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Salpeter SR, Greyber E, Pasternak GA, Salpeter EE

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[Intervention Review]

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus

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ABSTRACT

Background

Metformin is an oral anti-hyperglycemic agent that has been shown to reduce total mortality compared to other anti-hyperglycemic agents, in the treatment of type 2 diabetes mellitus. Metformin, however, is thought to increase the risk of lactic acidosis, and has been considered to be contraindicated in many chronic hypoxemic conditions that may be associated with lactic acidosis, such as cardiovascular, renal, hepatic and pulmonary disease, and advancing age.

Objectives

To assess the incidence of fatal and nonfatal lactic acidosis, and to evaluate blood lactate levels, for those on metformin treatment compared to placebo or non-metformin therapies.

Search methods

A comprehensive search was performed of electronic databases to identify studies of metformin treatment. The search was augmented by scanning references of identified articles, and by contacting principal investigators.

Selection criteria

Prospective trials and observational cohort studies in patients with type 2 diabetes of least one month duration were included if they evaluated metformin, alone or in combination with other treatments, compared to placebo or any other glucose-lowering therapy.

Data collection and analysis

The incidence of fatal and nonfatal lactic acidosis was recorded as cases per patient-years, for metformin treatment and for non-metformin treatments. The upper limit for the true incidence of cases was calculated using Poisson statistics. In a second analysis lactate levels were measured as a net change from baseline or as mean treatment values (basal and stimulated by food or exercise) for treatment and comparison groups. The pooled results were recorded as a weighted mean difference (WMD) in mmol/L, using the fixed-effect model for continuous data.

Main results

Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patients-years in the non-metformin group. Using Poisson statistics the upper limit for the true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. There was no

difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to non-metformin therapies.

Authors' conclusions

There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycemic treatments.

PLAIN LANGUAGE SUMMARY

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus

Metformin, a medication used to lower glucose levels in patients with diabetes mellitus, has long been thought to increase the risk for a metabolic disorder known as lactic acidosis. This review summarised data from all known comparative and observational studies lasting at least one month, and found no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use, or in 55,451 patient-years for those not on metformin. Average lactate levels measured during metformin treatment were no different than for placebo or for other medications used to treat diabetes. In summary, there is no evidence at present that metformin is associated with an increased risk for lactic acidosis when prescribed under the study conditions.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both (DeFronzo 1999). A consequence of this is chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative Review Groups'). For an explanation of methodological terms, see the main Glossary in *The Cochrane Library*.

Description of the intervention

Metformin is an anti-hyperglycemic agent that has been used with increasing frequency over the past several years, especially in obese or overweight patients with type 2 diabetes whose blood glucose levels cannot be controlled non-pharmacologically. There are three main questions that are being addressed. First, how does the drug affect total mortality and the development of long-term diabetes-related complications, and are these effects similar in all patient groups with type 2 diabetes? Secondly, what is the effect on cardiovascular risk factors such as obesity, dyslipidemia, and hypertension, and is this effect associated with changes in cardiovascular morbidity and mortality? The third question addresses concerns about the safety of the drug; specifically, what is the risk of fatal and nonfatal lactic acidosis associated with metformin use? These three questions are addressed in three separate reviews. The present review evaluates the risk of lactic acidosis attributed to metformin use, in comparison to placebo and other agents used for glycemic control in patients with type 2 diabetes. The reviews will be continually updated to include relevant new studies.

Adverse effects of the intervention

Adverse effects, principally gastrointestinal, are reported to occur in 20% to 30% of patients receiving metformin therapy and require discontinuation of the drug in less than 5% of patients (DeFronzo 1999). Diarrhea, nausea, vomiting, abdominal bloating, abdominal cramping or pain, flatulence, and anorexia are the most common gastrointestinal symptoms associated with metformin therapy. Other adverse effects reported are headache, agitation, dizziness, and tiredness.

Lactic acidosis is a rare, potentially fatal metabolic condition that can occur whenever substantial tissue hypoperfusion and hypoxia exist (Kreisberg 1980; Olivia 1970). Lactic acidosis is characterised by elevated blood lactate concentration (exceeding 45 mg/dl or 5.0 mEq/L), decreased blood pH (less than 7.35), and electrolyte disturbances with an increased anion gap. The mortality in reported cases have ranged from 8% to 50% (Bailey 1996; Laulau 2001; Misbin 1998). Biguanides are believed to decrease gluconeogenesis from alanine, pyruvate and lactate, and levels of lactic acid could accumulate under certain circumstances (Stang 1999). An earlier biguanide, phenformin, was withdrawn from the market because it was associated with a reported rate of lactic acidosis of 40 to 64 cases per 100,000 patient-years (DeFronzo 1999; Stang 1999). Metformin differs from phenformin in molecular structure and pharmacokinetics (Sulkin 1997). Metformin, unlike phenformin, is thought to enhance glucose oxidation without significantly affecting fasting lactate production in peripheral tissues (Cusi 1996).

The true incidence of lactic acidosis associated with metformin is not known. The Food and Drug Administration has estimated the rate of fatal or nonfatal lactic acidosis to be five cases per 100,000 persons treated over the course of one year (Misbin 1998). Population-based studies have estimated a rate of two to nine cases of lactic acidosis in metformin users per 100,000 person-years (Bodmer 2008; Campbell 1985; Stang 1999; Wilholm 1993). However, most of the reported cases have occurred in patients with severe acute conditions, such as renal failure, that could in themselves have caused the lactic acidosis (Brown 1998; Misbin 1998). In order to estimate the risk specifically attributable to metformin, the background rate of lactic acidosis in patients with type 2 diabetes who are not treated with metformin must be assessed. To this end, a database was used to measure incidence rates in patients with type 2 diabetes in the United States before metformin was introduced, and found a rate of nine cases per 100,000 person-years (Brown 1998). In addition, other population-based studies have found similar incidence rates for users of metformin as for other agents such as insulin or sulfonylureas (Aguilar 1992b; Bodmer 2008). This raises the question of whether patients with type 2 diabetes have an increased risk for developing lactic acidosis with metformin use compared to other glucose-lowering treatments.

How the intervention might work

Metformin hydrochloride is a biguanide that has been in clinical use for over 50 years (DeFronzo 1999; Sterne 1959). Unlike the sulfonylureas, biguanides do not have a hypoglycemic effect in healthy people and do not stimulate insulin release (Cusi 1996). Through its anti-hyperglycemic effect, metformin lowers both fasting and postprandial blood glucose concentrations in patients with type 2 diabetes. Although the precise mechanism of this effect has not been fully established, evidence suggests that the drug improves both peripheral and liver sensitivity to insulin, reduces basal liver glucose production and increases insulin-stimulated uptake and utilisation of glucose by peripheral tissues (AHFS 1999). Metformin, even in excessive dosage, normally does not lower glucose concentrations below euglycemia. Metformin accumulates in the wall of the intestine but does not appear to have clinically important effects on glucose absorption. In contrast, studies and systematic reviews have consistently shown that other diabetes treatments, including sulfonylureas and insulin, are associated with a substantial risk for clinically significant hypoglycemia (Bolen 2007; Hamnvik 2009).

Apart from its influence on carbohydrate metabolism, metformin is thought to have other positive effects related to type 2 diabetes and its long-term prognosis. There may be modest improvements in serum lipids, in particular reductions of fasting serum triglycerides as well as total and LDL-cholesterol concentrations. Additionally, therapy with metformin may be associated with weight loss or a stabilisation in weight gain. Suggested mechanisms for this effect include the absence of a hyperinsulinemic effect (which if present may increase appetite or lipogenesis) and decreased dietary intake caused by adverse gastrointestinal effects of metformin. There is inconclusive evidence at present on the effect of metformin on the

fibrinolytic system and platelet aggregation, that play a role in the development of coronary artery thrombosis (Palumbo 1998).

Studies of metformin

Several trials using metformin alone or in combination with other drugs in patients with type 2 diabetes mellitus have been published. The UK Prospective Diabetes Study (UKPDS) was the first big trial to assess long-term clinical outcomes related to metformin therapy in persons with type 2 diabetes. The study included overweight patients with newly diagnosed type 2 diabetes, mean age 53 years, who had no coronary artery disease or contraindication to treatment. The results indicated that metformin monotherapy led to a reduction in diabetes-related endpoints and also in diabetes-related mortality and total mortality, as compared to insulin, sulfonylurea therapy or diet alone (UKPDS-34 1998). There were no cases of lactic acidosis in any group.

More recently, a long-term trial evaluated the addition of metformin or placebo to insulin therapy and found that metformin was associated with a statistically significant 40% reduction in macrovascular morbidity and mortality compared with placebo (Kooy 2009a). The absolute risk reduction for macrovascular events for metformin compared with placebo was 6.1%, resulting in a number needed to treat of 16 to prevent one macrovascular endpoint, over the mean trial duration of 4.3 years. No cases of lactic acidosis were reported during the trial.

Several meta-analyses have been published evaluating the effect of metformin on glucose regulation, weight, diabetes-related outcomes, and mortality (Bolen 2007; Campbell 1995; Eurich 2007; Guthrie 1997; Johansen 1999; Saenz 2005). In the meta-analyses by Campbell, Johansen, Guthrie and Bolen, metformin and other anti-hyperglycemic treatments lowered blood glucose and glycosylated hemoglobin significantly compared with placebo, but body weight was substantially lower in the metformin group compared to other agents, including insulin and sulfonylureas. In addition, metformin was associated with significantly less clinically significant hypoglycemia than other agents. More recently, the Cochrane review by Saenz found that obese patients treated with metformin showed a significantly greater benefit than sulfonylureas or insulin for any diabetes-related outcome as well as for total mortality. Finally, the systematic review by Eurich evaluated patients with diabetes and congestive heart failure and a found that metformin was associated with a greater reduction in mortality and hospital admission compared with any other diabetes treatment.

Why it is important to do this review

The available data indicate that metformin use in patients with type 2 diabetes mellitus is associated with a reduction in cardiovascular morbidity and mortality, compared to insulin, sulfonylureas or diet alone (Eurich 2007; Kooy 2009a; Saenz 2005; UKPDS-34 1998). However, at present metformin use is considered to be contraindicated in many chronic conditions that may increase the risk of tissue anoxia (lack of oxygen) and the development of lactic acidosis, such as cardiovascular, renal, pulmonary and liver disease. These restrictions significantly reduce the number of patients who could benefit from metformin treatment. The present review assesses the risk of fatal and nonfatal lactic acidosis associated with metformin. Other adverse effects associated with metformin use are evaluated in another review.

OBJECTIVES

To assess the risk of fatal and nonfatal lactic acidosis associated with metformin use in persons with type 2 diabetes mellitus, compared to placebo or other glucose-lowering therapies. A secondary objective was to evaluate levels of blood lactate, measured at baseline and during treatment, for metformin compared to placebo or other hypoglycemic therapies.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective clinical trials in patients with type 2 diabetes mellitus were included if they evaluated metformin, alone or in combination with other treatments, compared to placebo or to any other glucose-lowering therapy, and lasted at least one month. Clinical trials were included even if they were not randomised or blinded. In addition, all observational cohort studies evaluating at least one month of metformin use were included in the analysis, as long as they provided the number of patients and the duration of treatment. The excluded trials lasting less than one month were evaluated separately to see if there were any cases of lactic acidosis.

Types of participants

Participants studied were adults with type 2 diabetes mellitus. 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 trial.

Types of interventions

Metformin, alone or in combination with other treatments, versus placebo or one of the following interventions used with the intention of lowering blood glucose levels:

- sulfonylurea (for example, glibenclamide);
- thiazolidinedione (for example, rosiglitazone);
- meglitinide (for example, repaglinide);
- alpha-glucosidase inhibitor (for example, acarbose, miglitol);
- dipeptidyl peptidase-4 inhibitor (for example, sitagliptin, vildagliptin);
- glucagon-like peptide-1 agonist (for example, exenatide, liraglutide);
- sodium-glucose cotransport inhibitor (for example, dapagliflozin)
- insulin;
- non-pharmacological intervention (for example, diet);
- any combination of the above.

Data on participants treated with phenformin were not included in the analysis for lactic acidosis, but were included in measurements of lactate levels.

Types of outcome measures

Primary outcomes

- death described as due to lactic acidosis;
- reported cases of nonfatal lactic acidosis, as defined by the investigator.

Secondary outcomes

- blood lactate levels for metformin compared to placebo or other non-biguanide therapies, and compared to phenformin.

Covariates, effect modifiers and confounders

Reported cases of renal failure or change in any hypoxic co-condition (e.g. pulmonary disease). If cases of lactic acidosis were to be identified, their association with concurrent illness would be assessed.

Search methods for identification of studies

Electronic searches

Two investigators (SS, EG) jointly developed search strategies with the help of an information service librarian and the Cochrane Metabolic and Endocrine Disorders Group Trials Search Coordinator.

A comprehensive search of the following databases was performed to identify relevant human clinical trials or meta-analyses:

- *The Cochrane Library* (issue 3, 2009);
- MEDLINE including OLDMEDLINE (until 10/2009);
- REACTIONS (until 10/2009);
- EMBASE (until 10/2009).

The described search strategy (see for a detailed search strategy Appendix 1) was used for MEDLINE. For use with EMBASE, *The Cochrane Library* and the other databases this strategy was slightly adapted.

Studies published in any language were included. No additional key words of relevance were identified during any of the electronic or other searches. If, in future searches, additional key works are found, electronic search strategies will be modified to incorporate these terms.

Searching other resources

In addition, attempts were made to contact authors of identified studies in order to obtain additional references, unpublished trials, ongoing trials or missing data not reported in the original trials. Similarly, the metformin manufacturer Bristol-Myers Squibb Company was contacted in order to retrieve information on metformin trials, published and unpublished.

The search was further augmented by scanning references of identified articles or reviews, and of abstracts at a clinical symposium, reported in the journal Diabetologia, Volume 43, Supplement 1, 2000. The Cumulated Index Medicus was used to search relevant articles from 1959 to 1965.

Data collection and analysis

Selection of studies

Two authors (GP, SS) independently reviewed the records found in the search. Full articles were retrieved for further assessment if the information given suggested that the study evaluated metformin use in patients with diabetes mellitus. If there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification. In addition, any potentially relevant clinical trials found from scanning references of identified articles or reviews were retrieved.

Two investigators (SS, EG) independently evaluated retrieved studies for inclusion, and consensus was reached in cases of dispute. For publications with additional information on participants included in another publication, the publication with the most information was chosen as the included article, the companion publications are provided in the reference list.

Data extraction and management

Data concerning details of study population, intervention and outcomes were extracted independently by two authors (SS, EG) using a standard data extraction form. The data extraction form included the following items:

- general information: published/unpublished, title, authors, contact address, language of publication, year of publication, duplicate publications, sponsoring, setting.
- trial characteristics: design, duration, randomisation (and method), blinding (single-, double- triple-blind), method and check of blinding.
- intervention(s): placebo included, interventions (dose, route, timing), comparison interventions (dose, route, timing), co-medications (dose, route, timing).
- patients: inclusion and exclusion criteria, total number and number in comparison groups, sex, age, selected baseline characteristics, diagnostic criteria, similarity of groups at baseline (including any co-morbidity), withdrawals or losses to follow-up (description), subgroups.
- outcomes: deaths thought due to lactic acidosis, nonfatal lactic acidosis, lactate levels, renal failure, worsening of hypoxemic co-conditions, length of follow-up, quality of reporting of outcomes.

Differences in data extraction were resolved by consensus, referring back to the original article. Cases of lactic acidosis were to be tabulated according to the investigator's report. In addition, information was sought from the authors of the primary studies.

Assessment of risk of bias in included studies

The methodological quality of each study was evaluated based on the quality criteria modified from Schulz, Jadad and Stroup (Jadad 1996; Schulz 1995; Stroup 2000). Studies were divided into five categories.

For randomised controlled trials, the following factors were studied:
1. Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?

2. Minimisation of performance bias - were the patients and people administering the treatment blind to the intervention?
2. Minimisation of attrition bias - a) were withdrawals and drop-outs completely described? b) was analysis by intention-to-treat?
4. Minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, trials were broadly subdivided into the following three categories:
A - all quality criteria met: low risk of bias.
B - one or more of the quality criteria only partly met: moderate risk of bias.
C - one or more criteria not met: high risk of bias.

For non-randomised trials, the following criteria were used:
D - Open-label non-randomised controlled trials
E - Observational cohort studies

Each trial was assessed independently by two authors (SS, EG), and consensus was reached in cases of disagreement. However, as no events were found in the results, sensitivity analyses using the quality assessments were not done.

Assessment of heterogeneity

Interstudy heterogeneity was to be tested for using the chi-squared statistic for the assumption of homogeneity, with the statistical significance set at $P < 0.1$. Possible sources of heterogeneity were to be assessed by subgroup and sensitivity analyses as described below. As no cases of lactic acidosis were found, this was not performed. Small study bias was tested for using funnel plots.

Data synthesis

The treatment effect for fatal and nonfatal lactic acidosis was expressed as a risk difference, by taking the incidence of events on metformin, alone or in combination with other treatments, and then subtracting the incidence of events on placebo or alternative treatments. If there were non-fatal events found, the first event would be considered for any one patient. We had planned to pool the results, using the fixed-effect model for dichotomous data. The risk difference could then be converted to the number needed to harm (NNH). In addition, the results could be expressed as the relative risk of lactic acidosis associated with metformin use, compared to placebo or non-metformin therapy. However, when no cases of lactic acidosis were found in either treatment group, the upper limit for the true incidence of lactic acidosis in the metformin group and the non-metformin group were calculated separately using Poisson statistics.

Once pooled results revealed no cases of lactic acidosis, it was decided to report on trials that measured blood lactate levels for metformin, compared to placebo or non-biguanide treatments, and also compared to phenformin. Three outcomes were analysed for the metformin group compared to the comparison groups: (1) the change in lactate levels from baseline to treatment, (2) the mean lactate levels recorded during treatment, and (3) the change in treatment lactate levels from a basal state to peak stimulation, either with food or exercise. The results were recorded as the weighted mean difference (WMD), in mmol/L, and pooled using the fixed-effect model for continuous data.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses in order to explore the association of lactic acidosis with the following factors:

- patients with hypoxemic co-conditions, e.g. chronic renal insufficiency (creatinine >1.5 mg/dl) or renal failure, congestive heart failure, liver disease, pulmonary diseases, and peripheral artery disease;
- age greater than 65 years;
- metformin use, given as monotherapy or in combination with other medications;
- different comparison interventions.

These analyses were not done as there were zero cases to analyse. Instead, information was obtained on how many patients were over the age of 65 or thought to have concomitant hypoxemic conditions.

Sensitivity analysis

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

- repeating the analysis excluding unpublished studies, non-randomised trials, and unblinded trials;
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies funded by industry sponsors.

The robustness of the results was also to be tested by repeating the analysis using different measures of effects size (risk difference, relative risk, etc.) and different statistical models (fixed-effect and random-effects models). As no cases of lactic acidosis were found, sensitivity analyses were not performed.

RESULTS

Description of studies

Results of the search

The electronic database search identified approximately 7000 articles, and of these 386 were potentially relevant studies on metformin use in patients with type 2 diabetes. After reviewing articles and bibliographies, the Cumulated Index Medicus, and abstracts at a clinical symposium, an additional 70 studies were identified. Of these 456 studies, 346 met inclusion criteria. No further articles were found by corresponding with authors, but information from one additional unpublished trial was received from Dr. Evertine Abbink, for a total of 347 included studies.

Missing data

Attempts were made to contact 102 of the authors for the comparative trials using the listed correspondence address, and 30 responses were received. All 30 of the respondents stated that they knew of no cases of lactic acidosis in any of their 34 trials. In addition, the metformin manufacturer Bristol-Myers Squibb Company responded, stating that they had no unpublished trials to

report. They provided a list of trials involving metformin, but none had been overlooked by the search.

Exclusion criteria of the studies

Of the 334 prospective studies, renal insufficiency (defined as a creatinine level of greater than 1.5 mg/dL) was listed as an exclusion criterion in 191 (57%), cardiovascular disease in 154 (46%), liver disease in 179 (54%), pulmonary disease in 46 (13%), and age greater than 65 years in 40 (12%).

Included studies

Studies and participants

Of the 347 studies analysed, 209 were prospective comparative trials, 125 were prospective cohort studies, and 13 were retrospective cohort studies. A total of 96,295 participants were followed for 125,941 patient-years, with 69,642 participants (70,490 patient-years) in the metformin group and 26,653 participants (55,451 patient-years) in the non-metformin group. The mean age of the participants in the metformin group was 57.1 (SD 8.8) years, with 61% men. In the non-metformin group, the mean age was 57.2 (SD 9.0) years, with 61% men. From the available data it was estimated that 26% of the participants were over the age of 65 years, who were followed for approximately 32,745 patient-years. The mean trial duration was 1.3 years, with a range from 0.1 to 10.7 years. The mean study size in the metformin group was 201 participants with a range of 6 to 11,014. The mean study size in the non-metformin group was 128 participants with a range of 8 to 2,897. The drop-out rate was estimated to be 9.2%.

Interventions

Metformin was given in daily doses of 1 to 3 grams, with the dosage titrated clinically. Comparison treatments included placebo, diet, insulin, glyburide (glibenclamide), gliclazide, glipizide, glimepiride, chlorpropamide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone, pioglitazone, vildagliptin, sitagliptin, saxagliptin, dapagliflozin, and guar gum.

Outcome measures

Outcomes measured included glycemic control (blood and urinary glucose, HbA1, HbA1c, insulin, and C-peptide levels), insulin sensitivity using a glucose clamp, weight, energy consumption, lipids, lipoproteins, fructosamine, free fatty acids, fibrinogen, plasminogen activator inhibitor, C-reactive protein, heart rate, blood pressure, lactate levels, bicarbonate, ketones, microalbuminuria, renal and liver function tests, crude mortality rate, time-related mortality, drug-related adverse events, death from hyper- or hypoglycemia, renal failure, diabetic eye disease, and cardiovascular endpoints (sudden death, myocardial infarction, stroke).

Only 19 trials were specifically designed to assess the incidence of lactic acidosis, but side effects or adverse events were described in almost all the trials. Attempts were made to reach the authors of the trials and 30 investigators replied, all confirming that there were no known cases of fatal or nonfatal acidosis in any of their 34 trials. Serum bicarbonate or lactate levels were measured in 123 of the included studies (45%). Of the comparative trials, 25 measured lactate levels while on metformin and non-metformin treatment (Bjorntorp 1978; Botha 1977; Campbell 1994; Cavallo-Perin 1989; Cryer 2005; Cusi 1996; Damsbo 1998; De Silva 1979; DeFronzo 1995; Fritsche 2000; Gregorio 1989; Gregorio 1990; Hother-Nielsen 1989; Inzucchi 1998; Jackson 1987; Josephkutty 1990; Klein 1991; McAlpine 1988; Nattrass 1977; Pedersen 1989; Rachmani 2002; Raptis 1996; Teupe 1991; Velussi 1992; Wu 1990).

Excluded studies

Studies were excluded for the following reasons: Ten were retrospective cohort studies that did not give information on the number of patients or the length of treatment (Charlton 2008; Cook 2005; Debry 1966a; Debry 1966b; Evans 2006; Masoudi 2005; Monami 2008a; Ong 2006; Sharabashi 2006; Simpson 2006), 33 were prospective cohort studies that did not give information on the number of patients or length of treatment (Bernard 1965; Berhanu 2007; Carpentier 1975; Chow 1995; Clauson 1996; Comaschi 2007; Comaschi 2008; Debry 1964; Derosa 2009; Eurich 2005b; Farah 2008; Forti 2008; Harris 2008; Hermansen 2007; Home 2009; Javaid 2007; Kamber 2008; Kim 2008; Komajda 2008; Lapina 2008; Lin 2008; Messens 1965; Messens 1966; Monami 2006; Muntoni 1965; Nauck 1993; Nauck 2009; Papa 2008; Rambert 1961; Seufert 2008; Sugawara 1962; Teitelbaum 1963; Yegnanarayan 2008), 41 prospective comparative trials were of less than one month duration (Bonfigli 1999; Bruneder 1978; Cacciapuoti 1991; Cunha 2008; English 2007; Faure 2008; Fery 1997; Galuska 1994; Gibson 1995; Gin 1982; Gin 1985; Gin 1989; Giugliano 1979; Gontier 2008; He 2009; Herman 2006; Herman 2006; Hong 2008; Irsigler 1978; Ismail 1978; Isnard 1996; Jansson 1996; Leslie 1987; Lim 1970; Magalhaes 2006; Orlikowska 1966; Panahloo 1995; Perriello 1994; Pilger 1978; Prager 1983; Rigas 1968; Rizkalla 1986; Sambol 1996; Scarpello 1998; Schaffalitzky 1979; Signore 1996; Slama 1984; Sum 1992; Trischitta 1983; Turner 1995; Zapecka-Dubno 1999), and 21 were retrospective analyses or reviews (Aguilar 1992b; Belsey 2008; Bodmer 2008; Chan 2009; Connolly 1996; Daniel 1997; Eurich 2005a; Guthrie 1997; Hirsch 2009; Johansen 1999; Lalau 1994; Lalau 1995; Mellbin 2008; Monami 2008; Nauck 1997; O'Connor 1998; Rao 2008; Runge 2008; Selby 1999; Tomioka 2007; Zhang 2009).

Risk of bias in included studies

The methodological quality evaluation of the studies was done using the criteria described above. Only information published in the trials was used to determine bias categories. An A low-risk of bias category was given to 32 trials, a B category to 63 trials, a C category to 84 trials, a D category for 30 trials, and an E category for 138 studies. Of the studies analysed, 94 were double-blind, randomised controlled trials (32 described the method of randomisation and allocation concealment). Another 115 were single-blind or open-label comparative trials (85 randomised and 30 non-randomised). The 138 cohort studies were all open-label and observational. The average drop-out rate was approximately 9%.

Effects of interventions

Incidence of lactic acidosis

When combining the data from cohort studies with the prospective comparative trials, there were no cases of fatal or nonfatal lactic acidosis reported in the metformin group, totaling 70,490 patient-years, and no cases in the non-metformin group, representing 55,451 patient-years. Using Poisson statistics with 95% confidence, the upper limit for the true incidence of metformin-associated lactic acidosis was 4.3 cases per 100,000 patient-years, and the upper limit for the incidence of lactic acidosis in the non-metformin

group was 5.4 cases per 100,000 patient-years. When combining data from metformin and non-metformin groups together the upper limit for the true incidence of lactic acidosis in all patients with type 2 diabetes was 2.4 cases per 100,000 patient-years.

Association with hypoxemic co-conditions

Another outcome to be assessed was the number of participants with worsening of their hypoxemic co-conditions during the trial. An accurate assessment of the incidence of renal failure or worsening of other conditions could not be made because two of the large trials did not provide adequate data (Fisman 2001; UKPDS-34 1998). On correspondence with the authors of these trials, this information could not be provided.

There was insufficient information to estimate the number of participants studied with hypoxemic co-conditions such as renal insufficiency, cardiovascular diseases, liver diseases, or pulmonary disease. Instead, each of the trials included in this analysis was characterized as to whether any of these conditions were listed as exclusion criteria. If the patients were listed as healthy or that standard contraindications were used, it was assumed that all of these conditions were excluded. Renal insufficiency was usually defined as a creatinine level of greater than 1.5 mg/dl. Of the 334 prospective studies, 143 (53%) allowed for the inclusion of renal insufficiency, following 37,360 patient-years of metformin use, and 324 (97%) allowed for the inclusion of at least one of the contraindications listed above. It was estimated from the available data that 26% of the participants in the studies were over the age of 65 years, who were followed for approximately 18,327 patient-years of metformin use.

Blood lactate levels

For those trials that provided the data, the baseline lactate level measured prior to metformin treatment was 1.13 ± 0.25 mmol/L. There was no difference in the net change of lactate levels from baseline for metformin compared to placebo or non-biguanide therapies, with a weighted mean difference (WMD) of 0.12 mmol/L (95% CI -0.01 to 0.25). The mean lactate level during metformin treatment was 1.24 ± 0.31 mmol/L, which was not significantly different from non-biguanide comparisons (WMD 0.04 mmol/L, 95% CI 0.00 to 0.13, P = 0.07), and was 0.75 mmol/L lower than with phenformin (95% CI -0.86 to -0.65). Lactate levels during metformin treatment, measured before and after stimulation (by a meal or strenuous exercise), were 2.3 ± 1.7 mmol/L. This was not significantly different for metformin compared to the non-biguanide group (WMD 0.09 mmol/L, 95% CI -0.03 to 0.22) or to phenformin (WMD -0.37 mmol/L, 95% CI -1.06 to 0.32). Four trials that measured lactate levels did not provide data to be analysed, but reported levels to be normal during metformin and non-metformin treatment (DeFronzo 1995; Fritsche 2000; Gregorio 1989; Raptis 1996).

