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Metformin monotherapy for adults with type 2 diabetes mellitus (Review)

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[Intervention Review]

Metformin monotherapy for adults with type 2 diabetes mellitus

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ABSTRACT

Background

Worldwide, there is an increasing incidence of type 2 diabetes mellitus (T2DM). Metformin is still the recommended first-line glucose-lowering drug for people with T2DM. Despite this, the effects of metformin on patient-important outcomes are still not clarified.

Objectives

To assess the effects of metformin monotherapy in adults with T2DM.

Search methods

We based our search on a systematic report from the Agency for Healthcare Research and Quality, and topped-up the search in CENTRAL, MEDLINE, Embase, WHO ICTRP, and ClinicalTrials.gov. Additionally, we searched the reference lists of included trials and systematic reviews, as well as health technology assessment reports and medical agencies. The date of the last search for all databases was 2 December 2019, except Embase (searched up 28 April 2017).

Selection criteria

We included randomised controlled trials (RCTs) with at least one year's duration comparing metformin monotherapy with no intervention, behaviour changing interventions or other glucose-lowering drugs in adults with T2DM.

Data collection and analysis

Two review authors read all abstracts and full-text articles/records, assessed risk of bias, and extracted outcome data independently. We resolved discrepancies by involvement of a third review author. For meta-analyses we used a random-effects model with investigation of risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, using 95% confidence intervals (CIs) for effect estimates. We assessed the overall certainty of the evidence by using the GRADE instrument.

Main results

We included 18 RCTs with multiple study arms (N = 10,680). The percentage of participants finishing the trials was approximately 58% in all groups. Treatment duration ranged from one to 10.7 years. We judged no trials to be at low risk of bias on all 'Risk of bias' domains. The main outcomes of interest were all-cause mortality, serious adverse events (SAEs), health-related quality of life (HRQoL), cardiovascular mortality (CVM), non-fatal myocardial infarction (NFMI), non-fatal stroke (NFS), and end-stage renal disease (ESRD).

Two trials compared metformin (N = 370) with insulin (N = 454). Neither trial reported on all-cause mortality, SAE, CVM, NFMI, NFS or ESRD. One trial provided information on HRQoL but did not show a substantial difference between the interventions.

Seven trials compared metformin with sulphonylureas. Four trials reported on all-cause mortality: in three trials no participant died, and in the remaining trial 31/1454 participants (2.1%) in the metformin group died compared with 31/1441 participants (2.2%) in the sulphonylurea group (very low-certainty evidence). Three trials reported on SAE: in two trials no SAE occurred (186 participants); in the other trial 331/1454 participants (22.8%) in the metformin group experienced a SAE compared with 308/1441 participants (21.4%) in the sulphonylurea group (very low-certainty evidence). Two trials reported on CVM: in one trial no CVM was observed and in the other trial 4/1441 participants (0.3%) in the metformin group died of cardiovascular reasons compared with 8/1447 participants (0.6%) in the sulphonylurea group (very low-certainty evidence). Three trials reported on NFMI: in two trials no NFMI occurred, and in the other trial 21/1454 participants (1.4%) in the metformin group experienced a NFMI compared with 15/1441 participants (1.0%) in the sulphonylurea group (very low-certainty evidence). One trial reported no NFS occurred (very low-certainty evidence). No trial reported on HRQoL or ESRD.

Seven trials compared metformin with thiazolidinediones (very low-certainty evidence for all outcomes). Five trials reported on all-cause mortality: in two trials no participant died; the overall RR was 0.88, 95% CI 0.55 to 1.39; P = 0.57; 5 trials; 4402 participants). Four trials reported on SAE, the RR was 0,95, 95% CI 0.84 to 1.09; P = 0.49; 3208 participants. Four trials reported on CVM, the RR was 0.71, 95% CI 0.21 to 2.39; P = 0.58; 3211 participants. Three trial reported on NFMI: in two trials no NFMI occurred and in one trial 21/1454 participants (1.4%) in the metformin group experienced a NFMI compared with 25/1456 participants (1.7%) in the thiazolidinedione group. One trial reported no NFS occurred. No trial reported on HRQoL or ESRD.

Three trials compared metformin with dipeptidyl peptidase-4 inhibitors (one trial each with saxagliptin, sitagliptin, vildagliptin with altogether 1977 participants). There was no substantial difference between the interventions for all-cause mortality, SAE, CVM, NFMI and NFS (very low-certainty evidence for all outcomes).

One trial compared metformin with a glucagon-like peptide-1 analogue (very low-certainty evidence for all reported outcomes). There was no substantial difference between the interventions for all-cause mortality, CVM, NFMI and NFS. One or more SAEs were reported in 16/268 (6.0%) of the participants allocated to metformin compared with 35/539 (6.5%) of the participants allocated to a glucagon-like peptide-1 analogue. HRQoL or ESRD were not reported.

One trial compared metformin with meglitinide and two trials compared metformin with no intervention. No deaths or SAEs occurred (very low-certainty evidence)
no other patient-important outcomes were reported.

No trial compared metformin with placebo or a behaviour changing interventions.

Four ongoing trials with 5824 participants are likely to report one or more of our outcomes of interest and are estimated to be completed between 2018 and 2024. Furthermore, 24 trials with 2369 participants are awaiting assessment.

Authors' conclusions

There is no clear evidence whether metformin monotherapy compared with no intervention, behaviour changing interventions or other glucose-lowering drugs influences patient-important outcomes.

PLAIN LANGUAGE SUMMARY

Is metformin an effective treatment for adults with type 2 diabetes?

Background
Type 2 diabetes is a condition that causes high levels of sugar in the blood. Blood sugar levels are controlled by insulin, a hormone made by the pancreas. Insulin instructs the liver, muscles and fat cells to remove sugar from the blood and store it. When the pancreas does not make enough insulin, or the body does not respond to insulin, too much sugar stays in the blood. Many medicines for treating type 2 diabetes are available. These aim to lower the amount of sugar in the blood and reduce long-term complications of diabetes. The first medicine that is usually prescribed to people with type 2 diabetes is metformin. Metformin works by reducing the amount of sugar that the liver releases into the blood. It also improves the way the body responds to insulin.

We wanted to find out whether metformin is an effective treatment for type 2 diabetes, and whether it causes any unwanted effects. We also wanted to compare its effects with other antidiabetic medicines, and with diets, exercise or both. The outcomes we were specifically interested in were death, serious unwanted events, health-related quality of life, death from cardiovascular causes, and non-fatal complications of diabetes (for example heart attacks, strokes or kidney failure).

What did we look for?
We searched medical databases for studies that:
— were randomised controlled trials: randomised controlled trials are medical studies where participants are put randomly into one of the treatment groups. This type of study provides the most reliable evidence about whether treatments make a difference;
— included people aged 18 years or older, with type 2 diabetes;

— compared metformin with: a placebo (fake treatment); no treatment; diet programmes to help people eat well; or another medicine that lowers blood sugar levels;
— lasted at least one year.

What did we find?
We found 18 studies with multiple study arme including a total of 10,680 participants. The studies lasted between one year and approximately 11 years. They compared metformin with:
— insulin injections (two studies);
— other medicines that lower blood sugar levels: sulphonylureas (seven studies); thiazolidinediones (seven studies); dipeptidyl peptidase-4 inhibitors (three studies); a glucagon-like peptide-1 analogue (one study); a meglitinide (one study);
— no treatment (two studies).

No study compared metformin with a placebo or with diet or exercise programmes.

Key results
Almost all studies investigated laboratory measurements of blood sugar control like fasting blood glucose. However, there was few information on patient-important outcomes such as death, serious unwanted events, health-related quality of life, death from cardiovascular causes, and non-fatal complications of diabetes when comparing metformin with other medicines that lower blood sugar levels, placebo or no intervention. The available data did not show any clear benefit or harm of metformin.

Four ongoing studies with 5824 participants will report one or more of our outcomes of interest andwill be completed between 2018 and 2024. Furthermore, 24 studies with 2369 participants could be used in a future update of our review once results are published.

Certainty of the evidence
All the studies in this review were poorly conducted. The number of participants in most treatment comparisons was small. Even if studies reported some data we have very little confidence in the results of the comparisons. Future studies may substantially change our findings.

How up to date is this review?
This evidence is up to date as of 2 December 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus insulin

Metformin monotherapy compared with insulin for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: insulin

Outcomes	Insulin	Metformin	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	**Not reported**				
Serious adverse events	**Not reported**				
Health-related quality of life (Short Form-36 version 2 questionnaire) Follow-up: 1 year	See comment		91 (1)	⊕⊖⊖⊖ **very low** [a]	No substantial difference in mental or physical health-related quality of life between the intervention groups
Cardiovascular mortality	**Not reported**				
Non-fatal myocardial infarction	**Not reported**				
Non-fatal stroke	**Not reported**				
End-stage renal disease	**Not reported**				

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels because of risk of bias and serious imprecision - see Appendix 15.

Summary of findings 2. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus sulphonylureas

Metformin monotherapy compared with sulphonylureas for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: sulphonylureas (glibenclamide/glyburide, gliclazide, glipizide, glimepiride)

Outcomes	Sulphonylureas (glibenclamide/glyburide, gliclazide, glipizide, glimepiride)	Metformin	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1-4 years	See comment		3129 (4)	⊕⊖⊖⊖ **very low** [a]	3 trials: no participant died (Campbell 1994; Derosa 2004; Erem 2014) 1 trial: 31/1454 participants (2.1%) in the metformin group died vs 31/1441 participants (2.2%) in the sulphonylurea group (Kahn 2006)
Serious adverse events (SAE) Follow-up: 1-4 years	See comment		3081 (3)	⊕⊖⊖⊖ **very low** [a]	2 trials: no SAE occurred (Derosa 2004; Erem 2014) 1 trial: 331/1454 participants (22.8%) in the metformin group experienced a SAE compared with 308/1441 participants (21.4%) in the sulphonylurea group (Kahn 2006)
Health-related quality of life	**Not reported**				
Cardiovascular mortality (CVM) Follow-up: 1-4 years	See comment		2940 (2)	⊕⊖⊖⊖ **very low** [a]	1 trial: no CVM was observed (Erem 2014) 1 trial: 4/1455 participants (0.3%) in the metformin group died of cardiovascular reasons vs 8/1447 participants (0.6%) in the sulphonylurea group (Kahn 2006)
Non-fatal myocardial infarction (NFMI)	See comment		3047 (3)	⊕⊖⊖⊖	2 trials: no NFMI occurred (Erem 2014; Yamanouchi 2005)

Follow-up: 1-4 years			**very low** [a]	1 trial: 21/1454 participants (1.4%) in the metformin group experienced a NFMI vs 15/1441 participants (1.0%) in the sulphonylurea group (Kahn 2006)
Non-fatal stroke (NFS) Follow-up: 1-4 years	See comment	72 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no NFS occurred (Yamanouchi 2005)
End-stage renal disease	**Not reported**			

CI: confidence interval; **NFMI**: non-fatal myocardial infarction; **NFS**: non-fatal stroke; **SAE**: serious adverse event.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels because of risk of bias and serious imprecision - see Appendix 16

Summary of findings 3. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus thiazolidinediones

Metformin monotherapy compared with thiazolidinediones for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: thiazolidinediones (pioglitazone, rosiglitazone)

Outcomes	Thiazolidinediones (pioglitazone, rosiglitazone)	Metformin monotherapy	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1-4 years	**16 per 1000**	**14 per 1000** (9 to 22)	**RR 0.88** (0.55 to 1.39)	4402 (5)	⊕⊖⊖⊖ **very low** [a]	2 trials: no deaths occurred (Erem 2014; Kiyici 2009) 1 trial contributed 65/71 events (91.5%) (Kahn 2006)

Serious adverse events (SAE) Follow-up: 1-4 years	**220 per 1000**	**209 per 1000** (184 to 239)	**RR 0.95** (0.84 to 1.09)	3208 (4)	⊕⊖⊖⊖ **very low** [a]	2 trials: no SAE occurred (Erem 2014; Kiyici 2009).
Health-related quality of life	**Not reported**					
Cardiovascular mortality (CVM) Follow-up: 1-4 years	**3 per 1000**	**2 per 1000** (1 to 7)	**RR 0.71** (0.21 to 2.39)	3211 (4)	⊕⊖⊖⊖ **very low** [a]	2 trials: no deaths due to cardiovascular reasons occurred (Erem 2014; Kiyici 2009)
Non-fatal myocardial infarction (NFMI) Follow-up: 1-4 years	See comment			3020 (3)	⊕⊖⊖⊖ **very low** [a]	2 trials: no NFMI occurred (Erem 2014; Yamanouchi 2005) 1 trial: 21/1454 participants (1.4%) in the metformin group experienced a NFMI vs 25/1456 participants (1.7%) in the thiazolidinedione group
Non-fatal stroke (NFS) Follow-up: 1-4 years	See comment			72 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no NFS occurred (Yamanouchi 2005)
End-stage renal disease	Not reported					

CI: confidence interval; **NFMI**: non-fatal myocardial infarction; **NFS**: non-fatal stroke; **RR:** risk ratio; **SAE**: serious adverse event.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels because of risk of bias and serious imprecision - see Appendix 17.

Summary of findings 4. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus dipeptidyl-peptidase 4 inhibitors

Metformin monotherapy compared with dipeptidyl peptidase-4 inhibitors for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, vildagliptin)

Outcomes	Dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, vildagliptin)	Metformin monotherapy	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1.5-2 years	See comment		1977 (3)	⊕⊖⊖⊖ **very low** [a]	1 trial: 5/328 (1.5%) participants in the metformin group died vs 2/335 (0.6%) participants in the saxagliptin group (Pfützner 2011) 1 trial: 1/364 (0.3%) participants in the metformin group died vs 0/179 in the sitagliptin group (Williams-Herman 2010) 1 trial: 4/252 (1.6%) participants in the metformin group died vs 3/519 (0.6%) in the vildagliptin group (Schweizer 2007)
Serious adverse events (SAE) Follow-up: 1.5-2 years	See comments		1977 (3)	⊕⊖⊖⊖ **very low** [a]	1 trial: 15/328 (4.5%) participants in the metformin group experienced a SAE vs 16/335 (4.8%) participants in the saxagliptin group (Pfützner 2011) 1 trial: 16/364 (4.4%) participants in the metformin group experienced a SAE vs 13/179 (7.2%) participants in the sitagliptin group (Williams-Herman 2010) 1 trial: 13/252 (5.2%) participants in the metformin group experienced a SAE vs 35/519 (6.7%) participants in the vildagliptin group (Schweizer 2007)
Health-related quality of life	**Not reported**				
Cardiovascular mortality (CVM) Follow-up: 1.5-2 years	See comment		1206 (2)	⊕⊖⊖⊖ **very low** [a]	1 trial: no deaths due to cardiovascular reasons occurred (Williams-Herman 2010). 1 trial: 3/328 (0.9%) participants in the metformin group died due to cardiovascular disease vs 2/335 (0.6%) participants in the saxagliptin group (Pfützner 2011)
Non-fatal myocardial infarction (NFMI)	See comment		543 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: 1/364 (0.3%) participants in the metformin group experienced a NFMI vs 0/179 participants in the sitagliptin group (Williams-Herman 2010)

Follow-up: 1.5-2 years				
Non-fatal stroke (NFS) Follow-up: 1.5-2 years	See comment	543 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no NFS occurred (Williams-Herman 2010)
End-stage renal disease	**Not reported**			

NFMI: non-fatal myocardial infarction; **NFS**: non-fatal stroke; **SAE**: serious adverse event.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels because of risk of bias and serious imprecision - see Appendix 18.

