2003	0	22	1	22	2.2%	0.33 [0.01, 7.76]
UKPDS 34 1998	32	277	35	342	25.8%	1.13 [0.72, 1.77]
Total (95% CI)		**2035**		**2108**	**100.0%**	**0.97 [0.60, 1.57]**
Total events	363		277			

Heterogeneity: Tau² = 0.18; Chi² = 16.15, df = 5 (P = 0.006); I² = 69%
Test for overall effect: Z = 0.14 (P = 0.89)

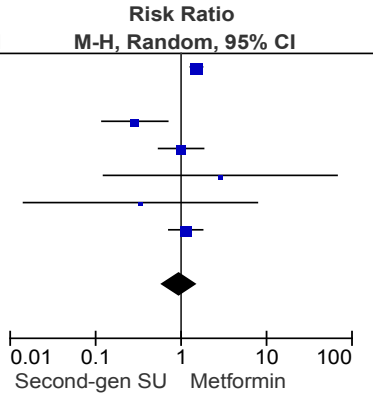
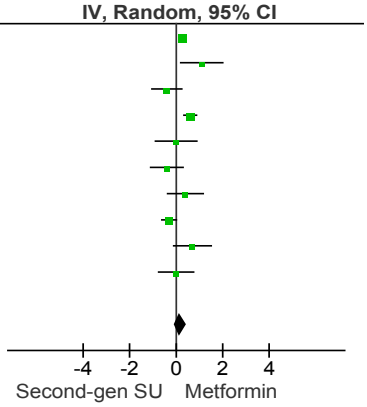


Fig 3f. Forest plot for intervention failure

Study or Subgroup	Sulphonylurea Mean	SD	Total	Metformin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ADOPT 2006	0.07	1.1	1310	-0.2	1.1	1352	18.8%	0.27 [0.19, 0.35]
Campbell 1994	9.7	1.9	24	8.6	1.2	24	5.9%	1.10 [0.20, 2.00]
Collier 1989	7	0.8	12	7.4	0.8	12	8.9%	-0.40 [-1.04, 0.24]
DeFronzo 1995	0.2	1.4	209	-0.4	1.4	210	15.9%	0.60 [0.33, 0.87]
Hermann 1991	7.9	0.8	10	7.9	1.3	12	6.0%	0.00 [-0.89, 0.89]
Hermann 1991a	-1.3	1.1	19	-0.9	1.1	19	8.1%	-0.40 [-1.10, 0.30]
Kamel 1997 (1)	7.3	1.1	17	6.9	0.7	6	7.2%	0.40 [-0.37, 1.17]
Lawrence 2004	6.6	0.5	20	6.9	0.5	20	15.1%	-0.30 [-0.61, 0.01]
Tessier 1999	6.8	1.6	18	6.1	0.7	18	6.8%	0.70 [-0.11, 1.51]
Tosi 2003	-0.5	1.3	20	-0.5	1.1	19	7.4%	0.00 [-0.75, 0.75]
Total (95% CI)			**1659**			**1692**	**100.0%**	**0.17 [-0.09, 0.44]**

Heterogeneity: Tau² = 0.09; Chi² = 31.65, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 1.30 (P = 0.19)

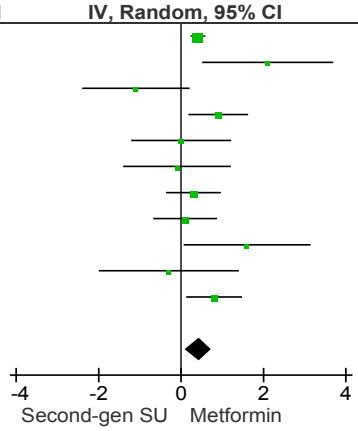


(1) Not described in abstract if the values are standard deviations or standard errors

Fig 4a. Forest plot for change in HbA1c from baseline

Study or Subgroup	Sulphonylurea Mean	SD	Total	Metformin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ADOPT 2006	-0.09	2.3	1334	-0.5	2	1394	25.0%	0.41 [0.25, 0.57]
Campbell 1994 (1)	9.2	3.7	24	7.1	1.3	24	3.6%	2.10 [0.53, 3.67]
Collier 1989	6.4	1.5	12	7.5	1.7	12	5.1%	-1.10 [-2.38, 0.18]
DeFronzo 1995	0.8	2.9	209	-0.1	4.3	210	11.8%	0.90 [0.20, 1.60]
Hermann 1991	7.2	1	10	7.2	1.8	12	5.7%	0.00 [-1.19, 1.19]
Hermann 1991a	-2.1	2.3	19	-2	1.7	19	5.1%	-0.10 [-1.39, 1.19]
Kamel 1997 (2)	8.1	0.9	17	7.8	0.6	6	13.0%	0.30 [-0.34, 0.94]
Lawrence 2004	7.4	1.4	20	7.3	1	20	10.9%	0.10 [-0.65, 0.85]
Tessier 1999	8	3.1	18	6.4	1.1	18	3.9%	1.60 [0.08, 3.12]
Tosi 2003	-3.1	2.4	20	-2.8	2.9	19	3.3%	-0.30 [-1.98, 1.38]
UKPDS 34 1998 (3)	8.5	4.5	212	7.7	2.1	262	12.7%	0.80 [0.14, 1.46]
Total (95% CI)			**1895**			**1996**	**100.0%**	**0.43 [0.10, 0.75]**

Heterogeneity: Tau² = 0.10; Chi² = 17.85, df = 10 (P = 0.06); I² = 44%
Test for overall effect: Z = 2.59 (P = 0.009)



(1) Numbers read from figure
(2) Not described in abstract if the values are standard deviations or standard errors
(3) Data after three years of follow-up

Fig 4b. Forest plot for change in fasting blood glucose from baseline

Study or Subgroup	Sulphonylurea Mean	SD	Total	Metformin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Collier 1989	23.6	1.4	12	24.5	1.6	12	39.5%	-0.90 [-2.10, 0.30]
Lawrence 2004	30.6	8.8	20	28.6	3.5	20	10.0%	2.00 [-2.15, 6.15]
Tosi 2003	0.3	0.9	20	-0.5	0.8	19	50.5%	0.80 [0.27, 1.33]
Total (95% CI)			**52**			**51**	**100.0%**	**0.25 [-1.21, 1.70]**

Heterogeneity: Tau² = 1.02; Chi² = 6.89, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 0.33 (P = 0.74)

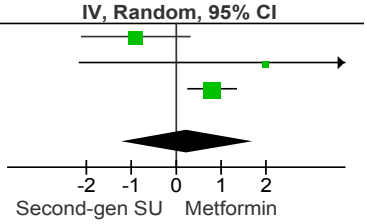


Fig 4c. Forest plot for change in body mass index from baseline

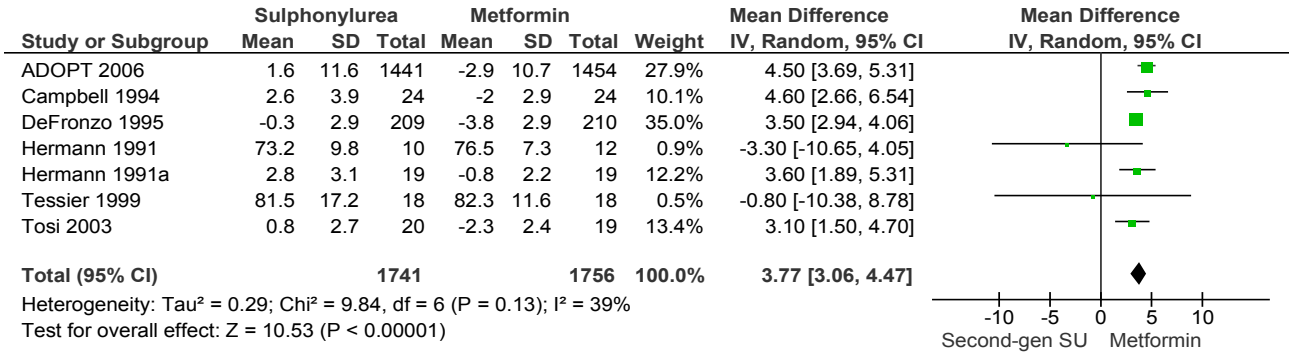


Fig 4d. Forest plot for change in weight from baseline

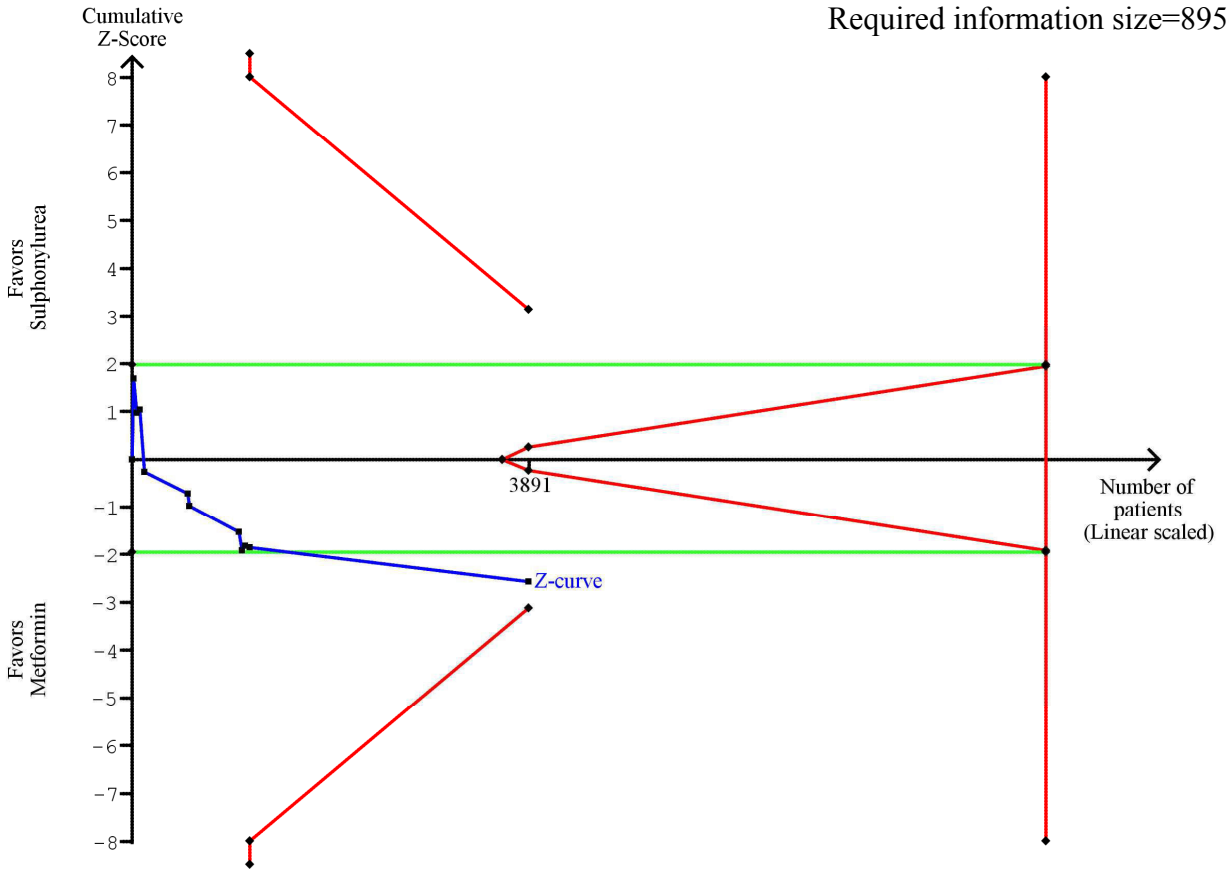


Fig 5a. Trial sequential analysis of the effect of second-generation sulphonylurea versus metformin in type 2 diabetes on fasting blood glucose (mmol/L) with a two-sided α=5% and a power of 80% anticipating a mean difference of 0.43 mmol/L and a diversity (D^2) of 81% as estimated in a random effects model. The solid blue cumulative Z curve indicate the cumulated Z score from the inverse variance model Z statistic, whenever a new trial is added. The solid blue cumulative Z curve does not cross the red trial sequential alpha spending monitoring boundaries. Horizontal green lines illustrate traditional level of statistical significance (P=0.05)

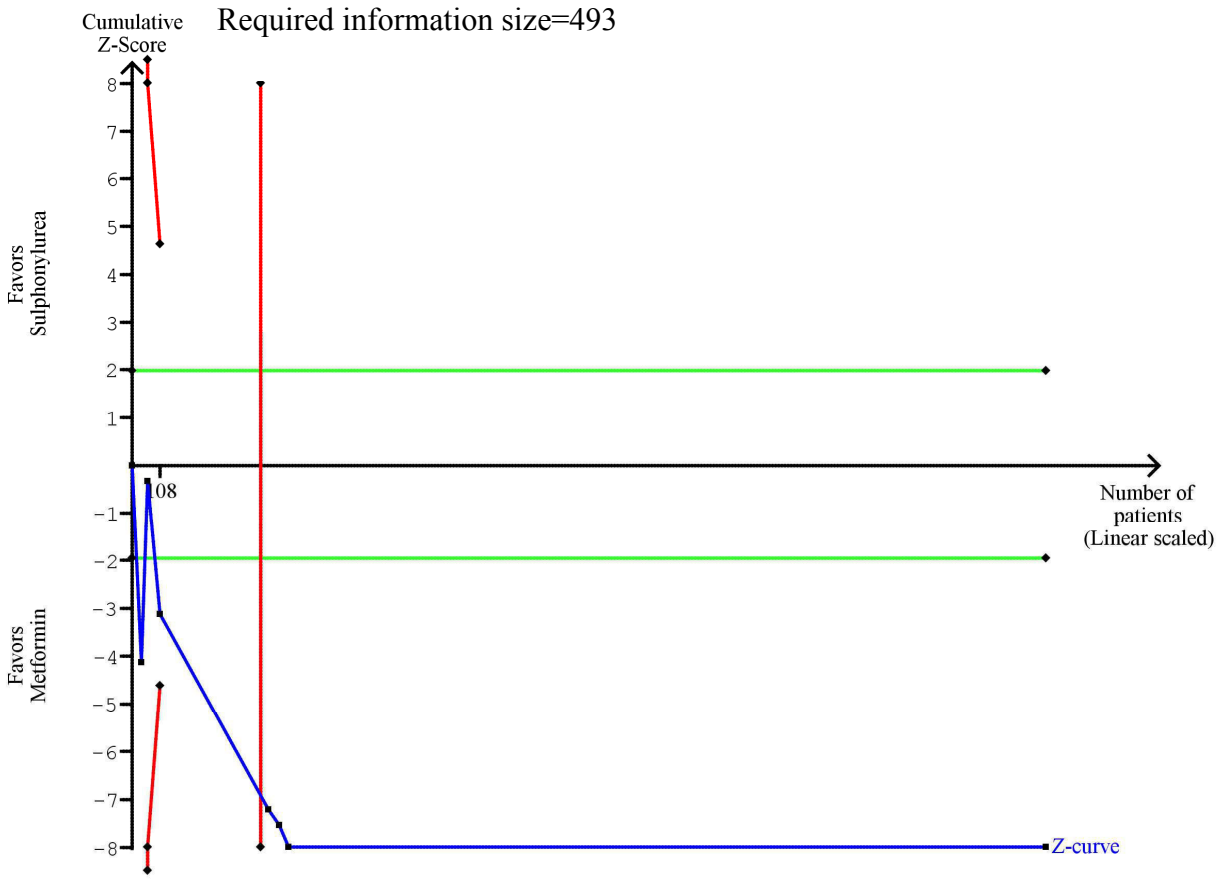


Fig 5b. Trial sequential analysis of the effect of second-generation sulphonylurea versus metformin in type 2 diabetes on weight (kg) with a two-sided α=5% and a power of 80% anticipating a mean difference of 3.77 kg and a diversity (D^2) of 65% as estimated in a random effects model. The solid blue cumulative Z curve indicate the cumulated Z score from the inverse variance model Z statistic, whenever a new trial is added. The solid blue cumulative Z curve crosses the red trial sequential alpha spending monitoring boundaries. Horizontal green lines illustrate traditional level of statistical significance (P=0.05)