Heterogeneity was noted in the three trials that measured lactate levels after stimulation by food or exercise during treatment with metformin or non-biguanide therapies, probably due to the fact that each was performed under different conditions. The results were not significantly different when the random-effects model was used (WMD 0.04 mmol/L, 95% CI -0.45 to 0.53). In addition, heterogeneity was noted in the three trials measuring mean lactate levels for metformin compared to phenformin treatment. When the random-effects model was used the difference was no longer statistically significant (-0.64 mmol/L, 95% CI -1.63 to 0.35).

Small study bias

Funnel plots of the effect size versus standard error were evaluated for the included trials in the analysis. The funnel plot used for the incidence of lactic acidosis was unable to provide evidence for or against the possibility of small study bias, since all of the trials found no cases of lactic acidosis. Funnel plots for the measurement of lactate levels showed no convincing evidence for significant small study bias.

DISCUSSION

Summary of main results

In order to evaluate the risk of lactic acidosis attributed to metformin use, pooled data from all known prospective comparative trials and observational cohort studies with durations of at least one month were analysed. No cases were found in 347 trials with 70,490 patient-years of metformin treatment. In fact, on review of 94 additional trials that were excluded from analysis (those that lasted less than one month or were of unclear duration) no cases of lactic acidosis were found. The risk difference for metformin compared to non-metformin treatment, calculated using Poisson statistics, was 0.00 per 100,000 patient-years (95% CI, -5.4 to +4.3). This indicates that the upper limit for the true incidence of metformin-associated lactic acidosis is 4 cases per 100,000 patient-years, and the upper limit for the incidence with other non-biguanide treatments is 5 per 100,000 patient-years. Of the trials that measured blood lactate levels, there was no significant difference for metformin compared to placebo or non-biguanide treatments, and was lower for metformin than for phenformin.

The mean duration of studies included in this review was 1.3 years, with a wide range from 1 month to 10.7 years. As no cases of lactic acidosis were found in any trial, the association of lactic acidosis with duration of treatment could not be assessed. In addition, excluded trials of less than one month duration were evaluated to see if lactic acidosis occurs shortly after initiation of treatment, and no cases were found.

At present, metformin is often considered to be contraindicated in patients with chronic renal insufficiency, liver function abnormalities, congestive heart failure, peripheral vascular disease, pulmonary disease, or age greater than 65, as these conditions may increase the risk of tissue anoxia and therefore the development of lactic acidosis. In this review, 324 (97%) of the 334 prospective studies allowed for the inclusion of patients with at least one of these contraindications, and 26% of all participants were estimated to be older than 65 years, with no adverse effects observed. However, it is not clear how many participants with each of these conditions were included in the trials, so the safety of metformin in the presence of these standard contraindications cannot be assessed. One trial (Rachmani 2002) questioned the standard contraindications by studying 393 patients, all with at least one contraindication to metformin use, and found no cases of lactic acidosis over four years of the trial duration. All of the patients in this trial had renal insufficiency, with mean plasma creatinine levels of 1.5 to 2.5 mg/dl (mean level 1.8 mg/dl).

Overall completeness and applicability of evidence

Metformin is a biguanide anti-hyperglycemic medicine that has been in use for over 50 years (Sterne 1959). Metformin treatment

in patients with type 2 diabetes has been shown to reduce cardiovascular events and mortality when compared to insulin, sulfonylureas or diet alone (Eurich 2007; Kooy 2009a; Saenz 2005; UKPDS-34 1998). Studies have consistently shown that treatments other than metformin, such as insulin and sulfonylureas, are associated with significant weight gain and a substantial risk for clinically significant hypoglycemia (Bolen 2007; Campbell 1995; Guthrie 1997; Hamnvik 2009; Johansen 1999).

Concern about the risk of lactic acidosis has led to recommendations that metformin be withheld in persons with chronic conditions that in themselves can cause lactic acidosis. These recommendations, if followed, would reduce the number of patients eligible to receive metformin by approximately one half (Brown 1998). It has been found that in clinical practice these standard contraindications are largely disregarded, with 54% to 73% of patients on metformin having at least one standard contraindication to treatment (Calabrese 2002; Holstein 1999; Sulkin 1997). In two studies, approximately 15% of patients on metformin admitted to a hospital had concurrent renal insufficiency (Calabrese 2002; Holstein 1999). In this meta-analysis, 97% of the studies allowed for at least one of the standard contraindications.

Metformin has been implicated as a cause of lactic acidosis because a related biguanide, phenformin, had been associated with several cases of lactic acidosis and was removed from the US market in 1977 (Aguilar 1992b). Despite their similarities, phenformin has a chemical structure significantly different from metformin. Unlike metformin, phenformin can impair oxidative phosphorylation in the liver, thereby increasing lactate production by anaerobic pathways (Cavallo-Perin 1989; Irsigler 1978; Pilger 1978; Sirtori 1994; Velussi 1992). In contrast, metformin inhibits hepatic gluconeogenesis without altering lactate turnover or lactate oxidation (Cusi 1996; Scheen 1996; Stacpoole 1998). In addition to the trials analysed in this review, several other trials have confirmed that metformin treatment does not significantly elevate blood lactate levels, even in the presence of renal impairment or advanced age (Connolly 1996; Debry 1964; Giugliano 1993; Irsigler 1978; Lalau 1990; Menzies 1989; Pagano 1983; Pilger 1978; Trischitta 1983).

At present the only evidence to indicate that metformin use is associated with lactic acidosis comes from reports of approximately 330 cases that have occurred in patients while on metformin treatment (Bergman 1978; Gan 1992; Lalau 1994; Luft 1978). The incidence of lactic acidosis occurring in patients on metformin has been estimated from population studies to be 2 to 9 cases per 100,000 patient-years (Bodmer 2008; Misbin 1998; Stang 1999; Wilholm 1993). Essentially all of the cases reported were in patients with severe underlying conditions that in themselves could have caused the lactic acidosis.

Lactic acidosis has also been reported in diabetic patients not treated with metformin, typically under conditions in which there is significant tissue hypoperfusion or hypoxia (Aguilar 1992b; Bodmer 2008). To assess the rate of lactic acidosis in diabetic patients on treatment other than metformin, a population study followed patients with type 2 diabetes who were treated in the USA prior to the introduction of metformin and after the withdrawal of phenformin (Brown 1998). This study found the rate of confirmed lactic acidosis to be approximately 10 per 100,000 patient-years, which is equivalent to that seen with metformin treatment. Another study evaluated all cases of metabolic non-ketotic acidosis in patients with type 2 diabetes that occurred during 600 emergency admissions to a University hospital (Aguilar 1992b). The rates of non-ketotic acidosis per 1000 emergency admissions were 29 for sulfonylureas, 48 for insulin, and no cases for those on metformin treatment. All cases of non-ketotic metabolic acidosis found were associated with severe precipitant disease that could have caused lactic acidosis. More recently, a nested case-control analysis using the United Kingdom General Practice Research Database found that the crude incidence rate for lactic acidosis in patients with diabetes was 3.3 cases per 100,000 person-years among users of metformin and 4.8 cases per 100,000 person-years among users of sulfonylureas (Bodmer 2008). The investigators of these observational studies concluded that it is the underlying systemic dysfunction and not the particular treatment that is the main determinant for the appearance of lactic acidosis. In support of that conclusion, the results of this review reveal that there is no evidence of an increased risk of lactic acidosis associated with metformin use, as compared with other diabetes treatments, when prescribed under the study conditions.

Potential biases in the review process

This review has several limitations. Essentially all the data included in this analysis were from published trials, and this may have produced biased results. A funnel plot of effect size versus standard error was unable to provide convincing evidence for significant small study bias, since no cases were found in any trial. It is interesting to note that many of the comparative trials included in the analysis were sponsored by pharmaceutical companies producing anti-hyperglycemic medications other then metformin, in which case a bias may be to publish adverse effects for metformin.

Another difficulty is that in order to assess the risk of a rare occurrence such as lactic acidosis, it may be necessary to evaluate more than 70,000 patient-years of metformin treatment. It is especially difficult to assess the risk of lactic acidosis in the presence of standard contraindications such as renal or hepatic insufficiency because it is unclear exactly how many of the participants had these conditions. For that reason, no conclusions can be made about the safety of metformin use in the presence of these conditions. Despite these limitations, the most important conclusion from this review is that, at present, there is no evidence from prospective comparative trials or observational cohort studies to support the hypothesis that metformin is associated with an increased risk for lactic acidosis.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from prospective comparative trials or from observational cohort studies that metformin treatment increases the incidence of lactic acidosis compared with other anti-hyperglycemic treatments. This review was not able to quantitatively assess the safety of metformin treatment in the presence of each of hypoxic co-conditions.

Implications for research

Large prospective, comparative trials are necessary in patients with type 2 diabetes mellitus who have conditions that are presently considered contraindications for its use. For example, a large

trial could be performed in patients known to have chronic renal insufficiency. Outcomes to be followed would include the incidence of lactic acidosis as well as diabetes-related complications and total mortality.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aarsand 1998

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: at least one year, then 12 weeks.
Participants	COUNTRY: Norway SETTING: Endocrinology center Treatment N: 28, with 14 on folate and 14 on placebo. Metformin + placebo AGE: 57+/-2.8. Metformin + folate AGE: 62+/-2.5. Metformin + placebo SEX: 79% men. Metformin + folate SEX: 71% men. INCLUSION: patients with type 2 DM, treated with metformin for a minimum of 1 year EXCLUSIONS: vitamin use that would interfere with the study.
Interventions	TREATMENT: metformin, at least 1g/day. One-half of patients on folate 0.25 mg/day + iron 60mg/day, and one-half on iron 60mg/day. COMPARISON: none.
Outcomes	Fasting homocysteine, cysteine, cysteinylglycine, vitamin B12, and folate.
Notes	

Aarsand 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Abbasi 1997

Methods	TRIAL DESIGN: Randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United States SETTING: research laboratory Treatment N: 15 Control N: 8. Treatment AGE: 53 +/-3 Control AGE: 51 +/-4 Treatment SEX: 64% men Control SEX: 87% males INCLUSION: Type 2 DM EXCLUSIONS: abnormal laboratory values, vascular disease
Interventions	TREATMENT: metformin-blind versus open-label metformin, dosage adjused clinically. COMPARISON: placebo
Outcomes	Fasting and postprandial glucose, insulin, and free fatty acids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Abbasi 1998

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient and research center Treatment N: 11 Control N: 0 AGE: not listed SEX: not listed INCLUSION: diet-treated type 2 DM EXCLUSIONS: laboratory abnormalities, diabetic vascular complications, or abnormal electrocardiogram
Interventions	TREATMENT: metformin 1-2.5 g/day COMPARISON: none
Outcomes	Plasma glucose, insulin, and free fatty acids.
Notes	

Abbasi 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Abbasi 2000

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2 years
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 110 Control N: 0 AGE: 27-85 SEX: not stated INCLUSION: type 2 DM with normal renal function EXCLUSIONS: renal insufficiency
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: none
Outcomes	Electrolytes, creatinine, plasma lactic acid
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Abbink 2001

Methods	TRIAL DESIGN: Double-blind randomised controlled trial - unpublished DURATION: 2 months
Participants	COUNTRY: Netherlands SETTING: outpatient Treatment N: 12 Control N: 12 AGE: unclear SEX: not listed. INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 500 mg TID COMPARISON: Glibenclamide
Outcomes	Glucose, HbA1.
Notes	

Abbink 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Abbink 2000

Methods	TRIAL DESIGN: Abstract of a double-blind randomised controlled trial DURATION: 2 months
Participants	COUNTRY: Netherlands SETTING: outpatient Treatment N: 12 Control N: 60 AGE: unclear SEX: not listed INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: glibenclaminde or glimerperide or acarbose
Outcomes	Vasodilator responses to diazoxide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Adamia 2007

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 6 months
Participants	COUNTRY: Georgia SETTING: Outpatient Treatment N: 26 Control N: 0 AGE: 59.7 SEX: 0% men INCLUSION: Type 2 DM, obese postmenopausal women EXCLUSIONS: None listed
Interventions	TREATMENT: Metformin, 1700 - 2500 mg/day
Outcomes	Leptin, adiponectin, insulin resistance
Notes	

Aguilar 1992a

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2 months
Participants	Country: Mexico. Setting: diabetes institute. Treatment N: 9. Control N: 0. Age: unclear. Sex: 26% men. Inclusion: type 2 DM with secondary failure to oral agents. Exclusions: insulin dependence.
Interventions	TREATMENT: metformin 1200 mg/day, chlorpropamide 375 mg/day, and bedtime insulin 0.1 U/kg/day COMPARISON: none
Outcomes	Fasting glucose, HbA1c, insulin dose, and glucose tolerance.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ahren 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial DURATION: 12 weeks
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 107 Control N; 0 AGE: 57.7 SEX: 45% men INCLUSION: type 2 DM EXCLUSIONS: clinically significant cardiovascular disease, carbohydrate disorders, elevated triglycerides
Interventions	TREATMENT: metformin plus vildgliptin or placebo
Outcomes	Beta-cell function and insulin sensitivity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Allen 1961

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 12 months

Allen 1961 *(Continued)*

Participants	COUNTRY: France SETTING: outpatient Treatment N: 57 Control N: 0 AGE: >40 SEX: not listed INCLUSION: poorly controlled DM EXCLUSION: none listed
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: none
Outcomes	Glycemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Amador-Licona 2000

Methods	TRIAL DESIGN: Prospective randomized controlled trial DURATION: 3 months
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 26 Control N: 23 AGE: < 65 years SEX: not listed INCLUSION: type 2 diabetes and incipient nephropathy EXCLUSION: hypertension, malignancy, hepatic or cardiovascular disorders
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: glibenclamide, dosage unclear
Outcomes	Metabolic control, blood pressure, unsulin, lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Andras 1962

Methods	TRIAL DESIGN: Prospective cohort study DURATION: approximately 1 month
Participants	COUNTRY: unclear

Andras 1962 *(Continued)*

	SETTING: outpatient Treatment N: 20 Control N: 0 AGE: not listed SEX: not listed INCLUSION: maturity-onset DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: none
Outcomes	Glycemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ascic-Buturovic 2008

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 6 months
Participants	COUNTRY: Bosnia SETTING: Outpatient Treatment N: 15 Control N: 0 AGE: 53.4 SEX: 60% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin and insulin, varying dosage
Outcomes	Glycemic control, weight
Notes	

Aviles-Santa 1999

Methods	TRIAL DESIGN: Randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United States SETTING: University clinic Treatment N: 21 Control N: 22 Treatment AGE: 53 +/-4 Control AGE: 54 +/-8 Treatment SEX: 28% men Control SEX: 45% men INCLUSION: Poorly controlled Type 2 DM on insulin

Aviles-Santa 1999 *(Continued)*

	EXCLUSIONS: pregnancy, creatinine > 1.5, hepatic enzymes double normal, medical conditions that could promote lactic acidosis.
Interventions	TREATMENT: Metformin + insulin COMPARISON: placebo + insulin
Outcomes	Weight, HbA1, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Azerad 1960

Methods	TRIAL DESIGN: Prospective cohort study DURATION: average 24 months
Participants	COUNTRY: France SETTING: outpatient Treatment N: 200 Control N: 0 AGE: not listed SEX: not listed INCLUSION: DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, with goal of 3 g/day, maximum 5 g/day. COMPARISON: none
Outcomes	Glycemia, and glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bacci 1961

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 3-6 months, average 4.5 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 42 Control N: 0 AGE: not listed SEX: not listed

Bacci 1961 *(Continued)*

	INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, dosage adjusted clinically COMPARISON: none
Outcomes	Glycemia and glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bailey 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial DURATION: 6 months
Participants	COUNTRY: United Kingdon SETTING: outpatient Treatment N: 568 Control N: 0 AGE: 57.9 SEX: 57% men INCLUSION: type 2 DM EXLCUSIONS: angina, congestive heart failure, hypertension
Interventions	TREATMENT: metformin, up to 3 gm daily or metformin 2.5 gm daily plus rosiglitazone 4 mg daily
Outcomes	Glycemic control, insulin resistance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Balasubramanian 2008

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 3 months
Participants	COUNTRY: India SETTING: Outpatient Treatment N: 213 Control N: 0 AGE: Not states SEX: Not stated INCLUSION: Type 2 DM

Balasubramanian 2008 *(Continued)*

	EXCLUSIONS: None listed
Interventions	Metformin 500 mg/day combined with lipitor 10 mg/day, in single pill
Outcomes	Glycemic control, weight, lipids, tolerability
Notes	

Bao 2009

Methods	TRIAL DESIGN: Open-label randomized controlled trial DURATION: 48 weeks
Participants	COUNTRY: China SETTING: Outpatient Treatment N: 22 Control N: 60 AGE: Not stated SEX: Not stated INCLUSION: Type 2 DM EXCLUSIONS: None listed
Interventions	TREATMENT: Metformin, 750-1500 mg/day COMPARISON: Repaglinide or Rosiglitazone
Outcomes	Glycemic and metabolic control
Notes	

Bastyr 2000

Methods	TRIAL DESIGN: Prospective randomized controlled trial DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 40 Control N: 91 Treatment age: 58.1 Control age: 55.7 Treatment SEX: 55% men Control SEX: 63% men INCLUSION: type 2 DM not controlled on sulfonylureas EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, 500 mg BID plus glyburide 10 mg BID COMPARISON: glyburide 10 mg BID plus insulin
Outcomes	Glycemic control
Notes	

Risk of bias

Bastyr 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Basu 2008a

Methods	TRIAL DESIGN: Double-blind randomized controlled trial DURATION: 4 months
Participants	COUNTRY: SETTING: Outpatient Treatment N: 15 Control N: 16 AGE: 56 SEX: 55% men INCLUSION: Type 2 DM EXCLUSIONS:
Interventions	TREATMENT: Metformin, 1 gm BID COMPARISON: Pioglitzaone, 45 mg/day
Outcomes	Insulin action
Notes	

Bauman 2000

Methods	TRIAL DESIGN: Prospective comparative study DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 14 Control N: 7 Treatment AGE: 49 Control AGE: 54 SEX: not stated INCLUSION: type 2 DM on oral sulfonylurea EXCLUSIONS: alcoholism, chronic renal failure, liver disease, cardiopulmonary disease
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: sulfonylurea, dosage unclear
Outcomes	Vitamin B12 measurements
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bayraktar 1996

Methods	TRIAL DESIGN: Crossover randomised controlled trial DURATION: 2 months
Participants	COUNTRY: Turkey SETTING: University clinic Treatment N: 36 Control N: 36 AGE: 30-63 SEX: 100% men INCLUSION : Type 2 DM with poor control EXCLUSIONS: microvascular or macrovascular complIcations, liver function abnormalities.
Interventions	TREATMENT: Metformin 500mg TID COMPARISON: acarbose
Outcomes	Insulin , c-peptide, fibrinogen, lipids, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Beisswenger 1999

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 30 Control N: 0 AGE: 62+/-8 SEX: 56% men INCLUSION: Type 2 DM, some on metformin treatment and some not EXCLUSIONS: renal or hepatic impairment or cardiac disease
Interventions	TREATMENT: metformin 500-2500 mg/day COMPARISON: none
Outcomes	HbA1c, methylglyoxal levels, D-lactate, and glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Belcher 2005

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 12 months
Participants	COUTNRY: United Kingdom SETTING: outpatient Treatment N: 917 Control N: 2796 Age: 57 +/- 9 Sex: 55% men Inclusion: type 2 DM Exlcusions: ALT levels greater than 2.5 times upper limit of normal
Interventions	TREATMENT: metformin 2500 mg/day COMPARISON: pioglitazone 45 mg/day
Outcomes	liver enzyme levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bell 1997

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 6 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 55 Control N: 0 AGE: 60.2+/-13 SEX: 45% men INCLUSION: patients with non-insulin-dependent DM treated with insulin EXCLUSIONS: creatinine > 1.5 mg/dl, or c-peptide < 0.8 ng/ml
Interventions	TREATMENT: metformin, 1-3 g/day, some with glyburide or insulin, dosage titrated clinically COM-PARISON: none
Outcomes	Insulin requirement, HbA1, BMI, and % successfully changed to oral therapy.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bermudez 2008

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 3 months
Participants	COUNTRY: Venezuela SETTING: Outpatient Treatment N: 189 Control N: 0 AGE: 58.3 SEX: Not stated INCLUSION: Type 2 DM EXCLUSIONS: Gestational diabetes, endocrine disorders, pancreatitis
Interventions	TREATMENT: Metformin, glimepiride and rosiglitazone, varying doses
Outcomes	Metabolic parameters
Notes	

Bermudez-Pirela 2007

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 2.5 months
Participants	COUNTRY: Venezuela SETTING: outpatient Treatment N: 53 Control N: 9 Treatment AGE: 52 Control AGE: 55.3 SEX: not states INCLUSION: type 2 DM EXCLUSIONS: Age > 60 years
Interventions	TREATMENT: metformin, 500 mg TID COMPARISON: metformin, 500 mg TID plus glimeperide 0.5 mg daily
Outcomes	Glycemic control, insulin, insulin resistance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Berne 2004

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of orlistat DURATION: 1 year
Participants	COUNTRY: Sweden SETTING: outpatient Treatment N: 220

Berne 2004 *(Continued)*

	Control N: 0 AGE: 59.1 SEX: 55% men INCLUSION: type 2 DM and obesity EXLCUSIONS: significant renal, peripheral vascular, gastrointestinal, respiratory or cardiac disease
Interventions	TREATMENT: metformin, dose unclear COMPARISON: none
Outcomes	Weight loss, glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Betteridge 2005

Methods	TRIAL DESIGN: Two prospective double-blind randomised controlled trials DURATION: 2 years
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 960 Control N: 319 AGE: not stated SEX: not stated INCLUSION: type 2 DM EXLCUSIONS: not listed
Interventions	TREATMENT: study 1: metformin, dosage unclear plus pioglitazone 15-45 mg daily. Study 2: metformin 850-2550 mg daily COMPARISON: study 1: metformin, dosage unclear plus gliclazide 80-320 mg daily. study 2: pioglitazone 15-45 mg daily
Outcomes	Lipids and lipoproteints
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Beyer 1975

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months

Beyer 1975 *(Continued)*

Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 24 Control N: 0 AGE: not listed SEX: 36% men INCLUSION: adult-onset DM EXCLUSION: none listed
Interventions	TREATMENT: metformin, dosage titrated clinically COMPARISON: none
Outcomes	Glucose and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bhansali 2005

Methods	TRIAL DESIGN: Prospective cohort study in a randomised trial of extended release metformin DURATION: 12 weeks
Participants	COUNTRY: India SETTING: outpatient Treatment N: 40 Control N: 0 AGE: 57.3 SEX: not stated INCLUSION: type 2 DM EXCLUSION: renal or hepatic dysfunction, congestive heart failure
Interventions	TREATMENT: metfromin, up to 2 gm daily COMPARISON: none
Outcomes	Glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bingle 1964

Methods	TRIAL DESIGN: Blinded randomised controlled trial (unclear if double-blind) DURATION: 2 months

Bingle 1964 *(Continued)*

Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 22 Control N: 22 AGE: unclear SEX: not listed INCLUSION: Type 2 DM not controlled on sulfonylureas EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 1-2 g/day + chlorpropamide COMPARISON: placebo + chlorpropamide
Outcomes	Plasma glucose and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bjorntorp 1978

Methods	TRIAL DESIGN: Prospective, cross-over comparative trial; not randomised DURATION: 8 weeks
Participants	COUNTRY: Sweden SETTING: outpatient Treatment N: 21 Control N: 21 AGE: 58 SEX: 52% men INCLUSION: Type 2 DM on long-term biguanide treatment EXCLUSIONS: abnormal renal function or liver function
Interventions	TREATMENT: Metformin, 1.5-3.0 g/day COMPARISON: phenformin, 50-100 mg/day (not analysed)
Outcomes	Fasting glucose and fasting lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Blonde 2002

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months

Blonde 2002 *(Continued)*

Participants	COUNTRY: United States SETTING: outpatient Treatment N: 476 Control N: 164 Age: 55.6 +/- 9.4 Sex: 57% men Inclusion: type DM uncontrolled on sulfnylurea treatment Exclusions: hepatic or renal dysfunction, congestive heart failure
Interventions	TREATMENT: metformin 1 g/day, with and without glyburide COMPARISON: glybruide 20 mg/day
Outcomes	HbA1, fasting glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Boronat 2000

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: average of 12 months
Participants	COUNTRY: Spain SETTING: Endocrine center Treatment N: 21 Control N: 0 AGE: unclear SEX: 5% men INCLUSION: obese insulin-treated patients with type 2 DM, also on metformin EXCLUSIONS: none listed
Interventions	TREATMENT: Insulin and metformin, dose adjusted clinically COMPARISON: none
Outcomes	HbA1c, weight, and insulin requirement.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bosi 2009

Methods	TRIAL DESIGN: Double-blind randomized controlled trial DURATION: 6 months

Bosi 2009 *(Continued)*

Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 879 Control N: 300 AGE: Not stated SEX: Not stated INCLUSION: Type 2 DM, treatment naive EXCLUSIONS: Pregnancy, coronary artery disease, renal or liver abnormalities
Interventions	TREATMENT: Metformin, 1 gm BID COMPARISON: Viladgliptin 50 mg/day
Outcomes	Glycemic control
Notes	

Botha 1977

Methods	TRIAL DESIGN: Open-label cross-over trial; not randomised DURATION: 1 month
Participants	COUNTRY: South Africa SETTING: general practice Treatment N: 21 Control N: 21 AGE: unclear SEX: not listed INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dose adjusted clinically COMPARISON: phenformin, buformin (not analysed), and untreated controls.
Outcomes	Heart rate, blood lactate, and lactate/pyruvate ratios, at baseline and with exercise.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Boyd 1992

Methods	TRIAL DESIGN: Randomised controlled trial DURATION: 6 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 8 Control N: 19 Treatment AGE: 64+/-6.2 Control AGE: 63.5+/-7.6 Treatment SEX: 37% men

Boyd 1992 *(Continued)*

	Control SEX: 68% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: glibenclamide or insulin
Outcomes	Insulin sensitivity, HbA1, weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Brazg 2007

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 1 month
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 28 Control N: 0 AGE: 55.9 SEX:36% men INCLUSION: Type 2 DM, poor control on metformin EXCLUSIONS: Not stated
Interventions	TREATMENT: Metformin, varying dose
Outcomes	Glycemic control, beta-cell function
Notes	

Brown 1999

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: average 11.6 months
Participants	COUNTRY: United States SETTING: patients in an HMO registry Treatment N: 3402 Control N: 0 AGE: > 30 SEX: 53% men INCLUSION: Type 2 DM on metformin treatment EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, 1000-2550 mg/day COMPARISON: none

Brown 1999 *(Continued)*

Outcomes	HbA1c, and fructosamine.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bruce 2006

Methods	TRIAL DESIGN: Prospective cohort study in a randomised trial of metformin and glybenclamide DURATION: 20 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 50 Control N: 0 IINCLUSION: type 2 DM, inadequately controlled EXCLUSIONS: renal, cardiac or hepatic diseae, obesity
Interventions	TREATMENT: metformin plus glubencalmide COMPARISON: none
Outcomes	Glycemic control, insulin sensitivity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Cairns 1977

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 39 Control N: 67 AGE: 57 SEX: 21% men INCLUSION: Type 2 DM EXCLUSIONS: renal failure, congestive heart failure
Interventions	TREATMENT: Metformin 850 mg BID COMPARISON: phenformin (not analysed)
Outcomes	Fasting glucose, body weight, and lipids

Cairns 1977 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Calle-Pascual 1995

Methods	TRIAL DESIGN: Open-label comparative trial; not randomised DURATION: 4 months
Participants	COUNTRY: Spain SETTING: outpatient Treatment N: 12 Control N: 24 AGE: unclear SEX: 50% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 850 mg TID COMPARISON: insulin or acarbose
Outcomes	Lipids, blood pressure, HbA1, body weight, insulin sensitivity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Campbell 1988

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 12 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 38 Control N: 24 AGE: 54+/-6.1 SEX: 64% men INCLUSION: Type 2 DM, diet failed EXCLUSIONS: congestive heart failure, renal failure, liver function abnormalities
Interventions	TREATMENT: Metformin, dosage adjusted clinically. COMPARISON: glipizide
Outcomes	Blood pressure, heart rate, microalbuminuria.

