Sulphonylurea monotherapy versus metformin in patients with type 2 diabetes: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses

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Abstract

Objectives Guidelines recommend metformin as the first line oral treatment for patients with type 2 diabetes. To compare the benefits and harms of sulphonylurea monotherapy versus metformin in randomized clinical trials of patients with type 2 diabetes.

Design Cochrane systematic review of randomized 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, and health technology assessments and contacted trial authors, pharmaceutical companies, and the US Food and Drug Administration homepage.

Criteria for trial selection Randomized clinical trials comparing sulphonylurea with metformin monotherapy 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 randomization, 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 14 trials with 4560 participants. All trials were judged as high risk of bias. Data on patient-important outcomes were sparse. Sulphonylurea versus metformin did not significantly affect all-cause mortality (relative risk (RR) 0.98, 95% confidence interval (CI) 0.61 to 1.58) or cardiovascular mortality (RR 1.47, 95% CI 0.54 to 4.01). Sulphonylurea compared with metformin significantly decreased the risk of non-fatal macrovascular outcomes (RR 0.67, 95% CI 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. No difference between the interventions was found in random-effects model for change in fasting blood

glucose or HbA1c. Sulphonylurea resulted in higher weight gain compared with metformin, a finding confirmed in trial sequential analysis. Sulfonylurea significantly increased mild hypoglycemia (RR 2.95, 95% CI 2.13 to 4.07; P<0.00001) and severe hypoglycemia (RR 5.64, 95% CI 1.22 to 26.00; P=0.03).

Conclusions There is some evidence suggesting that sulphonylurea compared with metformin may not affect all-cause or cardiovascular mortality while possibly decreasing the risk of non-fatal macrovascular outcomes and increase the risk of hypoglycemia in patients with type 2 diabetes. In general the amount of data is far too small and inconsistent to provide firm evidence concerning patient-important outcomes in relation to benefits and harms of sulphonylurea versus metformin monotherapy.

Introduction

The American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for treatment of type 2 diabetes recommends initiation of metformin at diagnosis, or soon after, along with lifestyle interventions.[1] In patients 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 seems to be 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 342 obese patients,[2] and on observational studies.[3-5]

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;6-8] 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;6-8]

The purpose of this systematic review was to assess whether the use of second- and third-generation sulphonylurea agents compared

with metformin are associated with a different risk of benefits and harms of patient-important outcomes in patients with type 2 diabetes.

Methods

This review follows the recommendations of the Cochrane Collaboration.[9] It is based on our published Cochrane protocol.[10] We included randomized clinical trials comparing sulphonylurea monotherapy versus other antidiabetic interventions, or placebo, or no intervention.[10;11] 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 and third-generation sulphonylurea versus metformin because, at present, it is the comparisons of greatest clinical relevance. The Cochrane version reports all comparisons.[11]

Search strategy

We searched the Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL in August 2011 for randomized clinical trials of sulphonylurea monotherapy versus other antidiabetic interventions or placebo or no intervention 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 contacted trial

authors for additional unpublished trials, 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 randomized 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.[10;11] We included trials irrespective of outcomes reported, language, or whether escape medicine was allowed if monotherapy failed.[10;11]

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.[9]

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.[10;11] 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, cardial or peripheral revascularization, microvascular outcomes as a composite outcome, nephropathy, retinal photocoagulation, adverse events, serious adverse events, drop-outs due to adverse events, mild hypoglycemia, severe hypoglycemia, 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.[10;11] We sought any relevant missing information from the original author(s) of the randomized 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.[10;11]

Translators extracted data from all relevant non-English articles.

Statistical analysis

We used Review Manager version 5.1.7 for statistical analysis.[12] 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.[13;14] 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.[10;11]

We examined heterogeneity with the I^2 statistic.[9] I^2 of 50% or more indicated substantial heterogeneity.[9]

Trial sequential analysis

Trial sequential analyses of a meta-analysis is similar to interim analyses of a single trial, where group sequential monitoring boundaries are used to decide whether a trial could be terminated early if a P value is sufficiently small to show the anticipated effect.[15–18] There is no reason why the standards for a meta-analysis should be less rigorous than those for a single trial. With trial sequential analysis analogous trial sequential monitoring boundaries can be applied to a meta-analysis.[15–19] Cumulative meta-analyses of trials are at risk of increasing 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.[18] 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,[10] 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 interventions. 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.[20]

Results

Results of the search and trial, participant, and intervention characteristics

We identified 11 049 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-five publications describing 14 randomized clinical trials met our inclusion criteria for the comparison of second-generation or third-generation sulphonylurea versus metformin.[2;21-44]

Most of the trials for this comparison were published in English. One trial was published in Chinese.[42] The trials included 4560 participants of whom 2244 were randomized to second-generation or third-generation sulphonylurea versus 2313 randomized to metformin monotherapy. However, one trial did not describe which intervention group three of the participants were randomized to.[31] Table 1 shows characteristics of the fourteen included trials, table 2 shows characteristics of the interventions, and table 3 shows baseline characteristics. The number of randomized participants in each trial ranged from 23 to 2902.[21-28;36] The duration of intervention varied from 24 weeks to 10.7 years. Six of the trials applied glibenclamide,[2;21-27;30-36;39;40] four trials applied gliclazide,[29;36-38] and one trial applied glipizide as second-generation sulphonylureas.[28] Three trials applied glimepiride as third-generation sulphonylurea.[42-44]

The United Kingdom Prospective Diabetes Study (UKPDS) 34 trial included overweight/obese participants with type 2 diabetes comparing intensive glycemic control with metformin versus intensive glycemic control with other antidiabetic interventions (chlorpropamide, glibenclamide, or insulin).[2;40;41] 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] Attempts to obtain the separate data on the sulphonylurea versus metformin were in vain.

Two of the trials had a cross over design.[31;39] We only used data from the first period. The remaining nine trials had a parallel design. Nine of the trials were open labelled,[2;28;29;31;37;38;40;42;43] and five trials were blinding investigators and participants.[21-27;30;32-36;39] Two trials did not describe the blinding of participants and investigators.[36;44] One of the trials involved an intervention arm with placebo, so we assumed this trial was designed to blind the investigators and participants.[36] The other trial not describing blinding was assumed to be open labelled.[44]

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.[9] 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.[21-27;32-35;39]

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.[21-27] All-cause mortality was not significantly influenced by the interventions (relative risk 0.98, 95% confidence interval 0.61 to 1.58; 8 trials, 3768

participants; I^2=0%, P=0.68; fig 2). Trial sequential analysis showed that only 2.3% of the diversity-adjusted required information size was accrued to detect or reject a 10% relative risk reduction.

Sensitivity analysis excluding the trial with the longest duration[21-27] 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 sulphonylurea was not significantly increased compared with metformin (relative risk 1.47, 95% confidence interval 0.54 to 4.01; 8 trials, 3768 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.[21-27] Trial sequential analysis showed that only 2.7% of the diversity-adjusted required information size to detect or reject a 10% relative risk reduction was accrued.

Sensitivity analysis excluding the trial with the longest duration[21-27] as well as 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 the Hermann et al. trial defined their outcome in a manner, which may have included cardiac outcomes of a non-atherosclerotic origin.[21-27;32-35] Tosi et al. reported that no cardiovascular events were observed during the trial.[39] Yamnouchi et al. reported no adverse cardiac events.[44] 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 sulphonylureas (relative risk 0.67, 95% confidence interval 0.48 to 0.93; P=0.02; 4 trials, 3094 participants; I^2=0%, P=0.53; fig 2). Trial sequential analysis showed that only 5% of the diversity-adjusted

required information size to detect or reject a 10% relative risk reduction was accrued and the trial sequential monitoring boundary for benefit was not crossed, meaning that firm evidence could not be established (fig 3).

Thirty-nine non-fatal myocardial infarctions were reported, of which 36 originated from the ADOPT trial.[21–27] 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). For the remaining 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.

Hypoglycemia

Mild hypoglycemia was significantly increased with sulfonylurea (relative risk 2.95, 95% confidence interval 2.14 to 4.07; P<0.00001; 6 trials, 4075 participants; I^2 =30%, P=0.22; fig 3). Trial sequential analysis showed that only 2.8% of the diversity-adjusted required information size to detect or reject a 10% relative risk increase was accrued (Web appendix 5). Due to the reporting in the trials, meta-analysis of moderate hypoglycemia could not be performed. Severe hypoglycemia showed significance for a lower risk with metformin (relative risk 5.64, 95%

confidence interval 1.22 to 25.99; P=0.03; 5 trials, 3656 participants; I^2=0%, P=0.62; fig 3). Trial sequential analysis showed that 0.1% of the diversity-adjusted required information size to detect or reject a 10% relative risk increase was accrued. Unfortunately, the UKPDS 34 publication did not report the number of participants with hypoglycemia in each of the intervention arms at the end of follow-up.[2;40;41] The data are therefore taken after one year of follow-up. Reporting of hypoglycemia in trials is listed in web appendix 6.