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Appendix 1. Search strategies

The Cochrane Library
#1 MeSH descriptor Diabetes mellitus, type 2 explode all trees
#2 MeSH descriptor Insulin resistance explode all trees
#3 ((impaired in All Text and glucose in All Text and toleranc* in All Text) or (glucose in All Text and intoleranc* in All Text) or (insulin* in All Text and resistanc* in All Text))
#4 (obes* in All Text near/6 diabet* in All Text)
#5 (MODY in All Text or NIDDM in All Text or TDM2 in All Text)
#6 ((non in All Text and insulin* in All Text and depend* in All Text) or (noninsulin* in All Text and depend* in All Text) or (non in All Text and insulindepend* in All Text) or noninsulindepend* in All Text)
#7 (typ* in All Text and (2 in All Text near/6 diabet* in All Text))
#8 (typ* in All Text and (II in All Text near/6 diabet* in All Text))
#9 (non in All Text and (keto* in All Text near/6 diabet* in All Text))
#10 (nonketo* in All Text near/6 diabet* in All Text)
#11 (adult* in All Text near/6 diabet* in All Text)
#12 (matur* in All Text near/6 diabet* in All Text)
#13 (late in All Text near/6 diabet* in All Text)
#14 (slow in All Text near/6 diabet* in All Text)
#15 (stabl* in All Text near/6 diabet* in All Text)
#16 (insulin* in All Text and (defic* in All Text near/6 diabet* in All Text))
#17 (plurimetabolic in All Text and syndrom* in All Text)
#18 (pluri in All Text and metabolic in All Text and syndrom* in All Text)
#19 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#20 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#21 (#19 or #20)
#22 MeSH descriptor Diabetes insipidus explode all trees
#23 (diabet* in All Text and insipidus in All Text)
#24 (#22 or #23)
#25 (#21 and not #24)
#26 MeSH descriptor Sulfonylurea compounds explode all trees
#27 (insulin? in All Text and secretagog* in All Text)
#28 (acetohexamid* in All Text or carbutamid* in All Text or chlorpropamid* in All Text or tolbutamid* in All Text or tolazamid* in All Text)
#29 (glipizid* in All Text or gliclazid* in All Text or glibenclamid* in All Text or glyburid* in All Text or gliquidon* in All Text or glyclopyramid* in All Text)
#30 glimepirid* in All Text
#31 (meglitinid* in All Text or repaglinid* in All Text or nateglinid* in All Text)
#32 (sulfonylurea* in All Text or sulphonylurea* in All Text)
#33 (glibenese* in All Text or minidiab* in All Text or glucotrol* in All Text or daonil* in All Text or euglucon* in All Text or glynase* in All Text)
#34 (#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
#35 (#25 and #34)

MEDLINE
1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/

3. exp Glucose Intolerance/
4. (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).tw,ot.
5. (obes$ adj3 diabet$).tw,ot.
6. (MODY or NIDDM or T2DM).tw,ot.
7. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,ot.
8. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet$).tw,ot.
9. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
10. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).tw,ot.
11. or/1-10
12. exp Diabetes Insipidus/
13. diabet$ insipidus.tw,ot.
14. 12 or 13
15. 11 not 14
16. exp Sulfonylurea Compounds/
17. exp Glyburide/
18. insulin? secretagog$.tw,ot.
19. (acetohexamid$ or Carbutamid$ or Chlorpropamid$ or Tolbutamid$ or Tolazamid$).tw,ot.
20. (Glipizid$ or Gliclazid$ or Glibenclamid$ or glyburid$ or Gliquidon$ or Glyclopyramid$).tw,ot.
21. glimepirid$.tw,ot.
22. (meglitinid$ or repaglinid$ or nateglinid$).tw,ot.
23. (sulfonylurea$ or sulphonylurea$).tw,ot.
24. (glibenese$ or minidiab$ or Glucotrol$ or daonil$ or euglucon$ or Glynase$).tw,ot.
25. or/16-24
26. 15 and 25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomi?ed.ab.
30. placebo.ab.
31. clinical trials as topic.sh.
32. randomly.ab.
33. trial.ti.
34. or/27-33
35. Meta-analysis.pt.
36. exp Technology Assessment, Biomedical/
37. exp Meta-analysis/
38. exp Meta-analysis as topic/
39. hta.tw,ot.
40. (health technology adj6 assessment$).tw,ot.
41. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
42. ((review$ 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.
43. or/35-42
44. (comment or editorial or historical-article).pt.
45. 43 not 44
46. 34 or 45

47. 26 and 46
48. (animals not (animals and humans)).sh.
49. 47 not 48

EMBASE
1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. (MODY or NIDDM or T2D or T2DM).tw,ot.
4. ((typ? 2 or typ? II or typ?II or typ?2) adj3 diabet*).tw,ot.
5. (obes* adj3 diabet*).tw,ot.
6. (non insulin* depend* or non insulin?depend* or noninsulin* depend* or noninsulin?depend*).tw,ot.
7. ((keto?resist* or non?keto*) adj3 diabet*).tw,ot.
8. ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw,ot.
9. (insulin* defic* adj3 relativ*).tw,ot.
10. insulin* resistanc*.tw,ot.
11. or/1-10
12. exp Diabetes Insipidus/
13. diabet* insipidus.tw,ot.
14. 12 or 13
15. 11 not 14
16. exp sulfonylurea derivative/
17. insulin? secretagog*.tw,ot.
18. exp acetohexamide/
19. exp carbutamide/
20. exp chlorpropamide/
21. exp tolbutamide/
22. exp tolazamide/
23. (acetohexamid* or carbutamid* or chlorpropamid* or tolbutamid* or tolazamid*).tw,ot.
24. exp glipizide plus metformin/ or exp glipizide/ or exp glibenclamide/
25. exp gliclazide/
26. exp gliquidone/
27. (glipizid* or gliclazid* or glibenclamid* or glyburid* or gliquidon* or glyclopyramid*).tw,ot.
28. exp glimepiride/
29. glimepirid*.tw,ot.
30. exp meglitinide/
31. exp repaglinide/
32. exp nateglinide/
33. (meglitinid* or repaglinid* or nateglinid*).tw,ot.
34. (sulfonylurea* or sulphonylurea*).tw,ot.
35. (glibenese* or minidiab* or glucotrol* or daonil* or euglucon* or glynase*).tw,ot.
36. or/16-35
37. 15 and 36
38. exp Randomized Controlled Trial/
39. exp Controlled Clinical Trial/
40. exp Clinical Trial/
41. exp Comparative Study/
42. exp Drug comparison/

43. exp Randomization/
44. exp Crossover procedure/
45. exp Double blind procedure/
46. exp Single blind procedure/
47. exp Placebo/
48. exp Prospective Study/
49. ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
50. (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
51. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
52. (cross over or crossover).ab,ti.
53. or/38-52
54. exp meta analysis/
55. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
56. ((review$ 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$)).ab,ti,ot.
57. exp Literature/
58. exp Biomedical Technology Assessment/
59. hta.tw,ot.
60. (health technology adj6 assessment$).tw,ot.
61. or/54-60
62. 53 or 61
63. 37 and 62
64. (comment or editorial or historical-article).pt.
65. 63 not 64

LILACS
(sulfonylurea OR sulphonylurea) [Words] and diabetes [Words] and not insipidus [Words]

Science Citation Index Expanded
1 TS=((impaired glucose toleranc*) or (glucose intoleranc*) or (insulin* resistanc*))
2 TS=(obes* SAME diabet*)
3 TS=(mody OR NIDDM OR TDM2)
4 TS=((non insulin* depend*) or (noninsulin* depend*) or (non insulindepend*)
or (noninsulindepend*))
5 TS=(typ* AND (2 SAME diabet*))
6 TS=(typ* AND (II SAME diabet*))
7 TS=(non AND (keto* SAME diabet*))
8 TS=(nonketo* SAME diabet*)
9 TS=(adult* SAME diabet*)
10 TS=(matur* SAME diabet*)
11 TS=(late SAME diabet*)
12 TS=(slow SAME diabet*)
13 TS=(stabl* SAME diabet*)
14 TS=(insulin and (defic* SAME diabet*))
15 TS=(plurimetabolic syndrom*)
16 TS=(pluri metabolic syndrom*)

17 #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
18 TS=(diabet* insipidus)
19 #17 NOT #18
20 TS=(insulin* secretagog*)
21 TS=(acetohexamid* or carbutamid* or chlorpropamid* or tolbutamid* or tolazamid*)
22 TS=(glipizid* or gliclazid* or glibenclamid* or glyburid* or gliquidon* or glyclopyramid*)
23 TS=(glimepirid*)
24 TS=(sulfonylurea* or sulphonylurea*)
25 TS=(glibenese* or minidiab* or glucotrol* or daonil* or euglucon* or glynase*)
26 #25 OR #24 OR #23 OR #22 OR #21 OR #20
27 #26 AND #19
28 TS=(((random* OR controlled OR clinical) AND trial*) OR placebo* OR meta-analysis)
29 #28 AND #27

CINHAL (Ovid SP)
S1 (MM "Diabetes Mellitus, Non-Insulin-Dependent")
S2 (MM "Insulin Resistance")
S3 (MM "Glucose Intolerance")
S4 (impaired glucos* toleranc* or glucos* intoleranc* or insulin resistan*) or TI (impaired glucos* toleranc* or glucos* intoleranc* or insulin resistan*)
S5 TX obes* N3 diabet* or TI obes* N3 diabet*
S6 TX (MODY or NIDDM or T2DM) or TI (MODY or NIDDM or T2DM)
S7 TX (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*) or TI (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*)
S8 TX ((typ? 2 or typ? II or typ?2 or typ?II) AND diabet*) or TI ((typ? 2 or typ? II or typ?2 or typ?II) AND diabet*)
S9 TX ((keto?resist* or non?keto*) AND diabet*) and TI ((keto?resist* or non?keto*) AND diabet*)
S10 TX ((late or adult* or matur* or slow or stabl*) AND onset AND diabet*) or TI ((late or adult* or matur* or slow or stabl*) AND onset AND diabet*)
S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S12 (MM "Diabetes Insipidus")
S13 TX diabet* insipidus or TI diabet* insipidus
S14 S12 or S13
S15 S11 NOT S14
S16 (MM "Sulfonylurea Compounds")
S17 (MM "Glyburide")
S18 TX insulin* secretagog* or TI insulin* secretagog*
S19 TX (acetohexamid* or Carbutamid* or Chlorpropamid* or Tolbutamid* or Tolazamid*) or TI (acetohexamid* or Carbutamid* or Chlorpropamid* or Tolbutamid* or Tolazamid*)
S20 TX (Glipizid* or Gliclazid* or Glibenclamid* or glyburid* or Gliquidon* or Glyclopyramid*) and TI (Glipizid* or Gliclazid* or Glibenclamid* or glyburid* or Gliquidon* or Glyclopyramid*)
S21 TX glimepirid* or TI glimepirid*
S22 TX (meglitinid* or repaglinid* or nateglinid*) or TI (meglitinid* or repaglinid* or nateglinid*)

S23 TX (sulfonylurea* or sulphonylurea*) or TI (sulfonylurea* or sulphonylurea*)
S24 TX (glibenese* or minidiab* or Glucotrol* or daonil* or euglucon* or glynase*) or TI (glibenese* or minidiab* or Glucotrol* or daonil* or euglucon* or glynase*)
S25 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
S26 S15 and S25
S27 TX (random* OR blind* OR placebo* OR group*) or TI (random* OR blind* OR placebo* OR group*)
S28 S26 and S27

Webappendix 2. Description of bias assessment

Risk of bias components based on the Cochrane risk of bias tool classification

Sequence generation

- Low risk of bias, if the allocation sequence is generated by a computer or random number table or similar
- Uncertain risk of bias, if the trial is described as randomised, but the method used for the allocation sequence generation was not described
- High risk of bias, if a system involving dates, names, or admittance numbers is used for the allocation of patients (quasi-randomised). Such studies were excluded.

Allocation concealment

- Low risk of bias, if the allocation of patients involves a central independent unit, on-site locked computer, or consecutively numbered sealed envelopes
- Uncertain risk of bias, if the trial is described as randomised, but the method used to conceal the allocation is not described
- High risk of bias, if the allocation sequence is known to the investigators who assigned participants or if the study is quasi-randomised. Such studies were excluded.

Blinding

- Low risk of bias, if the method of blinding is described
- Uncertain risk of bias, if the method of blinding is not described
- High risk of bias, if the participants or investigators are not blinded

Incomplete data outcomes

- Low risk of bias, if it is clearly described if there are any post-randomisation drop-outs or withdrawals and the reason for these drop-outs are described
- Uncertain risk of bias, if it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear
- High risk of bias, if the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis is performed, potentially inappropriate application of simple imputation, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size

Selective outcome reporting

- Low risk of bias, if all the pre-defined (primary and secondary) outcomes are mentioned in the trial's protocol or in a design article have been reported in the pre-specified way
- Uncertain risk of bias, if there is insufficient information to assess whether the risk of selective outcome reporting is present
- High risk of bias, if not all the pre-specified outcomes are reported or if the primary outcomes are changed or if some of the important outcomes are incompletely reported

Other Bias

Academic bias

- Low risk of bias, if the author of the trial has not conducted previous trials addressing the same interventions
- Uncertain risk of bias, if it is not clear if the author has conducted previous trials addressing the same interventions
- High risk of bias, if the author of the trial has conducted previous trials addressing the same interventions

Sponsor bias

- Low risk of bias, if the trial is unfunded or is not funded by an instrument or equipment or drug manufacturer
- Uncertain risk of bias, if the source of funding is not clear
- High risk of bias, if the trial is funded by an instrument or equipment or drug manufacturer

Webappendix 3. Excluded studies

Study	Reason for exclusion
Abbatecola et al 2006[1]	Not comparing intervention of interest*
Adetuyibi et al 1977[2]	Duration of intervention less than 24 weeks
Adlung et al 1974[3]	Not a randomised clinical trial
Ahuja et al 1973[4]	Not a randomised clinical trial
Akanuma et al 1988[5]	Not comparing interventions of interest
Almer 1984[6]	Not a randomised clinical trial
Alvarsson et al 2010[7-9]	Not comparing intervention of interest*
Aman et al 1977[10]	Not a randomised clinical trial
Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History (APPROACH) trial 2010[11-13]	Not comparing intervention of interest*
Baba et al 1983[14]	Not comparing intervention of interest
Balabolkin et al 1983[15]	Not a randomised clinical trial
Balabolkin et al 1988[16]	Not a randomised clinical trial
Banerji et al 1995[17]	Not including participants with type 2 diabetes
Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial[18]	Not comparing interventions of interest.
Bellomo et al 2011[19]	Duration of intervention less than 24 weeks
Belovalova et al 1990[20]	Not a randomised clinical trial
Ben et al 1988[21]	Not a randomised clinical trial
Berber et al 1982[22]	Duration of intervention less than 24 weeks
Bernas et al 1992[23]	Not a randomised clinical trial
Berry et al 1981[24]	Not a randomised clinical trial
Birkeland et al 1994[25]	Not comparing intervention of interest*
Birkeland et al 2002[26-28]	Not comparing intervention of interest*
Blumenbach et al 1976[29]	Not a randomised clinical trial
Bruns et al 1990[30]	Duration of intervention less than 24 weeks
Calvagno et al 1983[31]	Not a randomised clinical trial
Cefalu et al 1998[32]	Duration of intervention less than 24 weeks
Ceriello et al 2005[33]	Not a randomised clinical trial
Chan et al 1982[34]	Not comparing intervention of interest
Chandra et al 2008[35]	Not a randomised clinical trial. Authors asked and replied.
Charbonnel et al 2005[36;37]	Not comparing intervention of interest*
Chen et al 1987[38]	Not a randomised clinical trial
Coniff et al 1983[39]	Not comparing intervention of interest*
Cortinovis et al1998[40]	Not a randomised clinical trial
Dalzell et al 1986[41]	Not comparing intervention of interest*
Deng 2003[42]	Not comparing intervention of interest*
Derosa et al 2003[43]	Not comparing intervention of interest*
Derosa et al 2004[44]	Not comparing intervention of interest*
Derosa et al 2010[45]	Not comparing intervention of interest
Diehl et al 1985[46]	Not comparing intervention of interest*
Dills et al 1996[47]	Not comparing intervention of interest