Summary of findings 5. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus glucagon like peptide-1 analogues

Metformin monotherapy compared with glucagon like peptide-1 analogues for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: glucagon like peptide-1 analogues (dulaglutide)

Outcomes	Glucagon like peptide-1 analogues (dulaglutide)	Metformin monotherapy	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	See comment		807 (1)	⊕⊖⊖⊖	1 trial: no deaths occurred (Umpierrez 2014)

Follow-up: 1 year			**very low** [a]	
Serious adverse events (SAE) Follow-up: 1 year	See comment	807 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: 16/268 (6.0%) participants in the metformin group experienced a SAE vs 35/539 (6.5%) participants in the dulaglutide group (Umpierrez 2014)
Health-related quality of life	**Not reported**			
Cardiovascular mortality (CVM) Follow-up: 1 year	See comment	807 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no deaths due to cardiovascular reasons occurred (Umpierrez 2014)
Non-fatal myocardial infarction (NFMI) Follow-up: 1 year	See comment	807 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: 0/268 participants in the metformin group experienced a NFMI vs 1/539 (0.2%) participants in the dulaglutide group (Umpierrez 2014)
Non-fatal stroke (NFS) Follow-up: 1 year	See comment	807 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: 0/268 participants in the metformin group experienced a NFS vs 1/539 (0.2%) participants in the dulaglutide group (Umpierrez 2014)
End-stage renal disease	**Not reported**			

NFMI: non-fatal myocardial infarction; **NFS**: non-fatal stroke; **SAE**: serious adverse event.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels because of risk of bias and serious imprecision - see Appendix 19.

Summary of findings 6. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus meglitinides

Metformin monotherapy compared with another glucose-lowering drug for adults with type 2 diabetes
Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: meglitinide

Outcomes	Metiglinide (repaglinide)	Metformin monotherapy	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	**Not reported**				
Serious adverse events	See comment		112 (1)	See comment	1 trial: no SAE occurred (Derosa 2003)
Health-related quality of life	**Not reported**				
Cardiovascular mortality	**Not reported**				
Non-fatal myocardial infarction	**Not reported**				
Non-fatal stroke	**Not reported**				
End-stage renal disease	**Not reported**				

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels because of risk of bias and serious imprecision - see Appendix 20

BACKGROUND

Description of the condition

According to the International Diabetes Federation (IDF), 382 million people worldwide had diabetes in 2013, and this number is estimated to be 592 million by 2035 (Guariguata 2014). Type 2 diabetes mellitus (T2DM) is a condition characterised by insulin resistance and a relative deficiency of insulin secretion (Triplitt 2015). Long-term complications of T2DM are microvascular (e.g. nephropathy, retinopathy, neuropathy), as well as macrovascular (e.g. ischaemic heart disease, stroke, and ischaemia of the lower extremities). Mortality is increased among individuals with T2DM compared to people without T2DM. The main cause of the increased mortality is macrovascular disease (Almdal 2004; de Marco 1999; Stamler 1993).

Description of the intervention

People with T2DM are initially advised to follow behaviour changing ('lifestyle') interventions including weight loss and increased physical activity (ADA/EASD 2015). However, over time the majority of people with T2DM will require additional glucose-lowering pharmacological interventions. Currently, metformin is the recommended first-line glucose-lowering drug (ADA/EASD 2009). The pivotal trial underlying the recommendation of metformin as the first-line glucose-lowering drug was the UK Prospective Diabetes Study (UKPDS), which compared metformin as monotherapy with chlorpropamide, glyburide and insulin in a subgroup of overweight participants (N = 342 out of a total number of included participants of 4075) (UKPDS 1998). Intensive glycaemic control with metformin decreased the risk of diabetes-related outcomes compared with other glucose-lowering agents analysed in one combined group. Metformin is a biguanide originating from the plant *Galega officinalis* (Witters 2001). Metformin was first described in 1922, and was administered to humans for the first time in France in 1957. In 1972, Canada approved its use for T2DM and later, in 1994, it received approval for use in T2DM by the US Food and Drug Administration (FDA) (Corey 2007).

Adverse effects of metformin

The most common adverse effects of metformin are gastrointestinal disturbances, which are reported in 20% to 30% of people on metformin. However, the gastrointestinal disturbances only rarely necessitate discontinuation of metformin (DeFronzo 1999).

A potential complication of metformin use is lactic acidosis, a rare, but potentially fatal, metabolic condition that can occur whenever substantial tissue hypoxia exists (Kreisberg 1980). Lactic acidosis is characterised by elevated blood lactate concentrations (exceeding 5.0 mmol/L) and decreased blood pH (less than 7.35). The mortality is estimated to be about 50% (Huang 2016). A Cochrane Review did not show that metformin was associated with an increased risk of lactic acidosis or elevated lactate levels when compared to other glucose-lowering drugs (Salpeter 2010). However, several case reports of lactic acidosis in people receiving metformin have been published subsequently (Kalantar-Zadeh 2013; Schousboe 2012).

How the intervention might work

The exact mechanism(s) of action of metformin are not clearly elucidated. However, metformin is known to alter carbohydrate metabolism by stimulating glucagon-like peptide (GLP-1) secretion which inhibits glucagon secretion leading to suppressed basal hepatic glucose production (gluconeogenesis) (Rena 2017). Other mechanisms include improving insulin sensitivity in the liver and peripheral tissues, as well as increasing insulin-stimulated glucose uptake and utilisation in peripheral tissues (AHFS 1999). It has been proposed that its prime mode of action is via activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) enzyme (Cho 2015; Duca 2015).

Why it is important to do this review

A previously published systematic review on sulphonylurea monotherapy versus metformin monotherapy in people with T2DM did not show superiority of metformin monotherapy (Hemmingsen 2014). However, no updated review on metformin monotherapy compared with other glucose-lowering interventions in people with T2DM exists. In 2005, a Cochrane Review about metformin monotherapy was published (Saenz 2005). However, this systematic review is more than 10 years old and was consequently withdrawn. Therefore, a new systematic review with updated searches and newer methodology is warranted.

OBJECTIVES

To assess the effects of metformin monotherapy in adults with type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Adults (18 years or more) with type 2 diabetes mellitus (T2DM).

Diagnostic criteria for diabetes mellitus

In order to be consistent with changes in the classification of and diagnostic criteria for diabetes mellitus over the years, the diagnosis should be established using the standard criteria valid at the time of trial commencement (for example ADA 2003; ADA 2008; WHO 1998). Ideally, the diagnostic criteria should have been described. We used the trial authors' definition of diabetes mellitus if necessary. We planned to subject diagnostic criteria to a sensitivity analysis.

Types of interventions

We planned to investigate the following comparisons of intervention versus control/comparator.

Intervention

Metformin monotherapy.

Comparisons

- Placebo.

- No intervention.
- Diet.
- Other glucose-lowering drugs.

Concomitant interventions and glycaemic target had to be the same in both the intervention and comparator groups to establish fair comparisons.

If a trial included multiple arms, we included any arm that met the review inclusion criteria. We excluded studies comparing metformin monotherapy with first-generation sulphonylurea, as this compound is rarely used.

Minimum duration of intervention and follow-up

We included trials with at least one year's duration, irrespective of the post-intervention follow-up. The reason was that we were primarily interested in patient-important outcomes and not in short-term biochemical responses.

Summary of specific exclusion criteria

We excluded trials of the following category.

- Intervention period less than one year.
- Not type 2 diabetes mellitus.
- Other comorbidities.

Hypertension and hyperlipidaemia are conditions often associated with type 2 diabetes mellitus, and studies including people with these conditions were not excluded. Studies including people with other medical conditions, e.g. liver failure, were excluded.

Types of outcome measures

We did not exclude a trial if it failed to report one or several of our primary or secondary outcome measures. In cases where none of our primary or secondary outcomes were reported, we included the trial and contacted the corresponding author for supplementary data. If no additional data were available, we planned to provide some basic information in a supplementary table.

We investigated the following outcomes using the methods and time points specified below.

Primary outcomes

- All-cause mortality.
- Serious adverse events.
- Health-related quality of life.

Secondary outcomes

- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- End-stage renal disease.
- Blindness.
- Severe hypoglycaemia.

Explorative outcomes

- Anthropometric measures.
- Glycaemic control.
- Lactic acidosis.
- Amputation of lower extremity.
- Congestive heart failure.
- Cardiac revascularisation.
- Peripheral revascularisation.
- Socioeconomic effects.
- Intervention failure.

Method of outcome measurement

- All-cause mortality: defined as death from any cause.
- Serious adverse events: defined according to the International Conference on Harmonization Guidelines as, "any event that leads to death, that is life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which may have had jeopardised the patient or required intervention to prevent it" (ICH 1997), or as reported in trials.
- Health-related quality of life: defined as mental and physical quality of life and evaluated by a validated instrument such as Short-Form 36.
- Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, blindness: defined as reported in trials.
- End-stage renal disease: defined as dialysis, renal transplantation: defined as reported in trials.
- Severe hypoglycaemia: requiring assistance from another person.
- Anthropometric measures: defined as weight in kg or body mass index (BMI).
- Glycaemic control: defined as glycosylated haemoglobin A1c (HbA1c) or fasting plasma glucose (FPG).
- Lactic acidosis: defined as reported in trials.
- Amputation of lower extremity: defined as reported in trials.
- Congestive heart failure: defined as reported in trials.
- Cardiac revascularisation: defined as reported in trials.
- Peripheral revascularisation: defined as reported in trials.
- Socioeconomic effects: such as direct costs defined as admission/readmission rates, average length of stay, visits to general practitioner, accident/emergency visits; medication consumption; indirect costs defined as resources lost due to illness by the participant or their family member.
- Intervention failure: defined as requiring additional treatment.

Timing of outcome measurement

- At the end of the intervention period: health-related quality of life, anthropometric measures, glycaemic control.
- Any time after participants were randomised to intervention/comparator groups: all other outcomes.

Search methods for identification of studies

Electronic searches

In 2016, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review and meta-analysis (Maruthur 2016), based on an extensive AHRQ report (Bolen 2016), in which the authors evaluated the comparative effectiveness and safety of glucose-lowering interventions for people with T2DM, including

metformin monotherapy. This report included a systematic search of several databases up to April 2015 and a further update of the MEDLINE search up to December 2015.

Because the scientific publication output with regard to this review´ topic is immense (metformin is a widely used medication which has been available for several decades), we based the identification of eligible studies on the results of the AHRQ report and topped-up their search with our own search strategy from 2014 onwards. We placed no restrictions on the language of publication.
We searched the following literature databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (searched up to 2 December 2019).
- Ovid MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> (searched up to 2 December 2019).
- Embase Ovid <1974 to 2017 April 27> (searched up to 28 April 2017).

Additionally, we searched the following trials registers from inception onwards.

- ClinicalTrials.gov (searched up to 2 December 2019).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/) (searched up to 2 December 2019).

Details of all search strategies are presented in Appendix 1.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews of metformin monotherapy and health technology assessment reports. In addition, we contacted authors of included trials to identify any additional information on the retrieved trials and to determine if further trials existed, which we might have missed.

We also searched databases from regulatory agencies (European Medicines Agency (EMA), US Food and Drugs Administration (FDA)) (Hart 2012; Schroll 2015).

We did not use abstracts or conference proceedings for data extraction unless full data were available from trial authors because this information source does not fulfil the CONSORT requirements, which consist of "an evidence-based, minimum set of recommendations for reporting randomized trials" (CONSORT; Scherer 2007). We listed key data from abstracts in an appendix. We presented information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table.

Data collection and analysis

Selection of studies

Two review authors (FG and AT or LK) independently scanned the abstract, title, or both of every record we retrieved in the literature searches, to determine which trials we should assess further. We obtained the full text of all potentially relevant records. We resolved any disagreements through consensus or by recourse to a third review author (AT or LK). If we could not resolve a disagreement, we categorised the trial as a 'study awaiting classification' and contacted the trial authors for clarification. We presented an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009). We listed all articles excluded after full-text assessment in the 'Characteristics of excluded studies' table, and provided the reasons for exclusion.

Data extraction and management

For trials that fulfilled inclusion criteria, two review authors (FG and AT or LK) independently extracted key participant and intervention characteristics. We described interventions according to the 'template for intervention description and replication' (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017). We reported data on efficacy outcomes and adverse events using standardised CMED data extraction sheets. We resolved any disagreements by discussion or, if required, by consultation with a third review author (AT or LK) (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15; Appendix 16; Appendix 17; Appendix 18; Appendix 19; Appendix 20;Appendix 21).

We provided information about potentially relevant ongoing trials, including the trial identifier in the 'Characteristics of ongoing studies' table and in Appendix 7 'Matrix of trial endpoints' (publications and trial documents). We tried to find the protocol of each included trial and reported primary, secondary and other outcomes measured by the study personnel (objectively) in comparison with the data from the publications in Appendix 7.

We emailed all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We presented the results of this survey in Appendix 14. We then sought relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we maximised the information yield by collating all available data, and we used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we listed duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials were available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trials register, but no additional information (study results, publication or both) was available, we added this trial to the table 'Characteristics of studies awaiting classification'.

Assessment of risk of bias in included studies

Three review authors (FG and LK or AT) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus, or by consultation with a fourth review author (BH). If risk of bias items were insufficiently described to evaluate risk of bias in publications, trial protocols or other sources, we contacted the trial authors for clarification.

