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Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control (Review)

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[Intervention Review]

Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

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ABSTRACT

Background

It is unclear whether people with type 2 diabetes mellitus on insulin monotherapy who do not achieve adequate glycaemic control should continue insulin as monotherapy or can benefit from adding oral glucose-lowering agents to the insulin therapy.

Objectives

To assess the effects of insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin monotherapy for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and reference lists of articles. The date of the last search was November 2015 for all databases.

Selection criteria

Randomised controlled clinical trials of at least two months' duration comparing insulin monotherapy with combinations of insulin with one or more oral glucose-lowering agent in people with type 2 diabetes.

Data collection and analysis

Two review authors independently selected trials, assessed risk of bias, extracted data and evaluated overall quality of the evidence using GRADE. We summarised data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analyses according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions.*

Main results

We included 37 trials with 40 treatment comparisons involving 3227 participants. The duration of the interventions ranged from 2 to 12 months for parallel trials and two to four months for cross-over trials.

The majority of trials had an unclear risk of bias in several risk of bias domains. Fourteen trials showed a high risk of bias, mainly for performance and detection bias. Insulin monotherapy, including once-daily long-acting, once-daily intermediate-acting, twice-daily premixed insulin, and basal-bolus regimens (multiple injections), was compared to insulin in combination with sulphonylureas (17 comparisons: glibenclamide = 11, glipizide = 2, tolazamide = 2, gliclazide = 1, glimepiride = 1), metformin (11 comparisons), pioglitazone (four comparisons), alpha-glucosidase inhibitors (four comparisons: acarbose = 3, miglitol = 1), dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) (three comparisons: vildagliptin = 1, sitagliptin = 1, saxagliptin = 1) and the combination of metformin and glimepiride (one comparison). No trials assessed all-cause mortality, diabetes-related morbidity or health-related quality of life. Only one trial assessed patients' treatment satisfaction and showed no substantial differences between the addition of either glimepiride or metformin and glimepiride to insulin compared with insulin monotherapy.

Insulin-sulphonylurea combination therapy (CT) compared with insulin monotherapy (IM) showed a MD in glycosylated haemoglobin A1c (HbA1c) of -1% (95% confidence interval (CI) -1.6 to -0.5); P < 0.01; 316 participants; 9 trials; low-quality evidence. Insulin-metformin CT compared with IM showed a MD in HbA1c of -0.9% (95% CI -1.2 to -0.5); P < 0.01; 698 participants; 9 trials; low-quality evidence. We could not pool the results of adding pioglitazone to insulin. Insulin combined with alpha-glucosidase inhibitors compared with IM showed a MD in HbA1c of -0.4% (95% CI -0.5 to -0.2); P < 0.01; 448 participants; 3 trials; low-quality evidence). Insulin combined with DPP-4 inhibitors compared with IM showed a MD in HbA1c of -0.4% (95% CI -0.5 to -0.4); P < 0.01; 265 participants; 2 trials; low quality evidence. In most trials the participants with CT needed less insulin, whereas insulin requirements increased or remained stable in participants with IM.

We did not perform a meta-analysis for hypoglycaemic events because the included studies used different definitions.. In most trials the insulin-sulphonylurea combination resulted in a higher number of mild episodes of hypoglycaemia, compared to the IM group (range: 2.2 to 6.1 episodes per participant in CT versus 2.0 to 2.6 episodes per participant in IM; low-quality evidence). Pioglitazone CT also resulted in more mild to moderate hypoglycaemic episodes compared with IM (range 15 to 90 episodes versus 9 to 75 episodes, respectively; low-quality evidence. The trials that reported hypoglycaemic episodes in the other combinations found comparable numbers of mild to moderate hypoglycaemic events (low-quality evidence).

The addition of sulphonylureas resulted in an additional weight gain of 0.4 kg to 1.9 kg versus -0.8 kg to 2.1 kg in the IM group (220 participants; 7 trials; low-quality evidence). Pioglitazone CT caused more weight gain compared to IM: MD 3.8 kg (95% CI 3.0 to 4.6); P < 0.01; 288 participants; 2 trials; low-quality evidence. Metformin CT was associated with weight loss: MD -2.1 kg (95% CI -3.2 to -1.1), P < 0.01; 615 participants; 7 trials; low-quality evidence). DPP-4 inhibitors CT showed weight gain of -0.7 to 1.3 kg versus 0.6 to 1.1 kg in the IM group (362 participants; 2 trials; low-quality evidence). Alpha-glucosidase CT compared to IM showed a MD of -0.5 kg (95% CI -1.2 to 0.3); P = 0.26; 241 participants; 2 trials; low-quality evidence.

Users of metformin CT (range 7% to 67% versus 5% to 16%), and alpha-glucosidase inhibitors CT (14% to 75% versus 4% to 35%) experienced more gastro-intestinal adverse effects compared to participants on IM. Two trials reported a higher frequency of oedema with the use of pioglitazone CT (range: 16% to 18% versus 4% to 7% IM).

Authors' conclusions

The addition of all oral glucose-lowering agents in people with type 2 diabetes and inadequate glycaemic control who are on insulin therapy has positive effects on glycaemic control and insulin requirements. The addition of sulphonylureas results in more hypoglycaemic events. Additional weight gain can only be avoided by adding metformin to insulin. Other well-known adverse effects of oral glucose-lowering agents have to be taken into account when prescribing oral glucose-lowering agents in addition to insulin therapy.

PLAIN LANGUAGE SUMMARY

Combinations of insulin and oral glucose-lowering drugs for people with type 2 diabetes on insulin treatment

Introduction

Many guidelines on type 2 diabetes recommend a glycosylated haemoglobin A1c (HbA1c) level below 7%. HbA1c levels in the blood express glucose or glycaemic control over a longer time period (two to three months). During the course of type 2 diabetes it will get

more difficult to reach these levels with 'lifestyle' modification (diet, exercise or both) and oral glucose-lowering agents alone. Finally, a substantial number of people will need insulin therapy for better glycaemic control. Insulin therapy can be initiated as insulin alone, called monotherapy (which means that oral glucose-lowering medication will be stopped) or in combination with oral glucose-lowering agents. In the former case, oral blood glucose-lowering agents can be added at a later stage, if insulin monotherapy fails to achieve a good HbA1c level. Hypoglycaemia and weight gain are the most common and well known side effects of insulin therapy. Adding oral agents to insulin could reduce the required insulin dose and thus decrease these insulin-related side effects. However, there could be other side effects specific to the various oral blood glucose-lowering drugs.

Review question

To assess the effects of insulin monotherapy and the addition of an oral antidiabetic drug in people with type 2 diabetes already treated with insulin but not having good glycaemic control.

Background

It is unclear whether people with type 2 diabetes mellitus on insulin alone who do not achieve good glucose levels should continue with insulin alone or can benefit from adding an oral antidiabetic drug to their insulin therapy.

Study characteristics

All 37 included studies were randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups). Their duration ranged from 2 to 12 months. The total number of participants was 3227. Several types of insulin monotherapy (once-daily long- or intermediate-acting insulin, twice-daily premixed insulin, multiple injection therapy with short-acting insulin) were compared with different types of additional antidiabetic tablets: sulphonylureas (such as glibenclamide/glyburide), metformin, alpha-glucosidase inhibitors (such as acarbose), pioglitazone and DPP-4 inhibitors (such as saxagliptin).

Key results

The addition of oral agents to insulin monotherapy reduced HbA1c by 0.4% to 1%. Most combinations of oral antidiabetic agents with insulin resulted in a reduction in the necessary insulin dose per day whereas the insulin dose per day had to be increased or remained stable in participants with insulin monotherapy. In studies reporting hypoglycaemic episodes severe events were rare and mild to moderate hypoglycaemia was observed in similar numbers when comparing insulin monotherapy to the addition of oral antidiabetic agents to insulin. However, most studies adding sulphonylureas to insulin reported more hypoglycaemic episodes. Moreover, the addition of sulphonylureas to insulin resulted in an additional weight gain of 0.4 kg to 1.9 kg compared with -0.8 kg to 2.1 kg in the insulin monotherapy groups. Pioglitazone insulin combination therapy caused on average an increase in weight of 3.8 kg compared with insulin monotherapy. The difference in average weight gain with metformin insulin combination therapy compared with insulin monotherapy was 2.1 kg less in favour of the combination therapy. Gastro-intestinal side effects such as flatulence and diarrhoea were mostly reported with metformin and alpha-glucosidase inhibitors. Addition of pioglitazone to insulin compared with insulin monotherapy resulted in more cases of oedema (fluid retention in the body) and heart failure. Only one study assessed participants' treatment satisfaction and showed no substantial differences between the addition of glimepiride or metformin and glimepiride to insulin compared with insulin monotherapy. No study assessed all-cause mortality, diabetes-related morbidity or health-related quality of life.

This evidence is up to date as of November 2015.

Quality of the evidence

Almost a third of the studies had 30 or fewer participants. A lot of studies seemed to be underpowered and thus were probably not able to answer their own research question. This could mean that potentially important differences between intervention and control groups were not detected. Only five studies had a follow-up of 12 months.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Combinations of insulin and sulphonylureas compared with insulin monotherapy for diabetes mellitus

Patient: participants with type 2 diabetes mellitus
Settings: mostly secondary care outpatients and secondary care inpatients
Intervention: sulphonylureas plus insulin
Comparison: insulin monotherapy

Outcomes	Insulin monotherapy	Insulin plus sulphonylureas	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related morbidity	See comment	See comment	See comment	See comment	Not investigated
Health-related quality of life	See comment	See comment	See comment	See comment	Not investigated
Patient satisfaction	See comment	See comment	See comment	See comment	Not investigated
Adverse events: **a. mild hypoglycaemia** (**episodes per participant**) Follow-up: 12 weeks to 12 months **b. weight gain** (**kg**) Follow-up: 8 weeks to 12 months	a. range 2.0-2.6 b. the mean weight gain across control groups ranged from -0.8 kg to 2.1 kg	a. range 2.2-6.1 b. the mean weight gain across intervention groups ranged from 0.4 kg to 1.9 kg	a. 239 (8) b. 220 (7)	a. ⊕⊕◯◯ **low**[a] b. ⊕⊕◯◯ **low**[a]	a. Serious hypoglycaemic episodes were rare
HbA1c, change from baseline (%) Follow-up: 2 to 12 months	The mean change in HbA1c ranged across control groups from -1.5% to 3%	The mean change in HbA1c in the intervention groups was **1% lower** (1.6% lower to 0.5% lower)	316 (9)	⊕⊕◯◯ **low**[b]	-

CI: confidence interval; **HbA1c:** glycosylated haemoglobin A1c

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

[a]Downgraded by two levels because of risk of performance and detection bias and indirectness
[b]Downgraded by two levels because of risk of performance bias and indirectness

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of these defects is chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased.

The United Kingdom Prospective Diabetes Study (UKPDS) and its 10-year follow-up afterwards showed that tight glycaemic control can significantly reduce the development and progression of microvascular complications (Holman 2008; UKPDS 33; UKPDS 34). There is some inconsistency in the evidence of the effects of intensive treatment on macrovascular outcomes and mortality. Several large long-term clinical trials comparing standard with intensive therapy did not show a significant reduction of cardiovascular outcomes and mortality (ACCORD 2008; ADVANCE 2008; Duckworth 2009; Kooy 2009). Intensive glycaemic control reduced the risk of microvascular complications but increased the risk of hypoglycaemia. Many guidelines on type 2 diabetes recommend a glycosylated haemoglobin A1c (HbA1c) below 7% for the majority of people with type 2 diabetes, however, a patient-centred approach is more and more advocated, with the intent to encourage an appreciation of the variable and progressive nature of type 2 diabetes, the specific role of each drug, the patient and disease factors that drive clinical decision making and the constraints imposed by age and comorbidity (Inzucchi 2012). During the course of type 2 diabetes it will get more difficult to reach the HbA1c target levels with 'lifestyle' modification (diet, exercise or both) and oral glucose-lowering agents alone. Finally, a substantial number of individuals will need insulin therapy for better glycaemic control (Turner 1999; Wright 2002).

Description of the intervention

Since the natural course of type 2 diabetes causes progressive decline of the pancreatic ß-cell function, finally oral glucose-lowering agents may not suffice and exogenous insulin will be required in a substantial number of people. At that stage insulin therapy can be initiated as insulin alone, that is monotherapy (which means that oral glucose-lowering medication will be stopped) or in combination with oral glucose-lowering agents. In the former category of people, oral blood glucose-lowering agents can be added at a later stage, if monotherapy fails to achieve a sufficient HbA1c level. The latter intervention is the intervention under study in this review.

Adverse effects of the intervention

Hypoglycaemia, injection site reactions and weight gain are the most common and well known adverse effects of insulin therapy. Experimental and observational trials have shown that exogenous insulin may lead to increased atherosclerosis (Muis 2005; Ruige 1998; Stout 1990). Weight gain is another frequently reported adverse effect of insulin, with weight gain ranges from 0.3 kg to 3.8 kg. Several Dutch trials reported no effect or no negative effects on health-related quality of life after starting insulin treatment (De Grauw 2001; De Sonnaville 1998; Goddijn 1999; Goudswaard 2004a). On the other hand, many people with type 2 diabetes (and healthcare providers) are reluctant to initiate insulin therapy. People with type 2 diabetes may be afraid of hypoglycaemia and weight gain, they may be uncomfortable with daily injections, they might experience restrictions in lifestyle and feelings of guilt and failure (Brunton 2005; Hunt 1997; Korytkowski 2002; Snoek 2002). In addition, primary care patients treated with insulin reported higher diabetes-related distress compared with oral- or diet-treated patients, which is stable over time and might be difficult to alter (Delahanty 2007; Karlsen 2014).

How the intervention might work

In the 1990s three reviews were executed comparing insulin monotherapy with insulin-oral glucose-lowering agents combination therapy (Johnson 1996; Peters 1991; Pugh 1992). The reviews did not distinguish between insulin-treated and insulin-naive participants. Besides, they only focused on sulphonylureas in combination with insulin therapy and excluded trials with other oral agents. Their conclusions differed. Peters 1991 concluded that combination therapy has no additional value for insulin-treated people with type 2 diabetes, since it improved glycaemic control only slightly and it did not produce normal blood glucose concentrations. But Pugh 1992 and Johnson 1996 concluded that insulin combination therapy with sulphonylureas was more appropriate than insulin monotherapy because it was more efficacious and may be more cost-effective. A more comprehensive review on the combination of insulin and oral glucose-lowering agents in insulin-naive and insulin-treated patients did not meet Cochrane criteria (Yki-Jarvinen 2001). It showed that in most trials glycaemic control was better and less insulin was required with the combination of insulin and oral glucose-lowering agents compared with insulin alone. Notably, the difference in the required insulin dose between insulin monotherapy and the combination therapy was smaller in participants who were already being treated with insulin than in insulin-naive participants.

Why it is important to do this review

In 2004 a Cochrane Review was published on the comparison of insulin monotherapy versus combinations of insulin and oral glucose-lowering agents in insulin-naive people with type 2 diabetes with poor glycaemic control despite maximal dosages of oral glucose-lowering agents (Goudswaard 2004b). The authors con-

cluded that bedtime Neutral Protamine Hagedorn (NPH) insulin combined with oral glucose-lowering agents provides comparable glycaemic control to insulin monotherapy, but with less weight gain if metformin was used.

Up to now, no definitive answer has been available with regard to the comparison of insulin monotherapy versus combinations of insulin and oral glucose-lowering agents in people with type 2 diabetes already on insulin therapy. In other words: is the adding of an oral glucose-lowering agent to insulin beneficial with regard to outcomes such as glycaemic control, weight gain, hypoglycaemia, insulin dosage, health-related quality of life and other outcome parameters? This systematic review will try to clarify the benefits of adding an oral blood glucose-lowering agent to insulin monotherapy in people already on insulin therapy.

OBJECTIVES

To assess the effects of insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin monotherapy for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a minimal follow-up period of two months.

Types of participants

Participants with type 2 diabetes mellitus (according to the appropriate diagnostic criteria at the time) already on insulin therapy and inadequate glycaemic control. To be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (for example ADA 1997; ADA 1999; WHO 1980; WHO 1985; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, we used the study authors' definition of diabetes mellitus.

Types of interventions

Intervention

Combinations of insulin with one or more oral glucose-lowering agent(s).

Control

Insulin monotherapy.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Diabetes-related morbidity
- Adverse events

Secondary outcomes

- Health-related quality of life
- Patient satisfaction
- Glycosylated haemoglobin A1c (HbA1c)
- Fasting glucose
- Lipids
- Insulin dose

Method and timing of outcome measurement

- Mortality: defined as all-cause and diabetes-related (cardiovascular mortality, mortality due to end-stage renal disease or due to amputation) and measured at baseline and follow-up with a minimum duration of two months.
- Diabetes-related morbidity: defined as myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in at least one eye, or cataract extraction and measured at baseline and follow-up with a minimum duration of two months.
- Adverse events such as hypoglycaemic episodes, weight gain, gastrointestinal symptoms, heart failure and measured at baseline and follow-up with a minimum duration of two months.
- Health-related quality of life: evaluated by a validated instrument and measured at baseline and follow-up with a minimum duration of two months.
- Patient satisfaction: evaluated by a validated instrument and measured at baseline and follow-up with a minimum duration of two months.
- HbA1c: measured at baseline and follow-up with a minimum duration of two months.
- Fasting glucose: defined as after a period of eight hours of not eating or drinking with the exception of water and measured at baseline and follow-up with a minimum duration of two months.
- Lipids: defined as total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol,

triglycerides and measured at baseline and follow-up with a minimum duration of two months.

- Insulin dose: defined as once-daily long-acting, once-daily intermediate-acting, twice-daily premixed insulin, and basal-bolus regimen (multiple injections) and measured at baseline and follow-up with a minimum duration of two months.

Summary of findings

We present a 'Summary of findings' table to report the following outcomes, listed according to priority.

- All-cause mortality.
- Diabetes-related mortality.
- Diabetes-related morbidity.
- Health-related quality of life.
- Patient satisfaction.
- Adverse events.
- HbA1c.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception of each database to the specified date and placed no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL issue 10, October 2015, 18.11.2015)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (18.11.2015)
- Embase 1974 to 2015 November 17 (18.11.2015)
- ClinicalTrials.gov (18.11.2015)
- World Health Organization (WHO) ICTRP (International Clinical Trials Registry Platform - http://apps.who.int/trialsearch/) (18.11.2015), including:
    - Australian New Zealand Clinical Trials Registry (2 November 2015)
    - Chinese Clinical Trial Registry (2 November 2015)
    - ClinicalTrials.gov (2 November 2015)
    - EU Clinical Trials Register (EU-CTR) (2 November 2015)
    - ISRCTN (2 November 2015)
    - The Netherlands National Trial Register (3 November 2015)
    - Brazilian Clinical Trials Registry (ReBec) (13 October 2015)
    - Clinical Trials Registry - India (13 October 2015)
    - Clinical Research Information Service - Republic of Korea (13 October 2015)
    - Cuban Public Registry of Clinical Trials (13 October 2015)
    - German Clinical Trials Register (13 October 2015)
    - Iranian Registry of Clinical Trials (4 August 2015)
    - Japan Primary Registries Network (19 October 2015)
    - Pan African Clinical Trial Registry (13 October 2015)
    - Sri Lanka Clinical Trials Registry (13 October 2015)
    - Thai Clinical Trials Register (TCTR) (13 October 2015)

We also searched the excluded trials from the Cochrane Review with the same objective as ours except in insulin-naive people with type 2 diabetes (Goudswaard 2004b).

If we had detected additional relevant key words during any of the electronic or other searches, we would have modified the electronic search strategies to incorporate these terms and document the changes.

Searching other resources

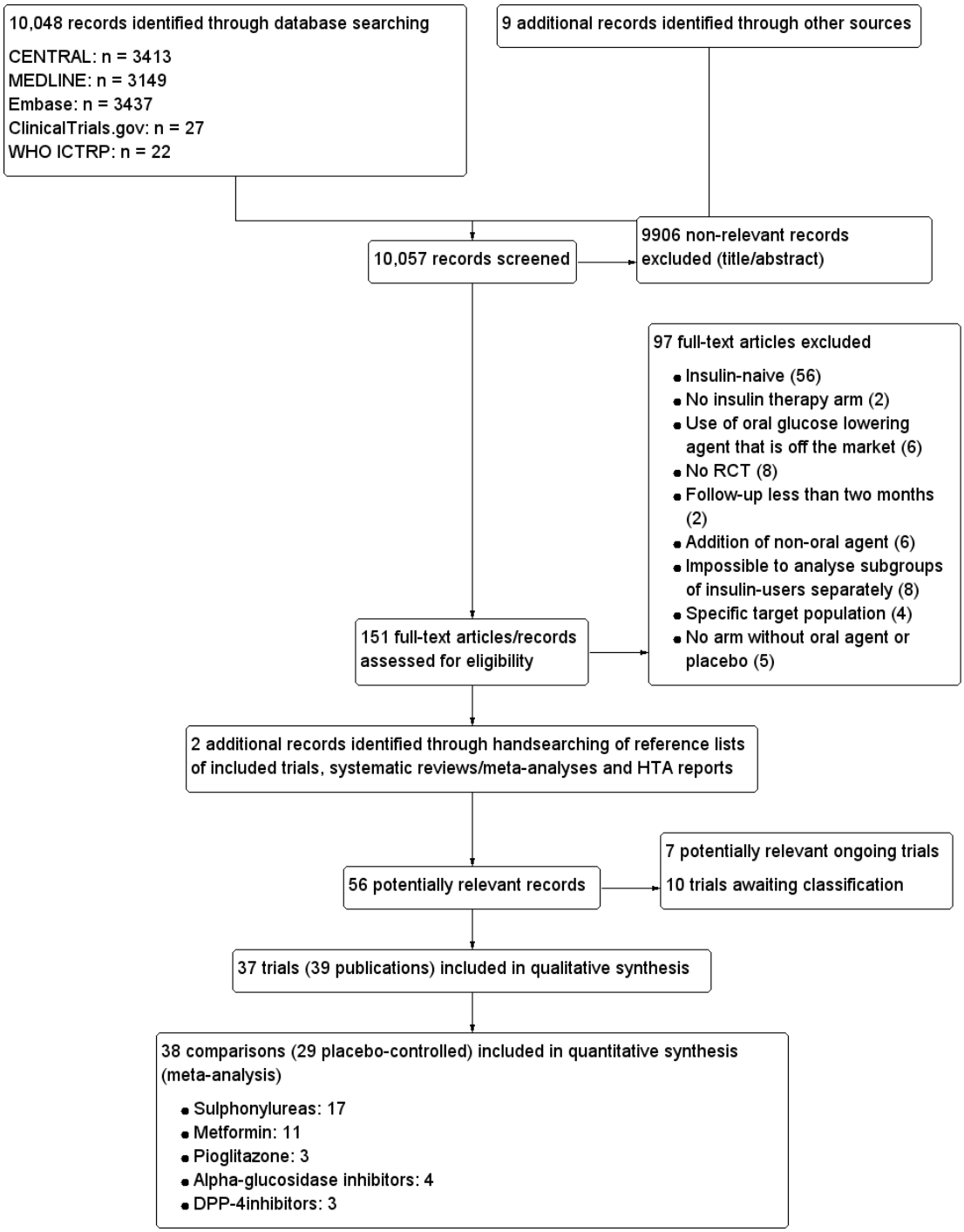
We tried to identify additional trials by searching the reference lists of included trials.

Data collection and analysis

Selection of studies

One review author (MA) first screened titles and abstracts to remove duplicates and obviously irrelevant records. Then two review authors (MA, AG or RV) independently scanned the abstract, title, or both, of the retriever records, to determine which trials should be assessed further. We investigated all potentially-relevant articles as full text. Full articles were retrieved for further assessment if the information given suggested that the trial included participants with type 2 diabetes mellitus, compared insulin with a combination of insulin with oral glucose lowering agent(s), assessed one or more relevant clinical outcome measure(s), and used random allocation to the comparison groups. We resolved any discrepancies through consensus or recourse to a third review author (KG or GR). If resolution of a disagreement was not possible, we added the article to those 'awaiting assessment' and we contacted trial authors for clarification. We present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of trial selection (Figure 1) (Liberati 2009).

Figure 1. Study flow diagram.



Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximised yield of information by collating all available data and used the most complete data set aggregated across all known publications. In case of doubt, we prioritised the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Data extraction and management

For trials that fulfilled inclusion criteria, two review authors (MA and AK or MD or AG or RV) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8) with any disagreements to be resolved by discussion, or, if required, by a third party (KG). We provide information including trial identifier about potentially relevant ongoing trials in the table 'Characteristics of ongoing studies'.

We sent an email request to authors of included trials to enquire whether they were willing to answer questions regarding their trials. Thereafter, we sought relevant missing information on the trial from the authors of the article, if required.

Assessment of risk of bias in included studies

Two review authors (MA and AK or MD or AG) assessed each trial independently. Possible disagreement was resolved by consensus, or with consultation with a third party in case of disagreement. We explored the influence of individual bias criteria in a sensitivity analysis (see Sensitivity analysis). In case of disagreement, we consulted the rest of the group and made a judgement based on consensus. We investigated risk of bias due to carry-over effect in cross-over trials during data-extraction.

We used the Cochrane 'risk of bias' assessment tool (Higgins 2011b; Higgins 2011a) and investigated the following risk of bias criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other potential sources of bias.

We judged 'risk of bias' criteria as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011b). We present a 'Risk of bias' graph (Figure 2) and a 'Risk of bias summary' figure (Figure 3). We assessed the impact of individual risk of bias domains on trial results at the endpoint and trial levels. In case of high risk of selection bias, all endpoints investigated in the associated trial were marked as 'high risk'.

Figure 2. 'Risk of bias' graph (blank cells indicate that the particular outcome was not investigated in some studies)

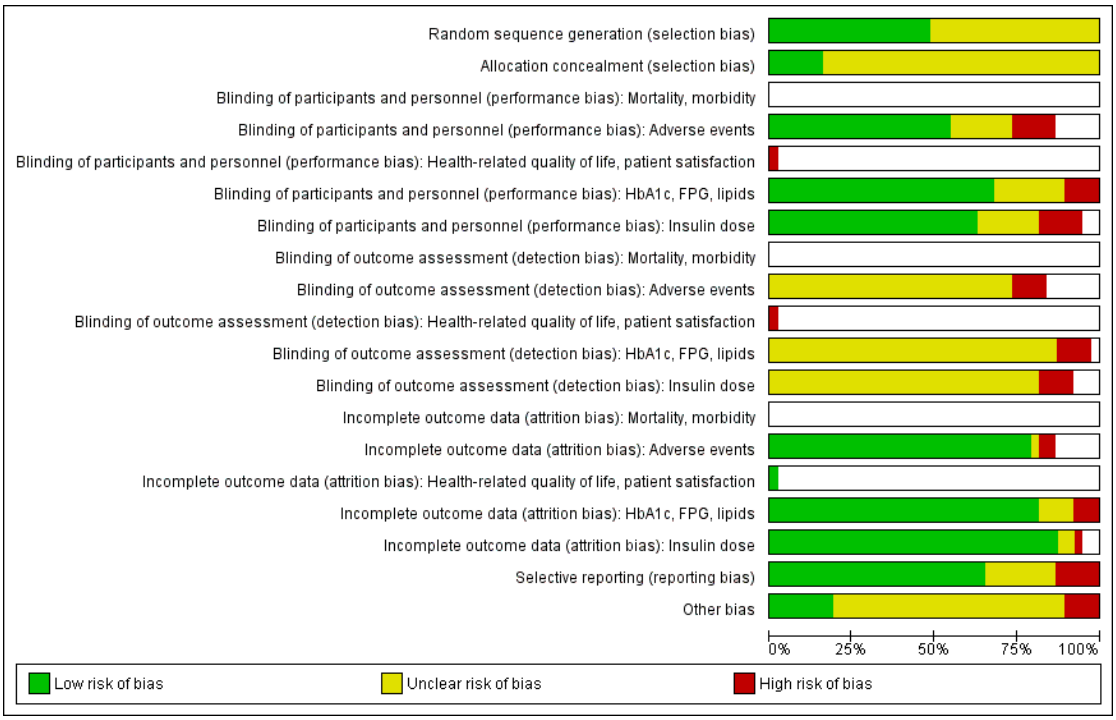
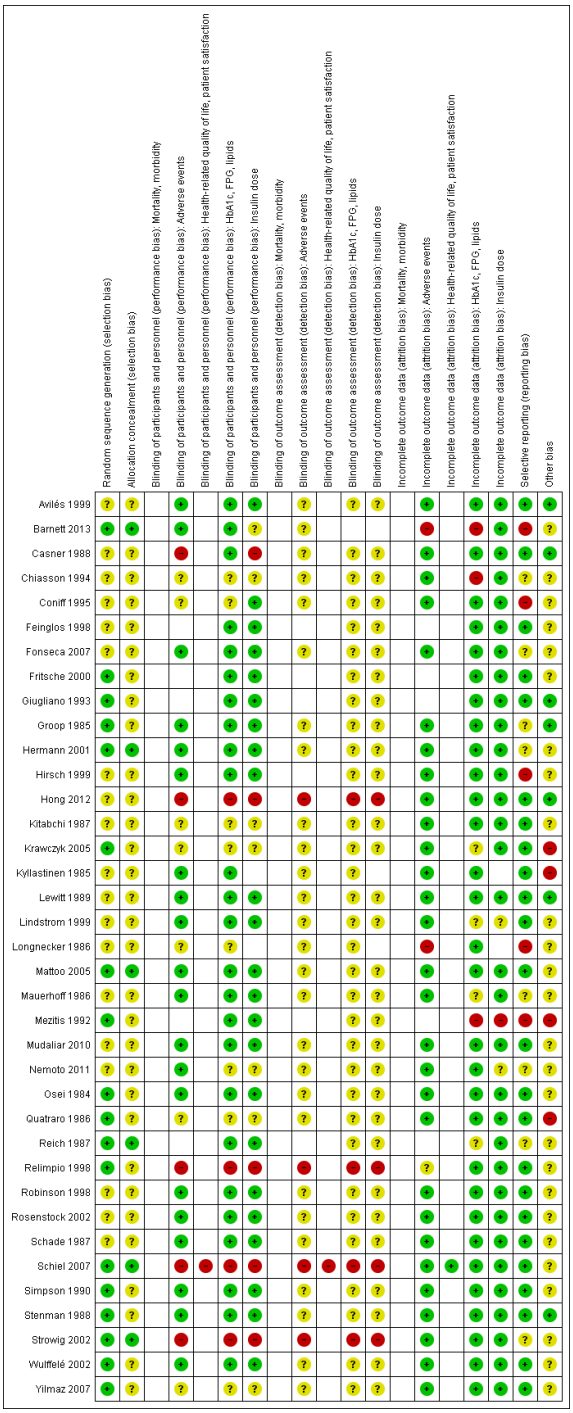


Figure 3. 'Risk of bias' summary (blank cells indicate that the study did not report that particular outcome)



For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessors) we evaluated the risk of bias separately for each outcome (Hróbjartsson 2013). We noted whether outcomes were measured subjectively or objectively, for example if body weight was measured by participants or trial personnel.

We considered the implications of missing outcome data from individual participants per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

We defined the following endpoints as subjective outcomes.

- Health-related quality of life.
- Patient satisfaction.

We defined the following endpoints as objective outcomes.

- All-cause mortality.
- Diabetes-related morbidity.
- Adverse events.
- HbA1c.
- Fasting glucose.
- Lipids.
- Insulin dose.

Measures of treatment effect

Continuous data

The results are expressed as mean differences (MD) with 95% confidence intervals (CIs).

For trials that did not provide HbA1c change-from-baseline values, we computed these data from baseline and post-treatment values, if necessary extracted from graphs. When standard deviations of mean differences from the main outcome HbA1c were not provided in 11 publications (Barnett 2013; Casner 1988; Fonseca 2007; Giugliano 1993; Hirsch 1999; Mattoo 2005; Osei 1984; Quatraro 1986; Relimpio 1998; Strowig 2002; Yilmaz 2007), we computed these data assuming a general correlation coefficient that was derived from baseline and post-treatment outcomes for HbA1c in trials that presented accompanying standard deviations. We computed matching standard deviations in SPSS 15.0 with a formula (formula 1), which included a general correlation coefficient of 0.5. This figure was 0.1 point lower than the correlation coefficient that was calculated from trials that provided information on change scores including standard deviations, and which appeared to be 0.6 in most trials (formula 2) (Armitage 2002). We used the same method and formula for assessing the standard deviation of the differences of fasting glucose for seven trials (Avilés 1999; Casner 1988; Mattoo 2005; Relimpio 1998; Schiel 2007; Strowig 2002; Yilmaz 2007), weight for six trials (Barnett 2013; Casner 1988; Krawczyk 2005; Mauerhoff 1986; Relimpio 1998; Strowig 2002), total cholesterol for five trials (Giugliano 1993; Osei 1984; Relimpio 1998; Strowig 2002; Yilmaz 2007), HDL-cholesterol for six trials (Giugliano 1993; Mattoo 2005; Osei 1984; Relimpio 1998; Strowig 2002; Yilmaz 2007) and triglycerides for six trials (Fonseca 2007; Giugliano 1993; Osei 1984; Relimpio 1998; Strowig 2002; Yilmaz 2007). We included a correlation coefficient of 0.3 for fasting glucose, 0.9 for weight gain, 0.8 for HDL-cholesterol and 0.6 for total cholesterol and triglycerides.

Formula 1: SPSS syntax for computing standard deviations of changes from baseline values of HbA1c:

SD = sqrt (sd˙tr˙b^2 + sd˙tr˙p^2 - (2 x corr x sd˙tr˙b x sd˙tr˙p)).

Abbreviations:

sd = standard deviation

sqrt = square root

sd˙tr˙b = standard deviation of mean baseline HbA1c

sd˙tr˙p = standard deviation of mean post-treatment HbA1c

corr = correlation coefficient between baseline and post-treatment values of HbA1c

Formula 2: SPSS syntax for computing correlation coefficient between baseline and post-treatment values of HbA1c:

corr˙tr = (hba1cbsd^2 + hba1cptsd^2 - sddiff˙tr^2) / (2 x hba1cbsd x hba1cptsd).

Abbreviations:

corr˙tr = correlation coefficient between baseline and post-treatment values of HbA1c

hba1cbsd = standard deviation of mean baseline HbA1c

hba1cptsd = standard deviation of mean post-treatment HbA1c

sddiff˙tr = standard deviation of change from baseline HbA1c

Unit of analysis issues

We pooled the results of mean difference and standard error of the parallel group and the cross-over trials using the generic inverse variance (GIV) method. In addition, we also used the non-GIV method in order to give insight into the number of participants included in each trial and the range of mean values. For the cross-over trials we calculated the correlation coefficient for within-participants difference based on the trial results of Robinson 1998, and estimated the standard error as described in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We then imputed this correlation coefficient in the other trials. When standard deviations of mean differences were not provided in the publications, we computed these data assuming a correlation coefficient that was derived from intervention and control outcomes in trials that presented accompanying standard deviations (HbA1c: Fritsche 2000; Kitabchi 1987; Kyllastinen 1985; Lewitt 1989; Schade 1987; Stenman 1988; fasting glucose: Fritsche 2000; Kyllastinen 1985; Lewitt 1989; Longnecker 1986; Robinson 1998; Stenman 1988; weight:

Kitabchi 1987; Kyllastinen 1985; Lindstrom 1999; Robinson 1998; Schade 1987; Stenman 1988; total cholesterol: Groop 1985; Kitabchi 1987; Lindstrom 1999; Stenman 1988; HDL-cholesterol: Groop 1985; Lindstrom 1999; Stenman 1988; triglycerides: Groop 1985; Kitabchi 1987; Lindstrom 1999; Stenman 1988).

Formula 3: SPSS syntax for computing correlation coefficient in cross-over trials

corr˙tr = (sd˙tr˙pa^2 + sd˙tr˙pb^2 - sddiff˙tr^2) / (2 x sd˙tr˙pa x sd˙tr˙pb).

Abbreviations:

corr˙tr = correlation coefficient between intervention and control values

sd˙tr˙pa = standard deviation of mean value after intervention

sd˙tr˙pb = standard deviation of mean value after control

sddiff˙tr = standard deviation of within-participant difference between intervention and control measurements

Dealing with missing data

We carefully evaluated important numerical data such as screened, eligible and randomised participants, as well as intention-to-treat (ITT) and per-protocol (PP) population. We investigated attrition rates, for example dropouts, losses to follow-up and withdrawals. We critically appraised issues of missing data, ITT and PP and compared them to specification of primary outcome parameters and power calculation.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the trials with regard to different clinical parameters: patient characteristics, duration of disease, interventions and outcome. In the event of substantial clinical or methodological heterogeneity, we did not combine trial results by means of meta-analysis. We identified statistical heterogeneity by visual inspection of the forest plots, by using a standard Chi² test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity was specifically examined with the I² statistic (Higgins 2002; Higgins 2003), where I² values of 75% and more indicate a considerable level of heterogeneity (Deeks 2011). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual trial characteristics and those of subgroups of the main body of evidence. We did not report the results of meta-analysis with a considerable level of statistical heterogeneity (I² greater than 75%).

Assessment of reporting biases

If we included 10 trials or more investigating a particular outcome, we used funnel plots to assess small trial effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We therefore interpreted results carefully Sterne 2011).

Data synthesis

We summarised data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analyses according to the statistical guidelines referenced in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Unless there was good evidence for homogeneous effects across trials, we primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions (*Deeks 2011.

Quality of evidence

We present the overall quality of the evidence for each outcome as specified in types of outcome measures under 'Summary of findings' according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results. Two review authors (MA and AK or MD or AG) independently rated the quality for each outcome. We present a summary of the evidence in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and the rating of the overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We present results on the outcomes as described in the Types of outcome measures section. If meta-analysis was not possible, we presented results in a narrative format in the 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses if one of the primary outcome parameters demonstrated statistically significant differences between intervention groups. In any other case, subgroup analyses would have been clearly marked as a hypothesis-generating exercise.

We planned to carry out the following subgroup analyses.

- Different oral glucose-lowering agent(s) and different types of insulin.
- Timing and frequency of insulin injections.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of very long trials (defined as equal to or greater than 24 weeks or six months) and the influence of trials with high risk of bias (defined as high risk of performance bias and detection bias because of not blinding researchers, or high risk of attrition bias because of incomplete outcome data, or both) on the effect size, to establish how much they dominated the results. Moreover, we compared the results of trials with a parallel design with the results of trials with a cross-over design. We also planned to perform sensitivity analyses by restricting the analysis to published trials or restricting the analysis to trials using the following filters: diagnostic criteria; imputation; language of publication; source of funding (industry versus other); and country.

We also tested the robustness of the results by repeating the analysis using different measures of effect size (RR, odds ratio (OR), etc.) and different statistical models (fixed-effect and random-effects models).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies and Table 1.

Results of the search

The search strategy provided 10,048 citations. After exclusion of duplicates and trials not related to the objective of the review, two review authors (MA, AG or RV) independently assessed the remaining abstracts. One of the authors of this review (AG) has conducted a similar Cochrane Review, that also compares insulin monotherapy to insulin combined with oral glucose-lowering agents, though in insulin-naive type 2 diabetes patients (Goudswaard 2004b). One author (MA) scanned the title, abstract and text of the excluded trials of that review. Seven excluded trials were related to the objective of the current review and did not appear in the search. We found two additional records in the references of included articles. We obtained the full text of 151 potentially relevant trials, of which 37 (39 publications) fulfilled the inclusion criteria (for details see Figure 1).

Included studies

All 37 included trials were randomised controlled trials, of which 26 had a parallel design and 11 a cross-over design (Feinglos 1998; Fritsche 2000; Groop 1985; Kitabchi 1987; Kyllastinen 1985; Lewitt 1989; Lindstrom 1999; Longnecker 1986; Robinson 1998; Schade 1987; Stenman 1988). Thirteen trials were conducted in the United States of America, three were conducted in Finland, two each in the United Kingdom, Sweden, Germany and Italy, and one each in Canada, Poland, Turkey, Australia, Belgium, Spain, Korea, Japan and the Netherlands. Another four trials were conducted in two or more countries. All trials were, if stated, conducted in secondary care. All were published in English, except one in Polish (Krawczyk 2005). More than 80% of the trials were sponsored by pharmaceutical companies.

The total number of participants was 3227 (range 9 to 566), with 0% to 100% men. Gender was not reported in four trials (Coniff 1995; Hirsch 1999; Mezitis 1992; Quatraro 1986). Participants ranged from 29 to 83 years of age and the duration of diabetes ranged from less than 1 to 31 years.

We evaluated 37 trials providing 40 comparisons between insulin monotherapy and insulin-oral glucose-lowering agents combination therapy. Insulin monotherapy was compared to insulin therapy in combination with:

- sulphonylureas; n = 17 comparisons (glibenclamide = 11, glipizide = 2, tolazamide = 2, gliclazide = 1, glimepiride = 1);
- metformin; n = 11 comparisons;
- combination of metformin and sulphonylureas; n = 1 comparison;
- pioglitazone; n = 4 comparisons;
- alpha-glucosidase inhibitors; n = 4 comparisons (acarbose n = 3, miglitol n = 1);
- dipeptidyl peptidase-4 inhibitors (DPP 4-inhibitors); n = 3 comparisons (vildagliptin n = 1, sitagliptin n = 1, saxagliptin n = 1).

One trial on pioglitazone (Rosenstock 2002) compared the combination of insulin therapy with pioglitazone 15 mg as well as pioglitazone 30 mg to placebo. Insulin therapy was applied as a once-daily, twice-daily, and/or a multiple-daily injection regimen. In almost all trials that reported the insulin regimens, participants received a different number of injections per day. Nine trials included participants who used a once-daily insulin regimen (Barnett 2013; Longnecker 1986; Mattoo 2005; Mudaliar 2010; Osei 1984; Quatraro 1986; Reich 1987; Simpson 1990; Stenman 1988), in the other trials all participants received two or more injections per day. The total trial duration of all trials ranged from 2 to 12 months. The mean follow-up of an intervention period of the cross-over trials varied from two to four months.

All except one trial (Mauerhoff 1986) reported glycaemic control as mean values of glycosylated haemoglobin A1c (HbA1c). Ten trials provided change-from-baseline values for HbA1c with standard deviations or errors (Coniff 1995; Fonseca 2007; Fritsche 2000; Hong 2012; Nemoto 2011; Relimpio 1998; Robinson 1998; Rosenstock 2002; Schiel 2007; Wulffelé 2002;). Fasting blood glucose values were not reported in two trials (Coniff 1995; Mezitis 1992). Eleven trials provided change-from-baseline values for body weight with standard deviations or errors (Coniff 1995; Fonseca 2007; Fritsche 2000; Hong 2012; Mattoo 2005; Mudaliar 2010; Relimpio 1998; Robinson 1998; Strowig 2002; Wulffelé

2002; Yilmaz 2007). Change in insulin requirement was reported in all trials, except one (Chiasson 1994). No trial assessed patient-reported outcomes like general well-being or health-related quality of life. Only one trial assessed patient treatment satisfaction (Schiel 2007). Eight trials reported data on total cholesterol, HDL-cholesterol and/or triglycerides. All but 13 trials (Fritsche 2000; Giugliano 1993; Groop 1985; Kitabchi 1987; Krawczyk 2005; Kyllastinen 1985; Lewitt 1989; Lindstrom 1999; Longnecker 1986; Mezitis 1992; Mudaliar 2010; Osei 1984; Quatraro 1986) in some way provided information on hypoglycaemic events. Almost half of the trials reported information on other adverse effects.