Dowey et al 1979[48]	Not a randomised clinical trial
Drouin et al 2000[49]	Not comparing intervention of interest
Drouin et al 2004[50]	Not comparing intervention of interest
Duprey et al 1971[51]	Not a randomised clinical trial
Ebeling et al 2001[52]	Not comparing intervention of interest*
Engelhardt 1965[53]	Includes also participants with normal glucose tolerance
Esposito et al 2004[54]	Not comparing intervention of interest*
Feinböck et al 2003[55]	Not comparing intervention of interest*
Ferner et al 1991[56]	Not a randomised clinical trial
Fineberg et al 1980[57]	Not comparing intervention of interest*
Foley et al 2009[58;59]	Not comparing intervention of interest*
Forst et al 2003[60]	Not comparing intervention of interest*
Forst et al 2005[61;62]	Not comparing intervention of interest*
Forst et al 2011[63]	Not a randomised clinical trial
Fuchs 1973[64]	Duration of intervention less than 24 weeks in publication. Not comparing intervention of interest*
Garber et al 2002[65;66]	Duration of intervention less than 24 weeks
Garber 2003[67]	Duration of intervention less than 24 weeks
Gargiolo et al 2001[68]	Not a randomised clinical trial
Giles et al 2008[69]	Not comparing intervention of interest
Giles et al 2010[70]	Not comparing intervention of interest
Goldberg et al 1996[71]	Duration of intervention less than 24 weeks
Groop et al 1989[72]	Not comparing intervention of interest
Gudat et al 1998[73]	Not a randomised clinical trial
Gurling 1970[74]	Not a randomised clinical trial
Happ et al 1974[75]	Duration of intervention less than 24 weeks
Hanefeld 2007[76-78]	Not comparing intervention of interest*
Harrower 1985[79]	Not comparing intervention of interest*
Haupt et al 1974[80]	Not a randomised clinical trial
Hoffmann 1990[81;82]	Not comparing intervention of interest*
Hoffmann et al 1994[83]	Not comparing intervention of interest*
Hollander et al 1992[84]	Not comparing intervention of interest*
Hollander et al 2001[85]	Duration of intervention less than 24 weeks
Howes 2000[86]	Not a randomised clinical trial
Hristov et al 2002[87]	Not a randomised clinical trial
Hussain 2007[88]	Not comparing intervention of interest
Inukai et al 2005[89]	Not comparing intervention of interest
Irsigler et al 1979[90]	Duration of intervention less than 24 weeks
Ishizuka et al 1994[91]	Not a randomised clinical trial
Jackson et al 1969[92]	Not a randomised clinical trial
Jain et al 2006[93]	Not comparing intervention of interest*
Jerums et al 1987[94]	Not comparing intervention of interest
Jibran et al 2006[95]	Not comparing intervention of interest*
Johnston et al 1970[96]	Duration of intervention less than 24 weeks
Johnston et al 1997[97]	Not comparing intervention of interest*

Josephkutty et al 1990[98]	Duration of intervention less than 24 weeks
Joshi et al 2002[99]	Duration of intervention less than 24 weeks
Kakhnovskii et al 1993[100]	Not a randomised clinical trial
Kaku et al 2011[101-104]	Not comparing intervention of interest*
Kanda 1998[105]	Not comparing intervention of interest*
Kanoun et al 1996[106]	Not a randomised clinical trial
Kovacevic et al 1997[107]	Not comparing intervention of interest*
Langenfeld et al 2005[108]	Not comparing intervention of interest
Lecomte et al 1977[109]	Duration of intervention less than 24 weeks
Levy et al 1995[110]	Duration of intervention less than 24 weeks
Li et al 2009[111]	Not comparing intervention of interest
Lim et al1970[112]	Duration of intervention less than 24 weeks
Lindbjerg et al 1976[113]	Duration of intervention less than 24 weeks
Liu et al 1985[114]	Duration of intervention less than 24 weeks
Lomuscio et al 1994[115]	Not a randomised clinical trial
Madsbad et al 2001[116]	Not comparing intervention of interest*
Mafauzy 2002[117]	Duration of intervention less than 24 weeks
Marbury et al 1999[118]	Not comparing intervention of interest*
Mazzone et al 2006[119]	Not comparing intervention of interest
Memisogullari et al 2009[120]	Not comparing intervention of interest*
Meneilly 2011[121]	Duration of intervention less than 24 weeks
Mogensen et al 1976[122]	Not comparing intervention of interest
Nakamura et al 2000[123]	Duration of intervention less than 24 weeks
Nakamura et al 2004[124]	Not comparing intervention of interest*
Nakamura et al 2006[125]	Not comparing intervention of interest*
Nathan et al 1988[126]	Not comparing intervention of interest*
Nikkilä et al 1982[127]	Not comparing intervention of interest
Nissen et al 2008[128]	Not comparing intervention of interest
Noury et al 1991[129]	Duration of intervention less than 24 weeks
Omrani et al 2005[130]	Assume not a randomised clinical trial
Osei et al 2003[131]	Not including participants with type 2 diabetes
Papa et al 2006[132]	Duration of intervention less than 24 weeks
Pagano et al 1995[133-135]	Not comparing intervention of interest*
Perez et al 2006[136]	Not comparing intervention of interest
Perriello et al 2007[137;138]	Not comparing intervention of interest*
Quatraro et al 1990[139]	Not comparing intervention of interest
Rao et al 2010[140]	Not comparing intervention of interest
Repaglinide studies[141-143]	Not comparing intervention of interest*
Rosenstock et al 1993[144]	Not comparing intervention of interest
Rosenthal et al 2002[145-147]	Not comparing intervention of interest*
Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial[148]	Not comparing intervention of interest
Rupprecht et al 1993[149]	Not a randomised clinical trial
Saadatnia et al 2009[150]	Not a randomised clinical trial
Salman et al 2001[151]	Not comparing intervention of interest*
Sami et al 1996[152]	Not comparing intervention of interest

Sasahara et al 1999[153]	Not a randomised clinical trial
Schernthaner et al 2004[154]	Not comparing intervention of interest
Seck et al 2010[155]	Not comparing intervention of interest
Segal et al 1997[156]	Not comparing intervention of interest*
Shihara et al 2011[157;158]	Not comparing intervention of interest*
Shinoda et al 2009[159]	We assume not a randomised clinical trial. Attempt made to contact authors.
Speiser et al 1989[160]	Duration of intervention less than 24 weeks
Spengler et al 1992[161-165]	Not comparing intervention of interest*
Sung et al 1999[166]	Not comparing intervention of interest*
Sutton et al 2002[167;168]	Not comparing intervention of interest*
Tan et al 2004[169]	Not comparing intervention of interest*
Tan et al 2004a[170]	Not comparing intervention of interest*
Tan et al 2005[171]	Not comparing intervention of interest*
Tang et al 2004[172]	Not comparing intervention of interest*
Teramoto et al 2007[173]	Not comparing intervention of interest*
The Liraglutide Effect and Action in Diabetes-3 (LEAD-3)[174-179]	Not comparing intervention of interest*
Tolman et al 2009[180]	Not comparing intervention of interest
Tovi et al 1998[181]	Not comparing intervention of interest
Toyota et al 1997[182]	Duration of intervention less than 24 weeks
Tsumara 1995[183]	Not comparing intervention of interest
Umpierrez et al 1997[184]	Not exclusively include patients with type 2 diabetes
University Group Diabetes Program[185-187]	Not comparing intervention of interest*
United Kingdom Diabetes Study 1998[188-192]	Not comparing intervention of interest*
Van de Laar et al 2004[193]	Not comparing intervention of interest*
Vray et al 1995[194]	Duration of intervention less than 24 weeks
Wang et al 1994[195]	Duration of intervention less than 24 weeks
Watanabe et al 2005[196]	Not comparing intervention of interest*
Wolffenbuttel et al 1989[197]	Not comparing intervention of interest*
Wolffenbuttel et al 1999[198]	Not comparing intervention of interest*
Wu et al 2010[199]	Duration of intervention less than 24 weeks
Yamanouchi et al 2005[200]	Not comparing intervention of interest*
Yang et al 2009[201]	Not including participants with type 2 diabetes
Zhang et al 2005[202]	Not comparing intervention of interest*
Zhou 1999[203]	Duration of intervention less than 24 weeks

* Included in the full Cochrane version of the review

Webappendix 4. Macrovascular definitions in trials

Study	Cardiovascular mortality	Cancer	Composite non-fatal macrovascular outcomes	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity
ADOPT 2006[204-210]	All cardiovascular deaths	Serious adverse event malignancies excluding skin cancer	Major adverse cardiovascular events (fatal and non-fatal myocardial infarction, congestive heart failure and stroke)	Non-fatal myocardial infarction	Only total stroke reported. Unknown whether it is fatal or non-fatal	ND
Campbell 1994[211]	ND	ND	ND	ND	ND	ND
Collier 1989[212]	ND	ND	ND	ND	ND	ND
DeFronzo 1995[213]	Death, possible due to myocardial infarction	ND	ND	ND	ND	ND
Hermann 1991[214]	ND	ND	ND	ND	ND	ND
Hermann 1991a[215-218]	One patient had a sudden death	ND	Cardiovascular adverse events	Non-fatal myocardial infarction	ND	ND
Kamel 1997[219]	ND	ND	ND	ND	ND	ND
Lawrence 2004[220]	Death due to myocardial infarction	ND	ND	Non-fatal myocardial infarction	ND	ND
Tessier 1999[221]	ND	ND	ND	ND	ND	ND
Tosi 2003[222]	ND	ND	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"	"No cardiovascular events was recorded during the study"
UKPDS 34[223-225]	ND	ND	ND	WHO clinical	Major stroke-	Major limb complicatio

				criteria with associated ECG/enzyme changes or new pathological Q wave (ICD 9 Code 410)	stroke with symptoms that persisted for more than one month (ICD 430 to 434.9 and 436)	ns- requiring amputation of digit or limb for any reason (ICD codes 5.845 to 5.848)

Webappendix 5. Hypoglycaemia and adverse events definitions in trials

Study	Mild hypoglycaemia	Severe hypoglycaemia	Adverse events	Serious adverse events	Drop-outs due to adverse events
ADOPT 2006[204-210]	Hypoglycaemia requiring minor intervention	Hypoglycaemia requiring medical intervention	Adverse events	Event that was fatal, life-threatening, or disabling, resulted in hospitalisation or prolonged hospital stay, was associated with congenital abnormality, cancer, or a drug overdose (intentional or accidental), or was suggested by the investigator as serious or suggested any substantial hazard, contraindication, side effect, or precaution	Drop-outs due to adverse events
Campbell 1994[211]	ND	ND	ND	ND	ND
Collier 1989[212]	Mild hypoglycaemic episodes	ND	ND	ND	ND
DeFronzo 2005[213]	ND	ND	ND	ND	Withdrawal due to adverse effects
Hermann 1991[214]	ND	ND	ND	Serious adverse events	ND
Hermann 1991a[215-218]	Hypoglycaemia, including tremor. No one had severe hypoglycaemia	Serious, long-lasting hypoglycaemia	Adverse events	ND	Withdrawn due to adverse events
Kamel 1997[219]	ND	ND	ND	ND	ND

Lawrence 2004[220]	ND	ND	ND	ND	ND
Tessier 1999[221]	ND	ND	ND	ND	ND
Tosi 2003[222]	Mild symptoms, suggestive of hypoglycaemia	Severe episodes of hypoglycaemia	Adverse events	Serious adverse events	Drop-outs due to adverse events
UKPDS 34[223-225]	Hypoglycaemic episodes were defined as minor if the patient was able to treat the symptoms unaided. Data in meta-analysis after one year of follow-up	Major if third-party help or medical intervention was necessary. Data in meta-analysis after one year of follow-up	ND	ND	ND

ADOPT= A Diabetes Outcome Progression Trial; NR= not reported; UKPDS= United Kingdom Prospective Diabetes Study

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RESEARCH

Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

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Abstract

Objectives To compare the benefits and harms of metformin and insulin versus insulin alone as reported in randomised clinical trials of patients with type 2 diabetes.

Design Systematic review of randomised clinical trials with meta-analyses and trial sequential analyses.

Data sources The Cochrane Library, Medline, Embase, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature, and Cumulative Index to Nursing and Allied Health Literature until March 2011. We also searched abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes Congresses, contacted relevant trial authors and pharmaceutical companies, hand searched reference lists of included trials, and searched the US Food and Drug Administration website.

Review methods Two authors independently screened titles and abstracts for randomised clinical trials comparing metformin and insulin versus insulin alone (with or without placebo) in patients with type 2 diabetes, older than 18 years, and with an intervention period of at least 12 weeks. We included trials irrespective of language, publication status, predefined outcomes, antidiabetic interventions used before randomisation, and reported outcomes.

Results We included 26 randomised trials with 2286 participants, of which 23 trials with 2117 participants could provide data. All trials had high risk of bias. Data were sparse for outcomes relevant to patients. Metformin and insulin versus insulin alone did not significantly affect all cause mortality (relative risk 1.30, 95% confidence interval 0.57 to 2.99) or cardiovascular mortality (1.70, 0.35 to 8.30). Trial sequential analyses showed that more trials were needed before reliable conclusions could be drawn regarding these outcomes. In a fixed effect model, but not in a random effects model, severe hypoglycaemia was significantly more frequent with metformin and insulin than with insulin alone (2.83, 1.17 to 6.86). In a random effects model, metformin and insulin resulted in reduced HbA_{1c}, weight gain, and insulin dose, compared with insulin alone; trial sequential analyses showed sufficient evidence for a HbA_{1c} reduction of 0.5%, lower weight gain of 1 kg, and lower insulin dose of 5 U/day.

Conclusions There was no evidence or even a trend towards improved all cause mortality or cardiovascular mortality with metformin and insulin, compared with insulin alone in type 2 diabetes. Data were limited by the severe lack of data reported by trials for patient relevant outcomes and by poor bias control.

Introduction

Metformin is a glucose lowering drug that, among other mechanisms, is supposed to work by enhancing insulin action mainly in the liver.[1] Metformin is often recommended as the first line drug in patients with type 2 diabetes.[2] Because of disease progression, a substantial proportion of these patients eventually end up on insulin, at which point doctors are recommended to continue metformin use.[2] The rationale behind this combination mainly relates to suggested beneficial metabolic effects, such as reduced blood glucose and body weight.[2-4]

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Web appendix: Search strategy and excluded studies

The United Kingdom Prospective Diabetes Study suggested a beneficial effect of metformin monotherapy, compared with conventional (diet) treatment, on cardiovascular disease and mortality after about 10 years in overweight patients with type 2 diabetes.[5] These findings were partly supported by the Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME) trial comparing combined metformin and insulin versus insulin alone.[6] However, other trials have suggested that metformin combined with sulphonylurea (that is, insulin secretagogues) versus sulphonylurea alone could increase mortality.[5 7] Thus, the effect of metformin combined with other glucose lowering drugs such as insulin providing regimens on patient relevant outcomes might differ from its effects during monotherapy.

Whether oral glucose lowering drugs should be continued when initiating insulin remains unclear.[8 9] An insulin sparing effect has been observed when using oral glucose lowering drugs with insulin.[9] However, the progressive nature of type 2 diabetes with its decline in endogenous insulin secretion could result in patients with advanced disease more closely resembling type 1 diabetes, in which adjunct treatment with, for example, metformin, has not proven to improve glycaemic control.[10] Thus, despite international recommendations to use metformin in combination with insulin in patients with type 2 diabetes and therefore the possible widespread use of this treatment regimen worldwide, insufficient and contradictory data exist in the literature to justify this policy.[2]

Previous meta-analyses of glucose lowering drugs have included trials of insulin in combination with various glucose lowering compounds such as metformin, but have not addressed the specific effect of metformin and insulin in this respect.[11-13] In the light of these considerations and the growing number of patients with type 2 diabetes receiving insulin worldwide, we compared the benefits and harms of metformin and insulin versus insulin alone in randomised clinical trials.