Campbell 1988 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Campbell 1994

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 52 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 24 Control N: 24 Treatment AGE: 57+/-10 Control AGE: 57+/-9 Treatment SEX: 33% men Control SEX: 33% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, 500 mg BID to 3,000 mg/day maximum. COMPARISON: glipizide, 5 mg/day to 39 mg/day maximum BID
Outcomes	Glucose, HbA1, lipids, lactate levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Canivet 1962

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: average 66 months
Participants	COUNTRY: France SETTING: outpatient Treatment N: 180 Control N: 0 AGE: not listed SEX: not listed INCLUSION: DM, 180 treated with metformin EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, dose unclear COMPARISON: some patients treated with other agents, not analysed

Canivet 1962 *(Continued)*

Outcomes	Plasma glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Carpentier 1975

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 6 months
Participants	COUNTRY: Belgium SETTING: outpatient Treatment N: 11 Control N: 0 AGE: 58.8 SEX: 45% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 1.5 g/day + arginine infusion 11.7 mg/kg/min COMPARISON: none
Outcomes	Blood glucose, free fatty acids, and glycagon.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Carter 2005

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 26 Control N: 16 Age: not stated Sex: not stated Inclusion: poorly controlled overweight patients with type 2 DM Exlcusions: not stated
Interventions	TREATMENT: metformin 1.5 to 3 g/day COMPARISON: placebo
Outcomes	C-reactive proteitn, complement factor C3

Carter 2005 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Cavallo-Perin 1989

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 10 Control N: 10 AGE: 51+/-2.1 SEX: 60% men INCLUSION: Type 2 DM EXCLUSIONS: liver or kidney disease, heart failure, other drugs, or chronic infection
Interventions	TREATMENT: Metformin 850 mg BID CONTROL: phenformin 50 mg BID (not analysed)
Outcomes	Weight, glucose, HbA1, and blood lactate levels at different times of day.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Cefalu 2002

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4.5 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 91 Control N: 91 Age: 35-70 Sex: not stated Inclusion: type 2 DM Exclusion: not stated
Interventions	TREATMENT: metformin 850 mg TID with and without glipizide CONTROL: glipizide 20 mg/day
Outcomes	Glycemic control, body weight, abdominal fat distribution, PAI-1 levels
Notes	

Cefalu 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ceriello 2005

Methods	TRIAL DESIGN: 4 prospective double-blind randomised controlled trials DURATION: 1 year
Participants	COUNTRY: United States SETTING: multi-center Treatment N: 298 Control N: 541 Treatment AGE: 55.6 Control AGE: 57 Treatment SEX: 80% men Control SEX: 71% men INCLUSION: type 2 DM, 35-75 years, poorly controlled EXLCUSIONS: heart attack or stroke
Interventions	TREATMENT: metformin, alone or in combination with other medications COMPARISON: pioglitazone, gliclazide, sulfonylureas
Outcomes	Glycemic control, insulin sensitvity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Chakrabarti 1965

Methods	TRIAL DESIGN: Single-blind crossover comparative trial; not randomised DURATION: 2 months placebo, 4 months treatment
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 27 Control N: 27 AGE: 56.3 SEX: 95% men INCLUSION: Type 2 DM with coronary artey disease, claudication EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 500 mg TID COMPARISON: placebo
Outcomes	Cholesterol, plasma fibrinogen.

Chakrabarti 1965 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Chalmers 2007

Methods	TRIAL DESIGN: Ongoing prospective observational cohort DURATION: 3 years
Participants	COUNTRY: United Kingdom SETTING: Outpatient Treatment N: 178 Control N: 0 AGE: 54.1 SEX: Not stated INCLUSION: Type 2 DM, 35-80 years, poor control EXCLUSIONS: None listed
Interventions	TREATMENT: Metformin, with glicazide, repaglinide or pioglitazone, varying doses
Outcomes	Deterioration of glycemic control
Notes	

Chan 1993

Methods	TRIAL DESIGN: Crossover randomised controlled trial DURATION: 4 weeks
Participants	COUNTRY: Hong Kong and United Kingdom SETTING: outpatient Treatment N: 24 Control N: 24 AGE: 48.5+/-2.4 SEX: 50% men INCLUSION: Type 2 DM EXCLUSIONS: renal insufficiency, hypertension
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: glybenclanide
Outcomes	Weight, body mass index (BMI), lipids, blood pressure, systemic vascular resistance index.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Charpentier 2001

Methods	TRIAL DESIGN: Prospective double-blind randomised controlled trial DURATION: 20 weeks
Participants	COUNTRY: France SETTING: outpatient Treatment N: 222 Control N: 150 Treatment AGE: 56.7 Control AGE: 55.4 Treatment SEX: 60% men Control SEX: 58% men INCLUSION: type 2 DM age 35-70, poorly controlled EXCLUSIONS: severe chronic disease, morbid obesity, major cardiovascular event
Interventions	TREATMENT: metformin with or without glimepiride COMPARISON: Glimepiride
Outcomes	Glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Chiasson 1994

Methods	TRIAL DESIGN: Randomised controlled trial of acarbose versus placebo. Metformin in non-randomised treatment strata. DURATION: 1 year
Participants	COUNTRY: Canada SETTING: multicenter Treatment N: 83 Control N: 271 Treatment AGE: 57.4+/-1.1 Control AGE: 57+/-1.1 Treatment SEX: 51% men Control SEX: 58% men INCLUSION: Type 2 DM EXCLUSIONS: gastrointestinal disease, various medications
Interventions	TREATMENT: Main: acarbose versus placebo Treatment strata: metformin (dosage adjusted clinically), diet, sulfonylurea, insulin
Outcomes	Postprandaial glucose, HbA1, lipds, c-peptide levels.
Notes	

Risk of bias

Chiasson 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Chiasson 2001

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 36 weeks
Participants	COUNTRY: Canada SETTING: multicenter Treatment N: 156 Control N: 162 Treatment AGE: 57.9+/-8.6 Control AGE: 57.3+/-9 Treatment SEX: 77% men Control SEX: 74% men INCLUSION: Type 2 DM EXCLUSIONS: cardiovascular events, gastrointestinal disease, history of lactic acidosis, major debilitating disease
Interventions	TREATMENT: Metformin, dosage adjusted clinically, or metformin + miglitol. COMPARISON: miglitol or placebo
Outcomes	Fasting and postprandial glucose, HbA1, insulin, weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cho 1992

Methods	TRIAL DESIGN: Open-label comparative trial; not randomised DURATION: 36 days
Participants	COUNTRY: Korea SETTING: University center Treatment N: 22 Control N: 27 AGE: unclear SEX: 47% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 0.5-1.5 g/day COMPARISON: insulin or sulfonylurea
Outcomes	Plasma t-PA and PAI-1 antigen

Cho 1992 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ciraldi 2002

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 14 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 11 Control N: 10 Treatment AGE: 30-70 years Control AGE: 30-70 years SEX: not stated INCLUSION: type 2 DM, poorly controlled EXCLUSIONS: patients listed as "healthy"
Interventions	TREATMENT: metformin 2550 mg daily COMPARISON: troglitazone 600 mg daily
Outcomes	Glucose transport, insulin signaling
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Civera 2008

Methods	TRIAL DESIGN: Open-label randomized controlled trial DURATION: 6 months
Participants	COUNTRY: Spain SETTING: Outpatient Treatment N: 24 Control N: 13 AGE: 40-70 SEX: Not stated INCLUSION: Type 2 DM, poor control EXCLUSIONS: Pregnancy, morbid obesity, renal or hepatic failure, pulmonary or cardiac disease
Interventions	TREATMENT: Metformin and repaglinide, with or without insulin COMPARISON: NPH insulin
Outcomes	Glycemic control

Civera 2008 *(Continued)*

Notes	

Clarke 1965

Methods	TRIAL DESIGN: Prospective cohort study DURATION: Average 21 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 108 Control N: 0 AGE: > 30 to < 60 SEX: 38% men INCLUSION: DM, treatment failures with sulfonyureas EXCLUSIONS: ketonuria, bicarbonate < 17 mEq/L, or serious organic disease
Interventions	TREATMENT: metformin, 1 g/day COMPARISON: none
Outcomes	Glycemica, glycosuria, and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Clarke 1968

Methods	TRIAL DESIGN: Crossover randomised controlled trial DURATION: 1 year
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 139 Control N: 139 Treatment AGE: 59 Control AGE: 57 SEX: not listed INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 1-3 g/day COMPARISON: chlorpropamide
Outcomes	Weight, blood glucose.
Notes	

Risk of bias

Clarke 1968 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Clarke 1977

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 1 year
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N:131 Control N: 146 Treatment AGE: 60 Control AGE: 60 Treatment SEX: 31% men Control SEX: 31% men INCLUSION: Newly diagnosed Type 2 DM EXCLUSIONS: malignancy, congestive heart failure, obesity, other hypoglycemic medications.
Interventions	TREATMENT: Metformin, 1-3 g/day COMPARISON: chlorpropamide
Outcomes	Blood glucose, weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Collier 1989

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Scotland SETTING: outpatient Treatment N: 12 Control N: 12 Treatment AGE: 53.3 Control AGE: 55.5 SEX: 50% men INCLUSION: Type 2 DM EXCLUSIONS: abnormal renal function, smokers, aspirin.
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: gliclazide
Outcomes	Platelet density profiles and aggregability studies.
Notes	

Collier 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Cosic 2001

Methods	TRIAL DESIGN: Prospective comparative trial DURATION: 8 weeks
Participants	COUNTRY: Yugoslavia SETTING: outpatient Treatment N: 23 Control N: 23 AGE: not stated SEX: not stated INCLUSION: type 2 DM EXCLSUIONS: not stated
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: placebo
Outcomes	Plasma xanthine oxidase, thiobarbituric acid-reactive substance, lactate and frutosamine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Cryer 2005

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 12 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 7227 Control N: 1505 Age: 58.5 +/- 13 Sex: 37% men Inclusion: type 2 DM suboptimally controlled on diet or sulfonylurea Exclusions: standard
Interventions	TREATMENT: metformin 2.6 g/day CONTROL: usual care
Outcomes	Serious adverse effects such as lactic acidosis
Notes	

Cryer 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Cusi 1996

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 15 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 10 Control N: 10. Treatment AGE: 51+/-3 Control AGE: 54+/-3 Treatment SEX: 40% men Control SEX: 60% men INCLUSION: Type 2 DM, with body weight stable EXCLUSION: sedentary or strenuous activities, renal disease, hepatic disease or other significant organ system disease
Interventions	TREATMENT: Metformin 500 mg BID to 2500 mg/day maximum + glibenclamide, dose on clinical grounds COMPARISON: glibenclamide + placebo
Outcomes	Glucose, HbA1, lipids, blood lactate.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

D'Argenzio 1996

Methods	TRIAL DESIGN: Open-label, nonrandomised comparative trial DURATION: 6 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 23 Control N: 57 AGE: 56 SEX: 40% men INCLUSION: Poorly controlled Type 2 DM EXCLUSIONS: cardiac, liver or renal disease, contraindication to oral hypoglycemic medications
Interventions	TREATMENT: Metformin, dosage adjusted clinically + glibenclamide COMPARISON: glibenclamide or diet

D'Argenzio 1996 *(Continued)*

Outcomes	Basal glucose, HbA1, renal and liver functions, lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Damsbo 1998

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Sweden SETTING: outpatient Treatment N: 9 Control N: 9 Treatment AGE: 51 Control AGE: 53 Treatment SEX: 78% men Control SEX: 66% men INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: abnormal renal, liver fucntion, or cardiac function
Interventions	TREATMENT: Metformin 1-3 g/day COMPARISON: placebo
Outcomes	Insulin sensitivity, plasma glucose, insulin, c-peptide, free fatty acids, lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Davidson 2000

Methods	TRIAL DESIGN: Abstract; randomised controlled trial, placebo-controlled; unclear if single-blind
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 484 Control N: 161 AGE: not listed SEX: not listed INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage adjusted clinically, versus metformin + glyburide

Davidson 2000 *(Continued)*

	COMPARISON: glyburide or placebo
Outcomes	HbA1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Davies 2007

Methods	TRIAL DESIGN: Prospective observational cohort of metformin, in an open-label randomized controlled trial DURATION: 4 months
Participants	COUNTRY: United Kingdom SETTING: Outpatient Treatment N: 82 Control N: 0 AGE: 57.4 SEX: 44% men INCLUSION: Type 2 DM, 20 - 80 years EXCLUSIONS: Recent heart attack or stroke, renal insufficiency, morbid obesity
Interventions	TREATMENT: Metformin and insulin, with and without regalinide
Outcomes	Glycemic control, hypoglycemia, weight
Notes	

De Silva 1979

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 2 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 21 Control N: 20 AGE: 55 SEX: 32% men INCLUSION: Type 2 DM EXCLUSIONS: renal or liver abnormalities
Interventions	TREATMENT: Metformin 1.5 g/day + placebo COMPARISON: clofibrate + placebo
Outcomes	Fasting glucose, urinary glucose, lipids and fibrinogen.
Notes	

De Silva 1979 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

DeFronzo 1991

Methods	TRIAL DESIGN: Open-label cross-over trial DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 14 Control N: 14 AGE: 60+/-3 SEX: 71% men INCLUSION: Obese and lean type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 1-2.5 g/day COMPARISON: no metformin
Outcomes	Insulin sensitivity, glucose tolerance test, continuous indirect calorimetry, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

DeFronzo 1995

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 29 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 566 Control N: 355 Treatment AGE: 53+/-1 Control AGE: 55+/-1 Treatment SEX: 43% men Control SEX: 49% men INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: creatinine > 1.4, abnormal liver functions, cardiovascular disease
Interventions	TREATMENT: Metformin 850 mg TID or metformin + glyburide COMPARISON: glyburide or placebo
Outcomes	HbA1c, fasting and postprandial glucose

DeFronzo 1995 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Derosa 2003

Methods	TRIAL DESIGN: Open-label randomised trial DURATION: 12 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 56 Control N: 56 Age: 54 +/- 9 Sex: 50% men Inclusion: type 2 DM Exclusion: hypertension, heart disease, abnormal renal function, or drugs that interact with treatment
Interventions	TREATMENT: metformin 2.5 g/day COMPARISON: repaglinide 4 mg/day
Outcomes	Fasting plasma insulin, postprandial plasma insulin, lipid profile, homocysteine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Derosa 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of metformin plus rosiglitazone or glimepiride DURATION: 1 year
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 99 Control N: 0 AGE: 53 SEX: 50% men INCLUSION: type 2 DM with metabolic syndrome EXCLUSIONS: renal, hepatic cardiovascular and cerebrovacular disease
Interventions	TREATMENT: metformin, 1.5 mg daily plus rosiglitazone or glimepitride COMPARISON: none

Derosa 2005 *(Continued)*

Outcomes	Body mass index, glucose, lipids, homocysteine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Derosa 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of metformin plus pioglitazone or rosiglitazone DURATION: 1 year
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 96 Control N: 0 INCLUSION: type 2 DM with metabolic syndrome and poor glycemic control EXCLUSIONS: renal or cardiovascular disease
Interventions	TREATMENT : metformin up to 3 gm daily plus pioglitazone or rosiglitazone
Outcomes	Body mass index, glycemic control, insulin sensitivity, lipids, homocysteine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Derosa 2007

Methods	TRIAL DESIGN: Prospective observational cohort in an open-lable randomized controlled trial DURATION: 12 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 238 Control N: 0 AGE: 55 SEX: 50% men INCLUSION: Type 2 DM, poor control, overweight EXCLUSIONS: history of ketoacidosis, liver or kidney abnormalities, congestive heart failure, coronary artery disease
Interventions	TREATMENT: Metformin, with nateglinide or glibencalime
Outcomes	Prothrombotic factors

Derosa 2007 *(Continued)*

Notes	

Derosa 2008

Methods	TRIAL DESIGN: Prospective observational cohort in a single-blind randomized controlled trial DURATION: 6 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 117 Control N: 0 AGE: 56 SEX: 47% men INCLUSION: Type 2 DM, tolerant or intolerant of metformin EXCLUSIONS: ketoacidosis, liver or kidney abnormalities
Interventions	TREATMENT: Metformin, with or without rosiglitazone
Outcomes	Insulin resistance, glycemic control
Notes	

Derosa 2009a

Methods	TRIAL DESIGN: Double-blind randomized controlled trial DURATION: 15 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 202 Control N: 69 AGE: Not stated SEX: 49% men INCLUSION: Type 2 DM, overweight EXCLUSIONS: ketoacidosis, liver or kidney abnormalities
Interventions	TREATMENT: metformin, 2 gm/day alone or with piioglitazone or glimeperide COMPARISON: Pioglitazone, 15 mg/day
Outcomes	
Notes	

Dies 1978

Methods	TRIAL DESIGN: Prospective cohort study DURATION: at least 5 years
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 25

Dies 1978 *(Continued)*

	Control N: 0 AGE: 56 SEX: 35% men INCLUSION: adult-onset DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 560 mg/day + chlorpropamide 175 mg/day COMPARISON: none
Outcomes	Fasting and postprandial glucose, glycosuria, and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Donnelly 1960

Methods	TRIAL DESIGN: Prospective cohort study DURATIONS: average 6 months
Participants	COUNTRY: Ireland SETTING: outpatient Treatment N: 25 Control N: 0 AGE: 21-77 Sex: 22% men INCLUSION: type 2 DM EXCLUSION: ketonuria or infection
Interventions	TREATMENT: metformin, dosage adjusted clinically COMPARISON: none
Outcomes	Glycosuria
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Dornan 1991

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 8 months
Participants	COUNTRY: United Kingdom SETTING: university clinic Treatment N: 30

Dornan 1991 *(Continued)*

	Control N: 30 Treatment AGE: 55+/-1 Control AGE: 55+/-1 Treatment SEX: 53% men Control SEX: 30% men INCLUSION: Diet-treated Type 2 DM EXCLUSIONS: ketonuria, renal or liver dysfunction, congestive heart failure
Interventions	TREATMENT: Metformin 500 mg QD-TID COMPARISON: placebo
Outcomes	Glucose, BMI, c-peptide, blood pressure, lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Douek 2005

Methods	TRIAL DESIGN: Prospective randomised placebo-controlled trial DURATION: 1 year
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 92 Control N: 91 Treatment AGE: 58 Control AGE: 58 Treatment SEX: 67% men Control SEX: 63% men INCLUSION: type 2 DM on maximal oral agents EXLCUSIONS: chronic renal insufficiency, hepatic diseaes, pulmonary disease, age > 75
Interventions	TREATMENT: metformin 2 gm daily COMPARISON: placebo
Outcomes	Glycemic control, weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Eguchi 2007

Methods	TRIAL DESIGN: Prospective randomised cross-over trial DURATION: 12 weeks

Eguchi 2007 *(Continued)*

Participants	COUNTRY: Japan SETTING: outpatient Treatment N: 12 Control N: 13 Treatment AGE: 61 Control AGE: 61 Treatment SEX: 83% men Control SEX: 54% men INCLUSION: early DM with impaired glucose tolerance EXCLUSIONS: chronic renal insufficiency, hepatic disease, congestive heart failure, stroke
Interventions	TREATMENT: metformin 500-750 mg dailu COMPARISON: pioglitazone 15 mg daily
Outcomes	Insulin resistance, lipids, hemostatic factors, inflammatory markers
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Einhorn 2000

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trail of metformin plus pioglitazone DURATION: 16 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 328 Control N: 0 AGE: 56 SEX: 57% men INCLUSION: type 2 DM EXCLUSIONS: renal, hepatic or cardiovascular disease
Interventions	TREATMENT: metformin, dosage unclear, with or without pioglitazone
Outcomes	Glycemic control, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Elkeles 1991

Methods	TRIAL DESIGN: 1) Open-label cross-over randomised controlled trial 2) Single-blind crossover trial DURATION: 3 months, then 6 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 63 Control N: 49 AGE: < 70 years SEX: 64% men INCLUSION: Type 2 DM EXCLUSIONS: renal or liver disease
Interventions	TREATMENT: 1) Metformin, dosage adjusted clinically 2) Metformin COMPARISONS: 1) glibenclamide 2) placebo
Outcomes	Serum lipids, lipoproteins, glucose, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Erdem 2008

Methods	TRIAL DESIGN: Open-label randomized controlled trial DURATION: 3 months
Participants	COUNTRY: Turkey SETTING: Outpatient Treatment N: 44 Control N: 15 AGE: 55 SEX: 39% men INCLUSION: Type 2 DM EXCLUSIONS: obesity, liver or renal abnormalities, chronic disease
Interventions	TREATMENT: metformin, 2 gm/day COMPARISON: pioglitazone, 15 mg/day
Outcomes	Plasma visfatin levels
Notes	

Eriksson 2006

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 4 weeks
Participants	COUNTRY: Sweden SETTING: outpatient

Eriksson 2006 *(Continued)*

	Treatment N: 18 Contyrol N: 5 AGE: 64 SEX: not stated INCLUSION: type 2 DM EXCLUSIONS: age > 75
Interventions	TREATMENT: metformin, doseage unclear COMPARISON: placebo
Outcomes	Glucose tolerance, lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Eriksson 2007

Methods	TRIAL DESIGN: Single-blind randomized controlled trial DURATION: 1 month
Participants	COUNTRY: Sweden SETTING: Outpatient Treatment N: 16 Control N: 5 AGE: 64 SEX: 78% men INCLUSION: Type 2 DM, 46-74 years EXCLUSIONS: obesity
Interventions	TREATMENT: metformin, 2 gm/day COMPARISON: placebo
Outcomes	Glucose tolerance tests, plasminogen-activator inhibitor, leptin levels
Notes	

Erle 1999

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION:
Participants	COUNTRY: SETTING: Treatment N: Control N: AGE: SEX: INCLUSION: Type 2 DM EXCLUSIONS:

Erle 1999 *(Continued)*

Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glyburide COMPARISON: placebo + glyburide
Outcomes	Glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ersoy 2008

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 3 months
Participants	COUNTRY: Turkey SETTING: Outpatient Treatment N: 24 Control N: 0 AGE: 20-65 years SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: type 1 diabetes, kidney or liver disease, pregnancy
Interventions	TREATMENT: metformin, varying dose
Outcomes	weight, glycemic control
Notes	

Esposito 2008

Methods	TRIAL DESIGN: Prospective observational cohort in an open-label randomized controlled trial DURATION: 9 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 116 Control N: 0 AGE: 30-70 years SEX: notstated INCLUSION: Type 2 DM, on stable dose metformin and sulfonylurea EXCLUSIONS: uncontrolled hypertension, liver or kidney abnormalities
Interventions	TREATMENT: metformin, varying dose, with NPH or glargine insulin
Outcomes	Glycemic control
Notes	

Fanghanel 1996

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 30 Control N: 30 Treatment AGE: 52.1+/- 8.8 Control AGE: 51.2+/-8.5 Treatment SEX: 40% men Control SEX: 30% men INCLUSION: Type 2 DM, obese EXCLUSIONS: abnormal liver functions, cardiomyopathy, lung disease
Interventions	TREATMENT: Metformin 850 mg BID-TID COMPARISON: insulin BID
Outcomes	Lipids, HbA1, blood pressure, BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Fanghanel 1998

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 12 weeks
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 30 Control N: 30 AGE: 49+/-9.6 SEX: 38% men INCLUSION: Type 2 DM with sulfonylurea failure EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 0.85-2.5 g/day COMPARISON: insulin
Outcomes	Plasma glucose, fibrinogen, body mass index.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Feinglos 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of glipazide DURATION: 16 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 122 Control N: 0 AGE: 58.1 SEX: 43% men INCLUSION: type 2 DM inadequately controlled on metformin EXCLUSIONS: renal, hepatic, cardiovascular or gastrointestinal dysfunction
Interventions	TREATMENT: metformin, doase unclear with or without glipazide
Outcomes	Glucose, HbA1c, insulin, weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ferner 1988

Methods	TRIAL DESIGN: Open-label nonrandomised comparative trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 6 Control N: 12 Treatment AGE: 56 Control AGE: 56 Treatment SEX: 67% men Control SEX: 50% men INCLUSION: Type 2 DM EXCLUSIONS: other medication, ketosis, ketonuria
Interventions	TREATMENT: Metformin, dose adjusted clilnically COMPARISON: tolbutamide or diet
Outcomes	Insulin sensitivity under euglycemic insulin clamp
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Fisman 2001

Methods	TRIAL DESIGN: Open-label nonrandomised comparative trial DURATION: 7.7 years
Participants	COUNTRY: Israel SETTING: research institute Treatment N: 332 Control N: 1943 Treatment AGE: 60.1+/-6.5 Control AGE: 59.9+/-6.6 Treatment SEX: 66% men Control SEX: 76% men INCLUSION: Type 2 DM with coronary artery disease EXCLUSIONS: pacemaker, cerebrovascular disease, malignant disease, estrogen replacement, and insulin treatment
Interventions	TREATMENT: Metformin or metformin + sulfonylurea, dose adjusted clinically COMPARISON: sulfonylurea or diet
Outcomes	Crude mortality rate, time-related mortality, and cause of death
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Fonseca 2000

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised controlled trial of rosiglitazone DURATION: 6.5 months
Participants	COUNTRY: United States SETTING: mulitcenter outpatient Treatment N: 348 Control N: 0 AGE: 58+/-9 SEX: 68% men INCLUSION: type 2 DM EXCLUSIONS: renal or hepatic disease, angina, congestive heart failure, abnormal laboratory result, or chronic use of insulin
Interventions	TREATMENT: metformin 2.5 g/day + placebo, metformin + rosiglitazone 4 mg/day, or metformin + rosiglitazone 8 mg/day.
Outcomes	HbA1c, fasting glucose, insulin sensitivity, weight, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Fonseca 2000 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Formoso 2008

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 13 Control N: 13 AGE: 58 SEX: 50% men INCLUSION: Type 2 DM, newly diagnosed EXCLUSIONS: hypertension, abnormal function of an organ system
Interventions	TREATMENT: metformin, varying dose COMPARISON: glicazide, varying dose
Outcomes	in vivo oxidative stress, platelet activation
Notes	

Fritsche 2000

Methods	TRIAL DESIGN: Double-blind cross-over randomised controlled trial DURATION: 10 weeks
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 26 Control N: 26 AGE: 51+/-9 SEX: not listed INCLUSION: Severely obese type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + insulin COMPARISON: placebo + insulin
Outcomes	Glucose, insulin, c-peptide, HbA1c, lipids, weight, venous lactic acid.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Fujioka 2005

Methods	TRIAL DESIGN: 2 double-blind randomised controlled trials DURATION: 3 months and 4 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 663 Control N: 202 Age: 56 +/- 10 Sex: 50% men Inclusion: type 2 DM inadequately controlled on diet and exercise Exclusions: standard
Interventions	TREATMENT: metformin XR 500 -2000 mg/day COMPARISON: placebo
Outcomes	HbA1c, fasting glucose and insulin, lipid profiles
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Galeone 1998

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: Italy SETTING: diabetes referral center Treatment N: 57 Control N: 0 AGE: 61+/-3.4 SEX: 54% men INCLUSION: type 2 DM for at least 5 years EXCLUSIONS: hepatic or liver abnormalities, neurological, psychological or cardiac disease
Interventions	TREATMENT: metformin 1500 mg/day and glicazide 120mg/day COMPARISON: none
Outcomes	HbA1c, 24-hour glycosuria, and fasting and postprandial glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Gao 2008

Methods	TRIAL DESIGN: Prospective observational cohort of metformin in a randomised controlled trial DURATION: 3 months
Participants	COUNTRY: China SETTING: Outpatient Treatment N: 150 Control N: 0 AGE: 54.6 SEX: 50% men INCLUSION: Type 2 DM, 30-70 years EXCLUSIONS: kidney or liver abnormalties
Interventions	TREATMENT: metformin, varying dose, extended-release or immediate release
Outcomes	Glycemic control
Notes	

Gao 2009

Methods	TRIAL DESIGN: Propsective observational cohort of metformin in a double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: China, India, Korea and Taiwan SETTING: Outpatient Treatment N: 466 Control N: 0 AGE: 54.5 SEX: 45% men INCLUSION: Type 2 DM, poor control EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, and sulfonylureas, with exanatide or placebo
Outcomes	Glycemic control
Notes	

Garber 1997

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 11 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 222 Control N: 229 Treatment AGE: 57+/-10 Control AGE: 55+/-11 Treatment SEX: 62% men Control SEX: 56% men INCLUSION: Type 2 DM, not controlled EXCLUSIONS: significant disease or contraindication likely to affect diabetes

Garber 1997 *(Continued)*

Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: placebo
Outcomes	Fasting glucose and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Garber 2002

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 2 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 317 Control N; 321 Age: 56 +/- 10 Sex: 53% men Inclusion: type 2 DM that failed diet and exercise Exclusions: polyurea, weight loss, acidosis, insulin treatment
Interventions	TREATMENT: metformin 500 mg BID with and without glyburide CONTROL: gluburide 2.5 mg BID or placebo
Outcomes	HbA1, fasting and postprandial glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Garber 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of rosiglitazone DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 318 Control N: 0 AGE: 56 SEX: 61% men INCLUSION: type 2 DM inadequately controlled on metformin EXCLUSIONS: renal, cardiac or hepatic dysfunction

Garber 2006 *(Continued)*

Interventions	TREATMENT: metformin, dosage unclear with rosliglitazone or glibenclamide COMPARISON: none
Outcomes	Glucose, HbAic, hypoglycemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Garcia 1971

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2 years
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 23 Control N: 0 AGE: 53.6 SEX: 26% men INCLUSION: DM, treated with sulfonylureas EXCLUSIONS: none listed
Interventions	TREATMENT: metformin + chlorpropamide in combination, dosage titrated clinically COMPARISON: none
Outcomes	Fasting and postprandial glucose, glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Garcia-Soria 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 1 month
Participants	COUNTRY: United States, Mexico and Australia SETTING: Outpatient Treatment N: 174 Control N: 0 AGE: 52 SEX: 72% men INCLUSION: Type 2 DM EXCLUSIONS: type 1 diabetes, insulin-dependent type 2 diabetes