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; 5 trials, 3118 participants; I^2=0%, P=0.76; fig 3). The effect-estimate of serious adverse events did not show any significance (relative risk 0.94, 95% confidence interval 0.82 to 1.07; 5 trials, 3175 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.[21-27] Drop-outs due to adverse events were not significantly influenced by the interventions, but showed a tendency of favouring metformin (relative risk 1.18, 95% confidence interval 0.98 to 1.41; 8 trials, 3731 participants; I^2=0%, P=0.50; fig 3). Reporting of adverse events in trials is listed in web appendix 6.

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).[21-27] 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 1.00, 95% confidence interval 0.66 to 1.53; 9 trials, 4238 participants; fig 3), but showed significance in the fixed-effect model favouring metformin (relative risk 1.34, 95% confidence interval 1.16 to 1.55; P < 0.0001; I^2=59%, P=0.02).

Glycemic control

The change in HbA1c from baseline was not significantly different comparing sulphonylurea versus metformin in random-effects model (mean difference 0.06%, 95% confidence interval −0.16 to 0.29; 13 trials, 3632 participants; fig 4), but showed statistical significance in favour of metformin in the fixed-effect model (mean difference 0.20%, 95% confidence interval 0.13 to 0.28; P<0.00001; I^2=75%, P<0.00001). The change in fasting blood glucose from baseline did not show any statistical significance in the random-effects model (mean difference 0.22 mmol/L, 95% confidence interval −0.08 to 0.52; 14 trials, 4172 participants; I^2=62%, P=0.001; fig 4), but statistical significance favouring metformin was present in the fixed-effect model (mean difference 0.30 mmol/L, 95% confidence interval 0.18 to 0.43).

Weight

The change in weight from baseline was significantly changed in favour of metformin compared with sulphonylurea (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 (Web appendix 5). Change in body mass index from baseline did not show statistical significance (mean difference 0.13 kg/m^2, 95% confidence interval −0.69 to 0.94; 5 trials, 322 participants; I^2=51%, P=0.08; fig 4). However, only two 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.[39;43] For the remaining trials the end of follow-up values were used.[29;37;44] All 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 all of these trials.[29;37;44]

Discussion

Based on our published protocol, we identified and meta-analysed eleven randomized clinical trials comparing the effects of sulphonylurea versus metformin monotherapy in patients with type 2 diabetes.[10] No significant differences were found between sulphonylurea versus metformin monotherapy on all-cause or cardiovascular mortality, but data were sparse. In contrast, a potential benefit of sulphonylurea over metformin was observed in relation to for non-fatal macrovascular outcomes. This potential

benefit should however be interpreted with caution as the definitions of the composite cardiovascular outcome for the two trials contributing with data to this meta-analysis rendered it impossible to identify, exclusively, the number of events with atherosclerotic origin.[21-27;32-35] However, we cannot rule out the clinical relevance of the events reported in the trials – being of atherosclerotic origin or not – advocating for inclusion of all reported events in the present meta-analysis. Moreover, 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.[21-27;32-35;39] Meta-analyses of patient-important outcomes were based on very sparse data and did, except for non-fatal macrovascular outcomes and severe hypoglycemia, not show any significance of the effect estimates.

Metformin monotherapy seems to be associated with lower risk of hypoglycemia and less pronounced weight gain compared with sulphonylurea. However, only the changes in weight could be confirmed in the trial sequential analysis and thus constitutes the only firm evidence obtained from randomized clinical trials disregarding the risk of bias to support the choice of metformin over a sulphonylurea as monotherapy. The change in BMI from baseline did not show statistical significance for the comparison of sulphonylurea versus metformin, although we expected the latter to be of most benefit in this regard. The reason for lack of

statistical significance is probably due to the way of reporting and the few number of trials contributing with data.[29;37;39;43;44]

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 randomized trials.[10] 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[45-47] and by using trial sequential analyses to control the risks of random errors.[15;17;48;49]

The weaknesses of our analyses and conclusions mirror the weaknesses of the included trials. Most importantly, all of the included trials were judged as high risk of bias in one or more bias domains. Only three of the included trials were classified as having lower risk of bias according to randomization, allocation, and blinding. 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 versus other antidiabetic interventions.[50] However, this Cochrane review only included six randomized trials with a duration of the intervention of 24 weeks or more comparing second-generation or third-generation sulphonylurea versus metformin monotherapy.[2;28-30;32-35;38;40] 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) as they compared metformin with any comparator and therefore applied the combined group of insulin and sulphonylurea reported by the UKPDS. However, like our review, not for metformin versus sulphonylurea.[50] 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.[50] A combined analysis of UKPDS and non-UKPDS trials was not made. Despite this, the conclusion from that Cochrane review was that metformin might be beneficial regarding cardiovascular outcomes in overweight/obese patients

with type 2 diabetes.[50] For the comparison of sulphonylurea versus metformin, we found statistical significant lower risk of mild as well as severe hypoglycemia in favour of metformin, but no statistical significant change in terms of fasting blood glucose and HbA1c in random-effects model. The Cochrane review of metformin monotherapy found less hypoglycemia with metformin compared with sulphonylurea and improved glycemic control in terms of fasting blood glucose and HbA1c.[50] However, we did only find statistical significance for a lower fasting blood glucose and HbA1c in favour of metformin in the fixed-effect model. This questions this finding.

Several observational studies have indicated an increased risk of mortality and cardiovascular disease with sulphonylurea compared to metformin monotherapy.[3-5] Our data, based on randomized clinical trials, did not find increased mortality with sulphonylurea 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 randomized clinical trials are needed. An observational study has indicated that sulphonylureas may be associated with different risks of macrovascular disease with gliclazide, putatively, exhibiting greatest beneficial outcome profile.[4] In the current analysis, we were unable to differentiate effects between different types of 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 randomized to either sulphonylurea versus metformin monotherapy.[40] However, to our knowledge, these data have never been reported separately. Instead, the participants randomized to sulphonylurea and insulin are reported together, which preclude direct comparison of sulphonylurea versus metformin.[2;40] The largest trial, reporting patient-important outcomes for sulphonylurea monotherapy compared with metformin, is the ADOPT trial.[21-27] This trial showed statistically 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.[24]

In our Cochrane review we also compared first-generation sulphonylurea versus metformin.[11] However, no meta-analyses could

be performed versus metformin for any of the patient-important outcomes due to lack of data.[11]

A recent randomized 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 after around 3 years.[51] 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 in our systematic review. Implementing the patient-important data from Hong et al. into our meta-analysis did not change the significance of the effect estimates for the primary outcomes or for non-fatal myocardial infarction, although 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 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 randomized trials with low risk of bias, and, in particular, in broader populations, to clarify the benefits and harms of sulphonylurea versus metformin 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;52;53] 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 sulphonylurea versus 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, have all together made sulphonylurea as monotherapy less used.[2;40;54] Sulphonylurea is now largely prescribed as a part of a combination regime.[54] The use of sulphonylurea has to a large extent been replaced with the novel, and with respect to hard outcome variables, as yet, unproven but more expensive dipeptidyl peptidase IV-inhibitors.[54] 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 randomized long-term trials assessing patient-important outcomes.

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 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 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 systematic review in The Cochrane Database of Systematic Reviews 2013, Issue 4. 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

SSL, AV, and TA have equity in Novo Nordisk A/S. SSL and AV received fees from Novo Nordisk A/S for speaking. TA was employed at Steno Diabetes Centre, Gentofte, Denmark during development of the protocol and the review. Steno Diabetes Centre is owned by Novo Nordisk A/S. SSL and AV were employed at Steno Diabetes Centre 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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Data sharing

No additional data available.