We used the Cochrane 'Risk of bias' assessment tool (Higgins 2017), assigning assessments of low, high, or unclear risk of bias (for details, see Appendix 2; Appendix 3). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* according to the criteria and associated categorisations contained therein *(* Higgins 2017).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We distinguished between self-reported, investigator-assessed and adjudicated outcome measures.

We considered the following to be self-reported outcomes.

- Health-related quality of life.
- Severe hypoglycaemia, as reported by participants.
- Anthropometric measures, as reported by participants.
- Glycaemic control, as reported by participants.

We considered the following outcomes to be investigator-assessed.

- All-cause mortality.
- Serious adverse events.
- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- End-stage renal disease.
- Blindness.
- Amputation of lower extremity.
- Cardiac revascularisation.
- Peripheral revascularisation.
- Severe hypoglycaemia.
- Anthropometric measures.
- Glycaemic control.
- Lactic acidosis.
- Amputation of lower extremity.
- Congestive heart failure.
- Cardiac revascularisation.
- Peripheral revascularisation.
- Socioeconomic effects.

Risk of bias for a trial across outcomes

Some 'Risk of bias' domains, such as selection bias (sequence generation and allocation sequence concealment), affected the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we marked all endpoints investigated in the associated trial as being at high risk. Otherwise, we would not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These were the main summary assessments that we incorporated into our judgments about the certainty of the evidence in the 'Summary of findings' tables. We defined outcomes as at low risk of bias when most information came from trials at low risk of bias, unclear risk when most information came from trials at low or unclear risk of bias and high risk when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two trials were available for a comparison and a given outcome, we expressed dichotomous data as a risk ratio (RR) with 95% confidence interval (CI). We also intended to use odds ratio (OR) with 95% CI if appropriate.For continuous outcomes measured on the same scale (e.g. HbA1c), we estimated the intervention effect using the mean difference (MD) with 95% CI. For continuous outcomes measuring the same underlying concept (e.g. health-related quality of life) but using different measurement scales, we planned to calculate the standardised mean difference (SMD). The scales measuring health-related quality of life could go in different directions. In some scales, values would increase with improved health-related quality of life, whereas in other scales, values would decrease with improved health-related quality of life. To adjust for the different directions of the scales, we planned to multiply scales that reported better health-related quality of life using decreasing values by –1. We intended to re-express the SMDs into the unit of the Short Form-36 (SF-36) questionnaire. This would have been done by using standard deviations from a clinical trial in participants with T2DM providing data for a pooled standard deviation for baseline and change from baseline.

If included, we would have expressed time-to-event data as hazard ratio (HR) with 95% CI. We would have calculated HRs with the generic inverse variance method with 95% CI.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison or appropriately reduced the sample size so that the same participants did not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011).

We planned to re-analyse cluster-RCTs that had not appropriately adjusted for potential clustering of participants within clusters in their analyses. The variance of the intervention effects would be inflated by a design effect. Calculation of a design effect would involve estimation of an intracluster correlation coefficient (ICC). We planned to obtain estimates of ICCs through contact with authors or impute them by using either estimates from other included trials that reported ICCs or external estimates from empirical research (e.g. Bell 2013). We would have examined the impact of clustering using sensitivity analyses.

Dealing with missing data

When possible, we requested missing data from the authors of the included trials. We carefully evaluated data such as screened, randomly assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In trials where the standard deviation (SD) of the outcome was not available at follow-up or could not be recreated, we standardised by the average of the pooled baseline standard deviation from those trials in which this information was reported.

In trials where means and SDs were not reported and the method mentioned above, and we did not receive the necessary information from trial authors, we imputed SDs by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005).

We investigated the impact of imputation on meta-analyses by performing sensitivity analyses, and we reported per outcome which trials were included with imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as a pooled effect estimate.

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I^2 statistic (Higgins 2003), which quantified inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002)).

When we found heterogeneity, we attempted to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

Had we included 10 or more trials investigating a particular outcome, we planned to use funnel plots to assess small-trial effects. Several explanations could account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. Therefore, we planned to interpret the results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display) a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration to the whole distribution of effects and presented a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we planned to use the Peto's odds ratio method, provided that there was no substantial imbalance between intervention and comparator group sizes and intervention effects were not exceptionally large. In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017; Hoffmann 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out the following subgroup analyses with investigation of interactions (Altman 2003).

- Comparing trials of long duration (two years or longer) to trials of short duration (less than two years).
- Comparing trials including exclusively obese participants (defined as BMI ≥ 30) to trials including obese and non-obese participants.
- Comparing trials at low risk of bias to trials at high risk of bias.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published trials.
- Very long or large trials to establish the extent to which they dominate the results.
- Trials using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

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

Certainty of the evidence

We presented the overall certainty of the evidence for each outcome specified under 'Types of outcome measures: Summary of findings' according to the GRADE approach (Guyatt 2008). The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Two review authors (BH and BR) independently rated the certainty of the evidence for each outcome.

'Summary of findings' table

We presented a summary of the evidence in a 'Summary of findings' table according to the GRADE approach (Guyatt 2008). We included an appendix entitled 'Checklist to aid

consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we would have used the GRADEpro Guideline Development Tool (GDT) software and presented evidence profile tables as an appendix (GRADEproGDT 2015). We presented results for the outcomes as described in the Types of outcome measures section. If meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of the evidence using footnotes and we made comments to aid the reader's understanding of the Cochrane Review where necessary.

We created the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017; Schünemann 2017), along with Review Manager (RevMan 5.3) table editor (RevMan 2014).

The intervention presented in the 'Summary of findings' table was metformin monotherapy and comparators were placebo, no intervention, behaviour changing interventions and other glucose-lowering drugs or combinations of glucose-lowering drugs.

Our 'Summary of findings' tables and conclusions were based on the results of trials with a low risk of bias in all risk of bias domains (Higgins 2017; Lundh 2017; Moher 1998; Savovic 2012; Schulz 1995; Wood 2008). We reported the following outcomes, listed according to priority.

- All-cause mortality.
- Serious adverse events.
- Health-related quality of life.
- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- End-stage renal disease.

RESULTS

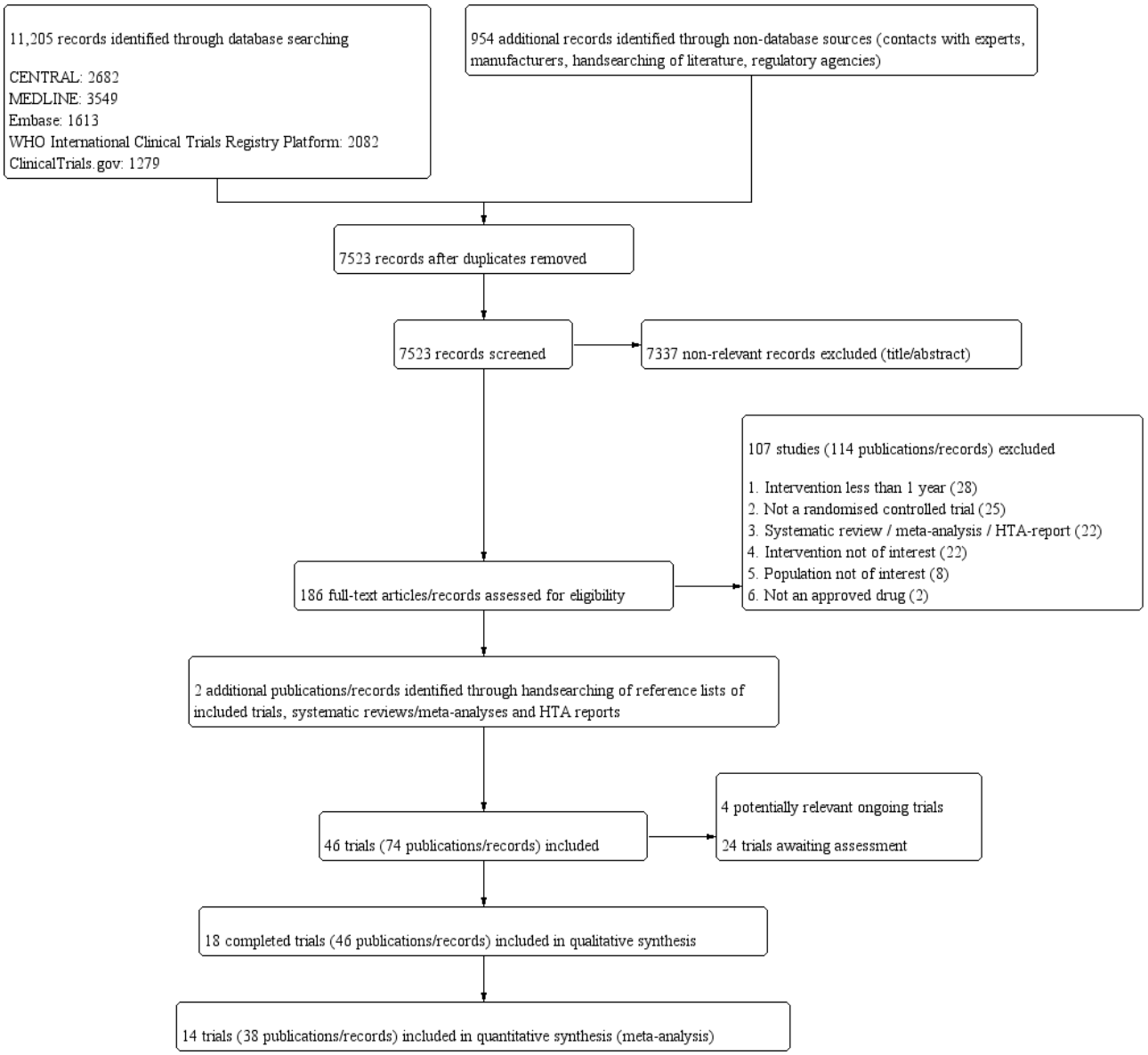
Description of studies

For a detailed description of trials, see the Table 1, 'Characteristics of included studies', 'Characteristics of excluded studies, and 'Characteristics of ongoing studies' sections.

Results of the search

For an overview of trial selection, please see Figure 1.

Figure 1. Trial flow diagram.



Our database searches identified 11,205 records. We excluded the majority of records on the basis of the title and abstract because they clearly did not meet inclusion criteria. We assessed a total of 186 full-text articles/records for eligibility. Handsearching of reference lists of included trials and systematic reviews/meta-analyses identified two additional publications/records (Derosa 2003; Wang 2005). After screening, 46 trials published in 74 publications/records met our inclusion criteria. We included a total of 18 completed trials published in 46 publications/records in qualitative synthesis. Among them, we included 14 completed trials published in 38 publications/records in meta-analyses.

Twenty-four of the 46 trials that met our inclusion criteria were published exclusively in English. The remaining 22 trials were published either exclusively or partly in other languages; one in Russian (Onuchin 2010), two in French (Campbell 1994; Teupe 1991), 10 in Chinese (ChiCTR-IOR-16007720; ChiCTR-IOR-17011477; ChiCTR-IPR-16009666; ChiCTR-IPR-17010811; ChiCTR-TCH-10001013; ChiCTR-TRC-11001331; ChiCTR1800018825; ChiCTR1900021632; Ma 2015; Zhang 2009) and nine in Japanese (JPRN-UMIN000000689; JPRN-UMIN000000771; JPRN-UMIN000001085; JPRN-UMIN000001891; JPRN-UMIN000002099; JPRN-UMIN000003563; JPRN-UMIN000006504; JPRN-UMIN000010624; JPRN-UMIN000014775).

We excluded 107 studies described in 114 publications. The most frequent reason for exclusion was "intervention less than 1 year" which concerned 28 studies. We identified four potentially relevant ongoing trials (see 'Characteristics of ongoing studies') and 24 trials awaiting assessment (see 'Characteristics of studies awaiting classification'). Most of the studies classified as awaiting classification were clinical trials which were completed, but not yet published.

Handsearching the reference list of a previous Cochrane Review on metformin monotherapy did not provide any additional trials (Saenz 2005).

We did not obtain additional references from contacting authors of included trials, screening references from the MEDLINE (Ovid SP) email alert service or searching databases from the European Medicines Agency. Searching the Food and Drug Aministration (FDA) provided additional information on one of the included trials (Campbell 1994; FDA 1994). It was not explicitly stated that the trial published by Campbell and colleagues and the trial in the FDA report was the same. In the FDA report a trial number was available. No trial number was available from the journal publication. However, we judged this to be the same trial as trial duration, country, intervention, number of participants, mean age and number of included men/women were identical between the two references (Campbell 1994; FDA 1994). Another study was identified from the FDA (trial number MET/D/86/BERGI) (FDA 1994). This study compared metformin with diet and had a two-year duration. However, it was unclear from the FDA document whether this study was randomised and how many participants were included. We did not identify any published version of this study. Weight was the only reported outcome. Therefore, we excluded this study (FDA 1994).

Included studies

A detailed description of the characteristics of included trials is presented elsewhere (see 'Characteristics of included studies' and Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 21). The following is a succinct overview.

Source of data

All 18 included trials were published in medical journals. One trial had additional information in a FDA document (Campbell 1994).

Seven trials provided a protocol in a trial register (Bilezikian 2013; Kahn 2006; Pfützner 2011; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010) or in a design paper (UKPDS 34 1998).

We contacted all authors of included trials and trials awaiting assessment by email if contact information was available (see 'Appendix 14'). Most of the references classified as awaiting classification were protocols for randomised clinical trials which were completed several years ago, but no publication could be retrieved. We received additional data for only one included trial (Schweizer 2007). In addition, if important information was lacking on excluded trials, we contacted authors for clarification (see 'Appendix 14').

Comparisons

No trials compared metformin monotherapy with placebo or diet. Two trials compared metformin monotherapy with no intervention (Kiyici 2009; Teupe 1991). Seven trials compared metformin monotherapy with sulphonylureas (Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006; Rahman 2011; UKPDS 34 1998; Yamanouchi 2005). Two trials compared metformin monotherapy with insulin (Onuchin 2010; UKPDS 34 1998). Seven trials compared metformin monotherapy with thiazolidinediones (Bilezikian 2013; Derosa 2009; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004; Yamanouchi 2005). Three trials compared metformin monotherapy with dipeptidyl peptidase 4-inhibitors (Pfützner 2011; Schweizer 2007; Williams-Herman 2010). One trial compared metformin monotherapy with a glucagon-like peptide 1-analogue (Umpierrez 2014). One trial compared metformin monotherapy with meglitinides (Derosa 2003).

Three trials had additional comparators that were not of interest to this review (Onuchin 2010; Pfützner 2011; Williams-Herman 2010). One trial had two separate metformin monotherapy arms with different doses (Williams-Herman 2010).