Garcia-Soria 2008 *(Continued)*

Interventions	TREATMENT: metformin with PHX1149 or placebo
Outcomes	Glycemic control
Notes	

Gerich 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of sibutramine DURATION: 6 months
Participants	COUNTRY: Turkey SETTING: outpatient Treatment N: 60 Control N: 0 AGE: 49.3 SEX: 0% men INCLUSION: obese women with type 2 DM and poor glycemic control EXCLUSIONS: hypertension, glaucoma, antidepressant medications
Interventions	TREATMENT: metformin, doase unclear, with or without sibutramine
Outcomes	Weight, glucose, insulin, waist circumference, blood presure, lipids
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Giugliano 1993

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 27 Control N: AGE: not listed Sex: 23% men INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: intercurrent illness, age > 70, creatinine > 1.2 mg/dl, ischemic or wasting disease
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: placebo
Outcomes	HbA1, lipids, c-peptide, blood pressure, and BMI.
Notes	

Giugliano 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gokcel 2001

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of nateglinide or glyburide DURATION: 2 years
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 428 Control N: 0 AGE: 53.1 SEX: 50% men INCLUSION: type 2 DM, drug naive EXCLUSIONS: renal or hepatic disiease or congestive heart failure
Interventions	TREATMENT: metformin, dosage unclear, with nateglinide or glyburide COMPARISON: none
Outcomes	Glucose, HbA1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Goke 2008

Methods	TRIAL DESIGN: Double-blind randomised controlled trial, extension of a previous study DURATION: 1 year
Participants	COUNTRY: Multinational, in Americas and Europe SETTING: Multicenter outpatient Treatment N: 158 Control N: 304 AGE: 54 SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, 2 gm/day COMPARIOSON: vildagliptin 100 mg/day
Outcomes	Glycemic control, weight, safety
Notes	

Goldstein 2003

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4.5 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 163 Control N: 84 Inclusions: type 2 DM inadequately controlled on sulfonylurea Exclusions: renal and hepatic dysfunction, cardiovascular diseaese, acidosis or long-term insulin treatment
Interventions	TREATMENT: metformin 2 g/day with or without glipizide CONTROL: glipizide 30 mg/day
Outcomes	BMI, HbA1, fasting glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Goldstein 2007

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Mutinational SETTING: Muticenter, outpatient Treatment N: 1091 Control N: 340 AGE: 18-78 years SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: unstable cardiac disease
Interventions	TREATMENT: metformin varying dosease, with or without sitagliptin COMPARISON: Sitaglitpin 500 mg/day or placebo
Outcomes	Glycemic control
Notes	

Gonzalez-Ortiz 2004

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Mexico SETTING: outpatient Treatment N: 67

Gonzalez-Ortiz 2004 *(Continued)*

	Control N: 37 Age: 53 +/- 7 Sex: 52% men Inclusion: type 2 DM with secondary failure to monotherapy with glibenclamide Exlcusions: cardiovascular, renal or hepatic dysfunction, insulin treatment, pregnancy
Interventions	TREATMENT: metformin 1-2 gm/day with or without glimepiride 2-4 mg/day COMPARISON: Glimipiride 2-4 mg/day
Outcomes	HbA1c, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Goodman 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Mutinational in United States and Europe SETTING: Muticenter, outpatient Treatment N: 618 Control N: 0 AGE: 54.5 SEX: 57% men INCLUSION: Type 2 DM, 18-78 years EXCLUSIONS: liver disease, significant kidney dysfunction
Interventions	TREATMENT: metformin, varying doses, with vildagliptin 100 md/day or placebo
Outcomes	Glycemic control, safety
Notes	

Gottlieb 1962

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 6 months
Participants	COUNTRY: United Kingdom SETTING: inpatient then outpatient Treatment N: 39 Control N: 0 AGE: 21 - >80 SEX: 58% men INCLUSION: patients with DM, poorly controlled on previous regimen EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 1-3 g/day COMPARISON: none

Gottlieb 1962 *(Continued)*

Outcomes	Weight, and glycemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Gottschalk 2007

Methods	TRIAL DESIGN: Prospective single-blind randomised cotnrolled trial DURATION: 6 monghs
Participants	COUNTRY: Multi-national SETTING: multi-center outpatient Treatment N: 131 Control N: 132 Treatment AGE: 13.8 Control AGE: 13.8 Treatment SEX: 34% men Control SEX: 33% men INCLUSION: adolescents with DM, poorly controlled EXCLUSION: history of ketoacidosis, medications that affect glucose metabolism, renal or hepatic disease
Interventions	TREATMENT: metformin 500-1000 mg BID COMPARISON: glimepiride 1-8 mg daily
Outcomes	Glycemic control, lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Grant 1991

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 weeks
Participants	COUNTRY: United Kingdom SETTING: Treatment N: 21 Control N: 17 Treatment AGE: 59.5+/-9 Control AGE: 63.2+/-9.6 SEX: not listed INCLUSION: Type 2 DM

Grant 1991 *(Continued)*

	EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, low and high dose COMPARISON: placebo
Outcomes	Plasminogen activator inhibitor, BMI, glucose, HbA1, insulin, lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Grant 1996

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 52 Control N: 23 AGE: not listed SEX: not listed INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: insulin therapy, BMI < 25, fasting glucose < 6 mmol/L
Interventions	TREATMENT: Metformin 3 g/day COMPARISON: placebo
Outcomes	Lipids, HbA1, insulin, BMI, plasminogen activator inhibitor.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Grant 1998

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 27 Control N: 17 AGE: not listed SEX: not listed INCLUSION: Type 2 DM

Grant 1998 *(Continued)*

	EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 1.5 g/day or metformin 3 g/day COMPARISON: placebo
Outcomes	Plasma insulin, glucose, lipids, and factor VII levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gregorio 1989

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 5 weeks
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 53 Control N: 53 AGE: not listed SEX: not listed INCLUSION: Type 2 DM, poor control EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + sulfonylurea COMPARISON: placebo + sulfonylurea
Outcomes	Weight, lipids, insulin, HbA1, and lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gregorio 1990

Methods	TRIAL DESIGN: Single-blind comparative trial. Patients were their own controls DURATION: 5 weeks
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 20 Control N: 10 AGE: 50-63 Treatment SEX: 45% men Control SEX: 40% men

Gregorio 1990 *(Continued)*

	INCLUSION: Type 2 DM with poor control EXCLUSIONS: heptic, renal or vascular disease
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + sulfonylurea COMPARISON: placebo + sulfonylurea
Outcomes	Glucose, insulin, c-peptide, fructosamine, lipids, lactate, pyruvate, alanine, and glycerol.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Gregorio 1997

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 6 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 68 Control N: 0 AGE: 67+/-1.2 SEX: 43% men INCLUSION: type 2 DM EXCLUSIONS: liver or renal abnormality, respiratory insufficiency or congestive heart failure
Interventions	TREATMENT: metformin 2350 mg/day COMPARISON: none
Outcomes	Lactate, free fatty acids, lipids, insulin, c-peptide, plasma metformin, and glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Groop 1989

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Finland SETTING: outpatient Treatment N: 12 Control N: 12 AGE: not listed SEX: not listed

Groop 1989 *(Continued)*

	INCLUSION: Type 2 DM EXCLUSIONS: cardiac, renal, hepatic or endocrine disease, intercurrent illness
Interventions	TREATMENT: Metformin 500 mg TID + glibenclamide COMPARISON: insulin
Outcomes	Glucose, lipids, weight, BMI, basal hepatic glucose production
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Groop 1991

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Finland SETTING: outpatient Treatment N: 12 Control N: 24 Treatment AGE: 60+/-2 Control AGE: 59+/-2 Treatment SEX: 50% men Control SEX: 50% men INCLUSION: Type 2 DM with sulfonylurea failure EXCLUSIONS: intercurrent illness, hepatic, renal or cardiac disease
Interventions	TREATMENT: Metformin 1.5 g/day + glibenclamide. COMPARISON: insulin
Outcomes	Blood glucose, HbA1, lipids, energy expenditure, glucose and fat oxidation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Guillausseau 1997

Methods	TRIAL DESIGN: Open-label, nonrandomised comparative trial DURATION: at least 3 months
Participants	COUNTRY: France SETTING: outpatient Treatment N: 26 Control N: 36

Guillausseau 1997 *(Continued)*

	Treatment AGE: 60+/-10 Control AGE: 60+/-12.9 Treatment SEX: 73% men Control SEX: 63% men INCLUSION: Type 2 DM on sulfonylurea EXCLUSIONS: none listed
Interventions	TREATMENT: Metfomin, dosage adjusted clinically + gliclazide COMPARISON: gliclazide
Outcomes	Fasting and postprandial glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Gupta 2009

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 17 Control N: 34 AGE: 35-75 years SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, varying dose, plus weight loss COMPARISON: pioglitazone plus weight loss
Outcomes	Weight, components of metabolic syndrome
Notes	

Gursoy 2000

Methods	TRIAL DESIGN: Abstract of a prospective cohort study DURATION: 3 months
Participants	COUNTRY: Turkey SETTING: outpatient Treatment N: 20 Control N: 0 AGE: 49+/-8 SEX: 80% men INCLUSION: obese and nonobese patients with type 2 DM EXCLUSIONS: none listed

Gursoy 2000 *(Continued)*

Interventions	TREATMENT: Metformin 2.5 g/day COMPARISON: none
Outcomes	Insulin sensitivity, lipid profiles, lactate, and BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hamann 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 596 Control N: 0 AGE: not stated SEX: not stated INCLUSION: Type 2 DM, overweight, inadequately treated with metformin EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, 2 gm/day, with rosiglitazone or sulfonylurea
Outcomes	Gycemic control
Notes	

Haupt 1991

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: Germany SETTING: multicenter outpatient Treatment N: 1823 Control N: 0 AGE: 64.8 SEX: 39% men INCLUSION: type 2 DM, poorly controlled EXCLUSIONS: nephropathy, previous treatment with metformin, and insulin-dependence
Interventions	TREATMENT: metformin 850-2550 mg/day + sulfonylurea, dosage titrated clinically COMPARISON: none
Outcomes	Postprandial glucose, HbA1, weight, blood pressure, and lipids.
Notes	

Haupt 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Heine 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised of exenatide or insulin DURATION: 6 months
Participants	COUNTRY: Multi-national SETTING: outpatient Treatment N: 551 Control N: 0 AGE: 59 SEX: 55% men INCLUSION: type 2 DM inadequately controlled EXCLUSIONS: renal or hepatic disease, malignancy
Interventions	TREATMENT: metformin, dosage unclear, with exenatide or insulin COMPARISON: none
Outcomes	Glucose, HbA1, safety, tolerability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Herman 1961

Methods	TRIAL DESIGN: Prospective cohort study DURATION: approximately 1 month
Participants	COUNTRY: South Africa SETTING: outpatient Treatment N: 47 Control N: 0 AGE: not listed SEX: not listed INCLUSION: maturity-onset DM, juvenile-onset patients were studied but not analysed EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 1.5-3 g/day COMPARISON: none
Outcomes	Fasting glucose and glucose tolerance.
Notes	

Herman 1961 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hermann 1991a

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Sweden SETTING: outpatient Treatment N: 122 Control N: 45 AGE: 60 SEX: 64% men INCLUSION: Type 2 DM EXCLUSIONS: cardiac, renal or hepatic disease, alcohol abuse, severe chronic disease
Interventions	TREATMENT: Metformin 1 g BID or metformin + glibenclamide COMPARISON: glibenclamide
Outcomes	Fasting glucose, HbA1, weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hermann 1991b

Methods	TRIAL DESIGN: Open-label crossover randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Sweden SETTING: outpatient Treatment N: 22 Control N: 22 AGE: 59 SEX: 72% men INCLUSION: Type 2 DM EXCLUSIONS: renal or liver dysfunction
Interventions	TREATMENT: Metformin 0.5-3 g/day COMPARISON: glibenclamide
Outcomes	Fasting glucose, lipds, c-peptide, HbA1.
Notes	

Hermann 1991b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hermann 1994a

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 3 months.
Participants	COUNTRY: Sweden SETTING: regional health centers Treatment N: 110 Control N: 34 AGE: 34-74 SEX: 64% men INCLUSION: Type 2 DM EXCLUSIONS: contraindications to the medications, or insulin requirements
Interventions	TREATMENT: Metformin or metformin, dosage adjusted clinically, + glibenclamide COMPARISON: glibenclamide
Outcomes	Fasting glucose, body weight, and c-peptide levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hermann 1994b

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Sweden SETTING: regional health centers Treatment N: 108 Control N: 36 AGE: 60 SEX: 63% men INCLUSION: Type 2 DM EXCLUSIONS: insulin treatment, contraindications to the medications
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: glibenclamide
Outcomes	Fasting glucose, c-peptide levels, HbA1, blood pressure.
Notes	

Hermann 1994b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Higginbotham 1979

Methods	TRIAL DESIGN: Double-blind cross-over randomised controlled trial DURATION: 2 months
Participants	COUNTRY: Australia SETTING: outpatient Treatment N: 17 Control N: 17 AGE: 31-79 SEX: 29% men INCLUSION: Type 2 DM EXCLUSIONS: renal or liver insufficiency, retinopathy
Interventions	TREATMENT: Metformin, dosage unclear COMPARISON: glibenclamide
Outcomes	Fasting and postprandial glucose, weight, insulin and lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hirsch 1999

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 5 months
Participants	COUNTRY: United States SETTING: research center Treatment N: 25 Control N: 25 AGE: not listed SEX: not listed INCLUSION: Type 2 DM with poor control on insulin EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 2.5 g/day COMPARISON: placebo
Outcomes	Weight, HbA1, insulin, c-peptide, or insulin dose.
Notes	

Hirsch 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hoffmann 1997

Methods	TRIAL DESIGN: randomised controlled trial. Single blind with respect to metformin treatment DURATION: 6 months
Participants	COUNTRY: SETTING: multicenter Treatment N: 31 Control N: 63 Treatment AGE: 55.9 Control AGE: 59.2 Treatment SEX: 45% men Control SEX: 28.5% men INCLUSION: Type 2 DM, previously on diet EXCLUSIONS: renal, liver or cardiovascular disease, malignancy, pregnancy, infection
Interventions	TREATMENT: Metformin 850 mg BID COMPARISON: acarbose or placebo.
Outcomes	Fasting and postprandial glucose, insulin, lipids, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hollenbeck 1991

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: United States SETTING: Veteran's Administration outpatient Treatment N: 9 Control N: 0 AGE: 63+/-3 SEX: 89% men INCLUSION: Type 2 DM, with elevated triglycerides EXCLUSIONS: significant diseases or medication that could interfere with carbohydrate metabolism
Interventions	TREATMENT: Metformin 2.5 g/day COMPARISON: none
Outcomes	HbA1c, plasma insulin, free fatty acids, triglyceride, and lipids.

Hollenbeck 1991 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Holman 1987

Methods	TRIAL DESIGN: crossover randomised controlled trial DURATION: 2 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 18 Control N: 45 AGE: 57+/-11 SEX: 33% men INCLUSION: Type 2 DM EXCLUSIONS: cardiovascular disease
Interventions	TREATMENT: Metformin, dosage adjusted clinically, or metformin + sulfonylurea COMPARISON: sulfonylurea or sulfonylurea + insulin versus insulin
Outcomes	Fasting glucose, c-peptide, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Home 2007

Methods	TRIAL DESIGN: Prospective double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: 5 European countries SETTING: outpatient Treatment N: 162 Control N: 160 Treatment AGE: 57.2 Control AGE: 56.9 Treatment SEX: 52% men Control SEX: 85% men INCLUSION: type 2 DM poorly controlled EXCLUSIONS: history of acidosis, congestive heart failure, coronary artery disease, hypertension
Interventions	TREATMENT: metformin plus insulin plus rosiglitazone COMPARISON: placebo plus insulin

Home 2007 *(Continued)*

Outcomes	Glycemic control, treatment satisfaction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Horton 2000

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 350 Control N: 351 AGE: 56-59 Treatment SEX: 58% men Control SEX: 61% men INCLUSION: Type 2 DM EXCLUSIONS: renal impairment, significant diabetic complications
Interventions	TREATMENT: Metformin 500 mg TID or metformin + nateglininde COMPARISON: nateglinide or placebo
Outcomes	Fasting glucose, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Horton 2004

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 193 Control N: 297 Age: 57 +/- 1.1 Sex: 60% men Inclusion: type 2 DM, treatment naive Exclusions: renal dysfunction, diabetic complications
Interventions	TREATMENT: metformin 500 mg TID with and without nateglinide COMPARISON: nateglinide 120 mg before meals

Horton 2004 *(Continued)*

Outcomes	HbA1, fasting and postprandial glucose, post-load insulin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hother-Nielsen 1989

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 4 weeks
Participants	COUNTRY: Denmark SETTTING: outpatient Treatment N: 9 Control N: 9 AGE: not listed SEX: not listed INCLUSION: Obese patients with Type 2 DM EXCLUSIONS: renal or liver dysfunction
Interventions	TREATMENT: Metformin 500 mg TID COMPARISON: placebo
Outcomes	Insulin requirements, glucose, insulin, lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hsieh 2007

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of slow-release or regular-release metformin DURATION: 12 weeks
Participants	COUNTRY: Taiwan SETTING: outpatient Treatment N: 55 Control N: 0 AGE: 57.8 SEX: 50% men INCLUSION: type 2 DM EXCLUSIONS: renal, hepatic, cardiovascular disease or chronic obstructive lung disease
Interventions	TREATMENT: Metformin, slow-release or regular-release 2g daily

Hsieh 2007 *(Continued)*

	COMPARISON: none
Outcomes	Glucose, HbA1, c-reactive protein, insulin resistance, adipocytokines
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hsu 2007

Methods	TRIAL DESIGN: Prospective cohort study of metformin and gliclazide in a randomised trial of Agaricus blazei Murill extract DURATION: 12 weeks
Participants	COUNTRY: Taiwan SETTING: outpatient Treatment N: 60 Control N: 0 AGE: 56.8 SEX: 50% men INCLUSION: type 2 DM EXCLUSIONS: hepatic dysfunction, creatinine > 2, acute myocardial infarction
Interventions	TREATMENT: metformin, dosage unclear, with gliclazine, with or without Agaricus blazei Murill extract COMPARISON: none
Outcomes	Insulin resistance, adiponectin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hu 2008

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 2 months
Participants	COUNTRY: China SETTING: Outpatient Treatment N: 30 Control N: 30 AGE: not stated SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: none listed

Hu 2008 *(Continued)*

Interventions	TREATMENT: metformin plus insulin COMPARISON: insulin plus rosiglitazone
Outcomes	N-terminal pro-brain natriuretic peptide
Notes	

Hundal 2000

Methods	TRIAL DESIGN: Prospective cohort study of metformin DURATION: 12 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 7 Control N: 0 AGE: not stated SEX: not stated INCLUSION: type 2 DM EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, doase unclear COMPARISON: none
Outcomes	Glucose production rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Hussain 2006

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Iraq SETTING: Outpatient Treatment N: 31 Control N: 32 AGE: 49.1 SEX: 54% men INCLUSION: Type 2 DM, poorly controlled EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin plus melatonin, zinc acetate COMPARISOM: placebo plus metatonin, zinc acetate
Outcomes	Glycemic control
Notes	

Imano 1998

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Japan SETTING: outpatient Treatment N: 13 Control N: 17 Treatment AGE: 66+/-8 Control AGE: 62+/-13 Treatment SEX: 23% men Control SEX: 29% men INCLUSION: Type 2 DM with microalbuminuria EXCLUSIONS: abnormal liver function
Interventions	TREATMENT: Metformin 500 mg TID COMPARISON: troglitazone
Outcomes	Lipids, blood pressure, BMI, fasting and postprandial glucose, albumin-to-creatinine ratio.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Inzucchi 1998

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 29 Control N: 24 Treatment AGE: 51+/-13 Control AGE: 56+/-12 Control SEX: 43% men Treatment SEX: 47% men INCLUSION: Type 2 DM EXCLUSIONS: abnormal renal or hepatic function, recent atherosclerotic event
Interventions	TREATMENT: Metformin 1g BID COMPARISON: troglitazone
Outcomes	Postprandial glucose, HbA1, glucose tolerance, insulin, c-peptide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Inzucchi 1998 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Jackson 1962

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: approximately 1 month
Participants	COUNTRY: South Africa SETTING: outpatient Treatment N: 26 Control N: 0 AGE: not listed SEX: not listed INCLUSION: mild, not-ketosis-prone DM EXCLUSIONS: ketosis
Interventions	TREATMENT: Metformin 1-3 g/day COMPARISON: none.
Outcomes	Glycemia, and dose of sulfonylurea.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Jackson 1987

Methods	TRIAL DESIGN: Single-blind cross-over trial DURATION: 4.9 months average
Participants	COUNTRY: United Kingdom SETTING: general practice Treatment N: 10 Control N: 10 AGE: 56.6+/-1.9 SEX: 100% men INCLUSION: Type 2 DM, nonobese EXCLUSIONS: excessive physical activity or a metabolic disorder
Interventions	TREATMENT: Metformin, dose adjusted clinically COMPARISON: placebo
Outcomes	Plasma glucose, hepatic glucose output, forearm glucose uptake, and blood lactate levels.
Notes	

Risk of bias

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

Jackson 1987 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Jadzinsky 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial, pase 3 DURATION: 6 months
Participants	COUNTRY: Multinational SETTING: Mulitcenter, outpatient Treatment N: 971 Control N: 335 AGE: 52 SEX: 49% men INCLUSION: Type 2 DM, 18-77 years EXCLUSIONS: Severe congestive heart failure, kidney or liver abnormalities, ketoacidosis
Interventions	TREATMENT: metformin, 1 gm/day, with or without saxagliptin COMPARISON: Saxagliptin
Outcomes	Glycemic control
Notes	

Jager 2005

Methods	TRIAL DESIGN: Prospective double-blind randomised controlled trial DURATION: 16 weeks
Participants	COUNTRY: Netherlands SETTING: multi-center outpatient Treatment N: 150 Control N: 163 Treatment AGE: 63 Control AGE: 59 Treatment SEX: 44% men Control SEX: 52% men INCLUSION: type 2 DM EXCLUSIONS: history of acidosis, chronic renal insufficiency, congestive heart failure
Interventions	TREATMENT: metformin plus insulin COMPARISON: placebo plus insulin
Outcomes	Markers of endothelial function, inflammatory activity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Janka 2007

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 6 months
Participants	COUNTRY: multi-national SETTING: outpatient Treatment N: 67 Control N: 63 Treatment AGE: 69.3 Control AGE: 69.6 Treatment SEX: 64% men Control SEX: 48% men INCLUSION: type elderly patients age > 65 with 2 DM poorly controlled EXCLUSIONS: history of acidosis, obesity
Interventions	TREATMENT: metformin plus glimepiride plus insulin COMPARISON: insulin
Outcomes	Glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Jeppesen 1994

Methods	TRIAL DESIGN: Open-label cross-over trial DURATION: 12 weeks glipizide and 8 weeks metformin added
Participants	COUNTRY: United States SETTING: research center Treatment N: 16 Control N: 16 AGE: 57+/-3 SEX: 63% men INCLUSION: Type 2 DM, poorly controlled EXCLUSIONS: patients not "in good health".
Interventions	TREATMENT: Metformin, dosage adjusted clinically + glipizide COMPARISON: glipizide
Outcomes	Postprandial and steady-state glucose, lipids, free fatty acids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Johansen 1984

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 8 weeks
Participants	COUNTRY: Denmark SETTING: outpatient Treatment N: 10 Control N: 10 AGE: 59 SEX: 30% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin 500 mg/day + placebo/day. COMPARISON: acarbose + placebo
Outcomes	Postprandial glucose, HbA1, urinary glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Johnson 1993

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 8 Control N: 12 AGE: 58+/-8 SEX: 62% men INCLUSION: Newly diagnosed obese untreated Type 2 DM EXCLUSIONS: renal or hepatic abnormalities
Interventions	TREATMENT: Metformin 0.85-2.5 g/day COMPARISON: placebo
Outcomes	Insulin sensitivity, HbA1, insulin, c-peptide, skeletal muscle biopsy, glucose synthetase activity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Johnson 1998

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: average 9 months
Participants	COUNTRY: United States SETTING: Diabetes center chart review Treatment N: 124 Control N: 0 AGE: not listed SEX: not listed INCLUSION: patients with type 2 DM treated with metformin EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 500-2500 mg/day, with other medications as needed COMPARISON: none.
Outcomes	Insulin dose, BMI, and HbA1c.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Jones 2000 b

Methods	TRIAL DESISN: Abstract: open-label extension study of a randomised controlled trial. DURATION: 30 months
Participants	COUNTRY: United States. SETTING: outpatient. Treatment N: Control N: Age: not listed. Sex: not listed. Inclusion: Type 2 DM. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + rosiglitazone. COMPARISON: rosiglitazone
Outcomes	Lipds, HbA1c, beta-cell function.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Jones 2000a

Methods	TRIAL DESIGN: Abstract of a prospective cohort trial. Some data reported in Fonseca 2000. Remaining data analysed DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient

Jones 2000a *(Continued)*

	Treatment N: 102 Control N: 0 AGE: not listed SEX: not listed INCLUSION: type 2 DM, poorly controlled on metformin EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, dosage adjusted clinically + placebo, or metformin + rositglitazone 4 mg/day, or metformin + rosiglitazone 8 mg/day
Outcomes	Fasting glucose and BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Jones 2002

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 42 Control N: 40 Age: 14 +/- 1.8 Sex: 30% men Inclusion: pediatric patients age 10-16 with type 2 DM Exclusions: creatinine > 76 mcmole/L, hepatic dysfunction
Interventions	TREATMENT: metformin up to 2 g/day COMPARISON: placebo
Outcomes	Fasting glucose, HbA1c
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Josephkutty 1990

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient

Josephkutty 1990 *(Continued)*

	Treatment N: 20 Control N: 20 Treatment AGE: 76.5 Control AGE: 80.5 Treatment SEX: 30% men Control SEX: 30% men INCLUSION: Type 2 DM patients, aged 65 or older EXCLUSIONS: renal or liver function abnormalities, recent congestive heart failure
Interventions	TREATMENT: Metformin 1g BID COMPARISON: tolbutamide
Outcomes	Fasting insulin, glucose, lactate levels, lipids and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Josse 1995

Methods	TRIAL DESIGN: randomised controlled trial of acarbose versus placebo. Metformin in nonrandomised treatment strata DURATION: 12 months
Participants	COUNTRY: Canada SETTING: outpatient Treatment N: 83 Control N: 271 AGE: 57.4+/-1.1 SEX: 64% men INCLUSION: Type 2 DM EXCLUSION: debilitating disease, gastrointestinal disease
Interventions	TREATMENT: Main: acarbose versus placebo. Treatment strata: Metformin (dosage adjusted clinically), diet, sulfonylureas, insulin
Outcomes	Postprandial glucose, HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Jung 2005

Methods	TRIAL DESIGN: Open-label randomised controlled trial

Jung 2005 *(Continued)*

	DURATION: 6 months
Participants	COUNTRY: South Korea SETTING: outpatient Treatment N: 13 Control N: 14 Age: 57 +/- 10 Sex: 45% men Inclusion: type 2 DM on sulfonyluera Exlcusions: standard
Interventions	TREATMENT: metformin 1 g/day COMPARISON: rosiglitazone 4 mg/day
Outcomes	Anthropometric parameters, fasting plasma glucose, HbA1, lipid profile, adiponectin, resistin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Juurinen 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Finland SETTING: Outpatient Treatment N: 88 Control N: 0 AGE: 55.9 SEX: 57% men INCLUSION: Type 2 DM, 20-75 years EXCLUSIONS: Ketoacidosis, alcohol or drugs, pregnancy, major systemic disease
Interventions	TREATMENT: metformin and insulin, with nateglinide 120 mg TID or placebo
Outcomes	Glycemic control
Notes	

Kabadi 2006

Methods	TRIAL DESIGN: Prospective comparative study DURATION: 16 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 24 Control N: 14 AGE: not stated

Kabadi 2006 *(Continued)*

	SEX; not stated INCLUSION: type 2 DM poorly controlled EXLCUSIONS: hepatic or renal dysfunction
Interventions	TREATMENT: metformin, dosage unclear, with or without glimepiride COMPARISON: glimepiride
Outcomes	Glycemic control, weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kadoglou 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Greece SETTING: Outpatient Treatment N: 70 Control N: 0 AGE: 65.3 SEX: 40% men INCLUSION: Type 2 DM, 50-70 years, poor control EXCLUSIONS: microvascular or macrovascular disease, congestive heart failure, over kidney or liver impairment
Interventions	TREATMENT: metformin and glicazide, with rosiglitazone or control
Outcomes	Novel cardiovascular risk factors
Notes	

Kahn 2006

Methods	TRIAL DESIGN: Prospective double-blind randomised trial DURATION: 4 years
Participants	COUNTRY: multi-national SETTING: outpatient Treatment N: 1454 Control N: 2897
Interventions	TREATMENT: metformin 1 gm BID COMPARISON: rosliglitazone 4 mg BID or glyburide 7.5 mg BID
Outcomes	Monotherapy failure