Further details are listed in the Table Characteristics of included studies.

Excluded studies

Reasons for exclusion of trials are given in Characteristics of excluded studies. Main reasons for exclusion were that participants were insulin-naive, trials used a non-appropriate trial design, and non-oral agents were added to insulin therapy.

Ongoing studies

We found seven ongoing trials, four with a subgroup for the combination insulin-DPP IV inhibitor (sitagliptin = 1, vildagliptin = 1, saxagliptin = 2) versus insulin monotherapy, one with a thiazolidinedione (rosiglitazone) combined therapy and one with the combination insulin-ipragliflozin (approved in Japan). More details of these trials are given in Characteristics of ongoing studies.

Risk of bias in included studies

All trials included in this review had some methodological weaknesses according to the criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), and thus showed unclear or high risk of bias in several risk of bias domains (Figure 2; Figure 3).

Allocation

Only six trials (Barnett 2013; Hermann 2001; Mattoo 2005; Reich 1987; Schiel 2007; Strowig 2002) fully reported the method of randomisation and allocation concealment. For the remaining trials it was not possible to judge whether the sequence generation was adequate and if the allocation to the intervention and control groups was concealed.

Blinding

The method of blinding was stated as open in four trials (Hong 2012; Relimpio 1998; Schiel 2007; Strowig 2002). The majority of the trials were double-blinded. Mostly, it was unclear whether the researcher or the outcome assessor was blinded in addition to the participant. Risk of performance and detection bias was high for some outcomes in five trials (Casner 1988; Hong 2012; Relimpio 1998; Schiel 2007; Strowig 2002).

Incomplete outcome data

Eleven trials (Feinglos 1998; Fritsche 2000; Giugliano 1993; Kitabchi 1987; Krawczyk 2005; Lindstrom 1999; Mauerhoff 1986; Mezitis 1992; Mudaliar 2010; Quatraro 1986; Simpson 1990), with rather small trial populations ranging from 12 to 50 participants, did not mention whether there were dropouts or whether there was excessive loss to follow-up. In thirteen trials (Avilés 1999; Barnett 2013; Casner 1988; Coniff 1995; Groop 1985; Hirsch 1999; Kyllastinen 1985; Lewitt 1989; Longnecker 1986; Osei 1984; Robinson 1998; Stenman 1988; Strowig 2002), dropouts were reported but no intention-to-treat analysis was executed or it was unclear whether it was done. In thirteen trials (Chiasson 1994; Fonseca 2007; Hermann 2001; Hong 2012; Mattoo 2005; Nemoto 2011; Reich 1987; Relimpio 1998; Rosenstock 2002; Schade 1987; Schiel 2007; Wulffelé 2002; Yilmaz 2007) dropouts were reported and intention-to-treat analysis was performed.

Selective reporting

We judged five trials (Barnett 2013; Coniff 1995; Hirsch 1999; Longnecker 1986; Mezitis 1992) to be at a high risk of bias for selective reporting, because some predefined outcomes were not reported. These outcomes (like level of liver enzymes or hormones) were often unimportant for the objective of this review.

Other potential sources of bias

The sample size of trials ranged from 9 to 566 participants. Thirteen of the 37 trials had 30 or fewer participants. Only eight trials (Casner 1988; Chiasson 1994; Hermann 2001; Hong 2012; Mattoo 2005; Schade 1987; Schiel 2007; Wulffelé 2002) discussed power calculations. This might mean that potential significant differences across groups were difficult to detect. Follow-up periods differed between trials, ranging from 2 to 12 months. The outcome values of the trials with a short follow-up might have been different if the trial had been continued for a longer period. In all cross-over trials a cross-over design was suitable and no risks of a carry-over effect were found. Most trials were funded by pharmaceutical companies and often the overall outcome was in favour of the product of the sponsoring company.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: sulphonylureas; **Summary of findings 2** Summary of findings: metformin; **Summary of findings 3** Summary of findings: pioglitazone; **Summary of findings 4** Summary of findings: alpha-glucosidase inhibitors; **Summary of findings 5** Summary of findings: DPP-4 inhibitors

We categorised comparisons according to the oral glucose-lowering agent that was added to insulin therapy. In the included trials we distinguished five groups of oral glucose-lowering agents: sulphonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors and dipeptidyl-peptidase (DPP) 4-inhibitors. Categorisation regarding mode of insulin therapy (once-daily, twice-daily, or multiple daily injections) was not possible due to the often mixed use of number of insulin injections in participants in a trial or due to lack of reporting. We used a random-effects model for the meta-analyses.

None of the included trials assessed the primary outcomes of all-cause mortality, diabetes-related mortality or diabetes-related morbidity.

None of the included trials assessed the secondary outcome, health-related quality of life. Only one trial assessed patient satisfaction.

Insulin monotherapy versus insulin plus sulphonylurea

Primary outcomes

Adverse events: hypoglycaemia

Heterogeneity in the definitions used between trials, and the quality of reporting of hypoglycaemia precluded the pooling of data.

Eight trials reported hypoglycaemic events, quantitatively or qualitatively (Casner 1988; Feinglos 1998; Mauerhoff 1986; Reich 1987; Schade 1987; Schiel 2007; Simpson 1990; Stenman 1988). Feinglos 1998 only reported the number of hypoglycaemic events for the total group: 69 mild events, six moderate events (glucose ranging from 1.2 to 3.0 mmol/L) and one severe event requiring assistance from another individual. Simpson 1990 reported that four out of nine participants on combination therapy had to reduce their treatment drug because of hypoglycaemic symptoms. Stenman 1988 reported more mild hypoglycaemic events with combination therapy (6.1 ± 1.0 events per participant; n = 13) than with insulin monotherapy (2.6 ± 1.0 events per patient; n = 8; P < 0.01). No severe hypoglycaemic reactions requiring medical treatment occurred in this trial. Mauerhoff 1986 and Schade 1987 also counted more hypoglycaemic events with combination therapy than with insulin monotherapy (107 versus 25 and 6 versus 1, respectively). However, Reich 1987 counted more events in insulin monotherapy than with combination therapy (10 versus 5 (of which three were biochemically confirmed)). Schiel 2007 reported a similar number of mild hypoglycaemic episodes per participant (glimepiride 2.2 (37 episodes) versus insulin monotherapy 2.0 (34 episodes)). No episodes of severe hypoglycaemia (i.e. the need for intravenous glucose or glucagon injection) were reported in this trial. Casner 1988 qualitatively reported similar rates of mild hypoglycaemia for both regimens.

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, and four of the eight trials were funded by a pharmaceutical company. In addition, heterogeneity in the definitions used between trials precluded pooling of data. Serious hypoglycaemic episodes were rare.

Other adverse events

One trial investigating the addition of sulphonylurea to insulin therapy reported one myocardial infarction during the insulin-sulphonylurea combination period (Schade 1987).

Adverse events: weight gain

Seven trials (intervention period ranging from two months to one year) reported data on weight change. In six comparisons (Casner 1988; Kyllastinen 1985; Lindstrom 1999; Mauerhoff 1986; Schade 1987; Stenman 1988) the addition of glibenclamide was compared with insulin monotherapy and in one trial tolazamide was added (Kitabchi 1987). The addition of sulphonylureas to insulin resulted in an additional weight gain of 0.4 kg to 1.9 kg compared to -0.8 kg to 2.1 kg in the insulin monotherapy group (220 participants; 7 trials; low-quality evidence; Analysis 1.1). The mean difference (MD) in weight change from baseline for the insulin-sulphonylurea combination therapy compared to insulin monotherapy of the trials with a parallel design (1.1 kg (95% CI -3.1 to 5.3; P = 0.60; 86 participants; 2 trials) showed a weight gain, whereas the MD in weight change from baseline of the trials with a cross-over design ranged between -1 kg to 0.4 kg (134 participants; 5 trials; Analysis 1.1; Analysis 1.2).

The sensitivity analysis for the effect of trial duration indicated that, after excluding the only long-term trial (Casner 1988), the effect on weight remained largely the same. Also, the sensitivity analysis excluding trials with high risk of bias (Casner 1988; Kitabchi 1987; Kyllastinen 1985; Stenman 1988) indicated that these trials had only very modest effects on the association between insulin-sulphonylurea combination therapy and change in weight.

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, and four of the six trials were funded by a pharmaceutical company.

Secondary outcomes

HbA1c and fasting glucose

In 12 comparisons the addition of glibenclamide to insulin therapy was compared to insulin monotherapy. In two comparisons (Feinglos 1998; Simpson 1990) glipizide was added, in two comparisons tolazamide was added (Kitabchi 1987; Longnecker 1986), in one comparison glimepiride was added (Schiel 2007) and in one comparison gliclazide was added (Quatraro 1986). We pooled data in a meta-analysis on HbA1c from nine comparisons (glibenclamide n = 6, gliclazide n = 1, glimepiride n = 1, tolazamide n = 1), with the intervention period ranging from 2 to 12 months (Analysis 1.4). Insulin-sulfphonylurea combination therapy compared with insulin monotherapy was associated with a pooled MD in lowering of HbA1c of -1.0% (95% CI -1.6 to -0.5; P = 0.0003; participants = 316 participants; 9 trials; Analysis 1.3 and Analysis 1.4). In one trial (Casner 1988) metabolic control (glycohaemoglobin) increased less in the intervention than in the control group after a follow-up of one year. In addition, it was not clear whether glycohaemoglobin referred to HbA or HbA1c. After exclusion of this trial the MD did not change substantially.

Insulin-sulphonylurea combination was also associated with a MD in lowering of fasting glucose of -2.29 mmol/L (95% CI -3.23 to -1.35; P < 0.00001; 205 participants; 6 trials; Analysis 1.5 and Analysis 1.6). This was calculated with pooled data from three different sulphonylurea compounds (glibenclamide, glimepiride, tolazamide).

The sensitivity analysis excluding long-term trials (Casner 1988; Quatraro 1986) indicated that there was some impact of long-term trials on the effect on HbA1c. Without these trials, insulin-sulphonylurea combination therapy was associated with a MD in lowering of HbA1c of -0.8% (95% CI -1.2 to -0.3; P = 0.001) compared to insulin monotherapy. There was no impact of the long-term trial (Casner 1988) on the effect on fasting glucose; the MD in lowering of fasting glucose was -2.41 mmol/L (95% CI -3.44 to -1.37; P < 0.00001).

All trials pooled in the meta-analysis on HbA1c and fasting glucose, except Schade 1987, had a high risk of bias in some domain. The MD in HbA1c of the trials with a parallel design was higher compared to the MD in HbA1c of the trials with a cross-over design (-1.3% (95% CI -2.6 to 0.1; P = 0.06; 150 participants; 4 trials) versus -1% (95% CI -1.4 to -0.5; P < 0.00001; 166 participants; 5 trials) (Analysis 1.4). We had to impute SDs for all cross-over trials.

In contrast, for fasting glucose, the pooled effect of trials with a parallel design was substantially lower -1.02 mmol/L (95% CI -2.48 to 0.44; P = 0.17; 71 participants; 2 trials) compared to the pooled effect of the trials with a cross-over design -2.73 mmol/L (95% CI -3.70 to -1.75; P < 0.00001; 134 participants; 4 trials; Analysis 1.5 and Analysis 1.6).

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, and four of the nine trials were funded by a pharmaceutical company.

Lipids

We pooled data from five trials in a meta-analysis on total cholesterol (Groop 1985; Kitabchi 1987; Lindstrom 1999; Osei 1984; Stenman 1988). Insulin-sulphonylurea combination therapy compared to insulin monotherapy was associated with a MD in change from baseline in total cholesterol of -0.04 mmol/L (95% CI -0.2 to 0.1; P = 0.52, 132 participants; 5 trials; Analysis 1.7 and Analysis 1.8). The same trials showed comparable results for HDL-cholesterol and triglycerides: the MD was -0.1 mmol/L (95% CI -0.2 to 0.1; P = 0.31; 108 participants; Analysis 1.9 and Analysis 1.10) and 0.04 mmol/L (95% CI -0.2 to 0.3; P = 0.76; 132 participants; Analysis 1.11 and Analysis 1.12), respectively.

Insulin dose

Heterogeneity in type of insulin (short-, intermediate- and long-acting), units of quantification and the quality of reporting precluded the pooling of data.

Kyllastinen 1985; Longnecker 1986; Osei 1984 reported a fixed insulin dose during the trial period. Casner 1988 reported a decreased mean insulin dose over the trial period in the insulin-sulphonylurea therapy group of -4 U and an increase in the insulin dose in the placebo group of 12 U. Almost no change in mean insulin amount was reported by Mauerhoff 1986: -0.04 difference in insulin dose in the insulin-sulphonylurea-treated participants versus 0.02 in the placebo-treated participants. Kitabchi 1987 reported a mean (SD) insulin amount of 0.7 (0.01) U/kg body weight in the insulin-sulphonylurea therapy group versus 0.9 (0.08) U/kg body weight in the placebo group at six months. In case of unexplained hypoglycaemia, insulin dose was changed in the trial by Lewitt 1989 and Stenman 1988. Lewitt 1989 reported a mean decrease in insulin amount of -4 U after the insulin-sulphonylurea period versus -1 U after the placebo period. Stenman 1988 reported a 2 U to 4 U/visit increase by reported hypoglycaemia or if fasting glucose was less than 6.0 mmol/L, after the insulin-sulphonylurea period a mean (SD) of 24 (3) U was found compared with 32 (4) U after the placebo period. Lindstrom 1999 reported a mean (SD) of 54 (7) U at the end of the run-in period, which decreased to 45 (8) U after the insulin-sulphonylurea therapy period versus an increase to 61 (6) after the placebo period. Quatraro 1986 reported a mean decrease of 33 U (mean (SD): 57 (4) U) after insulin-SU therapy versus a mean decrease of 3 U (mean (SD): 85 (6) U) after placebo treatment. Schade 1987 reported comparable mean (SD) insulin dose after the insulin-sulphonylurea period (54 (6) U) and the placebo period (55

(6) U). Schiel 2007 reported a mean (95%CI) decrease in insulin dose in the insulin-sulphonylurea therapy group from 36 (10 to 62) to 26 (10 to 54) compared with no change in the placebo group from 31 (14 to112) U at both measurements.

Insulin monotherapy versus insulin plus metformin

Primary outcomes

Adverse events: hypoglycaemia

Heterogeneity in the definitions used between trials, and the quality of reporting of hypoglycaemia precluded the pooling of data. All but three trials (Fritsche 2000; Giugliano 1993; Krawczyk 2005) reported hypoglycaemic events, quantitatively or qualitatively. Hirsch 1999 and Robinson 1998 only reported that no severe hypoglycaemia occurred. Relimpio 1998 reported qualitatively that some minor hypoglycaemic events took place in both groups. Avilés 1999 reported three hypoglycaemic events in the insulin-metformin group (with blood glucose levels ranging from 3.1 to 3.9 mmol/L). Yilmaz 2007 reported a similar occurrence of hypoglycaemic events (n = 2 in both groups). None of the participants experienced severe hypoglycaemia in this trial. Hermann 2001 reported two versus zero hypoglycaemic events in the combination therapy group compared with the insulin monotherapy group. Also, Wulffelé 2002 reported comparable occurrences of hypoglycaemic events per person per month in both treatment groups (P = 0.477). Eight events in the metformin group and four in the control group required partner assistance, and none required medical assistance. Strowig 2002 reported less mild hypoglycaemia with insulin plus metformin compared to insulin alone (0.6 versus two episodes per participant per month; P < 0.01). In this trial, one participant taking insulin alone experienced six episodes of hypoglycaemia severe enough to require assistance, including emergency medical treatment.

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, five of the eight included trials were funded by a pharmaceutical company, and in one trial funding was unclear. In addition, heterogeneity in the definitions used between trials precluded pooling; serious hypoglycaemic episodes were rare. In the largest trial (n = 353; Wulffelé 2002) no substantial difference in hypoglycaemic episodes between groups was found.

Other adverse events

Seven trials regarding the addition of metformin reported the number of gastro-intestinal symptoms. The percentage of participants treated with insulin-metformin combination therapy having gastro-intestinal complaints ranged from 7% to 67%, and was mostly higher than in the insulin monotherapy group (Avilés 1999; Giugliano 1993; Hermann 2001; Hirsch 1999; Strowig 2002; Wulffelé 2002; Yilmaz 2007). Some trials mentioned that gastro-intestinal complaints resolved spontaneously. Hermann 2001 reported one myocardial infarction in the metformin-treated group.

Adverse events: weight gain

Data from seven trials (intervention period ranging from three to six months) were pooled in a meta-analysis on weight (Avilés 1999; Krawczyk 2005; Relimpio 1998; Robinson 1998; Strowig 2002; Wulffelé 2002; Yilmaz 2007). Insulin-metformin combination therapy compared to insulin monotherapy was associated with a MD of 2.1 kg less weight gain (95% CI -3.2 to -1.1 kg; P = 0.0001; 615 participants; 7 trials; Analysis 2.1 and Analysis 2.2). A sensitivity analysis for the effect of trial duration indicated that after excluding long-term trials (Avilés 1999; Krawczyk 2005; Yilmaz 2007) there was still less weight gain in the intervention group (-1.7 kg (95% CI -2.9 to -0.4); P = 0.009; 496 participants; 4 trials). All trials pooled in the meta-analysis on weight, except Wulffelé 2002, had some high or unclear risk of bias. The only cross-over trial that was used for pooling in the meta-analysis (Robinson 1998) had a similar result on weight gain compared to the trials with a parallel design.

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, five of the seven included trials were funded by a pharmaceutical company, and in one trial funding was unclear.

Secondary outcomes

HbA1c and fasting glucose

Eleven trials compared the addition of metformin to insulin therapy with insulin monotherapy. We pooled data from nine comparisons in a meta-analysis, with the intervention period ranging from two to six months (Avilés 1999; Fritsche 2000; Giugliano 1993; Hirsch 1999; Relimpio 1998; Robinson 1998; Strowig 2002; Wulffelé 2002; Yilmaz 2007). Insulin-metformin combination therapy compared to insulin monotherapy was associated with a MD in lowering of HbA1c of -0.9% (95% CI -1.2 to -0.5); P < 0.00001; 698 participants; 9 trials; Analysis 2.3 and Analysis 2.4).

Because of considerable heterogeneity it was not possible to pool the results of insulin-metformin combination therapy on fasting glucose. However, the MD in fasting glucose (insulin-metformin combination therapy compared with insulin monotherapy; n = 6 trials) ranged from -5.7 to 1.1 mmol/L. The sensitivity analysis excluding long-term trials (Avilés 1999; Giugliano 1993; Yilmaz

2007) indicated that these trials had hardly any impact on the association between insulin-metformin combination therapy and lowering of HbA1c (MD -0.8% (95% CI -1.3 to -0.3); P = 0.001).The sensitivity analysis excluding trials with high risk of bias (Hirsch 1999; Relimpio 1998; Strowig 2002) indicated that these trials also had almost no impact on the effect of insulin-metformin combination therapy on HbA1c (MD -1.0% (95% CI -1.3 to -0.6); P < 0.0001; 546 participants; 6 trials). The MD in HbA1c of the trials with a parallel design was smaller compared to the MD in HbA1c of the trials with a cross-over design (-0.8%, 95% CI -1.1 to -0.4; P < 0.0001; 634 participants; 7 trials; Analysis 2.4 versus -1.2%, 95% CI -2.1 to -0.2; P = 0.02; 64 participants; 2 trials; Analysis 2.3 and Analysis 2.4).

We rated this as low-quality evidence, because of indirectness and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, five of the nine included trials were funded by a pharmaceutical company, and in one trial funding was unclear.

Lipids

We pooled data from eight trials in a meta-analysis on total cholesterol (Avilés 1999; Fritsche 2000; Giugliano 1993; Relimpio 1998; Robinson 1998; Strowig 2002; Wulffelé 2002; Yilmaz 2007). Insulin-metformin combination therapy compared to insulin monotherapy was associated with a MD in decrease of total cholesterol of -0.3 mmol/L (95% CI -0.5 to -0.1; P = 0.01; 651 participants; Analysis 2.5 and Analysis 2.6). The same pooled trials showed the following MDs for differences in HDL-cholesterol and triglycerides: MD for HDL-cholesterol 0.0 mmol/L (95% CI -0.1 to 0.0); P = 0.65; 651 participants; Analysis 2.7 and Analysis 2.8 and MD for triglycerides -0.2 mmol/L (95% CI -0.4 to 0.1); P = 0.26; 651 participants; Analysis 2.9 and Analysis 2.10.

Insulin dose

Heterogeneity in type of insulin (short-, intermediate- and long-acting), units of quantification and the quality of reporting precluded the pooling of data.

Ten of the 11 trials provided information about insulin requirements. One trial did not report the numbers of insulin doses, it only mentioned that there were no differences in insulin requirements (Hirsch 1999). Insulin doses were titrated to predetermined glycaemic targets based on fasting, postprandial or both glucose values in five trials (Avilés 1999; Fritsche 2000; Hermann 2001; Strowig 2002; Wulffelé 2002). Avilés 1999 reported a decrease in insulin dose in participants treated with metformin of 5 U/d (95% CI -17 to 8; P > 0.2) and an increase in insulin dose of 23 U/d (95% CI 11 to 35; P < 0.001) in participants treated with placebo. Also, Strowig 2002 and Wulffelé 2002 reported a decrease in mean total daily insulin dose in the insulin plus metformin group (from 83 U at baseline to 82 U at week 16 and a change of 7 U (95% CI -6 to -9), respectively) and an increase in total daily insulin dosage in the group treated with insulin alone (from 80 U to 135 U and a change of 1 U (95% CI 0.3 to 3), respectively). Fritsche 2000 (cross-over trial) reported that total insulin requirements decreased by one-third during the metformin treatment (from 53 U (SD 10) to 35 U (SD 7); P = 0.006), while insulin requirements were unchanged during the placebo phase (metformin versus placebo; P = 0.02). In contrast, Hermann 2001 reported no change in mean daily insulin dose after treatment, neither after metformin treatment (0.8 U/kg/day at baseline versus 0.8 U/kg/day after treatment) nor after treatment with placebo (0.7 U/kg/day at baseline versus 0.8 U/kg/day after treatment). In two trials insulin doses were titrated if hypoglycaemia occurred (Relimpio 1998; Yilmaz 2007). Relimpio 1998 reported a small reduction in insulin dose during the trial in the insulin plus metformin group (from 0.63 U/kg (SD 0.1) at baseline to 0.6 U/kg (SD 0.2) at the end of trial), while in participants assigned to insulin there was an increase in insulin dose from 0.7 U/kg (SD 0.1) at baseline to 0.8 U/kg (SD 0.14) at the end of trial. Also, Yilmaz 2007 reported a decrease in participants treated with insulin in combination with metformin (4.2/day; P < 0.001) and an increase in total daily insulin dose in participants treated with insulin alone (12.8 U/day; P < 0.001). Three trials did not report any targets to which insulin doses were titrated (Giugliano 1993; Krawczyk 2005; Robinson 1998). Giugliano 1993 reported a decrease in daily insulin dose in participants treated with insulin in combination with metformin (from 90 U (SD 9) at baseline to 68 U (SD 18) at six months' follow-up) while the daily insulin dose remained constant in the participants treated with insulin and placebo (from 88 U (SD 9) at baseline to 86 U(SD 9) at six months' follow-up). Krawczyk 2005 also reported a decrease in insulin requirement in participants treated with insulin and metformin (from 0.6 U/kg (SD 0.1) at baseline to 0.6 U/kg (SD 0.2) at follow-up; P < 0.05). But in this trial, insulin requirements significantly increased from 0.6 U/kg (SD .0.1) at baseline to 0.6 U/kg (SD 0.2) at follow-up (P < 0.05) in the control group. Robinson 1998 (cross-over trial) reported a relatively constant daily insulin dosage in the insulin plus metformin phase as well as the insulin plus placebo phase (mean change during metformin -2 U; mean change during placebo +0.6 U).

Insulin monotherapy versus insulin plus glimepiride versus insulin plus metformin and glimepiride

Primary outcomes

Adverse events: hypoglycaemia

Schiel 2007 reported a comparable number of mild hypoglycaemic events with the addition of glimepiride and metformin to insulin (2.3 episodes per participant) and with insulin monotherapy (2.0

episodes per participant). No episodes of severe hypoglycaemia (that is, the need for intravenous glucose of glucagon injection) were reported.

Adverse events: weight gain

Schiel 2007 reported minor differences regarding weight gain between the addition of glimepiride and metformin to insulin and insulin monotherapy.

Secondary outcomes

Patient satisfaction

Schiel 2007 assessed patients' treatment satisfaction with the 'Diabetes Treatment Satisfaction Questionnaire'. They found no statistically significant differences between the addition of glimepiride to insulin, the addition of both metformin and glimepiride to insulin or insulin monotherapy.

HbA1c and fasting glucose

Insulin plus metformin and glimepiride (Schiel 2007) showed a greater reduction of HbA1c (-0.7% (SD 0.9)) than the addition of glimepiride to insulin alone (-0.4% (SD 0.5)) or compared with insulin monotherapy (-0.3% (SD 1.0)). The same applied to fasting glucose levels.

Lipids

Data on lipids were not collected.

Insulin dose

Schiel 2007 reported a decrease in insulin requirements in the insulin plus glimepiride and metformin group (from 65 U/day (SD 32) to 54 U/day (SD 37); P = 0.009), whereas there was an increase in the insulin monotherapy group (65 U/day (SD 34) to 71 U/day (SD 35); P = 0.009).

Insulin monotherapy versus insulin plus pioglitazone

Primary outcomes

Adverse events: hypoglycaemia

Heterogeneity in the definitions used between trials, and the quality of reporting of hypoglycaemia precluded the pooling of data. Two trials reported, quantitatively, hypoglycaemic events. Mattoo 2005 reported more subjective hypoglycaemia with insulin plus pioglitazone than with insulin monotherapy (90 events (63%) versus 75 (51%); P < 0.05). They reported that they found no differences in the number of clinical hypoglycaemic episodes (blood glucose < 2.8 mmol/L), but numbers were not reported. Rosenstock 2002 reported that 29 participants (15%) in the 30 mg pioglitazone group, 15 participants (8%) in the 15 mg pioglitazone group, and nine participants (5%) in the placebo group reported hypoglycaemia. All hypoglycaemic episodes were considered mild or moderate.

We rated this as low-quality evidence, because of serious risk of bias. Only one trial reported adequate randomisation and allocation concealment, blinding of the outcome assessor was unclear in all of the trials, and all of the trials were funded by a pharmaceutical company.

Other adverse events

Two trials regarding the addition of pioglitazone reported a higher frequency of oedema with the use of pioglitazone, which increased with dose. Mattoo 2005 reported percentages of 16% versus 4% (pioglitazone 30 mg versus placebo) and Rosenstock 2002 reported 18% and 13% versus 7% (pioglitazone 30 mg and 15 mg versus placebo). In addition, Rosenstock 2002 reported congestive heart failure for two participants receiving 15 mg pioglitazone and two participants receiving 30 mg pioglitazone.

We rated this as low quality evidence, because of indirectness, imprecision and risk of bias; only one from the two included trials reported adequate randomisation and allocation concealment, in all trials blinding of the outcome assessor was unclear and all trials were funded by a pharmaceutical company.

Adverse events: weight gain

We pooled data from two trials (intervention period ranging from three to six months) in a meta-analysis on weight (Mattoo 2005; Mudaliar 2010). Insulin-pioglitazone combination compared to insulin monotherapy was associated with more weight gain (MD 3.8 kg (95% CI 3.0 to 4.6); P < 0.00001; 288 participants; 2 trials; Analysis 3.3). The multi-intervention trial (Rosenstock 2002) showed a greater increase in weight (1.9 kg to 5.3 kg) with combination therapy than with insulin monotherapy (-0.04 kg to 0.9 kg). Weight increased with increasing dosage of pioglitazone.

We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. Only one of the three trials reported adequate randomisation and allocation concealment, in all trials blinding of the outcome assessor was unclear, and all trials were funded by a pharmaceutical company. Although the number of included participants in the meta analysis was low, the minimum of 1.9 kg weight gain is clinically relevant, because it may be partially caused by oedema.

Secondary outcomes

HbA1c and fasting glucose

Three trials (Mattoo 2005; Mudaliar 2010; Rosenstock 2002) compared the addition of pioglitazone to insulin therapy with insulin monotherapy. Because of missing SDs we could not perform a meta-analysis. The mean difference in HbA1c for insulin-pioglitazone combination therapy ranged from -0.5% to -1.0% and for insulin monotherapy from -0.6% to 0% (785 participants; Analysis 3.1).

We pooled data from three comparisons, with the intervention period ranging from three to six months, in a meta-analysis to investigate the effect on fasting glucose (Mattoo 2005; Mudaliar 2010; Rosenstock 2002). We only included the results of the comparison pioglitazone 30 mg versus placebo from Rosenstock 2002. We did not use the results of the comparison between the addition of pioglitazone 15 mg versus placebo in the meta-analysis because it comprised the same placebo group. Insulin-pioglitazone combination therapy showed a greater variation in change in fasting glucose (-1.5 mmol/L to 2.7 mmol/L) compared to insulin monotherapy (-0.6 mmol/L to 0.7 mmol/L) (624 participants; 3 trials; Analysis 3.2).

The sensitivity analysis excluding the long-term trial (Mattoo 2005) indicated that this trial had only a small impact on the association between insulin-pioglitazone combination therapy and lowering of fasting glucose (-2.1 mmol/L (95% CI -3.8 to -0.4); P = 0.02).

We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. Only one of the three trials reported adequate randomisation and allocation concealment, in all trials blinding of the outcome assessor was unclear, and all trials were funded by a pharmaceutical company.

Lipids

Two trials reported data on HDL-cholesterol and LDL-cholesterol (Mattoo 2005; Rosenstock 2002), Rosenstock 2002 also reported data on total cholesterol and triglycerides.

Mattoo 2005 reported a small mean (SE) increase in HDL-cholesterol in participants treated with insulin-pioglitazone combination therapy (from 1.2 (0.03) to 1.4 (0.02) mmol/L) and a small mean (SE) decrease in the placebo group (from 1.2 (0.03) to 1.2 (0.02) mmol/L). For LDL-cholesterol a small mean (SE) reduction in both groups was found (from 3.2 (0.1) to 3.2 (0.1) mmol/L in the insulin-pioglitazone combination therapy group versus 3.2 (0.1) to 3.1 (0.1) mmol/L in the placebo groups.

Rosenstock 2002 investigated two different doses of pioglitazone (15 mg and 30 mg). In this trial a mean change (SD) in total cholesterol of 1.4 (1.1) mg/dL in the 15 mg pioglitazone group and of 0.4 (1.1) mg/dL in the 30 mg pioglitazone group versus -0.7 (1.1) mg/dL in the placebo group was found. For HDL-cholesterol mean change (SD) of 7.1 (1.6) mg/dL in the 15 mg pioglitazone group and of 9.1 (1.6) mg/dL in the 30 mg pioglitazone group versus -0.2 (1.6) mg/dL in the placebo group was found. For LDL-cholesterol a mean change (SD) of 5.1 (1.7) mg/dL in the 15 mg pioglitazone group and of 2.8 (1.8) mg/dL in the 30 mg pioglitazone group versus -1.4 (1.7) mg/dL in the placebo group was found. For triglycerides a mean (SD) change of 5.4 (6.6) mg/dL in the 15 mg pioglitazone group and of -10.4 (6.5) mg/dL in the 30 mg pioglitazone group versus 13.3 (6.6) mg/dL in the placebo group was found.

Insulin dose

Heterogeneity in type of insulin (short, intermediate and long acting), units of quantification and the quality of reporting precluded the pooling of data.

All trials provided information about insulin requirements. Insulin doses were titrated to predetermined glycaemic targets based on fasting, postprandial or both glucose values in two trials (Mattoo 2005; Mudaliar 2010). Mattoo 2005 reported a mean (SE) reduction in insulin dose in participants treated with insulin in combination with pioglitazone of -0.2 U/d/kg (0.02) - P < 0.002; in participants treated with insulin in combination with placebo they found no change in insulin dose (from 0.9 U/d/kg (0.03) at baseline to 0.9 U/d/kg (0.02) at trial end point). Mudaliar 2010 also reported a decrease in insulin dose in the insulin plus pioglitazone group (from 105 U (SD 22) to 92 U (SD19)) but they found an increase in insulin dose in the insulin plus placebo group (from 114 U (SD 11) to 127 U (SD 16). Rosenstock 2002 investigated two different doses of pioglitazone (15 mg and 30 mg). In this trial insulin doses were only titrated if hypoglycaemia occurred. Total daily insulin dose remained stable in participants with insulin monotherapy (71 U (SD 34) at screening versus 70 U (SD 34) at the end of treatment), but decreased in participants with insulin-pioglitazone combination therapy (pioglitazone 15 mg: 70 U (SD 34) at screening versus 67 U (SD 34) at the end of treatment; pioglitazone 30 mg: 72 U(SD 39) at screening versus 64 U (SD33) at the end of treatment.

Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor

Primary outcomes

Adverse events: hypoglycaemia

Heterogeneity in the definitions used between trials, and the quality of reporting of hypoglycaemia precluded the pooling of data.

All trials reported, quantitatively, hypoglycaemic events. Chiasson 1994 reported one severe hypoglycaemic event in the insulin-acarbose group against three episodes in the insulin monotherapy

group. Coniff 1995 and Yilmaz 2007 reported that hypoglycaemic episodes were not statistically significantly different between the treatment groups, both trials reported no severe hypoglycaemic events. Nemoto 2011 also reported no statistically significant difference in the incidence of hypoglycaemia between the insulin-miglitol group and the insulin monotherapy group (39% versus 35%); all hypoglycaemic events in this trial were mild.

We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, three of the four trials were funded by a pharmaceutical company, in one trial there was a high risk of bias because of selective reporting (Coniff 1995), and in another because of incomplete outcome data (Chiasson 1994).

Other adverse events

All trials regarding the addition of alpha-glucosidase inhibitors reported higher frequencies of gastro-intestinal complaints in the alpha-glucosidase inhibitor group than under insulin monotherapy (Chiasson 1994; Coniff 1995; Nemoto 2011; Yilmaz 2007). Coniff 1995 and Nemoto 2011 reported percentages: flatulence 75% versus 35% and 21% versus 12%, diarrhoea 33% versus 13% and 14% versus 4%, respectively.

Adverse events: weight gain

Data from two trials were pooled in a meta-analysis on weight (Coniff 1995; Yilmaz 2007). Insulin-acarbose combination therapy compared to insulin monotherapy showed a MD of -0.5 kg weight change (95% CI -1.2 to 0.3); P = 0.26; 241 participants; 2 trials; Analysis 4.1).

We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, both trials were funded by a pharmaceutical company, and in one trial there was bias because of selective reporting (Coniff 1995).

Secondary outcomes

HbA1c and fasting glucose

Three trials compared (Chiasson 1994; Coniff 1995; Yilmaz 2007) the addition of acarbose to insulin therapy and one trial compared the addition of miglitol (Nemoto 2011) to insulin therapy with insulin monotherapy. We pooled data from three comparisons, with an intervention period of three to six months, in a meta-analysis (Coniff 1995; Nemoto 2011; Yilmaz 2007). Insulin-alpha-glucosidase inhibitor combination therapy was associated with a MD in lowering of HbA1c of -0.4% (95% CI -0.5 to -0.2); P < 0.00001; 448 participants; 3 trials; Analysis 4.2).

Chiasson 1994 and Yilmaz 2007, when comparing combination-therapy with insulin monotherapy, showed a MD of fasting glucose levels of 0.3 mmol/L (95% CI -0.7 to 1.4); P = 0.55; 113 participants; 2 trials; Analysis 4.3).

We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. In most trials randomisation and allocation concealment were unclear, in all trials blinding of the outcome assessor was unclear, all included trials were funded by a pharmaceutical company, and in one trial there was bias because of selective reporting (Coniff 1995).

Lipids

Yilmaz 2007 assessed total cholesterol, HDL-cholesterol and triglycerides at baseline and at the trial end point (six months). In this trial the mean (SD) total cholesterol decreased more in the insulin-only group (from 5.4 mmol/L (1.8) to 5.1 mmol/L (1.2)) compared to the insulin-acarbose combination therapy group (from 5.1 mmol/L (1.5) to 5.0 mmol/L (1.1)).

HDL-cholesterol did not change substantially in both groups after six months (in the insulin-only group from 1.3 mmol/L (0.2) to 1.3 mmol/L (0.2) and in the insulin-acarbose combination therapy group from 1.2 mmol/L (0.3) to 1.1 mmol/L (0.3).

Triglycerides were reduced in both groups at the trial end (in the insulin only group from 2.5 mmol/L (2.4) to 1.8 mmol/L (0.8) and in the insulin-acarbose combination therapy group from 2.1 mmol/L (1.4) to 1.8 mmol/L (0.9).

Insulin dose

Heterogeneity in type of insulin (short-, intermediate- and long-acting), units of quantification and the quality of reporting precluded the pooling of data.

Three of the four trials provided information about insulin requirements (Coniff 1995; Nemoto 2011; Yilmaz 2007). Insulin doses were titrated if hypoglycaemia occurred. Coniff 1995 reported a decrease in total daily insulin dose of 7 U (SD 2) in the insulin plus acarbose group (at baseline 57 U (SD 3)), whereas total daily insulin remained constant in the insulin plus placebo group (baseline: 62 U (SD3); change: 1 U (SD 2). In Nemoto 2011 the mean reduction of insulin dosage to avoid hypoglycaemia was 5 U in participants treated with insulin and miglitol and 2 U in participants treated with insulin and placebo. Yilmaz 2007 reported a decrease in participants treated with insulin in combination with acarbose (3 U/day; P = 0.035) and an increase in total daily insulin dose in participants treated with insulin alone (13 U/day; P < 0.001).

Insulin monotherapy versus insulin plus dipeptidyl peptidase 4 (DPP-4) inhibitor

Primary outcomes

Adverse events: hypoglycaemia

Heterogeneity in the definitions used between trials, and the quality of reporting of hypoglycaemia precluded the pooling of data.
Barnett 2013 reported lower rates of confirmed hypoglycaemia in the insulin-saxagliptin group compared to the placebo group (8 versus 5) and no severe episodes. Hong 2012 reported a higher percentage of hypoglycaemia in the insulin increase group compared to the insulin-sitagliptin combination group (18% versus 8%; severe 5% versus 2%). Fonseca 2007 reported highest rates of confirmed hypoglycaemia (2 versus 3 events per patient-year; P < 0.001; 23% versus 30% of the participants) and severe hypoglycaemia (0 versus 0.1 events per patient-year; P = 0.032; absolute number of events n = 6) with insulin-vildagliptin therapy compared to insulin monotherapy.
We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. Randomisation and allocation concealment were unclear in these trials, in two trials, blinding of the outcome assessor was unclear and one trial was without blinding, and two trials were funded by a pharmaceutical company.

Adverse events: weight gain

Two trials reported data on body weight change with conflicting results. Hong 2012 reported a weight loss for participants in the insulin-sitagliptin group of 0.7 kg (0.1 SD) versus a weight gain of 1.1 kg (0.4 SD) in the insulin monotherapy group. In contrast, in the trial of Fonseca 2007 the body weight of participants in both groups increased during the intervention period (insulin-vildagliptin: 1.3 kg (0.3 SD) versus insulin-placebo: 0.6 kg (0.3 SD) (Analysis 5.1).
We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. Randomisation and allocation concealment was unclear, in one trial, blinding of the outcome assessor was unclear, and another trial was without blinding and funded by a pharmaceutical company.

Secondary outcomes

HbA1c and fasting glucose

The pooled effect of insulin and DPP-4 inhibitor combination therapy compared to insulin monotherapy on HbA1c showed a MD of -0.4% (95% CI -0.5 to -0.4; 265 participants; 2 trials; Analysis 5.2) (Barnett 2013; Hong 2012).
Fonseca 2007 was the only trial with data on fasting plasma glucose. In this trial with 238 participants the MD was -0.6 mmol/L (95% CI -1.6 to 0.4) for insulin-vildagliptin therapy compared to insulin monotherapy.
We rated this as low-quality evidence, because of indirectness, imprecision and risk of bias. Randomisation and allocation concealment was unclear, in one trial blinding of the outcome assessor was unclear and the other was without blinding, and both were funded by a pharmaceutical company.

Lipids

No trials assessed change in lipids.

Insulin dose

Heterogeneity in type of insulin (short-, intermediate- and long-acting), units of quantification and the quality of reporting precluded the pooling of data.
Barnett 2013 reported a similar increase in mean (95% CI) insulin dose for participants treated with saxagliptin (6 U (4 to 7)) and those treated with placebo (7 U (5 to 9)). Fonseca 2007 reported an adjusted mean change from baseline to endpoint of 1 U/day (SD 2) in vildagliptin treated participants and 4 U/day (SD 2) in participants receiving placebo (between-group difference P = 0.315). Hong 2012 reported an overall mean decrease (95% CI) in insulin dose from baseline of 3 U (1 to 5) in the sitagliptin group versus an increase of 10 U (5 to 15) in the insulin increase group.

Sensitivity analyses

Repeating all meta-analyses with a fixed-effect model only yielded small differences compared to the results of the random-effects model. The results of the sensitivity analyses investigating the impact of very long trials and trials with high risk of bias are reported in the relevant paragraphs. Also, the results of the comparisons between trials with a parallel design and trials with a cross-over design are reported in the relevant paragraphs.

Subgroup analyses

We planned two subgroup analyses:

- different oral glucose lowering agent(s) and different types of insulin; and
- timing and frequency of insulin injections.

We divided our results into groups of the added oral glucose-lowering agents. Subgroup analyses regarding the diverse types, timing and frequency of insulin were not feasible. The required information was often not reported or the participant groups used different insulin types and regimens in one trial.