Overview of trial populations

For a detailed overview of trial populations, please see Table 1.

Ten trials provided a description of sample size calculation (Bilezikian 2013; Derosa 2004; Derosa 2009; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; UKPDS 34 1998; Umpierrez 2014; Yamanouchi 2005). Seven trials provided information on the number of screened/eligible participants (Bilezikian 2013; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; UKPDS 34 1998; Williams-Herman 2010).

A total of 10,680 participants were randomised to metformin monotherapy (M) or comparator groups. A total of 4041 participants were randomised to metformin monotherapy, and 6639 participants were randomised to comparator groups. The percentage of participants finishing the trial was approximately 58% in all groups (dropout-rate of 42%), approximately 61% in the metformin monotherapy groups and approximately 56% in the comparator groups. The total number of participants in the trials ranged from 48 participants (Campbell 1994) to 4360 participants (Kahn 2006). The number of participants randomised to the metformin monotherapy group ranged from 24 to 1455 participants, and from 24 to 1458 participants in the comparator groups.

Trial design

All 18 trials were randomised controlled trials (RCTs) with a parallel design.

Two trials compared metformin monotherapy versus no intervention (Kiyici 2009; Teupe 1991). The remaining 16 trials compared metformin monotherapy versus an active control.

Seven trials were multicentre trials (Derosa 2004; Derosa 2009; Kahn 2006; Schernthaner 2004; Schweizer 2007; UKPDS 34 1998; Williams-Herman 2010). Number of centres ranged from three to 488 centres. Five trials were single-centre trials (Campbell 1994; Derosa 2003; Erem 2014; Kiyici 2009; Rahman 2011). The remaining six trials did not report the number of centres.

Seven trials did not report in which country they were conducted (Bilezikian 2013; Erem 2014; Kiyici 2009; Onuchin 2010; Pfützner 2011; Schernthaner 2004; Schweizer 2007). Most of the remaining trials were conducted in Europe.

Eight trials were double-blinded for participants and personnel (Bilezikian 2013; Derosa 2009; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010). Seven trials had an open-label design (Campbell 1994; Derosa 2003; Derosa 2004; Erem 2014; Kiyici 2009; Onuchin 2010; UKPDS 34 1998). The remaining three trials did not report blinding status.

Eight trials were blinded for outcome assessors (Bilezikian 2013; Derosa 2009; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010). The remaining trials did not blind, or report blinding of outcome assessors.

The trials were performed between 1977 and 2012.

Duration of interventions ranged from one year to 10.7 years. Mean and median duration of intervention was approximately 100 weeks and 52 weeks, respectively.

Duration of follow-up ranged from one year to 10.7 years. Mean and median duration of follow-up was approximately 100 weeks and 54 weeks, respectively.

Twelve trials had a run-in period prior to the intervention (Bilezikian 2013; Campbell 1994; Derosa 2003; Derosa 2009; Kahn 2006; Onuchin 2010; Pfützner 2011; Rahman 2011; UKPDS 34 1998; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005).

No trials were terminated early.

Settings

All trials were conducted in outpatient clinics.

Participants

Most participants were White people.

All trials included participants with T2DM. Four trials did not report the duration of T2DM (Derosa 2004; Derosa 2009; Kiyici 2009, Rahman 2011). In the remaining 14 trials, mean and median duration of T2DM was approximately 3.7 years and 3.3 years, respectively.

Two trials included only female participants (Bilezikian 2013; Onuchin 2010). In the remaining trials, the percentage of female participants ranged from 41% to 74%.

Mean age of trial participants ranged from approximately 50.7 years to 64.0 years.

Mean HbA1c at baseline ranged from 6.4% to 11.8%. Mean BMI at baseline ranged from 24.7 kg/m^2 to 34 kg/m^2.

Three trials did not report cointerventions/comedications used by participants (Kahn 2006; Onuchin 2010; Rahman 2011). In the remaining trials, the most frequent cointervention/comedication was diet and exercise. Four trials reported comorbidities of participants (Derosa 2009; Erem 2014; Kiyici 2009; Onuchin 2010). The most frequent comorbidity was hypertension.

Major exclusion criteria across all trials were type 1 diabetes mellitus, history of cardiovascular disease, renal dysfunction, liver dysfunction, pregnancy/lactating, known allergy towards trial drugs and known substance abuse.

Diagnosis

Eleven trials did not report diagnostic criteria for T2DM. Across the remaining seven trials, several different diagnostic criteria were used: World Health Organization (WHO) 1999 (Onuchin 2010), American Diabetes Association (ADA) 2001 (Derosa 2004), ADA 2006 (Kiyici 2009), ADA 2010 (Erem 2014), European Association for the Study of Diabetes (EASD) 2007 (Derosa 2009) and trial author's definitions: fasting plasma glucose (FPG) greater than 8 mmol/L on two occasions two weeks apart on diet (Campbell 1994) and FPG greater than 6 mmol/L on two occasions (UKPDS 34 1998).

Interventions

All trials randomised participants to a metformin monotherapy arm.

Metformin monotherapy was administered orally as a single intervention arm in all but one of the trials (Schernthaner 2004), where it was administered as two intervention arms in total daily doses of 1000 mg/day and 2000 mg/day, respectively. In the remaining trials, the total daily dose of metformin monotherapy ranged from 750 mg/day to 3000 mg/day, and the average total daily dose was approximately 2050 mg/day.

Second-generation sulphonylureas were administered orally as glibenclamide in two trials (Kahn 2006; UKPDS 34 1998), where the total daily dose ranged from 15 mg/day to 20 mg/day, and the average total daily dose was 17.5 mg/day; as gliclazide in one trial (Erem 2014), where the total daily dose was 120 mg/day; and as glipizide in one trial where the total daily dose was 30 mg/day (Campbell 1994).

Third-generation sulphonylureas were administered orally as the comparator arm as glimepiride in three trials (Derosa 2004; Rahman 2011; Yamanouchi 2005), where the total daily dose ranged from 1 mg/day to 8 mg/day, and the average total daily dose was approximately 5 mg/day.

Insulin was administered subcutaneously in two trials (Onuchin 2010; UKPDS 34 1998). In one trial, insulin was administered as a long-acting insulin in doses of 0.2 to 0.4 International Units (IU)/kg body weight/day in addition to a short-acting insulin in doses of 1 IU/10 g carbohydrates to 1.5 IU/10 g carbohydrates (Onuchin 2010). In one trial, insulin was primarily administered as a long-acting insulin, and was supplemented by a short-acting insulin if the daily dose exceeded 14 IU or the pre-meal/bed-time home blood glucose measurements were more than 7 mmol/L.

Thiazolidinediones were administered orally as pioglitazone in four trials (Derosa 2009; Erem 2014; Schernthaner 2004; Yamanouchi 2005), where the total daily dose was 45 mg/day in all trials; and as rosiglitazone in three trials (Bilezikian 2013; Kahn 2006; Kiyici 2009), where the total daily dose ranged from 4 mg/day to 8 mg/day, and the average daily dose was approximately 6.5 mg/day.

Dipeptidyl dipeptidase 4-inhibitors were administered orally as saxagliptin in one trial (Pfützner 2011), where the total daily dose was 10 mg/day; as sitagliptin in one trial (Williams-Herman 2010), where the total daily dose was 100 mg/day; and as vildagliptin in one trial (Schweizer 2007), where the total daily dose was 100 mg/day.

Glucagon-like peptide 1 receptor analogues were administered subcutaneously in one trial in total weekly doses of dulaglutide 0.75 mg/week and 1.5 mg/week, respectively (Umpierrez 2014).

Meglitinides were administered orally as repaglinide in one trial (Derosa 2003), where the total daily dose was 4 mg/day.

'No intervention' was the comparator arm in two trials (Kiyici 2009; Teupe 1991).

We considered the intervention and comparator arms to be adequate in all but three of the trials, due to administering 'no intervention' (Kiyici 2009; Teupe 1991) or administering insufficient doses of metformin (Kiyici 2009; Yamanouchi 2005), both of which did not establish fair comparisons.

Rescue medication was administered as add-on glibenclamide in two trials (UKPDS 34 1998; Williams-Herman 2010); unspecified sulphonylurea in one trial (Bilezikian 2013); insulin in one trial (UKPDS 34 1998); pioglitazone in two trials (Pfützner 2011; Schweizer 2007); and an unspecified treatment in one trial (Umpierrez 2014). In one trial (UKPDS 34 1998), rescue medication was administered as add-on glibenclamide in the metformin arm and could be switched to insulin if hyperglycaemia persisted; continued sulphonylurea or add-on metformin in the comparator arm receiving sulphonylurea; and more complex insulin regimens in the comparator arm receiving basal insulin. In the remaining 11 trials, rescue medication was not administered.

Three trials administered only diet as a cointervention (Schernthaner 2004; Teupe 1991; UKPDS 34 1998). Six trials did not administer diet nor exercise as a cointervention (Bilezikian 2013; Campbell 1994; Kahn 2006; Onuchin 2010; Rahman 2011; Schweizer 2007). The remaining nine trials administered diet and exercise as cointerventions.

Special cointerventions were administered in one trial (Bilezikian 2013) orally as calcium and vitamin D in daily doses of 500 mg/day to 1000 mg/day and 400 IU/day, respectively.

Outcomes

Eight trials explicitly stated a primary outcome in the publication. Of these trials, five trials were registered in ClinicalTrials.gov (Bilezikian 2013; Kahn 2006; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010), and the remaining three did not have any available trial documents (Derosa 2004; Schernthaner 2004; Yamanouchi 2005). Nine trials did not state a primary outcome in the publication. Of these trials, one was registered in ClinicalTrials.gov (Pfützner 2011), and the remaining eight did not have any available documents describing the trial protocol (Campbell 1994; Derosa 2003; Derosa 2009; Erem 2014; Kiyici 2009; Onuchin 2010; Rahman 2011; Teupe 1991). One trial had a design article in which it was stated that metformin monotherapy would be compared separately with each sulphonylurea group for outcomes of interest for this review, however, these data were never reported (UKPDS 34 1998).

The most common primary outcome of the included trials was HbA1c.

The total number of explicitly stated outcomes collected in the trials ranged from three (UKPDS 34 1998) to 20 (Derosa 2003). The median number of explicitly stated outcomes in the trials was 11.

All but seven of the trials reported all-cause mortality (Derosa 2003; Derosa 2009; Onuchin 2010; Rahman 2011; Teupe 1991; UKPDS 34 1998; Yamanouchi 2005). All but seven of the trials reported serious adverse events (Campbell 1994; Derosa 2009; Onuchin 2010; Rahman 2011; Teupe 1991; UKPDS 34 1998; Yamanouchi 2005). All but eight of the trials reported adverse events (Campbell 1994; Derosa 2003; Derosa 2009; Kiyici 2009; Onuchin 2010; Rahman 2011; Teupe 1991; UKPDS 34 1998). Only one trial reported on health-related quality of life (Onuchin 2010). This trial applied the Short-form health survey 36 (Appendix 21).

Seven trials reported cardiovascular mortality (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009; Pfützner 2011; Umpierrez 2014; Williams-Herman 2010). Five trials reported non-fatal myocardial infarction (Erem 2014; Kahn 2006; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005). Three trials reported non-fatal stroke (Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005). No trials reported blindness or end-stage renal disease.

Eight trials reported body weight (Campbell 1994; Erem 2014; Kahn 2006; Rahman 2011; Schweizer 2007; Teupe 1991; Umpierrez 2014; Williams-Herman 2010). Seven trials reported BMI (Derosa 2004; Erem 2014; Kiyici 2009; Onuchin 2010; Rahman 2011; Umpierrez 2014; Yamanouchi 2005). All but three of the trials reported FPG (Derosa 2009; Onuchin 2010; Teupe 1991). All but three of the trials reported HbA1c (Derosa 2003; Derosa 2009; UKPDS 34 1998). Four trials reported congestive heart failure (Erem 2014; Kahn 2006; Umpierrez 2014; Yamanouchi 2005). Only one trial reported cardiac revascularisation (Yamanouchi 2005). Two trials reported peripheral revascularisation (Kahn 2006; Yamanouchi 2005). Six trials reported intervention failure (Kahn 2006; Pfützner 2011; Teupe 1991; UKPDS 34 1998; Umpierrez 2014; Yamanouchi 2005). No trials reported lactic acidosis, amputation of lower extremity or socioeconomic effects.

All but four of the trials provided a definition of endpoint measurement for at least one of our primary outcomes (Campbell 1994; Erem 2014; Rahman 2011; Teupe 1991) (see Appendix 9).

Excluded studies

We excluded 107 studies described in 114 references after evaluation of the full publication/record.

The main reasons for exclusion were: the duration of the intervention was less than one year (28 records); the study was not a RCT (25 records); the reference was a systematic review/meta-analysis/HTA report (22 records); the intervention was not of interest to the review (22 records); the population was not of interest to the review (eight records) and the study investigated a non-approved drug (two records). We identified another study from the FDA (trial number MET/D/86/BERGI) (FDA 1994). This study compared metformin with diet and had a two-year duration. However, it is unclear from the FDA document whether this study was randomised and how many participants were included. Weight was the only reported outcome. Therefore, we excluded this study (FDA 1994).

In three cases we contacted the authors of the study for clarification and received an answer confirming the exclusion of the study (ChiCTR-IPR-17010825; ChiCTR-TRC-12002505; ChiCTR-IOR-16009296). In three cases we contacted the authors of the study for clarification and did not receive a reply (ChiCTR-IPR-17010825; JPRN-UMIN000004367; Kanazawa 2009). However, after finding additional information on these trials, we were able to exclude them.

For further details, see 'Characteristics of excluded studies'.