Table 1. Characteristics of the included trials

Trial	Location	Design	No of participants sulphonylurea/metformin (total) participants	Duration of intervention
ADOPT, 2006[21–27]	North America, Europe, and Canada	Parallel Blinding investigators and participants	1447/1455 (2902)	4 years
Campbell et al., 1994[28]	United Kingdom	Parallel Open label	24/24 (48)	1 year
Collier et al 1989[29]	NR	Parallel Open label	12/12 (24)	6 months
DeFronzo et al., 1995[30]	United States of America	Parallel Blinding investigators and participants	209/210 (419)	29 weeks
Derosa et al., 2004[43]	Italy	Parallel Open label	81/83 (164)	12 months (+ 8 weeks titration period)
Hermann et al., 1991[31#]	Sweden	Cross over Open label	10/12 (25)	6 months
Hermann et al., 1991a[32–35]	Sweden	Parallel Blinding investigators and participants	34/38 (72)	6 months+ 2–12 weeks
Kamel et al., 1997[36]*****	Turkey	Parallel Blinding investigators and participants	17/6 (23)	24 weeks
Lawrence et al., 2004[37]	United Kingdom	Parallel Open label	22/21 (43)	24 weeks
Tang et al., 2004[42]	China	Parallel Open label	33/29 (62)	6 months
Tessier et al., 1999[38%]	Canada	Parallel Open label	19/20 (39)	24 weeks
Tosi et al., 2003[39]	Italy	Cross over Blinding investigators and participants	22/22 (44)	6 months

UKPDS 34, 1998[2;40;41]	United Kingdom	Parallel Open label	277/342 (619)	10.7 years
Yamanouchi et al., 2005[44]	Japan	Parallel NR, we assume open label	37/39 (76)	12 months

ADOPT=A Diabetes Outcome Progression Trial; NR=not reported; UKPDS=United Kingdom Prospective Diabetes Study
[#]Number of participants randomized 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[21-27]	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[28]	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[29]	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[30]	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	Escape medicine not allowed, participants excluded	Combination of metformin plus glibenclamide

		adding a 500 mg tablet to be taken at lunch. After three 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 four weeks the daily dose was increased to 2500 mg by adding a second 500 mg tablet to the breakfast dose. Glibenclamide placebo		
Derosa et al., 2004[43]	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)	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)	Escape medicine allowed	
Hermann et al., 1991[31]	Glibenclamide, po., 1.75-10.5 mg daily	Metformin, po., 0.5-3 gram	NR	
Hermann et al., 1991a[32-35]	Glibenclamide, po., initial 3.5 mg. Up to 14.0 mg. Tablets given shortly before breakfast and if daily dosis	Metformin, po., initial 1 gram. 1.0-3.0 gram in two doses a day - shortly before breakfast and evening meal.	Escape medicine allowed	Combination of metformin plus glibenclamide

	exceeded 7 mg then divided between breakfast and evening meal Placebo metformin	Placebo glibenclamide		
Kamel et al., 1997[36]	Gliclazide and Glibenclamide	Metformin	NR	Acarbose and placebo
Lawrence et al., 2004[37]	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
Tang et al., 2004[42]	Glimepiride, po., 1 to 2 mg/day	Metformin, po., 750 to 1500 mg/day	NR	
Tessier et al., 1999[38]	Gliclazide, po., titrated to glycemic 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 glycemic target. Metformin dosage was 750, 1500 and 2250 mg (divided into three doses) one with each meal	NR	
Tosi et al., 2003[39]	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	Metformin, po., starting dose was 1 tablet before lunch, consisting of metformin 500 mg. The subsequent steps were 1 tablet twice daily	Escape medicine not allowed, participants excluded	Combination of metformin plus glibenclamide

	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	(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		
UKPDS 34, 1998[2;40;41]	Glibenclamide, po., 2.5–20 mg	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 or nausea occurred, patients reduced the dose to that which previously did not cause symptoms	Escape medicine allowed	Chlorpropamide and insulin

Yamanouchi et al., 2005[44]	Glimepiride, po., 1.0 to 2.0 mg/day	Metformin, po., tablet a 250 mg, 750 mg/day	Escape medicine allowed	Pioglitazone

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[21–27#]	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[28]	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[29]	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[30¤]	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)
Derosa et al., 2004[43]	NR, but all participants had to be diagnosed within 6 months from entry to the trial	54 (10)/ 56 (9)	8.5 (1.2)/ 8.4 (1)	27.6 (1.2)/ 28.1 (1.5)
Hermann et al., 1991[31&]	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[32–35?]	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[36]	NR	NR	Gliclazide: 8.4 (1.1); glibenclamide: 8.4 (1.1); metformin: 8.4 (0.5)	NR
Lawrence et al., 2004[37!]	NR	63.5 (11.4)/ 59.5	7.9 (0.9)/ 8.0 (0.9)	28.7 (28.3–34.4)/

		(9.3)		29.2 (28.1–31.6)
Tang et al., 2004[42]	NR	56.4 (8.8)/ 53.8 (9.7)	6.8 (1.6)/ 7.2 (1.4)	23.3 (1.7)/ 24.6 (2.2)
Tessier et al., 1999[38%]	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[39]	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;40;41]	All newly diagnosed	53 (9)/ 53 (8)	7.2 (1.5)/ 7.3 (1.5)	31.5 (4.4)/ 31.6 (4.2)
Yamanouchi et al., 2005[44]	3.3 (2.6)/ 3.0 (2.5)	55.6 (9.3)/ 54.7 (9.8)	9.8 (0.7)/ 9.9 (0.7)	25.6 (3.5)/ 26.2 (3.8)

ADOPT=A Diabetes Outcome Progression Trial; NR=not reported; 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[21-27]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate
Campbell et al., 1994[28]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear
Collier et al., 1989[29]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
DeFronzo et al., 1995[30]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Inadequate
Derosa et al., 2004[43]	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear
Hermann et al., 1991[31]	Adequate	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Inadequate
Hermann et al., 1991a[32-35]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Inadequate
Kamel et al., 1997[36]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear
Lawrence et al., 2004[37]	Unclear	Unclear	Inadequate	Adequate	Adequate	Unclear	Adequate	Inadequate
Tang et al., 2004[42]	Unclear	Unclear	Inadequate	Inadequate	Unclear	Unclear	Adequate	Adequate
Tessier et	Unclear	Unclear	Inadequate	Inadequate	Adequate	Unclear	Adequate	Inadequate

al., 1999[38]								
Tosi et al., 2003[39]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate	Inadequate
UKPDS 34, 1998[2;40;41]	Adequate	Adequate	Inadequate	Adequate	Unclear	Inadequate	Adequate	Inadequate
Yamanouchi et al., 2005[44]	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unclear	Adequate	Unclear

ADOPT=A Diabetes Outcome Progression Trial; UKPDS=United Kingdom Prospective Diabetes Study

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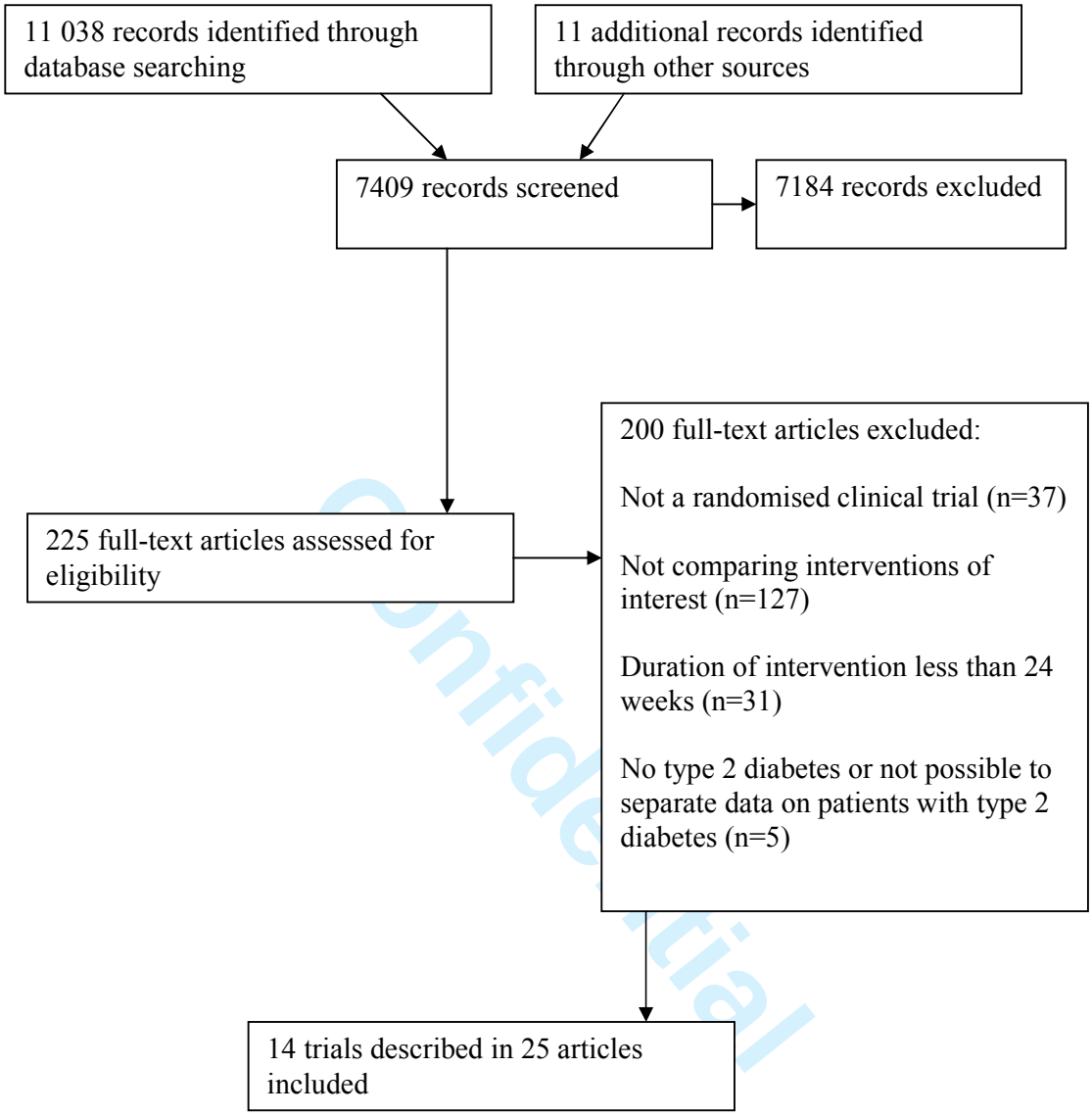