Methods

The present review followed the Cochrane Collaboration's recommendations for preparation of systematic reviews of interventions[14] and was based on a previously published protocol.[15]

Search strategy

We searched the Cochrane Library, Medline, Embase, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature, and Cumulative Index to Nursing and Allied Health Literature until March 2011 (web appendix). We also searched abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes Congresses. We contacted relevant pharmaceutical companies, and searched the US Food and Drug Administration website for unpublished randomised trials relevant to the review. We also scanned reference lists of included trials and systematic reviews, meta-analyses, and health technology assessment reports. We contacted experts to request for information on additional trials.

Study selection

Two authors (BH and LLC or TA) independently screened titles and abstracts according to the inclusion criteria. Randomised clinical trials were included if they compared metformin and insulin versus insulin alone (with or without placebo) in patients with type 2 diabetes older than 18 years, and had an intervention period of at least 12 weeks. We included trials irrespective of language, publication status, predefined outcomes, antidiabetic interventions used before randomisation, and reported outcomes. We excluded intervention groups including concomitant use of glucose lowering drugs other than metformin or insulin.

Data extraction and risk of bias assessment

Two authors (BH and LLC or TA) independently extracted data from the included trials using standard forms, and assessed the risk of bias according to the Cochrane Collaboration.[14] They assessed the following risk of bias domains: generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.[15] Each item was classified as low, unclear, or high risk of bias.[15] The involvement of a third author (JW or CG) resolved any discrepancies. Data extraction and assessment for all relevant non-English articles were obtained through translated texts.

The primary outcomes in this review were all cause mortality and cardiovascular mortality.[15] The secondary outcomes were macrovascular and microvascular diseases assessed as composite outcomes and in separate (non-fatal myocardial infarction, non-fatal stroke, abdominal aorta aneurism, amputation of lower extremity, cardial or peripheral revascularisation, manifestation and progression of nephropathy, end stage renal disease, manifestation and progression of retinopathy, or retinal photocoagulation) adverse events, cancer, quality of life, costs of intervention, insulin dose, glycaemic control, weight, and blood pressure.[15]

Statistical analysis

We did statistical analysis using Review Manager[16] according to our protocol.[15] The medians reported in the included trials were assumed to be close to the arithmetic mean. If not reported, the standard deviation of the changes from baseline to the end of follow-up was calculated with a correlation coefficient from the largest and longest trial with all available data for each continuous variable in each intervention group.[14 17 18] Reported standard errors and confidence intervals were converted to standard deviations.

We used both a random effects model and a fixed effect model.[19 20] In case of discrepancy between the two models, we reported both results. We examined heterogeneity with the I^2 statistic ($I^2 \geq 50\%$ indicated substantial heterogeneity).[14] To clarify the influence of missing data, we conducted scenario analyses for the "worst best" case and "best worst" case for the primary outcomes.

We did subgroup analyses for primary and secondary outcomes if significant effect estimates were present using a test of interaction. These analyses were done according to risk of bias (low *v* high risk), study design (blinding *v* no blinding of participants and investigators), previous insulin treatment (insulin naive *v* previous insulin treatment), insulin regimen (fixed *v* variable regimens in intervention groups), body mass index at baseline (<30 *v* ≥30), duration of interventions (<two years *v* ≥two years), metformin use at trial entry (allowed *v* not allowed), and publication status (published *v* unpublished trials).

Trial sequential analysis

Trial sequential analysis of a meta-analysis is conceptually similar to interim analyses in a single trial, which use monitoring boundaries to decide whether the trial has obtained a sufficiently low P value to show a reliable effect.[21-25] Cumulative

meta-analyses of trials are at risk of producing random errors because of sparse data and repetitive testing on accumulating data.[23-27] Trial sequential analysis depends on the quantification of the required information size.[25]

The trial sequential analysis was done to maintain an overall 5% risk of a type I error and 20% of the type II error. On the basis of criteria decided a priori, we calculated the required information size (adjusted for diversity) to detect or reject an intervention effect of a 10% relative risk reduction, considered as a clinically relevant effect corresponding to a numbers needed to treat of about 200.[21-25 28] However, if the required information size was very large, we also performed post hoc trial sequential analysis, with a 30% relative risk reduction. For the continuous outcomes of glycated haemoglobin (HbA_{1c}), weight gain, and insulin dose, we estimated the required information sizes to detect or reject a reduction of 0.5%, 1 kg, and 5 U/day, respectively. We used software Trial Sequential Analysis, version 0.8.[27]

Differences between planned protocol and review

The subgroup analysis conducted on the secondary outcomes showing significance was not defined in our protocol.[15] The subgroup analyses for insulin regimen (fixed *v* variable) as well as metformin use at trial entry (allowed *v* not allowed) were not described in our protocol.[15] We did not do subgroup analyses for mean age younger than 65 years compared with 65 years or older and for insulin type prescribed. We extracted data but did not report data for cancer, fasting blood glucose, and blood pressure. When the estimated required information size (to show or refute a 10% relative risk reduction) was very large, we did a trial sequential analysis for a 30% relative risk reduction. The estimated required information sizes based on small anticipated reductions in the surrogate outcomes of HbA_{1c}, weight gain, and insulin dose of 0.5%, 1 kg, and 5 U/day, respectively, were chosen post hoc to substantially challenge the effect on these outcomes, in view of sparse data and repetitive testing.

Results

Results of the search and trial, participant, and intervention characteristics

We identified 7993 references through electronic and hand searches (fig 1⇓). After excluding the duplicate reports, we screened 5613 references. Most references did not identify relevant trial reports. Thirty publications describing 26 randomised clinical trials met our inclusion criteria, randomly assigning 2286 patients to metformin and insulin versus to insulin alone. Three trials could not provide data for the meta-analysis because they only described the total number of patients who underwent randomisation.[29 30] Accordingly, 23 trials (2117 participants) provided data for our analyses. Schnack and colleagues did not report the total number of randomised patients, but only the number with available data at the time of publication of the abstract.[31]

Twenty five trials were published in English and one in Russian. One trial was only published as abstracts,[29 32 33] one in a single abstract,[31] and one in a letter.[34] All trial authors were contacted, but only a few provided additional data. We included two crossover trials, and the authors were unable to provide data before the crossover.[30 35] Tables 1 and 2⇓ ⇓ show baseline characteristics of the included trials.

Twelve trials included insulin naive participants (table 3⇓).[3 4 29 31 36-42 43] Fifteen trials allowed metformin at trial entry either as monotherapy or in combination with other antidiabetic drugs (table 3).[4 6 29 30 35-45 46] We were unable to retrieve information about the duration of metformin intervention before randomisation. The total daily dose of metformin in the intervention groups varied between 1000 mg and 2550 mg. Insulin regimens differed between the trials, and also varied between the intervention groups within some trials (table 3).[3 18 36 39 40 42 43 45-47] Three trials prescribed a fixed and identical insulin regimen in both intervention groups.[48-50]

Altuntas and colleagues reported three intervention groups: insulin lispro and metformin, insulin lispro and neutral protamine Hagedorn insulin, and human regular insulin and neutral protamine Hagedorn insulin.[43] In our analysis, we merged the data from the two insulin only groups into one dataset.[43] The South Danish Diabetes Study reported two different kinds of insulin treatments (neutral protamine Hagedorn insulin and insulin aspart) in combination with different oral antidiabetic drugs. For this study,[44] we reported the two types of insulin preparations in combination with metformin or placebo separately: neutral protamine Hagedorn insulin in combination with metformin or placebo (SDDSa), and insulin aspart in combination with metformin or placebo (SDDSb).

Bias risk assessment

Five trials had low risk of bias regarding both sequence generation and allocation concealment (table 4⇓).[6 38 39 44 47] Healthcare providers and participants were blinded in 10 trials,[4 6 30 34 35 44 48-50] and not blinded in 16.[3 18 29 31 36-42 43-47 51] Only two trials[6 44] described adequate sequence generation, allocation concealment, and blinding of participants and investigators, which our protocol had prespecified as trials with lower risk of bias.[15] The trials did not report the funding source, or report funding from the pharmaceutical industry. Based on all the domains assessed, none of the included trials had a low risk of bias.

All cause mortality

Sixteen trials with 1627 participants reported all cause mortality, of which five reported 21 deaths (fig 2⇓). Metformin and insulin versus insulin alone did not significantly affect all cause mortality (relative risk 1.30, 95% confidence interval 0.57 to 2.99; heterogeneity I^2=0%, P=0.77). Trial sequential analysis indicated that only 2.93% of the required information size was accrued to detect or reject a 30% reduction in relative risk.

The "best worst" case scenario for all cause mortality showed a significant difference in favour of metformin combined with insulin (relative risk 0.35, 95% confidence interval 0.13 to 0.95, P=0.04). However, the "worst best" case scenario showed a significant effect favouring insulin alone (4.27, 1.74 to 10.45, P=0.001). Test of interaction for subgroup differences did not show any significance regarding bias (P=0.90), blinding of investigators and participants (P=0.90), duration of interventions (P=0.90), body mass index (P=0.83), previous insulin treatment (P=0.89), or metformin use allowed at trial entry (P=0.56).

Subgroup analysis according to insulin regimen used was not possible because the three trials with fixed insulin regimens in intervention groups reported no fatal events.[48-50] We also could not analyse publication status because all the included trials were published. A separate analysis of the trials using placebo control groups (the HOME trial[6] and South Danish Diabetes Study[44]) did not show any significant effect of metformin and insulin (relative risk 1.27, 95% confidence interval 0.50 to 3.22).

Cardiovascular mortality

Fifteen trials with 1498 participants reported on cardiovascular mortality, of which three trials reported six deaths (fig 2). The effect of metformin and insulin versus insulin alone was non-significant (relative risk 1.70, 95% confidence interval 0.35 to 8.30; heterogeneity I^2=0%, P=0.52). Trial sequential analysis indicated that only 0.65% of the required information size was accrued to detect or reject a 30% reduction in relative risk.

The "best worst" case scenario showed significant benefit for metformin and insulin compared with insulin alone (relative risk 0.25, 95% confidence interval 0.09 to 0.73, P=0.01). The "worst best" case scenario showed significant harm for metformin and insulin (7.45, 3.08 to 18.03, P<0.001). Test of interaction for subgroup differences did not show any significance regarding bias (P=0.48), blinding of investigators and participants (P=0.50), duration of intervention (P=0.50), body mass index (P=0.25), previous insulin treatment (P=0.99), or metformin use allowed at trial entry (P=0.51). The HOME trial was the only placebo controlled trial to report any deaths due to cardiovascular disease.[6] We could not analyse the insulin regimen used because the three trials with fixed insulin regimens reported no fatal events.[48-50] We also could not analyse publication status because all the included trials were published.

Macrovascular and microvascular complications

The reporting of macrovascular and microvascular complications was infrequent, and all the outcomes assessed showed non-significant effect estimates (data not shown). We also observed a non-significant effect for the composite macrovascular outcome (relative risk 0.98, 0.79 to 1.22; heterogeneity I^2=0, P=0.44; three trials). Only one trial reported data for the composite microvascular outcome, and showed no significant effect of metformin and insulin versus insulin alone.[6]

Hypoglycaemia

Most trials reported hypoglycaemia data in a format that could not be included in a meta-analysis.[3 6 29 36 38 40 43 47 48] Eleven trials with 1303 participants reported severe hypoglycaemia (fig 3⇓). Only three trials reported severe hypoglycaemia in 24 patients (metformin and insulin, 18; placebo and insulin, six). The remaining eight trials reported no serious hypoglycaemic events. Although the random effects model did not show a significant effect (relative risk 2.43, 95% confidence interval 0.54 to 10.85), the fixed effects model did (2.83, 1.17 to 6.86; heterogeneity I^2=43%, P=0.17), suggesting that metformin and insulin was associated with an increased number of patients with severe hypoglycaemia. Separate analysis of the two trials providing data for severe hypoglycaemia using placebo did not show a significant effect in the random effects model (3.59, 0.75 to 17.33), but showed significance in favour of insulin alone in the fixed effects model (3.56, 1.34 to 9.48, P=0.01).

As the largest and longest trial, the HOME trial did not report the number of participants with serious hypoglycaemia at the end of the intervention period. However, after 4.3 years of treatment, researchers saw no significant difference in severe hypoglycaemia between intervention groups (0.3 severe hypoglycaemic events per person per year, for each group).[6]

We extracted data for mild hypoglycaemia from six trials (869 participants; fig 3), which showed no significant effect of metformin and insulin versus insulin alone (relative risk 1.01, 95% confidence interval 0.85 to 1.20; heterogeneity I^2=27%, P=0.23). Meta-analysis of the trials applying placebo did not substantially change this estimate (0.97, 0.83 to 1.14).

Adverse events

Only six trials reported adverse events, and showed no significant difference between intervention groups (relative risk 1.28, 95% confidence interval 0.69 to 2.37; heterogeneity I^2=75%, P=0.003). Hermann and colleagues conducted the only placebo controlled trial reporting adverse events, and did not find any significant difference in effect between the interventions.[50] The effect of dropouts owing to adverse events was close to significance in the random effects model when comparing metformin and insulin versus insulin alone (1.53, 0.99 to 2.36, P=0.05); this effect and was significant in the fixed effect model (1.69, 1.13 to 2.52, P=0.01; heterogeneity I^2=1%, P=0.43). Meta-analysis of the trials using placebo did not substantially change the estimate (1.41, 0.72 to 2.76).

Six trials reported four serious adverse events. The definition of serious adverse events varied among trials. The effect estimate was non-significant (relative risk 1.92, 0.33 to 11.35; heterogeneity I^2=0%, P=0.43). Hermann and colleagues conducted the only placebo controlled trial reporting any serious adverse events, and did not show any significant difference between the interventions.[50]

Quality of life

Three trials reported quality of life or wellbeing; all found no significant differences regarding these outcomes.[4 40 41] Only Douek and colleagues reported quality of life assessments in a format that was suitable for a meta-analysis.[4]

Insulin dose

Twelve trials reported changes in insulin dose (fig 4⇓). Insulin dose was significantly reduced when metformin was combined with insulin, compared with insulin alone (mean difference −18.65 U/day, 95% confidence interval −22.70 to −14.60, P<0.001; heterogeneity I^2=81%, P<0.001). Trial sequential analysis showed that sufficient evidence was established to show even a small reduction of 5 U/day, with crossing of the trial sequential alpha spending monitoring boundary (fig 5⇓).

Subgroup analysis of the trials according to risk of bias did not show any significant differences in the effect estimate for insulin dose (P=0.19, test of interaction). Separate analysis of trials using placebo according to blinding of participants and investigators suggested a more pronounced reduction of insulin use (mean difference −21.01 U/day, 95% confidence interval −23.88 to −18.15, P<0.001) compared with trials not using placebos (open label design) (−16.78 U/day, −22.07 to −11.49, P<0.001). However, tests of interaction did not show any significant differences between subgroups in relation to the blinding of investigators and participants (P=0.17), previous insulin treatment (P=0.15), insulin regimen (P=0.67), and duration of intervention (P=0.19; although only one trial with a duration of intervention of two years or more was included in the analysis).[6] Trials with participants who had a body mass index of less than 30 at baseline showed a smaller reduction in daily insulin dose (−13.36 U/day, −18.52 to −8.20, P<0.001) than those with participants who had a body mass index of 30 or more (−21.76 U/day, −26.99 to −16.53, P<0.001). Test of interaction showed significance for the subgroup differences according to body mass index (P=0.03), but not significant according to metformin use at trial entry (P=0.88). Subgroup analysis of publication status was not possible.

Glycaemic control

Twenty trials reported changes in HbA_{1c}. The achieved percentage of HbA_{1c} decreased with metformin and insulin compared with insulin alone (mean difference −0.60%, 95% confidence interval −0.89 to −0.31, P<0.001; 20 trials; heterogeneity I^2=82%, P<0.001) (fig 6⇓). Standard deviations of the changes had to be calculated for most trials. Trial sequential analysis showed that sufficient evidence was available to show a reduction of 0.5% in HbA_{1c}, with crossing of the trial sequential monitoring boundary in favour of metformin and insulin (fig 5).