Reporting bias

We did not create funnel plots, because we were not able to include 10 trials or more for a given outcome.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Combinations of insulin and metformin compared with insulin monotherapy for diabetes mellitus

Patient: participants with type 2 diabetes mellitus
Settings: mostly secondary care outpatients and secondary care inpatients
Intervention: metformin plus insulin
Comparison: insulin monotherapy

Outcomes	Insulin monotherapy	Insulin plus metformin	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related morbidity	See comment	See comment	See comment	See comment	Not investigated
Health-related quality of life	See comment	See comment	See comment	See comment	Not investigated
Patient satisfaction	See comment	See comment	See comment	See comment	Not investigated
Adverse events: **a. mild hypoglycaemia** (**episodes per participant**) Follow-up: 12 weeks to 12 months **b. weight gain** (**kg**) Follow-up: 12 weeks to 12 months	a. see comment b. the mean weight gain across control groups ranged from 0 kg to 4.4 kg	a. see comment b. the mean weight gain across intervention groups was **2.1 kg lower** (3.2 kg lower to 1.1 kg lower)	a. 590 (8) b. 615 (7)	a. ⊕⊕◯◯ **low**[a] [b.] ⊕⊕◯◯ **low**[a]	a. comparable occurrences of hypoglycaemic events, severe hypoglycaemic episodes were rare
HbA1c, change from baseline (**%**) Follow-up: 3.5 to 6 months	The mean change in HbA1c across control groups ranged from -1.6% to 0.5%	The mean change in HbA1c in the intervention groups was **0.9% lower** (1.2% lower to 0.5% lower)	698 (9)	⊕⊕◯◯ **low**[b]	-

CI: confidence interval; **HbA1c:** glycosylated haemoglobin A1c

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

[a]Downgraded by two levels because of risk of performance and detection bias and indirectness
[b]Downgraded by two levels because of risk of performance bias and indirectness

Combinations of insulin and pioglitazone compared with insulin monotherapy for diabetes mellitus

Patient: participants with type 2 diabetes mellitus
Settings: mostly secondary care outpatients and clinical research centre
Intervention: pioglitazone plus insulin
Comparison: insulin monotherapy

Outcomes	Insulin monotherapy	Insulin plus pioglitazone	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related morbidity	See comment	See comment	See comment	See comment	Not investigated
Health-related quality of life	See comment	See comment	See comment	See comment	Not investigated
Patient satisfaction	See comment	See comment	See comment	See comment	Not investigated
Adverse events: **a. mild to moderate hypoglycaemia** (**episodes per participant**) Follow-up: 16 weeks to 6 months **b. weight gain** (**kg**) Follow-up: 16 weeks to 6 months **c. oedema** (**%**) Follow-up: 16 weeks to 6 months	a. range 9-75 b. the mean weight gain across control groups ranged from 0.2 kg to 1.7 kg c. range 4%-7%	a. range 15-90 b. the mean weight gain in the intervention groups was**3.8 kg higher** (3.0 kg higher to 4.6 kg higher) c. range 16%-18%	a. 760 (2) b. 288 (2) c. 760 (2)	a. ⊕⊕◯◯ **low**[a] b. ⊕⊕◯◯ **low**[b] c. ⊕⊕◯◯ **low**[b]	a. the proportion of all hypoglycaemic episodes was higher in the pioglitazone-insulin combination group compared to insulin monotherapy; serious hypoglycaemic episodes were rare b. the minimum of 1.9 kg weight gain is clinically relevant, because it may have been partially caused by oedema c. pioglitazone was asso-

					ciated with a higher frequency of oedema which increased with dose. In addition, Rosenstock 2002 reported congestive heart failure for two participants receiving 15 mg pioglitazone and two participants receiving 30 mg pioglitazone
HbA1c, change from baseline (%) Follow-up: 12 weeks to 6 months	See comment	See comment	785 (3)	⊕⊕◯◯ **low**[c]	The mean difference in HbA1c for insulin-pioglitazone combination therapy ranged from -0.5% to -1.0% and for insulin monotherapy from -0.6% to 0%

CI: confidence interval; **HbA1c:** glycosylated haemoglobin A1c

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

[a] Downgraded by two levels because of risk of performance bias, indirectness and imprecision
[b] Downgraded by two levels because of unclear risk of bias in several risk of bias domains, indirectness and imprecision
[c] Downgraded by two levels because of unclear risk of bias in several risk of bias domains, indirectness and imprecision

Combinations of insulin and alpha-glucosidase inhibitors compared with insulin monotherapy for diabetes mellitus

Patient: participants with type 2 diabetes mellitus
Settings: mostly secondary care outpatients
Intervention: alpha-glucosidase inhibitors plus insulin
Comparison: insulin monotherapy

Outcomes	Insulin monotherapy	Insulin plus alpha-glucosidase inhibitors	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related morbidity	See comment	See comment	See comment	See comment	Not investigated
Health-related quality of life	See comment	See comment	See comment	See comment	Not investigated
Patient satisfaction	See comment	See comment	See comment	See comment	Not investigated
Adverse events: **a. mild hypoglycaemia** (**% of participants**) Follow-up: 24 weeks to 12 months **b. weight gain** (**kg**) Follow-up: 24 weeks to 12 months	a. range 0%-35% b. The mean weight gain across control groups ranged from +0.7 kg to +3.6 kg	a. range 0%-39% b. the mean weight gain in the intervention groups was**0.5 kg lower** (1.2 kg lower to 0.3 kg higher)	a. 583 (4) b. 241 (2)	a) ⊕◯◯◯**low**[a] b) ⊕◯◯◯**low**[a]	a. serious hypoglycaemic episodes were rare
HbA1c, change from baseline (%) Follow-up: 3 to 6 months	The mean change in HbA1c across control groups ranged from -1.1% to 0.04%	The mean change in HbA1c in the intervention groups was **0.4% lower** (0.5% lower to 0.2% lower)	448 (3)	⊕◯◯◯**low**[a]	-

CI: confidence interval; **HbA1c:** glycosylated haemoglobin A1c

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

[a] Downgraded by two levels because of unclear or high risk of bias in several risk of bias domains, indirectness and imprecision

Combinations of insulin and dipeptidyl peptidase 4 inhibitors compared with insulin monotherapy for diabetes mellitus

Patient: participants with type 2 diabetes mellitus
Settings: mostly secondary care outpatients
Intervention: dipeptidyl peptidase 4 (DPP-4) inhibitors plus insulin
Comparison: insulin monotherapy

Outcomes	Insulin monotherapy	Insulin + DPP4-inhibitor	No of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related mortality	See comment	See comment	See comment	See comment	Not investigated
Diabetes-related morbidity	See comment	See comment	See comment	See comment	Not investigated
Health-related quality of life	See comment	See comment	See comment	See comment	Not investigated
Patient satisfaction	See comment	See comment	See comment	See comment	Not investigated
Adverse events: **a. hypoglycaemia** (% of participants) Follow-up: 24 weeks to 52 weeks **b. weight gain** (kg) Follow-up: 24 weeks to 52 weeks	a. range 5%-30% (0%-5% severe) b. the mean weight gain across control groups ranged from 0.6 kg to 1.1 kg	a. range 8%-23% (0%-2% severe) b. the mean weight gain in the intervention groups ranged from -0.7 kg to 1.3 kg compared to 0.6 kg to 1.1 kg in the insulin (+ placebo) monotherapy group	a. 503 (3) b. 362 (2)	a) ⊕⊕◯◯ **low**[a] b) ⊕⊕◯◯ **low**[a]	
HbA1c, change from baseline (%) Follow-up: 24 weeks to 52 weeks	The mean change in HbA1c across control groups ranged from -0.2% to -0.3%	The mean change in HbA1c in the intervention groups was **0.4% lower** (0.5% lower to 0.4% lower)	265 (2)	⊕⊕◯◯ **low**[a]	

CI: confidence interval; **DPP-4:** dipeptidyl peptidase 4; **HbA1c:** glycosylated haemoglobin A1c

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

[a] Downgraded by two levels because of unclear or high risk of bias in several risk of bias domains, indirectness and imprecision

DISCUSSION

Summary of main results

We included 37 RCTs with 3227 participants in this review. The addition of an oral glucose-lowering agent to the treatment of people with type 2 diabetes, who were already on insulin therapy, had a beneficial effect on glycosylated haemoglobin A1c (HbA1c) levels . Sulphonylureas had a positive effect on fasting glucose levels. Combination therapy also led to a reduction of the insulin requirements in most trials on insulin-sulphonylurea, insulin-metformin, insulin-pioglitazone, as well as insulin-alpha-glucosidase inhibitor combination therapy. Besides the benefits of an improved glycaemic control and lower required insulin doses, the addition of oral glucose-lowering agents had some unwanted effects. Insulin therapy in combination with pioglitazone resulted in a higher frequency of hypoglycaemic events compared to insulin monotherapy. The combination with pioglitazone caused more weight gain compared to insulin monotherapy. On the other hand, weight gain appeared less when metformin was added. A substantial proportion of participants using metformin experienced gastrointestinal adverse effects. These adverse effects partly resolved spontaneously, however. Alpha-glucosidase inhibitor-users also experienced some gastro-intestinal adverse effects. A substantial proportion of the pioglitazone-users developed oedema, in a few cases combined with heart failure.

Overall completeness and applicability of evidence

The included trials shared an outcome measure of glycaemic control, often accompanied by some other diverse outcome measures. None of the included trials reported the effects on the primary outcomes, diabetes-related morbidity and all-cause mortality, as well as on health-related quality of life and only one reported patient satisfaction. Although the trials were of overall low quality, they could answer questions regarding some outcome measures. One of our objectives was to distinguish the effects between the different oral glucose-lowering agents and insulin regimens. The categorisation in insulin schemes was not possible, since most trials included participants with several kinds of insulin regimens without discriminating between them or without specification of the insulin regimens. In 11 of the 17 trials that investigated sulphonylureas, glibenclamide was added. Glibenclamide is associated with an increased risk of hypoglycaemic events compared to other sulphonylureas (Gangji 2007). So, the number of hypoglycaemic events in this review might be higher than expected with the use of other sulphonylureas.

There are some general barriers for the applicability of the evidence from this review. Abnormal liver and renal function limits the use of many oral agents. Therefore, in most trials participants with renal or liver failure were excluded. In the included trials, patient care reflected trial circumstances instead of routine daily care. This could mean that the participants received a more structured care which may have resulted in more educated and compliant participants. These features may have contributed to the reaching of better glycaemic control and other positive consequences, such as less weight gain and less hypoglycaemia.

The participants ranged in age from 29 to 83 years, and the duration of diabetes ranged from less than 1 to 31 years. These numbers are fairly comparable to the numbers of the type 2 diabetes patients with insufficient glycaemic control on insulin therapy that are currently treated for diabetes in daily practice.

The addition of alpha-glucosidase inhibitors had a small effect on HbA1c (-0.4%), but resulted in a reduction of insulin requirement ranging from 3 to 7 units per day. The baseline HbA1c was approximately 7.6% in the group of alpha-glucosidase inhibitors, compared to 10.7% in the sulphonylurea, 9.0% in the metformin and DPP-4, and 8.3% in the pioglitazone group. Apparently, the participants receiving alpha-glucosidase inhibitors had a better glycaemic control at baseline than the other groups. It is not likely that a pronounced lowering of HbA1c would still be possible in these participants. This indicates the importance of perceiving features of a trial population when interpreting results.

Quality of the evidence

All included trials were RCTs, of which 26 had a parallel design and 11 had a cross-over design. The total number of participants was 3227 (range 9 to 566), with 0% to 100% men. A third of the trials had 30 or fewer participants, partly due to the number of participants in the cross-over trials (mean n = 18 (range 9 to 33)). A lot of trials seemed to have been underpowered and only eight trials discussed power calculations. This might mean that potential significant differences across groups were not detected.

Follow-up periods differed between trials, ranging from 2 to 12 months. Only five trials had a follow-up of 12 months. The outcome values of the trials with a short follow-up might have been different if the trial had continued for longer. We performed sensitivity analyses in which we explored the influence of very long trials on the effect size, to establish how much they dominated the results. These analyses showed that a longer follow-up somewhat strengthened the effects, but that it did not change the direction. Long-term effects on diabetes-related morbidity and all-cause mortality particularly remained unclear.

Many trials had a serious risk of bias in some risk of bias domains, in addition randomisation, allocation concealment and blinding of the outcome assessor was often unclear. Most trials were funded by pharmaceutical companies and often the overall outcome was in favour of the product of the sponsoring company. Some argue that systematic bias favours products which are made by the company funding the research. Explanations include the selection

of an inappropriate comparator to the product being investigated and publication bias (Lexchin 2003).

Potential biases in the review process

It is possible that trials concerning our objective were not published. Only one author did the first rough selection of possible appropriate trials in the references obtained by the searches. This approach might have caused some selection bias.

Agreements and disagreements with other studies or reviews

Yki-Jarvinen 2001 draws some similar conclusions in a non-systematic review with 25 comparisons in previously insulin-treated type 2 diabetes patients. She showed better glycaemic control with the addition of metformin, sulphonylurea and thiazolidinediones compared to the treatment of insulin-treated type 2 diabetes patients. Metformin was associated with less weight gain, whereas the addition of sulphonylureas showed no difference and the combination with thiazolidinediones caused more weight gain than insulin alone. The occurrence of hypoglycaemia was sparsely described in the trials included in Yki-Jarvinen 2001. The trials reported more hypoglycaemic events with sulphonylurea (one trial) and thiazolidinediones (three trials) and fewer with metformin (one trial). There was no definite conclusion in favour of one treatment over the other with respect to the effects on lipids.

Goudswaard 2004b executed a Cochrane Review in insulin-naive patients with the same objectives as ours. They did not include trials that observed combination therapy with thiazolidinediones. In contrast to our finding that combination therapy gives better glycaemic control, they found similar glycaemic control in combination therapy and insulin monotherapy. They demonstrated, as we did, a beneficial effect of metformin and no effect of sulphonylurea on weight gain. An explanation of the difference between Goudswaard 2004b and our review could be the difference in the history of insulin therapy of the included participants. The participants in our review experienced a period of failing oral agents after which insulin monotherapy was started and the majority was included at the moment they did not reach the aimed glycaemic control with insulin monotherapy. Unfortunately we did not have enough data about the duration of insulin therapy at the moment of inclusion. Goudswaard concluded that the start of insulin treatment with or without the continuation of oral agents had positive effects on glycaemic control. However, the additional effect of the combination of insulin with oral glucose-lowering agents on glycaemic control in insulin-naive patients was small. To conclude: the effectiveness of adding oral glucose-lowering agents to insulin therapy is differential depending on whether they are administered in insulin-naive patients or in patients who are already on insulin therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Adding oral glucose-lowering agents to insulin therapy in people with type 2 diabetes with inadequate glycaemic control reduces glycosylated haemoglobin A1c (HbA1; range: -0.4% to -1.0%; low quality evidence). In most trials the participants with combination therapy needed less insulin, whereas insulin requirements increased or remained stable in participants with insulin monotherapy. Because adding an oral glucose-lowering agent may also lead to weight gain, more hypoglycaemic events and other adverse effects like gastro-intestinal complaints, oedema and heart failure (all low quality evidence), it is important that clinicians meticulously weight the advantages of combination therapy against possible negative effects in every individual patient. The evidence presented in this review is of 'low quality', therefore there is still uncertainty about the estimate of effect presented, and further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Implications for research

As the majority of the included trials seemed to be underpowered and follow-up was often short (< 12 months in all but five of the trials). Multi-centre trials with a long follow-up focusing on diabetes-related morbidity and mortality and all-cause mortality as outcome measures are needed.

None of the included trials assessed health-related quality of life. Future trials investigating the effects on patient-reported outcomes, like health-related quality of life, health status, wellbeing and treatment satisfaction are also needed. We have found seven ongoing trials, four with a subgroup for the combination insulin-DPP IV inhibitor versus insulin monotherapy, one with a thiazolidinedione combined therapy and one with the combination insulin-ipragliflozin (approved in Japan).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Avilés 1999

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio:** 1:1 **Superiority design**
Participants	**Inclusion criteria**: type 2 diabetes diagnosed after 30 years of age and treated for at least 2 years with at least 50 units of insulin per day, age at enrolment younger than 70 years and HbA1c level ≥ 8% **Exclusion criteria**: pregnant women; women trying to become pregnant; patients with a serum creatinine concentration greater than 132.6 mmol/L (1.5 mg/dL) or hepatic enzyme levels greater than twice the upper limit of normal; and patients with medical conditions that could promote lactic acidoses such as renal or hepatic disease, congestive heart failure or chronic obstructive pulmonary disease **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin: intervention 96.2 ± 44.9 U/day, control 96.9 ± 43.3 U/day **Titration period**: 8 weeks
Outcomes	**Outcomes reported in abstract of publication**: **Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, fasting plasma glucose), C-peptide, body weight, lipids, insulin dose, adverse events (hypoglycaemia)
Study details	**Run-in period**: 8 weeks to titrate metformin in maximal dosage **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Bristol-Myers-Squibb **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the efficacy of metformin in combination with insulin in patients with type 2 diabetes mellitus poorly controlled with insulin therapy alone"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate

Avilés 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "Patients who met the inclusion criteria were randomly assigned in a double-blind fashion to receive metformin or placebo in addition to their current insulin therapy"
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "Patients who met the inclusion criteria were randomly assigned in a double-blind fashion to receive metformin or placebo in addition to their current insulin therapy"
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "Patients who met the inclusion criteria were randomly assigned in a double-blind fashion to receive metformin or placebo in addition to their current insulin therapy"
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: it is unclear if the outcome assessor were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is unclear if the outcome assessor were blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: it is unclear if the outcome assessor were blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: in table 3 of the article the incidence of adverse events is listed for both groups
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: data were collected, analysed and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: was reported
Selective reporting (reporting bias)	Low risk	**Comment**: data on blood pressure, medical history and the physical examination is not reported. However this is not likely to bias the results of the other outcomes

Avilés 1999 (*Continued*)

Other bias	Low risk	**Comment**: no incomplete outcome data (attrition bias) Diabetes-related mortality

Barnett 2013

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 2:1** **Equivalence design** **Controlled clinical trial (CCT): a Phase IIIb, extension of RCT**
Participants	**Inclusion criteria**: Men and women aged 18-78 years with T2DM, fasting C-peptide C 0.8 ng/mL, body mass index (BMI) B45 kg/m2, and inadequate glycaemic control (HbA1c 7.5%-11.0%) on a stable regimen of insulin (30-150 U/day, with B 20% variation in total daily dose for C 8 weeks before screening) **Exclusion criteria**: poorly controlled diabetes (e.g. marked polyuria and polydipsia with 10% weight loss during the 3 months before screening); history of diabetic ketoacidosis or hyperosmolar nonketotic coma; history of significant cardiovascular disease or haemoglobinopathy; contraindications to DPP-4 inhibitors, metformin, or insulin; or pregnancy, breast feeding, or not using an acceptable method of birth control **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: unclear **Treatment before study**: intermediate-acting insulin, long-acting (basal) insulin, or a premixed formulation in which rapid- or short-acting insulin constituted one component was permitted. Participants could also be taking metformin if the daily dose was stable for C 8 weeks before screening **Titration period**: 4 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): mean change from baseline to 52 weeks in HbA1c
Study details	**Total study duration**: 56 weeks **Run-in period**: 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Bristol-Myers-Squibb and AstraZeneca **Publication status**: peer-reviewed journal
Stated aim of study	To evaluate the safety and efficacy of the DPP4 inhibitor saxagliptin vs placebo as add-on therapy in type 2 diabetes inadequately controlled with insulin with or without metformin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Patients were stratified based on metformin use at enrolment and randomised 2:1 via an interactive voice response system using a blocked randomisation schedule to receive saxagliptin 5 mg (Onglyza, Bristol-Myers Squibb Company, Princeton, NJ, USA, and AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) or placebo once daily as add-on to baseline therapy with insulin or insulin plus metformin."
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "To maintain blinding to patients and physicians, saxagliptin and placebo tablets were identical in appearance, and bottles were printed with a blinded label."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "To maintain blinding to patients and physicians, saxagliptin and placebo tablets were identical in appearance, and bottles were printed with a blinded label."
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Comment**: FGP and lipids not assessed
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Quote from publication**: "To maintain blinding to patients and physicians, saxagliptin and placebo tablets were identical in appearance, and bottles were printed with a blinded label."
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	High risk	**Comment**: no exact SDs are reported as text only in the figures
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	High risk	**Comment**: no exact SDs are reported as text only in the figures **Comment**: incomplete for FPG and lipids
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: available

Selective reporting (reporting bias)	High risk	**Comment**: no exact SDs are reported as text only in the figures
Other bias	Unclear risk	**Comment**: sponsoring by a pharmaceutical company

Casner 1988

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with non-insulin-dependent diabetes previously treated with an oral hypoglycaemic agent, currently receiving at least 25 U insulin/day with a fasting blood glucose value of 140 mg/dL or greater **Exclusion criteria**: history of allergic reactions to sulphonylurea therapy or a serious debilitating disease that would limit ability to participate in the study **Diagnostic criteria**: NDDG 1979
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin: intervention 65.9 U/day and control 66.9 U/day **Titration period**: variable
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, oral glucose tolerance test, fasting blood glucose), side effects, C-peptide, insulin dose, weight
Study details	**Total study duration**: 1 year **Run-in period**: variable **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Upjohn Company and an intramural grant from Texas Tech Health Sciences Center **Publication status**: peer-reviewed journal
Stated aim of study	Can the combination of a sulphonylurea and insulin improve glycaemic control? If this is true, can it be done with lower doses of exogenous insulin? Can the effect be maintained over a long period of time?
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate

Casner 1988 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "Patients and physicians were blinded regarding laboratory results and study medication but not on insulin" **Comment**: so patients were not blinded for their weight gain (this is the only adverse event mentioned)
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "Patients and physicians were blinded regarding laboratory results and study medication but not on insulin" **Comment**:
Blinding of participants and personnel (performance bias) Insulin dose	High risk	**Quote from publication**: "Patients and physicians were blinded regarding laboratory results and study medication but not on insulin"
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: it is unclear if the outcome assessment was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is unclear if the outcome assessment was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: it is unclear if the outcome assessment was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain was reported for both groups
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: data were reported for both groups
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data were reported for both groups
Selective reporting (reporting bias)	Low risk	**Comment**: data which was collected was also reported
Other bias	Low risk	**Comment**: no other concerns

Chiasson 1994

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with non-insulin-dependent diabetes of at least 6 months, HbA1c > 7%, normal renal and hepatic function **Exclusion criteria**: poor controlled hypertension, documented gastrointestinal disease, taking medication likely to alter gut motility or absorption, taking medications to lower lipid levels **Diagnostic criteria**: WHO 1985
Interventions	**Number of study centres**: 7 **Treatment before study**: insulin, dose is not stated in the publication **Titration period**: 6 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, oral glucose tolerance test, fasting blood glucose), side effects, hypoglycaemia, C-peptide, lipids, blood count, biochemistry, vitamins, minerals
Study details	**Total study duration**: 12 months **Run-in period**: 6 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Miles Canada **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "to evaluate the long-term efficacy of acarbose, an alpha-glucosidase inhibitor, in improving glycaemic control in patients with non-insulin-dependent diabetes mellitus"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded

Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: (from the abstract) " Design: a 1-year, multicenter, randomised, double-blind, placebo-controlled study" (from the main text) "Acarbose or placebo was taken with the first sip of the liquid meal" **Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Quote from publication**: (from the abstract) " Design: a 1-year, multicenter, randomised, double-blind, placebo-controlled study" (from the main text) "Acarbose or placebo was taken with the first sip of the liquid meal" **Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: it is not clear whether the physician or the outcome assessor is besides the participants blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: none
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	High risk	**Comment**: data on lipids is only mentioned, no analyses is performed or shown
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data were presented for both groups
Selective reporting (reporting bias)	Unclear risk	**Comment**: more figures than tables, that causes unclear reporting
Other bias	Unclear risk	**Comment**: funded in part by a pharmaceutical company

Coniff 1995

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes of at least 6 months, stable body weight, not receiving sulphonylurea for at least 2 months **Exclusion criteria**: not stated **Diagnostic criteria**: WHO 1985
Interventions	**Number of study centres**: multicentre, number of centres not mentioned, 4 centres are mentioned in the acknowledgements **Treatment before study**: insulin: 56.8 (SE3.4) IU/day (intervention), 62.2 (SE3.3) IU/day **Titration period**: 6 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, glucose tolerance tests, fasting blood glucose), insulin requirements **Secondary outcomes** (as stated in the publication): lipids, hypoglycaemic episodes
Study details	**Total study duration**: 6 weeks pretreatment, 24 weeks double-blind, 6 weeks follow-up (discontinuation acarbose) **Run-in period**: 6 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Miles pharmaceutical division **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To determine whether a forced titration of acarbose (from 50 to 300 mg three times daily) administered over a 24-week period, in conjunction with diet and insulin therapy, improves glycaemic control and reduce daily insulin requirements in insulin-requiring type II diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Quote from publication**: (abstract and main text): "This double-blind, randomised, multicenter, placebo-controlled

		study..." (main text) "The double-blind endpoint was defined as last visit observation for each patients" **Comment**: at all measurement occasions the efficacy and safety tests were assessed. However it is not clear whether the physician or the outcome assessor was blinded in addition to the participants
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: (abstract and main text): "This double-blind, randomised, multicenter, placebo-controlled study..." (main text)"The double-blind endpoint was defined as last visit observation for each patients" **Comment**: at all measurement occasions the efficacy and safety tests were assessed. However it is not clear whether the physician or the outcome assessor was blinded in addition to the participants
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Comment**: data are reported
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Quote from publication**: (abstract and main text): "This double-blind, randomised, multicenter, placebo-controlled study..." (main text) "The double-blind endpoint was defined as last visit observation for each patient" **Comment**: at all measurement occasions the efficacy and safety tests were assessed. However it is not clear whether the physician or the outcome assessor was blinded in addition to the participants
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: (abstract and main text): "This double-blind, randomised, multicenter, placebo-controlled study..." (main text) "The double-blind endpoint was defined as last visit observation for each patient" **Comment**: at all measurement occasions the efficacy and safety tests were assessed. However it is not clear whether the physician or the outcome assessor was blinded in addition to the participants

Coniff 1995 (*Continued*)

Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Quote from publication**: (abstract and main text): "This double-blind, randomised, multicenter, placebo-controlled study..." (main text)"The double-blind endpoint was defined as last visit observation for each patients" **Comment**: at all measurement occasions the efficacy and safety tests were assessed. However it is not clear whether the physician or the outcome assessor was blinded in addition to the participants
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from publication**: "Most adverse events involved.....There were no significant differences between treatment groups in the incidence of adverse events related to other body systems "
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data were reported
Selective reporting (reporting bias)	High risk	**Comment**: serum lipids and SGOT and SGPT values were not reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Feinglos 1998

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: insulin-requiring type 2 diabetes, total daily insulin dose $\geq$ 40 units, insulin monotherapy $\geq$ 1 year prior to the study **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin NPH and regular 80.8 (range 40-210) U/day **Titration period**: 1 week
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (plasma glucose, HbA1c), C-peptide, plasma free insulin levels, lipoprotein (TC, TG, HDL, LDL, VLDL)

Feinglos 1998 (*Continued*)

	, insulin dose, BMI
Study details	**Total study duration**: 8 months **Run-in period**: 1 week **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Pfizer Pharmaceuticals, Lifescan, National Center for Research Resources **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To determine the effect(s) on glucose control, insulin dose and circulating insulin levels of the addition of a sulphonylurea (glipizide) to the treatment regimen of patients with insulin-requiring type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "This study was a double-blind crossover comparison of insulin and placebo vs. insulin and glipizide. " **Comment**: probably the participant and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "This study was a double-blind crossover comparison of insulin and placebo vs. insulin and glipizide. " **Comment**: probably the participant and the personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: it is unclear if the outcome assessor was blinded

Feinglos 1998 (*Continued*)

Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: all outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: all outcome data were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Fonseca 2007

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: participants had to have received only injectable insulin for at least 3 months, at a dose of at least 30 U/day for a minimum of 4 weeks prior to enrolment. Age 18-80 years, HbA1c 7.5-11.0%, fasting plasma glucose < 15 mmol/L and BMI 22-45 kg/m² **Exclusion criteria**: people with type 1 diabetes, diabetes resulting from pancreatic injury or secondary forms of diabetes. People with acute metabolic diabetic complications within the past 6 months, serious cardiac conditions or clinically significant liver disease. Any of the following laboratory abnormalities: alanine transaminase > 3 x the upper limit of normal; direct bilirubin > 1.3 x the upper limit of normal; serum creatinine > 220 μmol/L; fasting triacylglycerol > 7.9 mmol/L **Diagnostic criteria**: based on the investigator's diagnosis and on the patient's medical record
Interventions	**Number of study centres**: 68 **Treatment before study**: insulin: intervention 81.2 ± 44.8 U/day and control 81.9 ± 49.4 U/day **Titration period**: 4 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, fasting plasma glucose), insulin dose and number of injections, fasting lipids, bodyweight
Study details	**Total study duration**: 24 weeks **Run-in period**: 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Novartis **Publication status**: peer-reviewed journal

Stated aim of study	Quote from publication: "To assess the efficacy and tolerability of vildagliptin added to added to insulin therapy in patients with type 2 diabetes."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "This was a 24-week, randomised, double-blind, placebo-controlled, parallel-group study...." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "All assessments were made by central laboratories." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "This was a 24-week, randomised, double-blind, placebo-controlled, parallel-group study...." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain and hypoglycaemia were collected and reported

Fonseca 2007 (*Continued*)

Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: data on all outcome measures were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose was collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: post-treatment BMI not reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Fritsche 2000

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: not clearly defined: severe obesity, moderate glycaemic control, intensive insulin therapy with regular specialist consultations for regimen adaptation for at least 6 months prior to inclusion **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: insulin: NPH 26 ± 6 U/day and regular 27 ± 5 U/day control: insulin: NPH 20 ± 4 U/day and regular 26 ± 4 U/day **Titration period**: 6 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, blood glucose levels, OGTT), insulin dose, lipids, C-peptide, lactate
Study details	**Total study duration**: 24 weeks **Run-in period**: 6 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Lipha Pharmaceuticals (medication) **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To examine the effect of adjunct metformin in 13 severely obese type 2 diabetes patients in sub optimal glucaemic control pretreated with intensified insulin therapy" on glycaemic control, insulin dosage, lipid profile and bodyweight
Notes	

Fritsche 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Patients were randomly assigned to either metformin or placebo treatment (double-blind)...."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "patients were randomised in a double-blind fashion..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "patients were randomised in a double-blind fashion..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: all outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: all outcome data were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funding by a pharmaceutical company

Giugliano 1993

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: age at diagnosis > 40 years, duration of disease > 3 years, duration of previous response to oral drugs > 1 year, inadequate metabolic control even when on maximal doses of sulphonylurea **Exclusion criteria**: age > 70 years, creatinine > 1.2 mg/dL, ischaemic of wasting disease, acute severe diseases **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1? **Treatment before study**: intervention: insulin: lente + regular 2 dd 90 ± 9 U/day; control: insulin lente + regular 2 dd 88 ± 9.4 U/day **Titration period**: 4 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, daily glucose levels), lipids, blood pressure, body weight, insulin dose, beta-cell function (C-peptide, insulin)
Study details	**Total study duration**: 7 months **Run-in period**: 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: not reported **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the effectiveness and safety of metformin in obese type 2 diabetic patients poorly controlled by conventional insulin therapy."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Phase II (double-blind) patients were randomly assigned to continue to receive placebo or to treatment with metformin for six months"
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "Phase II (double-blind) patients were randomly assigned to continue to receive placebo or to treat-

Giugliano 1993 (*Continued*)

		ment with metformin for six months **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "Phase II (double-blind) patients were randomly assigned to continue to receive placebo or to treatment with metformin fro six months" **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: all outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: no
Other bias	Low risk	**Comment**: no

Groop 1985

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: onset of non-ketotic diabetes after the age of 35 years, treated with oral antidiabetic drugs for at least 1 year before insulin therapy was started due to secondary drug failure **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 0.75 ± 0.11 IU/kg per day **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): insulin dose and bodyweight, glycaemic control (HbA1c, FBG, blood glucose profile), serum insulin levels, C-peptide, lipids

Groop 1985 (*Continued*)

Study details	**Total study duration**: 24 weeks (2 x 8 = 16 weeks intervention) **Run in period:** 8 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: none **Publication status**: peer review journal
Stated aim of study	Quote from publication: "To investigate the metabolic effects of the combination of insulin and sulphonylurea (glibenclamide) during controlled long-term therapy in NIDDM patients whose hyperglycaemia could not be controlled by insulin alone."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "...the patients were randomly allocated to 8 weeks of treatment with ....."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "In a double-blind cross-over study we compared the effect of...." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "In a double-blind cross-over study we compared the effect of...." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "In a double-blind cross-over study we compared the effect of...." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Groop 1985 (*Continued*)

Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data of adverse events (myocardial infarct, weight gain) were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: all outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: all data on insulin dose were collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: unclear graphical reporting of data
Other bias	Low risk	**Comment**: none

Hermann 2001

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with insulin therapy > 1 year. BMI > 27 kg/m2 for men and > 25 kg/m2 for women. HbA1c value higher than the upper reference limit + 2%. Insulin dose 0.4-1.0 U/kg/day. C-peptide after 1 mg glucagon intravenously > 0.6 nmol/L **Exclusion criteria**: treatment with oral antidiabetic agents within the last 6 months. Presence of any of the usual contraindications for metformin. Abnormal serum creatinine concentration. Transaminases > 2 x the upper reference limit. Overconsumption of alcohol **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 3 **Treatment before study**: insulin: intervention 0.75 ± 0.28 U/kg/day and control 0.73 ± 0.23 U/kg/day **Titration period**: 2 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, FBG), bodyweight and BMI, insulin dose, lipids **Secondary outcomes** (as stated in the publication): waist-hip ratio, blood pressure, fibrinogen, C-peptide, serum B12, compliance

Hermann 2001 (*Continued*)

Study details	**Total study duration**: 15 months **Run-in period:** 12 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: none **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To assess the adjunct effect of metformin to insulin in type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "...the patients entered a 12-month double-blind treatment phase randomly allocated to metformin or placebo in parallel groups and as adjunct to their current insulin therapy"
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "Randomization was performed by center in block of four."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "The study was a 12-month double-blind placebo-controlled trial..." **Comment**: probably the participants and personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "The study was a 12-month double-blind placebo-controlled trial..." **Comment**: probably the participants and personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "The study was a 12-month double-blind placebo-controlled trial..." **Comment**: probably the participants and personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Hermann 2001 (*Continued*)

Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on adverse events were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: data were reported graphically, unclear
Other bias	Unclear risk	**Comment**: medication was funded by a pharmaceutical company

Hirsch 1999

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with less than optimal control on insulin therapy alone **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin: dose not stated **Titration period**: not stated
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, FPG), bodyweight, blood pressure, insulin dose, fasting insulin levels, fasting C-peptide, hypoglycaemia
Study details	**Total study duration**: 5 months **Run-in period:** no **Study terminated early (for benefit/because of adverse events):** no

Hirsch 1999 (*Continued*)

Publication details	**Language of publication**: English **Funding source**: Bristol-Myers-Squibb **Publication status**: peer-reviewed journal	
Stated aim of study	Quote from publication: "To prospectively evaluate the efficacy of metformin added to insulin for patients with type 2 diabetes with less than optimal glycaemic control on insulin alone."	
Notes	Publication is a letter	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "... a 5-month single-center prospective double-blind placebo-controlled study" **Comment**: probably the participants and personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "... a 5-month single-center prospective double-blind placebo-controlled study" **Comment**: probably the participants and personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "... a 5-month single-center prospective double-blind placebo-controlled study" **Comment**: probably the participants and personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Hirsch 1999 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on adverse events were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: the outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	High risk	**Comment**: short report of the trial
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Hong 2012

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: type 2 diabetes mellitus; age 30-70 years; HbA1c 7.5%-11.0%; fasting plasma glucose (FPG) < 15 mmol/L (270 mg/dL) and body mass index (BMI) 18-35 kg/m2. Female participants had to be non-fertile or of childbearing potential using a medically approved birth control method **Exclusion criteria**: type 1 diabetes, gestational diabetes or diabetes with identifiable secondary causes, significant renal impairment (estimated creatinine clearance < 50 ml/min) or elevated (> 100) alanine or aspartate aminotransferase (ALT or AST). Participants who were taking medications, aside from antidiabetic medications, known to affect glycaemic control, such as glucocorticoids were also excluded **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 2 **Treatment before study**: insulin injections for at least 3 months; at a dose of at least 10 U/day and for a minimum of 4 weeks prior to enrolment **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): change in HbA1c (from baseline to 24 weeks) **Secondary outcomes** (as stated in the publication): proportion of participants achieving HbA1c < 7%, body weight, waist circumference, change in insulin dose, change in C-peptide, safety (AE, SAE, hypoglycaemia, liver/renal function)
Study details	**Total study duration**: 24 weeks **Study terminated early (for benefit/because of adverse events):** no

Publication details	**Language of publication**: English **Funding source**: non commercial; National Research Foundation **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "This study compared the efficacy and tolerability of adding sitagliptin, an oral dipeptidyl peptidase-4 inhibitor, and an up to 20% increase in insulin dose in patients with uncontrolled type 2 diabetes on insulin therapy."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not mentioned in the publication
Allocation concealment (selection bias)	Unclear risk	**Comment**: not mentioned in the publication
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Comment**: participants and personnel were not blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	High risk	**Comment**: participants and personnel were not blinded
Blinding of participants and personnel (performance bias) Insulin dose	High risk	**Comment**: participants and personnel were not blinded
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Comment**: the outcome assessor was not blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	High risk	**Comment**: the outcome assessor was not blinded
Blinding of outcome assessment (detection bias) Insulin dose	High risk	**Comment**: the outcome assessor was not blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: all end points shown
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: all end points shown

Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: all end points shown
Selective reporting (reporting bias)	Low risk	**Comment**: none
Other bias	Low risk	**Comment**: none

Kitabchi 1987

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: obese (130%-200% IBW) women with type 2 diabetes mellitus on prior insulin therapy who were poorly controlled but without severe diabetic complications **Exclusion criteria**: history of diabetic ketoacidosis **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 0.89 ± 0.07 U/kg/BW **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, FBG, 2-hour post prandial glucose), bodyweight, insulin requirement, total cholesterol, triglyceride, C-peptide
Study details	**Total study duration**: 6 months **Run-in period:** no **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: NIH, Abe Goodman Fund for Diabetes Research, Eli Lilly, Upjohn Company **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To assess the efficacy of combined NPH and tolazamide in enhancing insulin secretion and tissue sensitivity in obese patients with type 2 diabetes mellitus who were maintained at the same weight and glycaemic index during both phases of the study."
Notes	Several young participants with long-term insulin use and without severe obesity

Risk of bias

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

Kitabchi 1987 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**: unclear if it was a blinded trial
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**: unclear if it was a blinded trial
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**:unclear if it was a blinded trial
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**: unclear if it was a blinded trial
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**: unclear if it was a blinded trial
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Quote from publication**: "In a randomised cross-over trial, ..." **Comment**: unclear if it was a blinded trial
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were reported
Selective reporting (reporting bias)	Low risk	**Comment**: outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Krawczyk 2005

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: type 2 diabetes patients, diabetes duration of at least 5 years, BMI > 30, Insulin > 40 IU/day **Exclusion criteria**: contraindication for metformin, body weight change > 5 kg last year **Diagnostic criteria**: age > 35 years at diagnosis and at least 1 year of effective treatment with oral glucose-lowering agents
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 2dd, 59.5 (15.4) IU/day intervention, 55.6 (16.3) IU/day control **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, glucose) , bodyweight, insulin dose, WHR
Study details	**Total study duration**: 6 months **Run-in period**: none **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: Polish **Funding source**: not reported **Publication status**: unknown
Stated aim of study	Quote from publication: "To assess the influence of adding metformin to insulin monotherapy on metabolic control in type 2 diabetes patients."
Notes	Statistical methods not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: randomisations in two groups of 20 participants
Allocation concealment (selection bias)	Unclear risk	**Comment**: randomisations in blocks of 4 (20 participants per group)
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Comment**: it is unclear if the study was blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is unclear if the study was blinded

Krawczyk 2005 (*Continued*)

Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Comment**: it is unclear if the study was blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: it is unclear if the study was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: it is unclear if the study was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: it is unclear if the study was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: weight gain was reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	High risk	**Comment**: statistical methods were not described

Kyllastinen 1985

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: elderly patients, type 2 diabetes inadequately controlled by insulin **Exclusion criteria**: surgical operation; lack of co-operation **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 58 ± 3 IU/day (n = 1 once daily, n = 8 twice daily) **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, FPG), daily insulin dose, C-peptide, bodyweight, triglyceride, total cholesterol, HDL-cholesterol, Na, K, creatinine, chloride

Kyllastinen 1985 (*Continued*)

Study details	**Total study duration**: 4 months **Run-in period: none** **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: none **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To determine whether glibenclamide could improve glycaemic control in patients not adequately controlled by insulin."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "A double blind, cross over trial was assigned ...after randomisation patients were given either glibenclamide or placebo....5 patients started with glibenclamide and 4 with placebo" **Comment**: probably the participants and personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "A double blind, cross over trial was assigned...after randomisation patients were given either glibenclamide or placebo....5 patients started with glibenclamide and 4 with placebo" **Comment**: probably the participants and personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Kyllastinen 1985 (*Continued*)

Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	High risk	**Comment**: only 9 participants included

Lewitt 1989

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: insulin treated participants who were not ketosis prone and had previous primary or secondary oral hypoglycaemic failure **Exclusion criteria**: combined insulin-sulphonylurea therapy **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 47.3 ± 21.3 U/day. Insulin regimen: once or twice daily **Titration period**: none
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, self-monitored fasting and postprandial glucose), BMI, C-peptide, insulin dosage
Study details	**Total study duration**: 6 months **Run-in period: none** **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: none **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To determine which patient characteristics best predict a beneficial response to combined Insulin-gliburide therapy."
Notes	
Risk of bias	

Lewitt 1989 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "Glyburide was compared with placebo in a double-blind crossover design" **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "Glyburide was compared with placebo in a double-blind crossover design" **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "Glyburide was compared with placebo in a double-blind crossover design" **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported

Lewitt 1989 (*Continued*)

Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Low risk	**Comment**: none

Lindstrom 1999

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: participants with type 2 diabetes with insulin monotherapy for 6-36 months **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: unclear **Treatment before study**: insulin 54.5 ± 6.9 U/day (at the end of the run-in period) Insulin regimen: four times daily, regular plus intermediate insulin **Titration period**: 4-8 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (blood glucose, HbA1c), insulin dose, C-peptide, lipoproteins, IGF-1, SHBG, serum testosterone
Study details	**Total study duration**: 7-8 months **Run-in period:** 4-8 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Swedish Medical Research Council, Swedish Diabetes Association, County Council of Östergötland, Novo Nordisk Insulin Fund **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To study whether changes in endogenous insulin secretion at the same glycaemic control affect the plasma concentration of lipoproteins in patients with type 2 diabetes mellitus."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate

Lindstrom 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "...in this randomised double-blind crossover study." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "...in this randomised double-blind crossover study." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "...in this randomised double-blind crossover study." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Unclear risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: also funded by pharmaceutical company

Longnecker 1986

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: severely hyperglycaemic patients with type 2 diabetes with insulin monotherapy failed to sulphonylurea therapy Controls were nondiabetic women comparable with patients in age and weight **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin 64 ± 5.6 U/day (insulin regimen: once or twice daily, regular and/or isophane insulin) **Titration period**: 1 week
Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, fasting blood glucose), plasma glucose and C-peptide before and after standardised meal, weight, C-peptide, drug compliance, side effects
Study details	**Total study duration**: 20 weeks **Run-in period:** 1 week **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Public Health Service Grant, ADA, Upjohn **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the efficacy of adding tolazamide, an oral agent, to insulin in a group of severely hyperglycaemic patients with NIDDM, all of whom had previously failed to respond to therapy with oral sulfonylurea agent alone."
Notes	Carry-over effect not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Quote from publication**: (from the abstract) "Using a double-blind crossover design, ..." **Comment**: probably the participants and