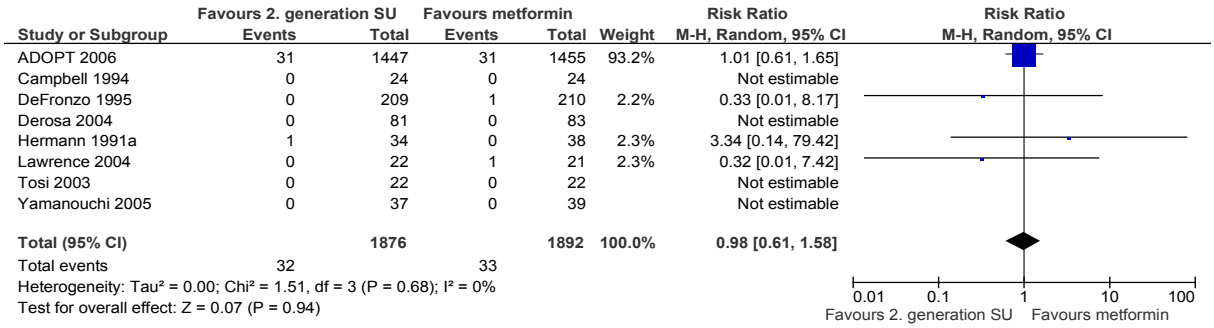


Fig 2a. Forest plot for all-cause mortality

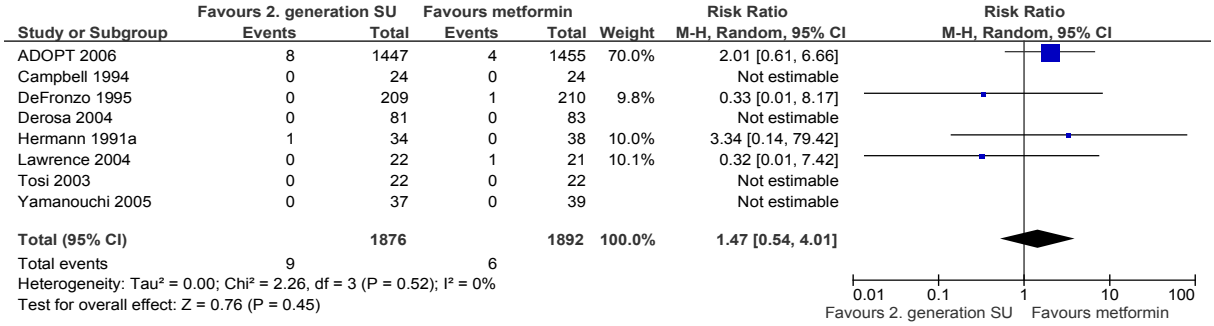


Fig 2b. Forest plot for cardiovascular mortality

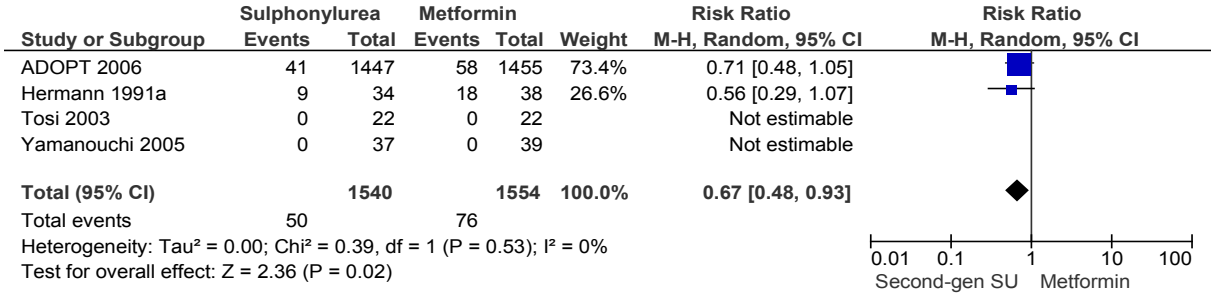
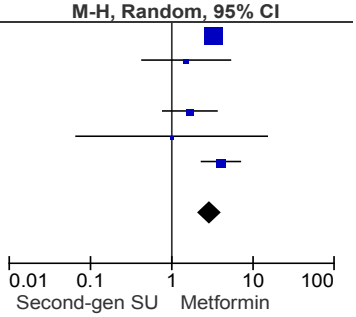


Fig 2c. Forest plot for non-fatal macrovascular outcomes

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	549	1447	167	1455	56.2%	3.31 [2.82, 3.87]
DeFronzo 1995	6	209	4	210	6.0%	1.51 [0.43, 5.26]
Derosa 2004	0	81	0	83		Not estimable
Hermann 1991a	12	34	8	38	13.9%	1.68 [0.78, 3.61]
Tosi 2003	1	22	1	22	1.4%	1.00 [0.07, 15.00]
UKPDS 34 1998 (1)	49	212	15	262	22.5%	4.04 [2.33, 6.99]
Total (95% CI)		**2005**		**2070**	**100.0%**	**2.95 [2.14, 4.07]**
Total events	617		195			

Heterogeneity: Tau² = 0.04; Chi² = 5.69, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 6.59 (P < 0.00001)

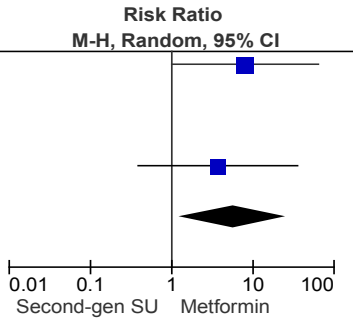


(1) Data after one year of follow-up

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]
Derosa 2004	0	81	0	83		Not estimable
Hermann 1991a	0	34	0	38		Not estimable
Tosi 2003	0	22	0	22		Not estimable
UKPDS 34 1998 (1)	3	212	1	262	45.9%	3.71 [0.39, 35.38]
Total (95% CI)		**1796**		**1860**	**100.0%**	**5.64 [1.22, 25.99]**
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)



(1) Data after one year of follow-up

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]
Yamanouchi 2005	1	37	0	39	0.0%	3.16 [0.13, 75.16]
Total (95% CI)		**1552**		**1566**	**100.0%**	**0.99 [0.97, 1.01]**
Total events	1353		1380			

Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 4 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)

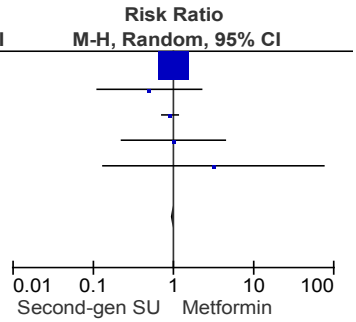


Fig 3c. Forest plot for adverse events

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]
Derosa 2004	0	81	0	83		Not estimable
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)		**1582**		**1593**	**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)