Kahn 2006 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kaku 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 40 weeks
Participants	COUNTRY: Japan SETTING: Outpatient Treatment N: 169 Control N: 0 AGE: 52.5 SEX: 39% men INCLUSION: Type 2 DM, 20-65 tears EXCLUSIONS: liver or kidney abnormalities, congestive heart failure, serious disease
Interventions	TREATMENT: metformin, 500 -750 mg.day, with pioglitazone 15 mg/day or placebo
Outcomes	Glycemic control, insulin resistance, cardiovascular risk factors
Notes	

Kann 2006

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Multi-national SETTING: outpatient Treatment N: 128 Control N: 127 Treatment AGE: 61.5 Control AGE: 61 Treatment SEX: 54% men Control SEX: 49% men INCLUSION: type 2 DM, insulin-naive EXLCUSIONS: renal, hepatic, cardiovascular disiease
Interventions	TREATMENT: metformin 2 gm BID plus insulin COMPARISON: glimepiride plus insulin
Outcomes	Glycemic control, hypoglycemia
Notes	

Risk of bias

Kann 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Karlsson 2005

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Finland SETTING: outpatient Treatment N: 9 Control N: 21 Age: 58 +/- 2.1 Sex: 80% men Inclusion: newly diagnosed type 2 DM Exclusions: cardiovascular, renal or hepatic dysfunction, anemia
Interventions	TREATMENT: 2 g/day COMPARISON: rosiglitazone 4 mg BID or placebo
Outcomes	Euglycemic clamp measurements, skeletal muscle biopsies, insulin receptor substrate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kawai 2008

Methods	TRIAL DESIGN: Open-label, nonrandomised, comparative trial DURATION: 6 months
Participants	COUNTRY: Japan SETTING: Outpatient Treatment N: 69 Control N: 28 AGE: 58.8 SEX: 70% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, 500 - 750 mg/day COMPARISON: pioglitazone 15 mg/day
Outcomes	Weight, metabolic parameters
Notes	

Khanolkar 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised trial DURATION: 6 months
Participants	COUNTRY: United Kingdom SETTING: Outpatient Treatment N: 50 Control N: 0 AGE: 57.5 SEX: not state INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, varying doses, with rosiglitazone 4 mg/day or glicazide 80 mg/day
Outcomes	Ciculating platelet activity
Notes	

Kiayias 1999

Methods	TRIAL DESIGN: Comparative trial; not randomised DURATION: 3 months
Participants	COUNTRY: Greece SETTING: outpatient Treatment N: 33 Control N: 16 AGE: 64.6+/-9.5 SEX: 51% men INCLUSION: Poorly controlled type 2 DM EXCLUSIONS: proteinuria, smokers, various medications
Interventions	TREATMENT: Metformin, dosage adjusted clinically, or metformin + sulfonylurea COMPARISON: sulfonylurea
Outcomes	Lipoprotein (a) levels, lipids, HbA1.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Kim 2002

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 7 Control N: 7

Kim 2002 *(Continued)*

	Age: 56 +/- 1 Sex: 79% men Inclusion: type 2 DM Exlcusions: standard
Interventions	TREATMENT: metformin 2.5 g/day COMPARISON: troglitazone 600 mg/day
Outcomes	Glucose disposal rate, HbA1, fasting glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kim 2007

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 12 weeks
Participants	COUNTRY: Korea SETTING: outpatient Treatment N: 60 Control N: 60 Treatment AGE: 57.6 Control AGE: 56.5 Treatment SEX: 50% men Control SEX: 53% men INCLUSION: type 2 DM EXCLUSIONS: renal disease, coronary artery disease, stroke, peripheral artery disease, malignancy
Interventions	TREATMENT: metformin 1000 mg daily plus glimepiride COMPARISON: rosiglitazone plus glimepiride
Outcomes	Insulin sensitivity, beta-cell function, adiponectin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kirk 1999

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 14 weeks
Participants	COUNTRY: United States SETTING: outpatient

Kirk 1999 *(Continued)*

	Treatment N: 15 Control N: 16 Treatment AGE: 50.5 Control AGE: 54.5 Treatment SEX: 64% men Control SEX: 31% men INCLUSION: Type 2 DM EXCLUSIONS: women of childbearing potential, renal or hepatic disease, alcohol abuse, various medications
Interventions	TREATMENT: Metformin 0.5-1 g BID COMPARISON: troglitazone 200-400 mg/day.
Outcomes	HbA1, fasting glucose and C-peptide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Klein 1975

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 4 months
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 60 Control N: 0 AGE: not listed SEX: 48% men INCLUSION: maturity-onset DM EXCLUSION: none listed
Interventions	TREATMENT: Metformin, dosage titrated clinically, some with chlorpropamide COMPARISON: none
Outcomes	Glucose, weight, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Klein 1991

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 1 year

Klein 1991 *(Continued)*

Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 16 Control N: 19 Treatment AGE: 68+/-10 Control AGE: 66+/-11 Treatment SEX: 27% males Control SEX: 20% males INCLUSION: Type 2 DM with failure with sulfonylurea EXCLUSIONS: renal insufficiency with creatinine > 1.2, acute or severe disease, various medications
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + sulfonylurea COMPARISON: insulin + sulfonylurea
Outcomes	Weight, blood pressure, insulin, c-peptide, HbA1, lipids, liver and renal function, and lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kooy 2009a

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4.3 years
Participants	COUNTRY: Netherland SETTING: Multicenter outpatient Treatment N: 196 Control N: 195 AGE: 61.5 SEX: 46% men INCLUSION: Type 2 DM, 30-80 years EXCLUSIONS: ketoacidosis, pregnancy, creatinine clearance <50, class 3 or 4 congestive heart failure, serious medical illness
Interventions	TREATMENT: metformin 850 mg 1-3 times/day, with insulin COMPARISON: placebo with insulin
Outcomes	Weight, glycemic control, microvascular and macrovascular events
Notes	

Kudolo 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of ginkgo biloba DURATION: 12 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 10 Control N: 0

Kudolo 2006 *(Continued)*

	AGE: 39.2 SEX: not stated INCLUSION: type 2 DM EXCLUSIONS: major cardiovascular, hepatic or endocrine disease
Interventions	TREATMENT: metformin dosage unclear, with or without ginkgo biloba COMPARISON: none
Outcomes	Pharmacokinetics of metformin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Kusaka 2008

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Japan SETTING: Outpatient Treatment N: 18 Control N: 17 AGE: 62 SEX: 60% men INCLUSION: Type 2 DM EXCLUSIONS: Cardiovascular disease, kidney or liver abnormalities, severe diabetic complications
Interventions	TREATMENT: metformin, 750 mg/day COMPARISON: pioglitazone 15-30 mg/day
Outcomes	Plasma ghrelin levels
Notes	

Kvapil 2006

Methods	TRIAL DESIGN: Prospective cohort study of metfomin in a randomised trial of insulin DURATION: 16 weeks
Participants	COUNTRY: Multi-national SETTING: outpatient Treatment N: 115 Control N: 0 AGE: 56.5 SEX: 50% men INCLUSION: type 2 DM EXCLUSIONS: hepatic, renal or cardiac disase
Interventions	TREATMENT: metformin, dosage titrated up, with or without glibenclmide and with or without biphasic insulin

Kvapil 2006 *(Continued)*

	COMPARISON: none
Outcomes	Glucose, HbA1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lalau 1990

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2 months.
Participants	COUNTRY: France SETTING: outpatient Treatment N: 24 Control N: 0 AGE: 74+/-1.5 SEX: 67% men INCLUSION: patients over the age of 70 with type 2 DM EXCLUSIONS: creatinine clearance < 30 ml/min
Interventions	TREATMENT: metformin, 1770-2550 mg/day COMPARISON: none
Outcomes	Creatinine clearance, lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lalor 1990

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: hospital clinic Treatment N: 38 Control N: 38 AGE: 58 SEX: 46% men INCLUSION: Obese patients with type 2 DM EXCLUSIONS: previous treatment with metformin or guar
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + placebo

Lalor 1990 *(Continued)*

	COMPARISON: Guar + placebo
Outcomes	Fasting glucose, weight, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lam 1998

Methods	TRIAL DESIGN: Prospective cohort trial with 91% on metformin DURATION: 6 months
Participants	COUNTRY: China SETTING: three-center outpatient Treatment N: 90 Comparison N: 0 AGE: 35-70 SEX: 45% men INCLUSION: Type 2 DM with poor control on oral hypoglycemics EXCLUSIONS: abnormal liver and renal function, significant diseases or conditions, ketonuria,abnormal gutmotility, lactose intolerance, pregnancy and lactation
Interventions	TREATMENT: 91% on metformin, dosage adjusted clinically, + acarbose, 150-300 mg/day, or metformin + placebo COMPARISON: 9% on other oral agents + acarbose or placebo. These patients not analysed.
Outcomes	Fasting and postprandial glucose, HbA1c, insulin levels, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Laurenti 1992

Methods	TRIAL DESIGN: Open-label comparative trial DURATION: 6 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 30 Control N: 30 AGE: 38-63 SEX: not listed INCLUSION: Type 2 DM with poor control on sulfonylurea

Laurenti 1992 *(Continued)*

	EXCLUSIONS: congestive heart failure, nephropathy, liver function abnormalities
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glibenclamide COMPARISON: sulfonylurea alone
Outcomes	Fasting and postprandial glucose, insulin, fructosamine, and BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lawrence 2004

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 20 Control N: 10 Age: 60 +/- 9 Sex: 60% men Inclusion: overweight type 2 DM Exclusions: Creatinine > 150 mcmole/L, congestive heart failure, hepatic dysfunction
Interventions	TREATMENT: metformin 500 mg BID COMPARISON: pioglitazone 30 mg/day or glicazine 80 mg.day
Outcomes	HbA1, lipid profile, glucose, BMI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lean 1983

Methods	TRIAL DESIGN: Prospective cohort study or metformin in a randomised controlled trial of ciclazindol DURATION: 2 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 10 Control N: 0 AGE: 42-68 SEX: 30% men INCLUSION: obese patients with type 2 DM, treated with metformin EXCLUSIONS: hepatic or renal impairment, heart disease, psychiatric or alcohol problems
Interventions	TREATMENT: metformin 500 mg BID + placebo or metformin + ciclazindol 25-75 mg/day

Lean 1983 *(Continued)*

	COMPARISON: none
Outcomes	Plasma insulin, triglycerides, lactate pyruvate, and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lee 1998

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 24 weeks
Participants	COUNTRY: United States SETTING: University center Treatment N: 24 Control N: 120 Treatment AGE: 59+/-3 Control AGE: 61+/-2 SEX: 0 men INCLUSION: Obese type 2 DM EXCLUSIONS: major illnes, cardiac, renal or hepatic disorder, medicine known to affect body weight or cholesterol metabolism
Interventions	TREATMENT: Metformin 850 mg BID COMPARISON: placebo
Outcomes	Food consumption and weight loss
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lewin 2007

Methods	TRIAL DESIGN: Prospective double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United Stated SETTING: outpatient multi-center Treatment N: 457 Control N: 152 Treatment AGE: 18-79 years Control AGE: 18-79 Treatment SEX: not stated Control SEX: not stated

Lewin 2007 *(Continued)*

	INCLUSION: type 2 DM EXCLUSIONS: renal insufficiency, untreated cardiovascular or hepatic disease Treatment N: 4
Interventions	TREATMENT: metformin extended-release 1500-2000 mg daily plus sulfonylurea COMPARISON: sulfonylurea monotherapy
Outcomes	Glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Li 2009

Methods	TRIAL DESIGN: Prospective observational cohort DURATION: 3 months
Participants	COUNTRY: China SETTING: Outpatient Treatment N: 30 Control N: 0 AGE: 40-70 years SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: major diabetic complications
Interventions	TREATMENT: metformin, varying doses
Outcomes	Fibroblast growth factor-21 levels
Notes	

Lingvay 2007

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 12 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 19 Control N: 0 AGE: 43.7 SEX: 83% men INCLUSION: type 2 DM with hepatic steatosis EXCLUSION: renal or hepatic disease
Interventions	TREATMENT: metformin, dosage unclear, with insulin

Lingvay 2007 *(Continued)*

Outcomes	Hepatic triglyceride content
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

List 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Canada, Mexico, Puerto Rico SETTING: Muticenter outpatient Treatment N: 56 Control N: 333 AGE: 53.5 SEX: 40% men INCLUSION: Type 2 DM EXCLUSIONS: kidney insufficiency
Interventions	TREATMENT: metformin XR COMPARISON: Dapaglitfozin, varying doses, placebo
Outcomes	Glycemic control, weight, glucosuria, osmolarity and volume changes
Notes	

Lord 1983

Methods	TRIAL DESIGN: Open-label cross-over trial with untreated controls DURATION: 4 weeks
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 8 Control N: 8 AGE: 61+/-5 SEX: 38% men INCLUSION: Obese, type 2 DM EXCLUSIONS: abnormal renal or liver function
Interventions	TREATMENT: Metformin 500 mg TID COMPARISON: no metformin
Outcomes	Glucose tolerance test, urinary glucose, and HbA1.
Notes	

Risk of bias

Lord 1983 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Luna 2006

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 1 month
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 6 Control N: 0 AGE: 50 SEX: 66% men INCLUSION: type 2 DM EXCLUSIONS: renal, cardiovascular or neurologic problems
Interventions	TREATMENT: metformin, 1000 mg BID COMPARISON: none
Outcomes	Atypical protein kinase C activation in muscle
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lund 2007

Methods	TRIAL DESIGN: Prospective double-blind cross-over randomised trial DURATION: 16 weeks
Participants	COUNTRY: Denmark SETTING: outpatient Treatment N: 48 Control N: 48 Treatment AGE: 59 Control AGE: 63 Treatment SEX: 75% men Control SEX: 79% men INCLUSION: non-obese patients with type 2 DM EXCLUSIONS: renal insufficiency, clinical heart failure
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: repaglinide, dosage unclear
Outcomes	Glycemic control, c-reactive protein, adiponectin
Notes	

Lund 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Lund 2008

Methods	TRIAL DESIGN: Double-blind randomised cross-over trial DURATION: 4 months and 4 months
Participants	COUNTRY: Denmark SETTING: Outpatient Treatment N: 83 Control N: 82 AGE: 61.4 SEX: 76% men INCLUSION: Type 2 DM, nonobese, insulin-naive EXCLUSIONS: ketoacidosie, ketonuria
Interventions	TREATMENT: metformin 1 gm BID COMPARISON: repaglinide 2 mg TID
Outcomes	Non-glycemic cardiovascular risk markers, inflammatory and endothelial markers
Notes	

Lunetta 1996

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 1 month
Participants	COUNTRY: Italy SETTING: outpatient clinic Treatment N: 12 Control N: 0 AGE: 55+/-5 SEX: 50% men INCLUSION: Type 2 DM for at least one year, with good glycemic control EXCLUSIONS: diabetic neuropathy, gastroparesis or diarrhea
Interventions	TREATMENT: metformin 850 mg BID, then a single dose of metformin 850 mg or placebo COMPARISON: none
Outcomes	Postprandial glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Makimattila 1999

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 12 months
Participants	COUNTRY: Finland SETTING: outpatient Treatment N: 13 Control N: 39 Treatment AGE: 54+/-2 Control AGE: 58+/-3 SEX: not listed INCLUSION: Type 2 DM EXCLUSIONS: congestive heart failure, cardiovascular disase, seizure, liver disease unrelated to DM
Interventions	TREATMENT: Metformin 2 g/day + insulin NPH QHS COMPARISON: insulin BID
Outcomes	Weight gain, urinary glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Manzella 2004

Methods	TRIAL DESIGN: Blinded randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 60 Control N: 60 Age: 57 +/- 11 Sex: 55% men Inclusion: obese type 2 DM Exclusions: coronary artery disease
Interventions	TREATMENT: metformin 850 mg BID COMPARISON: placebo
Outcomes	Fasting glucose, insulin, triglyceride, free fatty acids, insulin resistance by HOMA method
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Marena 1994

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 6 weeks
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 10 Control N: 10 AGE: 60.8+/-10.7 SEX: 60% men INCLUSION: Type 2 DM with poor control EXCLUSIONS: hepatic, renal, pulmonary or cardiac dysfunctions
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glibenclamide COMPARISON: placebo + glibenclamide
Outcomes	Fasting glucose, HbA1, weight, insulin sensitivity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Marfella 1996

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2 months
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 10 Control N: 0 AGE: 47+/-0.8 SEX: 50% men INCLUSION: newly diagnosed patients with type 2 DM, with mild hyperglycemia EXCLUSIONS: evidence of microvascular or macrovascular complications
Interventions	TREATMENT: Metformin 1700 mg/day COMPARISON: none
Outcomes	Weight, glucose, HbA1, insulin, lipids, blood pressure, heart rate, platelet aggregation, blood viscosity, blood filterability, epinephrine, and norepinephrine.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mari 2006

Methods	TRIAL DESIGN: Prospectiv cohort study DURATION: 30 weeks
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 73 Control N: 0 AGE: 54 SEX: not stated INCLUSION: type 2 DM EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, dosage unclear, with or without exenatide COMPARISON: none
Outcomes	Beta-cell function, insulin secretion rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Marre 2002

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: France, Belgium, Netherlands, Denmark, Portugal SETTING: outpatient Treatment N: 308 Control N: 103 Age: 58 +/- 11 Sex: 60% men Inclusion: type 2 DM inadequately controlled on metformin Exclusions: creatinine 127 mcmole/L, hypoxic states, hepatic dysfunction
Interventions	TREATMENT: metformin 2.5 g/day with and without glibenclamide COMPARISON: glimenclamide 20 mg/day
Outcomes	HbA1, fasting glucose, fructosamine, lipid profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mashavi 2008

Methods	TRIAL DESIGN: Observational cohort or metformin in a double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Israel SETTING: Outpatient Treatment N: 60 Control N: 0 AGE: 60.9 SEX: 47% men INCLUSION: Type 2 DM EXCLUSIONS: coronary artery disease, creatinine >2, liver abnormalities
Interventions	TREATMENT: metformin, high dose, plus folate, vitamin B12, vitamin B6 or placebo
Outcomes	Homocysteine levels, small artery elasticity
Notes	

Mather 2001

Methods	TRIAL DESIGN: Prospective randomised placebo-controlled tral
Participants	COUNTRY: Canada, United States SETTING: outpatient Treatment N: 29 Control N: 15 Treatment AGE: 50.7 Control AGE: 54.8 Treatment SEX: 54% men Control SEX: 73% men INCLUSION: type 2 DM without metabolic syndrome EXCLUSIONS: metabolic syndrome
Interventions	TREATMENT: metformin 500 mg BID COMPARISON: placebo
Outcomes	Endothelial function
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Matthews 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of pioglitazone DURATION: 1 year
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 630

Matthews 2005 *(Continued)*

	Control N: 0 AGE: 56.5 SEX: 50% men INCLUSION: type 2 DM poorly controlled EXCLUSIONS: acidosis, myocardial infarction, congestive heart failure
Interventions	TREATMENT: metformin, dosage unclear with pioglitazone or gliclazide COMPARISON: none
Outcomes	Glucose, HbA1, lipids, urinary albumin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

McAlpine 1988

Methods	TRIAL DESIGN: Open-label crossover trial DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 27 Control N: 27 AGE: 58 SEX: 57% men INCLUSION: Type 2 DM EXCLUSIONS: significant renal or hepatic impairment, various medications
Interventions	TREATMENT: Metformin, dosage adjusted clinically COMPARISON: glicazide
Outcomes	Weight, fasting and postprandial glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

McBain 1988

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months

McBain 1988 *(Continued)*

Participants	COUNTRY: Scotland. SETTING: outpatient. Treatment N: 14. Control N: 20. Treatment age: 56.5. Control age:56.3. Treatment sex: 36% men. Control sex: 35% men. Inclusion: Type 2 DM. Exclusions: low weight, Abnormal renal function, liver function.
Interventions	TREATMENT: Metformin 500mgBID. COMPARISON: glipizide 5mg/day.
Outcomes	Calcium and magnesium levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

McIntyre 1991

Methods	TRIAL DESIGN: Open-label cross-over trial DURATION: 6 weeks
Participants	COUNTRY: Australia SETTING: outpatient Treatment N: 9 Control N: 9 AGE: 48-75 SEX: 44% men INCLUSION: Type 2 DM EXCLUSIONS: renal or liver abnormalities
Interventions	TREATMENT: metformin 1.5-3 g/day COMPARISON: diet
Outcomes	Postprandial glucose, total insulin, and c-peptide levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mehta 1963

Methods	TRIAL DESIGN: Prospective cohort study DURATION: approximately 1 month.
Participants	COUNTRY: India SETTING: outpatient Treatment N: 41 Control N: 0 AGE: not listed

Mehta 1963 *(Continued)*

	SEX: not listed INCLUSIONS: patients with DM on medications other than metformin EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage unclear COMPARISON: none.
Outcomes	Glycemia, glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Menzies 1989

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: United Kingdom SETTING: outpatient Treatment N: 64 Control N: 0 AGE: 64+/-9 SEX: 41% men INCLUSION: obese patients with type 2 DM EXCLUSIONS: ketosis, or abnormal electrolytes or renal function
Interventions	TREATMENT: Metformin 1.5-2 g/day or 2.5-3 g/day COMPARISON: none
Outcomes	Plasma glucose, HbA1, and lactate.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mesirabi 2005

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 8 weeks
Participants	COUNTRY: India SETTING: outpatient Treatment N: 101 Control N: 0 AGE: 56 SEX: 66% men

Mesirabi 2005 *(Continued)*

	INCLUSION: type 2 DM EXLCUSIONS: none
Interventions	TREATMENT: Metformin, dosage unclear, with pioglitazone plus glimepiride COMPARISON: none
Outcomes	Glucose, HbA1, lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Moses 1999a

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 22 weeks
Participants	COUNTRY: Australia SETTING: outpatient Treatment N: 54 Control N: 28 Treatment AGE: 57.8 Control AGE: 60.3 Treatment SEX: 63% men Control SEX: 54% men INCLUSION: Type 2 DM with poor control on metformin EXCLUSIONS: clincally significant renal insufficiency, abnormal liver functions, cardiac diasease, history of lactic acidosis
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + placebo; or metformin + repaglinide COMPARISON: repaglinide + placebo
Outcomes	Fasting glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mourao-Junior 2006

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 6 months
Participants	COUNTRY: Brasil SETTING: outpatient Treatment N: 47

Mourao-Junior 2006 *(Continued)*

	Control N: 0 AGE: 58.9 SEX: 55% men INCLUSION: type 2 DM with metabolic syndrome EXCLUSIONS: none stated
Interventions	TREATMENT: metfomrin, dosage unclear, plus insulin COMPARISON: none
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Mughal 2000

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 12 weeks
Participants	COUNTRY: Karachi SETTING: outpatient Treatment N: 30 Control N: 0 AGE: 53.3 SEX: 65% men INCLUSION: type 2 DM with suboptimal control EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, up to 3 gm daily COMPARISON: none
Outcomes	Weight, lipids, glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Munk 1975

Methods	TRIAL DESIGN: Open-label comparative trial TRIAL DURATION: 6 months
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 40

Munk 1975 *(Continued)*

	Control N: 20 AGE: unclear SEX: 55% males INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage unclear, or metformin + insulin COMPARISON: Sulfonylurea
Outcomes	Lipids, liver function studies, and glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Nagi 1993

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United States. SETTING: outpatient. Treatment N: 27. Control N: 27. Age: 56.8 +/-8.9. Sex: not listed. Inclusion: Type 2 DM. Exclusions: cardiovascular disease, thromboembolic disease, renal or hepatic disease, retinopathy.
Interventions	TREATMENT: Metformin, dosage adjusted clinically. COMPARISON: placebo
Outcomes	Fasting glucose, lipids, BMI, insulin, c-peptide, blood pressure, plasminogen activator inhibitor, and other factors
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nar 2009

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Turkey SETTING: Outpatient Treatment N: 19 Control N: 15 AGE: 46.9 SEX: 74% men INCLUSION: Type 2 DM, obese, not on meds, with nonalcoholic fatty liver disease

Nar 2009 *(Continued)*

	EXCLUSIONS: liver or kidney abnormalities, virall hepatitis
Interventions	TRRATMENT: metformin, varying doses COMPARISON: lifestyle changes
Outcomes	plasma leptin levels, weight, degree of fatty liver disease
Notes	

Natali 2004

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Italy SETTING: outpatient: Treatment N: 28 Control N: 46 Age: 58 +/- 9 Sex: 70% men Inclusion: type 2 DM Exclusions: renal or hepatic dysfrunction, congestive heart failure
Interventions	TREATMENT: Metformin 500 mg TID COMPARISON: placebo
Outcomes	Insulin sensitivity by euglycemic clamp, fat-free mass, response to acetycholine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Nattrass 1977

Methods	TRIAL DESIGN: Open-label, cross-over comparative trial DURATION: 1 month
Participants	Country: United Kingdom. Setting: outpatient. Treatment N: 6. Control N: 6. Age: 50-57. Sex: 67% men. Inclusion: Type 2 DM longer than 3 years. Exclusions: hepatic or renal disease.
Interventions	TREATMENTt: Metformin 500mg TID. COMPARISON: intervention: phenformin 50mg BID (not analysed) or glibenclamide, 2.5-5mg/day.
Outcomes	Blood glucose, lactate, pyruvate, 3-hydroxybutyrate, acetoacetate,ketones, lactato pyruvate ratios, and cyclic AMP.
Notes	

Risk of bias

Nattrass 1977 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Nauck 2007

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Multinational SETTING: Multicenter, outpatient Treatment N: 1172 Control N: 0 AGE: 56.7 SEX: 59% men INCLUSION: Type 2 DM, 18-78 years, not on meds EXCLUSIONS: type 1 diabetes, recnet insulin use, kidney abnormalities
Interventions	TREATMENT: metformin, varying dose, with sitaglitpin 100 mg/day or glipizide 5-20 mg/day
Outcomes	Glycemic control, weight
Notes	

Nauck 2009a

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Multinational SETTING: Multicenter, outpatient Treatment N: 1091 Control N: 0 AGE: 55 SEX: 51% men INCLUSION: Type 2 DM, 18-80 years, poor control EXCLUSIONS: kidney impairment, cancer, congestive heart failure, coronary artery disease
Interventions	TREATMENT: metformin, 1 gm BID, with liraglutide, glimerpiride or placebo
Outcomes	Glycemic control, safety
Notes	

Nauck 2009b

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Multinational SETTING: Multicenter outpatient

Nauck 2009b *(Continued)*

	Treatment N: 527 Control N: 0 AGE: 55 SEX: 47.9% men INCLUSION: Type 2 DM, 18-80 years, poor control EXCLUSIONS: kidney impairment, congestive heart failure, cancer
Interventions	TREATMENT: metformin, varying doses, with alogliptin 12.5 mg/day or placebo
Outcomes	Glycemic control, safety
Notes	

Nauck 2009c

Methods	TRIAL DESIGN: Observational cohort of metformin in double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Multinational SETTING: Multicenter outpatient Treatment N: 306 Control N: 0 AGE: 52 SEX: 49% men INCLUSION: Type 2 DM, 18-75 years EXCLUSIONS: liver or kidney abnormalities, gastrointestinal disease, significant coronary artery disease
Interventions	TREATMENT: metformin, varying doses, with taspoglutide, varying dosease or placebo
Outcomes	Glycemic control, weight
Notes	

Niazi 1998

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 5 months
Participants	COUNTRY: Pakistan. SETTING: outpatient. Treatment N: 18. Control N: 36. Treatment age: 50 +/-11. Control age: 48 +/-11. Treatment sex: 61% men. Control sex: 56% men. Inclusion: Type 2 DM with sulfonylurea failure. Exclusions: cardiomegaly, lung disease, malnutrition, infection, various medications.
Interventions	TREATMENT: Metformin 0.5-3g/day. COMPARISON: insulin
Outcomes	Lipids, blood pressure, weight, and BMI.
Notes	

Risk of bias

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

Niazi 1998 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Nosadini 1987

Methods	TRIAL DESIGN: Open-label trial with patients as own controls DURATION: 1 month
Participants	COUNTRY: Italy. SETTING: outpatient. Treatment N: 7. Control N: 7. Age: 46 +/-5. Sex: 57% men. Inclusion: Type 2 DM. Exclusions: age > 65.
Interventions	TREATMENT: Metformin 850mg TID. COMPARISON: diet
Outcomes	Glucose turnover and insulin binding
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Noury 1991

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: France. SETTING: outpatient. Treatment N: 30. Control N: 27. Age: 55 +/-9.1. Treatment sex: 53% men. Control sex: 44% men. Inclusion: Type 2 DM. Exclusions: renal or hepatic disease.
Interventions	TREATMENT: Metformin 1700mg/day. COMPARISON: glicazide
Outcomes	Blood glucose, insulin levels, and weight loss
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ohira 2007

Methods	TRIAL DESIGN: Prospective observational cohort trial DURATION: 3 months
Participants	COUNTRY: Japan SETTING: Outpatient Treatment N: 28 Control N: 0

Ohira 2007 *(Continued)*

	AGE: 61.2 SEX: 61% men INCLUSION: Type 2 DM, taking sulfonylureas EXCLUSIONS: none listed
Interventions	TREATMENT: metformin 500 mg BID with sulfonylurea
Outcomes	Lipoprotein lipase mass levels, LDL cholesterol particle size
Notes	

Ohnhaus 1983

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 1.5 months
Participants	COUNTRY: Switzerland. SETTING: outpatient. Treatment N: 12. Control N: 12. Age: not listed. Sex: not listed. Inclusion: Type 2 DM pts on phenprocoumon. Exclusions: none listed.
Interventions	TREATMENT: Metformin 850mg TID. COMPARISON: diet
Outcomes	Phenprocoumon pharmacokinetic
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ozata 2001

Methods	Prospective cohort study DURATION: 3 months
Participants	COUNTRY: Turkey SETTING: outpatient Treatment N: 20 Control N: 0 AGE: not stated SEX: 100% men INCLUSION: Obese men with type 2 DM EXLCUSIONS: renal or cardiac disease Treatment N
Interventions	TREATMENT: metformin 850 mg TID COMPARISON: none
Outcomes	Waist circumference, body mass index, follicle-stimulating hormine, leptin
Notes	

Ozata 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Pala 2007

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label nonrandomised comparative, cross-over trial DURATION: 3 months, 3 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 30 Control N: 0 AGE: 65 SEX: 23% men INCLUSION: Type 2 DM EXCLUSIONS: recent insulin use, congestive heart failure, kidney or respiratory insufficiency, pregnancy
Interventions	TREATMENT: metformin, varying dose, with insulin before or after meals
Outcomes	Glycemic control
Notes	

Panikar 2007

Methods	TRIAL DESIGN: Prospective observational cohort trial DURATION: 2 years
Participants	COUNTRY: India SETTING: Outpatient Treatment N: 373 Control N: 0 AGE: 48.5 SEX: 45% men INCLUSION: Type 2 DM, new onset EXCLUSIONS: cardiac, kidney or liver insufficiency
Interventions	TREATMENT: metformin, 500 mg TID, with gliclazide 800 mg TID and pioglitazone 30 mg/day
Outcomes	Glycemic control
Notes	

Papathanassiou 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-lable randomised controlled trial

Papathanassiou 2009 *(Continued)*

	DURATION: 6 months
Participants	COUNTRY: Greece SETTING: Outpatient Treatment N: 28 Control N: 0 AGE: 63.2 SEX: 22% men INCLUSION: Type 2 DM, treated with metformin EXCLUSIONS: kidney, liver or heart disease, congestive heart failure
Interventions	TREATMENT: metformin, plus glimepiride 4 mg/day or pioglitazone 30 mg/day
Outcomes	Flow-mediated dilation of the brachial artery, vascular endothelial function
Notes	

Pavo 2003

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 8 months
Participants	COUNTRY: Russia SETTING: outpatient Treatment N: 100 Control N: 105 Age: 55 +/- 9 Sex: 50% men Inclusion: recently diagnosed type 2 DM naive to oral medications Exclusions: hepatic and renal dysfunction, congestive heart failure
Interventions	TREATMENT: metformin 2.5 g/day COMPARISON: pioglitazone 45 mg/day or placebo
Outcomes	HbA1c, fasting glucose, insuliln resistance by HOMA method
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Peacock 1984

Methods	TRIAL DESIGN: Prospective cohort study DURATION: at least 3 months
Participants	Country: United Kingdom. Setting: outpatient setting. Treatment N: 33. Control N: 0. Age: 58. Sex: 60% men. Inclusion: patients with type 2 DM, treated with high doses or oral hypoglycemics. Exclusions: history or ketosis or good control on oral agents.