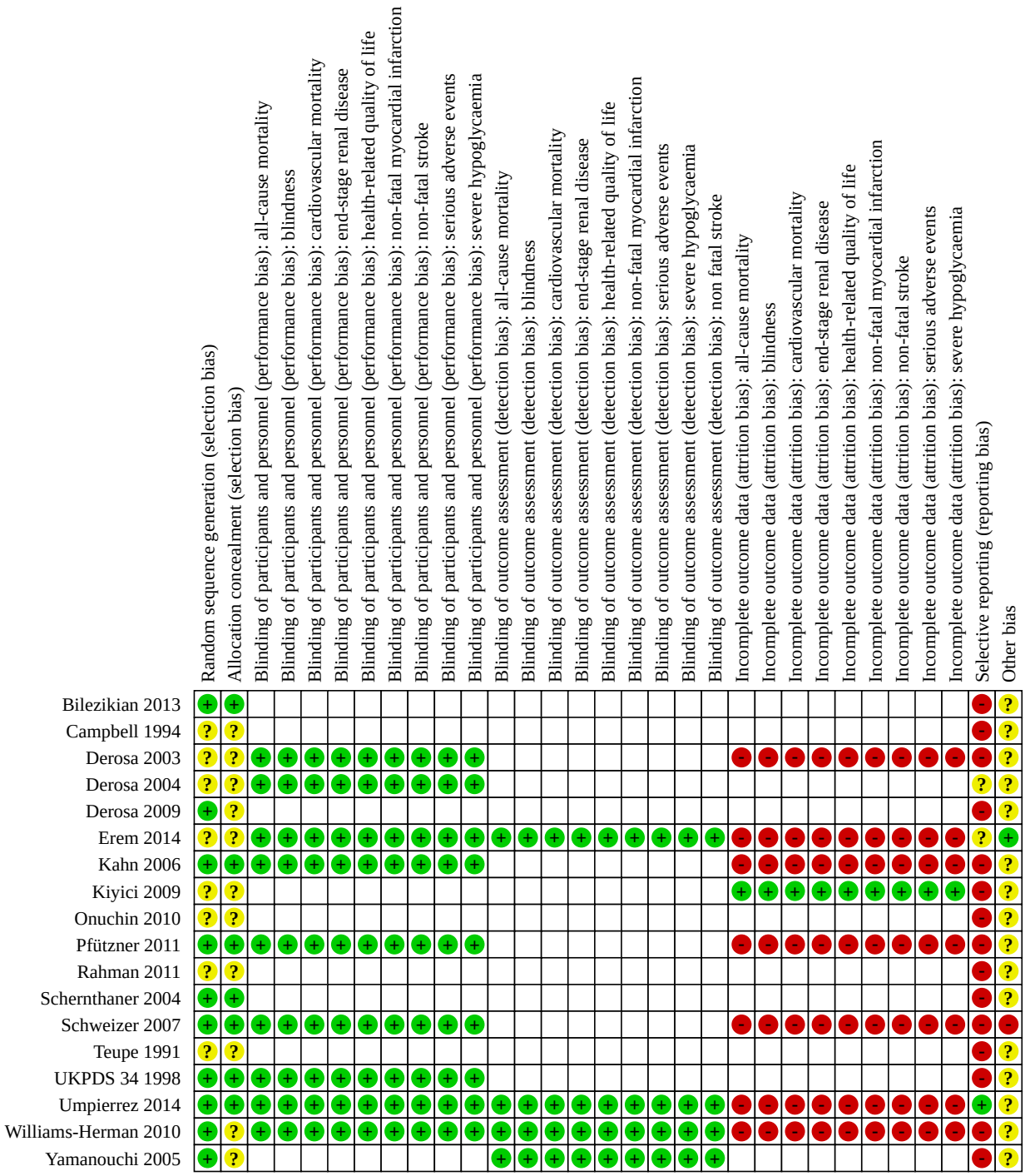
Risk of bias in included studies

For details on the risk of bias of the included trials see Characteristics of included studies table.

For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials see Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included trials (blank cells indicate that the particular outcome was not measured in some trials).

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included trial ((blank cells indicate that the particular outcome was not measured in some trials)



Allocation

We judged seven trials to be of low risk of bias regarding random sequence generation and allocation concealment (Bilezikian 2013; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; UKPDS 34 1998; Umpierrez 2014). We judged three trials to be of low risk of bias regarding the method of random sequence generation

and of unclear risk of bias for method of allocation concealment due to inadequate description of allocation concealment (Derosa 2009; Williams-Herman 2010; Yamanouchi 2005). We judged the remaining eight trials to be of unclear risk of bias for both the method of random sequence generation and allocation concealment due to the trials only being described as randomised with no further description.

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the risk of selection bias. All trials reported only some of our key prognostic variables. However, we did not identify any important baseline imbalances in the studies. Therefore, all of our original assessments of risk of selection bias remained the same after evaluating study baseline data.

Blinding

Eight trials were double-blinded for participants and personnel (Bilezikian 2013; Derosa 2009; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010). No trials were single-blinded only for participants. Seven trials had an open-label design (Campbell 1994; Derosa 2003; Derosa 2004; Erem 2014; Kiyici 2009; Onuchin 2010; UKPDS 34 1998). The remaining three trials did not report blinding procedures.

Eight trials were blinded for outcome assessors (Bilezikian 2013; Derosa 2009; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010). The remaining trials did not blind or did not report blinding of outcome assessors.

Health-related quality of life was only reported in one trial (Onuchin 2010). This trial was not blinded, and as the outcome is self-reported, we classified it as high risk of bias. Cardiovascular mortality and non-fatal stroke were adjudicated outcome measurements in one trial (Umpierrez 2014), and non-fatal myocardial infarction was an adjudicated outcome measurement in two trials (Kahn 2006; Umpierrez 2014). For all other trials, these and the remaining outcomes were explicitly stated as or assumed to be investigator-assessed outcomes.

We judged health-related quality of life to be of high risk of performance and detection bias, since the one study that reported the self-reported outcome was open-labelled. For all other outcomes, we judged all trials to be of low risk of performance and detection bias, since we did not judge these investigator- or adjudicated-assessed outcomes to be influenced by a potential lack of blinding.

Incomplete outcome data

Losses to follow-up were present in 13 trials (Bilezikian 2013; Derosa 2003; Derosa 2004; Derosa 2009; Erem 2014; Kahn 2006; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Teupe 1991; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005), and attrition rates ranged from approximately 44% (Williams-Herman 2010) to 95% (Erem 2014). Two trials reported no losses to follow-up (Campbell 1994; Kiyici 2009). Three trials did not describe whether there were losses to follow-up (Onuchin 2010; Rahman 2011; UKPDS 34 1998).

Intention-to-treat analysis was used in seven trials (Bilezikian 2013; Derosa 2003; Kahn 2006; Pfützner 2011; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010). Of these trials, two trials used last-observation-carried forward (Bilezikian 2013; Umpierrez 2014), and the remaining trials did not report on how missing data were handled. Per-protocol analysis was used in three trials (Derosa 2004; Erem 2014; Yamanouchi 2005). The type of analysis was not reported in the remaining eight trials.

Of the 13 trials in which losses to follow-up were present, eight trials had a detailed description of reasons for participants' withdrawal (Bilezikian 2013; Derosa 2003; Derosa 2004; Kahn 2006; Schernthaner 2004; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005). One trial (Schweizer 2007) had a detailed description of participants' withdrawal in the first 52 weeks of intervention, but no description in the extension period. The remaining trials did not provide a detailed description.

We judged the following outcomes to be of low risk of attrition bias in one or more trials: all-cause mortality (Bilezikian 2013; Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006; Kiyici 2009; Pfützner 2011; Schernthaner 2004; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010) and cardiovascular mortality (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009; Pfützner 2011; Umpierrez 2014; Williams-Herman 2010). We judged serious adverse events to be of low risk of attrition bias in two trials (Kiyici 2009; Schernthaner 2004) and at high risk in nine trials (Bilezikian 2013; Derosa 2003; Derosa 2004; Erem 2014; Kahn 2006; Pfützner 2011; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010).

We judged the following outcomes to be of unclear or high risk of attrition bias in one or more trials: health-related quality of life (Onuchin 2010), non-fatal myocardial infarction (Erem 2014; Kahn 2006; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005), non-fatal stroke (Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005) and severe hypoglycaemia (Derosa 2003; Derosa 2004; Erem 2014; Kahn 2006; Pfützner 2011; Schweizer 2007; Umpierrez 2014; Williams-Herman 2010).

The reasons for judging an outcome to be of high risk of attrition bias in a trial included one or more of the following: high dropout rate; dropout rate not balanced between intervention arms; low percentage of participants included in the analysis; inappropriate type of analysis performed (e.g. per protocol); reasons for loss to follow-up not balanced between intervention arms; inappropriate method of imputing missing data (e.g. last-observation-carried-forward); the proportion of missing outcomes compared with the observed event risk was enough to induce clinically relevant bias in the intervention effect estimate.

Selective reporting

A trial protocol was available for seven trials (Bilezikian 2013; Kahn 2006; Pfützner 2011; Schweizer 2007; Umpierrez 2014; UKPDS 34 1998; Williams-Herman 2010).

We judged all but three of the trials to be of high risk of reporting bias for one or more outcome of interest for this review (Derosa 2004; Erem 2014; Umpierrez 2014).

We judged the following primary outcomes to be of high risk of selective outcome reporting bias in one or more trials: all-cause mortality (Derosa 2003; Derosa 2009; Onuchin 2010; Rahman 2011; Teupe 1991; UKPDS 34 1998; Yamanouchi 2005), health-related quality of life (Kahn 2006; UKPDS 34 1998) and serious adverse events (Derosa 2009; Onuchin 2010; Rahman 2011; Schweizer 2007;

Schernthaner 2004; Teupe 1991; UKPDS 34 1998; Yamanouchi 2005).

We judged the following secondary outcomes to be of high risk of selective outcome reporting bias in one or more trials: non-fatal myocardial infarction (Schweizer 2007; UKPDS 34 1998), cardiovascular mortality, non-fatal stroke, end-stage renal disease, blindness (UKPDS 34 1998) and severe hypoglycaemia (Campbell 1994; Derosa 2009; Onuchin 2010; Schweizer 2007; Yamanouchi 2005).

For details on the assessment of risk of reporting bias, see 'Characteristics of included studies', Appendix 2; Appendix 3; Appendix 7 and Appendix 8.

Other potential sources of bias

We judged 16 trials to be at unclear risk of funding bias due to either having received grants from a pharmaceutical company or not adequately describing sources of funding (Bilezikian 2013; Campbell 1994; Derosa 2003; Derosa 2004; Derosa 2009; Kahn 2006; Kiyici 2009; Onuchin 2010; Pfützner 2011; Rahman 2011; Schernthaner 2004; Teupe 1991; UKPDS 34 1998; Umpierrez 2014; Williams-Herman 2010; Yamanouchi 2005). We judged one trial to be at high risk of funding bias due to all authors being employees and stockholders of a pharmaceutical manufacturer funding the study and performing the concept, design, data analysis and write-up (Schweizer 2007). We judged one trial to be at low risk of funding bias due to having received grants only from a university (Erem 2014).

Effects of interventions

See: **Summary of findings 1** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus insulin; **Summary of findings 2** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus sulphonylureas; **Summary of findings 3** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus thiazolidinediones; **Summary of findings 4** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus dipeptidyl-peptidase 4 inhibitors; **Summary of findings 5** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus glucagon like peptide-1 analogues; **Summary of findings 6** Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus meglitinides

For more details please see Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

Baseline characteristics

For details of baseline characteristics, see Appendix 5 and Appendix 6.

Metformin monotherapy versus placebo

We did not identify any trials comparing metformin monotherapy with placebo.

Metformin monotherapy versus no intervention

We identified two trials comparing metformin monotherapy with no intervention (Kiyici 2009; Teupe 1991). Metformin was administered in doses ranging from 850 mg/day to 1700 mg/day and 'no intervention' did not use any glucose-lowering drug or placebo. With the exception of HbA1c, subgroup and sensitivity analyses were not possible due to a lack of data.

Primary outcomes

All-cause mortality

One trial reported all-cause mortality (Kiyici 2009). In the metformin group, 0/16 participants died compared with 0/15 participants in the no intervention group (very low-certainty evidence).

Serious adverse events

One trial reported serious adverse events (Kiyici 2009). In the metformin group, 0/16 participants experienced a serious adverse event compared with 0/15 participants in the no intervention group (very low-certainty evidence).

Health-related quality of life

Neither of the trials reported health-related quality of life.

Secondary outcomes

Cardiovascular mortality

One trial reported cardiovascular mortality (Kiyici 2009). In the metformin group, 0/16 participants died of cardiovascular reasons compared with 0/15 participants in the no intervention group (very low-certainty evidence).

Non-fatal myocardial infarction, non-fatal stroke, end-stage renal disease, blindness, severe hypoglycaemia

Neither of the included trials reported these outcomes.

Explorative outcomes

Anthropometric measures: body mass index (BMI)

One trial reported BMI (Kiyici 2009). In the metformin group, the mean BMI was 30.7 kg/m^2 (standard deviation (SD) 3.7) in 16 participants compared with 29.6 kg/m^2 (SD 3.2) in 15 participants in the no intervention group.

Anthropometric measures: body weight

One of the trials reported body weight (Teupe 1991). In the metformin group, the mean body weight was 85.1 kg (SD 10) in 25 participants compared with 81.0 kg (SD 11.7) in 29 participants in the no intervention group.

Glycaemic control: fasting plasma glucose (FPG)

One trial reported on FPG (Kiyici 2009). In the metformin group, the mean FPG was 6.4 mmol/L (SD 0.6) in 16 participants compared with 6.6 mmol/L (SD 1.0) in 15 participants in the no intervention group.

Glycaemic control: HbA1c The figures for the confidence intervals have been rounded up, and the number of participants refers only to the 'No intervention group.

Both of the included trials reported on HbA1c (mean difference (MD) -0.1%, 95% confidence interval (CI) -0.5 to 0.4; P = 0.81; 2 trials; 85 participants; Analysis 1.1).

Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.67; Analysis 1.2). Testing for subgroup difference according to obesity or presence of selection bias was not possible due to lack of data and both trials having an unclear risk of selection bias.

Intervention failure

One trial reported on intervention failure (Teupe 1991). In the metformin group, 0/50 participants experienced intervention failure compared with 4/50 participants (8.0%) in the no intervention group.

Lactic acidosis, amputation of lower extremity, congestive heart failure, cardiac revascularisation, peripheral revascularisation, socioeconomic effects

Neither of the included trials reported these outcomes.

Metformin monotherapy versus diet

We did not identify any trials comparing metformin monotherapy versus diet.

Metformin monotherapy versus insulin

We identified two trials comparing metformin monotherapy with insulin (Onuchin 2010; UKPDS 34 1998). Metformin was administered in doses ranging from 2500 mg/day to 2550 mg/day and insulin was administered in variable doses. One trial reported that 30 participants (8.7%) in the metformin group and 90 participants (30%) in the insulin group did not take the allocated medication either due to refusal of taking the medication or experiencing adverse effects after three years of the intervention (UKPDS 34 1998).
Subgroup and sensitivity analyses were not possible due to a lack of data.

Primary outcomes

All-cause mortality or serious adverse events

Neither of the trials reported all-cause mortality or serious adverse events.