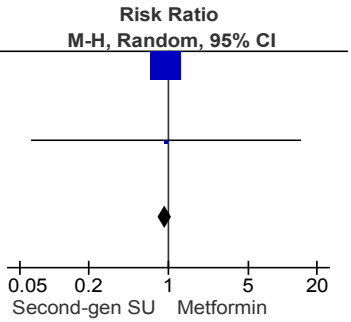


Fig 3d. Forest plot for serious adverse events

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	215	1447	178	1455	94.0%	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]
Derosa 2004	0	81	2	83	0.4%	0.20 [0.01, 4.20]
Hermann 1991a	3	34	9	38	2.1%	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)		**1858**		**1873**	**100.0%**	**1.18 [0.98, 1.41]**
Total events	227		196			

Heterogeneity: Tau² = 0.00; Chi² = 5.39, df = 6 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)

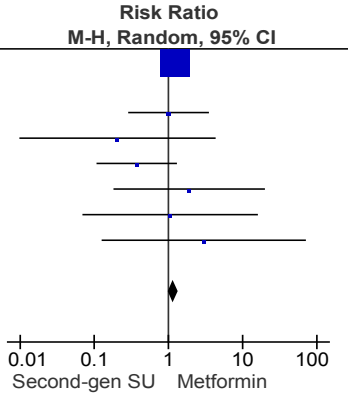
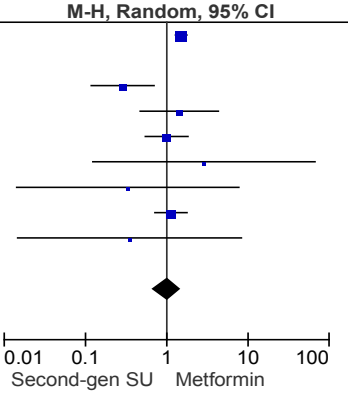


Fig 3e. Forest plot for drop-outs due to adverse events

Study or Subgroup	Sulphonylurea Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT 2006	311	1447	207	1455	29.9%	1.51 [1.29, 1.77]
Campbell 1994	0	24	0	24		Not estimable
DeFronzo 1995	6	209	21	210	13.1%	0.29 [0.12, 0.70]
Derosa 2004	7	81	5	83	9.9%	1.43 [0.47, 4.34]
Hermann 1991a	13	34	13	34	19.0%	1.00 [0.55, 1.83]
Lawrence 2004	1	22	0	21	1.7%	2.87 [0.12, 66.75]
Tosi 2003	0	22	1	22	1.7%	0.33 [0.01, 7.76]
UKPDS 34 1998 (1)	32	277	35	342	23.0%	1.13 [0.72, 1.77]
Yamanouchi 2005	0	37	1	39	1.7%	0.35 [0.01, 8.35]
Total (95% CI)		**2153**		**2230**	**100.0%**	**1.00 [0.66, 1.53]**
Total events	370		283			

Heterogeneity: Tau² = 0.15; Chi² = 16.87, df = 7 (P = 0.02); I² = 59%
Test for overall effect: Z = 0.02 (P = 0.98)

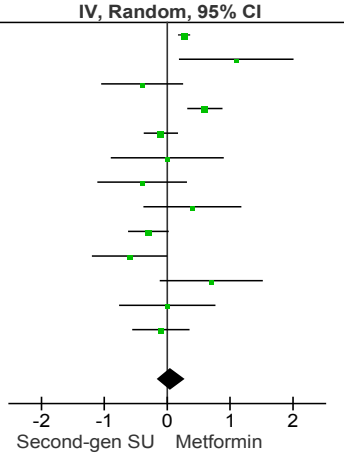


(1) Data after three years of follow-up

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	13.5%	0.27 [0.19, 0.35]
Campbell 1994	9.7	1.9	24	8.6	1.2	24	4.3%	1.10 [0.20, 2.00]
Collier 1989	7	0.8	12	7.4	0.8	12	6.5%	-0.40 [-1.04, 0.24]
DeFronzo 1995	0.2	1.4	209	-0.4	1.4	210	11.5%	0.60 [0.33, 0.87]
Derosa 2004	6.9	0.7	73	7	0.9	75	11.6%	-0.10 [-0.36, 0.16]
Hermann 1991	7.9	0.8	10	7.9	1.3	12	4.3%	0.00 [-0.89, 0.89]
Hermann 1991a	-1.3	1.1	19	-0.9	1.1	19	5.9%	-0.40 [-1.10, 0.30]
Kamel 1997 (1)	7.3	1.1	17	6.9	0.7	6	5.3%	0.40 [-0.37, 1.17]
Lawrence 2004	6.6	0.5	20	6.9	0.5	20	10.9%	-0.30 [-0.61, 0.01]
Tang 2004	6.1	1	33	6.7	1.3	29	7.1%	-0.60 [-1.18, -0.02]
Tessier 1999	6.8	1.6	18	6.1	0.7	18	4.9%	0.70 [-0.11, 1.51]
Tosi 2003	-0.5	1.3	20	-0.5	1.1	19	5.4%	0.00 [-0.75, 0.75]
Yamanouchi 2005	7.7	0.9	34	7.8	1	37	8.9%	-0.10 [-0.54, 0.34]
Total (95% CI)			**1799**			**1833**	**100.0%**	**0.06 [-0.16, 0.29]**

Heterogeneity: Tau² = 0.09; Chi² = 47.62, df = 12 (P < 0.00001); I² = 75%
Test for overall effect: Z = 0.55 (P = 0.58)

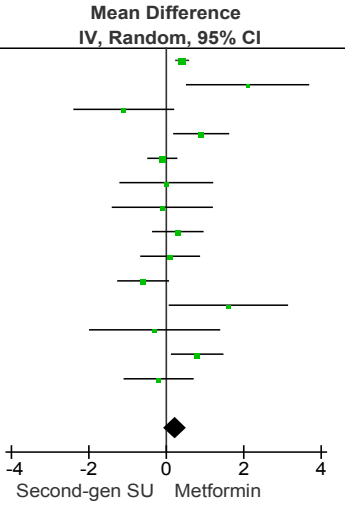


(1) Not described in abstract if the values are standard deviations or standard errors

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	15.0%	0.41 [0.25, 0.57]
Campbell 1994 (1)	9.2	3.7	24	7.1	1.3	24	3.0%	2.10 [0.53, 3.67]
Collier 1989	6.4	1.5	12	7.5	1.7	12	4.1%	-1.10 [-2.38, 0.18]
DeFronzo 1995	0.8	2.9	209	-0.1	4.3	210	8.5%	0.90 [0.20, 1.60]
Derosa 2004	6.8	1.4	73	6.9	0.8	75	12.7%	-0.10 [-0.47, 0.27]
Hermann 1991	7.2	1	10	7.2	1.8	12	4.6%	0.00 [-1.19, 1.19]
Hermann 1991a	-2.1	2.3	19	-2	1.7	19	4.1%	-0.10 [-1.39, 1.19]
Kamel 1997 (2)	8.1	0.9	17	7.8	0.6	6	9.2%	0.30 [-0.34, 0.94]
Lawrence 2004	7.4	1.4	20	7.3	1	20	8.0%	0.10 [-0.65, 0.85]
Tang 2004	6.3	1.4	33	6.9	1.2	29	9.1%	-0.60 [-1.25, 0.05]
Tessier 1999	8	3.1	18	6.4	1.1	18	3.2%	1.60 [0.08, 3.12]
Tosi 2003	-3.1	2.4	20	-2.8	2.9	19	2.7%	-0.30 [-1.98, 1.38]
UKPDS 34 1998 (3)	8.5	4.5	212	7.7	2.1	262	9.0%	0.80 [0.14, 1.46]
Yamanouchi 2005	8.8	1.8	34	9	2	37	6.7%	-0.20 [-1.08, 0.68]
Total (95% CI)			**2035**			**2137**	**100.0%**	**0.22 [-0.08, 0.52]**

Heterogeneity: Tau² = 0.15; Chi² = 33.80, df = 13 (P = 0.001); I² = 62%
Test for overall effect: Z = 1.43 (P = 0.15)