Peacock 1984 *(Continued)*

Interventions	TREATMENT: metformin, dosage unclear, + glibenclamide, dosage adjusted clinically. After 3 months, some were treated additionally with insulin. COMPARISON: none.
Outcomes	Fasting glucose, HbA1, and fasting c-peptide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Peacock 1986

Methods	TRIAL DESIGN: Comparative trial DURATION: 6 months
Participants	Country: United Kingdom. Setting: outpatient. Treatment N: 27. Control N: 20. Treatment age: 59.9 +/-2.1. Control age: 56.7 +/-2.1. Treatment sex: 59% men. Control sex: 66% men. Inclusion: Type 2 DM. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage unclear, + glibenclamide. COMPARISON: insulin
Outcomes	Platelet reactivity (ADP release, adrenaline release and NaAA threshold), and fasting glucose, HgA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Pedersen 1965

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 18 months
Participants	Country: Denmark. Setting: inpatient and outpatient. Treatment N: 20. Control N: 0. Age: not listed. Sex: not listed. Inclusion: maturity-onset DM. Exclusions: none listed.
Interventions	TREATMENT: metformin, dose titrated up clinically, 1-4g/day. COMPARISON: none.
Outcomes	Plasma glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Pedersen 1965 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Pedersen 1989

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 1 month
Participants	Country: Denmark. Setting: outpatient. Treatment N: 10. Control N: 10. Age: 53 +/-9. Sex: 20% men. Inclusion: Obese pts with Type 2 DM. Exclusions: renal or liver dysfunction.
Interventions	TREATMENT: Metformin 500mg TID. COMPARISON: placebo
Outcomes	Fasting and postprandial glucose, fructosamine, insulin, c-peptide, and adipocite insulin receptor binding.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Phillips 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 34 Control N: 17 AGE: 55 SEX: 76% men INCLUSION: Type 2 DM EXCLUSIONS: pregnancy, uncontrolled hypertension, treatment with more than one agent
Interventions	TREATMENT: metformin 1 gm BID, or 500 mg BID with rosiglitazone 2 mg BID COMPARIDON: rosiglitazone 4 mg BID
Outcomes	Adiponectin levels
Notes	

Pirart 1961

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 3 motnhs

Pirart 1961 *(Continued)*

Participants	Country: Belgium. Setting: outpatient. Treatment N: 107. Control N: 0. Age: not listed. Sex: not listed. Inclusion: type 2 DM, poorly controlled on a single agent. Exclusions: obesity.
Interventions	TREATMENT: metformin, unclear dose. COMPARISON: some patients treated with other agents, not analysed.
Outcomes	Glycemia, and glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Pitocco 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label randomised controlled trial DURATION: 2 months
Participants	COUNTRY: Italy SETTING: Outpatient Treatment N: 24 Control N: 0 AGE: not stated SEX: not stated INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin with pioglitazone 45 mg/day or control
Outcomes	Monocyte activation
Notes	

Ponssen 2000

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 5 months
Participants	Country: Netherlands. Setting: outpatient. Treatment N: 31. Control N: 62. Age: 62. +/-10. Sex: 77% men. Inclusion: Type 2 DM. Exclusions: renal insufficency with Creatinine clearance < 50 ml.min, hepatic disease, cardiovascular disease, alcohol abuse, various medications.
Interventions	TREATMENT: Metformin, dosage unclear, + insulin COMPARISON: placebo + insulin
Outcomes	Glucose, fructosamine, insulin requirements, lipds, BMI, and HbA1.
Notes	

Risk of bias

Ponssen 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pradhan 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial with open-label glargine insulin DURATION: 14 weeks
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 250 Control N: 250 AGE: 53.5 SEX: 25% men INCLUSION: Type 2 DM EXCLUSIONS: type 1 diabetes, pregnancy, congestive heart failure, liver or kidney abnormalties
Interventions	TREATMENT: metformin with or without glargine insulin COMPARISON: glargine insulin or placebo
Outcomes	CRP, inflammatory markers
Notes	

Prager 1986

Methods	TRIAL DESIGN: Open-label trial, cross-over, with patients as their own controls DURATION: 3 months control then 1 month metformin
Participants	Country: Austria. Setting: outpatient. Treatment N: 12. Control N: 12. Age: 35-62. Sex: 16% men. Inclusion: Type 2 DM. Exclusions: vascular disease, renal failure, liver function abnormalities.
Interventions	TREATMENT: Metformin 850mg TID. COMPARISON: diet
Outcomes	Insulin sensitivity, fasting glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Puchegger 1964

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months

Puchegger 1964 *(Continued)*

Participants	COUNTRY: Germany. SETTING: outpatient. Treatment N: 43. Control N: 0. Age:not listed. Sex: 28% men. Inclusion: patients with DM. Exclusions: none listed.
Interventions	TREATMENT: metformin, alone or in combination with insulin, dosage adjusted clinically. COMPARISON: none.
Outcomes	Plasma glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Rachmani 2002

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 48 months
Participants	COUNTRY: Israel SETTING: outpatient Treatment N: 195 Control N: 198 Age: 64.5 +/- 4 Sex: 60% neb Inclusion: type 2 DM with at least one traditional contraindication Exclusions: liver cirrhosis, actue myocardial infarction or pulmonary edema within previous 30 days, CO2 narcosis, malginancy
Interventions	TREATMENT: metformin, dose adjusted clinically COMPARISON: no metformin
Outcomes	Lactic acid levels, lactic acidosis, cardiovascular events, complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Rains 1988

Methods	TRIAL DESIGN: Single-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom/ SETTING: hospital clinic. Treatment N: 35. Control N: 70. Age: not listed. Sex: not listed. Inclusion: Type 2 DM. Exclusions: age > 70, BUN > 6 mmol/L, abnormal liver functions.
Interventions	TREATMENT: Metformin 1-3g/day. COMPARISON: placebo

Rains 1988 *(Continued)*

Outcomes	Plasma glucose, lipoproteins, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Rains 1989

Methods	TRIAL DESIGN: Open-label cross-over randomised controlled trial DURATION: 1.5 months
Participants	COUNTRY: United Kingdom. SETTING: diabetes clinic. Treatment N: 28. Control N: 14. Age: unclear. Sex: 64% men. Inclusion: Type 2 DM. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage unclear. COMPARISON: glibenclamide
Outcomes	Weight, lipds, glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Raptis 1996

Methods	TRIAL DESIGN: Open-label crossover randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Greece. SETTING: University center. Treatment N: 30. Control N: 30. Age: 60 +/-7.5. Sex: 57% men. Inclusion: Type 2 DM. Exclusions: cardiac, renal, hepatic failure, autoimmune disease.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glibenclanide. COMPARISON: phenformin + glibenclanide
Outcomes	Postprandial glucose, HgA1c, lipids, and blood lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Raskin 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label randomised controlled trial DURATION: 34 weeks
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 200 Control N: 0 AGE: 53.7 SEX: 42% men INCLUSION: Type 2 DM, insulin naive EXCLUSIONS: morbid obesity, HbAic >12
Interventions	TREATMENT: metformin 2500 mg/day plus pioglitazone 30-45 mg/day, with or without insulin
Outcomes	Glycemic control
Notes	

Raskin 2009a

Methods	TRIAL DESIGN: Observational cohort of metformin in a open-label randomised controlled trial DURATION: 26 weeks
Participants	COUNTRY: United States SETTING: Outpatient Treatment N: 561 Control N: 0 AGE: 54.8 SEX: 5% men INCLUSION: Type 2 DM EXCLUSIONS: significant disease history, pregnancy
Interventions	TREATMENT: metformin, varying doses with rosiglitazone 4 mg/day or replaglinide varying doses
Outcomes	Glycemic control
Notes	

Ratner 2006

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 82 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 150 Control N: 0 AGE: 54 SEX: 69% men INCLUSION: type 2 DM EXCLUSIONS: none stated

Ratner 2006 *(Continued)*

Interventions	TREATMENT: metformin, dosage unclear plus exenative COMPARISON: none
Outcomes	Percent of patient with HbA1 < 7
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Raz 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 30 weeks
Participants	COUNTRY: Multinational SETTING: Outpatient Treatment N: 190 Control N: 0 AGE: 55.2 SEX: 47% men INCLUSION: Type 2 DM, 18-78 years EXCLUSIONS: recent insulin, medications other than metformin, BMI <20 or >43
Interventions	TREATMENT: metformin 2550 mg/day with sitagliptin 100 mg/day or placebo
Outcomes	Glycemic control, safety
Notes	

Reaven 1992

Methods	TRIAL DESIGN: Nonrandomised open-label trial DURATION: 3 months
Participants	Country: United States. Setting: research center. Treatment N: 13. Control N: 13. Age: 57 +/-2. Sex: 77% men. Inclusion: Type 2 DM with poor control on sulfonylureas. Exclusions: Other drugs that effect lipids.
Interventions	TREATMENT: Metformin 0.5-2.5g/day. COMPARISON: glipizide.
Outcomes	Insulin sensitivity, glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Relimpio 1998

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Spain. SETTING: outpatient. Treatment N: 31. Control N: 29. Treatment age: 65 +/-8. Control age: 66 +/-6. Treatment sex: 21% men. Control sex: 40% men. Inclusion: Poorly controlled insulin-treated Type 2 DM. Exclusions: life-threatening condition, common contraindication to treatment, renal insufficiency.
Interventions	TREATMENT: Metformin, dosage adjusted clilnically, + insulin. COMPARISON: insulin increase.
Outcomes	Lipids, HbA1, and fasting glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Reyes 1969

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 1 month
Participants	COUNTRY: Mexico. SETTING: outpatient. Treatment N: 53. Control N: 0. Age: not listed. Sex: 28% men. Inclusion: DM, poorly controlled on sulonylureas. Exclusions: none listed
Interventions	TREATMENT: metformin, 1600-2400mg/day + chlorpropamide 500-750mg/day. COMPARISON: none
Outcomes	Glycemia, and glucosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Riccio 1991

Methods	TRIAL DESIGN: Prospective comparative trial, with control group for less than 1 month. Metformin data analysed DURATION: 4 weeks
Participants	COUNTRY: Italy. SETTING: medical center. Treatment N: 6. Control N: 0. Treatment age: 48+/-2. Sex: not listed. Inclusion: non-insulin-dependent type DM. Exclusion: none listed.

Riccio 1991 *(Continued)*

Interventions	TREATMENT: metformin 850mg BID. COMPARISON: none.
Outcomes	Basal and insulin-mediated glucose, free-fatty acid metabolism, and lipds.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ristic 2007

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Multinational SETTING: Multicenter outpatient Treatment N: 262 Control N: 0 AGE: 61.7 SEX: 53% men INCLUSION: Type 2 DM, poor control on metformin EXCLUSIONS: none listed
Interventions	TREATMENT: metformin, at least 1 gm/day, with hateglinide 180 mg TID or gliclazide 240 mg/day
Outcomes	Glycemic control
Notes	

Roberts 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a ranomised trial of glimepiride DURATION: 6 months
Participants	COUNTRY: United States SETTING: multi-center Treatment N: 170 Control N: 0 AGE: 56.5 SEX: 61.6 % men INCLUSION: type 2 DM EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, dosage unclear, with pioglitazone or rosiglitazone, with or without glimepiride COMPARISON: none
Outcomes	Lipids, glucose, HbA1, hypoglycemice
Notes	

Roberts 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Robinson 1998

Methods	TRIAL DESIGN: Double-blind crossover randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United Kingdom. SETTING: teaching hospital clinic. Treatment N: 35. Control N: 35. Treatment age: 61.3. Control age: 56.1. Treatment sex: 37% men. Control sex: 21% men. Inclusion: Insulin-treated Type 2 DM. Exclusions: childbearing age, another anihyperglycemic medication, renal insufficiency with creatinine > 125.
Interventions	TREATMENT: Metformin 1-2 g/day. COMPARISON: placebo
Outcomes	Fasting glucose, HbA1, lipids, weight, and blood pressure.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Roden 2005

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 917 Control N: 916 Age: 57 +/- 8.5 Sex: 55% men Inclusion: type 2 DM naive to metformin pioglitazone Exlcusions: not stated
Interventions	TREATMENT: metformin 2.5 g/day COMPARISON: pioglitazone 45 mg/day
Outcomes	Insulin sensitivity, fasting serum glucose and insulin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Roden 2005 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Roden 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 2 years
Participants	COUNTRY: Multinational in Europe, Australia, Canada SETTING: Multicenter outpatient Treatment N: 320 Control N: 319 AGE: 58 SEX: 52% men INCLUSION: Type 2 DM, 35-75 years, poor control EXCLUSIONS: symptomatic congestive heart failure, pancreatitis, cancer, heart attack, stroke
Interventions	TREATMENT: metformin and gliclazide COMPARISON: Pioglitazone and gliclazide
Outcomes	Adipose tissue insulin sensitivity
Notes	

Rodger 1995

Methods	TRIAL DESIGN: randomised controlled trial of acarbose vs placebo. Metformin in non-randomised treatment strata DURATION: 12 months
Participants	COUNTRY: Canada. SETTING: outpatient. Treatment N: 74. Control N: 242. Age: unclear. Sex: not listed. Inclusion: Type 2 DM. Exclusions: lactose intolerance, debilitating disease, gastrointestinal disease, various medications.
Interventions	TREATMENT: Main: acarbose vs placebo. Treatment strata: metformin (dosage adjusted clinically), diet, sulfonylurea, insulin.
Outcomes	Postprandial glucose, HbA1, insulin, and c-peptide.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	High risk	C - Inadequate

Rodriguez 2008

Methods	TRIAL DESIGN: Open-label prospective comparative trial DURATION: 6 months
Participants	COUNTRY: Spain

Rodriguez 2008 *(Continued)*

	SETTING: Outpatient Treatment N: 723 Control N: 851 AGE: 61.1 SEX: 50% men INCLUSION: Type 2 DM, poor control on 2 meds EXCLUSIONS: congestive heart failure, liver or kidney abnormaltities, ketoacidosis
Interventions	TREATMENT: Metformin and pioglitazone or sulfonylurea COMPARISON: sulfonylurea and pioglitazone
Outcomes	Glycemic control, tolerability
Notes	

Roger 1999

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: France. SETTING: community-based multi-center study. Treatment N: 127, with 63 on metformin + benflurex and 64 on metformin + placebo. Control N: 0. Age: not listed. Sex: not listed. Inclusion: obese patients with uncontrolled type 2 DM, treated with metformin. Exclusions: young patients, severe inervurrent illnes, kidney or liver failure, severehypertension, chronic pancreatitis,and alcoholism.
Interventions	TREATMENT: metformin 850mg BID + benflurex 150mg TID or metformin + placebo. COMPARISON: none.
Outcomes	Basal and stimulated insulin, HgA1, and body weight.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Rosak 2005

Methods	TRIAL DESIGN: Prospective study DURATION: 24 weeks
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 11,014 Control N: 0 AGE: not stated SEX: not stated INCLUSION: type 2 DM EXCLUSIONS: none
Interventions	TREATMENT: metformin, doage unclear plus roiglitazone COMPARISON: none

Rosak 2005 *(Continued)*

Outcomes	Weight, HbA1, blood pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Rosenstock 1998

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised controlled trial of acarbose DURATION: 6 months
Participants	COUNTRY: United States. SETTING: multicenter outpatient. Treatment N: 148. Control N: 0. Age: 56.7. Sex: 74% men. Inclusion: metformin-treated patients with type 2 DM. Exclusions: acute or chronic acidosis, persistent ketonuria, or a history of ketoacidosis.
Interventions	TREATMENT: metformin 2-2.5g/day + placebo or metformin +acarbosis 75-300mg/day. COMPARISON: none.
Outcomes	HbA1c, glucose, insulin, triglycerides, and plasma metformin levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Rosenstock 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of insulin glargine and rosiglitazone DURATION: 24 weeks
Participants	COUNTRY: Canada SETTING: outpatient Treatment N: 217 Control N: 0 AGE: 55.6 SEX: 65% men INCLUSION: type 2 DM EXCLUSIONS: hepatic, renal and cardiovascular disease
Interventions	TREATMENT: metformin, dosage unclear plus sulfonylurea with and without glargine insulin COMPARISON: none
Outcomes	Glucose, HbA1, hypoglycemia
Notes	

Rosenstock 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Russell-Jones 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Multinational SETTING: OUtpatient Treatment N: 581 Control N: 0 AGE: 57 SEX: 56% men INCLUSION: Type 2 DM EXCLUSIONS: recnet insulin use, liver or kidney abnormalities, cardiovascular disase, hypertension, cancer, pregnancy
Interventions	TREATMENT: Metformin and glimepiride, with liraglutide, glargine insulin or placebo
Outcomes	Glycemic control, weight
Notes	

Sahin 2007

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 6 weeks
Participants	VOUNTRY: Turkey SETTING: outpatient Treatment N: 74 Control N: 91 Treatment AGE: 58.4 Control AGE: 58.4 Treatment SEX: 42% men Control SEX: 38% men INCLUSION: type 2 DM EXCLUSIONS: renal insufficiency, congestive heart failure, stroke, cigarettes
Interventions	TREATMENT: metformin 850 mg BID COMPARISON: rosiglitazone 4 mg daily
Outcomes	Lipids, homocysteine, folate, vitamin B12 levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Sahin 2007 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Sanchez-Barba 1999

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 30 months
Participants	COUNTRY: Spain. SETIING: outpatient. Treatment N: 30. Control N: 0. Age: not listed. Sex: not listed. Inclusion: type 2 DM. Exclusions: none listed
Interventions	TREATMENT: metformin, dosage adjusted clinically + insulin, dosage adjusted clinically. COMPARISON: none
Outcomes	HgA1c, and plasma glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Santos 1995

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 2.5 months
Participants	COUNTRY: Brazil. SETTING: metabolic laboratory. Treatment N: 14. Control N: 0. Age: 44+/-2. Sex: 36% men. Inclusions: type 2 DM, on no medications. Exclusions: prior insulin treatment.
Interventions	TREATMENT: metformin 850mg BID. COMPARISON: none.
Outcomes	Fasting glucose, HbA1, fasting insuling, lipids, and insuling receptor tyrosine kinase activity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Schernthaner 2004

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 12 months
Participants	COUNTRY: 12 European countries SETTING: outpatient Treatment N: 597

Schernthaner 2004 *(Continued)*

	Control N; 597 Age: 57 +/- 9 Sex: 60% men Inclusion: poorly controlled type 2 DM Exlcusions: standard
Interventions	TREATMENT: metformin850 mg TID COMPARISON: pioglitazone 45 mg/day
Outcomes	HbA1c, fasting glucose and insulin, lipid profiles
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Schiel 2008

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Germany SETTING: Outpatient Treatment N: 18 Control N: 34 AGE: 65.6 SEX: 53% men INCLUSION: Type 2 DM, poor control EXCLUSIONS: liver or kidney abnormalities, pregnancy
Interventions	TREATMENT: metformin 850 mg BID with glimepiride and insulin COMPARISON: glargine insuline with or without glimepiride
Outcomes	Glycemic control
Notes	

Schneider 1990

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Germany. SETTING: outpatient. Treatment N: 18. Control N: 18. Treatment age: 60.4, Control age: 61.5. Treatment sex: 44% men. Control sex: 56% men. Inclusion: Patients with Type 2 DM and hyperlipoproteinemia. Exclusions: cardiovascular disease, pulmonary disease, hepatic or gastrointestinal diseaes, malignancy or psychiatric disorder.
Interventions	TREATMEN: Metformin, dosage adjusted clinically. COMPARISON: placebo
Outcomes	Lipids, and lipoproteins.

Schneider 1990 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schulte 1973

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 36 months
Participants	COUNTRY: Mexico. SETTING: outpatient. Treatment N: 53. Control N: 0. Age: 57. Sex: 33% men. Inclusion: adult-onset DM. Exclusions: none listed.
Interventions	TREATMENT: metformin + chlorpropamide, dose adjusted clinically. COMPARISON: none.
Outcomes	Fasting and postprandial glucose, weight, and glycosuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Schwartz 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of extended-release metformin DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 706 Control N: 0 AGE: 54.5 SEX: 50% men INCLUSION: type 2 DM EXCLUSIONS: renal, hepatic, cardiovascular or pulmonary disase
Interventions	TREATMENT: metformin, up to 2000 mg daily, in three extended-release regimens COMPARISON: none
Outcomes	Glucose, HbA1
Notes	

Risk of bias

Schwartz 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Schweizer 2007

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Multinational in Americas, Europe SETTING: Multicenter outpatient Treatment N: 253 Control N: 526 AGE: 53.2 SEX: 54% men INCLUSION: Type 2 DM EXCLUSIONS: type 1 diabetes, congestive heart failure, pregnancy, kidney dysfunction, cirrhosis, coronary artery disease
Interventions	TREATMENT: metformin 2 gm/day COMPARISON: vildagliptin 100 mg/day
Outcomes	Glycemic control
Notes	

Schweizer 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Multinational in Europe, Americas, Asia SETTING: Multicenter outpatient Treatment N: 166 Control N: 169 AGE: 71 SEX: 50% men INCLUSION: Type 2 DM, elderly, 65-93 years EXCLUSIONS: congestive heart failure, unstable coronary artery disease, cirrhosis, kidney dysfunction
Interventions	TREATMENT: metformin 1500 mg/day COMPARISON: vildagliptin 100 mg/day
Outcomes	Glycemic, safety, tolerability
Notes	

Scott 2008

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 18 weeks
Participants	COUNTRY: Multinational

Scott 2008 *(Continued)*

	SETTING: Multicenter outpatient Treatment N: 273 Control N: 0 AGE: 55 SEX: 58% men INCLUSION: Type 2 DM, 18-75 years EXCLUSIONS: kidney or liver abnormalities
Interventions	TREATMENT: metformin, with sitagliptin, rosiglitazone or placebo
Outcomes	Glycemic control, safety
Notes	

Sharma 2006

Methods	TRIAL DESIGN: Prospective double-blind randomised controlled trial DURATION: 12 weeks
Participants	COUNTRY: India SETTING: outpatient Treatment N: 15 Control N: 15 Treatment AGE: 47.7 Control AGE: 50.8 Treatment SEX: 67% men Control SEX: 53% men INCLUSION: type 2 DM, newly diagnosed EXCLUSIONS: renal insufficiency, pulmonary dysfunction, hepatic dysfunction, congestive heart failure
Interventions	TREATMENT: metformin 1 gm BID COMPARISON: pioglitazone 15 mg BID
Outcomes	Adiponectin, leptin
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

Shimpi 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: India SETTING: Outpatient Treatment N: 31 Control N: 0 AGE: 49.1 SEX: 48% men

Shimpi 2009 *(Continued)*

	INCLUSION: Type 2 DM EXCLUSIONS: kidney or liver abnormaltiies, pregnancy
Interventions	TREATMENT: metformin 1 gm/day with glimeperide or glibenclamice
Outcomes	Glycemic control
Notes	

Sieradzki 1999

Methods	TRIAL DESIGN: Acarbose trial. Metformin in nonrandomised treatment strata DURATION: 2 motnhs
Participants	COUNTRY: Poland. SETTING: outpatient. Treatment N: 106. Control N: 374. Age: 31-88. Sex: 44% men. Inclusion: Type 2 DM. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, +/- sulfonylurea + acarbose. COMPARISON: sulfonyurea + acarbose or acarbose
Outcomes	Fasting and posprandial glucose, urinary glucose, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stades 2000

Methods	TRIAL DESIGN: Retrospective cohort study
Participants	Country: Netherlands. Setting: outpatient clinic. Treatment N: 65. Control N: 0. Age: 64.5. Sex: not listed. Inclusion: patients with type 2 DM on metformin treatment for at least 6 months. Exclusions: insufficient follow-up time, or no HgA1c on record.
Interventions	Study duration: median 32 months. Treatment: metformin, dosage adjusted clinically. Comparison: none.
Outcomes	HbA1c and body weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stalhammar 1991

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 35 months
Participants	COUNTRY: Sweden. SETTING: Swedish population study. Treatment N: 81. Control N: 0. Age: 50-74 years. Sex: 51% men. Inclusion: Patients with type 2 DM receiving metformin. Exclusions: none listed
Interventions	TREATMENT: metformin, dosage adjusted clinically. COMPARISON: none.
Outcomes	HbA1c and BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Standl 2001

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of miglitol DURATION: 6 months
Participants	COUNTRY: multi-country SETTING: multi-center Treatment N: 154 Control N: 0 AGE: 61.5 SEX: 55% men INCLUSION: type 2 DM poorly controlled EXCLUSIONS: conditions that affect gastrointestinal motility
Interventions	TREATMENT: metformin, dosage unclear, plus glibenclamide with or without miglitol COMPARISON: none
Outcomes	Glucose, lipids, flatulence, diarrhea
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Sterne 1963

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 60 motnhs
Participants	COUNTRY: Germany. SETTING: outpatient. Age: not listed. Sex: not listed. Inclusions: maturity-onset DM. Exclusions: none listed.