Health-related quality of life

One trial reported health-related quality of life for both mental health and physical health measured using the SF-36 version 2 questionnaire (Onuchin 2010), for details see Appendix 21. The mean mental health in the metformin group was 36.4 (SD 7.9) in 46 participants compared with 33.9 (SD 8.6) in 45 participants in the insulin group (very low-certainty evidence). The mean physical health in the metformin group was 38.1 (SD 5.4) in 46 participants compared with 38.1 (SD 5.3) in 45 participants in the insulin group (very low-certainty evidence).

Secondary outcomes

Severe hypoglycaemia

One trial reported severe hypoglycaemia (UKPDS 34 1998). In the metformin group, 1/342 participants (0.3%) experienced severe hypoglycaemia compared with 1/409 participants (0.2%) in the insulin group. Data were reported after one year of follow-up. However, it was not clearly described how many participants were included in the analysis. Unfortunately, the UKPDS 34 did not report the number of participants with hypoglycaemia in each of the intervention arms at the end of the follow-up period.

Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, end-stage renal disease or blindness

Neither of the trials reported these outcomes.

Explorative outcomes

Anthropometric measures: body mass index (BMI)

One trial reported BMI (Onuchin 2010). In the metformin group, the mean BMI was 29.6 kg/m^2 (SD 5.2) in 46 participants compared with 32.1 kg/m^2 (SD 6.5) in 45 participants in the insulin group.

Glycaemic control: fasting plasma glucose (FPG)

One trial reported FPG (UKPDS 34 1998). In the metformin group, the mean FPG was 7.7 mmol/L (SD 2.1) in 262 participants compared with 7.0 mmol/L (SD 2.1) in 304 participants in the insulin group.

Glycaemic control: HbA1c

One trial reported HbA1c (Onuchin 2010). In the metformin group, the mean HbA1c was 7.1% (SD 0.6) in 46 participants compared with 8.1% (SD 0.9) in 45 participants in the insulin group.

Intervention failure

One trial reported on intervention failure (UKPDS 34 1998). In the metformin group, 25/342 participants (7.3%) experienced intervention failure compared with 38/409 participants (9.3%) in the insulin group. Data were reported after three years of the intervention.

Anthropometric measures: body weight, lactic acidosis, amputation of lower extremity, congestive heart failure, cardiac revascularisation, peripheral revascularisation, socioeconomic effects

Neither of the included trials reported these outcomes.

Metformin monotherapy versus sulphonylureas

We identified seven trials comparing metformin monotherapy with sulphonylureas (Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006; Rahman 2011; UKPDS 34 1998; Yamanouchi 2005). Metformin was administered in doses ranging from 750 mg/day to 3000 mg/day. Sulphonylureas were administered as glibenclamide in two trials (Kahn 2006; UKPDS 34 1998) in doses ranging from 15 mg/day to 20 mg/day; gliclazide in one trial (Erem 2014) in a dose of 120 mg/day; glipizide in one trial (Campbell 1994) in a dose of 30 mg/day; and glimepiride in three trials (Derosa 2004; Rahman 2011; Yamanouchi 2005) in doses ranging from 1 mg/day to 8 mg/day.

Primary outcomes

All-cause mortality

Four trials (Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006) reported all-cause mortality (very low-certainty evidence). Three trials reported that 0/24, 0/75 and 0/19 participants in the metformin group died compared with 0/24, 0/73 and 0/19 participants in the sulphonylurea group, respectively (Campbell 1994; Derosa 2004; Erem 2014). In the remaining trial in the metformin group, 31/1454 participants (2.1%) died compared with 31/1441 participants (2.2%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

Serious adverse events

Three trials (Derosa 2004; Erem 2014; Kahn 2006) reported serious adverse events (very low-certainty evidence). Two trials reported that 0/75 and 0/19 participants in the metformin group experienced a serious adverse event compared with 0/73 and 0/19 participants in the sulphonylurea group, respectively (Derosa 2004; Erem 2014). In the remaining trial in the metformin group, 331/1454 participants (22.8%) experienced a serious adverse event compared with 308/1441 participants (21.4%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

One trial reported that 30 participants (8.7%) in the metformin group and 16 participants (8%) in the sulphonylurea group did not take the allocated medication either due to refusal of taking the medication or experiencing adverse effects after three years of the intervention (UKPDS 34 1998).

Health-related quality of life

None of the trials reported on this outcome.

Secondary outcomes

Cardiovascular mortality

Two trials (Erem 2014; Kahn 2006) reported cardiovascular mortality (very low-certainty evidence). One trial reported that 0/19 in the metformin group died of cardiovascular reasons compared with 0/19 in the sulphonylurea group (Erem 2014). In the other trial in the metformin group, 4/1455 participants (0.3%) died of cardiovascular reasons compared with 8/1447 participants (0.6%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

Non-fatal myocardial infarction

Three trials (Erem 2014; Kahn 2006; Yamanouchi 2005) reported non-fatal myocardial infarction (very low-certainty evidence). Two trials reported that 0/19 and 0/37 in the metformin group experienced a non-fatal myocardial infarction compared with 0/19 and 0/34 in the sulphonylurea group (Erem 2014; Yamanouchi 2005). In the remaining trial in the metformin group, 21/1454 participants (1.4%) compared with 15/1441 participants (1.0%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

Non-fatal stroke

One of the trials (Yamanouchi 2005) reported non-fatal stroke (very low-certainty evidence). In the metformin group, 0/37 participants experienced a non-fatal stroke compared with 0/34 participants in the sulphonylurea group.

Subgroup and sensitivity analyses were not possible due to a lack of data.

Severe hypoglycaemia

Four trials (Derosa 2004; Erem 2014; Kahn 2006; UKPDS 34 1998) reported that a total of 13 participants experienced severe hypoglycaemia: in the metformin group 2/1890 participants (0.1%) experienced severe hypoglycaemia compared with 11/1810 participants (0.6%) in the sulphonylurea group (RR 0.18 in favour of metformin, 95% CI 0.04 to 0.82; P = 0.03; 4 trials; 3700 participants; Analysis 2.1). The 95% prediction interval did not provide a meaningful estimate.

For one of the trials data were reported after one year of follow-up, and the number of participants included in the analysis was not clearly described (UKPDS 34 1998). Unfortunately, the UKPDS 34 did not report the number of participants with hypoglycaemia in each of the intervention arms at the end of the follow-up period.

Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.62; Analysis 2.2). Testing for subgroup differences according to sulphonylurea generation, obesity or presence of selection bias was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials did not substantially affect the effect estimate (RR 0.12, 95% CI 0.02 to 0.99; P = 0.05) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

End-stage renal disease or blindness

None of the included trials reported on these outcomes.

Explorative outcomes

Anthropometric measures: body mass index (BMI)

Four trials reported BMI (MD 0.6 kg/m^2 in favour of sulphonylureas, 95% CI 0.3 to 0.9; P < 0.001; 4 trials; 461 participants; Analysis 2.3) (Derosa 2004; Erem 2014; Rahman 2011; Yamanouchi 2005).

Testing for subgroup differences according to sulphonylurea generation did not indicate an interaction (P = 0.85; Analysis 2.3). Testing for subgroup differences according to duration of follow-up, presence of selection bias or obesity was not possible due to a lack of data.

The effect estimate was greatly influenced by the large weight of one trial (Derosa 2004). Sensitivity analysis showed that excluding this trial substantially affected the effect estimate (MD 0.02 kg/m^2, 95% CI -1.04 to 1.08; P = 0.98; 3 trials; 313 participants). This was most likely due to the slight baseline imbalances in BMI between the metformin and sulphonylurea group coupled with the considerably smaller variance in the results of this trial compared to the other trials in the meta-analysis. Sensitivity analyses based on very long or large trials, publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were of short duration (less than two years), published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Anthropometric measures: body weight

Four of the trials reported on body weight (MD -3.9 kg in favour of metformin, 95% CI -5.2 to -2.5; P < 0.001; 4 trials; 3185 participants; Analysis 2.4) (Campbell 1994; Erem 2014; Kahn 2006; Rahman 2011). Two of the trials reported the effect size as change from baseline (Campbell 1994; Kahn 2006).

Testing for subgroup differences according to sulphonylurea generation indicated an interaction (P = 0.002; Analysis 2.4). For second-generation sulphonylurea the effect estimate (MD -4.5 kg, 95% CI -5.2 to -3.9; P < 0.001; 3 trials; 2981 participants) was in favour of metformin. For third-generation sulphonylurea the effect estimate (MD -2.1 kg, 95% CI -3.5 to -0.6; P = 0.005; 1 trial; 204 participants) was also in favour of metformin. Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.42) (Analysis 2.5). Testing for subgroup differences according to presence of selection bias yielded the same subgroups and results as the subgroup analysis according to duration of follow-up. Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting the analysis to very long or large trials did not substantially affect the effect estimate (MD -4.5 kg, 95% CI -5.3 to -3.7; P < 0.001; 1 trial; 2895 participants) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

We detected substantial statistical heterogeneity between the trials (P = 0.02, I^2 = 69%). This could have been due to different types of comparator used (gliclazide, glipizide, glibenclamide, glimepiride), different doses of metformin (ranging from 2000 mg/day to 3000 mg/day), or different length of follow-up (ranging from one year to four years) across the trials.

Glycaemic control: fasting plasma glucose (FPG)

All trials reported FPG (random-effects MD -0.23 mmol/L, 95% CI -0.54 to 0.07; P = 0.13; fixed-effect MD -0.27 mmol/L in favour of metformin, 95% CI -0.41 to -0.14; P < 0.001; 7 trials; 3878 participants; Analysis 2.6). One of the trials reported data after three years of follow-up (UKPDS 34 1998). One trial reported FPG in both a published paper and a FDA document (Campbell 1994). In the publication, a total of 48 participants were included in the analysis. In the FDA report only 43 participants were included in the analysis. In the data from the FDA report, a larger reduction in FPG with glipizide was reported than reported in the published paper (2.8 mmol/L versus 3.2 mmol/L). In the FDA report it was concluded that metformin and glipizide were equally effective. In the published paper it was concluded that metformin gave greater reduction in FPG (Campbell 1994).

Testing for subgroup differences according to sulphonylurea generation did not indicate an interaction (P = 0.17; Analysis 2.6). Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.21; Analysis 2.7). Testing for subgroup differences according to presence of selection bias yielded the same subgroups and results as the subgroup analysis according to duration of follow-up. Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials did not substantially affect the effect estimate (MD -0.35 mmol/L in favour of metformin, 95% CI -0.51 to -0.19; P < 0.001; 1 trial; 2895 participants) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

We detected substantial statistical heterogeneity (P = 0.01, I^2 = 65%). This could have been due to different types of comparator used (gliclazide, glipizide, glibenclamide, glimepiride), different doses of intervention (ranging from 750 mg/day to 3000 mg/day), or comparator (ranging from 15 mg/day to 20 mg/day for glibenclamide and ranging from 2 mg/day to 8 mg/day for glimepiride) or different length of follow-up (ranging from one year to four years) across the trials.

Glycaemic control: HbA1c

Six trials reported HbA1c (random-effects MD -0.2%, 95% CI -0.5 to 0.02; P = 0.08; fixed-effect MD -0.2% in favour of metformin, 95% CI -0.3 to -0.1; P < 0.001; 6 trials; 3404 participants; Analysis 2.8) (Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006; Rahman 2011; Yamanouchi 2005).

One trial reported HbA1c in both a published paper and a FDA document (Campbell 1994). In the publication, a total of 48 participants were included in the analysis. In the FDA report only 43 participants were included in the analysis. In the FDA report it was concluded that there was a greater reduction in HbA1c with metformin, although this was not statistically significant. SD and number of participants in each intervention arm were not reported (Campbell 1994).

Testing for subgroup differences according to sulphonylurea generation indicated an interaction (P = 0.02; Analysis 2.8). For second-generation sulphonylurea the effect estimate (MD -0.5%, 95% CI -0.9 to -0.1; P = 0.01; 3 trials; 2981 participants) was in favour of metformin. For third-generation sulphonylurea the effect estimate (MD 0.1%, 95% CI -0.2 to 0.3; P = 0.64; 3 trials; 423 participants) was not in favour of either intervention. However, the CIs overlapped to a small degree indicating doubtful subgroup differences.

Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.98; Analysis 2.9). Testing for subgroup differences according to presence of selection bias yielded the same subgroups and results as the subgroup analysis according to duration of follow-up. Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials substantially affected the effect estimate (MD -0.24 in favour of metformin, 95% CI -0.35 to -0.13; P < 0.0001; 1 trials; 2895 participants) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible, since all the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Congestive heart failure

Three trials reported congestive heart failure (Erem 2014; Kahn 2006; Yamanouchi 2005). However, two trials reported that 0/19 and 0/37 participants in the metformin group experienced congestive heart failure compared with 0/19 and 0/34 participants in the sulphonylurea group, respectively (Erem 2014; Yamanouchi 2005). In the remaining trial, 19/1454 participants (1.3%) in the metformin group experienced congestive heart failure compared with 9/1441 participants (0.6%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

Cardiac revascularisation

Yamanouchi 2005 reported cardiac revascularisation. In the metformin group, 0/37 participants experienced cardiac revascularisation compared with 0/34 participants in the sulphonylurea group.

Subgroup and sensitivity analyses were not possible due to a lack of data.

Peripheral revascularisation

Two trials reported peripheral revascularisation (Kahn 2006; Yamanouchi 2005). Yamanouchi 2005 reported that in the metformin group 0/37 participants experienced peripheral revascularisation compared with 0/34 in the sulphonylurea group. In the remaining trial, 27/1454 participants (1.9%) in the metformin group experienced peripheral revascularisation compared with 31/1441 participants (2.2%) in the sulphonylurea group (Kahn 2006).

Subgroup and sensitivity analyses were not possible due to a lack of data.

Intervention failure

Three trials reported that a total of 576 participants experienced intervention failure: in the metformin group 233/1835 participants (12.7%) experienced intervention failure compared with 343/1755 participants (19.5%) in the sulphonylurea group (RR 0.66 in favour of metformin, 95% CI 0.57 to 0.77; P < 0.001; 3 trials; 3590 participants; Analysis 2.10) (Kahn 2006; UKPDS 34 1998; Yamanouchi 2005) . In one trial (UKPDS 34 1998), data were reported after three years of follow-up. In one trial the analysis included withdrawals that were excluded from the other analyses from the trial (Yamanouchi 2005).