Longnecker 1986 (*Continued*)

		the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: (from the abstract) "Using a double-blind crossover design, ..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	High risk	**Comment**: the effects on weight and side effects were not reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome date were collected and reported
Selective reporting (reporting bias)	High risk	**Comment**: the effects on weight and side effects were not reported
Other bias	Unclear risk	**Comment**: only 12 participants were included

Mattoo 2005

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with insulin therapy with or without oral antihyperglycaemic agents for ≥ 3 months, HbA1c ≥ 7,5% and ≥ 30 years at the time of diagnosis **Exclusion criteria**: type 1 DM, signs or symptoms of any chronic condition or drug or alcohol abuse, previous TZD, glucocorticoid, nicotinic acid or therapy for a malignancy (except basal cell or squamous cell cancer), breastfeeding, pregnancy, women of childbearing potential **Diagnostic criteria**: WHO
Interventions	**Number of study centres**: 39 **Treatment before study**: intervention: insulin 0.96 (0.03) U/day/kg, control insulin 0.92 (0.03) U/day/kg. Insulin regimen: once, twice, thrice or four times a day **Titration period**: 2 weeks lead-in (at the end oral agents were stopped) and 3 months insulin intensification period

Outcomes	**Primary outcome(s)** (as stated in the publication): glycaemic control (HbA1c, fasting blood glucose), lipids, hs-CRP, PAI-1, hypoglycaemia, bodyweight, insulin dose
Study details	**Total study duration**: 6 months **Run-in period:** 2 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Eli Lilly, Takeda Europe **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To determine the effect of pioglitazone 30 mg plus insulin versus placebo plus insulin on glycaemic control, the serum lipid profile, and selected cardiovascular risk factors in patients with type 2 diabetes mellitus whose disease was inadequately controlled with insulin therapy alone despite efforts to intensify such treatment."
Notes	Some participants also used oral antihyperglycaemic agents before study. Users and non-users were separated in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "randomised"
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "randomised with equal probability.... according to a central randomisation table generated by the study sponsor and administered by an automated interactive voice response system at all sites"
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "this 6-month, randomised, double blind, prospective, multicenter, placebo-controlled, parallel-group study was ...." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "this 6-month, randomised, double blind, prospective, multicenter, placebo-controlled, parallel-group study was ...." **Comment**: probably the participants and the personnel were blinded

Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "this 6-month, randomised, double blind, prospective, multicenter, placebo-controlled, parallel-group study was ...." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on adverse events and weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by pharmaceutical companies

Mauerhoff 1986

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with insulin therapy for ≥ 1 year **Exclusion criteria**: abnormal renal and hepatic functions, C-peptide > 0.2 pmol/mL **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: insulin 0.50 (0.07) U/day/kg, control insulin 0.44 (0.05) U/day/kg **Titration period**: 3 weeks lead-in

Outcomes	**Primary outcome(s)** (as stated in the publication): plasma glucose and C-peptide after standardised breakfast, HbA1c (no assessment for technical reasons), fasting cholesterol and triglyceride, hypoglycaemia, insulin requirements
Study details	**Total study duration**: 16 weeks **Run-in period:** 3 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Hoechst Belgium **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "We have studied the effect of the combination of a sulphonylurea (Hb 420 or glibenclamide) with insulin in 22 type 2 diabetic patients, treated with insulin and with residual insulin secretion."
Notes	Use of intervention medication Hb420 (galenic form of glibenclamide)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "The study was carried out double-blind....." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "The study was carried out double-blind....." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "The study was carried out double-blind....." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Mauerhoff 1986 (*Continued*)

Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on number of hypoglycaemia were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: HbA1c analyses not performed for technical reasons
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: HbA1c analyses not performed for technical reasons
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Mezitis 1992

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**HbA1c** before randomisation (% (SD)): intervention 8.7, control 8.6 **Inclusion criteria**: people with type 2 diabetes with insulin therapy for ≥ 1 year **Exclusion criteria**: endocrinologic disease other than diabetes mellitus, history of allergies to sulphonamides and/or insulin, history of impaired gastric emptying, active hepatic disease, renal disease significantly impairing creatinine clearance, current treatment with steroids, oestrogens, progestogens, beta-blockers, Ca-channel antagonists, diuretics, monoamine oxidase inhibitors, clonidine, probenecid, anticoagulants, NSAID **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin monotherapy, dosages not stated **Titration period**: yes, duration not stated
Outcomes	**Primary outcome(s)** (as stated in the publication): urinary C-peptide, HbA1c, lipids, insulin requirement, glycaemic profiles in response to test meals
Study details	**Total study duration**: 20 weeks **Run-in period:** unclear **Study terminated early (for benefit/because of adverse events):** no

Publication details	**Language of publication**: English **Funding source**: UpJohn, Boehringer Mannheim, Becton Dickinson **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To investigate the effects of addition of glibenclamide to the regimen of insulin-treated non-insulin-dependent diabetes mellitus (NIDDM) patients with regard to their overall insulin requirements and dosage schedule and to assess persistence of these effects."
Notes	A lot of data were missing: dose of glibenclamide, incomplete study design and baseline data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "random assignment to equal-sized parallel-groups"
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "The study was double-blinded with random assignment to equal-sized parallel-groups..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "The study was double-blinded with random assignment to equal-sized parallel-groups..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	High risk	**Comment**: outcomes of C-peptide, lipids and HbA1c assays were not reported

Mezitis 1992 (*Continued*)

Incomplete outcome data (attrition bias) Insulin dose	High risk	**Comment**: missing data on dose of glibenclamide
Selective reporting (reporting bias)	High risk	**Comment**: outcomes of C-peptide, lipids and HbA1c assays were not reported
Other bias	High risk	**Comment**: no data on adverse events and population size; funded by a pharmaceutical company

Mudaliar 2010

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: obese people with type 2 diabetes on insulin therapy alone and with HbA1c between 7.5% and 10% **Exclusion criteria**: history of peripheral oedema, cardiac, hepatic or renal problems, or had been treated with NSAIDs or diuretics within 21 days of screening **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin monotherapy (IU/day (SD)): intervention: 105 (22), control 114 (11) **Titration period**: 4 weeks: weight maintenance, carbohydrate diet
Outcomes	**Primary outcome(s)** (as stated in the publication): HbA1c, fasting plasma glucose, insulin dose, weight, total body water, extracellular fluid, renal measures, hormonal measures
Study details	**Total study duration**: 16-20 weeks **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Takeda pharmaceuticals, Veterans Medical Research Foundation, Department of Veterans Affairs and the VA San Diego Healthcare System, University of California San Diego Clin Res. Centre NIH Grant **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the effects of intensive insulin therapy alone or with added pioglitazone on renal salt/water balance and body fluid compartment shifts in type 2 diabetes."
Notes	Funded by pharmaceutical company

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "After the completion of the baseline studies, subjects were randomised (in a double-blind manner) to. .." **Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "After the completion of the baseline studies, subjects were randomised (in a double-blind manner) to. .." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "After the completion of the baseline studies, subjects were randomised (in a double-blind manner) to. .." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "After the completion of the baseline studies, subjects were randomised (in a double-blind manner) to. .." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Mudaliar 2010 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funding by pharmaceutical company; performed in clinical research centre

Nemoto 2011

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy alone, HbA1c $\geq$ 6.5%, outpatients, age at least 20 years **Exclusion criteria**: not stated **Diagnostic criteria**: plasma glucose level at either 1 or 2 h after meal was 180 mg/dL or higher; HbA1c $\geq$ 6.5%
Interventions	**Number of study centres**: not stated **Treatment before study**: insulin monotherapy (U/day (SD)): 31.7 (17.6) **Titration period**: 4-10 weeks observation period
Outcomes	**Primary outcome(s)** (as stated in the publication): meal tolerance test, plasma glucose AUC **Secondary outcomes** (as stated in the publication): HbA1c, 1,5 AG, glycoalbumin, hypoglycaemic symptoms **ADDITIONAL OUTCOMES**: safety
Study details	**Total study duration**: 16-22 weeks (4-10 weeks observation + 12 weeks treatment) **Run-in period:** 4-10 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Sanwa Kagaku Kenkyusyo Co Ltd **Publication status**: peer-reviewed journal

Stated aim of study	Quote from publication: "To investigate the efficacy of combination therapy with miglitol and insulin" in people with type 2 diabetes receiving insulin therapy	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "The enrolled patients were randomised to groups treated with miglitol or with placebo" **Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "We conducted a placebo-controlled double-blind comparative study..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: "We conducted a placebo-controlled double-blind comparative study..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Quote from publication**: "We conducted a placebo-controlled double-blind comparative study..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: adverse events were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: data on HbA1c were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Unclear risk	**Comment**: part of the results only described in figures, not in numbers
Selective reporting (reporting bias)	Unclear risk	**Comment**: part of the results only described in figures, not in numbers
Other bias	Unclear risk	**Comment**: funding unclear, possibly commercial

Osei 1984

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with serum glucose levels > 200 mg/dL and daily insulin requirement > 30 IU **Exclusion criteria**: renal and hepatic disease, allergies to sulphonylurea **Diagnostic criteria**: NDDG
Interventions	**Number of study centres**: 1 **Control (route, total dose/day, frequency)**: placebo, oral **Treatment before study**: intervention: insulin 60.3 (7.1) U/day, control insulin 50.27 (5.0) U/day (insulin regimen: once or twice daily, short-acting and/or intermediate insulin) **Titration period**: 4 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): fasting glucose, HbA1c and C-peptide, after OGTT serum glucose and C-peptide, lipids, lipoproteins, weight, dietary intake, compliance
Study details	**Total study duration**: 16 weeks **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: UpJohn, Core Laboratory, Central Ohio Diabetes Association **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate, in a double-blind, placebo-controlled manner, glucose and lipoprotein responses after long-term use of combination therapy in the

	management of insulin-treated patients with poorly controlled type 2 diabetes mellitus. "
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Patients were randomly assigned in a double-blind manner to receive either glyburide or placebo.. ."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "Patients were randomly assigned in a double-blind manner..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "Patients were randomly assigned in a double-blind manner..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "Patients were randomly assigned in a double-blind manner..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Osei 1984 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Quatraro 1986

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: insulin 90 (6) U/day, control insulin 88 (5) U/day Insulin regimen: twice or thrice daily, porcine lente and/or rapid-acting insulin **Titration period**: 2 months + 1-2 weeks inpatient period
Outcomes	**Primary outcome(s)** (as stated in the publication): diurnal glucose profile, HbA1c, C-peptide, glucagon stimulated C-peptide, insulin dose, weight
Study details	**Total study duration**: 14 months **Run-in period:** 2 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: none **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "We studied the influence of chronic sulphonylurea treatment on glucose metabolism and beta-cell secretory activity in diabetic patients requiring insulin after secondary failure to oral drugs."
Notes	

Quatraro 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "They were allocated at random into two groups, each consisting of 15 subjects..."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Comment**: unclear if the study was blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the study was blinded
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Comment**: unclear if the study was blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the study was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the study was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the study was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Quote from publication**: "weight remained stable throughout the study period. "
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported

Quatraro 1986 (*Continued*)

Other bias	High risk	**Comment**: different participant groups reported in figure and table

Reich 1987

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy **Exclusion criteria**: significant surgery within 3 months before entry into the study, major organ or system disease, medication use affecting glucose metabolism or sulphonylurea activity **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 2 **Treatment before study**: intervention: 36.5 (6.3) insulin, placebo: insulin 48.2 (4.0) U/day. Insulin regimen: only intermediate insulin **Titration period**: 12 days hospitalisation (after 6 weeks optimisation glycaemic control with insulin)
Outcomes	**Primary outcome(s)** (as stated in the publication): serum and urinary glucoses, HbA1c, urinary C-peptide, insulin dose, number of tablets prescribed, compliance
Study details	**Total study duration**: 5.5 months **Run-in period:** 12 days **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Upjohn **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To test the effect of combined glibenclamide-insulin therapy over 4 months in 20 patients after achieving good control of fasting glucose with diet and intermediate insulin alone."
Notes	Participants had adequate glycaemic control

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "randomised"
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "randomised by the hospital pharmacy"

Reich 1987 (*Continued*)

Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: (from abstract) "A placebo-controlled, double-blinded design..." **Comment**: Probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: (from abstract) "A placebo-controlled, double-blinded design..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: not all outcome values were reported, only graphical
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: insulin dose was collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: not all outcome values were reported, only graphical **Comment**: dropouts were described; intention-to-treat
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Relimpio 1998

Methods	**Parallel open-label randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: poorly controlled (HbA1c > 8%) people with type 2 diabetes on insulin therapy ($\geq$ 0.5 IU/kg body weight in 2 or more daily doses)) **Exclusion criteria**: life-threatening condition, contraindication for biguanides, serum creatinine < 132.6 μmol/L **Diagnostic criteria**: not stated

Relimpio 1998 (*Continued*)

Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: 47.9 (10) insulin, control: insulin 51.8 (9.6) U/day. Insulin regimen: twice or more daily, premixed soluble and NPH insulin or NPH insulin alone **Titration period**: 4 weeks increase metformin dose (1,275 g -> 2,550 g)
Outcomes	**Primary outcome(s)** (as stated in the publication): HbA1c, glucose, lipids, blood pressure, height, weight, BMI, insulin dose, serum creatinine, albumin excretion rate, uric acid, compliance
Study details	**Total study duration**: 4 months **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Novo Nordisk **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To compare the effect of adding metformin to insulin therapy with a moderate increase in insulin dose alone in insulin-treated, poorly controlled type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "... and were subsequently randomised (31 to insulin + metformin and 29 to insulin dose increase) "
Allocation concealment (selection bias)	Unclear risk	"patients were randomised into two study groups following an experimental design of open-label randomisation."
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "open-label randomisation"
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "open-label randomisation"
Blinding of participants and personnel (performance bias) Insulin dose	High risk	**Quote from publication**: "open-label randomisation"

Relimpio 1998 (*Continued*)

Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "open-label randomisation"
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "open-label randomisation"
Blinding of outcome assessment (detection bias) Insulin dose	High risk	**Quote from publication**: "open-label randomisation"
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Robinson 1998

Methods	**Two cross-over randomised controlled clinical trials** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: study I: DM2 patients with insulin monotherapy for at least 1 year after secondary failure of maximum dose oral antihyperglycaemic agents; study II: see study I plus taking metformin (100-2550 mg/day as the sole oral antihyperglycaemic agent for at least 1 year **Exclusion criteria**: women of childbearing age, unable to give informed consent **Diagnostic criteria**: fasting plasma glucose > 7.8 mmol/L on 2 occasions
Interventions	**Number of study centres**: 2 **Treatment before study**: study I: insulin 71 (47) U/day, study II : insulin 41 (16) U/day + metformin 1000-2550 **Titration period**: 6 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): HbA1c, glucose, lipids, blood pressure, insulin dose, hypoglycaemia

Robinson 1998 (*Continued*)

Study details	**Total study duration**: 12 weeks (intervention period study I) **Run-in period:** 6 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Lipha Pharmaceuticals **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To test the hypothesis that metformin therapy, given as an adjunct to insulin therapy, improves metabolic control in insulin-treated type 2 diabetes mellitus patients with sub optimal glycaemic control."
Notes	2 studies, only study I fulfilled our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "patients were randomised..." **Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: (from abstract) "Two randomised double-blind placebo-controlled crossover studies were run." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: (from abstract) "Two randomised double-blind placebo-controlled crossover studies were run." **Comment**:probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: (from abstract) "Two randomised double-blind placebo-controlled crossover studies were run." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Robinson 1998 (*Continued*)

Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were described
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Rosenstock 2002

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy (≥ 30 IU/day) for 4 months, 30-75 years, HbA1c ≥ 8.0%, fasting C-peptide > 0.7μg/l **Exclusion criteria**: history of ketoacidosis; unstable retinopathy, nephropathy or neuropathy; impaired hepatic and renal function; anaemia; unstable cardiovascular or cerebrovascular condition; concomitant lipid lowering medication must be taken for a stable dose > 60 days **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 79 **Treatment before study**: pioglitazone 15: 70.2 (34.0) insulin, pioglitazone 30: insulin 72.3 (38.5), placebo: insulin 70.7 (33.5) U/day (insulin regimen: 88% monotherapy) **Titration period**: insulin monotherapy: 2 weeks screening + 1 week single-blind placebo insulin with oral anti-diabetic (OAD) medication: 2 weeks screening + 4 weeks single-blind placebo (= washout)
Outcomes	**Primary outcome(s)** (as stated in the publication): HbA1c, glucose, C-peptide, lipids, insulin dose, safety profile: chemistry, haematology, urine analysis, vital signs, ECG, adverse events

Rosenstock 2002 (*Continued*)

Study details	**Total study duration**: 16 weeks **Run-in period:** 3 weeks for insulin users and 6 weeks for insulin + OAD users (last group discontinued oral agent at the beginning of the screening period **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Takeda Pharmaceuticals **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the ability of two doses of pioglitazone in combination with a stable insulin regimen to improve glycaemic control in patient whose type 2 diabetes remained poorly controlled despite current insulin therapy."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "... the 16-weeks double-blind treatment period" **Comment**: Probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "... the16-weeks double-blind treatment period" **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "During the single-blinded period, patients received their stable insulin regimens" **Quote from publication**: "... the16-weeks double-blind treatment period" **Comment**: the single-blind period refers to the run-in period and the 16-weeks to the treatment period. Probably the participants and the personnel were blinded

Rosenstock 2002 (*Continued*)

Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain and drug-related adverse events were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Schade 1987

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy (≥ 28 IU/day ≥ 3 months), C-peptide-positive on stimulation of endogenous insulin secretion (OGTT) **Exclusion criteria**: hepatic or renal disease or other major diseases that might impair participation, use of sulphonylurea or other drugs that alter glucose control within 1 month of the study **Diagnostic criteria**: NDDG
Interventions	**Number of study centres**: > 1? **Treatment before study**: 55.4 (6.0) IU/day (insulin regimen: 10/16 twice daily) **Titration period**: 4 weeks (washout)
Outcomes	**Primary outcome(s)** (as stated in the publication): OGTT, insulin- C-peptide, fasting blood glucose, HbA1c, ery-glu binding capacity, compliance, insulin dose, weight

Study details	**Total study duration**: 32 weeks **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Upjohn, NIH **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To examine the potential beneficial effect of the addition of a second-generation sulphonylurea to insulin therapy for poorly controlled type 2 diabetes. "
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication**: "The order of the two treatment regimens was randomised..." **Comment**: not possible to judge whether the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period."
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period."
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period."

Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period." **Comment**: unclear if "end of the study" meant the end of the treatment period or after outcome analysis
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period." **Comment**: unclear if "end of the study" meant the end of the treatment period or after outcome analysis
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Quote from publication**: "...neither the patient nor the investigators knew until the completion of the study which treatment regimen the patients were receiving during each 16-weeks period." **Comment**: unclear if "end of the study" meant the end of the treatment period or after outcome analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Schiel 2007

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes with inadequate glycaemic control (HbA1c ≥ 8.0% or FBG ≥ 6.6 mmol/L) on premix insulin therapy (≤ 5 years), diabetes duration > 5 years, BMI 27-35 **Exclusion criteria**: impaired hepatic or renal function, pregnancy, unable to understand the study, to cope or attend follow-up visits **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: mix insulin 75/25 or 70/30 A: 77.6 (32.1) , B: 64.9 (32.1), C: 65.2 (34.2) IU/day **Titration period**: 4 weeks
Outcomes	**Primary outcome(s)** (as stated in the publication): fasting blood glucose, HbA1c, treatment satisfaction, hypoglycaemia, adverse events, blood pressure, creatinine, liver enzymes
Study details	**Total study duration**: 20 weeks (4 + 16 wks) **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Sanofi-Aventis **Publication status**: peer review journal
Stated aim of study	Quote from publication: "To establish whether insulin plus OADs is effective in type 2 diabetes patients previously poorly controlled on premixed insulin therapy."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Randomization was performed..."
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "Randomization was performed by a central computer and patients were assigned (1:1:1) to one of the three treatment groups."
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."

Blinding of participants and personnel (performance bias) Health-related quality of life, patient satisfaction	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of participants and personnel (performance bias) Insulin dose	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of outcome assessment (detection bias) Health-related quality of life, patient satisfaction	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Blinding of outcome assessment (detection bias) Insulin dose	High risk	**Quote from publication**: "In a open, controlled, randomised, parallel-group, single-centre, 16-weeks pilot study..."
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain and hypoglycaemia were collected and reported
Incomplete outcome data (attrition bias) Health-related quality of life, patient satisfaction	Low risk	**Comment**: data on patient satisfaction were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Simpson 1990

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy, inadequate controlled (fasting glucose > 8.0 mmol/L **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: 36 (10-62) insulin , placebo: insulin 31 (14-112) U/day. Insulin regimen: once (n = 5) or twice daily (n = 15) **Titration period**: 2 months minimum run-in period in which oral medication was stopped
Outcomes	**Primary outcome(s)** (as stated in the publication): serum and urinary glucoses, HbA1c, urinary C-peptide, insulin dose, number of tablets prescribed, compliance
Study details	**Total study duration**: 2 months run-in and 8 weeks intervention **Run-in period:** 2 months **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Farmaitalia **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To assess the relative contribution of endogenous insulin secretion and peripheral insulin sensitivity when SU was given in combination with insulin to 'secondary failure' type 2 diabetes patients."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "patients were randomised to receive either glipizide 10 mg twice daily or placebo, in addition to usual insulin"
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "The treatment was blind to both the patient and investigators"

Simpson 1990 (*Continued*)

Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "The treatment was blind to both the patient and investigators"
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "The treatment was blind to both the patient and investigators"
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Stenman 1988

Methods	**Cross-over randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes failing on oral antidiabetic agents **Exclusion criteria**: hepatic, renal or pulmonary dysfunction; secondary diabetes **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: intervention: 34 (4) insulin, placebo: insulin 26 (3) U/day.

Stenman 1988 (*Continued*)

	Insulin regimen: once or twice daily intermediate or intermediate mixed with short-acting insulin **Titration period**: 4 months (2 weeks in hospital) initiation insulin therapy
Outcomes	**Primary outcome(s)** (as stated in the publication): HbA1c, fasting glucose, urinary glucose, C-peptide after glucagon, insulin dose, lipids, body weight, free insulin
Study details	**Total study duration**: 8 months: 4 months run-in and 4 months intervention **Run-in period:** 2 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Sigrid Juselius Foundation, Finnish Medical Association, Signe and Ane Gyllenberg foundation **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To examine the effect of the addition of glibenclamide to insulin therapy on glycaemic control and beta cell function."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "...the patients were randomised to a double-blind treatment with insulin in combination with glibenclamide or insulin and placebo for four months"
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "....the patients were randomised to a four-months double-blind cross-over treatment...." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "....the patients were randomised to a four-months double-blind cross-over treatment...." **Comment**: probably the participants and the personnel were blinded

Stenman 1988 (*Continued*)

Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "....the patients were randomised to a four-months double-blind cross-over treatment...." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain and hypoglycaemia were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: some data were only reported graphically
Other bias	Low risk	**Comment**: none

Strowig 2002

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy (≥ 30 IU/day), 24-70 years, HbA1c ≥ 7.0%, normal renal and hepatic function **Exclusion criteria**: not stated **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: metformin insulin 82.9 U/day, troglitazone insulin 96.5 U/day, control insulin 80.3 U/day. Insulin regimen: 2 or more daily, 70/30 mix insulin or intermediate and short-acting insulin **Titration period**: 4 weeks

Outcomes	**Primary outcome(s)** (as stated in the publication): insulin dose, lipids, HbA1c, glucose, C-peptide, body weight, Alat, Asat, medical history, physical exam, waist-hip measurement, 3-day food record, serum chemistry
Study details	**Total study duration**: 4 weeks run-in and 12 weeks intervention **Run-in period:** 4 weeks **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: Bristol Myers Squibb **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To evaluate the safety and efficacy of treatment with insulin alone, insulin plus metformin, or insulin plus troglitazone for 4 months in type 2 DM."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Subjects ... were randomly assigned ..."
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "Random assignment was determined by the sponsor who provided sealed sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) Adverse events	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion... "
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion... "
Blinding of participants and personnel (performance bias) Insulin dose	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion... "
Blinding of outcome assessment (detection bias) Adverse events	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion... "
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion...

		"
Blinding of outcome assessment (detection bias) Insulin dose	High risk	**Quote from publication**: "...were randomly assigned in an unmasked fashion... "
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on adverse events were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Unclear risk	**Comment**: medical history and physical exam were not reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Wulffelé 2002

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1** **Superiority design**
Participants	**Inclusion criteria**: people with type 2 diabetes on insulin therapy **Exclusion criteria**: significant surgery within 3 months before entry into the study, major organ or system disease, medication use affecting glucose metabolism or sulphonylurea activity **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 3 **Treatment before study**: intervention: 71 (33) insulin, placebo: insulin 70 (33) U/day. Insulin regimen: 4 times daily intermediate plus short-acting insulin or twice daily mix-insulin **Titration period**: 12 weeks (optimisation of insulin therapy, cessation of metformin, cessation of antihypertensive and lipid-lowering medication)
Outcomes	**Primary outcome(s)** (as stated in the publication): glucose, HbA1c, lipids, insulin dose, blood pressure, weight, BMI, waist-hip-ratio
Study details	**Total study duration**: 16 weeks **Run-in period:** 12 weeks **Study terminated early (for benefit/because of adverse events):** no (results of the interim analysis)

Publication details	**Language of publication**: English **Funding source**: Byk, Lifescan, Merck Lipha, MSD, Novo Nordsik **Publication status**: peer-reviewed journal
Stated aim of study	Quote from publication: "To investigate the metabolic effects of metformin, as compared with placebo, in type 2 diabetes patients intensively treated with insulin."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "...all subject were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Low risk	**Quote from publication**: "...all subjects were randomly assigned in a double-blind fashion..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Low risk	**Quote from publication**: "...all subjects were randomly assigned in a double-blind fashion..." **Comment**: probably the participants and the personnel were blinded
Blinding of participants and personnel (performance bias) Insulin dose	Low risk	**Quote from publication**: "...all subjects were randomly assigned in a double-blind fashion..." **Comment**: probably the participants and the personnel were blinded
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear if the outcome assessor was blinded

Wulffelé 2002 (*Continued*)

Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear if the outcome assessor was blinded
Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on adverse events were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were collected and reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funded by a pharmaceutical company

Yilmaz 2007

Methods	**Parallel randomised controlled clinical trial** **Randomisation ratio: 1:1:1** **Superiority design**
Participants	**Inclusion criteria**: people with poorly controlled type 2 diabetes on insulin monotherapy **Exclusion criteria**: severe hypertension, repeated hypoglycaemic episodes, severe cardiovascular and cerebrovascular disease, renal or hepatic failure, acute diabetic complications, incipient heart failure, pregnancy, breastfeeding **Diagnostic criteria**: not stated
Interventions	**Number of study centres**: 1 **Treatment before study**: insulin MIX 30/70 aspart/NPH **Titration period**: not stated
Outcomes	**Primary outcome(s)** (as stated in the publication): change in HbA1c **Secondary outcomes** (as stated in the publication): changes in insulin dosage, body weight, waist-to-hip ratio, lipids **ADDITIONAL OUTCOMES**: incidence of hypoglycaemia and side effects
Study details	**Total study duration**: 6 months **Run-in period**: unclear **Study terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication**: English **Funding source**: not stated **Publication status**: peer-reviewed journal

Stated aim of study	Quote from publication: "To investigate the glucose lowering effects of insulin alone, insulin plus metformin, insulin plus rosiglitazone, or insulin plus acarbose in subjects with type 2 diabetes mellitus and determine the type of treatment that would influence the serum level of total cholesterol, LDL-C, HDL-C, CRP and fibrinogen in these patients."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "After the initial assessment, subjects were randomly assigned to continue insulin therapy alone, or add acarbose (300 mg/day), or metformin (1,700 mg/day), or rosiglitazone (8 mg/day) to insulin therapy."
Allocation concealment (selection bias)	Unclear risk	**Comment**: not possible to judge whether the allocation to the intervention and control group was concealed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	**Comment**: unclear, not described
Blinding of participants and personnel (performance bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear, not described
Blinding of participants and personnel (performance bias) Insulin dose	Unclear risk	**Comment**: unclear, not described
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	**Comment**: unclear, not described
Blinding of outcome assessment (detection bias) HbA1c, FPG, lipids	Unclear risk	**Comment**: unclear, not described
Blinding of outcome assessment (detection bias) Insulin dose	Unclear risk	**Comment**: unclear, not described

Incomplete outcome data (attrition bias) Adverse events	Low risk	**Comment**: data on weight gain were collected and reported
Incomplete outcome data (attrition bias) HbA1c, FPG, lipids	Low risk	**Comment**: outcome data were collected and reported
Incomplete outcome data (attrition bias) Insulin dose	Low risk	**Comment**: data on insulin dose were reported
Selective reporting (reporting bias)	Low risk	**Comment**: all outcomes of interest were reported
Other bias	Unclear risk	**Comment**: funding not disclosed; differences in baseline data between groups; people with heart failure excluded

Note: where the judgement is 'Unclear' and the description is blank, the study did not report that particular outcome.
NPH: Neutral Protamine Hagedorn

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

Study	Reason for exclusion
Abraira 1998	Mixed population: insulin-naive and previously insulin-treated
Al-Shaikh 2006	Insulin-naive participants
Altuntas 2003	Insulin-naive participants
Bachman 1988	Insulin-naive participants
Barranco 2006	No insulin therapy arm
Berhanu 2007	Impossible to analyse subgroup of insulin-users separately
Bianchi 1996	Trial on combination of benfluorex with insulin
Buse 1998	Use of troglitazone (off the market)
Carta 1984	Insulin-naive participants
Castillo 1987	Insulin-naive participants

(*Continued*)

Charbonnel 2010	Impossible to analyse subgroup of insulin-users separately
Chazan 2001	Insulin-naive participants
Chow1995	Insulin-naive participants
Clauson 1995	Insulin-naive participants
Cortes 1993	Well-controlled population
Dashora 2007	Impossible to analyse subgroup of insulin-users separately
Davidson 2006	No arm without oral agent or placebo
De Luis 2001	No RCT
Douek 2005	Insulin-naive participants
Fonseca 2006	Insulin-naive participants
Fonseca 2008	Observational phase of RCT
Garg 2007	No RCT
Gerstein 2006	Insulin-naive participants
Goudswaard 2004a	Insulin-naive participants
Greco 1998	No RCT
Groop 1984	Insulin-naive participants
Groop 1991	Insulin-naive participants
Gutniak 1987	Insulin-naive participants
Hamelbeck 1982	Insulin-naive participants
Hermanns 2004	Follow-up less than 2 months
Hollander 2003	Adding of non-oral agent pramlintide
Hollander 2003a	Adding of non-oral agent pramlintide
Hollander 2004	Adding of non-oral agent pramlintide
Hollander 2007	Adding of rosiglitazone (off the market)

(*Continued*)

Holman 1987	Insulin-naive participants
Home 2007	Insulin-naive participants
Inoue1998	Insulin-naive participants
Jacob 2007	Impossible to analyse subgroup of insulin-users separately
Jacober 2006	Insulin-naive participants
Janka 2005	Insulin-naive participants
Janka 2007	Insulin-naive participants
Juurinen 2008	No RCT
Juurinen 2009	Impossible to analyse subgroup of insulin-users separately
Kabadi 2003	Insulin-naive participants
Kanda 1996	Insulin-naive participants
Kandalintseva 2008	Rosiglitazone combination therapy (off the market)
Karlander 1991	Insulin-naive participants
Kilo 2003	Insulin-naive participants
Kokic 2003	Insulin-naive participants
Kothny 2013	Impossible to analyse subgroup of insulin-users separately
Kvapil 2006	Insulin-naive participants
LAPToP 2004	Insulin-naive participants
Lins 1988	Insulin-naive participants
Liu 2003	Rosiglitazone combination therapy (off the market)
Lotz 1988	Insulin-naive participants
Lund 2009	Insulin-naive participants
Lundershausen 1987	Insulin-naive participants

(*Continued*)

Makimattila 1999	Insulin-naive participants
Mohan 1990	No RCT
Morrow 2011	Combination with ligarglutide (non-oral agent)
Olsson 2002	Insulin-naive participants
Ose 2005	Not RCT
Ozbek 2006	Well-controlled population
Pan 2007	Insulin-naive participants
Peacock 1984	Insulin-naive participants
Peyrot 2008	Addition of a non-oral agent pramlintide
Ponssen 2000	Mixed group: insulin-naive and previously insulin-treated participants
Pontiroli 1990	Insulin-naive participants
Poulsen 2003	Control group mixed: insulin- and insulin + metformin-treated
Raskin 2001	Addition of rosiglitazone (off the market)
Ravnik 1989	Insulin-naive participants
Ravnik 1995	Insulin-naive participants
Raz 2005	Insulin-naive participants
Riddle 1989	Mixed group: insulin-naive and previously insulin-treated participants
Riddle 1992	Insulin-naive participants
Riddle 1998	Insulin-naive participants
Riddle 2007	Adding of a non-oral agent pramlintide
Rosak 1985	Follow-up less than 2 months
Sachse 1984	Insulin-naive participants
Sangiorgio 2000	Not RCT
Schmidt 1986	Insulin-naive participants

(*Continued*)

Schnell 2006	Insulin-naive participants
Schwartz 1998	Use of troglitazone (off the market)
Sun 1995	Insulin-naive participants
Tamemoto 2007	Insulin-naive participants
Vilsboll 2010	Impossible to analyse subgroup of insulin-users separately
Willey 1994	Mixed group: insulin- and insulin + metformin-treated participants; trial on combination of insulin and dexfenfluramine
Wolffenbuttel 1991	Insulin-naive participants
Wolffenbuttel 1999	Insulin-naive participants
Wong 2005	Special population: type 2 diabetes participants with peritoneal dialysis
Wright 2002	Newly diagnosed type 2 diabetes participants
Yamada 2007	No arm without oral agent or placebo
Yki-Jarvinen 1992	Insulin-naive participants
Yki-Jarvinen 1999	Insulin-naive participants
Yki-Jarvinen 2013	Impossible to analyse subgroup of insulin-users separately
Yokoyama 2011	Two arms: continuation and discontinuation of glimepiride
Zargar 2002	Insulin-naive participants

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Fargren 2014

Methods	A single-centre, double-blind, randomised, placebo-controlled cross-over study
Participants	Participants with type 2 diabetes, mean age 59 + 6 (SD) years and mean HbA1c 7.7% + 0.8%, treated with exogenous insulin with or without oral antihyperglycaemic agents

Fargren 2014 (*Continued*)

Interventions	Participants received vildagliptin (50 mg twice a day) or placebo as add-on to insulin for 4 weeks in random order with a 4-week washout in between
Outcomes	Glucose, glucagon
Notes	-

Kaku 2014

Methods	Randomised, double-blind, 12-week comparative trial, followed by a 40-week, open-label phase
Participants	179 participants with type 2 diabetes
Interventions	Alogliptin and insulin versus placebo and insulin
Outcomes	HbA1c, body weight, hypoglycaemia
Notes	-

Mathieu 2015

Methods	Multicenter, randomised, double-blind, placebo-controlled, 24-week clinical trial
Participants	660 participants with type 2 diabetes and inadequate glycaemic control on insulin, with or without metformin (> 1500 mg/day) or sulfonylurea, for > 10 weeks. Participants could remain on metformin but not sulphonylurea after randomisation
Interventions	Sitagliptin 100 mg/day or placebo was administered concurrently with insulin glargine titration, targeting a fasting glucose of 4.0-5.6 mmol/L (72-100 mg/dL)
Outcomes	Insulin dose, HbA1c, hypoglycaemia, adverse effects
Notes	Subgroup analysis with insulin monotherapy needs to be checked

McGill 2015

Methods	Data for participants in two phase 3 trials with linagliptin who were receiving insulin were analysed separately (n = 811)
Participants	Type 2 diabetes mellitus participants with chronic kidney disease
Interventions	Linagliptin + insulin vs placebo + insulin
Outcomes	HbA1c, (severe) hypoglycaemia
Notes	Inadequate control needs to be checked

Ning 2014

Methods	Multicentre, double-blind, placebo-controlled trial
Participants	Participants with type 2 diabetes inadequately controlled (HbA1c 7.5%-11.0%) on stable therapy with long-acting, intermediate-acting or premixed insulin, with or without concomitant metformin
Interventions	Vildagliptin 50 mg twice a day (n = 146) or placebo (n = 147)
Outcomes	HbA1c, fasting blood glucose, BMI
Notes	Need to determine if subgroup analysis with insulin monotherapy is possible

Rosenstock 2009

Methods	26-week, double-blind, placebo-controlled study
Participants	People with type 2 diabetes inadequately controlled with insulin alone or combined with metformin
Interventions	Participants received alogliptin 12.5 mg (n = 131), alogliptin 25 mg (n = 129) or placebo (n = 130) once daily, as add-on to stable insulin therapy with or without metformin
Outcomes	HbA1c, body weight, hypoglycaemia, incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events
Notes	Need to determine whether subgroup analysis for insulin monotherapy group is possible

Sato 2015

Methods	24-week, prospective, randomised, open-labelled, controlled trial
Participants	Participants with type 2 diabetes who were suboptimally controlled despite receiving at least twice-daily injections of insulin were enrolled in the trial
Interventions	The participants were randomised to continuation of insulin treatment (insulin group) or addition of sitagliptin 50 mg-100 mg daily to insulin treatment
Outcomes	HbA1c, body weight, hypoglycaemia, treatment satisfaction
Notes	-

Sheu 2015

Methods	Randomised double-blind trial
Participants	Asian participants with type 2 diabetes mellitus inadequately controlled by basal insulin with/without oral agents
Interventions	Treatment with linagliptin 5 mg once daily or placebo. Basal insulin dose remained stable for 24 weeks, after which adjustments could be made according to the investigator's discretion to improve glycaemic control

Sheu 2015 (*Continued*)

Outcomes	HbA1c, adverse events
Notes	Need to determine if subgroup analysis with insulin monotherapy is possible

Srivanichakorn 2015

Methods	8-week randomised controlled trial
Participants	Participants with type 2 diabetes who had been treated with insulin for at least 3 years plus moderate to high doses of sulphonylureas
Interventions	Withdrawal of sulphonylureas (insulin monotherapy) (n = 16) or continuation (n = 16) of sulphonylureas
Outcomes	HbA1c, insulin secretion
Notes	Need to determine whether participants were adequately controlled

Takahashi 2015

Methods	Randomised controlled trial
Participants	Type 2 diabetes participants receiving twice-daily injections of premix analog insulin
Interventions	Group A, in which participants were switched to long-acting insulin glargine at 80% of the insulin dose in the previous treatment regimen (23 participants), or group B (21 participants), given 50% of the previous dose, concurrently with the oral dipeptidyl-peptidase 4 inhibitor sitagliptin
Outcomes	HbA1c, lipids, hyperglycaemia and nocturnal hypoglycaemia
Notes	Need to determine if participants were adequately controlled before randomisation

BMI: body mass index; HbA1c: glycosylated haemoglobin A1c

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

EUCTR2011-004622-96-ES

Trial name or title	Study to test the safety, tolerability, and effectiveness of sitagliptin when compared to placebo in reducing the amount of insulin (with or without metformin) needed per day, to control blood sugar, over a 24-week period
Methods	A phase III, multicenter, randomised, double-blind, placebo-controlled clinical trial to study the safety and insulin-sparing efficacy of the addition of sitagliptin in - Study to test the safety, tolerability, and effectiveness of sitagliptin when compared to placebo

EUCTR2011-004622-96-ES (*Continued*)

Participants	Participants with type 2 diabetes mellitus who have inadequate glycaemic control on insulin alone or in combination with metformin
Interventions	Sitagliptin compared with placebo on the change in insulin dose in IU per day in people with type 2 diabetes mellitus (T2DM) with inadequate glycaemic control on insulin with or without metformin, who titrate insulin glargine (treat-to-target)
Outcomes	Daily insulin dose, HbA1c, fasting plasma glucose, body weight
Starting date	23 December 2011
Contact information	
Notes	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc

IRCT201204229536N1

Trial name or title	The comparison glycaemic control in two group patient treated with insulin alone and insulin plus sulfonylurea [*title as provided by study investigators]*
Methods	
Participants	
Interventions	Insulin 0.2 U/kg /day and sulphonylurea with previous dose vs insulin 0.3 U/kg /day
Outcomes	Blood glucose, body weight, hypoglycaemic events
Starting date	
Contact information	
Notes	

JPRN-UMIN000011851

Trial name or title	The efficacy of vildagliptin on type 2 diabetic patients with basal-bolus insulin therapy in the short-term hospitalisation (single-center, randomised, open-label, controlled study)
Methods	Single-center, randomised, open-label, controlled study
Participants	Type 2 diabetes participants
Interventions	Insulin + vildagliptin vs insulin alone
Outcomes	Blood glucose, lipids

JPRN-UMIN000011851 (*Continued*)

Starting date	
Contact information	
Notes	

JPRN-UMIN000018784

Trial name or title	Comparison of the effects of insulin monotherapy and combination therapy with ipragliflozin and insulin on glucose toxicity in type 2 diabetes mellitus : a randomised controlled trial
Methods	Not specified
Participants	
Interventions	Combination therapy with ipragliflozin and insulin group. Oral administration of 50 mg ipragliflozin once a day, after breakfast. Multiple injection of rapid-acting insulin and long-acting insulin. Insulin monotherapy group: multiple injection of rapid-acting insulin and long-acting insulin
Outcomes	Glucose, insulin dose, lipids, body weight
Starting date	
Contact information	
Notes	

NCT00329225

Trial name or title	Rosiglitazone in subjects with type 2 diabetes mellitus who are inadequately controlled on insulin
Methods	A multicenter, randomised, double-blind, parallel-group, placebo-controlled clinical evaluation of insulin plus rosiglitazone (2 mg and 4 mg) compared to insulin plus placebo for 24 weeks
Participants	Participants with type 2 diabetes mellitus who are inadequately controlled on insulin
Interventions	Rosiglitazone + insulin vs insulin + placebo
Outcomes	HbA1c, fasting plasma glucose, lipids
Starting date	22 May 2006
Contact information	
Notes	GlaxoSmithKline

NCT00757588

Trial name or title	Safety and efficacy of saxagliptin plus insulin with or without metformin
Methods	Multicenter double-blind parallel-group randomised controlled trial, phase 3 trial
Participants	Type 2 diabetes with inadequate glycaemic control
Interventions	Saxagliptin (5 mg) + insulin vs placebo for saxagliptin + insulin
Outcomes	HbA1c, fasting glucose, insulin dose, blood pressure, (serious) adverse events (hypoglycaemia)
Starting date	22 September 2008
Contact information	
Notes	AstraZeneca

NCT02104804

Trial name or title	Evaluate the efficacy and aafety of aaxagliptin added to insulin monotherapy or to insulin combined with metformin in Chinese subjects with type 2 diabetes who have inadequate glycaemic control
Methods	Double-blind parallel-group randomised controlled trial, phase 3 trial
Participants	Type 2 diabetes participants who have inadequate glycaemic control on insulin alone or on insulin in combination with metformin
Interventions	Saxagliptin (5 mg) + insulin vs placebo for saxagliptin + insulin
Outcomes	HbA1c, fasting glucose, insulin dose, (serious) adverse events (hypoglycaemia)
Starting date	2 April 2014
Contact information	
Notes	AstraZeneca