A test of interaction found no significant subgroup difference between the two trials with lower risk of bias and the remaining trials with high risk of bias (P=0.81). Trials designed to blind participants and investigators showed a reduction in HbA_{1c} (mean difference −0.87%, 95% confidence interval −1.30 to −0.44, P<0.001) greater than that observed in trials without blinding (−0.30%, −0.62 to 0.01; P=0.06, test of interaction). Tests of interactions did not show significant subgroup differences according to previous insulin treatment (P=0.18), body mass index (P=0.07), and duration of intervention (P=0.72). Trials with variable insulin regimens in the intervention groups showed a smaller reduction in HbA_{1c} (−0.46%, −0.72 to −0.20, P<0.001) than trials with fixed insulin regimens (−1.44%, −1.72 to −1.17, P<0.001; P<0.001, test of interaction). Subgroup analyses of metformin use at trial entry did not show any significant effect (P=0.38, test of interaction). Subgroup analysis of publication status was not possible.

Weight

Both body mass index and weight gain were significantly reduced by metformin and insulin compared with insulin alone (body mass index, mean difference −1.27, 95% confidence interval −2.07 to −0.47, P=0.002, six trials (heterogeneity I^2=86%, P<0.001); weight gain, −1.68 kg, −2.22 to −1.13, P<0.001, 13 trials (I^2=36%, P=0.09)) (fig 7⇓). Trial sequential analysis showed that sufficient evidence was available to show a reduction of 1 kg in weight, with crossing of the trial sequential monitoring boundary for less weight gain with metformin and insulin than insulin alone (fig 5).

Tests of interaction of weight changes did not find any significant subgroup differences according to risk of bias (P=0.33), previous insulin treatment (P=0.27), or blinding of investigators and participants (P=0.45), or insulin regimen (P=0.51). The change in weight for trials using placebo was significant (mean difference −1.97 kg, 95% confidence interval −2.59 to −1.35, P<0.001). Separate analysis of trials with a duration of intervention of two years or longer showed a weight loss (−2.07 kg, −2.22 to −1.13, P<0.001). Tests of interactions for subgroup differences did not show any significance according to trial duration (P=0.33) or body mass index (P=0.62). Trials allowing participants to receive metformin at entry showed a less pronounced weight loss (−1.79 kg, −2.40 to −1.18, P<0.001) than trials not allowing metformin use (−2.93 kg, −4.13 to −1.74, P<0.001; P=0.03, test of interaction). Subgroup analysis of publication status was not possible.

Discussion

We identified 26 randomised clinical trials comparing the effects of metformin and insulin with insulin alone. Of these trials, 23 (n=2117 participants) provided sufficient information to be included in one or more meta-analyses. All trials had a high risk of bias, and only two were considered to have lower risk of bias. This finding could lead to a systematic overestimation of beneficial effects and an underestimation of adverse effects.[52-55] Nevertheless, metformin combined with insulin seem to be associated with a significant reduction in HbA_{1c}, weight gain, and insulin dose, compared with insulin alone. Although the influence of bias cannot be excluded, trial sequential analysis suggested evidence was sufficient for the effect, found in a random effects model, of metformin and insulin versus insulin alone on these surrogate outcomes. However, duration of intervention in the included trials was relatively short, and we were unable to explore whether these metabolic effects disappear, persist, or became more pronounced with time. Meta-analyses of patient relevant outcomes were based on very sparse data and did not show significant results. The accrued cumulated sample sizes of the included trials for the primary outcomes only constituted a very small fraction of the required information size calculated to establish firm evidence for the presence or absence of effect.

The present systematic review contains substantially more data than previous meta-analyses relevant to the topic.[11 12] Although our results seem to support the combination of metformin and insulin compared with insulin alone on HbA_{1c}, weight, and insulin dose, these variables are, at best, unvalidated surrogate indicators of a potentially reduced risk of microvascular and macrovascular complications.[56] Our results regarding patient relevant outcomes should be interpreted with caution. Several of these outcomes were rarely reported or not reported at all. Major drawbacks of the meta-analyses of patient relevant outcomes mirrored the weaknesses of the included trials, and highlighted the substantial lack of evidence on this topic. Most trials had a short duration (<two years) and we cannot exclude a potential legacy effect from the trials allowing metformin at baseline. However, we were unable to show any legacy effect apart from one on weight loss. These factors might have diluted a potential effect of metformin and insulin in two trials in the meta-analysis with a longer duration.

After combining all the evidence available from randomised clinical trials, we were unable to find any evidence or even a trend towards improved all cause mortality or cardiovascular mortality with metformin and insulin, compared with insulin alone. Point estimates of the risk ratios for all cause or cardiovascular mortality were greater than one (that is, favouring insulin alone); these risk ratios or the upper limits of their 95% confidence intervals spanned far beyond current safety limits such as 1.3 or 1.8, as used for evaluating drug safety by the US Food and Drug Administration.[57] This lack of evidence means that possible harm cannot be excluded according to current criteria. However, several factors limited the confidence in the effect estimates and confidence intervals in our meta-analyses, owing to insufficient information and consequent high risk of random errors.

The risk of having one or more severe hypoglycaemic events was significantly increased with metformin and insulin when applying the fixed effect model. The combination of metformin and insulin seemed to decrease HbA_{1c}, which might have explained the observed tendency of an increased risk of severe hypoglycaemia.[58 59] Furthermore, the largest and longest of the included trials, the HOME trial, did not find any difference in the number of severe hypoglycaemic events per person per year, implying that the observed potential harm might not be present during a longer intervention period.[6] We did not adjust the number of patients who had severe hypoglycaemia with the achieved HbA_{1c} in trials. Since both the achieved glycaemic level and the number of hypoglycaemic events are results of the interventions, it is not possible in real life to have only one outcome without the other. Thus, any conclusions from

statistically adjusting the risk of hypoglycaemia for results of achieved glycaemic control cannot be translated into clinical practice. Therefore, a possible signal of harm, when combining metformin and insulin could not be excluded from our meta-analysis, and should be investigated in future trials.

The risks of other severe and non-severe adverse events were not significant between the two interventions. However, the number of dropouts from adverse events was significantly higher for metformin and insulin than for insulin alone in the fixed effect model. When initiating metformin treatment, participants often have gastrointestinal disturbances.[1] The observed differences of the dropouts due to adverse events might have represented the initial adverse effects experienced when initiating metformin treatment, due to the short duration of the included trials. Therefore, the observed difference might have disappeared after the titration period of metformin, although no data were available to investigate this.

Strengths and limitations

Our systematic review has several strengths. We based it on a published protocol with rigid inclusion criteria for randomised clinical trials.[15] 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 to clarify methodological details and patient relevant outcomes, but only a few authors responded. We tried to evaluate the strength of the available evidence with comprehensive analyses of the risk of bias using subgroup analyses with test for subgroup differences and trial sequential analysis on all our primary and statistically significant secondary outcomes.[21-24] We evaluated the heterogeneity variance among trials.

The weaknesses of our analyses and conclusions mirror the weaknesses of the included trials. Our results should be interpreted with caution because almost all the trials had a high risk of bias.[52-55] Data were sparse for patient relevant outcomes. Most trials had short duration of the intervention and assessed metabolic efficacy as their primary outcome. Only two trials had intervention duration longer than one year,[6 44] and only one was designed to assess patient relevant outcomes.[6]

Subgroup analyses on the secondary outcomes showing significant results were post hoc. Nonetheless, the magnitude of HbA_{1c} reduction with metformin and insulin seemed to be more pronounced in trials designed to blind investigators and participants than in non-blinded trials. The extent to which this finding might be due to less aggressive titration of insulin doses in patients receiving both metformin and insulin in blinded trials than in non-blinded trials is unknown. Likewise, HbA_{1c} reductions were also more pronounced in trials using fixed insulin regimens than in those using variable regimens. The trials that used fixed regimens did not explain the exact meaning of this regimen; therefore, we cannot know if this regimen meant, for example, no changes in insulin type or dose. A fixed regimen strategy in terms of type or dose is probably unlikely to be found in clinical practice typically using unrestricted changes in insulin dose or type according to the individual needs of patients.

Despite these uncertainties and being a post hoc analysis, the data seem to raise a clinical dilemma: whether to reduce HbA_{1c} or change the insulin regimen (that is, mean difference in HbA_{1c} with variable regimen −0.46% *v* mean difference with fixed regimen −1.44%; P<0.001 for test of interaction). This choice can only be better guided by randomised trials assessing patient relevant outcomes as well. Also, our finding of the influence of obesity on the reduction in insulin dose reiterates the classic, but as yet unsolved, question of metformin being a drug that potentially benefits mainly obese patients.[5] Post hoc subgroup analysis of previous metformin treatment showed significant differences in the effect estimate of weight (P=0.03), showing a more pronounced weight reduction in trials not allowing metformin treatment at entry.

Because we aimed to assess the effect of metformin and insulin versus insulin alone irrespective of previous interventions, we included a diverse group of trials—for example, the percentage of patients who were insulin or metformin naive varied among trials. Furthermore, the prescribed insulin regimens varied markedly among trials, and some also varied between the intervention groups within the trials.[3 18 36 39 40 42 43 45-47] Some trials allowed participants to receive metformin at trial entry.[4 6 29 35-46] We were unable to estimate for how long these participants received metformin, and only a few trials reported the percentage of participants receiving metformin at entry. Even though our subgroup analysis did not support a potential legacy effect of metformin, such an effect cannot be ruled out, because the absence of evidence is not evidence of absence.

Results in relation to other studies and reviews

A Cochrane review compared the effect of metformin alone with placebo or no intervention and found only a few trials providing data for mortality and morbidity.[60] Accordingly, the review was inconclusive. A recent meta-analysis included a diverse group of trials of participants both with and without diabetes and showed a reduction of cardiovascular events with metformin (not necessarily alone) when compared with placebo, but, notably, not when compared with active comparators.[7] Another meta-analysis including 10 trials showed that metformin alone reduced fasting blood glucose and HbA_{1c} compared with placebo, but did not report any significant difference in weight change.[61] Another Cochrane review of 20 randomised clinical trials compared insulin and oral hypoglycaemic agents with insulin alone, but only few trials compared metformin and insulin with insulin alone.[12] As in our review, evidence in that Cochrane review was insufficient to make conclusions about long term complications and mortality. The previous meta-analyses also included trials with high risk of bias and of short duration, similar to our systematic review.

We found no significant effect on cardiovascular complications, which conflicts with the findings of the HOME trial. The HOME trial found that metformin and insulin compared with insulin alone significantly reduced the risk of a composite outcome of cardiovascular complications after a follow-up of four years and four months when adjusted for baseline confounders.[6] The reason for this difference cannot fully be elucidated. However, some obvious factors could be the differences in duration of intervention between trials with the lack of time to event analysis in a meta-analysis such as ours (without access to data at the patient level). Also, the sparse and possibly non-systematic or non-adjudicated reporting of events from studies other than the HOME trial could have been a confounder.

Moreover, the HOME trial reported baseline imbalances for some potentially important confounders, which could have influenced the results. The participants assigned to metformin and insulin were older (on average, five years) and had a history of cardiovascular disease more often than did the participants assigned placebo and insulin. On the other hand, the control group had more smokers than did the metformin and insulin group. The HOME trial authors found that the favourable effect

of metformin could be explained partly by the metformin associated changes in weight. The HOME trial did not report P values of the unadjusted events rates on macrovascular complications. Our analysis of macrovascular complications was mainly dominated by the results from the HOME trial reporting the unadjusted event rates.[6]

Observational studies comparing the effect of metformin and insulin with insulin monotherapy are sparse. We identified a Danish cohort study of patients with type 2 diabetes and heart failure (468 receiving metformin and insulin treatment, 3718 receiving insulin alone).[62] The study showed reduced mortality in the combination group compared with insulin monotherapy, but did not report other potential benefits or harms.[62]

Clinical implementations

Many perceived disadvantages of insulin treatment in type 2 diabetes seem to be minimised by concomitant treatment with metformin. Metformin and insulin versus insulin alone seems to cause favourable reductions in weight, HbA_{1c}, and insulin dose. However, we do not know of effects on patient relevant outcomes. The incomplete evidence on patient relevant outcomes is surprising, in view of current international consensus statements on diabetes clearly recommending the use of metformin and insulin in almost all patients with type 2 diabetes who initiate insulin treatment.[2 63] Furthermore, as noted above, a recent meta-analysis [7] did not confirm (P=0.89) the favourable effect of metformin on cardiovascular outcomes compared with other glucose lowering drugs, as observed in the UK Prospective Diabetes Study[5] and possible harm of additional metformin treatment in sulphonylurea treated patients was suggested.[7] Moreover, unlike insulin or sulphonylureas, metformin has not yet been shown to significantly reduce microvascular outcomes.[5 6 64]

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Contributors: BH undertook the searches and data analysis. BH, LLC, and TA participated in the selection of trials, data extraction, and quality assessment of trials. JW advised on statistical methods and data analyses. CG advised on statistical methods and interpretation of data. All authors developed the protocol, read and approved the final manuscript, and were involved in the development of the final review. BH and TA are the guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: the study received funding from the Copenhagen Insulin and Metformin Therapy Trial Group; LLC, SSL, AV, and TA have reported equity in Novo Nordisk A/S; SSL and AV have received fees from Novo Nordisk A/S for speech making; LLC was employed at Steno Diabetes Centre, Gentofte, Denmark, when the systematic review began; TA is employed at Steno Diabetes Center, which is an academic institution owned by Novo Nordisk A/S; BH, JW, and CG have no conflicts of interest to declare; after the initial draft of the present manuscript, SSL took up a position at Boehringer Ingelheim, Ingelheim, Germany.

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What is already known on this topic

Because of the progressive nature of type 2 diabetes, a substantial proportion of patients end up receiving insulin treatment

Current guidelines for diabetes treatment recommend combining metformin with insulin instead of using insulin alone

Previous meta-analyses have only included a few trials comparing metformin and insulin with insulin alone

What this study adds

The reporting of patient relevant outcomes was sparse

An influence of metformin and insulin versus insulin alone on all cause mortality or cardiovascular mortality could not be established, and more trials are needed to provide firm evidence for an effect or absence of an effect

Metformin and insulin treatment, compared with insulin alone, seems to be associated with a reduction in HbA_{1c}, weight gain, and insulin dose

Metformin and insulin seems to increase the risk of severe hypoglycaemia compared with insulin alone