Sterne 1963 *(Continued)*

Interventions	TREATMENT: metformin, dosage titrated clinically, alone or in combination with insulin or sulfonyrureas. COMPARISON: none
Outcomes	Glycemia, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stewart 2006

Methods	TRIAL DESIGN; Prospective cohort study of metformin in a randomised trial of rosiglitazone DURATION: 14 weeks
Participants	COUNTRY: Multi-national SETTING: multi-center Treatment N: 526 Control N: 0 AGE: 59 SEX: 55% men INCLUSION: type 2 DM inadequately controlled EXCLUSIONS: congestive heart failure, hypertension
Interventions	TREATMENT: metformin, up to 3 gm daily with or without rosiglitazone COMPARISON: none
Outcomes	Glucose, HbA1, C-reative protein, beta-cell function, blood pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stocker 2007

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 47 Control N: 45 Treatment AGE: 65 Control N: 64 Treatment SEX: 53% men Control SEX: 50% men

Stocker 2007 *(Continued)*

	INCLUSION: type 2 DM poorly controlled EXCLUSIONS: renal insufficiency, congestive heart failure, myocardial infarction
Interventions	TREATMENT: metformin 850 mg BID COMPARISON: rosiglitazone 4 mg dailure
Outcomes	c-reactive protein, carotid artery intimal thickening
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stratmann 1965

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 8 months
Participants	COUNTRY: Germany. SETTING: outpatient. Treatment N: 92. Control N: 0. Age: not listed. Sex: not listed. Inclusion: patients with DM, who have failed oral sulfonylureas. Exclusions: none listed.
Interventions	TREATMENT: metformin, dosage adjusted clinically. COMPARISON: none.
Outcomes	Level of glycemic control.m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Strowig 2002

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 4 months
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 27 Control N: 61 Age: 52 +/- 9 Sex: 50% men Inclusion: type 2 DM inadequately treated on insulin Exclusions: renal or hepatic dysfunction
Interventions	TREATMENT: metformin 2 g/day + insulin COMPARISON: insulin with or without troglitazone 600 mg/day

Strowig 2002 *(Continued)*

Outcomes	HbA1c, body weight, lipid profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Stumvoll 1995

Methods	TRIAL DESIGN: Prospective comparative trial, with control DURATION: 4 monthsgroup studied for less than 1 month. Metformin data analysed
Participants	Country: United States. Setting: outpatient. Treatment N: 10. Control N: 0. Age: 58+/-9. Sex: 60% men. Inclusion: healthy obese type 2 DM. Exclusions: none listed, but all were described as healthy.
Interventions	Study duration: 4 months. Treatment intervention: metfomin 800-2550mg/day. Comparison intervention: none.
Outcomes	HbA1, fasting glucose, weight, plasma glucose turnover, and lactate conversion to glucose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Sundaresan 1997

Methods	TRIAL DESIGN: Double-blind randomised controlled trial
Participants	COUNTRY: Australia. SETTING: outpatient. Treatment N: 14. Control N: 14. Age: 40-73. Sex: 64% men. Inclusion: Type 2 DM. Exclusions: BMI > 40 different from ideal body weight, vascular disease, microvscular disease.
Interventions	TREATMENT: Metformin 1-2g/day. COMPARISON: glibenclamicde
Outcomes	Norepinephrine levels, blood pressure, and forearm vascular resistance.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Swislocki 1999

Methods	TRIAL DESIGN: Retrospective cohort study DURATION: 5 motnhs
Participants	COUNTRY: United States. SETTING: Veteran's Administration Health Care system. Treatment N: 251. Comparison: 0. Age: mot listed. Sex: not listed. Inclusion: patients with type 2 DM receiving metformin. Exclusions: none listed.
Interventions	TREATMENT: metformin, doses adjusted clinically. COMPARISON: none.
Outcomes	HbA1c, weight and blood pressure.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Szanto 1964

Methods	TRIAL DESIGN: Open-label comparative trial DURATION: 9 months
Participants	COUNTRY: Ireland. SETTING: diabetes clinic. Treatment N: 10. Control N: 9. Age: 51-76. Sex: 45% men. Inclusion: Type 2 DM not controlled on sulfonylueas. Exclusions: hypoglycemia.
Interventions	TREATMENT: Metformin, dosage unclear. COMPARISON: phenformin (not analyses). Then acetohexamide-biguanide combination was given.
Outcomes	Weight, blood glucose, and insulin dose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Taylor 1982

Methods	TRIAL DESIGN: Nonrandomised open-label trial DURATION: 12 months
Participants	COUNTRY: United Kingdom. SETTING: outpatient. Treatment N: 23. Control N: 71. Age: 51-52 years. Treatment sex: 43% men. Control sex: 77% male. Inclusion: Type 2 DM, obese and nonobese. Exclusions: renal or hepatic disease.
Interventions	TREATMENT: Metformin (obese) 500mg TID. COMPARISON: glibenclamice (nonobese) 2.5-15mg/day.

Taylor 1982 *(Continued)*

Outcomes	Lipids and apolipoproteins
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Teranishi 2007

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Japan SETTING: Outpatient Treatment N: 20 Control N: 21 AGE: 59.7 SEX: 58% men INCLUSION: Type 2 DM EXCLUSIONS: renal failure, severe liver dysfunction, severe congestive heart failure
Interventions	TREATMENT: metformin 750 mg/day COMPARIDON: pioglitazone 30 mg/day
Outcomes	Glycemic control, intracellular lipid content in liver and skeletal muscle
Notes	

Tessari 1994

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 1 month
Participants	COUNTRY: Italy. SETTING: outpatient. Treatment N: 11. Control N: 6. Treatment age: 53 +/-3. Control age: 60 +/-3> Treatment sex: 55% men. Control sex: 33% men. Inclusion: Diet-treated Type 2 DM. ExclusionsL cardiovascular, gastrointestinal pulmonary or renal disease.
Interventions	TREATMENT: Metformin, dosage adjusted clinically. COMPARISON: placebo
Outcomes	Postprandial phenylalanine kinetics, weight, free fatty acids, BMI, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tessier 1999

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Canada. SETTING: outpatient. Treatment N: 18 Control N: 18. Treatment age: 59.1 +/- 7.1. Control age: 59.3 +/-7.3. Treatment sex: 16% men. Control sex: 44% men. Inclusion: Type 2 DM. Exclusions: acute cardiovascular or neurological events, malignancy, various medications.
Interventions	TREATMENT: Metformin 0.75-2.5g/day. COMPARISON: gliclazide
Outcomes	HbA1, fructosamine, glucose tolerance test.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Testa 1996

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: Italy. SETTING: outpatient clinic and metabolic laboratory. Treatment N: 80. Control N: 0. Age: 63+/-9.7. Sex: 63% men. Inclusion: type 2 DM with good glycemic control on sulfonylureas for at least 2 years.. Exclusions: previous insulin treatment
Interventions	TREATMENT: 1.2-1.7g/day. COMPARISON: none.
Outcomes	Plasminogen activator inhibitor, lipoprotein(a), and BMI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Teupe 1991

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 24 months
Participants	COUNTRY: Germany. SETTING: outpatient. Treatment N: 50. Control N: 50. Treatment age: 51.5 +/-10. Control age: 56 +/-8. Treatment sex: 40% males. . Control sex: 40% males. Inclusion: Type 2 DM, poor control. Exclusions: age > 70, creatinine > 1.2, iver cirhosis, ischemia or wasting disease, sever acute disease.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + diet. COMPARISON: diet

Teupe 1991 *(Continued)*

Outcomes	Weight, lipids, HbA1, c-peptide, and lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Tikkainen 2004

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: Finland SETTING: outpatient Treatment N: 11 Control N: 9 Age: 30.6 +/- 3.5 Sex: 35% men Inclusion: type 2 DM treated with diet Exclusions: cardiovascular or renal disease
Interventions	TREATMENT: metformin 1 g BID + placebo COMARISON: rosiglitazone 4 mg BID + placebo
Outcomes	HbA1c, insulin, free fatty acid, body weight, adiponectin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Topiak 2007

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of topiramate DURATION: 1 year
Participants	COUNTRY: Austria SETTING: outpatient Treatment N: 640 Control N: 0 AGE: 53 SEX: 58% men INCLUSION: obese patients with type 2 DM EXCLUSIONS: central nervous system of psychiatric illness
Interventions	TREATMENT: metformin, dosage unclear, with or without topiramate COMPARISON: none

Topiak 2007 *(Continued)*

Outcomes	Percent change in weight and HbA1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Tosi 2003

Methods	TRIAL DESIGN: Double-blind randomised controlled cross-over trial DURATION: 6 months for each treatment arm DURATION:
Participants	COUNTRY: Italy SETTING: outpatient Treatment N: 88 Control N: 88 Age: 57.3 +/- 7 Sex: 70% men Inclusion: type 2 DM Exclusions: severe cardiovascular, renal or hepatic disease, insulin treatment,
Interventions	TREATMENT: metformin 3 g/day with or without glibenclamide COMPARISON: glibenclamide 15 mg/day
Outcomes	HbA1c, fasting glucose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Triplitt 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of glargine insulin and rosiglitazone DURATION: 16 weeks
Participants	COUNTRY: United States SETTING: outpatient Treatment N: 20 Control N: 0 AGE: 47.5 SEX: 40% men INCLUSION: type 2 DM poorly controlled EXCLUSIONS: cardiac, hepatic or renal dysfunction

Triplitt 2006 *(Continued)*

Interventions	TREATMENT: metformin, dosage unclear, with glargine insulin or rosiglitazone COMPARISON: none
Outcomes	Glucose, HbA1, insulin resistance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Trischitta 1992

Methods	TRIAL DESIGN: randomised controlled trial cross-over DURATIPN: 2 months for each arm
Participants	COUNTRY: Italy. SETTING: outpatient. Treatment N: 20. Control N: 20. Age: 53.6 +/-2.1. Sex: not listed. Inclusion: Type 2 DM with sulfonylurea. Exclusions: renal, liver, cardiovascular or systemic disese.
Interventions	TREATMENT: Metformin 500mg TID. COMPARISON: insulin
Outcomes	Fasting and postprandial glucose, c-peptide, HbA1, weight, and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Trischitta 1998

Methods	TRIAL DESIGN: randomised controlled trial cross-over DURATION: 2 months
Participants	COUNTRY: Italy. SETTING: outpatient. Treatment N: 50. Control N: 50. Age: 55.7 +/-1.2. Sex: 24% men. Inclusion: Type 2 DM. Exclusions: none listed.
Interventions	TREATMENT: Metformin 850mg TID + glibenclamide. COMPARISON: insulin + glibenclamide
Outcomes	Fasting glucose, HbA1, c-peptide, and weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Turkmen 2007

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Turkey SETTING: Outpatient Treatment N: 16 Control N: 30 AGE: 55.9 SEX: 24% men INCLUSION: Type 2 DM EXCLUSIONS: kidney or liver abnormalities, congestive heart failure
Interventions	TREATMENT: metformin 1700 mg/day COMPARISON: Rosiglitazone 8 mg/day or control
Outcomes	Plasma brain natriuretic peptide levels, myocardial performance index
Notes	

Uehara 2001

Methods	TRIAL DESIGN: Prospective randomised controlled trial DURATION: 12 weeks
Participants	COUNTRY: Brazil SETTING: outpatient Treatment N: 13 Control N: 13 AGE: not stated SEX: not stated INCLUSION: overweight patient with type 2 DM and hypertension EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, dosage unclear COMPARISON: placebo
Outcomes	Glycemic control, insulin sensisitivy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

UKPDS-34 1998

Methods	TRIAL DESIGN: Open-label randomised controlled trial. DURATION: 6.6 - 10.7 years.
Participants	COUNTEY: United Kingdom SETTING: large multicenter. Treatment N: 683. Control N: 1631. Treatment age: 53 +/-8. Control age: 53 +/-8. Treatment sex: 46% men. Control sex: 46% men. Inclusion: Type 2 DM.

UKPDS-34 1998 *(Continued)*

	Exclusions: severe vascular disease, accelerated hypertension, renalfailure with creatinine > 175 mmol/L, life thretening disease, severe asthma, myocardial infarction in past year, current angina, congestive heart failure. n = 1704
Interventions	TREATMENT: Metformin 850mg QD-TID. Comparison: diet, sulfonylurea, or insulin
Outcomes	DM-related endpoint (sudden death, death for hyper- or hypoglycemia, myocardial infarction, stroke, renal failure, amputation, eye problems), diabetes-related death, all-cause mortality, HgA1, microalbuminuria.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Umpierrez 2006

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of pioglitazone or glimepiride DURATION: 6 months
Participants	COUNTRY: United States SETTING: outpatient TREATMENT N: 203 Control N: 0 AGE: 53 SEX: 55% men INCLUSION: type 2 DM inadequately controlled EXCLUSIONS: abnormal laboratory values including hematology, chemisty or urinalysis
Interventions	TREATMENT: metformin, dosage unclear, with glimepiride or pioglitazone COMPARISON: none
Outcomes	Glucose, HbA1, hypoglycemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Vahatalo 2007

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Finland SETTING: Outpatient

Vahatalo 2007 *(Continued)*

	Treatment N: 26 Control N: 26 AGE: 62 SEX: 67% men INCLUSION: Type 2 DM, 40-75 years EXCLUSIONS: kidney or liver abnormalities, severe congestive heart failure
Interventions	TREATMENT: metformin plus insulin COMPARISON: Insulin with or without glipizide
Outcomes	Glycemic control
Notes	

van der Meer 2009

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: Netherlands SETTING: Outpatient Treatment N: 39 Control N: 39 AGE: 56.4 SEX: 100% men INCLUSION: Type 2 DM, 45-65 years EXCLUSIONS: cardiovascular or liver disease
Interventions	TREATMENT: metformin, 1 gm BID COMPARISON: pioglitazone 30 mg/day
Outcomes	Echocardiographic function, myocardial substrate metabolism
Notes	

Van Gaal 2001

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of miglitol DURATION: 32 weeks
Participants	COUNTRY: Belgium SETTING: outpatient Treatment N: 152 Control N: 0 AGE: not stated SEX: not stated INCLUSION: type 2 DM inadequately controlled EXCLUSIONS: not stated
Interventions	TREATMENT: metformin, up to 2250 mg daily, with or without miglitol COMPARISON: none
Outcomes	Postprandial glucose, adverse effects
Notes	

Van Gaal 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Vannasaeng 1995

Methods	TRIAL DESIGN: Open-label trial of acarbose. Metformin in nonrandomised treatment strata DURATION: 6 months
Participants	COUNTRY: Thailand. SETTING: Outpatient. Treatment N: 24. Control N: 12. Age: 50.4 +/-1.5, Sex: 19% men. Inclusion: Type 2 DM. Exclusions: pregnancy, liver disorder, renal insufficiency with Creatinine > 2 mg/dl.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + sulfonylurea + acarbose. COMPARISON: sulfonylurea + acarbose
Outcomes	Fasting glucose, HbA1, lipids, insulin and c-peptide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Velojic-Golubovic 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in an open-label randomised controlled trial DURATION: 3 months
Participants	COUNTRY: Serbia SETTING: Outpatient Treatment N: 50 Control N: 0 AGE: 58.7 SEX: 60% men INCLUSION: Type 2 DM EXCLUSIONS: cardiovascular disease, liver or kidney abnormalities
Interventions	TREATMENT: metformin, varying dose, with biphasic or premixed insulin
Outcomes	Glycemic control
Notes	

Velussi 1992

Methods	TRIAL DESIGN: Open-label cross-over nonrandomised comparative trial

Velussi 1992 *(Continued)*

	DURATION: 4 months
Participants	COUNTRY: Italy. SETTING: general practive. Treatment N: 60. Control N: 60. Age: 68 +/- 3 Sex: 53% men. Inclusion: Type 2 DM with hypertension. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glibenclamide, doses on clinical grounds. COMPARISON: Phenformin + glibenclamide (not analysed).
Outcomes	Fasting glucose, HbA1c, basal C-peptide, glucosuria, and lactate levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Vigneri 1991

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 2 months
Participants	COUNTRY: Italy. SETTING: outpatient. Treatment N: 12. Control N: 12. Age: 52.3 +/-2.1 Sex: not listed. Inclusion: Type 2 DM with failure to sulfonylureas. Exclusions: none listed.
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + glyburide. COMPARISON: insulin + glyburide
Outcomes	Fasting and postprandial glucose, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Viljanen 2005

Methods	TRIAL DESIGN: Prospective double-blind randomised placebo-controlled trial DURATION: 6 months
Participants	COUNTRY: FInland SETTING: outpatient Treatment N: 12 Control N: 25 Treatment AGE: 57.8 Control AGE: 58.7 Treatment SEX: 58% men Control SEX: 72% men INCLUSION: type 2 DM EXLCUSIONS: renal or hepatic disease, hypertension, cardiovascular disease

Viljanen 2005 *(Continued)*

Interventions	TREATMENT: metformin 1 gm BID COMPARISON: rosiglitazone 4 mg BID or placebo
Outcomes	Subcutaneous adippose tissue glucose uptake
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Vukovic 2007

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 6 weeks
Participants	COUNTRY: Serbia SETTING: Outpatient Treatment N: 43 Control N: 46 AGE: 44.5 SEX: not listed INCLUSION: Type 2 DM EXCLUSIONS: non listed
Interventions	TREATMENT: metformin plus diet COMPARISON: Placebo plus diet
Outcomes	Glycemic control, insulin secretion
Notes	

Weissman 2005

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trail of rosilglitazone DURATION: 6 months
Participants	COUNTRY: Germany SETTING: outpatient Treatment N: 766 Control N: 0 AGE: 55.6 SEX; not stated INCLUSION: type 2 DM EXCLUSIONS: renal or hepatic disase, congestive heart failure
Interventions	TREATMENT: metformin 1000 -1500 mg daily with or without rosiglitazone COMPARISON: none
Outcomes	Glucose, HbA1
Notes	

Weissman 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Willey 1992

Methods	TRIAL DESIGN: Prospective cohort study
Participants	Country: Australia. Setting: outpatient. Treatment N: 38. Control N: 0. Age: 54+/-1.7. Sex: 44% men. Inclusion: overweight patients with type 2 DM, and HbA1c >normal. Exclusions: none listed.
Interventions	Trial duration: 3 months. Treatment intervention: metformin, 1-3g/day, + dexfenfluramine or metformin + placebo. Comparison: none.
Outcomes	Body weight, HbA1c, blood pressure, and fructosamine.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Willey 1994

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 3 months
Participants	COUNTRY: Australia. SETTING: diabetes center. Metformin treatment N: 20 (10 on dexfenfluramine, 10 on placebo). Age: 55+/-1.9. Sex: 30% men. Inclusion: Type 2 DM, overweight with poor control, on maximum dose metformin. Exclusions: none listed.
Interventions	TREATMENT: Metformin, 1-3g/day, + dexfluramine or metformin + placebo. COMPARISON: none.
Outcomes	Weight, BMI, and HbA1c.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Willms 1999

Methods	TRIAL DESIGN: randomised controlled trial. Single-blind for metformin versus other.

Willms 1999 *(Continued)*

	DURATION: 3 months
Participants	COUNTRY: Germany. SETTING: outpatient. Treatment N: 29. Control N: 60. Treatment ate: 53.4. Control age: 59.2. Treatment sex: 48% males. Control sex: 48% males. Inclusion: Type 2 DM. Exclusions: Severe hepatic or renal abnormalities, respiratory insufficiency, conditions that predispose to tissue anoxia.
Interventions	TREATMENT: MetfORmin 850mg BID. COMPARISON: acarbose or placebo
Outcomes	Body weight, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Wilson 1989

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 2 months
Participants	COUNTRY: United Kingdom. SETTING: outpatient. Treatment N: 15. Control N: 45. Age: 65 +/-2. Sex: 80% men. Inclusion: Type 2 DM on sulfonylureas. Exclusion: None listed.
Interventions	TREATMENT: Metformin 500mg TID. COMPARISON: guar 5gmTID.
Outcomes	Glucose, HbA1, and lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Wolever 1995

Methods	TRIAL DESIGN: Double-blind randomised controlled trial of acarbose versus placebo. Metformin in 1 of 4 non-randomized treatment strata. DURATION: 11 years
Participants	COUNTRY: Canada. SETTING: outpatient. Treatment N: 83. Control N: 271. Treatment age: 55.8. Control age 57.6. Treatment sex: 44% men. Control sex: 57% males. Inclusion: Type 2 DM. Exclusions: renal or liver abnormalities.
Interventions	TREATMENT: acarbos vs placebo. Treatment strata: Metformin (dosage adjusted clinically), diet, sulfonylurea, insulin
Outcomes	Lipids, HbA1, and serum acetate levels

Wolever 1995 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Wolever 2000

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 9 months
Participants	COUNTRY: Canada. SETTING: outpatient. Treatment N: 109. Control N: 90. Treatment age: 58.7 +/-1.1. Control age: 59.5 +/-1.1. Treatment sex: 80% men. Control sex: 69% men. Inclusion: Type 2 DM. Exclusions: insulin treatment, major debilitating disease, recent cardiovascular event or surgery, various medication, renal or liver idsease, emotional disorder.
Interventions	TREATMENT: Metformin 500 mgTID or metformin + miglitol. COMPARISON: miglitol or placebo
Outcomes	Serum folate and B12 levels, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wu 1990

Methods	TRIAL DESIGN: Prospective cohort study DURATION: 4 months
Participants	COUNTRY: United States. SETTING: inpatient and outpatient. Treatment N: 12. Control N: 0. Age: 56+/-3. Sex: 58% men. Inclusion: type 2 DM. Exclusion: significant illness, or medication that could affect carbohydrate metabolism.
Interventions	TREATMENT: metformin 2.5g/day. COMPARISON: none.
Outcomes	Fasting and postprandial glucose, HbA1c, insulin binding, lactate and lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Wulffele 2000

Methods	TRIAL DESIGN: Abstract of randomised controlled trial, placebo-controlled DURATION: 4 months
Participants	COUNTRY: Netherlands SETTING: outpatient Treatment N: 95 Control N: 95 AGE: not listed SEX: not listed INCLUSION: Type 2 DM treated with insulin EXCLUSIONS: none listed
Interventions	TREATMENT: Metformin, dosage unclear, + insulin COMPARISON: placebo + insulin
Outcomes	Daily dose insulin, and HbA1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wulffele 2002

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 48 months
Participants	COUNTRY: The Netherlands SETTING: outpatient Treatment N: 171 Control N: 182 Age: 60 +/- 10 Sex: 45% m4n Inclusion: type 2 DM controlled with insulin Exlcusions: renal insufficiency with GFR < 50, congestive heart failure
Interventions	TREATMENT: metformin, dose adjusted clinically, + insulin COMPARISON: placebo + insulin
Outcomes	Insulin requirements, lipid profile, glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Wulffele 2003

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: The Netherlands SETTING: outpatient Treatment N: 196 Control N; 194 Inclusion: type 2 DM Exlcusions: renal insufficiency with GFR < 50, congestive heart failure, pregnancy
Interventions	TREATMENT: metformin, dose adjusted clinically COMPARISON: placebo
Outcomes	Homocystein, folate, vitamin B12, body weight, glycemic control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Wulffele 2005

Methods	TRIAL DESIGN: Double-blind randomised controlled trial DURATION: 4 months
Participants	COUNTRY: THe Netherlands SETTING: outpatient Treatment N: 89 Control N: 93 Age: 58 +/- 11 Sex: 48% men Inclusion: type 2 DM Exclusions: congestive heart failure, serious illness, renal insufficiency with GFR < 50
Interventions	TREATMENT: metformin 2.5 g/day COMPARISON: placebo
Outcomes	Systolic, diastolic, mean blood pressure, 24-hour blood pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Yale 2001

Methods	TRIAL DESIGN: Prospective cohort study of metformin in a randomised trial of troglitazone

Yale 2001 *(Continued)*

	DURATION: 1 year
Participants	COUNTRY: Canada SETTING: mult-center Treatment N: 200 Control N: 0 AGE: 59 SEX: not stated INCLUSION: type 2 DM poorly controlled EXCLUSIONS: creatinine > 2, hepatic or cardiac disase, hypertension, anemia
Interventions	TREATMENT: metofmrin, dosage unclear, plus sulfonylurea, with or without troglitazone COMPARISON: none
Outcomes	Glucose, HbA1, lipids, insulin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Yamanouchi 2005

Methods	TRIAL DESIGN: Open-label randomised controlled trial DURATION: 12 months
Participants	COUNTRY: Japan SETTING: outpatient Treatment N: 39 Control N: 75 Age: 55.4 +/- 9 Sex: 55% men Inclusion: newly diagnosed type 2 DM Exclusions: standard
Interventions	TREATMENT: metformin750 mg/day COMPARISON: pioglitazone 30-45 mg/day or glimepiride 1-2 mg/day
Outcomes	Fasting glucose, free fatty acid, HbA1c, blood pressure, lipid profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Yener 2008

Methods	TRIAL DESIGN: Open-label randomised controlled trial

Yener 2008 *(Continued)*

	DURATION: 3 months
Participants	COUNTRY: Turkey SETTING: Outpatient Treatment N: 16 Control N: 23 AGE: 53.3 SEX: 54% men INCLUSION: Type 2 DM, 30-70 years EXCLUSIONS: hypertension, cardiovascular disase, pregnancy, morbid obesity, kidney or liver abnormalities
Interventions	TREATMENT: metformin 1700 mg/day COMPARISON: rosiglitazone 4 mg/day
Outcomes	Serum transforming growth factor-beta 1 levels
Notes	

Yki-Jarvinen 1999

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 1 year
Participants	COUNTRY: Finland SETTING: multicenter Treatment N: 48 Control N: 48 AGE: 58+/-1 SEX: not listed INCLUSION: Poorly controlled type 2 DM EXCLUSIONS: congestive heart failure, liver diseae, creatinine > 120
Interventions	TREATMENT: Metformin, dosage adjusted clinically, + placebo or metformin + glyburide COMPARISON: insulin + glyburide + placebo or BID insulin
Outcomes	Weight, HbA1, plasma glucose, insulin, lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Yu 1999

Methods	TRIAL DESIGN: randomised controlled trial DURATION: 4 weeks
Participants	COUNTRY: United States SETTING: research laboratory Treatment N: 10 Control N: 10

Yu 1999 *(Continued)*

	Treatment AGE: 49+/-9 Control AGE: 51+/-9 Treatment SEX: 70% men Control SEX: 80% men INCLUSION: Type 2 DM with suboptimal contol EXCLUSIONS: renal or liver abnormalities
Interventions	TREATMENT: Metformin 1-2.5 g/day COMPARISON: troglitazone
Outcomes	Fasting glucose, insulin sensitivity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Zinman 2009

Methods	TRIAL DESIGN: Observational cohort of metformin in a double-blind randomised controlled trial DURATION: 6 months
Participants	COUNTRY: United States, Canada SETTING: Outpatient Treatment N: 533 Control N: 0 AGE: 55 SEX: 57% men INCLUSION: Type 2 DM EXCLUSIONS: none listed
Interventions	TREATMENT: metformin and rosiglitazone with liraglutide 100 microliter injection weekly or placebo injection weekly
Outcomes	Glycemic control, safety
Notes	

BID= two times a day; BMI=body mass index; DM=diabetes mellitus; TID=three times a day

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

Study	Reason for exclusion
Aguilar 1992b	TRIAL DESIGN: Retrospective analysis
Belsey 2008	TRIAL DESIGN: Restrospective systematic review
Berhanu 2007	TRIAL DESIGN: Prospective observational study, with not all patients on metformin
Bernard 1965	TRIAL DESIGN: Prospective cohort, with varying durations of treatment

Study	Reason for exclusion
Bodmer 2008	TRIAL DESIGN: Retrospective case-control analysis
Bonfigli 1999	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Bruneder 1978	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Cacciapuoti 1991	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Chan 2009	TRIAL DESIGN: Restrospective analysis
Charlton 2008	TRIAL DESIGN: Prospective cohort tiral, with not all patients on metformin
Chow 1995	TRIAL DESIGN: Prospective cohort trial, that did not give length of treatment
Clauson 1996	TRIAL DESIGN: Prospective cohort trial, that did not give length of treatment
Comaschi 2007	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Comaschi 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Connolly 1996	TRIAL DESIGN: Retrospective analysis study
Cook 2005	TRIAL DESIGN: Retosepctive cohort study, of unclear duration
Cunha 2008	TRIAL DESIGN: Prospective comparative trial, with duration < one month
Daniel 1997	TRIAL DESIGN: Retrospective meta-analysis
Debry 1964	TRIAL DESIGN: Prospective cohort study, of varying durations
Debry 1966a	TRIAL DESIGN: Retrospective cohort study, with no durations given
Debry 1966b	TRIAL DESIGN: Retrospective cohort study, with no durations given
Derosa 2009	TRIAL DESIGN: Observational cohort study, with not all patients on metformin
English 2007	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Eurich 2005a	TRIAL DESIGN: Retrospective case-control.
Eurich 2005b	TRIAL DESIGN: Prospective comparative study, of varying durations
Evans 2006	TRIAL DESIGN: Retosepctive cohort study, of unclear duration
Farah 2008	TRIAL DESIGN: Observational cohort study, with unclear number of patients
Faure 2008	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Fery 1997	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Forti 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Galuska 1994	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month