Testing for subgroup differences according to sulphonylurea generation did not indicate an interaction (P = 0.36; Analysis 2.10). Testing for subgroup differences according to duration of follow-up or presence of selection bias yielded the same subgroups and results as the subgroup analysis according to sulphonylurea generation (Analysis 2.11). Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials did not substantially affect the effect estimate (RR 0.66, 95% CI 0.56 to 0.77; P < 0.001; 1 trial; 2895 participants) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

Lactic acidosis, amputation of lower extremity, socioeconomic effects

None of the included trials reported these outcomes.

Metformin monotherapy versus thiazolidinediones

We identified seven trials comparing metformin monotherapy versus thiazolidinediones (Bilezikian 2013; Derosa 2009; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004; Yamanouchi 2005). Metformin was administered in doses ranging from 750 mg/day to 3000 mg/day. Thiazolidinediones were administered as pioglitazone in four trials (Derosa 2009; Erem 2014; Schernthaner 2004; Yamanouchi 2005) in doses of 45 mg/day and as rosiglitazone in three trials (Bilezikian 2013; Kahn 2006; Kiyici 2009) in doses ranging from 4 mg/day to 8 mg/day.

Primary outcomes

All-cause mortality

Five trials (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004) reported that a total of 71 participants died: in the metformin group 33/2197 participants (1.5%) died compared with 38/2205 participants (1.7%) in the thiazolidinedione group (RR 0.88, 95% CI 0.55 to 1.39; P = 0.57; 5 trials; 4402 participants; very low-certainty evidence; Analysis 3.1) The 95% prediction interval ranged between 0.42 and 1.85.

In two trials there were no deaths (Erem 2014; Kiyici 2009), and one trial contributed 65/71 events (91.5%) (Kahn 2006).

Testing for subgroup differences according to thiazolidinedione type did not indicate an interaction (P = 0.76). Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.57; Analysis 3.2). Testing for subgroup differences according to presence of selection bias or obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials (Kahn 2006) did not substantially affect the effect estimate (RR 0.91, 95% CI 0.56 to 1.48; P = 0.71; 1 trial; 2910 participants). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Serious adverse events

Four trials (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009) reported that a total of 689 participants experienced a serious adverse event: in the metformin group 336/1600 participants (21.0%) experienced a serious adverse event compared with 353/1608 participants (22.0%) in the thiazolidinedione group (RR 0.95, 95% CI 0.84 to 1.09; P = 0.49; 4 trials; 3208 participants; very low-certainty evidence; Analysis 3.3). In two trials no serious adverse events occurred (Erem 2014; Kiyici 2009).

Testing for subgroup differences according to thiazolidinedione type was not possible due to lack of data. Testing for subgroup differences according to duration of follow-up did not indicate an

interaction (P = 0.64; Analysis 3.4). Testing for subgroup differences according to presence of selection bias or obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials (Kahn 2006) did not substantially affect the effect estimate (RR 0.96, 95%, CI 0.84 to 1.09; P = 0.52; 1 trial; 2910 participants). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

Health-related quality of life

None of the included trials reported on health-related quality of life.

Secondary outcomes

Cardiovascular mortality

Four trials (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009) reported that a total of 10 participants died of cardiovascular reasons: in the metformin group 4/1601 participants (0.2%) died of cardiovascular reasons compared with 6/1610 participants (0.4%) in the thiazolidinedione group (RR 0.71, 95% CI 0.21 to 2.39; P = 0.58; 4 trials; 3211 participants; very low-certainty evidence; Analysis 3.5). In two trials no deaths due to cardiovascular reasons occurred (Erem 2014; Kiyici 2009).

Testing for subgroup differences according to duration of follow-up did not indicate an interaction (P = 0.63: Analysis 3.6). Testing for subgroup differences according to thiazolidinedione type, presence of selection bias or obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials did not substantially affect the effect estimate (RR 0.80, 95% CI 0.22 to 2.98; P = 0.74; 1 trial; 2910 participants) (Kahn 2006). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding, and country were not possible. All the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

Non-fatal myocardial infarction

Three trials (Erem 2014; Kahn 2006; Yamanouchi 2005) reported non-fatal myocardial infarction (very low-certainty evidence). Two trials reported that 0/19 and 0/37 participants in the metformin group experienced a non-fatal myocardial infarction compared with 0/19 and 0/35 participants in the thiazolidinedione group, respectively (Erem 2014; Yamanouchi 2005). In the remaining trial (Kahn 2006), 21/1454 participants (1.4%) in the metformin group experienced non-fatal myocardial infarction compared with 25/1456 participants (1.7%) in the thiazolidinedione group.

Subgroup and sensitivity analysis could not be performed due to lack of data.

Non-fatal stroke

One trial (Yamanouchi 2005) reported non-fatal stroke. In the metformin group, 0/37 participants experienced non-fatal stroke compared with 0/35 participants in the thiazolidinedione group (very low-certainty evidence).

Subgroup and sensitivity analysis could not be performed due to lack of data.

Severe hypoglycaemia

Two trials reported severe hypoglycaemia (Erem 2014; Kahn 2006). Erem 2014 reported that 0/19 participants in the metformin group experienced severe hypoglycaemia compared with 0/19 participants in the thiazolidinedione group. In the remaining trial in the metformin group, 1/1454 participants (0.1%) experienced severe hypoglycaemia compared with 1/1456 (0.1%) in the thiazolidinedione group (Kahn 2006).

Subgroup and sensitivity analysis could not be performed due to lack of data.

End-stage renal disease or blindness

None of the included trials reported these outcomes.

Explorative outcomes

Anthropometric measures: body mass index (BMI)

Three trials (Erem 2014; Kiyici 2009; Yamanouchi 2005) reported BMI (MD -0.4 kg/m^2, 95% CI -2.3 to 1.6; P = 0.69; 3 trials; 145 participants; Analysis 3.7).

Testing for subgroup differences according to thiazolidinedione type did not indicate an interaction (P = 0.48). Testing for subgroup differences according to duration of follow-up, presence of selection bias, or obesity was not possible due to a lack of data.

Sensitivity analyses based on very long or large trials, publication status, language of publication, diagnostic criteria, source of funding and country were not possible, since all the trials had less than 1000 participants, were of one year duration, were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Anthropometric measures: body weight

Two trials (Erem 2014; Kahn 2006) reported body weight (random-effects MD -1.3 kg, 95% CI -15.2 to 12.7; P = 0.86; fixed-effect MD -7.6 kg in favour of metformin, 95% CI -8.3 to -6.9; P < 0.001; 2 trials; 2948 participants; Analysis 3.8).

Testing for subgroup differences according to thiazolidinedione type indicated an interaction (P = 0.002). For pioglitazone the effect estimate (MD 6.6 kg, 95% CI -2.3 to 15.5; P = 0.15; 1 trial; 38 participants) was not in favour of either intervention. For rosiglitazone the effect estimate (MD -7.7 kg, 95% CI -8.4 to -7.0; P < 0.001; 1 trial; 2910 participants) was in favour of metformin. Testing for subgroup differences according to duration of follow-up or presence of selection bias yielded the same subgroups and results as the subgroup analysis according to thiazolidinedione type. Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis was not possible due to a lack of data.

Glycaemic control: fasting plasma glucose (FPG)

Six trials (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004; Yamanouchi 2005) reported FPG (random-effects MD 0.32 mmol/L, 95% CI -0.21 to 0.84; P = 0.23; fixed-effect MD 0.52 mmol/L in favour of thiazolidinediones, 95% CI 0.38 to 0.65; P < 0.001; 6 trials; 4456 participants; Analysis 3.9).

Testing for subgroup differences according to thiazolidinedione type did not indicate an interaction (P = 0.25). Testing for subgroup differences according to duration of follow-up indicated an interaction (P = 0.01; Analysis 3.10). For the one trial of long duration (two years or more) the effect estimate (MD 0.73 mmol/L, 95% CI 0.57 to 0.89; P < 0.001; 1 trial; 2910 participants) was in favour of thiazolidinedione. For trials of short duration (less than two years) the effect estimate (MD 0.12 mmol/L, 95% CI -0.32 to 0.56; P = 0.59; 5 trials; 1546 participants) was not in favour of either intervention. Testing for subgroup differences according to presence of selection bias did not indicate an interaction (P = 0.89; Analysis 3.11). Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials (Kahn 2006) substantially affected the effect estimate (MD 0.73 mmol/L in favour of thiazolidinedione, 95% CI 0.57 to 0.89; P < 0.001; 1 trial; 2910 participants). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding, and country were not possible, since all the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding and were based in different countries.

We detected considerable heterogeneity between the trials (P < 0.001, I^2 = 85%). This could have been due to different types of comparator used (pioglitazone, rosiglitazone), different doses of intervention (ranging from 750 mg/day to 2550 mg/day) or comparator (ranging from 4 mg/day to 8 mg/day for rosiglitazone) or different length of follow-up (ranging from one year to four years) across the trials.

Glycaemic control: HbA1c

Six trials (Bilezikian 2013; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004; Yamanouchi 2005) reported HbA1c (MD 0.01%, 95% CI -0.2 to 0.2; P = 0.95; 6 trials; 4456 participants; Analysis 3.12).

Testing for subgroup differences according to thiazolidinedione type did not indicate an interaction (P = 0.26). Testing for subgroup differences according to duration of follow-up indicated an interaction (P < 0.001; Analysis 3.13). For the one trial of long duration (two years or more) the effect estimate (MD 0.3%, 95% CI 0.2 to 0.4; P < 0.001; 1 trial; 2910 participants) was in favour of thiazolidinediones. For trials of short duration (less than two years) the effect estimate (MD -0.1%, 95% CI -0.2 to 0.01; P = 0.07; 5 trials; 1546 participants) was not in favour of either intervention. Testing for subgroup differences according to presence of selection bias did not indicate an interaction (P = 0.65; Analysis 3.14). Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials (Kahn 2006) substantially affected the effect estimate (MD 0.3% in favour of thiazolidinediones, 95% CI 0.2 to 0.4; P < 0.001; 1 trial; 2910 participants). Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible, since all the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Congestive heart failure

Three trials (Erem 2014; Kahn 2006; Yamanouchi 2005) reported congestive heart failure. Two trials reported that 0/37 and 0/19 participants in the metformin group experienced congestive heart failure compared with 0/35 and 0/19 participants in the thiazolidinedione group, respectively (Erem 2014; Yamanouchi 2005). In the remaining trial, 19/1454 participants (1.3%) in the metformin group experienced congestive heart failure compared with 22/1456 participants (1.5%) in the thiazolidinedione group (Kahn 2006).

Testing for subgroup differences according to thiazolidinedione type, duration of follow-up, presence of selection bias, or obesity was not possible due to a lack of data.

Sensitivity analysis showed that restricting analysis to very long or large trials (Kahn 2006) contained the same trial data as in the main analysis. Sensitivity analyses based on publication status, language of publication, diagnostic criteria, source of funding and country were not possible, since all the trials were published in medical journals, published in English, used different or did not report diagnostic criteria, did not have sufficient data on source of funding, and were based in different countries.

Cardiac revascularisation

One trial reported cardiac revascularisation (Yamanouchi 2005). In the metformin group, 0/37 participants experienced cardiac revascularisation compared with 0/35 in the thiazolidinedione group.

Subgroup and sensitivity analysis could not be performed due to lack of data.

Peripheral revascularisation

Two trials reported data peripheral revascularisation (Kahn 2006; Yamanouchi 2005). One trial reported that 0/37 participants experienced peripheral revascularisation in the metformin group compared with 0/35 participants in the thiazolidinedione group (Yamanouchi 2005). In the remaining trial, 27/1454 participants (1.9%) in the metformin group experienced peripheral revascularisation compared with 36/1456 participants (2.5%) in the thiazolidinedione group (Kahn 2006).

Subgroup and sensitivity analysis could not be performed due to lack of data.

Intervention failure

Two of the included trials (Kahn 2006; Yamanouchi 2005) reported that a total of 352 participants experienced intervention failure: in the metformin group 208/1493 participants (13.9%) experienced intervention failure compared with 144/1494 participants (9.6%) in the thiazolidinedione group (RR 1.45 in favour of thiazolidinediones, 95% CI 1.18 to 1.77; P < 0.001; 2 trials; 2987 participants; Analysis 3.15). In one trial the results included withdrawals from the study which were excluded in all other analyses (Yamanouchi 2005).

Testing for subgroup differences according to thiazolidinedione type did not indicate an interaction (P = 0.78). Testing for subgroup differences according to duration of follow-up (Analysis 3.16) or presence of selection bias (Analysis 3.17) yielded the same subgroups and results as the subgroup analysis according to thiazolidinedione type. Testing for subgroup differences according to obesity was not possible due to a lack of data.

Sensitivity analysis was not possible due to a lack of data

Lactic acidosis, amputation of lower extremity, socioeconomic effects

None of the included trials reported these outcomes.

Metformin monotherapy versus dipeptidyl peptidase-4 inhibitors

We identified three trials comparing metformin monotherapy with a dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) (Pfützner 2011; Schweizer 2007; Williams-Herman 2010). Metformin was administered in doses ranging from 1000 mg/day to 2000 mg/day. DPP-4 inhibitors were administered as saxagliptin in doses of 10 mg/day in one trial (Pfützner 2011); vildagliptin in doses of 100 mg/day in one trial (Schweizer 2007); and sitagliptin in doses of 100 mg/day (Williams-Herman 2010). In one trial (Williams-Herman 2010), two doses of metformin were administered in two separate intervention groups. These doses were 1000 mg/day and 2000 mg/day, respectively. For all of the following results these groups were combined as one intervention group.

Primary outcomes

All-cause mortality

All of the included trials reported that a total of 15 participants died: in the metformin group 10/944 participants (1.1%) died compared with 5/1033 participants (0.5%) in the DPP-4 inhibitor group (3 trials; 1977 participants; very low-certainty evidence; Analysis 4.1). As each trial applied a different DPP-4 inhibitor it was inappropriate to pool results in a meta-analysis. For this reason, we also did not perform sensitivity or subgroup analysis. In one trial results were reported after 104 weeks of the intervention (Williams-Herman 2010). In one trial results were calculated using all-cause mortality from the first 52 weeks of intervention summed with all-cause mortality from the extension period (Schweizer 2007).

In the saxagliptin trial, 5/328 (1.5%) participants in the metformin group died compared with 2/335 (0.6%) participants in the saxagliptin group (Pfützner 2011).

In the sitagliptin trial, 1/364 (0.3%) participants in the metformin group died compared with 0/179 in the sitagliptin group (Williams-Herman 2010).

In the vildagliptin trial, 4/252 (1.6%) participants in the metformin group died compared with 3/519 (0.6%) in the vildagliptin group (Schweizer 2007).