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Tables

Table 1| Demographic characteristics of the included trials

Trial	No of participants*	Age (years)*	Duration of diabetes (years)*	HbA1c (%)*	Weight (kg)*	Body mass index*	Trial duration (months)
Altuntas et al, 2003[43]	20/40	53.8 (13.9)/54.7 (33.5)	5.2/8.2	10.1 (5.1)/9.5 (6.5)	NR	31.2 (34.9)/31.6 (14.5)	6
Avilés-Santa et al, 1999[48]	21/22	53.1 (9.4)/54.6 (7.8)	9.2 (6.4)/10.1 (4.7)	9.0 (1.4)/9.1 (1.5)	103.9 (25.2)/106.6 (12.2)	NR	6
Civera et al, 2007[36]	12/13	61.6 (9.2)/61.8 (10.2)	7.9 (3.3)/11.1 (6.7)	9.6 (0.7)/9.8 (1.1)	74.7 (8.0)/68.8 (14.7)	27.9 (3.8)/27.4 (4.8)	6
Douek et al, 2005[4]	92/91	58 (8.9)/58 (7.7)	9 (5.2)/10 (5.2)	9.7 (1.3)/10.0 (1.5)	88.5 (14.7)/91.1 (15.7)	30.9 (4.5)/31.5 (4.3)	12
Galvani et al, 2011[37]	15/15	55.2/61.4	NR	10.8 (0.7)/9.6 (0.7)	65.1/65.4	NR	3
Giugliano et al, 1992[49]	27/23	60 (1)/60.8 (1.1)	11.9 (1.2)/11.5 (1.2)	11.5 (1.2)/11.7 (1.3)	NR	33 (3.1)/32.7 (3.2)	6
Heine et al, 1995[29,32,33]	134†	NR	NR	13.6/13.4	NR	Both groups: 29.0 (3.0)	6
Hermann et al, 2001[50]	16/19	56.9 (10.2)/58.1 (9.7)	13 (3-13)/13 (4-25)	9.1 (1.3)/8.7 (1.0)	96.4 (16.6)/94.2 (9.4)	33.6 (3.5)/32.6 (3.8)	12
Hirsch et al, 1999[34]	25/25	NR	NR	8.6 (1.1)/9.0 (1.8)	NR	NR	5
HOME, 2009[6,17]	196/194	64 (10)/59 (11)	14 (9)/12 (8)	7.9 (1.2)/7.9 (1.2)	85 (16)/87 (15)	30 (5)/30 (5)	4.3
Kabadi et al, 2006[38]	12/8	54 (24.2)/53 (17.0)	13 (13.9)/13 (11.3)	9.4 (4.2)/9.6 (3.1)	98 (27)/103 (28.3)	34 (17.3)/35 (14.1)	6
Kokic et al, 2003[42]	29/29	62.3 (7.2)/63.6 (4.8)	9.5 (3.1)/10.5 (3.2)	10.0 (1.73)/9.21 (1.54)	NR	30.2 (4.8)/27.9 (3.9)	3
Kokic et al, 2010[45]	79/79	64.2 (8.4)/66.0 (12.7)	9.5 (3.6)/10.0 (6.2)	10.2 (2.1)/9.5 (2.0)	NR	28.9 (3.5)/28.5 (3.5)	6
Kvapil et al, 2005[39]‡	116/111	56.4 (9.0)/55.2 (10.3)	6.7 (5.7)/8.2 (7.1)	9.3 (1.3)/9.6 (1.5)	85.1 (15.1)/87.3 (16.5)	30.4 (4.0)/30.9 (4.5)	4
Onuchin et al, 2010[40]	44/45	61.4 (8.0)/61.1 (8.5)	8 (6-13)/9 (4-14)§	10.8 (1.6)/11.03 (1.9)	NR	32.3 (5.7)/31.1 (7.6)	12
Ponssen et al, 2000[35]	17/14	63.7 (10.0)/59.4 (9.7)	10 (96-276)‡	NR	72.2	NR	5 (before crossover)
Relimpio et al, 1998[18]	31/29	65.4 (7.9)/66.7 (6.2)	15.4 (7.9)/15.3 (6)	9.6 (1.4)/9.6 (1.2)	76.8 (12.6)/78.0 (12.9)	33 (4.7)/31.9 (4.5)	4
Robinson et al, 1998, study 1[30]	20¶	61.3 (7.1)	15 (7)	8.9 (1.0)	81.1 (16.9)	29.5 (3.5)	3(before crossover)
Robinson et al, 1998, study 2[30]	15¶	56.1 (8.9)	14 (6)	9.5 (1.2)	83.2 (12.7)	30.9 (3.8)	3 (before crossover
Schnack et al, 1996[31]	20/19**	63.3	11.3	10.0 (0.9)/9.7 (0.9)	77.2 (11.2)/81.1 (16.1)	NR	6
SDDSa, 2011[44,65]	45/46	55.4 (8.5)/55.8 (7.7)	8.2 (4.0)/7.3 (4.3)	8.9 (1.2)/8.7 (1.3)	105 (17.7)/100.2 (19.8)	35.7 (6.4)/34.0 (6.0)	24
SDDSb, 2011[44,65]	45/48	56.1 (8.2)/57.1 (8.5)	8.7 (4.5)/9.1 (5.5)	8.5 (1.2)/8.5 (1.2)	100.5 (17.9)/98.3 (16.6)	33.7 (6.1)/33.7 (5.0)	24
Strowig et al, 2002[47]	30/31	51.8 (10.5)/54.4 (9.1)	7.6 (4.1)/10.5 (7.3)	8.8 (1.2)/8.7 (1.6)	105.8 (22.4)/107.0 (26.7)	37.1 (6.6)/36.4 (9.0)	4
Ushakova et al, 2007[41]	100/104	58.4 (6.4)/58.0 (6.4)	8.4 (5.7)/9.9 (6.2)	10.4 (1.7)/10.4 (1.4)	78.4 (13.0)/79.3 (11.8)	29.2 (3.8)/29.8 (3.5)	4
Vähätalo et al, 2007[46]	26/11	NR	NR	10/9.8	81.7/85.1	NR	12
Yilmaz et al, 2007[51]	17/19	57.7 (8.5)/61.5 (12.0)	12.1 (7.7)/17.9 (11.5)	8.9 (1.2)/8.7 (1.6)	79.4 (14.1)/71.7 (16.0)	33.2 (6.1)/28.2 (5.9)	6
Yki-Järvinen et al, 1999[3,66]	23/24	57 (9.6)/58 (9.8)	NR	9.8 (1.9)/10.1 (2.0)	NR	28.9 (5.3)/28.5 (5.4)	12

NR=not reported; SDDS=South Danish Diabetes Study; SDDSa=intervention group in the South Danish Diabetes Study prescribed neutral protamine Hagedorn insulin in combination with metformin or placebo; SDDSb=intervention group in the South Danish Diabetes Study prescribed insulin aspart in combination with metformin or placebo; Robinson study 1=participants were exclusively treated with insulin at entry to trial and randomised to metformin or placebo in addition to insulin; Robinson study 2=participants received combination of metformin and insulin at entry to the trial, but after entry to the trial participants were randomised to receive either metformin or placebo.

Table 1 (continued)

Trial	No of participants*	Age (years)*	Duration of diabetes (years)*	HbA1c (%)*	Weight (kg)*	Body mass index*	Trial duration (months)

*Data are intervention group (insulin and metformin)/control group (insulin (and placebo)); data for continuous variables are mean (standard deviation) if reported, unless stated otherwise.

†Number of participants randomly assigned into four groups, of which only two were relevant for our review.

‡Baseline data only reported for participants exposed, not those who underwent randomisation.

§Interquartile range.

¶Data only reported for the total number of participants undergoing randomisation.

**More participants were randomly assigned to each group and only data for the one trial with available data reported.

Table 2| Baseline variables of the included trials‡Data are participants with hypertension at baseline.

Trial	Systolic and diastolic blood pressure (mm Hg)*	Cholesterol concentration (mmol/L)*			Triglyceride concentration (mmol/L)*	No of patients given aspirin, antihypertensive, or lipid lowering treatment	Previous cardiovascular disease*
		Total	Low density lipoprotein	High density lipoprotein			
Altuntas et al, 2003[43]	NR	5.8 (8.0)/5.3 (5.4)	3.3 (0.9)/3.1 (4.3)	1.3 (0.9)/1.1 (0.9)	3.6 (13.0)/2.2 (4.7)	NR	NR
Avilés-Santa et al, 1999[48]	NR	5.5 (1.0)/5.6 (1.5)	3.1 (0.8)/3.5 (1.1)	0.9 (0.3)/0.9 (0.3)	2.3 (1.3)/2.5 (2.1)	NR	NR
Civera et al, 2007[36]	146 (26)/78 (10); 152 (23)/81 (11)	NR	NR	NR	NR	NR	NR
Douek et al, 2005[4]	146 (20)/84 (11); 145 (19)/84 (11)	5.1 (0.96)/5.1 (0.98)	NR	1.1 (0.22)/1.1 (0.33)	2.9 (2.0)/2.5 (1.4)	NR	NR
Galani et al, 2011[37]	136.9/80.7; 136.4/79.8	NR	NR	NR	NR	NR	NR
Giugliano et al, 1992[49]	155 (20)/87.5 (10); 155(20)/85 (10)	5.9 (0.6)/6.03 (0.6)	NR	1.05 (0.3)/1.0 (0.3)	2.9 (0.9)/2.6 (0.5)	NR/5/NR NR/4/NR	NR
Heine et al, 1995[29,32,33]	NR	NR	NR	NR	NR	NR	NR
Hermann et al, 2001[50]	155 (17)/84 (8); 153 (17)/88 (9)	6.1 (1.2)/6.0 (1.3)	3.9 (0.8)/3.7 (1.3)	1.2 (0.3)/1.1 (0.3)	2.8 (1.7)/2.5 (1.3)	NR	19% of included participants
Hirsch et al, 1999[34]	NR	NR	NR	NR	NR	NR	NR
HOME, 2009[6,17]	160 (25)/86 (12); 159 (25)/86 (11)	5.5 (1.3)/5.4 (1.2)	3.6 (1.1)/3.4 (1.0)	1.3 (0.4)/1.3 (0.4)	1.7 (1.2)/1.9 (1.5)	NR/93/32 NR/75/31	59/53†
Kabadi et al, 2006[38]	NR	NR	NR	NR	NR	NR	NR
Kokic et al, 2003[42]	NR	NR	NR	NR	NR	NR	NR
Kokic et al, 2010[45]	NR	NR	NR	NR	NR	NR	NR
Kvapil et al, 2005[39]	NR	NR	NR	1.2 (0.3)/1.2 (0.3)	2.8 (2.4)/2.6 (2.5)	NR	NR
Onuchin et al, 2010[40]	161 (22.1)/93.2 (8.5); 161 (23.2)/94.9 (8.3)	6.3 (1.4)/6.5 (1.6)	NR	NR	3.4 (1.4)/3.0 (1.5)	NR	NR
Ponssen et al, 2000[35]	NR	NR	NR	NR	NR	NR	NR
Relimpio et al, 1998[18]	153.5 (24)/81.6 (10.8); 148.(24.8)/80 (14.4)	5.84 (1.0)/5.92 (1.2)	3.84 (0.51)/3.71 (1.15)	1.36 (0.18)/1.34 (0.35)	2.01 (1.1)/2.42(1.53)	NR/10/1 NR/7/5	13/13‡
Robinson et al, 1998, study 1[30]	138 (16)/78 (9)§	6.0 (1.1)	3.9 (1.2)	1.1 (0.3)	2.2 (1.3)	NR	NR
Robinson et al, 1998, study 2[30]	144 (23)/87 (11)§	6.4 (1.2)	4.1 (1.5)	1.2 (0.4)	2.5 (2.4)	NR	NR
Schnack et al, 1996[31]	NR	NR	NR	NR	NR	NR	NR
SDDSa, 2011[44,65]	NR	NR	NR	NR	NR	NR	NR
SDDSb, 2011[44,65]	NR	NR	NR	NR	NR	NR	NR
Strowig et al, 2002[47]	NR	4.9 (1.1)/4.9 (1.1)	2.8 (1.1)/2.8 (0.7)	0.8 (0.2)/1.0 (0.3)	2.5 (1.8)/2.0 (1.7)	NR	NR
Ushakova et al, 2007[41]	NR	NR	NR	NR	NR	NR	NR
Vähätalo et al, 2007[46]	NR	NR	NR	NR	NR	NR	NR
Yilmaz et al, 2007[51]	NR	4.6 (0.7)/5.4 (1.8)	2.5 (0.6)/3.2 (0.5)	1.3 (0.4)/1.3 (0.2)	1.7 (0.9)/2.5 (2.4)	NR	NR
Yki-Järvinen et al, 1999[3,66]	NR	5.9 (1.4)/5.8 (1.5)	NR	1.2 (0.5)/1.2 (0.5)	2.4 (1.9)/0.9 (2.4)	NR/2/NR	NR

NR=not reported; SDDS=South Danish Diabetes Study; SDDSa=intervention group in the South Danish Diabetes Study prescribed neutral protamine Hagedorn insulin in combination with metformin or placebo; SDDSb=intervention group in the South Danish Diabetes Study prescribed insulin aspart in combination with metformin or placebo; Robinson study 1=participants were exclusively treated with insulin at entry to trial and randomised to metformin or placebo in addition to insulin; Robinson study 2=participants received combination of metformin and insulin at entry to the trial, but after entry to the trial participants were randomised to receive either metformin or placebo.

*Data are intervention group (insulin and metformin)/control group (insulin (and placebo)); data for continuous variables are mean (standard deviation) if reported, unless stated otherwise.

†Data only for participants who completed the trial.

§Data only reported for the total number of participants undergoing randomisation.

Table 3| **Interventions in the included trials**

Trial	Participants allowed metformin treatment at entry?	Insulin naive participants at baseline	Insulin dose at baseline (U/day)		Trial regimen	
			Intervention	Control	Intervention	Control
Altuntas et al, 2003[43]	No; patients received diet and sulphonylurea	Yes	—	—	850 mg metformin, twice daily; insulin lispro (initial 0.3 U/kg per day, before meals)	Two regimens used: insulin lispro (initial 0.3 U/kg per day, before meals) and neutral protamine Hagedorn insulin (0.2 U/kg per day, at bedtime); human regular insulin (initial 0.3 U/kg per day, before meals) and neutral protamine Hagedorn insulin (initial 0.2 U/kg per day at bedtime)
Avilés-Santa et al, 1999[48]	NR	No	96.2 (44.9)	96.9 (43.4)	Metformin, twice daily, titrated up to 2000 mg; insulin type and regimen not changed from baseline	Placebo tablets; insulin type not changed from baseline
Civera et al, 2007[36]	Yes; oral antidiabetic drugs	Yes	—	—	850 mg metformin, twice daily; neutral protamine Hagedorn insulin (initial 0.2 U/kg per day, before dinner)	Neutral protamine Hagedorn insulin (initial 0.3 U/kg per day; two thirds before breakfast and one third before dinner)
Douek et al, 2005[4]	Yes; oral antidiabetic drugs	Yes	—	—	2 g metformin per day, divided into two doses; no management protocol for insulin, insulin type decided by investigator	Placebo tablets; no management protocol for insulin, insulin type decided by investigator
Galani et al, 2011[37]	Assuming yes; routine oral antidiabetic drugs	Yes	—	—	500 mg metformin per day; insulin isophane (fixed dose 10 U/day)	Insulin isophane (fixed dose 10 U/day)
Giugliano et al, 1992[49]	No	No	90 (9)	88 (9.4)	850 mg metformin, twice daily; insulin treatment as before randomisation	Placebo tablets; insulin treatment as before randomisation
Heine et al, 1995[29,32,33]	Yes; metformin and glipizide	Yes	NR	NR	Metformin; neutral protamine Hagedorn insulin (at bedtime)	Neutral protamine Hagedorn insulin (at bedtime)
Hermann et al, 2001[50]	No; exclusion criterion was oral antidiabetic treatment within past six months	No	72.3 (27)	68.8 (21.7)	850 mg metformin twice daily; insulin regimen unchanged from baseline	Placebo tablets; insulin regimen unchanged from baseline
Hirsch et al, 1999[34]	No; no oral antidiabetic drugs	No	NR	NR	2.5 g metformin; insulin	Placebo tablets; insulin
HOME, 2009[6,17]	Yes; metformin allowed only in combination with insulin	No	62 (29)	64 (25)	850 mg metformin up to three times per day; actrapid (before three main meals) and insulatard (at bedtime); alternatively, mixed insulin (before breakfast and dinner)	Placebo tablets; actrapid (before three main meals) and insulatard (at bedtime); alternatively, mixed insulin (before breakfast and dinner)
Kabadi et al, 2006[38]	Yes; metformin monotherapy, glimepiride monotherapy, or combination of both drugs	Yes	—	—	2.5 g metformin; biphasic insulin aspart 30/70 (initial dose 10 U, before dinner)	Placebo tablets; biphasic insulin aspart 30/70 (initial dose 10 U, before dinner)
Kokic et al, 2003[42]	Yes; oral antidiabetic drugs	Yes	—	—	Metformin; insulin lispro (thrice daily)	Biphasic insulin 30/70 (twice daily); neutral protamine Hagedorn insulin (at bedtime)
Kokic et al, 2010[45]	Assuming yes; NR	NR	—	—	Two doses of metformin; lispro insulin (before meals)	Biphasic insulin 30/70 (before breakfast and dinner); neutral protamine Hagedorn insulin (at bedtime)
Kvapil et al, 2005[39]	Yes; metformin monotherapy	Yes	—		Metformin maintained at pretrial dosages; biphasic insulin aspart 30/70 (initial dose 0.2 U/kg per day, before breakfast and dinner)	Biphasic insulin aspart 30/70 (dose 0.3 U/kg per day, before breakfast and dinner)
Onuchin et al, 2010[40]	Yes; oral antidiabetic drugs	Yes	—	—	1.5-2.5 g metformin per day; long acting insulin (initial 0.2-0.4 U/kg per day, two thirds before breakfast, one third at bedtime)	Long acting insulin (initial 0.2-0.4 U/kg per day, two thirds before breakfast, one third at bedtime); (actrapid 1-1.5 U/10 g carbohydrate, at meals)