(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
ADOPT 2006	1.6	11.6	1441	-2.9	10.7	1454	27.9%	4.50 [3.69, 5.31]
Campbell 1994	2.6	3.9	24	-2	2.9	24	10.1%	4.60 [2.66, 6.54]
DeFronzo 1995	-0.3	2.9	209	-3.8	2.9	210	35.0%	3.50 [2.94, 4.06]
Hermann 1991	73.2	9.8	10	76.5	7.3	12	0.9%	-3.30 [-10.65, 4.05]
Hermann 1991a	2.8	3.1	19	-0.8	2.2	19	12.2%	3.60 [1.89, 5.31]
Tessier 1999	81.5	17.2	18	82.3	11.6	18	0.5%	-0.80 [-10.38, 8.78]
Tosi 2003	0.8	2.7	20	-2.3	2.4	19	13.4%	3.10 [1.50, 4.70]
Total (95% CI)			**1741**			**1756**	**100.0%**	**3.77 [3.06, 4.47]**

Heterogeneity: Tau² = 0.29; Chi² = 9.84, df = 6 (P = 0.13); I² = 39%
Test for overall effect: Z = 10.53 (P < 0.00001)

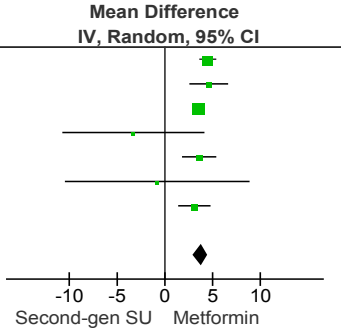


Fig 4c. Forest plot for change in weight from baseline

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	22.5%	-0.90 [-2.10, 0.30]
Derosa 2004	-0.7	3.4	73	-0.6	3.5	75	24.2%	-0.10 [-1.21, 1.01]
Lawrence 2004	30.6	8.8	20	28.6	3.5	20	3.6%	2.00 [-2.15, 6.15]
Tosi 2003	0.3	0.9	20	-0.5	0.8	19	37.0%	0.80 [0.27, 1.33]
Yamanouchi 2005	25.4	4	34	25.5	4.3	37	12.7%	-0.10 [-2.03, 1.83]
Total (95% CI)			**159**			**163**	**100.0%**	**0.13 [-0.69, 0.94]**

Heterogeneity: Tau² = 0.39; Chi² = 8.25, df = 4 (P = 0.08); I² = 51%
Test for overall effect: Z = 0.31 (P = 0.76)

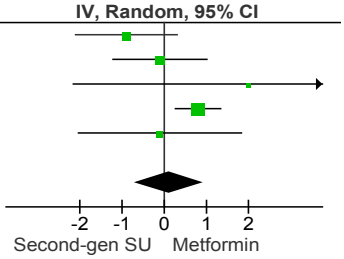


Fig 4d. Forest plot for change in body mass index from baseline

Web 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

Web 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 is generated by a computer or random number table or similar
- Uncertain risk of bias, if the trial is described as randomized, 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-randomized). 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 randomized, 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-randomized. 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-randomization 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

Web appendix 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 randomized clinical trial
Ahuja et al 1973[4]	Not a randomized clinical trial
Akanuma et al 1988[5]	Not comparing interventions of interest
Almer 1984[6]	Not a randomized clinical trial
Alvarsson et al 2010[7-9]	Not comparing intervention of interest*
Aman et al 1977[10]	Not a randomized 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 randomized clinical trial
Balabolkin et al 1988[16]	Not a randomized 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 randomized clinical trial
Ben et al 1988[21]	Not a randomized clinical trial
Berber et al 1982[22]	Duration of intervention less than 24 weeks
Bernas et al 1992[23]	Not a randomized clinical trial
Berry et al 1981[24]	Not a randomized 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 randomized clinical trial
Bruns et al 1990[30]	Duration of intervention less than 24 weeks
Calvagno et al 1983[31]	Not a randomized clinical trial
Cefalu et al 1998[32]	Duration of intervention less than 24 weeks
Ceriello et al 2005[33]	Not a randomized clinical trial
Chan et al 1982[34]	Not comparing intervention of interest
Chandra et al 2008[35]	Not a randomized clinical trial. Authors asked and replied.
Charbonnel et al 2005[36;37]	Not comparing intervention of interest*
Chen et al 1987[38]	Not a randomized clinical trial
Coniff et al 1983[39]	Not comparing intervention of interest*
Cortinovis et al1998[40]	Not a randomized 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 2010[44]	Not comparing intervention of interest
Diehl et al 1985[45]	Not comparing intervention of interest*
Dills et al 1996[46]	Not comparing intervention of interest

Dowey et al 1979[47]	Not a randomized clinical trial
Drouin et al 2000[48]	Not comparing intervention of interest
Drouin et al 2004[49]	Not comparing intervention of interest
Duprey et al 1971[50]	Not a randomized clinical trial
Ebeling et al 2001[51]	Not comparing intervention of interest*
Engelhardt 1965[52]	Includes also participants with normal glucose tolerance
Esposito et al 2004[53]	Not comparing intervention of interest*
Feinböck et al 2003[54]	Not comparing intervention of interest*
Ferner et al 1991[55]	Not a randomized clinical trial
Fineberg et al 1980[56]	Not comparing intervention of interest*
Foley et al 2009[57;58]	Not comparing intervention of interest*
Forst et al 2003[59]	Not comparing intervention of interest*
Forst et al 2005[60;61]	Not comparing intervention of interest*
Forst et al 2011[62]	Not a randomized clinical trial
Fuchs 1973[63]	Duration of intervention less than 24 weeks in publication. Not comparing intervention of interest*
Garber et al 2002[64;65]	Duration of intervention less than 24 weeks
Garber 2003[66]	Duration of intervention less than 24 weeks
Gargiolo et al 2001[67]	Not a randomized clinical trial
Giles et al 2008[68]	Not comparing intervention of interest
Giles et al 2010[69]	Not comparing intervention of interest
Goldberg et al 1996[70]	Duration of intervention less than 24 weeks
Groop et al 1989[71]	Not comparing intervention of interest
Gudat et al 1998[72]	Not a randomized clinical trial
Gurling 1970[73]	Not a randomized clinical trial
Happ et al 1974[74]	Duration of intervention less than 24 weeks
Hanefeld 2007[75-77]	Not comparing intervention of interest*
Harrower 1985[78]	Not comparing intervention of interest*
Haupt et al 1974[79]	Not a randomized clinical trial
Hoffmann 1990[80;81]	Not comparing intervention of interest*
Hoffmann et al 1994[82]	Not comparing intervention of interest*
Hollander et al 1992[83]	Not comparing intervention of interest*
Hollander et al 2001[84]	Duration of intervention less than 24 weeks
Howes 2000[85]	Not a randomized clinical trial
Hristov et al 2002[86]	Not a randomized clinical trial
Hussain 2007[87]	Not comparing intervention of interest
Inukai et al 2005[88]	Not comparing intervention of interest
Irsigler et al 1979[89]	Duration of intervention less than 24 weeks
Ishizuka et al 1994[90]	Not a randomized clinical trial
Jackson et al 1969[91]	Not a randomized clinical trial
Jain et al 2006[92]	Not comparing intervention of interest*
Jerums et al 1987[93]	Not comparing intervention of interest
Jibran et al 2006[94]	Not comparing intervention of interest*
Johnston et al 1970[95]	Duration of intervention less than 24 weeks
Johnston et al 1997[96]	Not comparing intervention of interest*