HbA1c: glycosylated haemoglobin A1c

DATA AND ANALYSES

Comparison 1. Insulin monotherapy versus insulin plus sulphonylurea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight (change from baseline)	7	220	Mean Difference (IV, Random, 95% CI)	0.57 [-2.52, 3.67]
1.1 Parallel-group trials	2	86	Mean Difference (IV, Random, 95% CI)	1.12 [-3.08, 5.32]
1.2 Cross-over trials	5	134	Mean Difference (IV, Random, 95% CI)	-0.08 [-4.66, 4.50]
2 Weight (change from baseline) [kg] GIV	7		Mean Difference (Random, 95% CI)	-0.13 [-0.57, 0.32]
2.1 Parallel-group	2		Mean Difference (Random, 95% CI)	1.12 [-3.08, 5.32]
2.2 Cross-over group	5		Mean Difference (Random, 95% CI)	-0.14 [-0.59, 0.31]
3 HbA1c (change from baseline)	9	316	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.56, -0.49]
3.1 Parallel-group trials	4	150	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.57, 0.06]
3.2 Cross-over trials	5	166	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.38, -0.56]
4 HbA1c (change from baseline) GIV	9		Mean Difference (Random, 95% CI)	-1.03 [-1.58, -0.47]
4.1 Parallel-group trials	4		Mean Difference (Random, 95% CI)	-1.25 [-2.57, 0.06]
4.2 Cross-over trials	5		Mean Difference (Random, 95% CI)	-0.97 [-1.42, -0.52]
5 Fasting glucose (change from baseline)	6	205	Mean Difference (IV, Random, 95% CI)	-2.28 [-3.23, -1.33]
5.1 Parallel-group trials	2	71	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.56, 0.61]
5.2 Cross-over trials	4	134	Mean Difference (IV, Random, 95% CI)	-2.72 [-3.66, -1.78]
6 Fasting plasma glucose (change from baseline) [mmol/L] GIV	6		Mean Difference (Random, 95% CI)	-2.29 [-3.23, -1.35]
6.1 Parallel-group	2		Mean Difference (Random, 95% CI)	-1.02 [-2.48, 0.44]
6.2 Cross-over group	4		Mean Difference (Random, 95% CI)	-2.73 [-3.70, -1.75]
7 Total cholesterol (change from baseline)	5	132	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.38, 0.32]
7.1 Parallel-group trials	1	22	Mean Difference (IV, Random, 95% CI)	0.26 [-0.49, 1.01]
7.2 Cross-over trials	4	110	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.50, 0.29]
8 Total cholesterol (change from baseline) [mmol/l] GIV	5		Mean Difference (Random, 95% CI)	-0.04 [-0.17, 0.09]
8.1 Parallel-group	1		Mean Difference (Random, 95% CI)	0.26 [-0.49, 1.01]
8.2 Cross-over group	4		Mean Difference (Random, 95% CI)	-0.05 [-0.18, 0.08]
9 HDL-cholesterol (change from baseline)	4	108	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.17, 0.03]
9.1 Parallel-group trials	1	22	Mean Difference (IV, Random, 95% CI)	0.0 [-0.27, 0.27]
9.2 Cross-over trials	3	86	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.20, 0.04]
10 HDL-Cholesterol (change from baseline mmol/L) GIV	4		Mean Difference (Random, 95% CI)	-0.05 [-0.15, 0.05]
10.1 Parallel-group	1		Mean Difference (Random, 95% CI)	0.0 [-0.27, 0.27]
10.2 Cross-over group	3		Mean Difference (Random, 95% CI)	-0.07 [-0.19, 0.06]
11 Triglyceride (change from baseline) [mmol/L] GIV	5		Mean Difference (Random, 95% CI)	0.04 [-0.21, 0.28]
11.1 Parallel-group	1		Mean Difference (Random, 95% CI)	-0.24 [-1.37, 0.89]
11.2 Cross-over group	4		Mean Difference (Random, 95% CI)	0.05 [-0.20, 0.30]

12 Triglycerides (change from baseline)	5	132	Mean Difference (IV, Random, 95% CI)	0.03 [-0.17, 0.22]
12.1 Parallel-group trials	1	22	Mean Difference (IV, Random, 95% CI)	-0.24 [-1.37, 0.89]
12.2 Cross-over trials	4	110	Mean Difference (IV, Random, 95% CI)	0.03 [-0.16, 0.23]

Comparison 2. Insulin monotherapy versus insulin plus metformin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight (change from baseline)	7	615	Mean Difference (IV, Random, 95% CI)	-2.12 [-3.19, -1.05]
1.1 Parallel-group trials	6	577	Mean Difference (IV, Random, 95% CI)	-2.45 [-3.61, -1.29]
1.2 Cross-over trials	1	38	Mean Difference (IV, Random, 95% CI)	-0.5 [-2.11, 1.11]
2 Weight (change from baseline) [kg] GIV	7		Mean Difference (Random, 95% CI)	-2.11 [-3.18, -1.05]
2.1 Parallel-group	6		Mean Difference (Random, 95% CI)	-2.45 [-3.61, -1.29]
2.2 Cross-over group	1		Mean Difference (Random, 95% CI)	-0.5 [-2.05, 1.05]
3 HbA1c (change from baseline)	9	698	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.20, -0.51]
3.1 Parallel-group trials	7	634	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.13, -0.41]
3.2 Cross-over trials	2	64	Mean Difference (IV, Random, 95% CI)	-1.16 [-2.13, -0.19]
4 HbA1c (change from baseline) [%] GIV	9		Mean Difference (Random, 95% CI)	-0.86 [-1.20, -0.51]
4.1 Parallel-group	7		Mean Difference (Random, 95% CI)	-0.77 [-1.13, -0.41]
4.2 Cross-over group	2		Mean Difference (Random, 95% CI)	-1.16 [-2.13, -0.18]
5 Total cholesterol (change from baseline)	8	651	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.41, -0.08]
5.1 Parallel-group trials	6	587	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.38, -0.02]
5.2 Cross-over trials	2	64	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.85, -0.09]
6 Total cholesterol (change from baseline) [mmol/L] GIV	8		Mean Difference (Random, 95% CI)	-0.29 [-0.50, -0.07]
6.1 Parallel-group	6		Mean Difference (Random, 95% CI)	-0.20 [-0.38, -0.02]
6.2 Cross-over group	2		Mean Difference (Random, 95% CI)	-0.57 [-0.94, -0.20]
7 HDL-cholesterol (change from baseline)	8	651	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.06, 0.04]
7.1 Parallel-group trials	6	587	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.05, 0.05]
7.2 Cross-over trials	2	64	Mean Difference (IV, Random, 95% CI)	0.00 [-0.25, 0.25]
8 HDL-cholesterol (change from baseline) [mmol/L]	8		Mean Difference (Random, 95% CI)	0.01 [-0.05, 0.08]
8.1 Parallel-group	6		Mean Difference (Random, 95% CI)	-0.00 [-0.05, 0.05]
8.2 Cross-over group	2		Mean Difference (Random, 95% CI)	0.04 [-0.22, 0.31]
9 Triglycerides (change from baseline)	8	651	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.22, 0.04]
9.1 Parallel-group trials	6	587	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.24, 0.11]
9.2 Cross-over trials	2	64	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.50, 0.16]
10 Triglyceride (change from baseline) [mmol/L] GIV	8		Mean Difference (Random, 95% CI)	-0.15 [-0.41, 0.11]
10.1 Parallel-group	6		Mean Difference (Random, 95% CI)	-0.07 [-0.24, 0.11]
10.2 Cross-over group	2		Mean Difference (Random, 95% CI)	-0.34 [-0.79, 0.11]

Comparison 3. Insulin monotherapy versus insulin plus pioglitazone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c (change from baseline)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Fasting glucose (change from baseline)	3	624	Mean Difference (IV, Random, 95% CI)	-0.07 [-3.61, 3.46]
3 Weight (change from baseline)	2	288	Mean Difference (IV, Random, 95% CI)	3.79 [2.97, 4.60]

Comparison 4. Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight (change from baseline)	2	241	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.22, 0.32]
2 HbA1c (change from baseline)	3	448	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.54, -0.24]
3 Fasting glucose (change from baseline)	2	113	Mean Difference (IV, Random, 95% CI)	0.33 [-0.74, 1.39]

Comparison 5. Insulin monotherapy versus insulin plus DPP-4 inhibitor

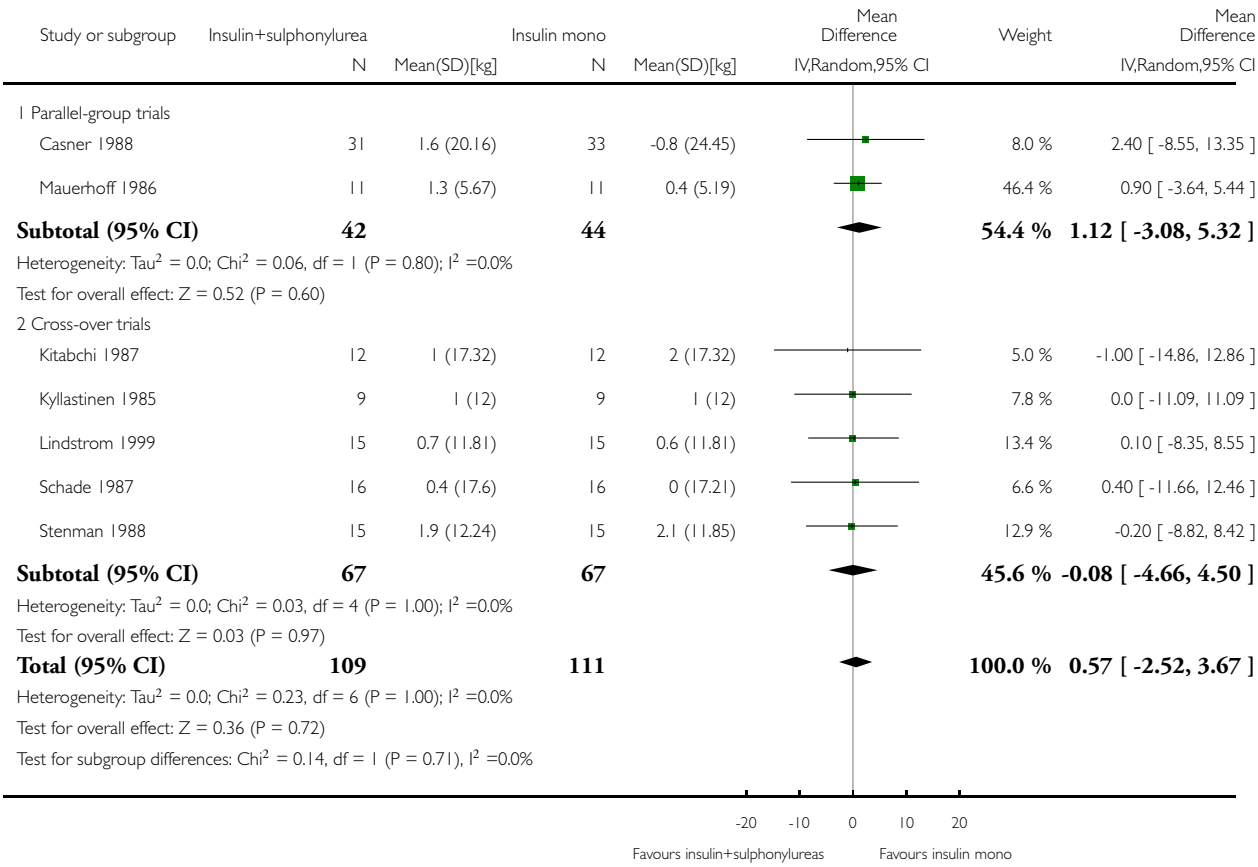
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight (change from baseline)	2	362	Mean Difference (IV, Random, 95% CI)	-0.55 [-1.00, 1.90]
2 HbA1c (change from baseline)	2	265	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.46, -0.35]
3 Fasting glucose (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 1 Weight (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 1 Weight (change from baseline)

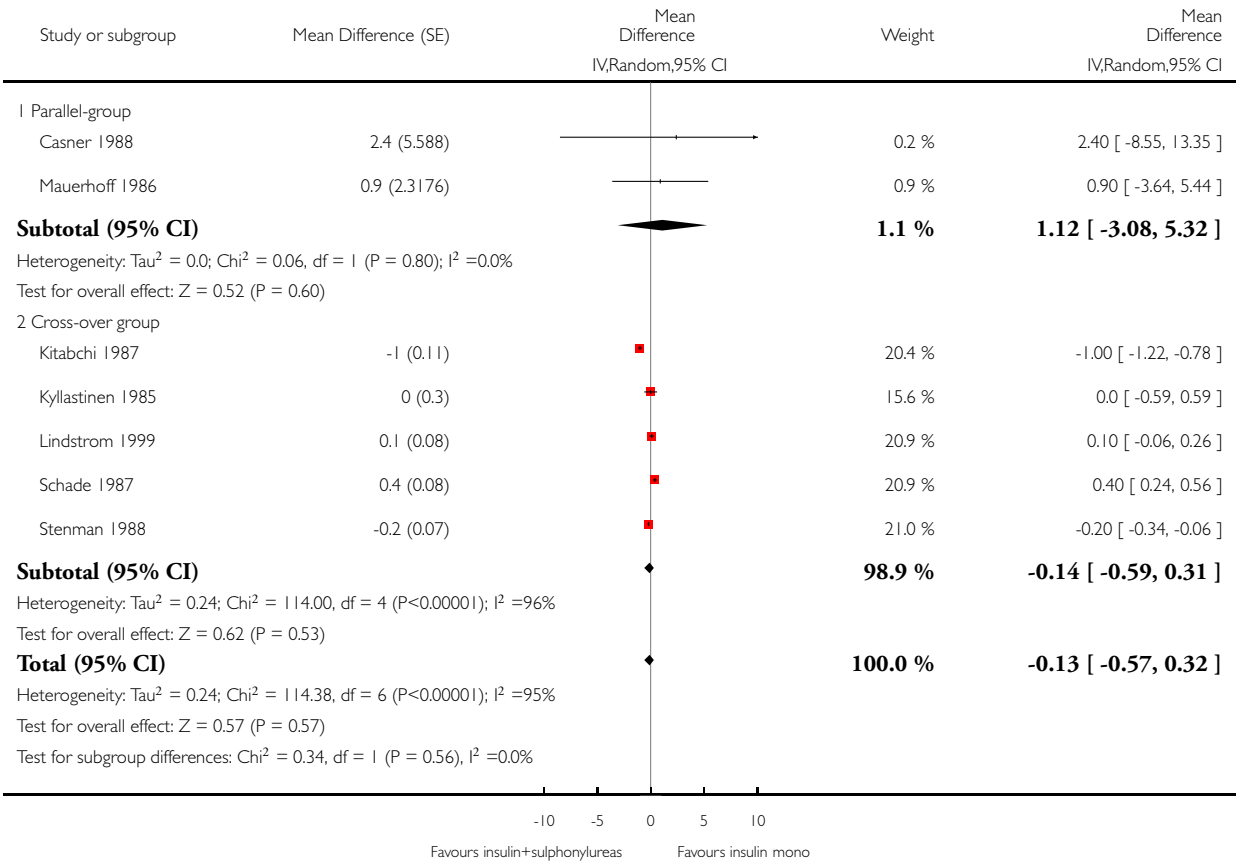


Analysis 1.2. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 2 Weight (change from baseline) [kg] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 2 Weight (change from baseline) [kg] GIV

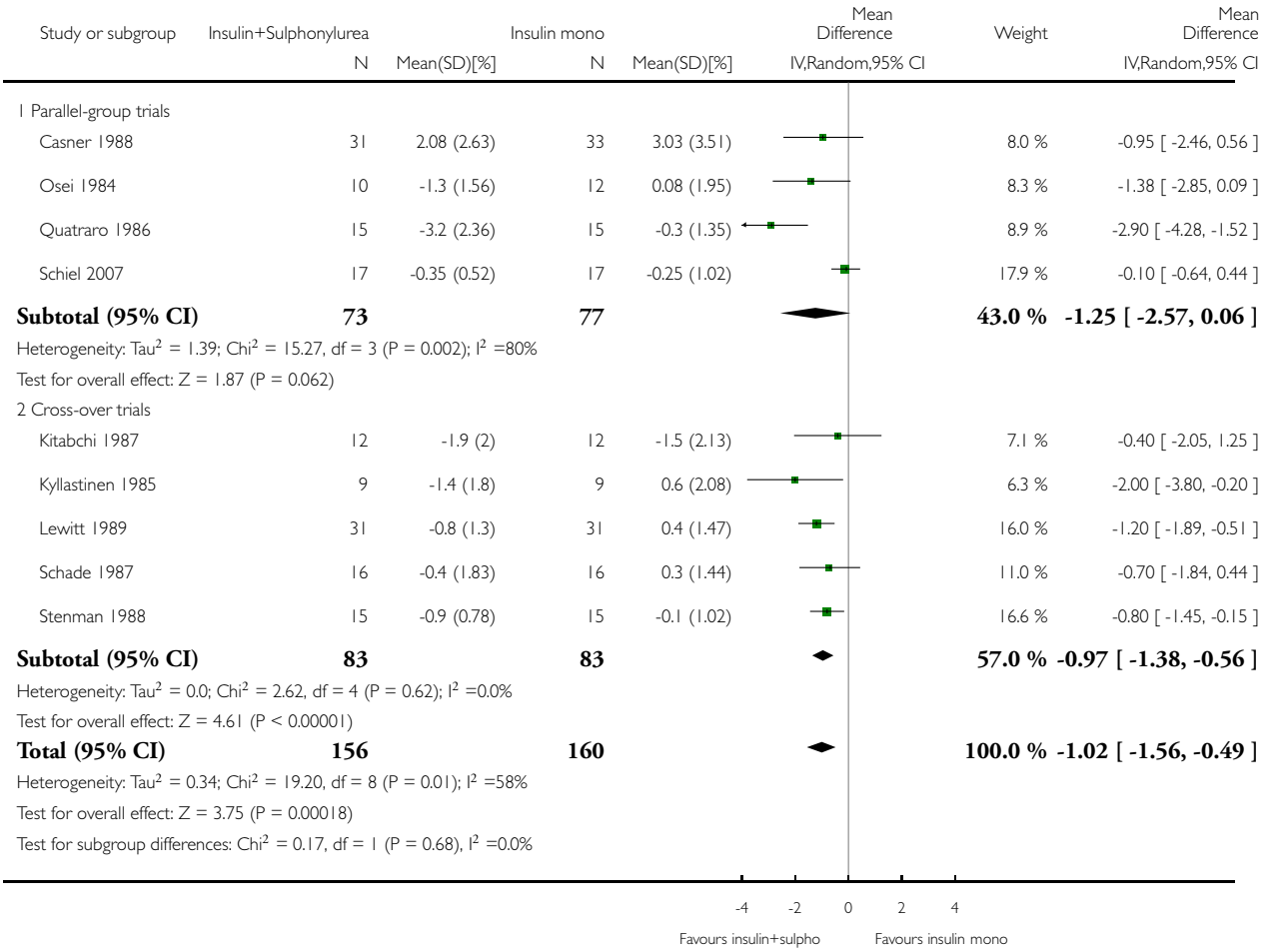


Analysis 1.3. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 3 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 3 HbA1c (change from baseline)

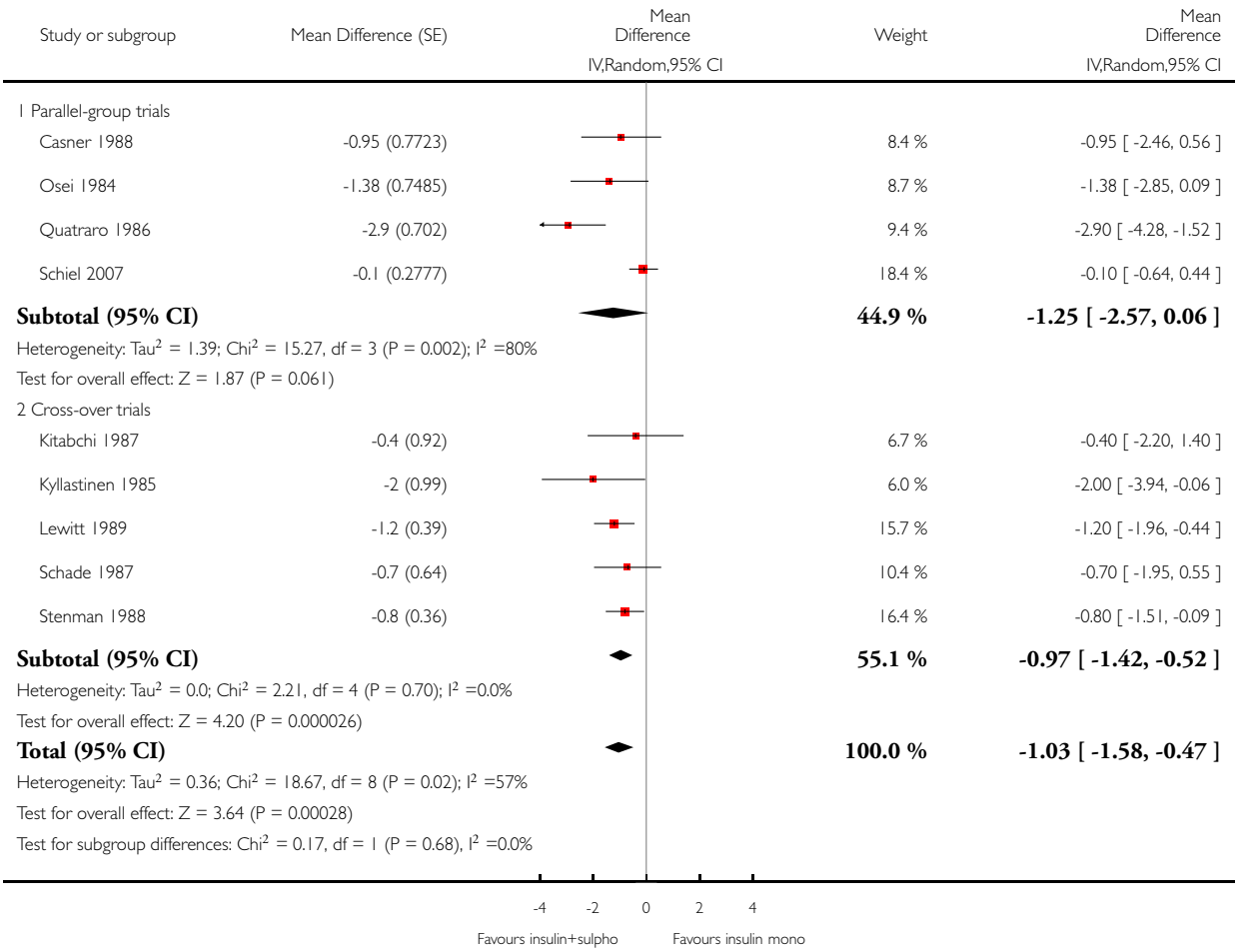


Analysis 1.4. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 4 HbA1c (change from baseline) GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 4 HbA1c (change from baseline) GIV

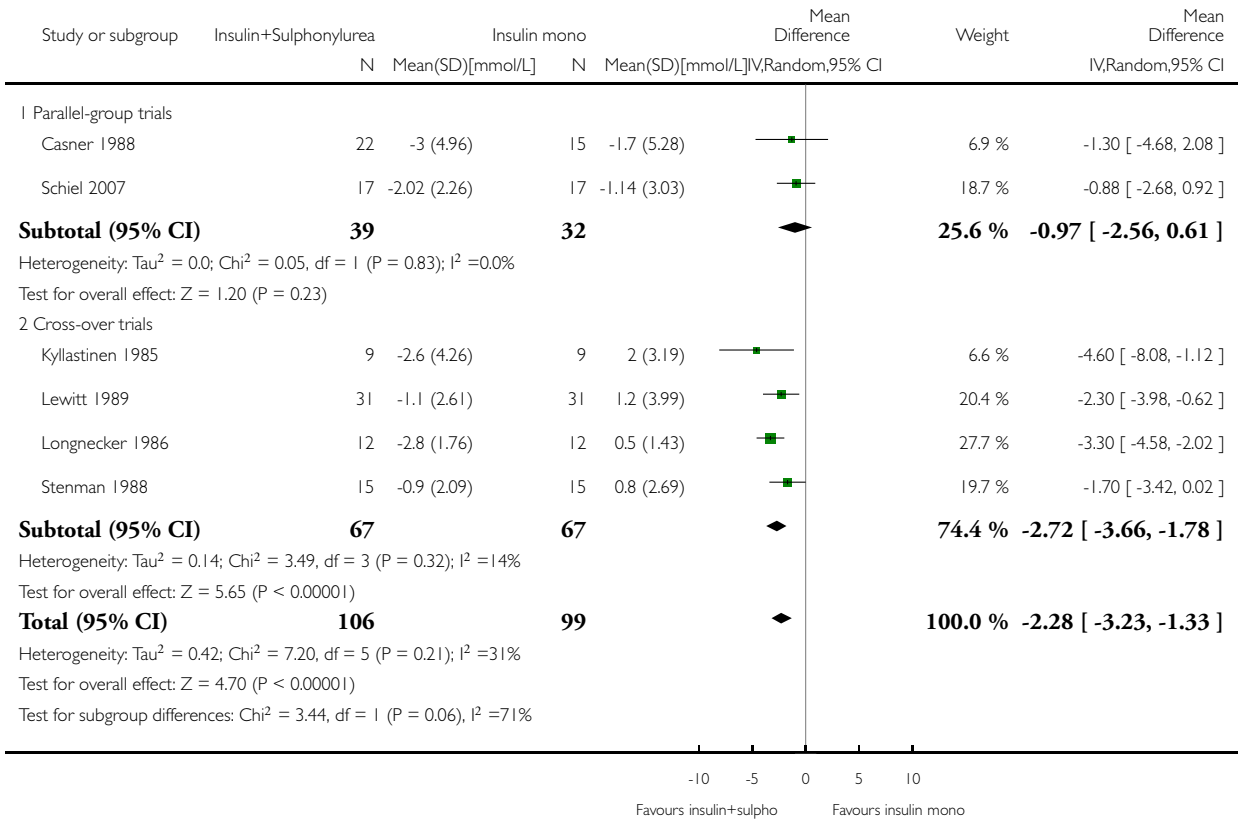


Analysis 1.5. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 5 Fasting glucose (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 5 Fasting glucose (change from baseline)

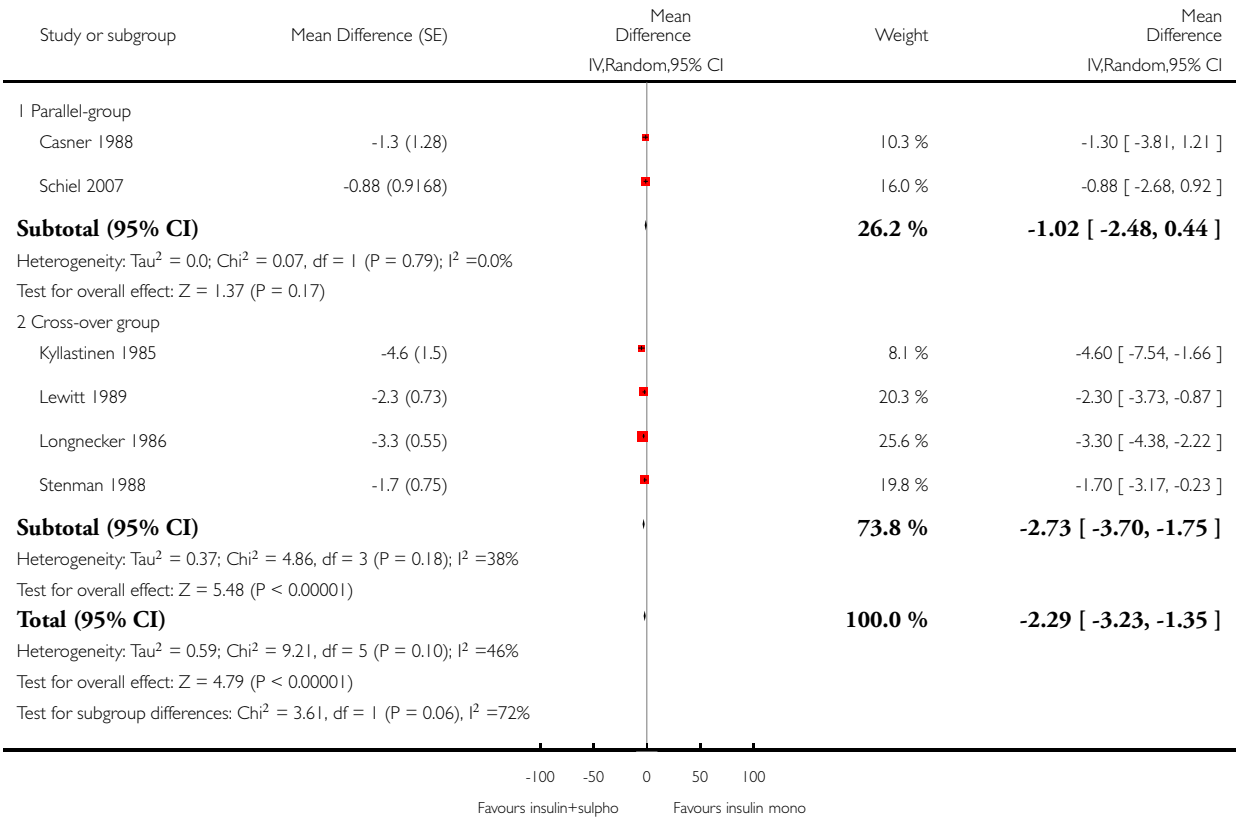


Analysis 1.6. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 6 Fasting plasma glucose (change from baseline) [mmol/L] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 6 Fasting plasma glucose (change from baseline) [mmol/L] GIV

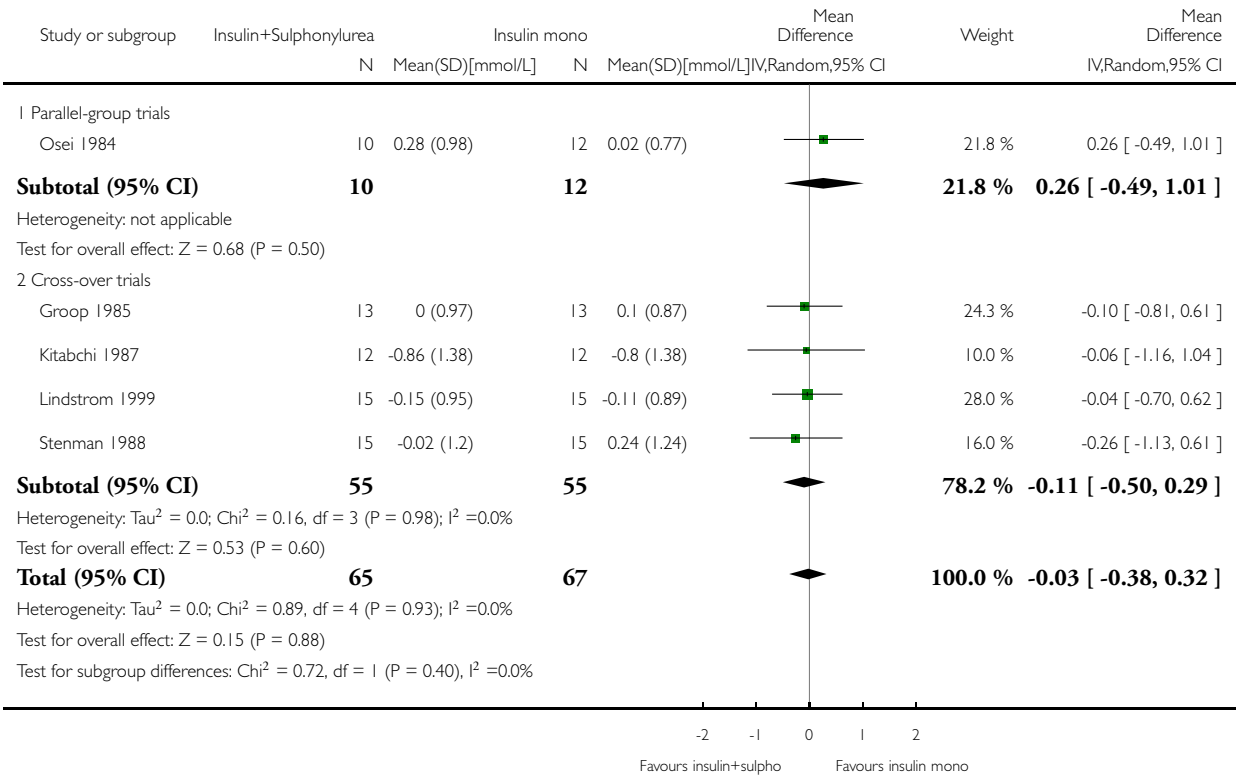


Analysis 1.7. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 7 Total cholesterol (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 7 Total cholesterol (change from baseline)

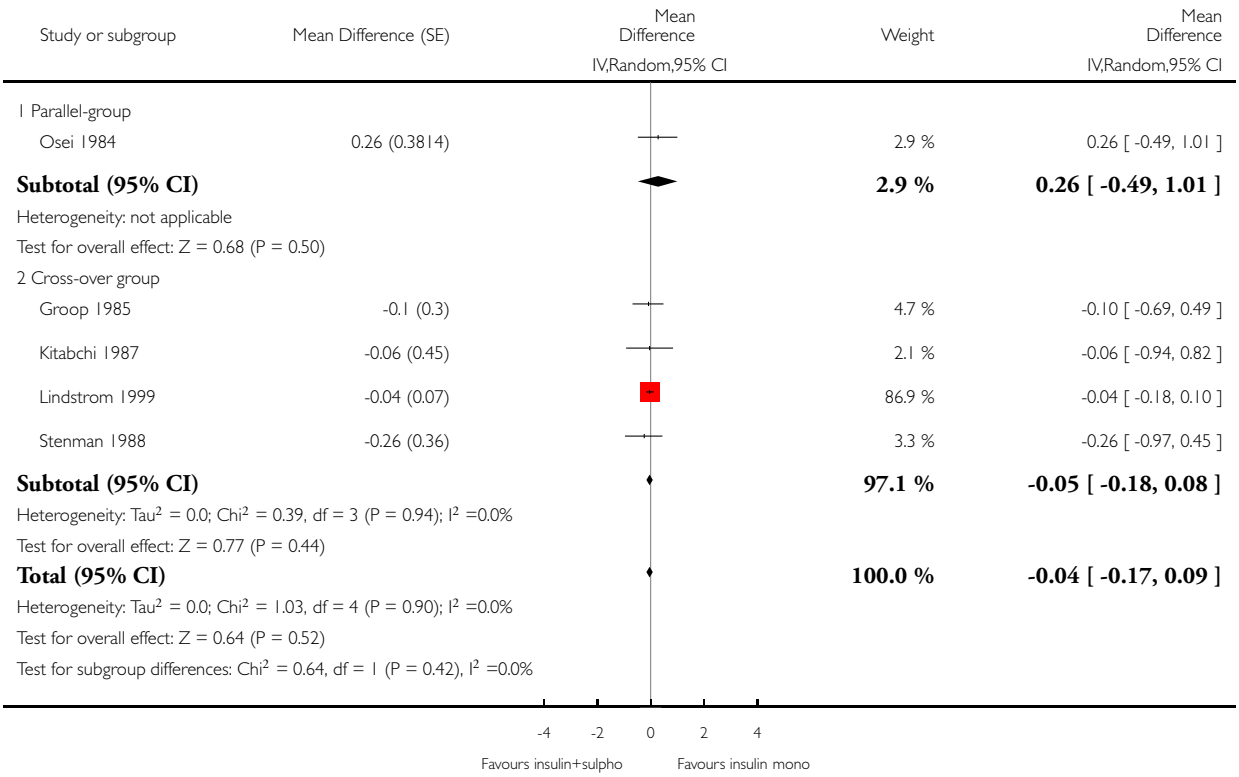


Analysis 1.8. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 8 Total cholesterol (change from baseline) [mmol/l] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 8 Total cholesterol (change from baseline) [mmol/l] GIV

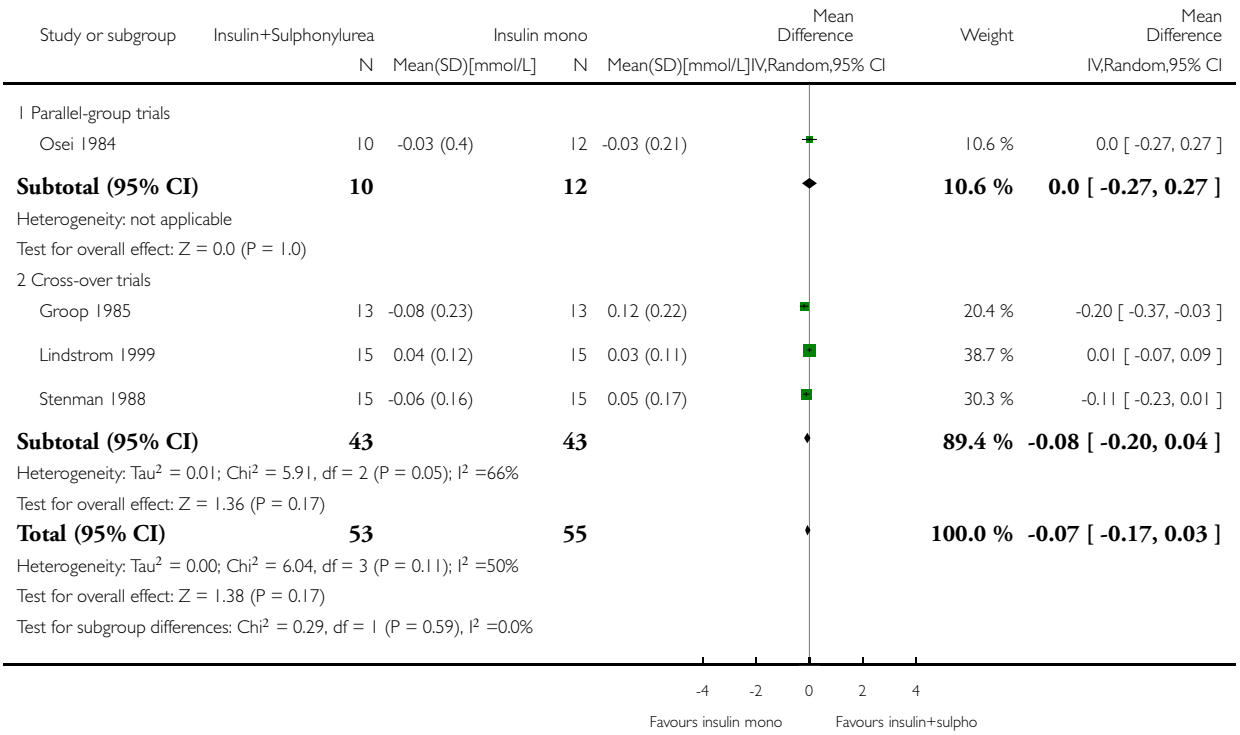


Analysis 1.9. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 9 HDL-cholesterol (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 9 HDL-cholesterol (change from baseline)



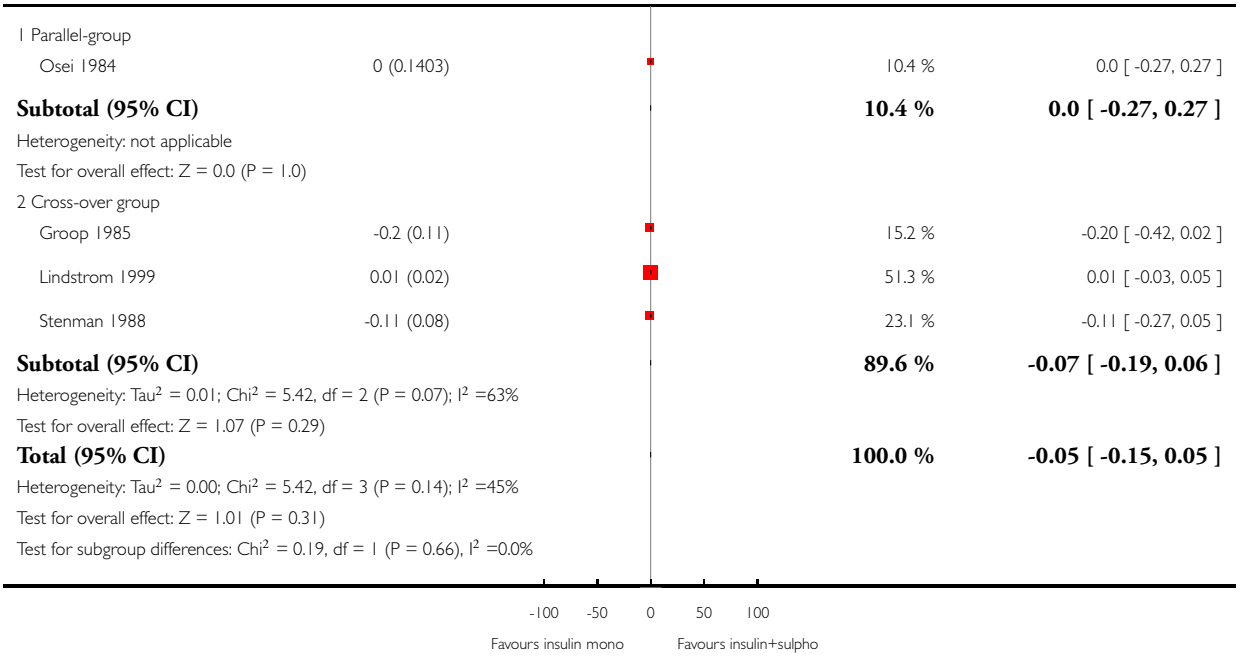
Analysis 1.10. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 10 HDL-Cholesterol (change from baseline mmol/L) GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 10 HDL-Cholesterol (change from baseline mmol/L) GIV

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group				
Osei 1984	0 (0.1403)		10.4 %	0.0 [-0.27, 0.27]
Subtotal (95% CI)			**10.4 %**	**0.0 [-0.27, 0.27]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P = 1.0)				
2 Cross-over group				
Groop 1985	-0.2 (0.11)		15.2 %	-0.20 [-0.42, 0.02]
Lindstrom 1999	0.01 (0.02)		51.3 %	0.01 [-0.03, 0.05]
Stenman 1988	-0.11 (0.08)		23.1 %	-0.11 [-0.27, 0.05]
Subtotal (95% CI)			**89.6 %**	**-0.07 [-0.19, 0.06]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 5.42, df = 2 (P = 0.07); I^2 =63%				
Test for overall effect: Z = 1.07 (P = 0.29)				
Total (95% CI)			**100.0 %**	**-0.05 [-0.15, 0.05]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.42, df = 3 (P = 0.14); I^2 =45%				
Test for overall effect: Z = 1.01 (P = 0.31)				
Test for subgroup differences: Chi^2 = 0.19, df = 1 (P = 0.66), I^2 =0.0%				