Study	Reason for exclusion
Gibson 1995	TRIAL DESIGN: Prospective comparative trial, as part of another UKPDS trial, with patients studied less than 1 month
Gin 1982	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Gin 1985	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Gin 1989	TRIAL DESIGN: Prospective cohort study, lasting less than 1 month
Giugliano 1979	TRIAL DESIGN: Prospective cohort study, lasting less than 1 month
Gontier 2008	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Guthrie 1997	TRIAL DESIGN: Retrospective meta-analysis
Harris 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
He 2009	TRIAL DESIGN: Randomized control trial, lasting less than 1 month
Herman 2006	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Hermansen 2007	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Hirsch 2009	TRIAL DESIGN: Retrospective analysis
Home 2009	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Hong 2008	TRIAL DESIGN: Prospective observational trial, lasting less than 1 month
Irsigler 1978	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Ismail 1978	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Isnard 1991	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Isnard 1996	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Jansson 1996	TRIAL DESIGN: Prospective cohort study, lasting less than 1 month
Javaid 2007	TRIAL DESIGN: Prospective comparative study, of varying durations
Johansen 1999	TRIAL DESIGN: Retrospective meta-analysis
Kamber 2008	TRIAL DESIGN: Prospective observational trial, with unclear number of patients
Kim 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Komajda 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Lalau 1994	TRIAL DESIGN: Retrospective analysis
Lalau 1995	TRIAL DESIGN: Retrospective analysis
Lapina 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin

Study	Reason for exclusion
Leslie 1987	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Lim 1970	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Lin 2008	TRIAL DESIGN: Prospective observational trial, with not all patients on metformin
Magalhaes 2006	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Masoudi 2005	TRIAL DESIGN: Retosepctive cohort study, of unclear duration
Mellbin 2008	TRIAL DESIGN: Retrospective analysis
Messens 1965	TRIAL DESIGN: Prospective cohort study of varying durations
Messens 1966	TRIAL DESIGN: Prospective cohort study of varying durations
Monami 2006	TRIAL DESIGN: Prospective comparative study, of varying durations
Monami 2008	TRIAL DESIGN: Retrospective meta-analysis
Monami 2008a	TRIAL DESIGN: Retrospective observational cohort study, of varying durations
Muntoni 1965	TRIAL DESIGN: Prospective cohort study, of varying durations
Nauck 1993	TRIAL DESIGN: Prospective cohort study, of unclear duration
Nauck 1997	TRIAL DESIGN: Retrospective review of 4 trials
Nauck 2009	TRIAL DESIGN: Prospective observational cohort trial, with not all patients on metformin
O'Connor 1998	TRIAL DESIGN: Retrospective meta-analysis
Ong 2006	TRIAL DESIGN: Retosepctive comparative study, of unclear duration
Orlikowska 1966	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Panahloo 1995	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Papa 2008	TRIAL DESIGN: Prospective observational cohort trial, with not all patients on metformin
Perriello 1994	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Pilger 1978	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Prager 1983	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Rambert 1961	TRIAL DESIGN: Prospective cohort study of varying durations.
Rao 2008	TRIAL DESIGN: Retrospective meta-analysis
Rigas 1968	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Rizkalla 1986	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Runge 2008	TRIAL DESIGN: Retrospective analysis

Study	Reason for exclusion
Sambol 1996	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Scarpello 1998	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Schaffalitzky 1979	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Selby 1999	TRIAL DESIGN: Retrospective analysis
Seufert 2008	TRIAL DESIGN: Prospecctive observational cohort trial, with not all patients on metformin
Sharabashi 2006	TRIAL DESIGN: Prospective cohort study, of unclear duration
Signore 1996	TRIAL DESIGN: Prospective cohort study, lasting less than 1 month
Simpson 2006	TRIAL DESIGN: Retosepctive comparative study, of unclear duration
Slama 1984	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Stefanovic 1999	TRIAL DESIGN: Prospective cohort study, of unclear duration
Sugawara 1962	TRIAL DESIGN: Prospective cohort study, of varying duration
Sum 1992	TRIAL DESIGN: Prospective cohort study, lasting less than 1 month
Teitelbaum 1963	TRIAL DESIGN: Prospective cohort study, of unclear duration
Tomioka 2007	TRIAL DESIGN: Restrospective analysis
Trischitta 1983	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Turner 1995	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Yegnanarayan 2008	TRIAL DESIGN: Observational cohort study, with not all patients on metformin
Zapecka-Dubno 1999	TRIAL DESIGN: Prospective comparative trial, lasting less than 1 month
Zhang 2009	TRIAL DESIGN: Retrospective meta-analysis

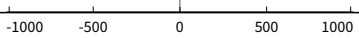
DATA AND ANALYSES

Comparison 1. Fatal/nonfatal lactic acidosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lactic acidosis incidence per patient-years (metformin minus non-metformin)	148	62960	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]

Analysis 1.1. Comparison 1 Fatal/nonfatal lactic acidosis, Outcome 1 Lactic acidosis incidence per patient-years (metformin minus non-metformin).

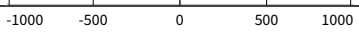
Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Hermann 1991a	0/55	0/29		0.16%	0[-0.05,0.05]
Horton 2000	0/175	0/176		0.74%	0[-0.01,0.01]
Moses 1999a	0/28	0/11		0.07%	0[-0.12,0.12]
Hermann 1994b	0/54	0/18		0.11%	0[-0.08,0.08]
Grant 1996	0/26	0/12		0.07%	0[-0.12,0.12]
Johnson 1993	0/2	0/1		0.01%	0[-0.73,0.73]
Grant 1991	0/3	0/2		0.01%	0[-0.53,0.53]
Schneider 1990	0/5	0/4		0.02%	0[-0.34,0.34]
Ponssen 2000	0/13	0/18		0.06%	0[-0.12,0.12]
De Silva 1979	0/7	0/4		0.02%	0[-0.31,0.31]
Johansen 1984	0/1	0/3		0.01%	0[-0.68,0.68]
Robinson 1998	0/9	0/9		0.04%	0[-0.19,0.19]
Marena 1994	0/1	0/1		0%	0[-0.85,0.85]
Abbasi 1997	0/4	0/2		0.01%	0[-0.5,0.5]
Yki-Jarvinen 1999	0/48	0/48		0.2%	0[-0.04,0.04]
Hirsch 1999	0/10	0/10		0.04%	0[-0.17,0.17]
Abbink 2000	0/2	0/10		0.01%	0[-0.44,0.44]
Wolever 2000	0/82	0/68		0.31%	0[-0.03,0.03]
Erle 1999	0/20	0/23		0.09%	0[-0.09,0.09]
Josephkutty 1990	0/5	0/5		0.02%	0[-0.31,0.31]
Dornan 1991	0/20	0/20		0.08%	0[-0.09,0.09]
Giugliano 1993	0/14	0/12		0.05%	0[-0.14,0.14]
Higginbotham 1979	0/3	0/3		0.01%	0[-0.46,0.46]
Lalor 1990	0/5	0/10		0.03%	0[-0.25,0.25]
Hother-Nielsen 1989	0/1	0/1		0%	0[-0.85,0.85]
Pedersen 1989	0/1	0/1		0%	0[-0.85,0.85]
Bingle 1964	0/4	0/4		0.02%	0[-0.37,0.37]
Damsbo 1998	0/2	0/2		0.01%	0[-0.6,0.6]
Sundaresan 1997	0/1	0/1		0%	0[-0.85,0.85]
Cavallo-Perin 1989	0/6	0/6		0.03%	0[-0.27,0.27]
Hermann 1994a	0/28	0/9		0.06%	0[-0.14,0.14]
DeFronzo 1995	0/342	0/214		1.11%	0[-0.01,0.01]
Nagi 1993	0/7	0/7		0.03%	0[-0.24,0.24]
Tessari 1994	0/1	0/1		0%	0[-0.85,0.85]
Fritsche 2000	0/5	0/5		0.02%	0[-0.31,0.31]
Gregorio 1989	0/6	0/6		0.03%	0[-0.27,0.27]
Cusi 1996	0/3	0/3		0.01%	0[-0.46,0.46]
Aviles-Santa 1999	0/11	0/11		0.05%	0[-0.16,0.16]
Garber 1997	0/85	0/18		0.13%	0[-0.07,0.07]
Chiasson 1994	0/83	0/271		0.53%	0[-0.02,0.02]
Makimattila 1999	0/13	0/16		0.06%	0[-0.13,0.13]
Groop 1989	0/6	0/6		0.03%	0[-0.27,0.27]
McBain 1988	0/7	0/13		0.04%	0[-0.19,0.19]
Taylor 1982	0/23	0/31		0.11%	0[-0.07,0.07]
Teupe 1991	0/100	0/100		0.42%	0[-0.02,0.02]
Tessier 1999	0/9	0/9		0.04%	0[-0.19,0.19]
Gregorio 1990	0/2	0/1		0.01%	0[-0.73,0.73]
Jeppesen 1994	0/3	0/4		0.01%	0[-0.42,0.42]
Fanghanel 1998	0/8	0/13		0.04%	0[-0.18,0.18]



Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Lee 1998	0/12	0/22		0.07%	0[-0.12,0.12]
Szanto 1964	0/2	0/4		0.01%	0[-0.5,0.5]
Hoffmann 1997	0/16	0/32		0.09%	0[-0.09,0.09]
Vigneri 1991	0/2	0/2		0.01%	0[-0.6,0.6]
Bayraktar 1996	0/3	0/3		0.01%	0[-0.46,0.46]
Munk 1975	0/20	0/10		0.06%	0[-0.14,0.14]
Relimpio 1998	0/10	0/1		0.01%	0[-0.61,0.61]
Ferner 1988	0/2	0/2		0.01%	0[-0.6,0.6]
DeFronzo 1991	0/4	0/4		0.02%	0[-0.37,0.37]
Inzucchi 1998	0/11	0/4		0.02%	0[-0.29,0.29]
Laurenti 1992	0/15	0/15		0.06%	0[-0.12,0.12]
Davidson 2000	0/81	0/27		0.17%	0[-0.05,0.05]
Wulffele 2000	0/32	0/32		0.13%	0[-0.06,0.06]
Niazi 1998	0/8	0/11		0.04%	0[-0.19,0.19]
Wolever 1995	0/83	0/271		0.53%	0[-0.02,0.02]
Bjorntorp 1978	0/2	0/2		0.01%	0[-0.6,0.6]
Nosadini 1987	0/1	0/1		0%	0[-0.85,0.85]
Trischitta 1992	0/3	0/3		0.01%	0[-0.46,0.46]
Lord 1983	0/1	0/1		0%	0[-0.85,0.85]
Jones 2000 b	0/174	0/428		1.04%	0[-0.01,0.01]
Rodger 1995	0/74	0/242		0.48%	0[-0.02,0.02]
Cairns 1977	0/4	0/6		0.02%	0[-0.32,0.32]
Josse 1995	0/83	0/271		0.53%	0[-0.02,0.02]
McIntyre 1991	0/1	0/1		0%	0[-0.85,0.85]
Raptis 1996	0/8	0/8		0.03%	0[-0.21,0.21]
Nattrass 1977	0/1	0/1		0%	0[-0.85,0.85]
Wilson 1989	0/3	0/6		0.02%	0[-0.38,0.38]
Elkeles 1991	0/13	0/11		0.05%	0[-0.15,0.15]
Clarke 1968	0/139	0/139		0.58%	0[-0.01,0.01]
Willms 1999	0/7	0/15		0.04%	0[-0.19,0.19]
Groop 1991	0/6	0/24		0.04%	0[-0.2,0.2]
Campbell 1988	0/31	0/24		0.11%	0[-0.07,0.07]
Reaven 1992	0/3	0/2		0.01%	0[-0.53,0.53]
Chan 1993	0/2	0/2		0.01%	0[-0.6,0.6]
Jackson 1987	0/4	0/4		0.02%	0[-0.37,0.37]
Velussi 1992	0/20	0/20		0.08%	0[-0.09,0.09]
Yu 1999	0/1	0/1		0%	0[-0.85,0.85]
Noury 1991	0/8	0/7		0.03%	0[-0.22,0.22]
Calle-Pascual 1995	0/4	0/8		0.02%	0[-0.3,0.3]
Ohnhaus 1983	0/2	0/2		0.01%	0[-0.6,0.6]
Trischitta 1998	0/8	0/10		0.04%	0[-0.19,0.19]
Grant 1998	0/14	0/9		0.05%	0[-0.16,0.16]
McAlpine 1988	0/7	0/7		0.03%	0[-0.24,0.24]
Fanghanel 1996	0/8	0/8		0.03%	0[-0.21,0.21]
Hermann 1991b	0/22	0/22		0.09%	0[-0.08,0.08]
Vannasaeng 1995	0/12	0/6		0.03%	0[-0.22,0.22]
Guillausseau 1997	0/6	0/9		0.03%	0[-0.23,0.23]
Holman 1987	0/3	0/8		0.02%	0[-0.36,0.36]
Kiayias 1999	0/8	0/5		0.03%	0[-0.27,0.27]
Rains 1989	0/2	0/2		0.01%	0[-0.6,0.6]
Imano 1998	0/3	0/4		0.01%	0[-0.42,0.42]
Boyd 1992	0/1	0/2		0.01%	0[-0.73,0.73]

Favours treatment -1000 -500 0 500 1000 Favours control

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Collier 1989	0/6	0/6		0.03%	0[-0.27,0.27]
Kirk 1999	0/4	0/5		0.02%	0[-0.34,0.34]
Campbell 1994	0/24	0/24		0.1%	0[-0.08,0.08]
Clarke 1977	0/131	0/146		0.58%	0[-0.01,0.01]
Klein 1991	0/25	0/25		0.11%	0[-0.07,0.07]
Peacock 1986	0/14	0/10		0.05%	0[-0.15,0.15]
Prager 1986	0/1	0/4		0.01%	0[-0.66,0.66]
Botha 1977	0/2	0/5		0.01%	0[-0.48,0.48]
Rains 1988	0/9	0/12		0.04%	0[-0.17,0.17]
UKPDS-34 1998	0/7239	0/11580		37.49%	0[-0,0]
D'Argenzio 1996	0/12	0/12		0.05%	0[-0.15,0.15]
Cho 1992	0/2	0/3		0.01%	0[-0.53,0.53]
Sieradzki 1999	0/18	0/63		0.12%	0[-0.08,0.08]
Abbink 2001	0/4	0/4		0.02%	0[-0.37,0.37]
Belcher 2005	0/917	0/2796		5.81%	0[-0,0]
Blonde 2002	0/146	0/50		0.31%	0[-0.03,0.03]
Carter 2005	0/13	0/8		0.04%	0[-0.18,0.18]
Cefalu 2002	0/26	0/26		0.11%	0[-0.07,0.07]
Chakrabarti 1965	0/7	0/5		0.02%	0[-0.28,0.28]
Chiasson 2001	0/119	0/124		0.51%	0[-0.02,0.02]
Cryer 2005	0/7227	0/1505		10.48%	0[-0,0]
Derosa 2003	0/65	0/65		0.27%	0[-0.03,0.03]
Fisman 2001	0/2556	0/14961		18.37%	0[-0,0]
Fujioka 2005	0/207	0/61		0.4%	0[-0.02,0.02]
Garber 2002	0/73	0/74		0.31%	0[-0.03,0.03]
Goldstein 2003	0/56	0/29		0.16%	0[-0.05,0.05]
Gonzalez-Ortiz 2004	0/17	0/9		0.05%	0[-0.15,0.15]
Horton 2004	0/97	0/149		0.49%	0[-0.02,0.02]
Jones 2002	0/13	0/12		0.05%	0[-0.14,0.14]
Jung 2005	0/7	0/7		0.03%	0[-0.24,0.24]
Karlsson 2005	0/5	0/11		0.03%	0[-0.25,0.25]
Kim 2002	0/2	0/2		0.01%	0[-0.6,0.6]
Lawrence 2004	0/10	0/20		0.06%	0[-0.14,0.14]
Manzella 2004	0/20	0/20		0.08%	0[-0.09,0.09]
Marre 2002	0/95	0/32		0.2%	0[-0.04,0.04]
Natali 2004	0/9	0/14		0.05%	0[-0.16,0.16]
Pavo 2003	0/62	0/65		0.27%	0[-0.03,0.03]
Rachmani 2002	0/780	0/792		3.31%	0[-0,0]
Roden 2005	0/917	0/916		3.86%	0[-0,0]
Schernthaner 2004	0/597	0/597		2.51%	0[-0,0]
Strowig 2002	0/9	0/20		0.05%	0[-0.15,0.15]
Tikkainen 2004	0/3	0/3		0.01%	0[-0.46,0.46]
Tosi 2003	0/44	0/44		0.19%	0[-0.04,0.04]
Wulffele 2002	0/684	0/728		2.97%	0[-0,0]
Wulffele 2003	0/60	0/60		0.25%	0[-0.03,0.03]
Wulffele 2005	0/27	0/29		0.12%	0[-0.07,0.07]
Yamanouchi 2005	0/39	0/75		0.22%	0[-0.04,0.04]
Total (95% CI)	**24739**	**38221**		**100%**	**0[-0,0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=147(P=1); I²=0%					
Test for overall effect: Not applicable					



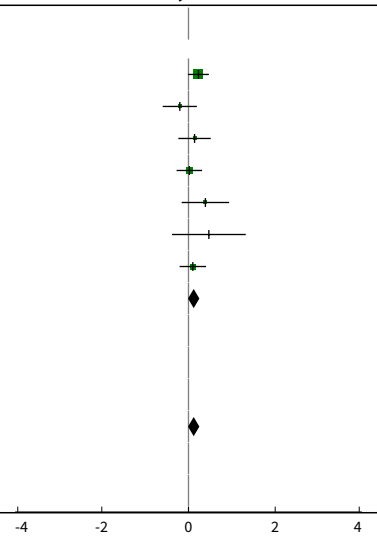
Favours treatment Favours control

Comparison 2. Blood lactate levels

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Net treatment effect, lactate levels (mmol/L)	7	222	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.01, 0.25]
1.1 Net treatment effect, lactate levels (metformin minus non-metformin, mmol/L)	7	222	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.01, 0.25]
2 Mean treatment lactate levels (mmol/L)	19	1547	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.13, -0.05]
2.1 Mean treatment lactate levels (metformin minus non-metformin, mmol/L)	16	1387	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.00, 0.09]
2.2 Mean treatment lactate levels (metformin minus phenformin, mmol/L)	3	160	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-0.86, -0.65]
3 Peak stimulated lactate levels (mmol/L)	4	92	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.05, 0.20]
3.1 Peak stimulated lactate levels (metformin minus non-metformin, mmol/L)	3	72	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.03, 0.22]
3.2 Peak stimulated lactate levels (metformin minus phenformin, mmol/L)	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.06, 0.32]

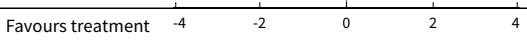
Analysis 2.1. Comparison 2 Blood lactate levels, Outcome 1 Net treatment effect, lactate levels (mmol/L).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Net treatment effect, lactate levels (metformin minus non-metformin, mmol/L)							
Campbell 1994	24	0.1 (0.4)	24	-0.2 (0.4)		29.85%	0.23[-0.01,0.47]
Cusi 1996	10	-0.2 (0.5)	10	0 (0.5)		11.1%	-0.2[-0.59,0.19]
Damsbo 1998	25	0 (0.7)	29	-0.1 (0.7)		12.37%	0.14[-0.23,0.51]
Gregorio 1990	20	0 (0.6)	10	0 (0.3)		19.98%	0.02[-0.27,0.31]
Josephkutty 1990	16	0.3 (0.8)	16	-0.1 (0.8)		5.76%	0.39[-0.16,0.94]
Klein 1991	10	0.4 (1)	10	-0 (1)		2.39%	0.47[-0.38,1.32]
Teupe 1991	9	0.1 (0.3)	9	-0 (0.3)		18.55%	0.1[-0.21,0.41]
Subtotal ***	**114**		**108**			**100%**	**0.12[-0.01,0.25]**
Heterogeneity: Tau^2=0; Chi^2=5.39, df=6(P=0.49); I^2=0%							
Test for overall effect: Z=1.79(P=0.07)							
Total ***	**114**		**108**			**100%**	**0.12[-0.01,0.25]**
Heterogeneity: Tau^2=0; Chi^2=5.39, df=6(P=0.49); I^2=0%							
Test for overall effect: Z=1.79(P=0.07)							



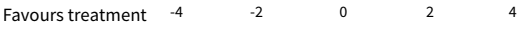
Analysis 2.2. Comparison 2 Blood lactate levels, Outcome 2 Mean treatment lactate levels (mmol/L).

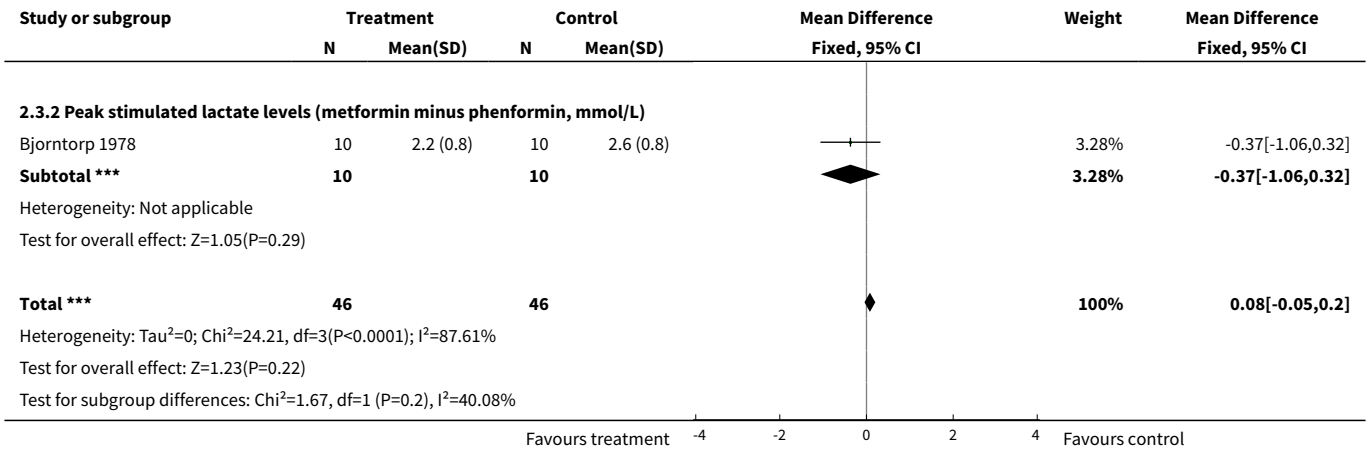
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 Mean treatment lactate levels (metformin minus non-metformin, mmol/L)							
Botha 1977	21	1.2 (0.4)	21	1.2 (0.4)		3.3%	-0.03[-0.26,0.2]
Campbell 1994	24	1 (0.4)	24	0.9 (0.2)		6.05%	0.09[-0.08,0.26]
Cryer 2005	456	1.7 (0.6)	114	1.6 (0.6)		11.5%	0.1[-0.02,0.22]
Cusi 1996	10	1 (0.3)	10	1.1 (0.3)		2.22%	-0.1[-0.38,0.18]
Damsbo 1998	9	0.8 (0.2)	9	0.7 (0.2)		4.63%	0.13[-0.06,0.32]
De Silva 1979	21	1.1 (0.6)	21	1.2 (0.7)		1.14%	-0.1[-0.49,0.29]
Gregorio 1990	20	0.9 (0.5)	20	0.9 (0.3)		3.43%	0.02[-0.21,0.25]
Hother-Nielsen 1989	9	1.6 (0.5)	9	1.4 (0.3)		1.2%	0.13[-0.25,0.51]
Jackson 1987	10	1.6 (0.2)	10	1.6 (0.2)		6.29%	0[-0.17,0.17]
Josephkutty 1990	10	1.8 (0.8)	10	1.5 (0.6)		0.45%	0.31[-0.31,0.93]
Klein 1991	16	1.6 (0.6)	16	1.5 (0.7)		0.83%	0.11[-0.35,0.57]
McAlpine 1988	21	1.6 (0.6)	21	1.3 (0.6)		1.58%	0.3[-0.03,0.63]
Nattrass 1977	6	0.9 (0.3)	6	0.9 (0.2)		1.75%	0.05[-0.27,0.37]
Pedersen 1989	10	1.6 (0.4)	10	1.4 (0.4)		1.85%	0.2[-0.11,0.51]
Rachmani 2002	195	1.5 (0.4)	198	1.5 (0.3)		35.6%	0[-0.07,0.07]
Teupe 1991	25	1.4 (0.6)	25	1.3 (0.5)		1.98%	0.12[-0.18,0.42]
Subtotal * **	**863**		**524**			**83.8%**	**0.04[-0,0.09]**
Heterogeneity: Tau^2=0; Chi^2=10.08, df=15(P=0.81); I^2=0%							
Test for overall effect: Z=1.79(P=0.07)							
2.2.2 Mean treatment lactate levels (metformin minus phenformin, mmol/L)							
Bjorntorp 1978	10	1 (0.2)	10	1.1 (0.2)		6.29%	-0.04[-0.21,0.13]
Cavallo-Perin 1989	10	1.3 (0.3)	10	1.7 (0.3)		2.6%	-0.37[-0.63,-0.11]
Velussi 1992	60	1.7 (0.4)	60	3.2 (0.5)		7.31%	-1.5[-1.65,-1.35]
Subtotal * **	**80**		**80**			**16.2%**	**-0.75[-0.86,-0.65]**
Heterogeneity: Tau^2=0; Chi^2=168.7, df=2(P<0.0001); I^2=98.81%							
Test for overall effect: Z=14.21(P<0.0001)							
Total * **	**943**		**604**			**100%**	**-0.09[-0.13,-0.05]**
Heterogeneity: Tau^2=0; Chi^2=367.09, df=18(P<0.0001); I^2=95.1%							
Test for overall effect: Z=4.08(P<0.0001)							
Test for subgroup differences: Chi^2=188.32, df=1 (P<0.0001), I^2=99.47%							



Analysis 2.3. Comparison 2 Blood lactate levels, Outcome 3 Peak stimulated lactate levels (mmol/L).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.3.1 Peak stimulated lactate levels (metformin minus non-metformin, mmol/L)							
Botha 1977	21	4.7 (0.5)	21	5.2 (0.4)		19.75%	-0.5[-0.78,-0.22]
Damsbo 1998	9	1 (0.2)	9	0.8 (0.1)		62.92%	0.21[0.05,0.37]
Nattrass 1977	6	1.2 (0.4)	6	0.8 (0.2)		14.05%	0.41[0.08,0.74]
Subtotal * **	**36**		**36**			**96.72%**	**0.09[-0.03,0.22]**
Heterogeneity: Tau^2=0; Chi^2=22.54, df=2(P<0.0001); I^2=91.13%							
Test for overall effect: Z=1.45(P=0.15)							





APPENDICES

Appendix 1. Search strategy

Search terms
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent. TYPE 2 DIABETES MELLITUS 1. Diabetes mellitus, non-insulin-dependent [MeSH, all subheadings and categories included] 2. NIDDM 3. (Non insulin* dep*) OR (Noninsulin* dep*) OR (Non insulin dep*) 4. (Typ* II diabet*) OR (Typ* 2 diabet*) OR (diabet* typ* 2) OR (diabet* typ* II) 5. #1 OR #2 OR #3 OR #4 METFORMIN 6. Biguanides [MeSH, all subheadings and categories included] 7. Biguanid* 8. Metformin [MeSH, all subheadings and categories included] 9. Glucophag* 10. Metformin* 11. #6 or #7 or #8 or #9 or #10 TYPE 2 DIABETES AND METFORMIN 12. #5 AND #11

WHAT'S NEW

Date	Event	Description
16 March 2010	New citation required but conclusions have not changed	Erratum author Salpeter EE: 'posthumous' deleted.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 2, 2002

Date	Event	Description
12 November 2009	New citation required but conclusions have not changed	The third update as of October 2009 revealed no cases of fatal or nonfatal lactic acidosis in over 70,000 patient-years of metformin use. Metformin did not significantly affect lactic acid levels.
11 November 2009	New search has been performed	An update search covering the period 2008 to October 8, 2009 identified 137 potentially relevant publications out of 1660 scanned references. From these 73 studies were included as new trials.
30 September 2007	New search has been performed	Second update: No cases of fatal or nonfatal lactic acidosis were found in over 50,000 patient-years of metformin use. Metformin did not significantly affect lactic acid levels.
31 August 2005	New search has been performed	This is an update of the first version of this review, published in issue 2, 2002.

CONTRIBUTIONS OF AUTHORS

SHELLEY SALPETER : Protocol development, trials selection, quality assessment of trials, data extraction, data analysis, manuscript preparation, management of references.

ELIZABETH GREYBER: Search strategy, quality assessment of trials, data extraction, manuscript preparation.

GARY PASTERNAK: Trials selection.

EDWIN SALPETER: Data analysis, statistical evaluation.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Santa Clara Valley Medical Center, USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acidosis, Lactic [*chemically induced] [mortality]; Cohort Studies; Contraindications; Diabetes Mellitus, Type 2 [*drug therapy]; Hypoglycemic Agents [*adverse effects]; Incidence; Lactic Acid [blood]; Metformin [*adverse effects]; Prospective Studies; Risk

MeSH check words

Humans