Josephkutty et al 1990[97]	Duration of intervention less than 24 weeks
Joshi et al 2002[98]	Duration of intervention less than 24 weeks
Kakhnovskii et al 1993[99]	Not a randomized clinical trial
Kaku et al 2011[100-103]	Not comparing intervention of interest*
Kanda 1998[104]	Not comparing intervention of interest*
Kanoun et al 1996[105]	Not a randomized clinical trial
Kovacevic et al 1997[106]	Not comparing intervention of interest*
Langenfeld et al 2005[107]	Not comparing intervention of interest
Lecomte et al 1977[108]	Duration of intervention less than 24 weeks
Levy et al 1995[109]	Duration of intervention less than 24 weeks
Li et al 2009[110]	Not comparing intervention of interest
Lim et al1970[111]	Duration of intervention less than 24 weeks
Lindbjerg et al 1976[112]	Duration of intervention less than 24 weeks
Liu et al 1985[113]	Duration of intervention less than 24 weeks
Lomuscio et al 1994[114]	Not a randomized clinical trial
Madsbad et al 2001[115]	Not comparing intervention of interest*
Mafauzy 2002[116]	Duration of intervention less than 24 weeks
Marbury et al 1999[117]	Not comparing intervention of interest*
Mazzone et al 2006[118]	Not comparing intervention of interest
Memisogullari et al 2009[119]	Not comparing intervention of interest*
Meneilly 2011[120]	Duration of intervention less than 24 weeks
Mogensen et al 1976[121]	Not comparing intervention of interest
Nakamura et al 2000[122]	Duration of intervention less than 24 weeks
Nakamura et al 2004[123]	Not comparing intervention of interest*
Nakamura et al 2006[124]	Not comparing intervention of interest*
Nathan et al 1988[125]	Not comparing intervention of interest*
Nikkilä et al 1982[126]	Not comparing intervention of interest
Nissen et al 2008[127]	Not comparing intervention of interest
Noury et al 1991[128]	Duration of intervention less than 24 weeks
Omrani et al 2005[129]	Assume not a randomized clinical trial
Osei et al 2003[130]	Not including participants with type 2 diabetes
Papa et al 2006[131]	Duration of intervention less than 24 weeks
Pagano et al 1995[132-134]	Not comparing intervention of interest*
Perez et al 2006[135]	Not comparing intervention of interest
Perriello et al 2007[136;137]	Not comparing intervention of interest*
Quatraro et al 1990[138]	Not comparing intervention of interest
Rao et al 2010[139]	Not comparing intervention of interest
Repaglinide studies[140-142]	Not comparing intervention of interest*
Rosenstock et al 1993[143]	Not comparing intervention of interest
Rosenthal et al 2002[144-146]	Not comparing intervention of interest*
Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial[147]	Not comparing intervention of interest
Rupprecht et al 1993[148]	Not a randomized clinical trial
Saadatnia et al 2009[149]	Not a randomized clinical trial
Salman et al 2001[150]	Not comparing intervention of interest*
Sami et al 1996[151]	Not comparing intervention of interest

Sasahara et al 1999[152]	Not a randomized clinical trial
Schernthaner et al 2004[153]	Not comparing intervention of interest
Seck et al 2010[154]	Not comparing intervention of interest
Segal et al 1997[155]	Not comparing intervention of interest*
Shihara et al 2011[156;157]	Not comparing intervention of interest*
Shinoda et al 2009[158]	We assume not a randomized clinical trial. Attempt made to contact authors.
Speiser et al 1989[159]	Duration of intervention less than 24 weeks
Spengler et al 1992[160-164]	Not comparing intervention of interest*
Sung et al 1999[165]	Not comparing intervention of interest*
Sutton et al 2002[166;167]	Not comparing intervention of interest*
Tan et al 2004[168]	Not comparing intervention of interest*
Tan et al 2004a[169]	Not comparing intervention of interest*
Tan et al 2005[170]	Not comparing intervention of interest*
Teramoto et al 2007[171]	Not comparing intervention of interest*
The Liraglutide Effect and Action in Diabetes-3 (LEAD-3)[172-177]	Not comparing intervention of interest*
Tolman et al 2009[178]	Not comparing intervention of interest
Tovi et al 1998[179]	Not comparing intervention of interest
Toyota et al 1997[180]	Duration of intervention less than 24 weeks
Tsumara 1995[181]	Not comparing intervention of interest
Umpierrez et al 1997[182]	Not exclusively include patients with type 2 diabetes
University Group Diabetes Program[183-185]	Not comparing intervention of interest*
United Kingdom Diabetes Study 1998[186-190]	Not comparing intervention of interest*
Van de Laar et al 2004[191]	Not comparing intervention of interest*
Vray et al 1995[192]	Duration of intervention less than 24 weeks
Wang et al 1994[193]	Duration of intervention less than 24 weeks
Watanabe et al 2005[194]	Not comparing intervention of interest*
Wolffenbuttel et al 1989[195]	Not comparing intervention of interest*
Wolffenbuttel et al 1999[196]	Not comparing intervention of interest*
Wu et al 2010[197]	Duration of intervention less than 24 weeks
Yang et al 2009[198]	Not including participants with type 2 diabetes
Zhang et al 2005[199]	Not comparing intervention of interest*
Zhou 1999[200]	Duration of intervention less than 24 weeks

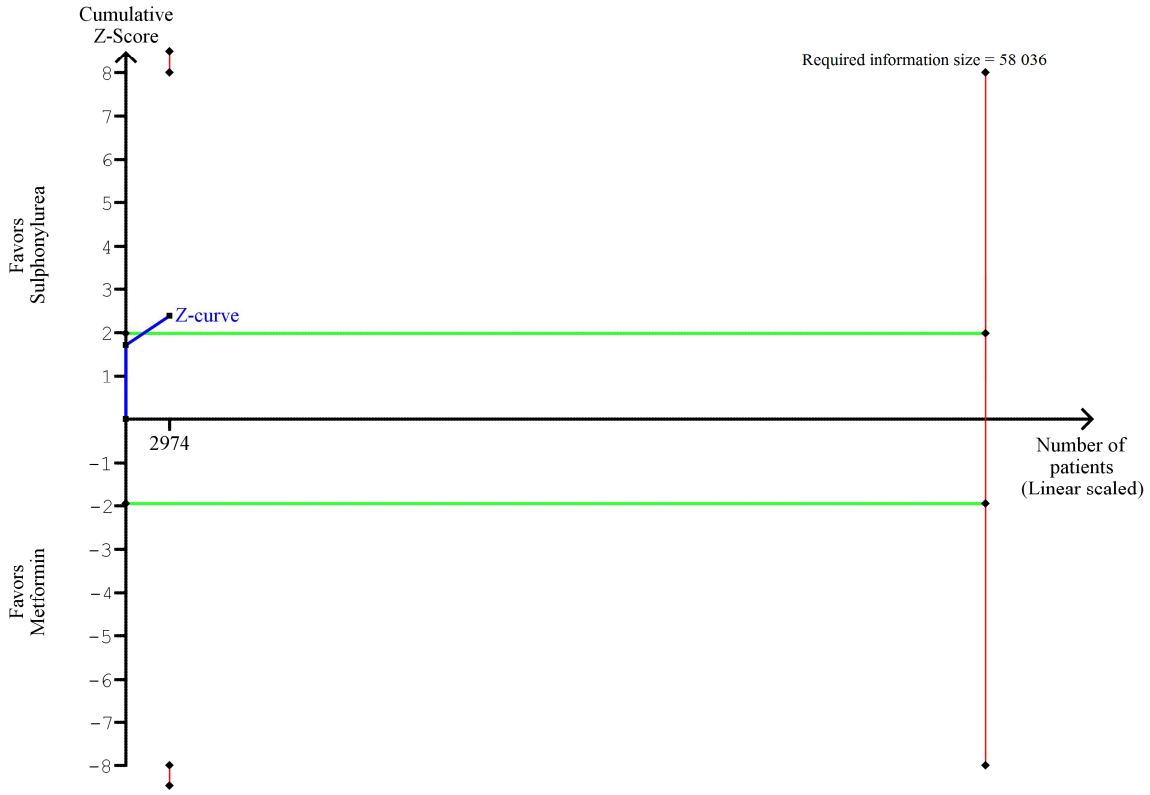
* Included in the full Cochrane version of the review