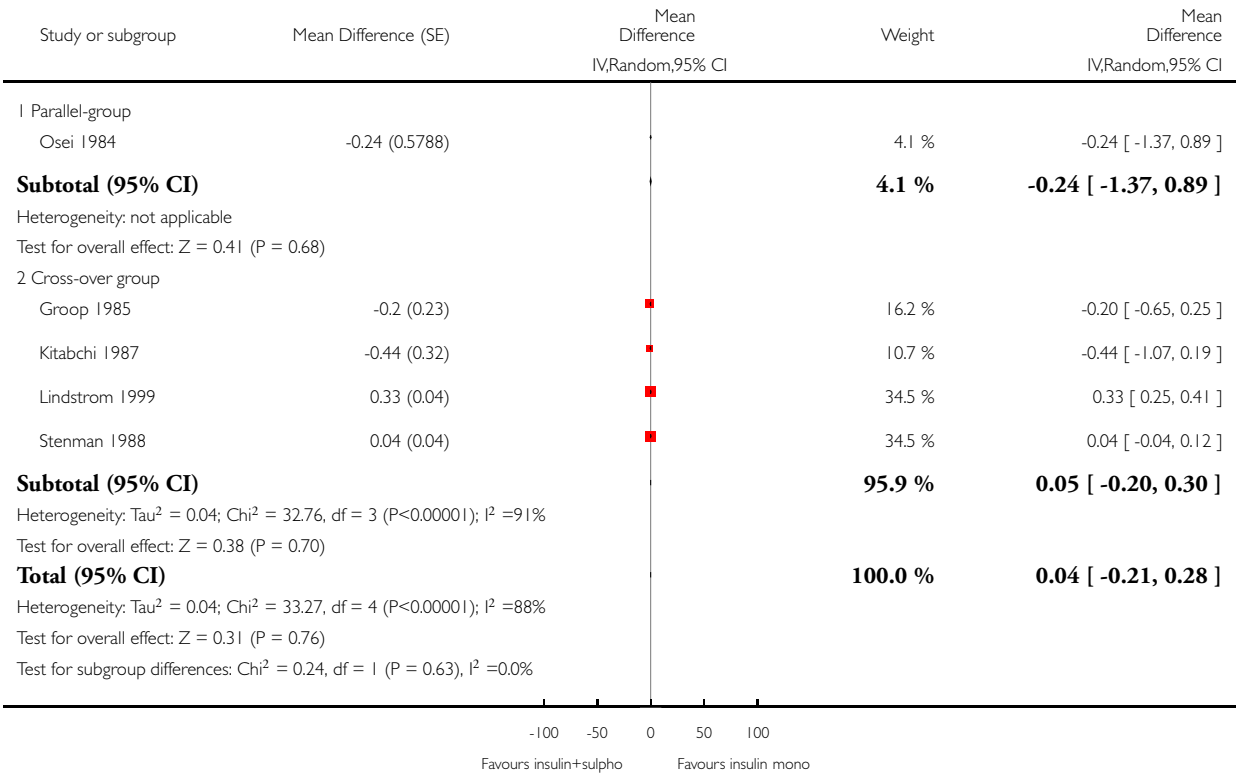


Analysis 1.11. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 11 Triglyceride (change from baseline) [mmol/L] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 11 Triglyceride (change from baseline) [mmol/L] GIV



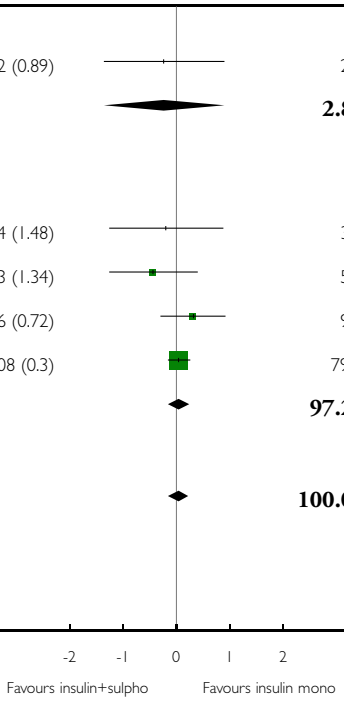
Analysis 1.12. Comparison 1 Insulin monotherapy versus insulin plus sulphonylurea, Outcome 12 Triglycerides (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 1 Insulin monotherapy versus insulin plus sulphonylurea

Outcome: 12 Triglycerides (change from baseline)

Study or subgroup	Insulin+Sulphonylurea N	Mean(SD)[mmol/L]	Insulin mono N	Mean(SD)[mmol/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group trials							
Osei 1984	10	-0.12 (1.64)	12	0.12 (0.89)		2.8 %	-0.24 [-1.37, 0.89]
Subtotal (95% CI)	**10**		**12**			**2.8 %**	**-0.24 [-1.37, 0.89]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.41 (P = 0.68)							
2 Cross-over trials							
Groop 1985	13	0.2 (1.29)	13	0.4 (1.48)		3.2 %	-0.20 [-1.27, 0.87]
Kitabchi 1987	12	-0.47 (0.61)	12	-0.03 (1.34)		5.2 %	-0.44 [-1.27, 0.39]
Lindstrom 1999	15	0.25 (0.97)	15	-0.06 (0.72)		9.7 %	0.31 [-0.30, 0.92]
Stenman 1988	15	0.12 (0.3)	15	0.08 (0.3)		79.0 %	0.04 [-0.17, 0.25]
Subtotal (95% CI)	**55**		**55**			**97.2 %**	**0.03 [-0.16, 0.23]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.21, df = 3 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 0.34 (P = 0.74)							
Total (95% CI)	**65**		**67**			**100.0 %**	**0.03 [-0.17, 0.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.43, df = 4 (P = 0.66); I^2 =0.0%							
Test for overall effect: Z = 0.26 (P = 0.79)							
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%							

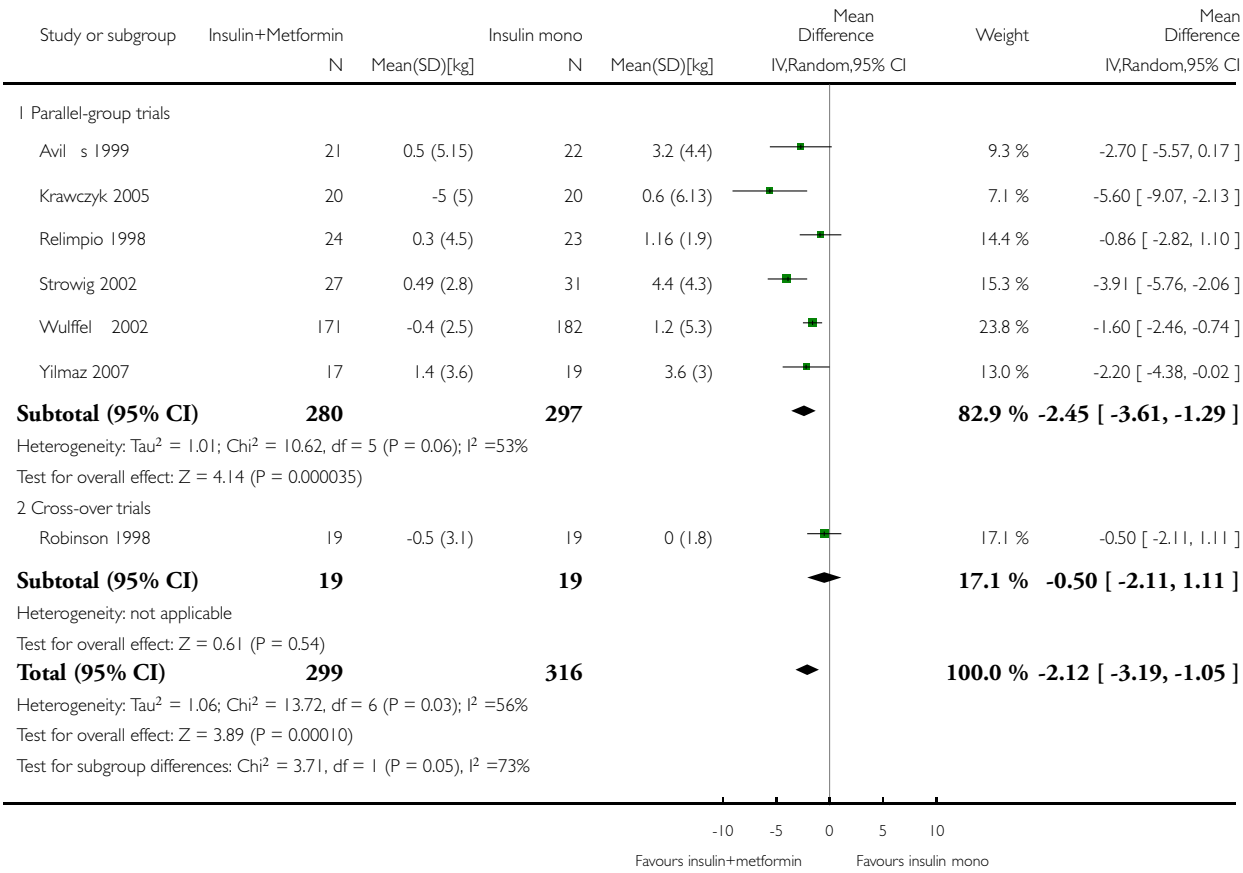


Analysis 2.1. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 1 Weight (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 1 Weight (change from baseline)

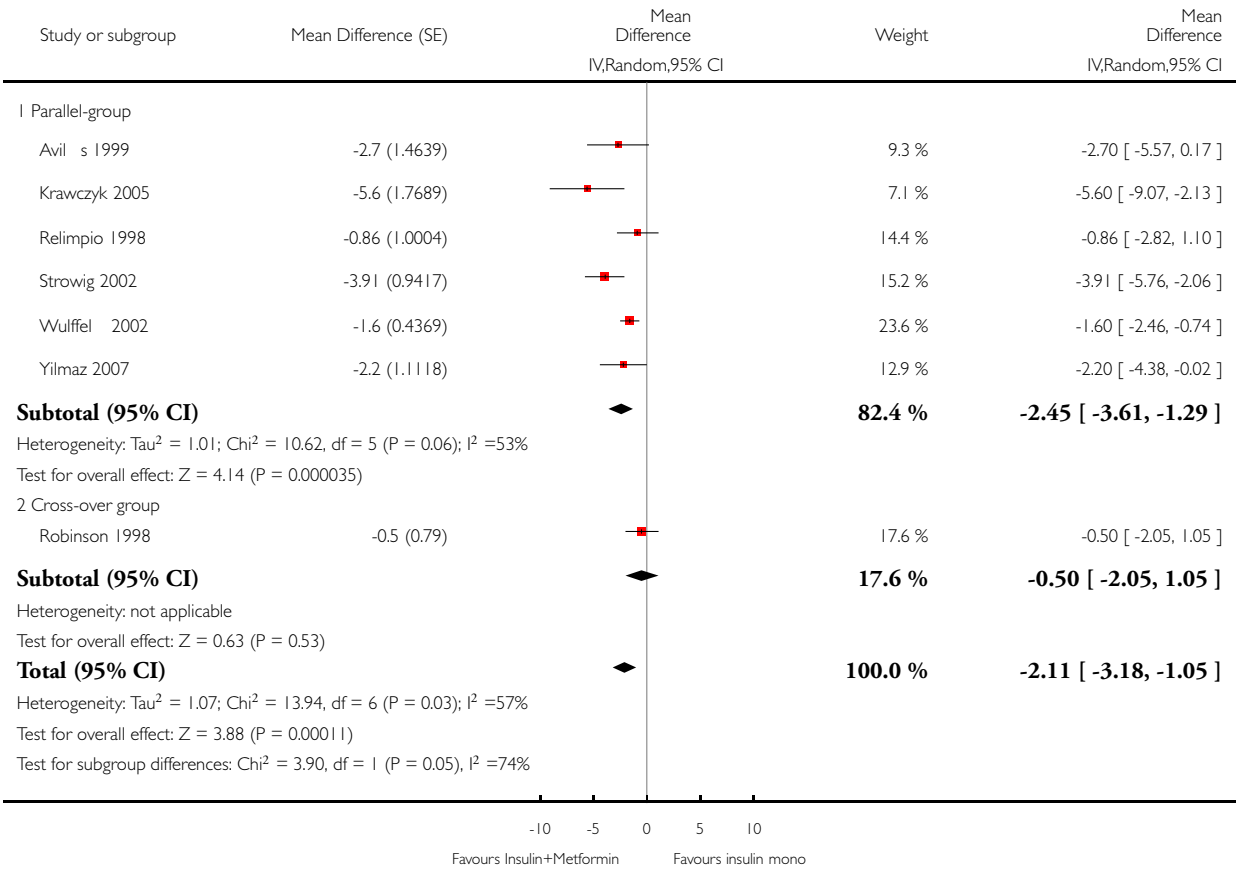


Analysis 2.2. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 2 Weight (change from baseline) [kg] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 2 Weight (change from baseline) [kg] GIV



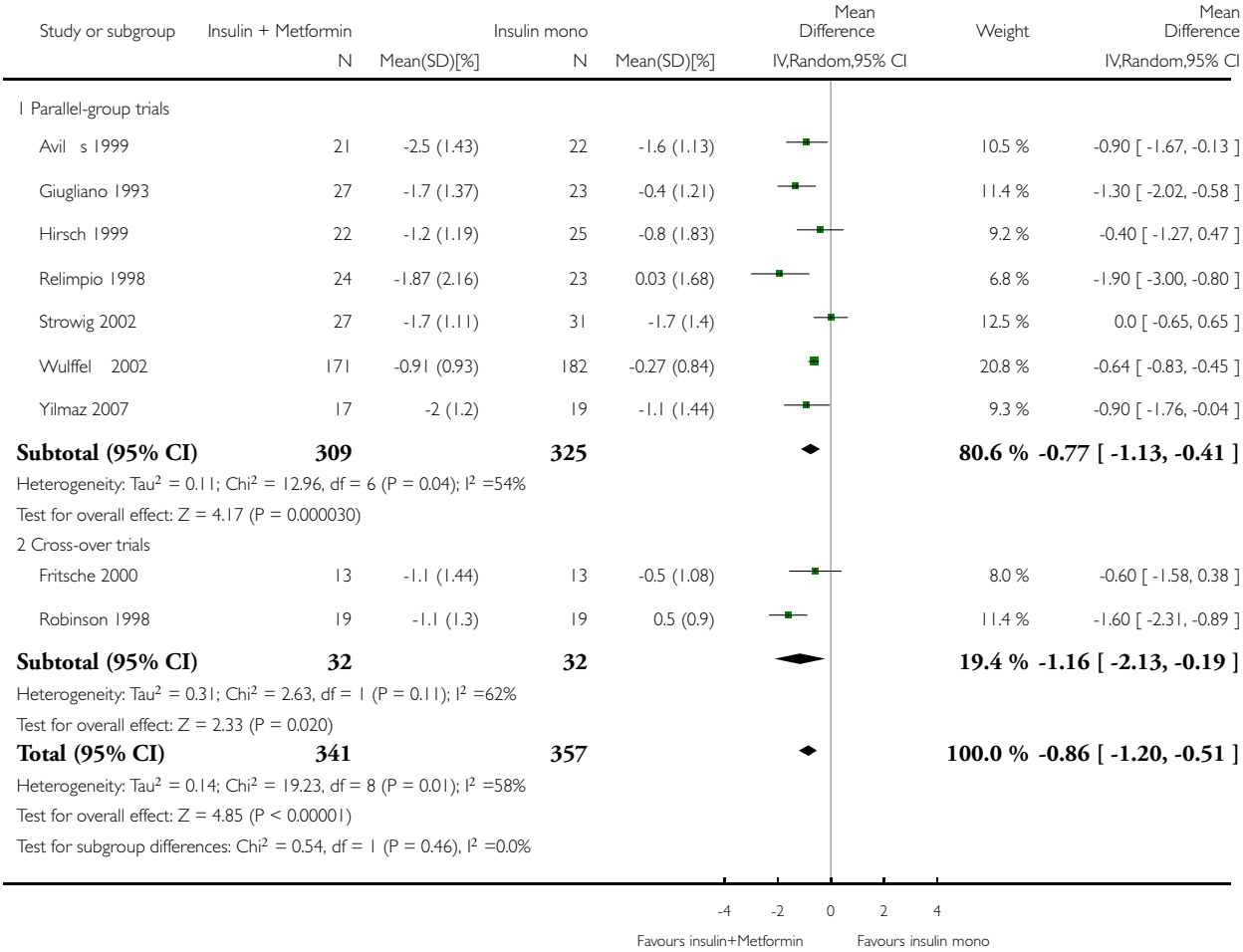
Analysis 2.3. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 3 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 3 HbA1c (change from baseline)

Study or subgroup	Insulin + Metformin N	Mean(SD)[%]	Insulin mono N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group trials							
Avil s 1999	21	-2.5 (1.43)	22	-1.6 (1.13)		10.5 %	-0.90 [-1.67, -0.13]
Giugliano 1993	27	-1.7 (1.37)	23	-0.4 (1.21)		11.4 %	-1.30 [-2.02, -0.58]
Hirsch 1999	22	-1.2 (1.19)	25	-0.8 (1.83)		9.2 %	-0.40 [-1.27, 0.47]
Relimpio 1998	24	-1.87 (2.16)	23	0.03 (1.68)		6.8 %	-1.90 [-3.00, -0.80]
Strowig 2002	27	-1.7 (1.11)	31	-1.7 (1.4)		12.5 %	0.0 [-0.65, 0.65]
Wulffel 2002	171	-0.91 (0.93)	182	-0.27 (0.84)		20.8 %	-0.64 [-0.83, -0.45]
Yilmaz 2007	17	-2 (1.2)	19	-1.1 (1.44)		9.3 %	-0.90 [-1.76, -0.04]
Subtotal (95% CI)	**309**		**325**			**80.6 %**	**-0.77 [-1.13, -0.41]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 12.96$, df = 6 (P = 0.04); $I^2 = 54\%$							
Test for overall effect: Z = 4.17 (P = 0.000030)							
2 Cross-over trials							
Fritsche 2000	13	-1.1 (1.44)	13	-0.5 (1.08)		8.0 %	-0.60 [-1.58, 0.38]
Robinson 1998	19	-1.1 (1.3)	19	0.5 (0.9)		11.4 %	-1.60 [-2.31, -0.89]
Subtotal (95% CI)	**32**		**32**			**19.4 %**	**-1.16 [-2.13, -0.19]**
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 2.63$, df = 1 (P = 0.11); $I^2 = 62\%$							
Test for overall effect: Z = 2.33 (P = 0.020)							
Total (95% CI)	**341**		**357**			**100.0 %**	**-0.86 [-1.20, -0.51]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 19.23$, df = 8 (P = 0.01); $I^2 = 58\%$							
Test for overall effect: Z = 4.85 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.54$, df = 1 (P = 0.46), $I^2 = 0.0\%$							

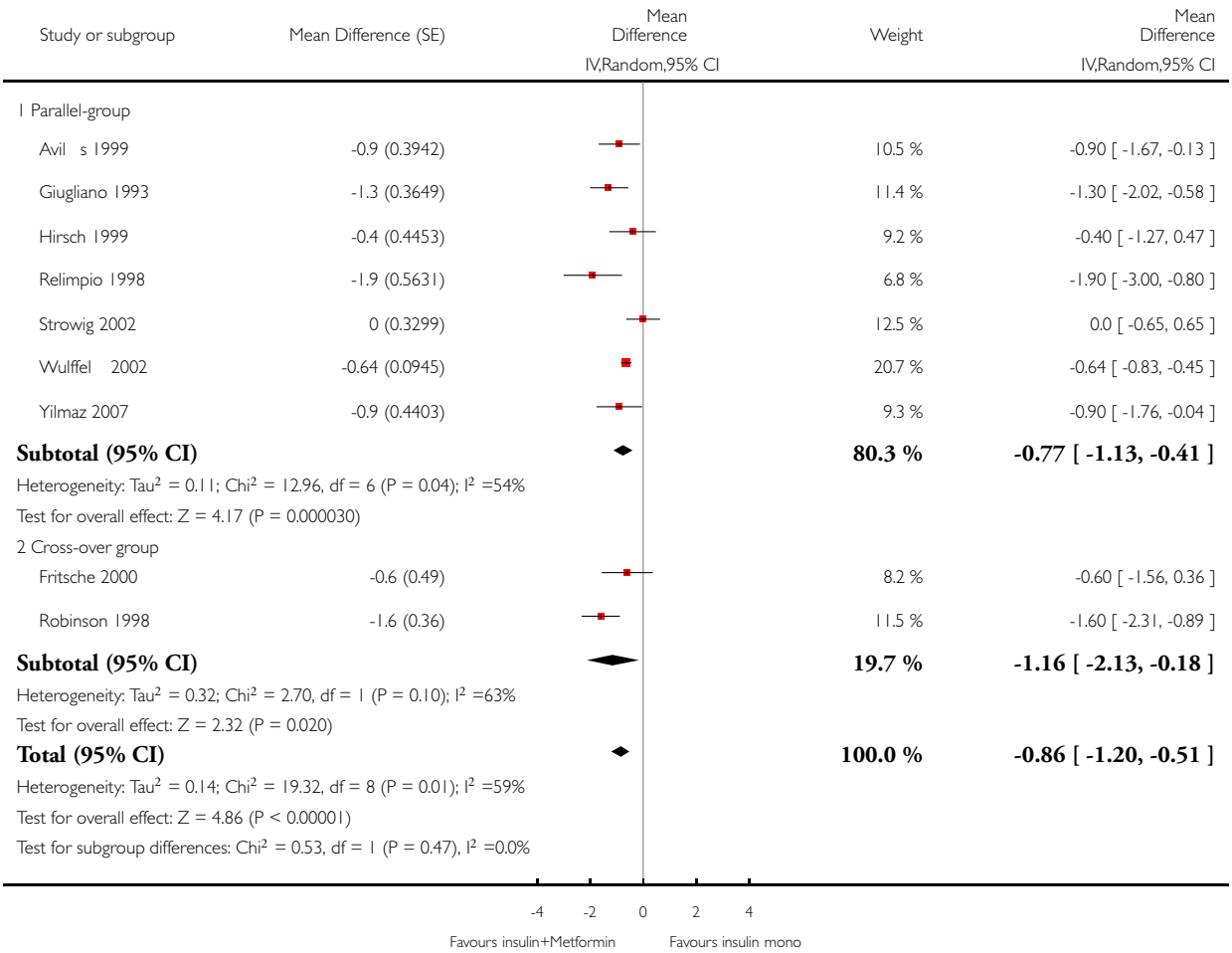


Analysis 2.4. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 4 HbA1c (change from baseline) [%] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 4 HbA1c (change from baseline) [%] GIV



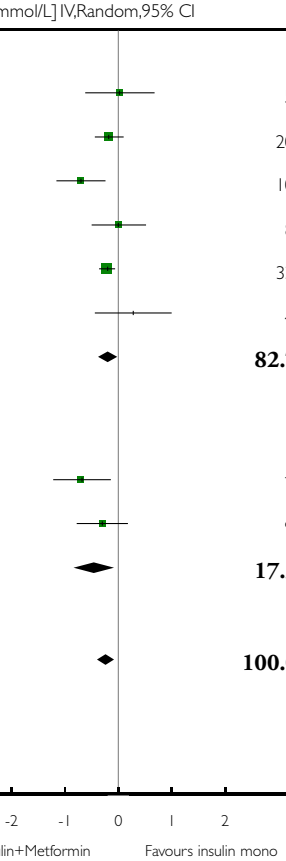
Analysis 2.5. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 5 Total cholesterol (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 5 Total cholesterol (change from baseline)

Study or subgroup	Insulin+Metformin N	Mean(SD)[mmol/L]	Insulin mono N	Mean(SD)[mmol/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group trials							
Avil s 1999	21	-0.51 (1.32)	22	-0.53 (0.79)		5.7 %	0.02 [-0.63, 0.67]
Giugliano 1993	27	-0.21 (0.48)	23	-0.03 (0.49)		20.5 %	-0.18 [-0.45, 0.09]
Relimpio 1998	24	-0.56 (0.89)	23	0.14 (0.72)		10.1 %	-0.70 [-1.16, -0.24]
Strowig 2002	27	0.04 (1.02)	31	0.04 (0.95)		8.6 %	0.0 [-0.51, 0.51]
Wulffel 2002	171	-0.25 (0.65)	182	-0.04 (0.75)		33.0 %	-0.21 [-0.36, -0.06]
Yilmaz 2007	17	-0.07 (0.61)	19	-0.34 (1.47)		4.8 %	0.27 [-0.45, 0.99]
Subtotal (95% CI)	**287**		**300**			**82.7 %**	**-0.20 [-0.38, -0.02]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.19$, df = 5 (P = 0.21); $I^2 = 30\%$							
Test for overall effect: Z = 2.19 (P = 0.029)							
2 Cross-over trials							
Fritsche 2000	13	-0.72 (0.65)	13	-0.03 (0.76)		7.8 %	-0.69 [-1.23, -0.15]
Robinson 1998	19	-0.3 (0.7)	19	0 (0.8)		9.6 %	-0.30 [-0.78, 0.18]
Subtotal (95% CI)	**32**		**32**			**17.3 %**	**-0.47 [-0.85, -0.09]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 10\%$							
Test for overall effect: Z = 2.44 (P = 0.015)							
Total (95% CI)	**319**		**332**			**100.0 %**	**-0.25 [-0.41, -0.08]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.20$, df = 7 (P = 0.18); $I^2 = 31\%$							
Test for overall effect: Z = 2.88 (P = 0.0040)							
Test for subgroup differences: $Chi^2 = 1.65$, df = 1 (P = 0.20), $I^2 = 39\%$							

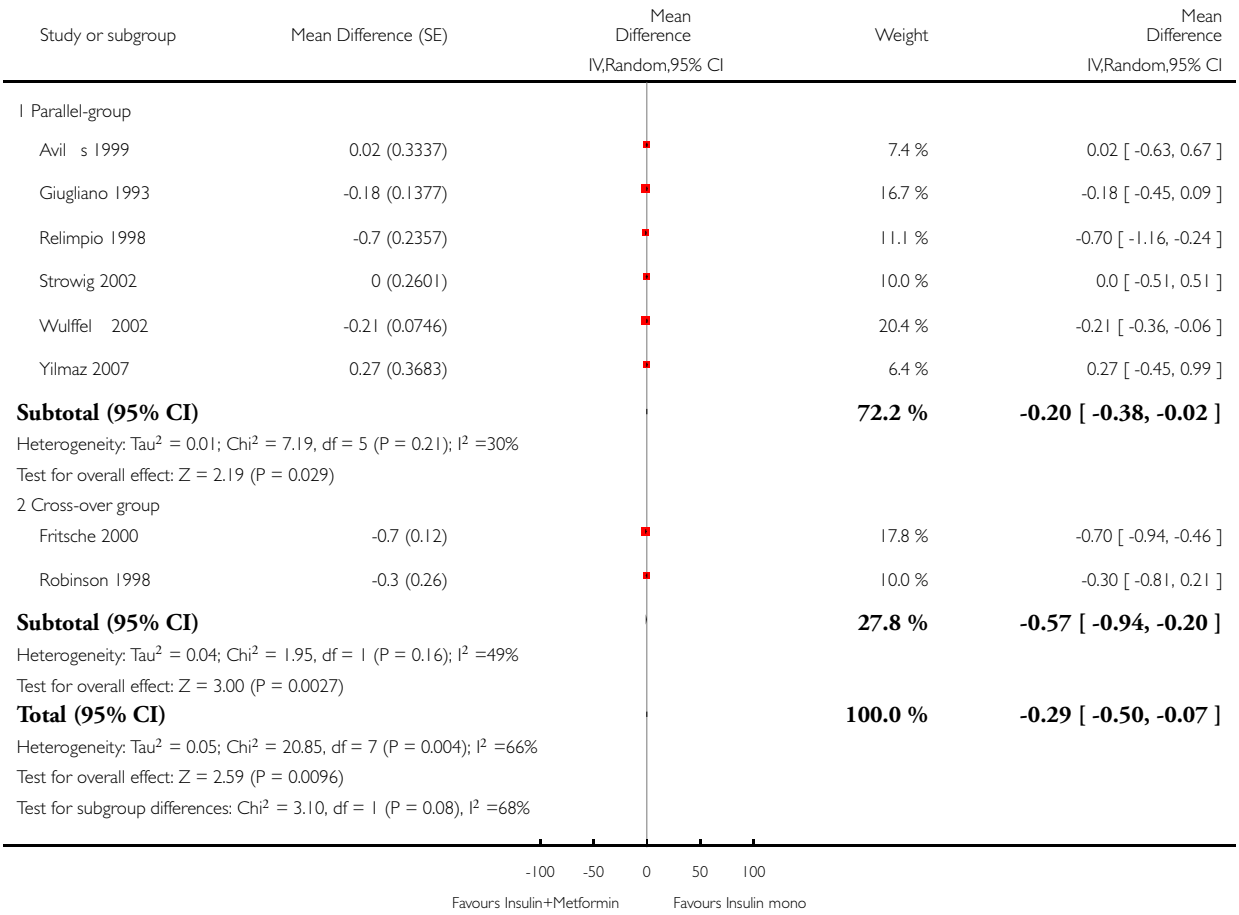


Analysis 2.6. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 6 Total cholesterol (change from baseline) [mmol/L] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 6 Total cholesterol (change from baseline) [mmol/L] GIV



Analysis 2.7. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 7 HDL-cholesterol (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 7 HDL-cholesterol (change from baseline)

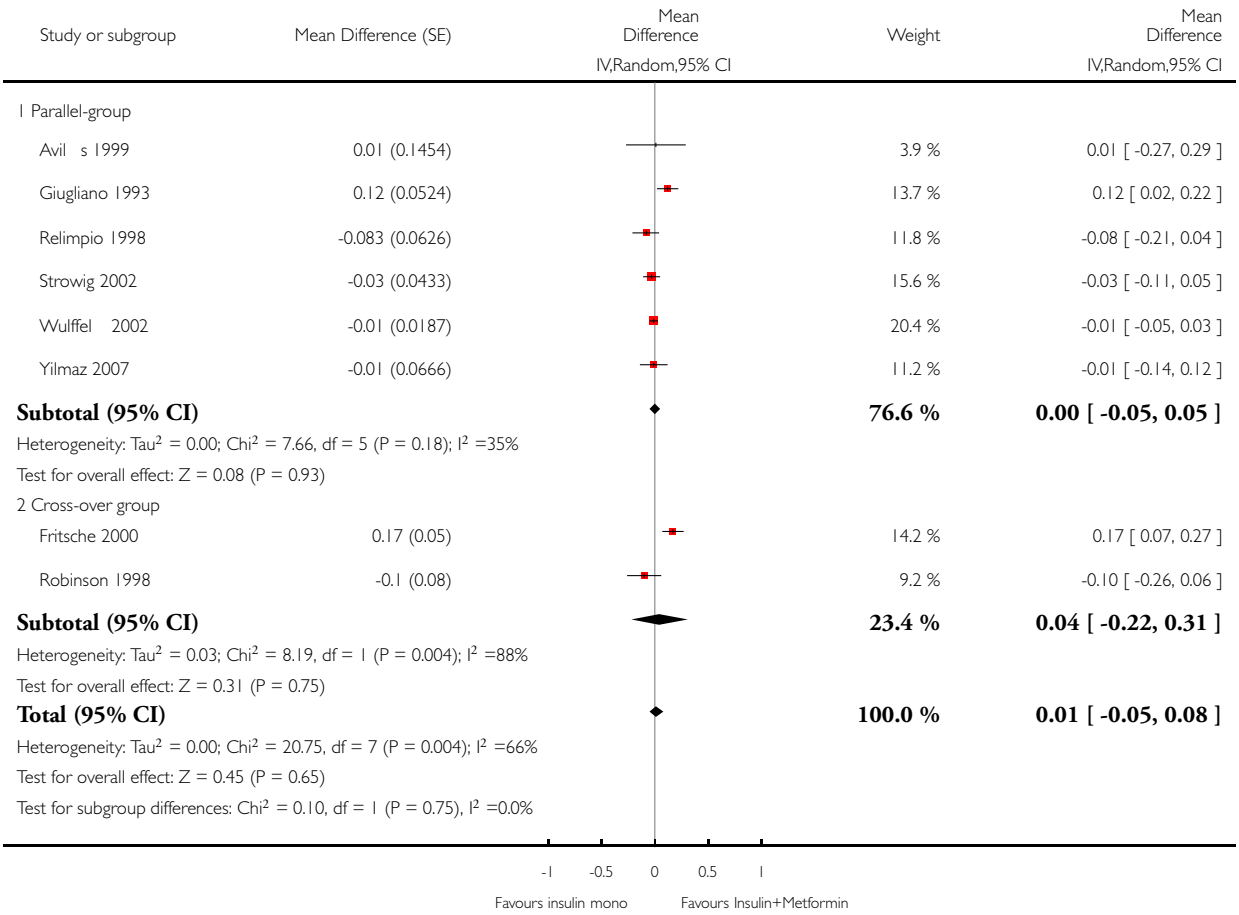
Study or subgroup	Insulin+Metformin N	Mean(SD)[mmol/L]	Insulin mono N	Mean(SD)[mmol/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group trials							
Avil s 1999	21	-0.1 (0.38)	22	-0.11 (0.56)		2.8 %	0.01 [-0.27, 0.29]
Giugliano 1993	27	0.13 (0.19)	23	0.01 (0.18)		13.7 %	0.12 [0.02, 0.22]
Relimpio 1998	24	-0.003 (0.17)	23	0.08 (0.25)		11.0 %	-0.08 [-0.21, 0.04]
Strowig 2002	27	0 (0.11)	31	0.03 (0.21)		16.9 %	-0.03 [-0.11, 0.05]
Wulffel 2002	171	-0.01 (0.18)	182	0 (0.17)		28.0 %	-0.01 [-0.05, 0.03]
Yilmaz 2007	17	0 (0.25)	19	0.01 (0.12)		10.1 %	-0.01 [-0.14, 0.12]
Subtotal (95% CI)	**287**		**300**			**82.4 %**	**0.00 [-0.05, 0.05]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.66$, df = 5 (P = 0.18); $I^2 = 35\%$							
Test for overall effect: Z = 0.08 (P = 0.93)							
2 Cross-over trials							
Fritsche 2000	13	-0.05 (0.29)	13	-0.21 (0.36)		3.5 %	0.16 [-0.09, 0.41]
Robinson 1998	19	0 (0.1)	19	0.1 (0.2)		14.1 %	-0.10 [-0.20, 0.00]
Subtotal (95% CI)	**32**		**32**			**17.6 %**	**0.00 [-0.25, 0.25]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.54$, df = 1 (P = 0.06); $I^2 = 72\%$							
Test for overall effect: Z = 0.03 (P = 0.98)							
Total (95% CI)	**319**		**332**			**100.0 %**	**-0.01 [-0.06, 0.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.58$, df = 7 (P = 0.08); $I^2 = 44\%$							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0.0\%$							

Analysis 2.8. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 8 HDL-cholesterol (change from baseline) [mmol/L].

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 8 HDL-cholesterol (change from baseline) [mmol/L]

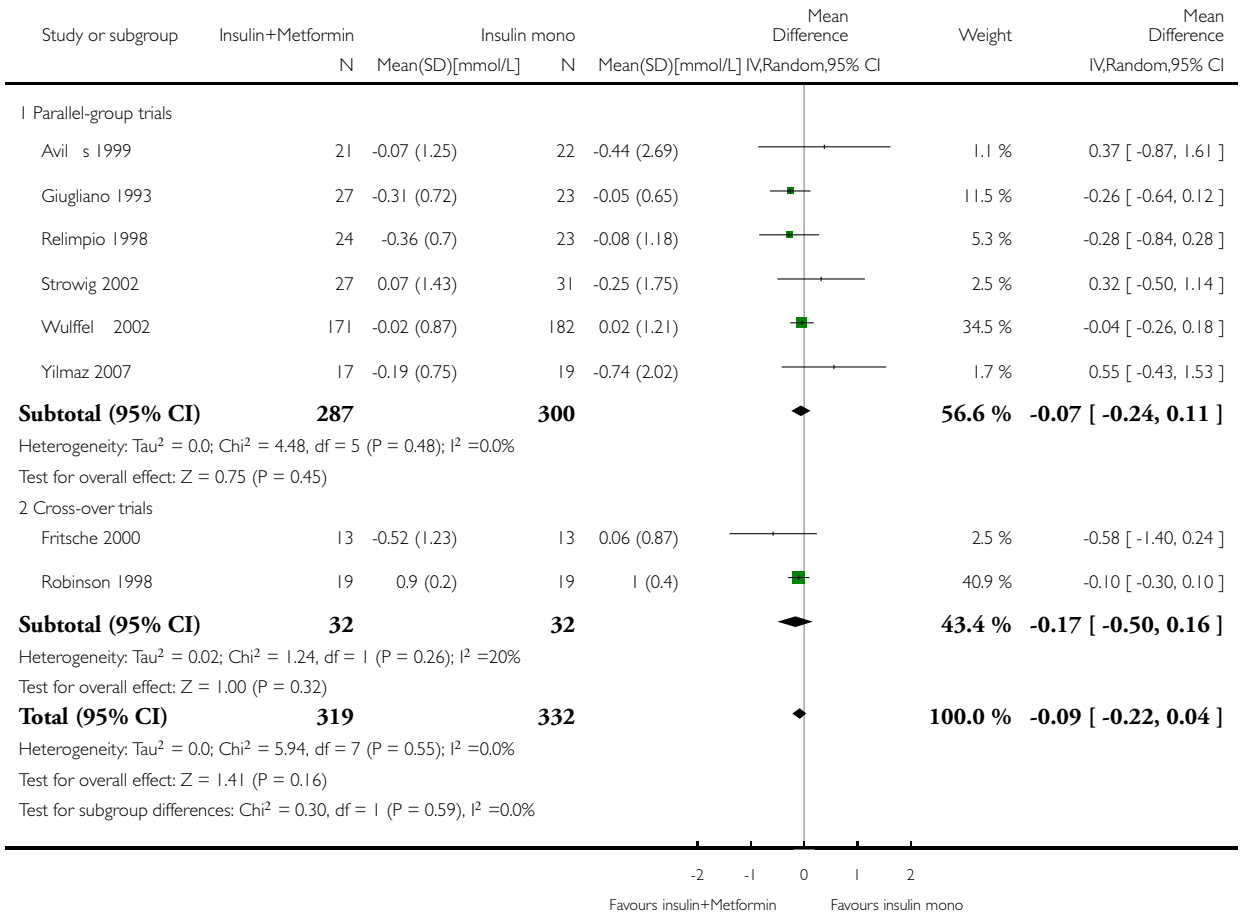


Analysis 2.9. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 9 Triglycerides (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 9 Triglycerides (change from baseline)



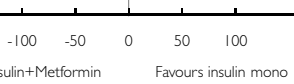
Analysis 2.10. Comparison 2 Insulin monotherapy versus insulin plus metformin, Outcome 10 Triglyceride (change from baseline) [mmol/L] GIV.