Table 3 (continued)

Trial	Participants allowed metformin treatment at entry?	Insulin naive participants at baseline	Insulin dose at baseline (U/day)		Trial regimen	
			Intervention	Control	Intervention	Control
Ponssen et al, 2000[35]	Yes; oral antidiabetic drugs	No	12 (0-96)*†	12 (0-96)*†	Metformin; mixed insulin 30/70 (twice daily)	Placebo tablets; mixed insulin 30/70 (twice daily)
Relimpio et al, 1998[18]	NR	No	47.9 (10)	51.8 (9.6)	Metformin, titrated up to 2550 mg/day, after four weeks; insulin regimen maintained	10% increase in insulin from baseline
Robinson et al, 1998, study 1[30]	No; no oral antidiabetic drugs	No	71 (47)*	71 (47)*	1 g metformin twice a daily; insulin	Placebo tablets; insulin
Robinson et al, 1998, study 2[30]	Yes; metformin in combination with insulin	No	41 (16)†	41 (16)†	1 g metformin twice a daily; insulin	Placebo tablets; insulin
Schnack et al, 1996[31]	No; sulphonylurea monotherapy	Yes	—	—	Metformin; mixed insulin (twice daily)	Mixed insulin (twice daily)
SDDSa, 2011[44,65]	Yes; oral antidiabetic drugs	No	NR	NR	Metformin, titrated to 2000 mg/day, in four weeks; neutral protamine Hagedorn insulin (naive use, initial dose 12 U/day; previous use, half previous daily dose)	Placebo tablets; neutral protamine Hagedorn insulin (naive use, initial dose 12 U/day; previous use, half previous daily dose)
SDDSb, 2011[44,65]	Yes; oral antidiabetic drugs	No	NR	NR	Metformin, titrated to 2000 mg/day, in four weeks; insulin aspart (naïve use, initial dose 4U before each main meal; previous use: initial dose 50% of previous daily dose divided in three, before each main meal)	Placebo tablets; insulin aspart (naïve use, initial dose 4U before each main meal; previous use: initial dose 50% of previous daily dose divided in three, before each main meal)
Strowig et al, 2002[47]	No; no oral antidiabetic drugs	No	82.9 (48.2)	80.3 (41.7)	Metformin, titrated to 2000 mg/day, in four weeks; insulin dose not increased, but dose decreased if frequent hypoglycaemia occurred	Insulin dose increased to achieve normal levels of glycaemia
Ushakova et al, 2007[41]	Yes; oral antidiabetic drugs	Yes	—	—	Metformin, titrated to 2000 mg/day; biphasic insulin aspart 30/70 (initial dose 0.3-0.5 U/kg per day, before breakfast and dinner)	Biphasic insulin aspart 30/70 (initial dose 0.3-0.5 U/kg per day, before breakfast and dinner)
Vähätalo et al, 2007[46]	Yes; oral antidiabetic drugs	No	21.1	42.7	Metformin, titrated to 2500 mg/day; neutral protamine Hagedorn insulin (at bedtime) or Lente insulin (at bedtime)	Neutral protamine Hagedorn insulin (in the morning and at bedtime)
Yilmaz et al, 2007[51]	No; no oral antidiabetic drugs	No	52.2 (13.6)	42.7 (14.3)	1700 mg metformin per day; biphasic insulin aspart 30/70 twice daily	Biphasic insulin aspart 30/70 twice daily
Yki-Järvinen et al, 1999[3,66]	No; inclusion criterion was previous treatment with glipizide or glyburide	Yes	—	—	2000 mg metformin divided in two doses; neutral human isophane (initial dose same as fasting blood glucose levels (mmol/L), before bedtime)	Neutral human isophane (initial dose same as fasting blood glucose levels (mmol/L), before bedtime); second injection of neutral human isophane insulin (before breakfast)

NR=not reported; SDDS=South Danish Diabetes Study; SDDSa=intervention group in the South Danish Diabetes Study prescribed neutral protamine Hagedorn insulin in combination with metformin or placebo; SDDSb=intervention group in the South Danish Diabetes Study prescribed insulin aspart in combination with metformin or placebo; Robinson study 1=participants were exclusively treated with insulin at entry to trial and randomised to metformin or placebo in addition to insulin; Robinson study 2=participants received combination of metformin and insulin at entry to the trial, but after entry to the trial participants were randomised to receive either metformin or placebo; intervention=group receiving insulin and metformin; control=group receiving insulin (and placebo). Data for continuous variables are mean (standard deviation) if reported, unless stated otherwise.

*Interquartile range.

†Number only reported for both intervention groups together.

Table 4| Risk of bias assessment of the included trials

Trial	Sequence generation	Allocation concealment	Blinding of participants and investigators	Blinding of outcome assessors	Complete outcome data	Selective outcome reporting	Academic bias	Sponsor bias
Altuntas et al, 2003[43]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear
Avilés-Santa et al, 1999[48]	Unclear	Unclear	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate
Civera et al, 2007[36]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear
Douek et al, 2005[4]	Unclear	Unclear	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate
Galani et al, 2011[37]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear
Giugliano et al, 1992[49]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear
Heine et al, 1995[29,32,33]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
Hermann et al, 2001[50]	Unclear	Unclear	Adequate	Adequate	Adequate	Unclear	Adequate	Unclear
Hirsch et al, 1999[34]	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Unclear
HOME, 2009[6,17]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Kabadi et al, 2006[38]	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unclear	Inadequate	Unclear
Kokic et al, 2003[42]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Inadequate	Unclear
Kokic et al, 2010[45]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear
Kvapil et al, 2005[39]	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate
Onuchin et al, 2010[40]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear
Ponssen et al, 2000[35]	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate
Relimpio et al, 1998[18]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate
Robinson et al, 1998, study 1[30]	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate
Robinson et al, 1998, study 2[30]	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate
Schnack et al, 1996[31]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
SDDS, 2011[44,65]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Strowig et al, 2002[47]	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate
Ushakova et al, 2007[41]	Unclear	Adequate	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate
Vähätalo et al, 2007[46]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear
Yilmaz et al, 2007[51]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear
Yki-Järvinen et al, 1999[3,66]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate

SDDS=South Danish Diabetes Study; Robinson study 1=participants were exclusively treated with insulin at entry to trial and randomised to metformin or placebo in addition to insulin; Robinson study 2=participants received combination of metformin and insulin at entry to the trial, but after entry to the trial participants were randomised to receive either metformin or placebo.

Figures

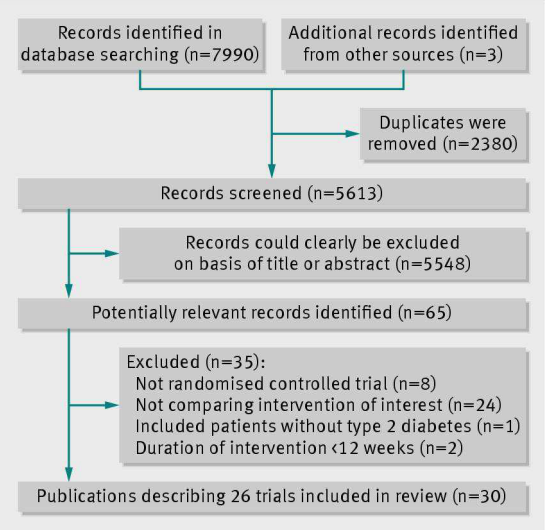

Fig 1 Identification of trials for inclusion

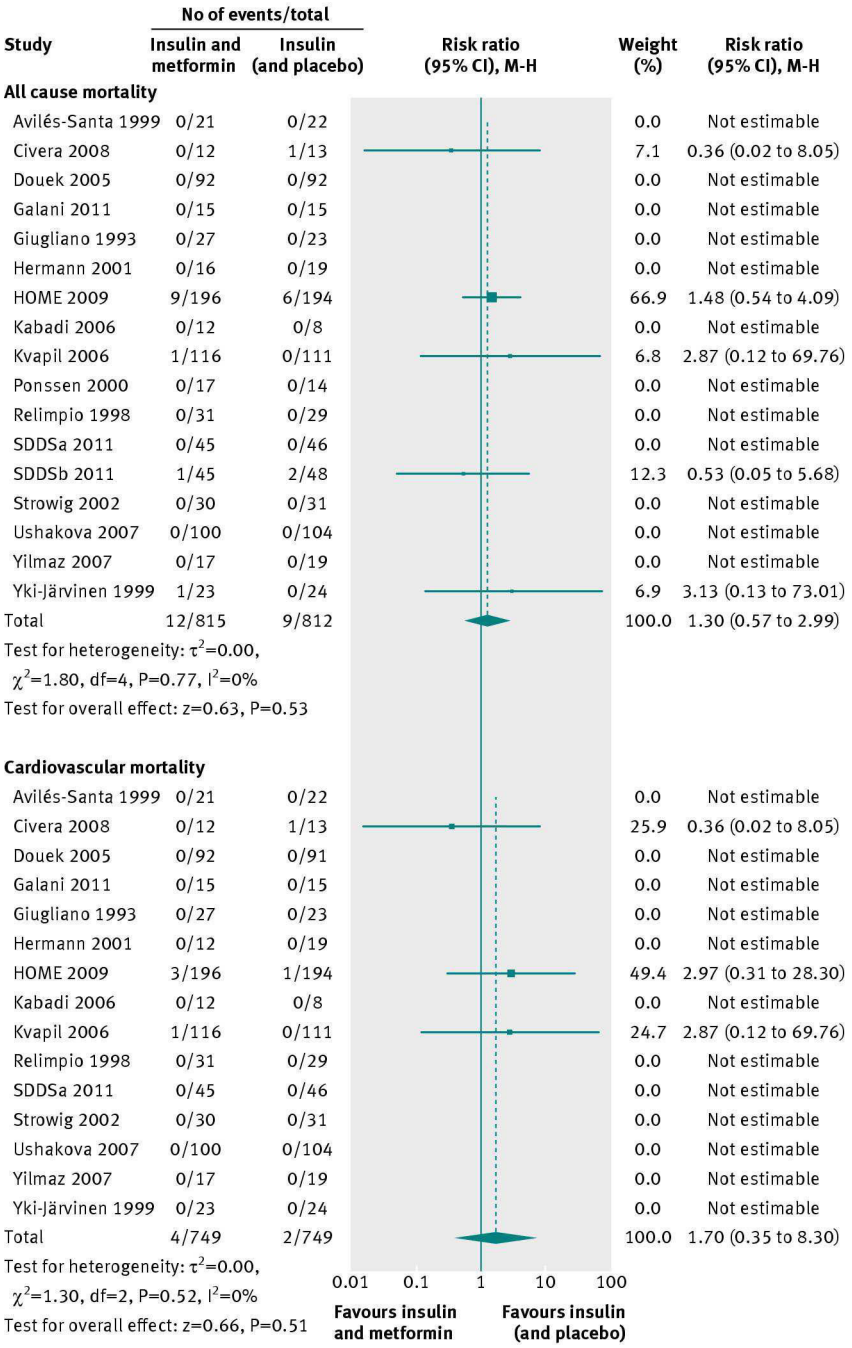

Fig 2 Forest plots for trial outcomes in all cause mortality and cardiovascular mortality. M-H=Mantel-Haenszel; CI=confidence interval. Random effects model used.

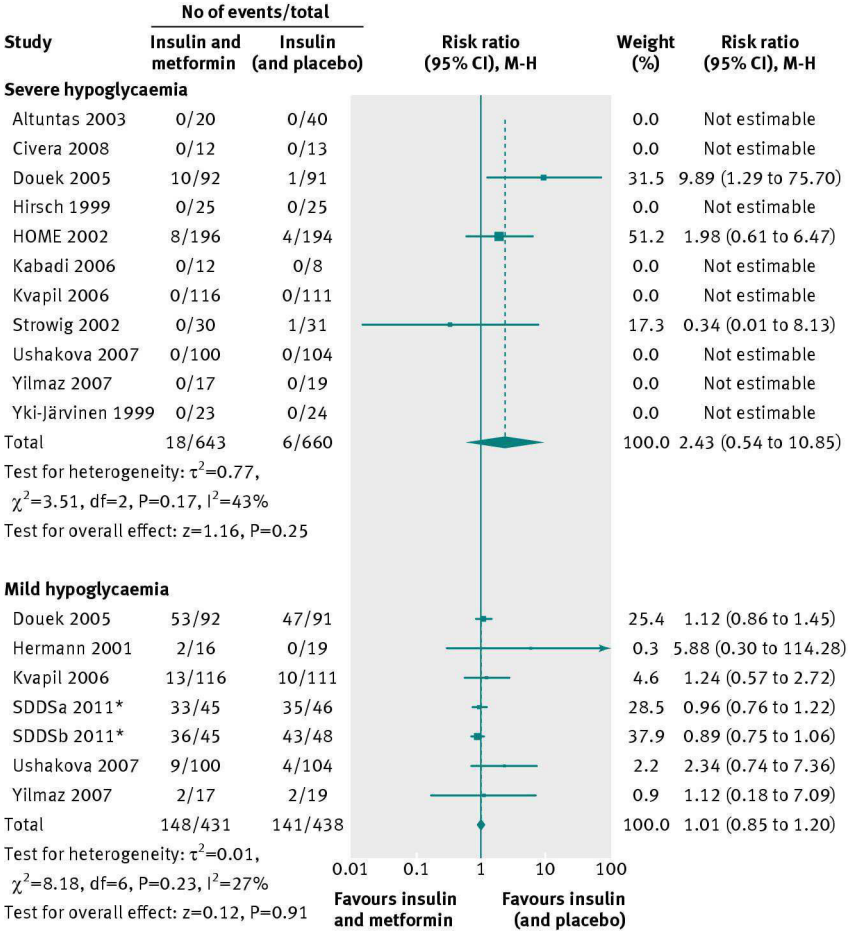

Fig 3 Forest plots for trial outcomes in severe hypoglycaemia and mild hypoglycaemia. M-H=Mantel-Haenszel; CI=confidence interval. Random effects model used. *Trial only reported hypoglycaemia and did not specify severity

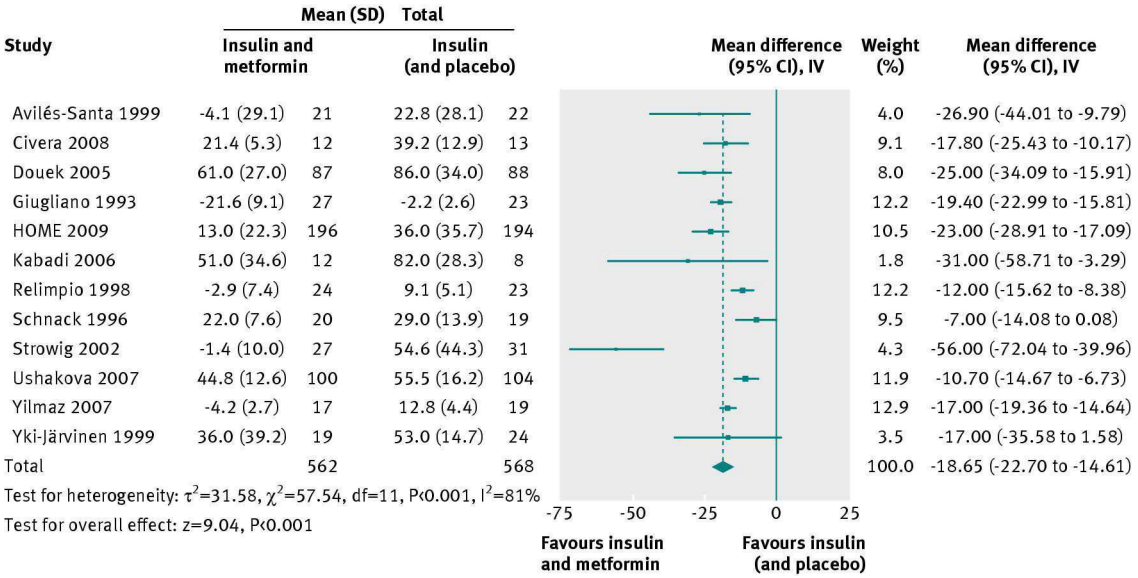

Fig 4 Forest plot for changes in insulin dose (U/day) from baseline to end of follow-up. IV=inverse variance; CI=confidence interval. Random effects model used