Web appendix 4. Macrovascular definitions in trials

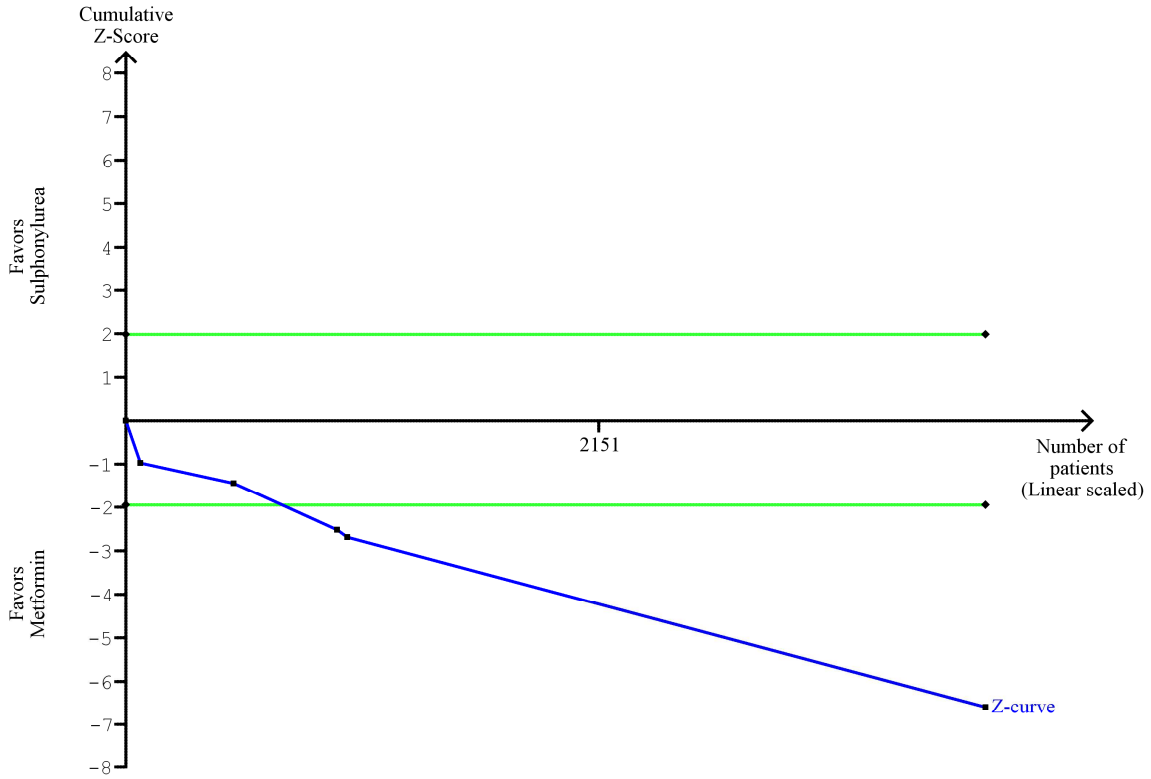
Study	Cardiovascular mortality	Cancer	Composite non-fatal macrovascular outcomes	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity
ADOPT 2006[201-207]	All cardiovascular deaths	Serious adverse event malignancies excluding skin cancer	Major adverse cardiovascular events (fatal 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[208]	ND	ND	ND	ND	ND	ND
Collier 1989[209]	ND	ND	ND	ND	ND	ND
DeFronzo 1995[210]	Death, possible due to myocardial infarction	ND	ND	ND	ND	ND
Derosa et al 2004[211]	ND	ND	ND	ND	ND	ND
Hermann 1991[212]	ND	ND	ND	ND	ND	ND
Hermann 1991a[213-216]	One patient had a sudden death	ND	Cardiovascular adverse events	Non-fatal myocardial infarction	ND	ND
Kamel 1997[217]	ND	ND	ND	ND	ND	ND
Lawrence 2004[218]	Death due to myocardial infarction	ND	ND	Non-fatal myocardial infarction	ND	ND
Tang et al 2004[219]	ND	ND	ND	ND	ND	ND
Tessier 1999[220]	ND	ND	ND	ND	ND	ND
Tosi 2003[221]	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[222-224]	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)
Yamanouchi et al 2005[225]	ND	ND	Adverse cardiac events	ND	ND	ND

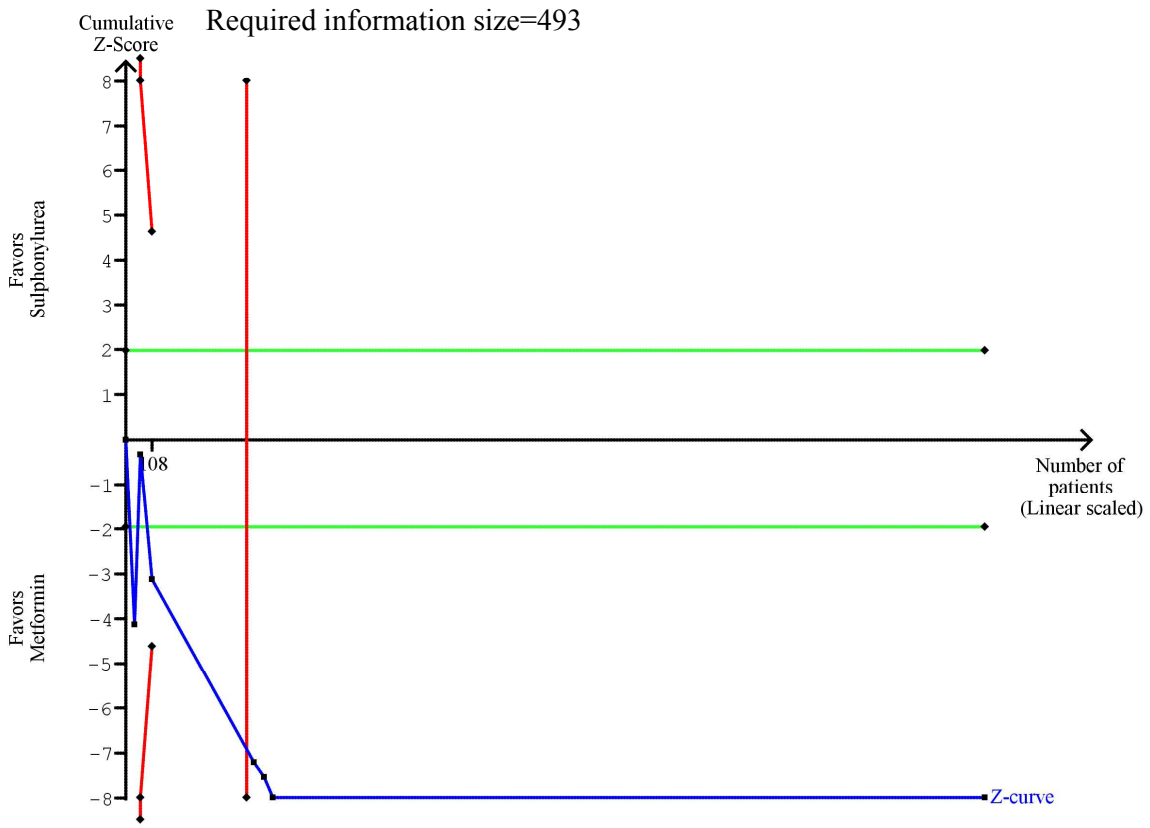
Web appendix 5



Web appendix 5a. Trial sequential analysis of the effect of second- and third-generation sulphonylurea versus metformin in type 2 diabetes on non-fatal macrovascular outcomes with a two-sided α=5%, a power of 80% anticipating, a control event proportion of 4.9%, a 10% relative risk reduction, and a diversity (D^2) of 0%. 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 crosses the red trial sequential alpha spending monitoring boundaries for a 10% relative risk reduction. Horizontal green lines illustrate traditional level of statistical significance (P=0.05)



Web appendix 5b. Trial sequential analysis of the effect of second- and third-generation sulphonylurea versus metformin in type 2 diabetes on non-fatal macrovascular outcomes with a two-sided α=5%, a power of 80% anticipating, a control event proportion of 9.4%, a 10% relative risk reduction, and a diversity (D^2) of 79%. 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 crosses the red trial sequential alpha spending monitoring boundaries for a 10% relative risk reduction. Horizontal green lines illustrate traditional level of statistical significance (P=0.05)



Web appendix 5c. Trial sequential analysis of the effect of second- and third-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)

Web appendix 6. 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[201-207]	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[208]	ND	ND	ND	ND	ND
Collier 1989[209]	Mild hypoglycaemic episodes	ND	ND	ND	ND
DeFronzo 2005[210]	ND	ND	ND	ND	Withdrawal due to adverse effects
Derosa et al 2004[211]	ND	ND	ND	ND	Drop-out due to transient side effects
Hermann 1991[212]	ND	ND	ND	Serious adverse events	ND
Hermann 1991a[213-216]	Hypoglycaemia, including tremor. No one had	Serious, long-lasting hypoglycaemia	Adverse events	ND	Withdrawn due to adverse events

	severe hypoglycaemia				
Kamel 1997[217]	ND	ND	ND	ND	ND
Lawrence 2004[218]	ND	ND	ND	ND	ND
Tang et al 2004[219]	ND	ND	ND	ND	ND
Tessier 1999[220]	ND	ND	ND	ND	ND
Tosi 2003[221]	Mild symptoms, suggestive of hypoglycaemia	Severe episodes of hypoglycaemia	Adverse events	Serious adverse events	Drop-outs due to adverse events
UKPDS 34[222-224]	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
Yamanouchi et al 2005[225]	ND	ND	ND	ND	Discontinuation of treatment due to oedema

ADOPT= A Diabetes Outcome Progression Trial; NR= not reported; UKPDS= United Kingdom Prospective Diabetes Study

References

(1) Abbatecola AM, Rizzo MR, Barbieri M, Grella R, Arciello A, Laieta MT et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology 2006; 67(2):235-240.

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