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 2 Insulin monotherapy versus insulin plus metformin

Outcome: 10 Triglyceride (change from baseline) [mmol/L] GIV

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Parallel-group				
Avil s 1999	0.37 (0.6351)		3.6 %	0.37 [-0.87, 1.61]
Giugliano 1993	-0.26 (0.1938)		15.0 %	-0.26 [-0.64, 0.12]
Relimpio 1998	-0.28 (0.2845)		10.9 %	-0.28 [-0.84, 0.28]
Strowig 2002	0.32 (0.4178)		6.9 %	0.32 [-0.50, 1.14]
Wulffel 2002	-0.04 (0.1117)		19.1 %	-0.04 [-0.26, 0.18]
Yilmaz 2007	0.55 (0.4978)		5.3 %	0.55 [-0.43, 1.53]
Subtotal (95% CI)			**60.9 %**	**-0.07 [-0.24, 0.11]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.48, df = 5 (P = 0.48); I^2 =0.0%				
Test for overall effect: Z = 0.75 (P = 0.45)				
2 Cross-over group				
Fritsche 2000	-0.56 (0.07)		20.9 %	-0.56 [-0.70, -0.42]
Robinson 1998	-0.1 (0.13)		18.2 %	-0.10 [-0.35, 0.15]
Subtotal (95% CI)			**39.1 %**	**-0.34 [-0.79, 0.11]**
Heterogeneity: Tau^2 = 0.09; Chi^2 = 9.71, df = 1 (P = 0.002); I^2 =90%				
Test for overall effect: Z = 1.49 (P = 0.14)				
Total (95% CI)			**100.0 %**	**-0.15 [-0.41, 0.11]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 27.58, df = 7 (P = 0.00026); I^2 =75%				
Test for overall effect: Z = 1.12 (P = 0.26)				
Test for subgroup differences: Chi^2 = 1.28, df = 1 (P = 0.26), I^2 =22%				



Analysis 3.1. Comparison 3 Insulin monotherapy versus insulin plus pioglitazone, Outcome 1 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 3 Insulin monotherapy versus insulin plus pioglitazone

Outcome: 1 HbA1c (change from baseline)

Study or subgroup	Pioglitazone + insulin		Insulin mono		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Mattoo 2005	128	-0.69 (0)	135	-0.08 (0)		Not estimable
Mudaliar 2010	12	-0.5 (0)	13	-0.6 (0)		Not estimable
Rosenstock 2002	333	-1 (0)	164	0 (0)		Not estimable

Analysis 3.2. Comparison 3 Insulin monotherapy versus insulin plus pioglitazone, Outcome 2 Fasting glucose (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 3 Insulin monotherapy versus insulin plus pioglitazone

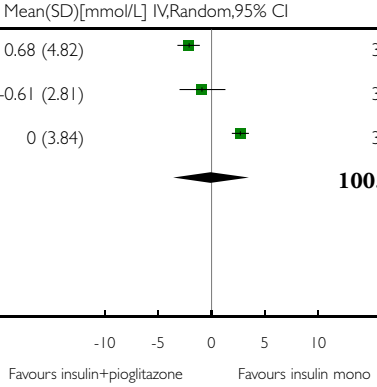
Outcome: 2 Fasting glucose (change from baseline)

Study or subgroup	Insulin + pioglitazone		Insulin mono		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[mmol/L]	N	Mean(SD)[mmol/L]	IV,Random,95% CI		IV,Random,95% CI
Mattoo 2005	128	-1.45 (3.96)	135	0.68 (4.82)		34.2 %	-2.13 [-3.19, -1.07]
Mudaliar 2010	12	-1.5 (2.7)	13	-0.61 (2.81)		31.2 %	-0.89 [-3.05, 1.27]
Rosenstock 2002	172	2.7 (3.93)	164	0 (3.84)		34.6 %	2.70 [1.87, 3.53]
Total (95% CI)	**312**		**312**			**100.0 %**	**-0.07 [-3.61, 3.46]**

Heterogeneity: $Tau^2 = 9.22$; $Chi^2 = 51.52$, df = 2 (P<0.00001); $I^2 = 96\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Insulin monotherapy versus insulin plus pioglitazone, Outcome 3 Weight (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 3 Insulin monotherapy versus insulin plus pioglitazone

Outcome: 3 Weight (change from baseline)

Study or subgroup	Insulin+ pioglitazone		Insulin mono		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[kg]	N	Mean(SD)[kg]	IV,Random,95% CI		IV,Random,95% CI
Mudaliar 2010	12	4.9 (4.5)	13	1.7 (0.7)		9.9 %	3.20 [0.63, 5.77]
Mattoo 2005	128	4.05 (4.03)	135	0.2 (2.92)		90.1 %	3.85 [3.00, 4.70]
Total (95% CI)	**140**		**148**			**100.0 %**	**3.79 [2.97, 4.60]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 9.15 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor, Outcome 1 Weight (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor

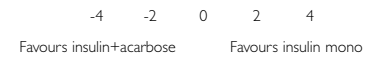
Outcome: 1 Weight (change from baseline)

Study or subgroup	Insulin + acarbose N	Mean(SD)[kg]	Insulin mono N	Mean(SD)[kg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Coniff 1995	103	0.3 (3.1)	104	0.7 (3.1)		83.8 %	-0.40 [-1.24, 0.44]
Yilmaz 2007	15	2.9 (2.7)	19	3.6 (3)		16.2 %	-0.70 [-2.62, 1.22]
Total (95% CI)	**118**		**123**			**100.0 %**	**-0.45 [-1.22, 0.32]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 1.14 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor, Outcome 2 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor

Outcome: 2 HbA1c (change from baseline)

Study or subgroup	Insuline + α - glucosidase N	Mean(SD)[%]	Insulin mono N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Coniff 1995	103	-0.57 (0.81)	104	-0.17 (0.82)		39.1 %	-0.40 [-0.62, -0.18]
Nemoto 2011	107	-0.37 (0.68)	100	0.04 (0.56)		59.2 %	-0.41 [-0.58, -0.24]
Yilmaz 2007	15	-0.6 (1.91)	19	-1.1 (1.44)		1.7 %	0.50 [-0.66, 1.66]
Total (95% CI)	**225**		**223**			**100.0 %**	**-0.39 [-0.54, -0.24]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.31$, df = 2 (P = 0.32); $I^2 = 13\%$

Test for overall effect: Z = 4.97 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor, Outcome 3 Fasting glucose (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 4 Insulin monotherapy versus insulin plus alpha-glucosidase inhibitor

Outcome: 3 Fasting glucose (change from baseline)

Study or subgroup	Insulin + acarbose		Insulin mono		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[mmol/L]	N	Mean(SD)[mmol/L]	IV,Random,95% CI		IV,Random,95% CI
Chiasson 1994	35	0.1 (2.96)	44	0.1 (3.32)		58.7 %	0.0 [-1.39, 1.39]
Yilmaz 2007	15	-1.48 (3.05)	19	-2.27 (1.31)		41.3 %	0.79 [-0.86, 2.44]
Total (95% CI)	**50**		**63**			**100.0 %**	**0.33 [-0.74, 1.39]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 1 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor, Outcome 1 Weight (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor

Outcome: 1 Weight (change from baseline)

Study or subgroup	Insulin + DPP-4 inhibitor		Insulin mono		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[kg]	N	Mean(SD)[kg]	IV,Random,95% CI		IV,Random,95% CI
Fonseca 2007	114	1.3 (0.3)	124	0.6 (0.3)		50.0 %	0.70 [0.62, 0.78]
Hong 2012	61	-0.7 (0.1)	63	1.1 (0.4)		50.0 %	-1.80 [-1.90, -1.70]
Total (95% CI)	**175**		**187**			**100.0 %**	**-0.55 [-3.00, 1.90]**

Heterogeneity: $Tau^2 = 3.12$; $Chi^2 = 1481.43$, df = 1 (P<0.00001); $I^2 = 100\%$

Test for overall effect: Z = 0.44 (P = 0.66)

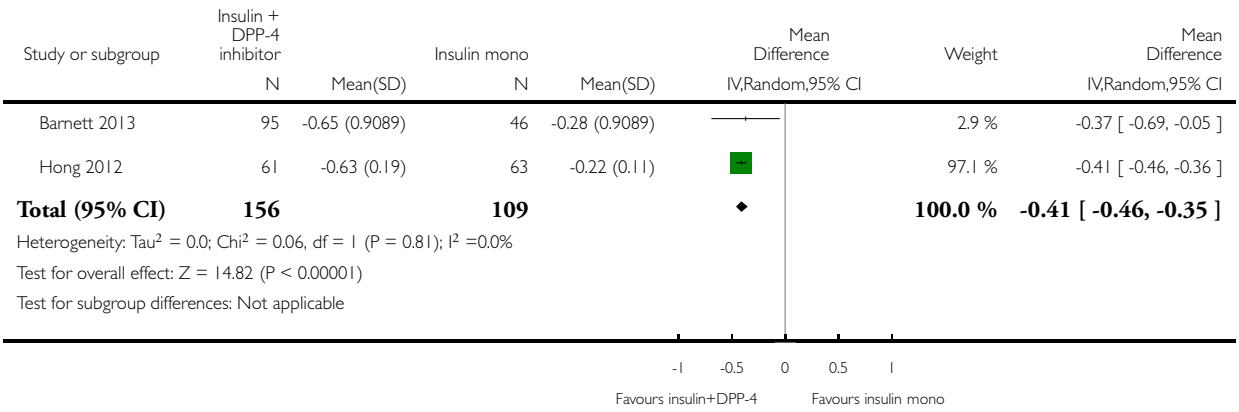
Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor, Outcome 2 HbA1c (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor

Outcome: 2 HbA1c (change from baseline)

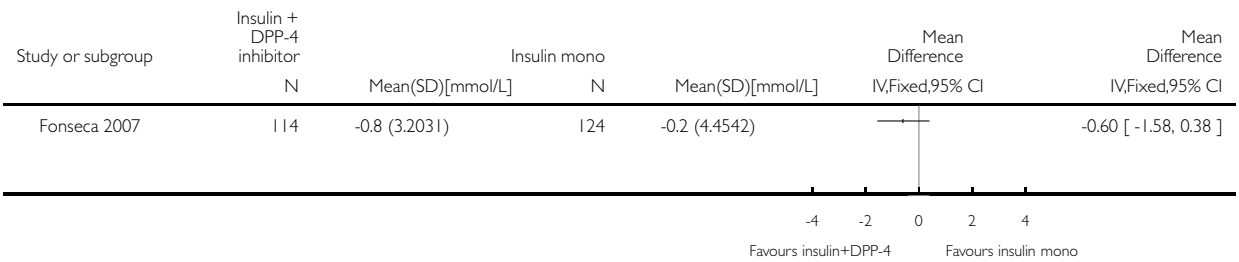


Analysis 5.3. Comparison 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor, Outcome 3 Fasting glucose (change from baseline).

Review: Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Comparison: 5 Insulin monotherapy versus insulin plus DPP-4 inhibitor

Outcome: 3 Fasting glucose (change from baseline)



ADDITIONAL TABLES

Table 1. Overview of study populations

	Intervention(s) and comparator(s)	Sample size[a]	Screened/ eligible (N)	Randomised (N)	Safety (N)	ITT (N)	Finishing study (N)	Randomised finishing study (%)	Follow-up time[b]
(1) Avilés 1999	I: metformin	-	54	22	22	-	21	95	24 weeks
	C: placebo			23	23	-	22	96	
	total:			**45**	**45**	**-**	**43**		
(2) Barnett 2013	I: saxagliptin	-	141	95	95	-	89	94	52 weeks
	C:placebo			46	46	-	45	98	
	total:			**141**	**141**	**-**	**134**		
(3) Casner 1988	I: glibenclamide	42 needed, 50 recruitment goal	83	31	31	31	31	100	1 year
	C: placebo			33	33	33	33	100	
	total:			**64**	**64**	**64**	**64**		
(4) Chiasson 1994[c]	I: acarbose	76 total, 38 per group	91	41	41	40	35	85	1 year
	C: placebo			50	50	42	44	88	
	total:			**91**	**91**	**82**	**79**		
(5) Coniff 1995	I: acarbose	-	-	103	103	-	103	100	24 weeks
	C: placebo			104	104	-	104	100	
	total:			**207**	**207**	**-**	**207**		
(6) Feinglos 1998[d]	I: glipizide	-	37			-			7 months
	C: placebo					-			
	total:			**29**	**29**	**-**	**29**	**100**	
(7) Fonseca 2007	I: vildagliptin	-	461	144	144		114	79	24 weeks

Table 1. Overview of study populations (*Continued*)

	C: placebo			152	152		124	82	
	total:			**296**	**296**	**290**	**238**		
(8) Fritsche 2000[d]	I: metformin	-	-						24 weeks
	C: placebo								
	total:			**13**	**13**	**-**	**13**	**100**	
(9) Giugliano 1993	I: metformin	-	50	27	27	-	27	100	7 months
	C: placebo			23	23		23	100	
	total:			**50**	**50**		**50**		
(10) Groop 1985[d]	I: glibenclamide	-	14						16 weeks (after 8 weeks run-in)
	C: placebo								
	total:			**14**	**14**	**-**	**13**	**93**	
(11) Hermann 2001	I: metformin	30, 15 in each group	37	16	16	16	12	75	12 months
	C: placebo			19	19	19	18	95	
	total:			**35**	**35**	**35**	**30**		
(12) Hong 2012	I: sitagliptin	140	-	70	61	61	61	87	24 weeks
	C: insulin increase			70	63	63	63	90	
	total:			**140**	**124**	**124**	**124**		
(13) Hirsch 1999	I: metformin	-	-	25	25	-	22	88	5 months
	C: placebo			25	25		25	100	
	total:			**50**	**50**		**47**		
(14) Kitabchi 1987[d]	I: tolazamide	-	12						6 months

Table 1. Overview of study populations (*Continued*)

	C: insulin alone								
	total:			**12**	**12**	**-**	**12**	**100**	
(15) Krawczyk 2005	I: metformin	-	-	20	20	20	20	100	6 months
	C: insulin alone			20	20	20	20	100	
	total:			**40**	**40**	**40**	**40**		
(16) Kyllastinen 1985[d]	I: glibenclamide	-	11						4 months
	C: placebo								
	total:			**9**	**9**	**-**	**9**	**100**	
(17) Lewitt 1989[d]	I: glibenclamide	-	31						6 months
	C: placebo								
	total:			**31**	**31**	**-**	**31**	**100**	
(18) Lindstrom 1999[d]	I: glibenclamide	-	-						6 months
	C: placebo								
	total:			**15**	**15**	**-**	**15**	**100**	
(19) Longnecker 1986[d]	I: tolazamide	-	12						20 weeks
	C: placebo								
	total:			**12**	**12**	**-**	**11**	**92**	
(20) Mattoo 2005	I: pioglitazone	250 (125 per treatment)	385	142	142	142	128	90	6 months
	C: placebo			147	147	147	135	92	
	total:			**289**	**289**	**289**	**263**		
(21) Mauerhoff 1986	I: glibenclamide	-	22	11	11	-	11	100	19 weeks

Table 1. Overview of study populations (*Continued*)

	C: placebo			11	11		11	100	
	total:			**22**	**22**		**22**		
(22) Mezitis 1992	I: glibenclamide	-	-	10	10	-	10	100	20 weeks
	C: placebo			10	10		10	100	
	total:			**20**	**20**	**-**	**20**		
(23) Mudaliar 2010	I: pioglitazone	-	-	12	12	-	12	100	12-16 weeks
	C: placebo			13	13		13	100	
	total:			**25**	**25**		**25**		
(24) Nemoto 2011	I: miglitol	-	276	107	107	107	100	93	16-22 weeks
	C: placebo			100	100	100	97	97	
	total:			**207**	**207**	**207**	**197**		
(25) Osei 1984	I: glibenclamide	-	22	10	10	-	6	60	16 weeks
	C: placebo			12	12		11	92	
	total:			**22**	**22**		**17**		
(26) Quartraro 1986	I: gliclazide	-	40	15	15	-	15	100	12 months
	C: insulin alone			15	15		15	100	
	total:			**30**	**30**		**30**		
(27) Reich 1987[e]	I: glibenclamide	-	20	10	10	-	9	90	4 months
	C: placebo			10	10		10	100	
	total:			**20**	**20**		**19**		
(28) Relimpio 1998	I: metformin	-	60	31	31	31	24	77	4 months

Table 1. Overview of study populations (*Continued*)

	C: insulin dose increase			29	29	23	23	79	
	total:			**60**	**60**	**60**	**47**		
(29) Robinson 1998[d]	I: metformin	-	-						30 weeks
	C: placebo								
	total:			**20**	**20**	**-**	**19**	**95**	
(30) Rosenstock 2002	I1: pioglitazone 15 mg	-	-	191	191	191	161	89	16 weeks
	I2: pioglitazone 30 mg			188	188	188	172	92	
	C: placebo			187	187	187	164	88	
	total:			**566**	**566**	**566**	**497**		
(31) Schade 1987[d]	I: glibenclamide	16	16						32 weeks
	C: placebo								
	total:			**16**	**16**	**16**	**15**	**94**	
(32) Schiel 2007	I1: glimepiride	60 (20 participants in each group)	54	17	17	17	17	100	20 weeks
	I2: glimepiride + metformin			18	18	16	16	89	
	C: insulin alone			17	17	17	17	100	
	total:			**52**	**52**	**50**	**50**		
(33) Simpson 1990	I: glipizide	-	20	9		-			4 months

Table 1. Overview of study populations (*Continued*)

	C: placebo			11					
	total:			**20**	**20**		**19**	**95**	
(34) Stenman 1988 [d]	I: glibenclamide	-	16						5 months
	C: placebo								
	total:			**16**	**16**	**-**	**15**	**94**	
(35) Strowig 2002	I1: metformin	-	92	30	30	-	27	90	4 months
	I2: troglitazone			31	31		30	97	
	C: insulin alone			31	31		31	100	
	total:			**92**	**92**		**88**		
(36) Wulffelé 2002	I: metformin	390	745	196	195	196	171	87	16 weeks
	C: placebo			194	193	194	182	94	
	total:			**390**	**388**	**390**	**353**		
(37) Yilmaz 2007	I1: acarbose	-	-	15	15	-	15	100	6 months
	I2: metformin			17	17		17	100	
	I3: rosiglitazone			15	15		15	100	
	C: insulin alone			19	19		19	100	
	total:			**66**	**66**		**66**		
Grand total	***All interventions***			***1856***[f]			***1677***[f]		
	All comparators			***1558***[f]			***1460***[f]		

Table 1. Overview of study populations (*Continued*)

	All interventions and comparators			***3227***			***2951***		

[a] According to power calculation in study publication or report
[b] Duration of intervention and/or follow-up under randomised conditions until end of study
[c] Subgroup of participants using insulin
[d] Cross-over study
[e] Three participants in the intervention group discontinued insulin
[f] Participants in cross-over trials were counted both in the intervention and comparator groups
- denotes not reported
C: comparator; I: intervention; ITT: intention-to-treat; N/A: not applicable

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)
#1 [mh "Diabetes mellitus"]
#2 diabet*:ti,ab,kw
#3 (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D):ti,ab,kw
#4 ((non and insulin* and depend*) or (noninsulin* and depend*) or (non and insulin?depend*) or noninsulin?depend*):ti,ab,kw
#5 ((insulin* and depend*) or insulin?depend*):ti,ab,kw
#6 {or #1-#5}
#7 [mh "Diabetes insipidus"]
#8 (diabet* and insipidus):ti,ab,kw
#9 #7 or #8
#10 #6 not #9
#11 [mh "Drug Therapy, Combination"]
#12 combin*:ti,ab,kw
#13 #11 or #12
#14 [mh "Sulfonylurea compounds"]
#15 [mh Biguanides]
#16 [mh Acarbose]
#17 [mh Thiazolidinediones]
#18 [mh Tolbutamide]
#19 [mh Metformin]
#20 [mh Chlorpropamide]
#21 [mh "Dipeptidyl-Peptidase IV inhibitors"]

(*Continued*)

#22 [mh Glyburide]
#23 [mh Tolazamide]
#24 [mh Carbutamide]
#25 [mh Acetohexamide]
#26 [mh Buformin]
#27 [mh Chlorhexidine]
#28 [mh Chloroguanide]
#29 [mh Phenformin]
#30 (biguanid* or sulfonylurea* or sulphonylurea* or acarbos*):ti,ab,kw
#31 (gliglacid* or glimepirid* or glibornurid* or gliguidon* or glisoxepid* or glipizid* or gliburid* or glyburid* or tolazamid*):ti,ab,kw
#32 (tolbutamid* or carbutamid* or chlorpropamid* or acetohexamid* or glibenclamid*):ti,ab,kw
#33 (metformin* or buformin* or chlorhexidin* or chlorguanid or phenformin*):ti,ab,kw
#34 (miglitol* or nateglinid* or repaglinid* or meglitinid* or glucobay):ti,ab,kw
#35 (troglitazone* or rosiglitazon* or pioglitazon* or thiazolidinedion* or glitazon*):ti,ab,kw
#36 (antidiabet* near/3 drug*):ti,ab,kw
#37 (antidiabet* near/3 herb*):ti,ab,kw
#38 (antidiabet* near/3 agent*):ti,ab,kw
#39 (antidiabet* near/3 compound*):ti,ab,kw
#40 (anti and (diabet* near/3 drug*)):ti,ab,kw
#41 (anti and (diabet* near/3 herb*)):ti,ab,kw
#42 (anti and (diabet* near/3 agent*)):ti,ab,kw
#43 (anti and (diabet* near/3 compound*)):ti,ab,kw
#44 (oral near/6 hypoglyc?emic):ti,ab,kw
#45 (oral near/6 antidiabet*):ti,ab,kw
#46 (oral near/6 antihyperglyc?emic):ti,ab,kw
#47 alpha-glucosidase-inhibitor*:ti,ab,kw
#48 (hypoglyc?emic near/3 drug*):ti,ab,kw
#49 (hypoglyc?emic near/3 herb*):ti,ab,kw
#50 (hypoglyc?emic near/3 agent*):ti,ab,kw
#51 (hypoglyc?emic near/3 compound*):ti,ab,kw
#52 (sitagliptin* or vildagliptin*):ti,ab,kw
#53 [mh "Glucagon-Like Peptides"]
#54 (glucagon-like and peptid*):ti,ab,kw
#55 (GLP1 or (GLP and 1)):ti,ab,kw
#56 (DPP-4 or DPP-IV or DPP4 or DPPIV):ti,ab,kw
#57 {or #14-#30}
#58 {or #13-#50}
#59 {or #51-#56}
#60 {or #57-#59}
#61 [mh Insulin]
#62 insulin*:ti,ab,kw
#63 #61 or #62
#64 #10 and #13 and #60 and #63

MEDLINE (Ovid SP)

1. exp Drug therapy combination/
2. combin*.tw,ot.
3. 1 or 2

(*Continued*)

4. exp Diabetes Mellitus/
5. diabet$.tw,ot.
6. (IDDM or NIDDM or MODY or T1DM or T2DM).tw,ot.
7. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw,ot.
8. (insulin$ depend$ or insulin?depend$).tw,ot.
9. or/4-8
10. exp Diabetes Insipidus/
11. diabet$ insipidus.tw,ot.
12. 10 or 11
13. 9 not 12
14. exp Sulfonylurea Compounds/
15. exp Biguanides/
16. exp Acarbose/
17. exp Thiazolidinediones/
18. exp Tolbutamide/ or exp Metformin/ or exp Chlorpropamide/ or exp Dipeptidyl-Peptidase IV Inhibitors/
19. exp Glyburide/ or exp Tolazamide/ or exp Carbutamide/ or exp Acetohexamide/
20. exp Buformin/ or exp Chlorhexidine/ or exp Chloroguanide/ or exp Phenformin/
21. (biguanid$ or sulfonylurea$ or sulphonylurea$ or acarbos$).tw,ot.
22. (gliglacide$ or glimepirid$ or glibornurid$ or gliguidon$ or glisoxepid$ or glipizid$ or gliburid$ or glyburid$ or tolazamid$).tw,ot.
23. (tolbutamid$ or carbutamid$ or chlorpropamid$ or acetohexamid$ or glibenclamid$ or glimepirid$).tw,ot.
24. (metformin$ or buformin$ or chlorhexidin$ or chlorguanid$ or phenformin$).tw,ot.
25. (miglitol$ or nateglinid$ or meglitinid$ or glucobay).tw,ot.
26. (troglitazon$ or rosiglitazon$ or pioglitazon$ or thiazolidinedion$ or glitazon$).tw,ot.
27. repaglinid$.tw,ot.
28. ((antidiabet$ or anti diabet$) adj3 (drug$ or herb$ or agent$ or compound$)).tw,ot.
29. (oral adj6 (hypoglycemic or antidiabetic or antihyperglycemic)).tw,ot.
30. alpha-glucosidase-inhibitor$.tw,ot.
31. (hypoglyc?emic adj3 (drug$ or herb or agent$ or compound$)).tw,ot.
32. (sitagliptin$ or vildagliptin$).tw,ot.
33. exp Glucagon-Like Peptide 1/
34. glucagon-like peptid$ 1.tw,ot.
35. (GLP1 or GLP 1).tw,ot.
36. (DPP-4 or DPP-IV or DPP4 or DPPIV).tw,ot.
37. or/14-36
38. exp Insulin/
39. insulin$.tw,ot.
40. 38 or 39
41. 3 and 13 and 37 and 40
42. Meta-analysis.pt.
43. exp Review/
44. exp Technology Assessment, Biomedical/
45. exp Meta-analysis/
46. exp Meta-analysis as topic/
47. hta.tw,ot.
48. (health technology adj6 assessment$).tw,ot.
49. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
50. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo

(*Continued*)

or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot.
51. or/42-50
52. randomized controlled trial.pt.
53. controlled clinical trial.pt.
54. randomi?ed.ab.
55. placebo.ab.
56. drug therapy.fs.
57. randomly.ab.
58. trial.ab.
59. groups.ab.
60. or/52-59
61. 51 or 60
62. 41 and 61
63. (animals not (animals and humans)).sh.
64. 62 not 63
65. (comment or editorial or historical-article).pt.
66. 64 not 65

Embase (Ovid SP)

1. exp Drug combination/
2. combin*.tw,ot.
3. 1 or 2
4. exp Diabetes Mellitus/
5. diabet$.tw,ot.
6. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw,ot.
7. (insulin* depend* or insulin?depend*).tw,ot.
8. (IDDM or NIDDM or MODY or T1DM or T2DM or T1d or T2D).tw,ot.
9. or/4-8
10. exp Diabetes Insipidus/
11. diabet* insipidus.tw,ot.
12. 10 or 11
13. 9 not 12
14. exp sulfonylurea derivative/
15. exp biguanide derivative/
16. exp acarbose/
17. exp 2,4 thiazolidinedione derivative/
18. (biguanid* or sulfonylurea* or sulphonylurea* or acarbos*).tw,ot.
19. (gliglacide* or glimeprid* or glibornurid* or gliguidon* or glisoxepid* or glipizid* or gliburid* or glyburid* or tolazamid*).tw,ot.
20. (metformin* or buformin* or chlorhexidin* or chlorguanid* or phenformin*).tw,ot.
21. (troglitazon* or rosiglitazon* or pioglitazon* or thiazolidinedion* or glitazon*).tw,ot.
22. (miglitol* or nateglinid* or repaglinid* or meglitinid* or glucobay).tw,ot.
23. ((antidiabet* or anti diabet*) adj3 (drug* or herb* or agent* or compound*)).tw,ot.
24. (oral adj6 (hypoglyc?emic or antidiabetic or antihyperglyc?emic)).tw,ot.
25. alpha-glucosidase-inhibitor*.tw,ot.
26. (hypoglyc?emic adj3 (drug* or herb* or agent* or compound*)).tw,ot.
27. (sitagliptin* or vildagliptin*).tw,ot.
28. exp glucagon like peptide 1/
29. glucagon-like peptid* 1.tw,ot.

(*Continued*)

30. (GLP 1 or GLP1).tw,ot.
31. (DPP-4 or DPP-IV or DPP4 or DPPIV).tw,ot.
32. (biguanid* or sulfonylurea* or sulphonylurea* or acarbos*).tw,ot.
33. exp glimepiride/
34. exp glibornuride/
35. exp glisoxepide/
36. glibenclamide/ or metformin/ or glipizide/ or tolbutamide/
37. exp tolazamide/
38. exp carbutamide/
39. exp chlorpropamide/
40. exp acetohexamide/
41. exp buformin/
42. (tolbutamid* or carbutamid* or chlorpropamid* or acetohexamid* or glibenclamid* or glimepirid*).tw,ot.
43. exp chlorhexidine/
44. proguanil/
45. exp phenformin/
46. exp miglitol/
47. exp nateglinide/
48. exp meglitinide/
49. exp troglitazone/
50. exp rosiglitazone/
51. exp pioglitazone/
52. exp 2,4 thiazolidinedione derivative/
53. exp glitazone derivative/
54. exp alpha glucosidase inhibitor/
55. exp sitagliptin/
56. exp vildagliptin/
57. or/14-56
58. exp insulin/
59. insulin*.tw,ot.
60. 58 or 59
61. exp Randomized Controlled Trial/
62. exp Controlled Clinical Trial/
63. exp Clinical Trial/
64. exp Comparative Study/
65. exp Drug comparison/
66. exp Randomization/
67. exp Crossover procedure/
68. exp Double blind procedure/
69. exp Single blind procedure/
70. exp Placebo/
71. exp Prospective Study/
72. ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
73. (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
74. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
75. (cross over or crossover).ab,ti.
76. or/61-75
77. exp meta analysis/
78. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.

(*Continued*)

79. ((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$)).ab,ti,ot. 80. exp Literature/ 81. exp Biomedical Technology Assessment/ 82. hta.tw,ot. 83. (health technology adj6 assessment$).tw,ot. 84. or/77-83 85. 76 or 84 86. 3 and 13 and 57 and 60 and 85 87. (comment or editorial or historical-article).pt. 88. 86 not 87 89. limit 88 to human
WHO ICTRP (Standard search)
diabet* AND insulin monotherapy OR diabet* AND insulin alone
ClinicalTrials.gov (Advanced search)
Search Terms: (((diabetes OR diabetic) AND ("type 2" OR "type II")) OR T2D OR T2DM) AND ("insulin monotherapy" OR "insulin alone") **Study Type:** Interventional Studies

Appendix 2. Description of interventions

	Intervention(s) (route, frequency, total dose/day)	Comparator(s) (route, frequency, total dose/day)
Avilés 1999	Insulin as before treatment of at least 50 U insulin/day + **metformin**, oral, 2500 mg/day, 5 tablets of 500 mg daily	Insulin as before treatment of at least 50 U insulin/day + **placebo**, 5 tablets daily
Barnett 2013	Insulin (premixed 67.4%, intermediate 16.8%, long-acting 11.6%, intermediate + long-acting 1.1%, intermediate + premixed 1.1, long-acting + premixed 1.1) 53.6 U (range 30-150) daily dose + **saxagliptin**, oral, 5 mg daily	Insulin (premixed 54.3%, intermediate 21.7%, long acting 13.0%, intermediate + long-acting 6.5%, intermediate + premixed 4.3, long-acting + premixed 0) 55. 3 U (range 30-149) daily dose + **placebo** daily
Casner 1988	NPH insulin twice a day, total of at least 25 U insulin/day + **glibenclamide**, oral, 3.39 ± 0.22 mg/day	NPH insulin twice a day, total of at least 25 U insulin/day + **placebo**, oral, 3.28 ± 0.28 mg/day
Chiasson 1994	Insulin (type and dose not mentioned) + **acarbose**, oral, 3 times a day, 50 mg to 200 mg/day	Insulin (type and dose not mentioned) + **placebo,** oral, 3 times a day

(*Continued*)

Coniff 1995	Insulin (type and dose not mentioned) + **acarbose**, oral, 3 times a day 50 mg to 300 mg/day	Insulin (type and dose not mentioned) + **placebo**, oral, 3 times a day
Feinglos 1998	Insulin (regular or NPH: 1 participant; daily, 26 participants; twice a day, 2 participants: 3 times a day, dose not mentioned) + **glipizide**, oral, 5-40 mg/day, daily or twice a day	Insulin (regular or NPH: 1 participant; daily, 26 participants twice a day, 2 participants 3 times a day, dose not mentioned) + **placebo**, oral
Fonseca 2007	Injectable insulin (type not mentioned) of at least 30 U/day + **vildagliptin**, oral, 100 mg/day, twice a day 50 mg	Injectable insulin (type not mentioned) of at least 30 U/day + **placebo**, oral, twice a day
Fritsche 2000	NPH insulin twice a day (dose not mentioned) + **metformin**, oral, daily 850 mg - 3 times a day	NPH insulin twice a day (dose not mentioned) + **placebo**, oral, daily - 3 times a day
Giugliano 1993	Regular and lente insulin, mean dose 90 (9 SD) U/day, twice a day + **metformin**, oral, 850 mg twice daily	Regular and lente insulin, mean dose 90 (9 SD) U/day, twice a day + **placebo**, oral, twice daily
Groop 1985	Insulin (type and dose not mentioned) + **glibenclamide**, oral, 10 mg/day, twice a day 5 mg	Insulin (type and dose not mentioned) + **placebo**, oral, twice a day
Hermann 2001	Insulin (rapid-acting + NPH or premixed) 0.75 (0.28 SD) U/kg/day + **metformin**, oral, 2 weeks daily 850 mg, thereafter twice a day 850 mg	Insulin (rapid-acting + NPH or premixed) 0.73 (0.23 SD) U/kg/day + **placebo**, oral, 2 weeks daily, thereafter twice a day
Hirsch 1999	Insulin (type and dose not mentioned) + **metformin**, oral, 2.5 gram/day, frequency not stated	Insulin (type and dose not mentioned) + **placebo**, oral, frequency not stated
Hong 2012	Insulin (glargine, glargine + rapid-acting, NPH + regular) at least 10 U/day + **sitagliptin**, oral, 100 mg/day	**Increase insulin** (glargine, glargine + rapid-acting, NPH + regular) by $\geq$ 10% at random at the start of the intervention and again by $\geq$ 10% at 12 weeks if their HbA1c was not within target ($\leq$ 7%) If glargine insulin 20 U daily was used, the dose increased to $\geq$ 22 U daily and to $\geq$ 24 U daily at 12 weeks. If 20-10 U mixed insulin was used twice a day, the dose was increased to $\geq$ 22-11 U twice a day and $\geq$ 24-12 U twice a day at 12 weeks
Kitabchi 1987	Insulin (NPH, dose not mentioned) + **tolazamide**, oral, 1000 mg/day, twice a day 500 mg	NPH insulin alone
Krawczyk 2005	Insulin (type not mentioned) 57.5 (15.8 SD) U + **metformin** 1500 mg once daily	Insulin alone (type not mentioned) 59.5 (15.4 SD) U
Kyllastinen 1985	Insulin (type not mentioned) mean dose 58 (3 SD) U daily + **glibenclamide**, oral, 10 mg/day, twice a day 5 mg	Insulin (type not mentioned) mean dose 58 (3 SD) U daily + **placebo**, oral, twice daily

(*Continued*)

Lewitt 1989	Insulin (14 participants on daily, 17 on twice a day, 12 mixed, 19 premixed or intermediate-acting insulin) mean dose 47 (21 SD) U + **glibenclamide**, oral, 15 mg/day, 10 mg in the morning and 5 mg in the evening	Insulin (14 participants on daily, 17 on twice a day, 12 mixed, 19 premixed or intermediate-acting insulin) mean dose 47 (21 SD) U + **placebo**, oral, twice daily
Lindström 1999	Soluble insulin (total dose 100 U/ml 3 times a day) + intermediate-acting insulin (100 U/ml daily) + **glibenclamide**, oral, 10.5 mg/day, 3 times daily 3.5 mg	Soluble insulin (total dose 100 U/ml three times a day) + intermediate-acting insulin (100 U/ml daily) +**placebo**, oral 3 times daily
Longnecker 1986	Insulin (5 participants daily insulin injection: 1 participant on isophane insulin suspension alone (40 U daily), 4 participants on isophane insulin suspension (48 (8 SD) U) + regular insulin injections (23 (9 SD) U); 6 participants twice a day insulin injections: mean morning dose 38 (6 SD) U (regular, isophane suspension, or both) + mean afternoon dose 25 (7 SD) U (regular, isophane suspension, or both) + **tolazamide**, oral, 1000 mg, twice daily 250 mg	Insulin (5 participants daily insulin injection: 1 participant on isophane insulin suspension alone (40 U daily), 4 participants on isophane insulin suspension (48 (8 SD) U) + regular insulin injections (23 (9 SD) U); 6 participants DIB insulin injections: mean morning dose 38 (6 SD) U (regular, isophane suspension, or both) + mean afternoon dose 25 (7 SD) U (regular, isophane suspension, or both) + **placebo**, oral, twice daily
Mattoo 2005	Insulin (type and dose not mentioned) + **pioglitazone** 30 mg	Insulin (type and dose not mentioned) + **placebo**, oral
Mauerhoff 1986	Usual insulin (type and dose not mentioned) + Hb420 (galenic form of **glibenclamide**) 7 mg before breakfast and 3.5 mg before supper	Usual insulin (type and dose not mentioned) + **placebo**, oral
Mezitis 1992	Biosynthetic human insulin (dose not mentioned) + **glibenclamide**, oral, twice daily 2 tablets (dose not mentioned)/day	Biosynthetic human insulin + **placebo**, oral
Mudaliar 2010	Insulin (type and dose not mentioned) + **pioglitazone**, oral, 30 mg for 4 weeks, then titrated to 45 mg	Insulin (type and dose not mentioned) + **placebo**, oral
Nemoto 2011	Insulin (type and dose not mentioned) + **miglitol**, oral, 50 mg 3 times a day	Insulin (type and dose not mentioned) + **placebo**, oral, 3 times a day
Osei 1984	Insulin (intermediate-acting insulin alone or in combination with short-acting insulin twice a day (dose not mentioned)) + **glibenclamide**, oral, 5-20 mg once daily	Insulin (intermediate-acting insulin alone or in combination with short-acting insulin twice a day (dose not mentioned)) + **placebo**, oral
Quartraro 1986	Monocomponent porcine insulin (mean dose 95 (2 SD) U daily) + **gliclazide** 40-240 mg once daily	Insulin alone (mono component porcine insulin (mean dose 95 (2 SD) U daily))
Reich 1987	Insulin (intermediate-acting, dose not mentioned) + **glibenclamide,** oral, 5-40 mg once daily	Insulin (intermediate-acting, dose not mentioned) + **placebo**, oral

(*Continued*)

Relimpio 1998	Insulin (premixed formulation of soluble and NPH or NPH only, twice a day in 23 participants and 3 times a day in 1 participant) + **metformin** 1275-2550 mg once daily	Insulin dose increase (premixed formulation of soluble and NPH or NPH only, twice a day in 22 participants and 3 times a day in 1 participant), **insulin increase** by 10%
Robinson 1998	Trial 1: insulin (type and dose not mentioned) + **metformin** 1000 mg/day increasing to 2000 mg /day	Insulin (type and dose not mentioned) + **placebo**
Rosenstock 2002	I1: insulin (type and dose not mentioned) + **pioglitazone** 15 mg once daily I2: insulin (type and dose not mentioned) + **pioglitazone** 30 mg once daily	Insulin (type and dose not mentioned) + **placebo** once daily
Schade 1987	Insulin (intermediate-acting or short-acting) mean dose at least 28 U/day (daily or twice a day) + **glibenclamide** 20 mg once daily	Insulin (intermediate-acting or short-acting, mean dose at least 28 U/day, daily or twice a day) + **placebo**, oral
Schiel 2007	I1: insulin glargine (before treatment dose) + **glimepiride 3** mg/day I2: insulin glargine (before treatment dose) + **glimepiride** 3 mg/day + **metformin** 1700 mg/day	Insulin alone (75/25 or 70/30 premixed human insulin)
Simpson 1990	Usual insulin soluble + isophane twice a day or soluble + zinc-complexed insulin daily or twice a day) + **glipizide** 10 mg twice a day	Usual insulin soluble + isophane twice a day or soluble + zinc-complexed insulin daily or twice a day) + **placebo**, oral
Stenman 1988	Insulin (intermediate-acting daily or twice a day or intermediate- and short-acting daily) + **glibenclamide**, oral, 15 mg once daily	Insulin (intermediate-acting daily or twice a day or intermediate- and short-acting daily) + **placeb**o, oral
Strowig 2002	I1: insulin (type and dose not mentioned) + **metformin**, oral, 2000 mg once daily I2: insulin (type and dose not mentioned) + **troglitazone**[a] , oral, 600 mg once daily	Insulin alone (type and dose not mentioned)
Wulffelé 2002	Insulin (Actrapid + Insulatard 4 times daily or mixed Actrapid (10%-50%) + Insulatard (90%-50%) twice a day) + **metformin**, oral, 3 x 850 mg once daily	Insulin (Actrapid + Insulatard 4 times daily or mixed Actrapid (10%-50%) + Insulatard (90%-50%) twice a day) + **placebo**, oral
Yilmaz 2007	I1: insulin (mixed 30% insulin aspart + 70% NPH insulin twice a day) + **acarbose**, oral, 300 mg once daily I2: insulin (mixed 30% insulin aspart + 70% NPH insulin twice a day) + **metformin**, oral, 1700 mg once daily	Insulin alone (mixed 30% insulin aspart + 70% NPH insulin twice a day)

(*Continued*)

	I3: insulin (mixed 30% insulin aspart + 70% NPH insulin twice a day) + **rosiglitazone**[a] , oral, 8 mg once daily	

[a] off the market
I: intervention; NPH: Neutral Protamine Hagedorn; SD: standard deviation; U: units

Appendix 3. Baseline characteristics (I)

	Intervention (s) and comparator(s)	Duration of intervention	Description of participants	Country	Setting	Ethnic groups (%)	Duration of diabetes (mean/range years (SD), or as reported)
Avilés 1999	I: metformin	24 weeks	Participants with poorly controlled type 2 diabetes on insulin therapy	USA	Secondary care outpatients	White: 49 African-American: 23 Hispanic :23 Other: 5	9.2 (6.4)
	C: placebo					White: 68 African-American: 18 Hispanic: 14	10.1 (4.7)
Barnett 2013	I: saxagliptin	52 weeks	Inadequately controlled type 2 diabetes individuals with insulin alone (subgroup in the publication)	Canada, Hungary, India, Mexico, Poland, Russia, South Africa, UK	Multiple choices possible	White: 84.2 Black: 6.3 Asian: 7.4 Other: 2.1	12.1 (6.3)
	C: placebo					White: 76.1 Black: 10.9 Asian: 6.5 Other: 6.5	10.3 (6.4)
Casner 1988	I: glibenclamide	12 months	Participants with type 2 diabetes on insulin therapy	USA	Unclear	Hispanic: 84 Non-Hispanic white: 10 Non-Hispanic black: 6	14.3 (0.1)
	C: placebo					Hispanic: 94 Non-His-	10.9 (0.1)

(*Continued*)

						panic white: 6	
Chiasson 1994	I: acarbose	12 months	Participants with type 2 diabetes (26% pretreated with insulin, only results of	Canada	Secondary care outpatients	-	-
	C: placebo					-	-
	all:					White: 92	12.9 (0.8 SE)
Coniff 1995	I: acarbose	24 weeks	Insulin pretreated participants with type 2 diabetes	Canda, USA	Not stated	-	-
	C: placebo						
Feinglos 1998	I: glipizide	3 months	Participants with type 2 diabetes	USA	Secondary care inpatients and	-	
	C: placebo						
	all:						15 (3 - 30)
Fonseca 2007	I: vildagliptin	24 weeks	Participants with type 2 diabetes inadequately controlled by insulin	Finland, Germany, Spain, USA	Unclear	Black: 15 White: 70 Hispanic + Latino: 12 Other: 3	14.4 (8.6)
	C: placebo					Black: 11 White: 72 Hispanic + Latino: 15 Other: 2	14.9 (8.4)
Fritsche 2000	I: metformin	10 weeks	Severely obese participants with type 2 diabetes on	Germany	Secondary care inpatients and outpatients	-	
	C: placebo						
	all:					-	10 (8)
Giugliano 1993	I: metformin	6 months	Obese type 2 diabetes on insulin therapy	Italy	Secondary care outpatients	-	11.9 (1.2)
	C: placebo						11.5 (1.2)
Groop 1985	I: glibenclamide	8 weeks	Poorly controlled participants with	Finland	Secondary care outpatients	-	

(*Continued*)

			type 2 diabetes on insulin				
	C: placebo						
	all:						8 (1)
Hermann 2001	I: metformin	12 months	Overweight and obese type 2 diabetes participants on insulin therapy	Sweden	Secondary care outpatients	-	13 (3 - 31)
	C: placebo						13 (4 - 25)
Hirsch 1999	I: metformin	5 months	Participants with type 2 diabetes and sub optimal insulin therapy	USA	Secondary care outpatients	-	-
	C: placebo					-	-
Hong 2012	I: Sitagliptin	24 weeks	Participants with uncontrolled type 2 diabetes on insulin therapy	Korea	Secondary care outpatients	-	15.9 (10.5)
	C: insulin increase						15.8 (9.9)
Kitabchi 1987	I: tolazamide	3 months	Obese insulin-requiring participants with type 2 diabetes	USA	Secondary care inpatients and outpatients	-	
	C: insulin alone						
	all:						10 (1)
Krawczyk 2005	I: metformin	6 months	Obese insulin-requiring participants with type 2 diabetes	Poland	Secondary care outpatients	-	12.2 (4.8)
	C: insulin alone						11.9 (5.9)
Kyllastinen 1985	I: glibenclamide	2 months	Elderly participants with type 2 diabetes on in-	Finland	Secondary care outpatients	-	
	C: placebo						
	all:						11 (1)
Lewitt 1989	I: glibenclamide	3 months	Insulin-treated type 2 diabetes par-	Australia	Secondary care	-	-

(*Continued*)

			ticipants		outpatients		
	C: placebo						
Lindström 1999	I: glibenclamide	3 months	Type 2 diabetes participants on insulin	Sweden	Unclear	-	
	C: placebo						
	all:						10.5 (1.2)
Longnecker 1986	I: tolazamide	8 weeks	Type 2 diabetes participants on in-	USA	Secondary care outpatients	-	
	C: placebo						
	all:						12 (2)
Mattoo 2005	I: pioglitazone	6 months	Type 2 diabetes participants on insulin monotherapy	Australia, Belgium, Canada, New Zealand, Romania, Spain	Secondary care outpatients	White: 97	13.6 (6.8)
	C: placebo					White: 97	13.4 (6.1)
Mauerhoff 1986	I: glibenclamide	16 weeks	Type 2 diabetes participants on insulin monotherapy	Belgium	Secondary care outpatients	-	11 (2)
	C: placebo						10 (2)
Mezitis 1992	I: glibenclamide	20 weeks	Type 2 diabetes participants on insulin monotherapy	USA	Secondary care outpatients	-	-
	C: placebo						
Mudaliar 2010	I: pioglitazone	12 to 16 weeks	Type 2 diabetes participants on insulin monotherapy	USA	Clinical research centre	-	-
	C: placebo						
Nemoto 2011	I: miglitol	24 weeks	Type 2 diabetes participants on in-	Japan	Secondary care outpatients	-	
	C: placebo						
	all:						15.1 (8.5)

(*Continued*)