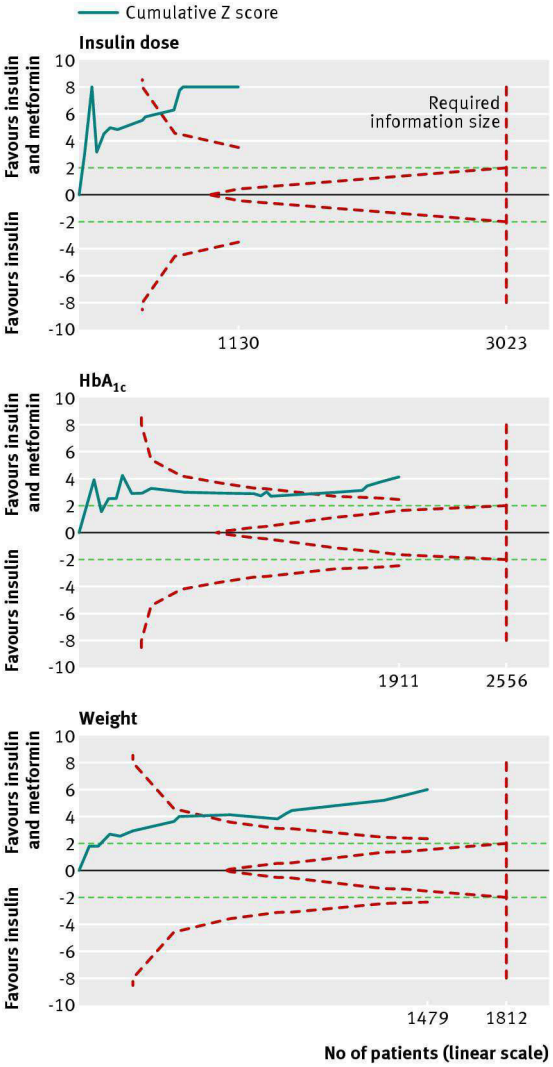

Fig 5 Trial sequential analysis of effect of metformin and insulin versus insulin alone in type 2 diabetes on insulin dose, HbA_{1c}, and weight. The required information size (and adjacent trial sequential alpha spending monitoring boundaries) for insulin dose was calculated based on a two sided α=5%; power of 80%; a minimal relevant difference of –5 U/day; a standard deviation of 17.6 U/day; and a diversity of 87% as estimated in a random effects model. The required information size (and the adjacent trial sequential alpha spending monitoring boundaries) for HbA_{1c} was calculated based on a two sided α=5%; power of 80%; a minimal relevant difference of –0.5%; a standard deviation of 1.6%; and a diversity of 80% as estimated in a random effects model. The required information size (and the adjacent trial sequential alpha spending monitoring boundaries) for weight was calculated based on a two sided α=5%; power of 80%; a minimal relevant difference of –1 kg; a standard deviation of 7.96 kg; and a diversity of 48% as estimated in a random effects model. The solid blue cumulative Z curves indicate the cumulated Z score from the inverse variance model Z statistic, whenever a new trial is added. The solid blue cumulative Z curves all cross the dashed red trial sequential alpha spending monitoring boundaries. Horizontal dotted green lines illustrate traditional level of statistical significance (P=0.05)

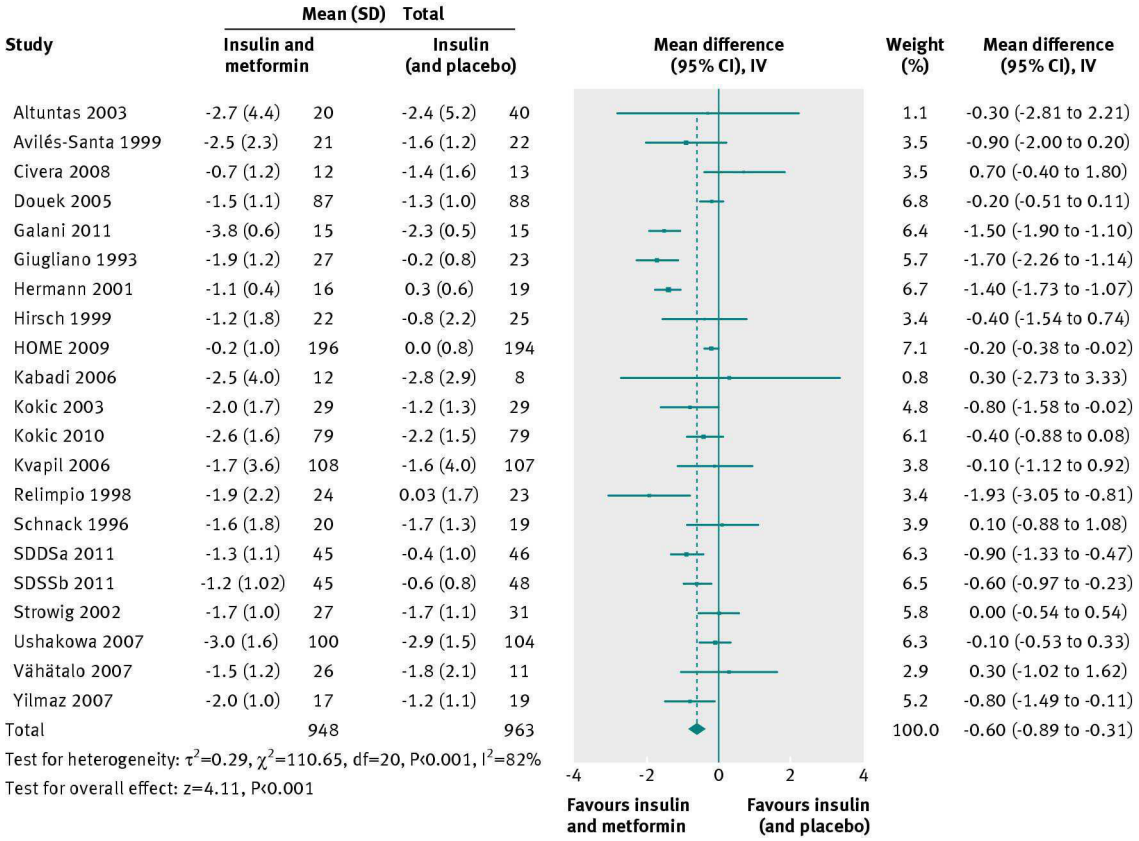

Fig 6 Forest plot for changes in HbA_{1c} (%) from baseline to end of follow-up. IV=inverse variance; CI=confidence interval. Random effects model used

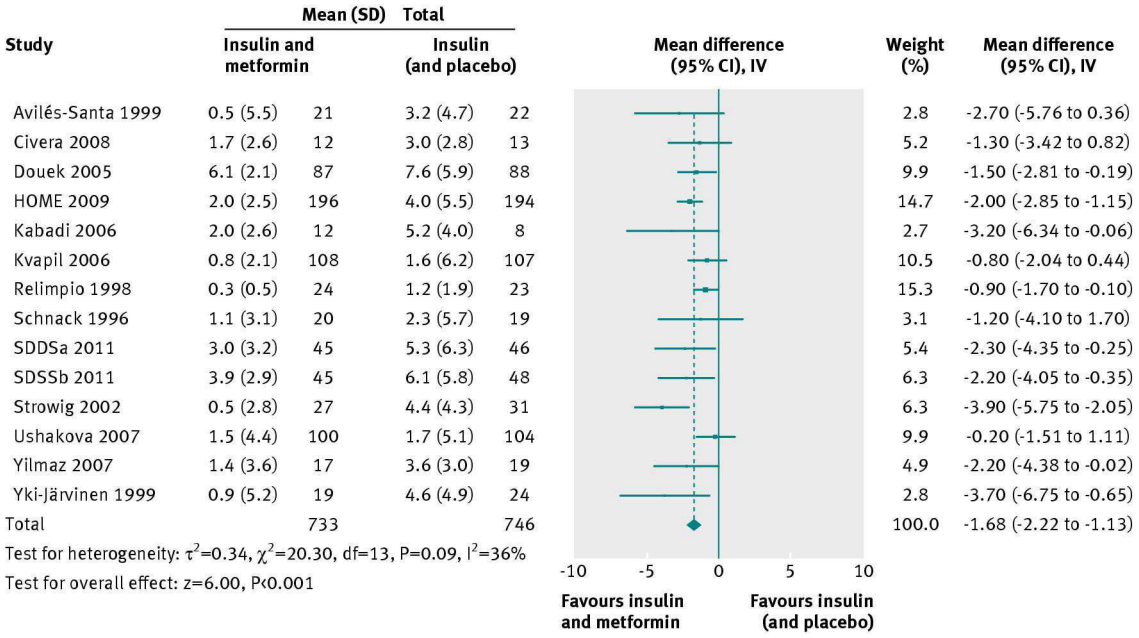

Fig 7 Forest plot for changes in weight (kg) from baseline to end of follow-up. IV=inverse variance; CI=confidence interval. Random effects model used

Web appendix: Search strategy and excluded studies

Appendix 1. Search terms

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2011) in The Cochrane Library
#1 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees 6549
#2 MODY OR NIDDM OR T2DM 1348
#3 non insulin* depend* OR noninsulin* depend* OR non insulin?depend* OR noninsulin?depend* 3259
#4 (typ* 2 OR typ* II) near/3 diabet* 8930
#5 (keto?resist* OR non?keto*) near diabet* 0
#6 (late OR adult* OR matur* OR slow OR (stabl*) near/3 onset) AND diabet* 12046
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 17474
#8 MeSH descriptor Diabetes Insipidus explode all trees 41
#9 diabet* insipidus 117
#10 (#8 OR #9) 117
#11 (#7 AND NOT #10) 17375
#12 MeSH descriptor Biguanides explode all trees 2419
#13 metformin* OR glucophag* OR biguanid* 1865
#14 (#12 OR #13) 3088
#15 MeSH descriptor Insulin explode all trees 7405
#16 insulin* 16568
#17 (#15 OR #16) 16568
#18 (#11 AND #14 AND #17) 851

MEDLINE (Ovid SP) (1950 to March 2011)
1. exp Diabetes Mellitus, Type 2/
2. (MODY or NIDDM or T2DM).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. ((typ* 2 or typ* II) adj3 diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. ((keto?resist* or non?keto*) adj6 diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Diabetes Insipidus/
9. diabet* insipidus.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. 8 or 9
11. 7 not 10
12. exp Biguanides/
13. (metformin* or glucophag* or biguanid*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. 12 or 13
15. exp Insulin/
16. insulin*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. 15 or 16
18. 11 and 14 and 17
19. (random* or blind* or placebo* or meta-analysis).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. 18 and 19

EMBASE (Ovid SP) (1980 to March 2011)
1. exp diabetes mellitus/
2. (MODY or NIDDM or T2DM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
3. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
4. ((typ* 2 or typ* II) adj3 diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
5. ((keto?resist* or non?keto*) adj6 diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
6. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp diabetes insipidus/
9. diabet* insipidus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
10. 8 or 9
11. 7 not 10
12. exp biguanide/
13. (metformin* or glucophag* or biguanid*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
14. 12 or 13
15. exp INSULIN/
16. insulin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
17. 15 or 16
18. 11 and 14 and 17
19. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
20. 18 and 19

Science Citation Index Expanded (1900 to March 2011)
13 1,215 #12 AND #11
12 >100,000 TS=(random* or blind* or placebo* or meta-analysis)
11 2,880 #10 AND #9 AND #8
10 >100,000 TS=(insulin*)
9 10,099 TS=(metformin* or glucophag* or biguanid*)
8 97,316 #6 NOT #7
7 6,161 TS=diabet* insipidus
6 97,504 #5 OR #4 OR #3 OR #2 OR #1
5 2,932 TS=(((late or adult* or matur* or slow or stabl*) SAME onset) AND diabet*)
4 0 TS=((keto?resist* or non?keto*) SAME diabet*)
3 79,124 TS=((typ* 2 or typ* II) SAME diabet*)
2 15,360 TS=(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*)
1 14,877 TS=(MODY or NIDDM or T2DM)

Latin American Caribbean Health Sciences Literature (1982 to March 2011)
metformin [Words] and insulin [Words]

Cumulative Index to Nursing & Allied Health Literature (March 2011)
S1 MW Diabetes Mellitus
S2 TX MODY OR NIDDM OR T2DM
S3 TX non insulin* depend* OR noninsulin* depend* OR non insulin?depend* OR noninsulin?depend*
S4 TX (typ* 2 OR typ* II) AND diabet*
S5 TX (keto?resist* OR non?keto*) AND diabet
S6 TX (late OR adult* OR matur* OR slow OR stabl*) AND onset AND diabet*
S7 S1 or S2 or S3 or S4 or S5 or S6
S8 MW Diabetes insipidus

S9 TX diabet* insipidus
S10 S8 or S9
S11 S7 NOT S10
S12 MW metformin
S13 TX metformin* OR glucophag* OR biguanid*
S14 S12 or S13
S15 MW insulin
S16 TX insulin*
S17 S15 or S16
S18 S11 and S14 and S17
S19 TX random* or blind* or placebo* or meta-analysis
S20 S18 and S19

Appendix II. Excluded studies

Study	Reason for exclusion
Barnett et al, 2006[1]	Not comparing interventions of interest
Chan et al, 2009[2]	Not a randomised clinical trial
Chow et al, 1995[3]	Not comparing interventions of interest
Ebel, 2005[4]	Not a randomised clinical trial
Fahrbach et al, 2008[5]	Not comparing interventions of interest
Fonseca, 2009[6]	Not a randomised clinical trial
Fritsche et al, 2010[7]	Not comparing interventions of interest
Garber et al, 1997[8]	Not comparing interventions of interest
Gardner et al, 1995[9]	Not comparing interventions of interest
Gin et al, 2003[10]	Duration of the intervention less than 12 weeks
Gregorio et al, 1989[11]	Not comparing interventions of interest
Goudswaard et al, 2004[12]	Not comparing interventions of interest
Guthrie, 1997[13]	Not a randomised clinical trial
Hermann et al, 1999[14]	Not a randomised clinical trial
Home et al, 2007[15]	Not comparing interventions of interest
Jaber et al, 2002[16]	Not a randomised clinical trial
James et al, 2005[17]	Not comparing interventions of interest
Janka et al, 2005[18]	Not comparing interventions of interest
Janka et al, 2007[19]	Not comparing interventions of interest
Kantola et al, 2000[20]	Not including patients with type 2 diabetes
Kilo et al, 2007[21]	Not comparing interventions of interest
Kooy, 2009[22]	Editorial. Not a randomised clinical trial
Liao et al, 2010[23]	Duration of the intervention less than 12 weeks
Ligthelm et al, 2011[24]	Not comparing interventions of interest
Mäkimattila et al, 1999[25]	Patients continue sulphonylurea from baseline
Perriello et al, 1997[26]	Not comparing interventions of interest
Pradhan et al, 2009[27]	Patients continue oral antidiabetic interventions from baseline
Riddle et al, 2011[28]	Not comparing interventions of interest
Schiel et al, 2007[29]	Not comparing interventions of interest
Tong et al, 2002[30]	Not comparing interventions of interest
Vilsboll et al, 2009[31]	Not comparing interventions of interest
Wolffenbuttel et al, 2009[32]	Not comparing interventions of interest
Wulffele et al, 2002[33]	Not a randomised clinical trial
Xu et al, 2001[34]	Patients continue oral antidiabetic interventions from baseline
Yki-Järvinen et al, 2006[35]	Not comparing interventions of interest

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