Osei 1984	I: glibenclamide	16 weeks	Type 2 diabetes participants on insulin monotherapy	USA	Secondary care inpatients and outpatients	-	12.3 (1.2)
	C: placebo						12.9 (1.6)
Quartraro 1986	I: gliclazide	12 months	Type 2 diabetes participants on insulin monotherapy	Italy	Secondary care inpatients and outpatients	-	12.1 (1.4 SE)
	C: insulin alone						11.8 (1.3 SE)
Reich 1987	I: glibenclamide	4 months	Type 2 diabetes participants on insulin monotherapy	USA	Secondary care inpatients and outpatients	-	9.0 (3.1)
	C: placebo						9.7 (3.3)
Relimpio 1998	I: metformin	4 months	Type 2 diabetes participants on insulin monotherapy	Spain	Secondary care outpatients	-	15.4 (7.7)
	C: insulin dose increase						15.3 (6.0)
Robinson 1998	I: metformin	12 weeks	Type 2 diabetes participants on insulin monotherapy	UK	Secondary care outpatients	-	Study 1: 15 (7) Study 2: 14 (6)
	C: placebo						
Rosenstock 2002	I1: pioglitazone 15 mg	16 weeks	Type 2 diabetes participants on insulin ± oral antidiabetic medication. Those participants on insulin + oral antidiabetic medication discontinued the oral drug at the beginning of the screening period. In addition the run-in period for	USA	Unclear	White: 75	-

(*Continued*)

			those participants was 6 weeks instead of 3 for the participants on insulin monotherapy				
	I2: pioglitazone 30 mg					White: 73	-
	C1: placebo					White: 71	-
Schade 1987	I: glibenclamide	16 weeks	Type 2 diabetes participants on insulin	USA	Secondary care outpatients	-	-
	C: placebo						-
	all:						10 (1)
Schiel 2007	I1: glimepiride	16 weeks	Type 2 diabetes participants on insulin monotherapy	Germany	Secondary care outpatients	-	15.3 (8.4)
	I2: glimepiride + metformin						14.2 (8.0)
	C1: insulin alone						16.3 (6.7)
Simpson 1990	I: glipizide	8 weeks	Type 2 diabetes participants on insulin monotherapy	UK	Secondary care outpatients	-	9 (2 - 18)
	C: placebo						10 (1 - 20)
Stenman 1988	I: glibenclamide	4 months	Type 2 diabetes participants on insulin	Finland	Secondary care inpatients and outpatients	-	-
	C: placebo						-
	all:						9.8 (4.7)
Strowig 2002	I1: metformin	4 months	Type 2 diabetes participants on insulin monotherapy	USA	Unclear	White: 52 Afro-American: 15 Hispanic: 30 Other: 4	7.6 (4.1)
	I2: troglitazone					White: 57 Afro-American: 17 Hispanic: 27	11.6 (6.8)

(*Continued*)

	C1: insulin alone					White: 55 Afro-American: 29 Hispanic: 16	10.5 (7.3)
Wulffelé 2002	I: metformin	16 weeks	Type 2 diabetes participants on insulin monotherapy	The Netherlands	Secondary care outpatients	-	14.0 (8.4)
	C1: placebo						12.0 (8.0)
Yilmaz 2007	I1: acarbose	6 months	Type 2 diabetes participants on insulin monotherapy	Turkey	Secondary care outpatients	-	13.9 (7.2)
	I2: metformin						12.1 (7.7)
	I3: rosiglitazone						12.1 (7.9)
	C1: insulin alone						

- denotes not reported
C: comparator; I: intervention; SD: standard deviation; SE: standard error

Appendix 4. Baseline characteristics (II)

	Intervention(s) and comparator (s)	Sex (female %)	Age (mean years (SD); (range))	HbA1c (mean % (SD); (range))	Comedications/ Cointerventions (%)	Comorbidities (%)
Avilés 1999	I: metformin	71	53.1 (9.4); (35-69)	9 (1.4); -	-	-
	C: placebo	55	54.6 (7.8); (36-70)	9.1 (1.5); -		
Barnett 2013	I: saxagliptin	60	58.7 (10.0); (29-77)	8.7 (0.9); (7-11)	-	-
	C: placebo	59	57.8 (10.9); (30-75)	8.7 (0.8); (7-11)		
Casner 1988	I: glibenclamide	65	55.8 (0.1); -	10.9 (0.5 SE); -	-	-
	C: placebo	79	60.0 (0.1); -	11.4 (0.4 SE); -		

(*Continued*)

Chiasson 1994	I: acarbose	-	-	-	-	-
	C: placebo	-	-	-		
	all:	39	56.6 (0.9); -	7.7 (0.2 SE); -		
Coniff 1995	I: acarbose	-	-	6.4 (0.1 SE); -	-	-
	C: placebo	-	-	6.6 (0.1 SE); -		
Feinglos 1998	I: glipizide	-	-	-	-	-
	C: placebo	-	-	-		
	all:	59	56 (39 - 68); (39-68)	12.1 (5.4-21.2);		
Fonseca 2007	I: vildagliptin	52	59.6 (10.3); -	8.4 (1.0); -	-	-
	C: placebo	45	58.9 (10.8); -	8.4 (1.1); -		
Fritsche 2000	I: metformin			8.5 (0.4 SE); -	-	-
	C: placebo			8.1 (0.4 SE); -		
	all:	69	51 (9); -			
Giugliano 1993	I: metformin			11.5 (1.2); -	Antihypertensive drugs (ACE-inhibitor or calcium antagonist) : 5	-
	C: placebo			11.7 (1.3); -	Antihypertensive drugs (ACE-inhibitor or calcium antagonist) : 4	
	all:	62	60 (2); -			
Groop 1985	I: glibenclamide			-	Antihypertensive drugs (n = 4)	Background retinopathy and signs of sensory neuropathy (n = 5)
	C: placebo					

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	all:	46	56 (1); (49-61)		31	38
Hermann 2001	I: metformin	56	56.9 (10.2); -	9.1 (1.3); -	-	Hypertension (n = 10) 27 Ischaemic heart disease (n = 7) 19 diabetic nephropathy (n = 1) 3
	C: placebo	37	58.1 (9.7); -	8.7 (1.0); -		
Hirsch 1999	I: metformin	-	-	8.6 (0.2 SE); -	-	-
	C: placebo	-	-	9.0 (0.4 SE); -		
Hong 2012	I: sitagliptin	53.7	58.8 (14.3); -	9.2 (1.0); -	Sulphonylurea: 24.6 Glinides (short-acting insulin secretagogues): 13.1 Metformin: 45.9 Thiazolidinedione: 6.6 Alpha-glucosidase inhibitor: 31.1 Glargine only: 47.5 Glargine plus rapid acting insulin: 23 NPH plus regular insulin: 29.5	Retinopathy: 16.4 Neuropathy: 21.3
	C: insulin increase	50.9	59.6 (13.0); -	9.2 (1.1); -	Sulphonylurea: 23.8 Glinides (short acting insulin secretagogues): 15.9 Metformin: 41.3 Thiazolidinedione: 3.2 Alpha-glucosidase inhibitor: 42.9	Retinopathy: 14.3 Neuropathy: 23.8

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					Glargine only: 49.2 Glargine plus rapid-acting insulin: 17.5 NPH plus regular insulin: 33.3	
Kitabchi 1987	I: tolazamide	-	-	-	-	-
	C: insulin alone	-	-	-		
	all:	100	51 (3); (34-66)	10.7 (0.7 SE); (8.7-15.5)		
Krawczyk 2005	I: metformin	60	55.8 (8.1); -	8.6 (1.9); -	-	-
	C: insulin alone	40	58.4 (6.0); -	8.4 (1.6); -		
Kyllastinen 1985	I: glibenclamide			13.8 (0.6 SE); -	Dose kept constant throughout trial	Heart failure: 89 Hypertension: 44 Hypothyroidism: 11 Psychiatric illness: 11 Chronic obstipation: 33 Retinopathy: 22 Elevated creatinine: 33
	C: placebo			13.5 (0.8 SE); -	-	-
	all:	78	73 (2); (66-80)			
Lewitt 1989	I: glibenclamide				-	-
	C: placebo					
	all:	15	67 (5); (59-78)	9.9 (1.3); (7.3-13.3)		
Lindström 1999	I: glibenclamide			-	-	-
	C: placebo			-		
	all:	33	59 (2); (48-71)	-		

(*Continued*)

Longnecker 1986	I: tolazamide	92	62 (2.4); (48-76)		-	-
	C: placebo	100	54 (2.9); (43-65)			
	all:			12.7 (0.8); (9-16.3)		
Mattoo 2005	I: pioglitazone	56	58.8 (7.4); -	8.9 (0.1 SE); -	-	-
	C: placebo	57	58.9 (6.9); -	8.8 (0.1 SE); -		
Mauerhoff 1986	I: glibenclamide	63	62 (2); -	-; -	-	-
	C: placebo	27	59 (4); -	-; -		
Mezitis 1992	I: glibenclamide	-	-; 46-68	8.7; (4.4-8.2)	-	-
	C: placebo	-	-; 46-68	8.6; (4.4-8.2)		
Mudaliar 2010	I: pioglitazone			7.6 (0.3); -	-	-
	C: placebo			7.8 (0.3); -		
	all:	19	58 (2); -	-; 7.5-10		
Nemoto 2011	I: miglitol				-	-
	C: placebo					
	all:	42	59.9 (10.7); -	7.9 (1); -		
Osei 1984	I: glibenclamide	60	58.6 (2.7); -	10.9 (0.6 SE); -	-	-
	C: placebo	83	56.3 (1.2); -	10.4 (0.4 SE); -		
Quartraro 1986	I: gliclazide	-	56 (1.9 SE); (39-70)	12.0 (0.6)	-	-
	C: insulin alone		57 (1.9 SE); (39-70)	11.8 (0.4)		
Reich 1987	I: glibenclamide	0	58.7 (2.8); (39-69)	8.9 (0.7 SE); (7.2-13.4)	-	-
	C: placebo	0	56.8 (3.7); (29-69)	10.0 (1.0 SE); (6.7-12.8)		

(*Continued*)

Relimpio 1998	I: metformin	79	65.4 (7.9); -	9.6 (1.4); -	ACE inhibitors: 42 Thiazides: 8 Fibric acid: 8 HMG-CoA inhibitors: 4	-
	C: insulin dose increase	65	66.7 (6.2); -	9.6 (1.2); -	ACE inhibitors: 30 Thiazides: 17 Fibric acid: 17 HMG-CoA inhibitors: 22	-
Robinson 1998	I: metformin	Study 1: 63	Study 1: 61.3 (7.1); -	Study 1: 8.9 (1.0 SE); -	-	Trial 1: Retinopathy (n = 9) 47 Neuropathy (n = 6) 32 Proteinuria (n = 1)
	C: placebo					-
Rosenstock 2002	I1: pioglitazone 15 mg	54	56.9 (10.4); (29-75)	9.8 (0.1 SE); -	Oral anti-diabetic medication before study: total 12 evenly distributed among the treatment arms (metformin: 8, glibenclamide: 2, glipizide: 2) Lipid-lowering drugs: 28	-
	I2: pioglitazone 30 mg	50	57.5 (9.9); (29-75)	9.8 (0.1 SE); -	Lipid-lowering drugs: 22	-
	C1: placebo	55	56.8 (3.7); (29-75)	9.8 (0.1 SE); -	Lipid-lowering drugs: 21	-
Schade 1987	I: glibenclamide				-	-
	C: placebo					
	all:	56	51 (3); (35-66)	10.6 (0.4); -		

(*Continued*)

Schiel 2007	I1: glimepiride	53	61.7 (10.7); -	8.2 (0.7); -	-	-
	I2: glimepiride + metformin	44	65.4 (8.5); -	8.1 (0.9); -		
	C1: insulin alone	47	69.8 (6.4); -	8.1 (0.8); -		
Simpson 1990	I: glipizide		65 (-); (53 - 75)	10.6 (-); (10-16. 4)	-	-
	C: placebo		62 (-); (50 - 78)	12.0 (-); (7.6-4. 9)		
	all:	32				
Stenman 1988	I: glibenclamide				-	-
	C: placebo					-
	all:	13	58 (6.6); (45-68)	9.2 (0.2); (9.9-15.8)		Coronary heart disease (n = 1) 7 Hypertension (n = 3) 20
Strowig 2002	I1: metformin	44	51.8 (10.5); -	8.8 (1.2); -	Lipid-lowering drugs: 30	-
	I2: troglitazone	57	51.7 (8.0); -	8.5 (1.2); -	Lipid-lowering drugs: 43	
	C1: insulin alone	52	54.4 (9.1); -	8.7 (1.6); -	Lipid-lowering drugs: 26	
Wulffelé 2002	I: metformin	56	63.2 (9.8); -	7.9 (1.2); -	-	-
	C: placebo	50	58.9 (11.1); -	7.9 (1.2); -		
Yilmaz 2007	I1: acarbose	53	62.6 (6.6); (34-80)	-	-	-
	I2: metformin	66	57.7 (8.5); (34-80)	-		
	I3: rosiglitazone	88	57.6 (8.8); (34-80)	-		
	C1: insulin alone	63	61.5 (12.0); (34-80)	-		

(*Continued*)

- denotes not reported
C: comparator; HbA1c: glycosylated haemoglobin A1c; I: intervention; NPH: Neutral Protamine Hagedorn; SD: standard deviation; SE: standard error

Appendix 5. Matrix of study endpoints

Characteristic Study ID	Primary[a] endpoint (s)	Secondary[b] endpoint (s)	Other[c] endpoint (s)
Avilés 1999	-	-	Glycaemic control, insulin dose requirements, study drug tolerance, body weight, blood pressure, lipid and lipoprotein profiles, C-peptide
Barnett 2013	Change in HbA1c from baseline to 52 weeks follow-up	Mean change from baseline in total daily insulin dose at 52 weeks	Safety end points including adverse events, hypoglycaemia and weight gain
Casner 1988	-	-	Fasting blood glucose, HbA1c, C-peptide, glucose tolerance test, side effects, compliance
Chiasson 1994	-	-	HbA1c, glucose, C-peptide, lipids, glucose tolerance test, safety, blood count, biochemistry, vitamins/minerals, hypoglycaemia
Coniff 1995	HbA1c, insulin requirements	Glucose tolerance test, postprandial glucose area under the curve	Lipids, hypoglycaemia
Feinglos 19987	-	-	Glucose, HbA1c, C-peptide, plasma insulin, lipids
Fonseca 2007	HbA1c	Fasting glucose, insulin dose, insulin injections, lipids, body weight	-
Fritsche 2000	-	-	Glucose tolerance test, HbA1c, glucose, C-peptide, insulin dose, lipids

(*Continued*)

Giugliano 1993	-	-	Body weight, blood pressure, HbA1c, lipids, glucose profile, safety
Groop 1985	-	-	Body weight, glucose, HbA1c, lipids, glucose tolerance test, serum free insulin, plasma glucagon, insulin tolerance test, glucose profiles
Hermann 2001	HbA1c	-	Fasting glucose, body weight, BMI, waist-hip ratio, blood pressure, insulin dose, C-peptide, lipids, biochemistry, adverse events, compliance
Hong 2012	Change in HbA1c (from baseline to 24 weeks)	Proportion of participants achieving HbA1c < 7%, body weight, waist circumference, change in insulin dose, change in C-peptide, safety (AE, SAE, hypoglycaemia, liver/renal function)	-
Hirsch 1999	-	-	HbA1c, glucose, body weight, blood pressure, insulin dose, insulin levels, C-peptide, hypoglycaemia
Kitabchi 1987	-	-	HbA1c, glucose, body weight, C-peptide, insulin dose, insulin antibodies, chemistry, triglycerides
Krawczyk 2005	-	-	HbA1c, glucose, insulin dose, waist-hip ratio, body weight
Kyllastinen 1985	-	-	Glucose, HbA1c, insulin dose, C-peptide, body weight, biochemistry, lipids
Lewitt 1989	-	-	HbA1c, glucose, BMI, C-peptide, insulin dose
Lindström 1999	-	-	Insulin dose, glucose, HbA1c, plasma insulin, C-peptide, lipoproteins, IGF-1, testosterone, SHBG

(*Continued*)

Longnecker 1986	-	-	HbA1c, glucose, C-peptide, body weight, compliance, side effects
Mattoo 2005	-	-	HbA1c, glucose, lipids, CRP, hypoglycaemia, body weight, cardiovascular risk markers
Mauerhoff 1986	-	-	Glucose, C-peptide, insulin dose, hypoglycaemia
Mezitis 1992	-	-	Insulin dose, C-peptide, HbA1c, lipids, glucose profiles
Mudaliar 2010	-	-	HbA1c, glucose, insulin dose, weight, total body water, extracellular fluid, renal and hormonal measures
Nemoto 2011	-	-	Meal tolerance test, HbA1c, 1, 5 AG, glycoalbumin, hypoglycaemia, safety
Osei 1984	-	-	Compliance, dietary intake, weight, glucose, HbA1c, tolerance tests
Quartraro 1986	-	-	Glucose profile, HbA1c, insulin dose, weight, C-peptide
Reich 1987	-	-	HbA1c, glucose, chemistry, urinalyses
Relimpio 1998	-	-	Weight, BMI, blood pressure, HbA1c, lipids, insulin dose, biochemistry, compliance
Robinson 1998	-	-	Glucose, HbA1c, creatinine, lipids, blood pressure, insulin dose, hypoglycaemia
Rosenstock 2002	-	-	HbA1c, glucose, C-peptide, lipids, ECG, chemistry, haematology, vital signs, adverse events
Schade 1987	-	-	HbA1c, glucose, insulin dose, C-peptide, free insulin, erythrocyte-glucose binding, compliance

(*Continued*)

Schiel 2007	HbA1c	Glucose, treatment satisfaction, hypoglycaemia, adverse events	Blood pressure, creatinine, liver enzymes
Simpson 1990	-	-	HbA1c, C-peptide, serum insulin, lipids, glucose, body weight, BMI
Stenman 1988	-	-	HbA1c, glucose, body weight, lipids, C-peptide, free insulin
Strowig 2002	-	-	HbA1c, glucose, liver enzymes, body weight, chemistry, C-peptide, lipids, waist-hip ratio
Wulffelé 2002	HbA1c, insulin dose	BMI, body weight, lipids, blood pressure	Hypoglycaemia
Yilmaz 2007	HbA1c	Insulin dose, body weight, waist-hip ratio, lipids	Hypoglycaemia, side effects

[a,b] verbatim statement in the publication
[c] not explicitly stated as primary or secondary endpoint (s) in the publication
- denotes not reported
BMI: body mass index; HbA1c: glycosylated haemoglobin A1c

Appendix 6. Adverse events (I)

	Intervention(s) and comparator (s)	Participants included in analysis (N)	Deaths (N)	Deaths (%)	Participants with adverse events (N)	Participants with adverse events (%)	Participants with severe/ serious adverse events (N)	Participants with severe/ serious adverse events (%)
Avilés 1999	I: metformin	22	-	-	3	14	-	-
	C: placebo	23	-	-	-	-	-	-
Barnett 2013	I: saxagliptin	95	1	1.1	61	64.2	9	9.5
	C: placebo	46	0	0	32	69.6	3	6.5

(*Continued*)

Casner 1988	I: glibenclamide	31	-		-	-	-	0
	C: placebo	33	-		-	-	-	0
Chiasson 1994	I: acarbose	35	-	-	1	2.4	0	0
	C: placebo	44	-	-	3	2.9	0	0
Coniff 1995	I: acarbose	103	-	-	78	76	0	0
	C: placebo	104	-	-	36	35	0	0
Feinglos 1998	I: glipizide		-			-		-
	C: placebo							-
	all:	29	-	-	69 episodes of hypoglycaemia	-	1	-
Fonseca 2007	I: vildagliptin	144	1	0.7	-	81.3	-	8.3
	C: placebo	152	1	0.7	-	82.9	-	9.2
Fritsche 2000	I: metformin	-	-	-	0	0	0	0
	C: placebo	-	-	-	0	0	0	0
	all:	13	-	-	0	0	0	0
Giugliano 1993	I: metformin	27	-	-	2	7.4	0	0
	C: placebo	23	-	-	-	-	-	-
Groop 1985	I: glibenclamide	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
	all:	13	-	-	-	-	-	-
Hermann 2001	I: metformin	16	-	-	9	-	-	-
	C: placebo	19	-	-	6	-	-	-

(*Continued*)

Hong 2012	I: sitagliptin	61	-	-	-	34.4	1	-
	C: insulin increase	63	-	-	-	36.5	4	-
Hirsch 1999	I: metformin	25	-	-	3	12	0	0
	C: placebo	25	-	-	0	-	0	0
Kitabchi 1987	I: tolazamide		-	-	-	-	-	-
	C: NPH alone		-	-	-	-	-	-
	all:	12	-	-	-	-	-	-
Krawczyk 2005	I: metformin	20	-	-	-	-	-	-
	C: insulin alone	20	-	-	-	-	-	-
Kyllastinen 1985	I: glibenclamide	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
	all:	9	-		-	-	-	-
Lewitt 1989	I: glibenclamide		-	-	-	-	-	-
	C: placebo		-	-	-	-	-	-
	all:	31	-	-	-	-	-	-
Lindström 1999	I: glibenclamide	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
	all:	15	-	-	-	-	-	-
Longnecker 1986	I: tolazamide	-	-	-	0	0	0	0
	C: placebo	-	-	-	0	0	0	0

(*Continued*)

	all:	11	-	-	0	0	0	0
Mattoo 2005	I: pioglitazone	128	0	0	109	76.8	-	-
	C: placebo	135	1	0.7	98	66.7	-	-
Mauerhoff 1986	I: glibenclamide	11	0	0	107 episodes	-	-	-
	C: placebo	11	0	0	25 episodes	-	-	-
Mezitis 1992	I: glibenclamide	10	-	-	-	-	-	-
	C: placebo	10	-	-	-	-	-	-
	all:	20	-	-	-	-	-	-
Mudaliar 2010	I: pioglitazone	12	-	-	-	-	-	-
	C: placebo	13	-	-	-	-	-	-
Nemoto 2011	I: miglitol	107	-	-	122 episodes	78.5	-	-
	C: placebo	100	-	-	91 episodes	76	-	-
Osei 1984	I: glibenclamide	6	-	-	-	-	-	-
	C: placebo	11	-	-	-	-	-	-
Quartraro 1986	I: gliclazide	15	0	0	-	-	-	-
	C: insulin alone	15	0	0	-	-	-	-
Reich 1987	I: glibenclamide	10	1	10	3 (5 episodes)	30	-	-
	C: placebo	10	0	0	10 episodes	-	-	-
Relimpio 1998	I: metformin	24	-	-	-	-	-	-
	C: insulin dose increase	23	-	-	-	-	-	-

(*Continued*)

Robinson 1998	I: metformin	-	-	-	-	-	0	0
	C: placebo	-	-	-	-	-	0	0
	all:	19	-	-	-	-	0	0
Rosenstock 2002	I1: pioglitazone 15 mg	191	-	-	-	78.4	-	-
	I2: pioglitazone 30 mg	188	-	-	-		-	-
	C: placebo	187	-	-	-	74.3	-	
Schade 1987	I: glibenclamide	16			6	37.5	0	0
	C: placebo	16			1	6.3	0	0
Schiel 2007	I1: glimepiride	17	-	-	-	59	0	0
	I2: glimepiride + metformin	18	-	-	-	72	0	0
	C: insulin	17	-	-	-	77	0	0
Simpson 1990	I: glipizide	9	-	-	4	44.4	-	-
	C: placebo	10	-	-	0	0	-	-
Stenman 1988	I: glibenclamide	15	0	0	13	86.7	0	0
	C: placebo	15	0	0	8	53.3	0	0
Strowig 2002	I1: metformin	27	0	0	-	-	2	6.7
	I2: troglitazone	30	0	0	-	-	0	0
	C: insulin	31	0	0	-	-	1	3.2
Wulffelé 2002	I: metformin	171	1	0.6	1 episode per participant per month: 31	1 episode per participant per month: 18	8 episodes	-

(*Continued*)

					2 episodes per participant per month: 12 3 episodes per participant per month: 9 ≥ 4 episodes per participant per month: 11	2 episodes per participant per month: 7 3 episodes per participant per month: 5 ≥ 4 episodes per participant per month: 6		
	C: placebo	182	0	0	1 episode per participant per month: 30 2 episodes per participant per month: 11 3 episodes per participant per month: 11 ≥ 4 episodes per participant per month: 7	1 episode per participant per month: 16 2 episodes per participant per month: 6 3 episodes per participant per month: 6 ≥ 4 episodes per participant per month: 4	4 episodes	
Yilmaz 2007	I1: acarbose	15	0	0	3	20	0	0
	I2: metformin	17	0	0	5	29.4	0	0
	I3: rosiglitazone	15	0	0	3	20	0	0
	C: insulin alone	19	0	0	3	15.8	0	0

- denotes not reported
C: comparator; I: intervention; NPH: Neutral Protamine Hagedorn

Appendix 7. Adverse events (II)

	Intervention(s) and comparator (s)	Participants included in analysis (N)	Participants discontinuing study due to adverse events (N)	Participants discontinuing study due to adverse event (%)	Participants hospitalised (N)	Participants hospitalised (%)	Participants with outpatient treatment (N)	Participants with outpatient treatment (%)
Avilés 1999	I: metformin	21	0	0	0	0	-	-
	C: placebo	22	0	0	0	0	-	-
Barnett 2013	I: saxagliptin	95	3	3.2	-	-	-	-
	C: placebo	46	1	2.2	-	-	-	-
Casner 1988	I: glibenclamide	31	0	0	0	-	-	-
	C: placebo	33	0	0	0	-	-	-
Chiasson 1994	I: acarbose	35	11	27	-	-	-	-
	C: placebo	44	12	23	-	-	-	-
Coniff 1995	I: acarbose	103	9	9	-	-	-	-
	C: placebo	104	4	4	-	-	-	-
Feinglos 1998	I: glipizide	-	0	0	-	-		-
	C: placebo	-	0	0	-			
	all:	29	0	0	-	-	-	-
Fonseca 2007	I: vildagliptin	114	-	6.3	-	-	-	-
	C: placebo	124	-	0.7	-	-	-	-
Fritsche 2000	I: metformin	-	-	0	-	-	-	-
	C: placebo	-	-	0	-	-	-	-
	all:	13	-	0	-	-	-	-

(*Continued*)

Giugliano 1993	I: metformin	27	0	0	-	-	-	-
	C: placebo	23	0	0	-	-	-	-
Groop 1985	I: glibenclamide	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
Hermann 2001	I: metformin	16	4	-	-	-	-	-
	C: placebo	19	1	-	-	-	-	-
Hirsch 1999	I: metformin	25	3	12	-	-	-	-
	C: placebo	25	0	0	-	-	-	-
Hong 2012	I: sitagliptin	61	0	0	-	-	-	-
	C: insulin increase	63	0	0	-	-	-	-
Kitabchi 1987	I: tolazamide	-	0	0	-	-	-	-
	C: NPH alone	-	0	0	-	-	-	-
	all:	12	0	0	-	-	-	-
Krawczyk 2005	I: metformin	20	-	-	-	-	-	-
	C: insulin alone	20	-	-	-	-	-	-
Kyllastinen 1985	I: glibenclamide	-	0	0	-	-	-	-
	C: placebo	-	0	0	-	-	-	-
	all:	9	0	0	-	-	-	-
Lewitt 1989	I: glibenclamide	-	0	0	-	-	-	-
	C: placebo	-	0	0	-	-	-	-

(*Continued*)

	all:	31	0	0	-	-	-	-
Lindström 1999	I: glibenclamide	-	0	0	-	-	-	-
	C: placebo	-	0	0	-	-	-	-
	all:	15	0	0	-	-	-	-
Longnecker 1986	I: tolazamide	-	0	0	-	-	-	-
	C: placebo	-	0	0	-	-	-	-
	all:	11	0	0	-	-	-	-
Mattoo 2005	I: pioglitazone	128	7	4.9	-	-	-	-
	C: placebo	135	3	2	-	-	-	-
Mauerhoff 1986	I: glibenclamide	11	0	0	-	-	-	-
	C: placebo	11	0	0	-	-	-	-
Mezitis 1992	I: glibenclamide	10	-	-	-	-	-	-
	C: placebo	10	-	-	-	-	-	-
Mudaliar 2010	I: pioglitazone	12	0	0	-	-	-	-
	C: placebo	13	0	0	-	-	-	-
Nemoto 2011	I: miglitol	107	7	6.5	-	-	-	-
	C: placebo	100	3	3	-	-	-	-
Osei 1984	I: glibenclamide	6	4	40	-	-	-	-
	C: placebo	11	1	8.3	-	-	-	-
Quartraro 1986	I: gliclazide	15	0	0	-	-	-	-
	C: insulin alone	15	0	0	-	-	-	-

(*Continued*)

Reich 1987	I: glibenclamide	10	0	0	-	-	-	-
	C: placebo	10	0	0	-	-	-	-
Relimpio 1998	I: metformin	24	0	0	-	-	-	-
	C: insulin dose increase	23	0	0	-	-	-	-
Robinson 1998	I: metformin	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
	all:	19	1	5	-	-	-	-
Rosenstock 2002	I1: pioglitazone 15 mg	191	-	2.6	-	-	-	-
	I2: pioglitazone 30 mg	188	-	3.2	-	-	-	-
	C: placebo	187	-	1.6	-	-	-	-
Schade 1987	I: glibenclamide	16	0	0	-	-	-	-
	C: placebo	16	0	0	-	-	-	-
Schiel 2007	I1: glimepiride	17	0	0	-	-	-	-
	I2: glimepiride + metformin	18	2	11.1	-	-	-	-
	C: insulin	17	0	0	-	-	-	-
Simpson 1990	I: glipizide	9	0	0	-	-	-	-
	C: placebo	10	0	0	-	-	-	-
Stenman 1988	I: glibenclamide	15	0	0	-	-	-	-
	C: placebo	15	0	0	-	-	-	-

(*Continued*)

Strowig 2002	I1: metformin	27	2	6.7	-	-	-	-
	I2: troglitazone	30	0	0	-	-	-	-
	C: insulin	31	0	0	-	-	-	-
Wulffelé 2002	I: metformin	171	20	10.2	-	-	-	-
	C: placebo	182	6	3.1	-	-	-	
Yilmaz 2007	I1: acarbose	15	0	0	-	-	-	-
	I2: metformin	17	0	0	-	-	-	-
	I3: rosiglitazone	15	0	0	-	-	-	-
	C: insulin alone	19	0	0	-	-	-	-

- denotes not reported
C: comparator; I: intervention; NPH: Neutral Protamine Hagedorn

Appendix 8. Adverse events (III)

	Intervention(s) and comparator(s)	**Participants included in analysis (N)**	**Participants with hypoglycaemic episodes (N)**	**Participants with hypoglycaemic episodes (%)**	**Participants with nocturnal hypoglycaemic episodes (N/%)**	**Participants with severe/serious hypoglycaemic episodes (N/%)**	**Definition of severe/serious hypoglycaemia**	**Participants with specific adverse events (N)**	**Participants with specific adverse events (%)**
Avilés 1999	I: metformin	21	3	13.6	-	0	-	-	-
	C: placebo	22	0	10	-	0		-	-
Barnett 2013	I: saxagliptin	95	Reported: 22 Confirmed: 8	23.2 8.4	-	-	-	Urine tract infection: 7	Urine tract infection: 7.4

(*Continued*)

								Nasopharyngitis: 6 Upper resp. tract infection: 6 Headache: 5 Bronchitis: 4 Pharyngitis: 3 Influenza: 3 Hypertension: 4 Pain in extremity: 3	Nasopharyngitis: 6.3 Upper resp. tract infection: 6.3 Headache: 5.3 Bronchitis: 4.2 Pharyngitis: 3.2 Influenza: 3.2 Hypertension: 4.2 Pain in extremity: 3.2
	C: placebo	46	Reported: 15 Confirmed: 5	32.6 10.9	-	-		Urine tract infection: 1 Nasopharyngitis: 1 Upper resp. tract infection: 5 Headache: 1 Bronchitis: 0 Pharyngitis: 3 Influenza: 2 Hypertension: 4 Pain in extremity: 2	Urine tract infection: 2.2 Nasopharyngitis: 2.2 Upper resp. tract infection: 10.9 Headache: 2.2 Bronchitis: 0 Pharyngitis: 6.5 Influenza: 4.3 Hypertension: 8.7 Pain in extremity: 4.3
Casner 1988	I: glibenclamide	31	"complains compatible with	-	-	0	-	-	-

(*Continued*)

			mild hypoglycaemia were not different between the two groups."						
	C: placebo	33	-	-	-	0		-	-
Chiasson 1994	I: acarbose	35	-	2.4	-	/2.4	Required correction of hypoglycaemia	-	Flatulence: 73.2 Diarrhoea: 43.6 Abdominal discomfort: 25.0
	C: placebo	44	-	6.0	-	/6.0		-	Flatulence: 39.0 Diarrhoea: 20.3 Abdominal discomfort: 8.8
Coniff 1995	I: acarbose	103	0	0	-	-	-	Digestive system: 78 Flatulence: 34	Digestive system: 76 Flatulence: 33
	C: placebo	104	0	0	-	-		Digestive system: 36 Flatulence: 14	Digestive system: 35 Flatulence: 13
Feinglos 1998	I: glipizide	-	-	-	-	-	Requiring assistance from another person		-
	C: placebo	-	-	-		-			
	all:	29	69 total episodes, number of participants not mentioned	-	-	1/		-	-

(*Continued*)

Fonseca 2007	I: vildagliptin	114	-	22.9	-	0	Requiring assistance of another party	-	-
	C: placebo	124	-	29.6	-	-		-	-
Fritsche 2000	I: metformin	-	0	0	0	0	-	-	-
	C: placebo	-	0	0	0	0		-	-
	all:	13	0	0	0	0		-	-
Giugliano 1993	I: metformin	27	0	0	-	-	-	Diarrhoea: 2	Diarrhoea: 7.4
	C: placebo	23	0	0	-	-		Diarrhoea: -	Diarrhoea: -
Groop 1985	I: glibenclamide	-	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-		-	-
	all:	13	-	-	-	-		-	-
Hermann 2001	I: metformin	16	2	-	-	0	-	Diarrhoea: 6 Flatulence: 1 Epigastic pain: 0 Anorexia: 2 Constipation: 1 Sweating: 0 GI-event: 8	-
	C: placebo	19	0	-	-	0		Diarrhoea: 1 Flatulence: 3 Epigastric pain: 1 Anorexia: 1 Constipa-	-

(*Continued*)

								tion: 1 Sweating: 1 GI-event: 5	
Hirsch 1999	I: metformin	25	-	-	-	0	-	Gastrointestinal side effects: 3	Gastrointestinal side effects: 12.0
	C: placebo	25	-	-	-	0		Gastrointestinal side effects: 0	Gastrointestinal side effects: 0
Hong 2012	I: sitagliptin	61	-	8.2	-	1.6	Any episode requiring assistance from another party with plasma glucose value < 3.0 mmol/L (54 mg/dL)	-	-
	C: insulin increase	63	-	17.5	-	4.8		-	-
Kitabchi 1987	I: tolazamide	-	-	-	-	-	-	-	-
	C: NPH alone	-	-	-	-	-		-	-
Krawczyk 2005	I: metformin	20	-	-	-	-	-	-	-
	C: insulin alone	20	-	-	-	-		-	-
Kyllastinen 1985	I: glibenclamide	-	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-		-	-
Lewitt 1989	I: glibenclamide	-	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-		-	-

Lindström 1999	I: glibenclamide	-	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-		-	-
	all:	15	-	-	-	-		-	-
Longnecker 1986	I: tolazamide	-		0	0	0	-	-	-
	C: placebo	-		0	0	0		-	-
	all:	11		0	0	0		-	-
Mattoo 2005	I: pioglitazone	128	109	63.4	-	-	Requiring assistance	Oedema: 20	Oedema: 14.1
	C: placebo	135	98	51.0	-	-		Oedema: 5	Oedema: 3.4
Mauerhoff 1986	I: glibenclamide	11	107 episodes	-	-	-	-	-	-
	C: placebo	11	25 episodes	-	-	-		-	-
Mezitis 1992	I: glibenclamide	10	-	-	-	-	-	-	-
	C: placebo	10	-	-	-	-		-	-
Mudaliar 2010	I: pioglitazone	12	-	-	-	-	-	-	-
	C: placebo	13	-	-	-	-		-	-
Nemoto 2011	I: miglitol	107	122 episodes	39.3	13 episodes	-	-	-	Flatulence: 20.6 Diarrhoea: 14.0 Abdominal distension: 15.0
	C: placebo	100	91 episodes	35.0	29 episodes	-		-	Flatulence: 12.0 Diarrhoea: 4.0 Abdominal distension: 4.0

(*Continued*)

Osei 1984	I: glibenclamide	6	-	-	-	-	-	-	-
	C: placebo	11	-	-	-	-		-	-
Quartraro 1986	I: gliclazide	15	-	-	-	-	-	-	-
	C: insulin alone	15	-	-	-	-		-	-
Reich 1987	I: glibenclamide	10	3 (5 episodes)	30.0	-	-	-	-	-
	C: placebo	10	10 episodes	-	-	-		-	-
Relimpio 1998	I: metformin	24	-	-	-	0	-	-	-
	C: insulin dose increase	23	-	-	-	0		-	-
Robinson 1998	I: metformin	-	-	-	-	0	-	-	Diarrhoea: 5.0 Mild abdominal bloating: 5.0
	C: placebo	-	-	-	-	0		-	Diarrhoea: 0 Mild abdominal bloating: 0
	all:	19	-	-	-	0		-	-
Rosenstock 2002	I1: pioglitazone 15 mg	191	-	7.9	-	0	-	-	Oedema: 12.6
	I2: pioglitazone 30 mg	188	-	15.4	-	0		-	Oedema: 17.6
	C: placebo	187	-	4.8	-	0		-	Oedema: 7.0

(*Continued*)

Schade 1987	I: glibenclamide	16	6	37.5	-	-	-	-	-
	C: placebo	16	1	6.3	-	-		-	-
Schiel 2007	I1: glimepiride	17	-	59	-	0	Need for intravenous glucose or glucagon	0	0
	I2: glimepiride + metformin	18	-	72	-	0		Gastrointestinal discomfort: 2	Gastrointestinal discomfort: 11.1
	C: insulin	17	-	77	-	0		0	0
Simpson 1990	I: glipizide	9	4	44.4	-	-	-	-	-
	C: placebo	10	0	0	-	-		-	-
Stenman 1988	I: glibenclamide	15	13	86.7	-	0	-	-	-
	C: placebo	15	8	53.3	-	0		-	-
Strowig 2002	I1: metformin	27	0.6 episodes per participant per month	-	-	0	Third party assistance	-	Gastrointestinal side effects: 67
	I2: troglitazone	30	1.7 episodes per participant per month	-	-	0		-	Gastrointestinal side effects:36.7
	C: insulin	31	2 episodes per participant per month	-	-	1/3.2		-	Gastrointestinal side effects: 13
Wulffelé 2002	I: metformin	171	-	36.8	-	-	Third party assistance	Diarrhoea: 9 Flatulence: 4 Pruritus: 1 Headaches: 1	-

(*Continued*)

								Pyrosis: 0 Nausea: 1	
	C: placebo	182	-	32.4	-	-		Diarrhoea: 2 Flatulence: 1 Pruritus: 0 Headaches: 0 Pyrosis: 1 Nausea: 0	-
Yilmaz 2007	I1: acarbose	15	1	6.7	-	0	Unable to treat themselves	Flatulence and bloating: 2	Flatulence and bloating: 13.3
	I2: metformin	17	2	11.8	-	0		Gastrointestinal side effects: 3	Gastrointestinal side effects: 17.7
	I3: rosiglitazone	15	2	13.3	-	0		Pretibial oedema: 1	Pretibial oedema: 6.7
	C: insulin alone	19	2	10.5	-	0		Pretibial oedema: 1	Pretibial oedema: 5.3

- denotes not reported
C: comparator; I: intervention; NPH: Neutral Protamine Hagedorn

CONTRIBUTIONS OF AUTHORS

Rimke C Vos (RV): methodology, statistical analysis and review development.

Marielle JP van Avendonk (MA): protocol development, searching for trials, trial selection, quality assessment of trials, data extraction, methodology, statistics and review development.

Hanneke Jansen (HJ): quality assessment of trials, data extraction and review development.

Alex N Goudswaard (AG): protocol development, trial selection, quality assessment, data extraction and review development.

Maureen Van den Donk (MD): methodology, statistics, data extraction and review development.

Kees Gorter (KG): data extraction and review development.

Anneloes Kerssen (AK): data extraction and review development.

Guy EHM Rutten (GR): review development.

DECLARATIONS OF INTEREST

RV: an unrestricted grant for a study in type 2 diabetes patients on insulin therapy (support of self-managment by triggers) is received by Sanofi. An unrestricted grant is received for a study on the long term effects of a self management education course for patients with type 2 diabetes by the European Foundation for the Study of Diabetes.

MA: received a reimbursement from Sanofi-Aventis for attending a congress and printing her thesis (2010) and she received royalties from publisher Bohn Stafleu van Loghum for authorship of a book: "Leven met diabetes mellitus type 2".

HJ: has no conflict of interest.

AG: received an unrestricted research grant from Novo Nordisk in 1999.

MD: has no conflict of interest.

KG: has no conflict of interest.

AK: has no conflict of interest.

GR: received a grant for a study project from Sanofi-aventis. Besides he received honoraria from Novo Nordisk for lecturing and attending (inter-) national board meetings.

SOURCES OF SUPPORT

Internal sources

- University Medical Center Utrecht, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Terminology was changed from 'oral hypoglycaemic agents' to 'oral glucose-lowering agents'.

Type of outcome measures

We deleted from secondary outcome measures 'the percentage of participants achieving good glycaemic control (HbA1c less than 7%) without hypoglycaemic events', blood pressure and body-mass index, because reporting about these outcomes was rare.

Data collection and analysis

We changed second reviewer from AG to AK for data extraction, assessment of risk of bias and data entry. Dichotomous data were not identified, therefore this part was omitted. RV and MA, contributed equally to the data analyses and the review development.
Analyses of cross-over trials were specified.
We changed the sensitivity analyses. We did not repeat the analysis excluding unpublished trials, because only published trials were included. We did not repeat the analysis excluding trials using different filters i.e. diagnostic criteria, language of publication, source of funding (industry versus other) and country. Not all trials reported diagnostic criteria and only one trial was not published in English. Almost all trials were funded by a pharmaceutical company. The trials were mainly performed in Western-European countries and the United States. We did not expect large differences in the results between these countries.

Declarations of interest

Changed from 'None known' to 'GR has received research grants from Sanofi-Aventis and honoraria form Novo Nordisk for lecturing and attending (inter-)national board meetings. In 1999, AG has received an unrestricted research grant from Novo Nordisk. MA received a reimbursement from Sanofi-Aventis for attending a congress and printing her thesis' and royalties from publisher Bohn Stafleu van Loghum for authorship of a book: "Leven met diabetes mellitus type 2".

NOTES

Part of the background, the methods section, appendices, additional tables and figures 1 to 3 of this review are based on a standard template established by Cochrane Metabolic and Endocrine Disorders.