Serious adverse events

All of the included trials reported that a total of 108 participants experienced a serious adverse event: in the metformin group 44/944 participants (4.7%) experienced a serious adverse event compared with 64/1033 participants (6.2%) in the DPP-4 inhibitor group (3 trials; 1977 participants; very low-certainty evidence; Analysis 4.2). As each trial applied a different DPP-4 inhibitor it was inappropriate to pool results in a meta-analysis. For this reason, we also did not perform sensitivity or subgroup analysis. In one trial results were reported after 52 weeks of intervention (Schweizer 2007). In one trial results were reported after 104 weeks of intervention and excluded data for participants who initiated glycaemic rescue therapy (Williams-Herman 2010).

In the saxagliptin trial, 15/328 (4.5%) participants in the metformin group experienced a serious adverse event compared with 16/335 (4.8%) participants in the saxagliptin group (Pfützner 2011).

In the sitagliptin trial, 16/364 (4.4%) participants in the metformin group experienced a serious adverse event compared with 13/179 (7.2%) participants in the sitagliptin group (Williams-Herman 2010).

In the vildagliptin trial, 13/252 (5.2%) participants in the metformin group experienced a serious adverse event compared with 35/519 (6.7%) participants in the vildagliptin group (Schweizer 2007).

Health-related quality of life

None of the included trials reported on health-related quality of life.

Secondary outcomes

Cardiovascular mortality

Two trials (Pfützner 2011; Williams-Herman 2010) reported on cardiovascular mortality (very low-certainty evidence). One trial reported that in the metformin group 0/364 participants died from cardiovascular reasons compared with 0/179 participants in the DPP-4 inhibitor group (Williams-Herman 2010). In the remaining trial, 3/328 participants (0.9%) in the metformin group died from cardiovascular reasons compared with 2/335 participants (0.6%) in the DPP-4 inhibitor group (Pfützner 2011). In Pfützner 2011 one additional participant in the metformin group died from sudden death which was not classified as cardiovascular mortality. Williams-Herman 2010 reported results after 104 weeks of intervention.

Non-fatal myocardial infarction

One trial reported non-fatal myocardial infarction (Williams-Herman 2010). In the metformin group, 1/364 participants (0.3%) experienced a non-fatal myocardial infarction compared with 0/179 participants in the DPP-4 inhibitor group (very low-certainty evidence). Results were reported after 104 weeks of intervention.

Non-fatal stroke

One trial reported non-fatal stroke (Williams-Herman 2010). In the metformin group, 0/364 participants experienced a non-fatal stroke compared with 0/179 participants in the DPP-4 inhibitor group (very low-certainty evidence). Results were reported after 104 weeks of intervention.

Severe hypoglycaemia

All of the included trials reported severe hypoglycaemia. Two trials reported that in the metformin group 0/328 participants and 0/252 participants experienced severe hypoglycaemia compared with 0/335 and 0/519 participants in the DPP-4 inhibitor group, respectively (Pfützner 2011; Schweizer 2007). In the remaining trial, 3/364 participants (0.8%) in the metformin group experienced severe hypoglycaemia compared with 0/179 participants in the DPP-4 inhibitor group (Williams-Herman 2010). Schweizer 2007

reported results after 52 weeks of intervention. Williams-Herman 2010 reported results after 104 weeks of intervention.

End-stage renal disease or blindness

None of the included trials reported these outcomes.

Explorative outcomes

Anthropometric measures: body weight

All of the included trials reported body weight. However, as each trial applied a different DDP-4 inhibitor, no meta-analysis was performed (Analysis 4.3). All trials favoured metformin. In one trial (Pfützner 2011), SD was not reported and had to be imputed by combining the SDs from the two other trials in the analysis. Schweizer 2007 reported results after 52 weeks of intervention and adjusted for baseline HbA1c values. Williams-Herman 2010 reported results after 104 weeks of intervention and excluded participants that required rescue medication in the initial 24 weeks and/or the subsequent 30 weeks of the intervention. Pfützner 2011 reported results after 76 weeks of intervention.

Sensitivity and subgroup analysis were not possible due to a lack of data.

Glycaemic control: fasting plasma glucose (FPG)

All of the included trials reported on FPG. However, as each trial applied a different DDP-4 inhibitor, no meta-analysis was performed (Analysis 4.4). All studies showed a reduction in FPG in favour of metformin.

Sensitivity and subgroup analysis were not possible due to a lack of data.

Glycaemic control: HbA1c

All of the included trials reported on HbA1c. However, as each trial applied a different DDP-4 inhibitor, no meta-analysis was performed (Analysis 4.5).

Sensitivity and subgroup analysis were not possible due to a lack of data.

Intervention failure

One trial reported on intervention failure (Pfützner 2011). In the metformin group, 105/328 participants (32.0%) experienced intervention failure compared with 155/335 participants (46.3%) in the DPP-4 inhibitor group.

Sensitivity and subgroup analysis were not possible due to a lack of data.

Lactic acidosis, amputation of lower extremity, congestive heart failure, cardiac revascularisation, peripheral revascularisation, socioeconomic effects

None of the included trials reported these outcomes.

Metformin monotherapy versus glucagon like peptide-1 analogues

One trial compared metformin monotherapy with a glucagon like peptide-1 analogue (GLP-1) (Umpierrez 2014). Metformin was administered in a doses 1500 mg/day to 2000 mg/day. GLP-1 was administered as dulaglutide. Two different doses of dulaglutide were administered in the two separate comparator groups. These doses were 0.75 mg/week and 1.5 mg/week, respectively. For all of the following results these groups were combined as one comparator group.

Primary outcomes

All-cause mortality

In the metformin group, 0/268 participants died compared with 0/539 participants in the GLP-1 group (very low-certainty evidence).

Serious adverse events

In the metformin group, 16/268 participants (6.0%) experienced a serious adverse event compared with 35/539 participants (6.5%) in the GLP-1 group (RR 0.92, 95% CI 0.52 to 1.63; P = 0.77; very low-certainty evidence).

Health-related quality of life

The included trial did not report health-related quality of life.

Secondary outcomes

Cardiovascular mortality

In the metformin group, 0/268 participants died of cardiovascular reasons compared with 0/539 participants in the GLP-1 group (very low-certainty evidence). The results were reported after 53 weeks of follow-up.

Non-fatal myocardial infarction

In the metformin group, 0/268 participants experienced a non-fatal myocardial infarction compared with 1/539 participants (0.2%) in the GLP-1 group (RR 0.67, 95% CI 0.03 to 16.37; P = 0.81; very low-certainty evidence).

Non-fatal stroke

In the metformin group, 0/268 participants experienced a non-fatal stroke compared with 1/539 (0.2%) participants in the GLP-1 group (RR 0.67, 95% CI 0.03 to 16.37; P = 0.81; very low-certainty evidence).

Severe hypoglycaemia

In the metformin group, 0/268 participants experienced severe hypoglycaemia compared with 0/539 participants in the GLP-1 group.

End-stage renal disease or blindness

The included trial did not report these outcomes.

Explorative outcomes

Anthropometric measures: body mass index (BMI)

In the metformin group, the mean change of baseline BMI was -0.8 kg/m^2 (SD 1.8) in 267 participants compared with -0.6 kg/m^2 (SD 1.7) in 536 participants in the GLP-1 group. The result was adjusted for country, prior diabetes-medication usage, baseline value, visit, treatment-by-visit and patient as a random-effects in a mixed-effects, repeated measures analysis.

Anthropometric measures: body weight

In the metformin group, the mean change of baseline body weight was -2.2 kg (SD 4.7) in 267 participants compared with -1.5 kg (SD 4.8) in 536 participants in the GLP-1 group. The result was adjusted for country, prior diabetes-medication usage, baseline value, visit,

treatment-by-visit and patient as a random-effects in a mixed-effects, repeated measures analysis.

Glycaemic control: fasting plasma glucose (FPG)

In the metformin group, the mean change of baseline FPG was -1.15 mmol/L (SD 1.95) in 194 participants compared with -1.28 mmol/L (SD 2.04) in 417 participants in the GLP-1 group. The result was adjusted for country, prior diabetes-medication usage, baseline value, visit, treatment-by-visit and patient as a random-effects in a mixed-effects, repeated measures analysis.

Glycaemic control: HbA1c

In the metformin group, the mean change of baseline HbA1c was -0.5% (SD 1.1) in 265 participants compared with -0.6% (SD 1.1) in 530 participants in the GLP-1 group (MD 0.1%, 95% CI -0.1 to 0.3; P = 0.1805). The result was adjusted for country, prior diabetes-medication usage, baseline value, visit, treatment-by-visit and patient as a random-effects in a mixed-effects, repeated measures analysis.

Congestive heart failure

In the metformin group, 1/268 participants (0.4%) experienced congestive heart failure compared with 0/539 participants in the GLP-1 group.

Intervention failure

In the metformin group, 14/268 participants (5.2%) experienced intervention failure compared with 20/539 participants (3.7%) in the GLP-1 group.

Lactic acidosis, amputation of lower extremity, cardiac revascularisation, peripheral revascularisation, socioeconomic effects

The included trial did not report these outcomes.

Metformin monotherapy versus meglitinides

We identified one trial comparing metformin monotherapy with meglitinide (Derosa 2003). Metformin was administered in doses of 1500 mg/day to 2500 mg/day. Meglitinide was administered as repaglinide in doses of 2 mg/day to 4 mg/day.

Primary outcomes

All-cause mortality

The trial did not report this outcome.

Serious adverse events

In the metformin group, 0/56 participants experienced a serious adverse event compared with 0/56 participants in the meglitinide group (very low-certainty evidence).

Health-related quality of life

The trial did not report this outcome.

Secondary outcomes

Severe hypoglycaemia

In the metformin group, 0/56 participants experienced severe hypoglycaemia compared with 0/56 participants in the meglitinide group.

Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, end-stage renal disease, blindness

The trial did not report these outcomes.

Explorative outcomes

Glycaemic control: fasting plasma glucose (FPG)

In the metformin group, the mean FPG was 7.6 mmol/L (SD 0.94) in 49 participants compared with 7.7 mmol/L (SD 1.22) in 53 participants in the meglitinide group.

Subgroup analyses

We performed several subgroup analyses. Please see under comparison and outcome of interest.

Sensitivity analyses

We performed several sensitivity analyses. Please see under comparison and outcome of interest.

Assessment of reporting bias

We did not draw funnel plots since there were no analyses with 10 trials or more for a particular outcome.

Ongoing trials

We identified four ongoing RCTs that could potentially provide data of interest for our review. The estimated trial completion dates were: NCT01001962 (January 2020), NCT01779362 (August 2019), NCT02853630 (December 2018) and NCT03982381 (September 2024). Three of the trials (NCT01001962; NCT01779362; NCT02853630) are expected to have been completed, but no results have been published. The ongoing trials will include approximately 5824 participants. All of the ongoing trials are investigating one or more outcomes of interest to this review.

For further details, see 'Characteristics of ongoing studies'.

Studies awaiting assessment

We identified 24 RCTs awaiting assessment. All of the trials were expected to have been completed, but no results were published. The trials included approximately 2369 participants. The majority of the studies awaiting assessment investigated one or more outcomes of interest to this review.

For further details, see 'Characteristics of studies awaiting classification'.

DISCUSSION

Summary of main results

This review investigated metformin monotherapy compared with no intervention, placebo, diet or glucose-lowering drugs in people with T2DM. We included 18 trials with a total of 10,680 randomised participants. We judged no trials to be at low risk of bias for all 'Risk of bias' domains. The amount of evidence for our primary and secondary outcomes was very limited. Neither metformin nor any of the comparators were clearly favoured in any of the outcomes as specified in the Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6. There were fewer

reported cases of severe hypoglycaemia with metformin compared to sulphonylurea. Furthermore, metformin was favoured in the majority of our explorative outcomes. However, many of these results suffered from lack of data and heterogeneity, and were not robust in sensitivity analyses.

Overall completeness and applicability of evidence

We conducted an extensive search for trials in databases and from non-database sources with no restrictions on language or outcomes reported in trials, and we tried to retrieve additional information on all trials. Additionally, we handsearched reference lists of all trials, which identified two additional publications to be included. The US Food and Drug Administration (FDA) also provided additional information of an included trial (Campbell 1994).

For each trial we contacted one or more authors to obtain supplemental data on outcomes and 'Risk of bias' domains and to specify whether further trials existed. Only one author replied and provided additional data (Schweizer 2007).

Diagnostic criteria for T2DM were primarily established using the criteria from the World Health Organization (WHO) and American Diabetes Association (ADA). Eleven trials did not report diagnostic criteria for T2DM.

Selection bias may generally be present in randomised controlled trials (RCTs) because the participants could be healthier and more motivated than the population from which they are sampled. However, a Cochrane systematic review demonstrated that participants in RCTs had similar clinical outcomes compared with patients who did not participate (Vist 2008).

We were not able to include patient-important data from the longest follow-up period in the UKPDS trial (UKPDS 34 1998). The importance of the UKDPS trial is based on the length of the intervention: about 10 years. According to the design description, the researchers planned to compare the subgroup of overweight and obese participants randomly assigned to receive insulin or sulphonylureas or metformin monotherapy. However, to our knowledge, these data have not been reported separately. Instead, the participants assigned to sulphonylureas or insulin were grouped together, which precludes direct comparison of sulphonylureas with metformin and insulin with metformin. However, in some of the co-publications, some information on outcomes with relevance (e.g. severe hypoglycaemia, glycaemic control) for this review could be retrieved after one to three years of follow-up. The largest trial reporting patient-important outcomes for sulphonylurea monotherapy compared with metformin was the A Diabetes Outcome Progression Trial (ADOPT) trial (Kahn 2006).

We could not include mortality or macrovascular complications from the UKPDS trial, therefore our review consists exclusively of trials that did not predefine mortality or cardiovascular complications as their primary outcome and instead reported them as adverse events (deaths). This might have led to bias arising from trial design features, such as lack of adjudication of events.

Quality of the evidence

We judged all trials to be at unclear or high risk of bias for at least one of the 'Risk of bias' domains. The description or procedure of randomisation was inadequate in 11 trials (Campbell 1994; Derosa 2003; Derosa 2004; Derosa 2009; Erem 2014; Kiyici 2009; Onuchin 2010; Rahman 2011; Teupe 1991; Williams-Herman 2010; Yamanouchi 2005).

All but two trials (Derosa 2004; Umpierrez 2014) inadequately reported one or more outcomes of interest for our review, and we consequently judged them to be at high risk of selective outcome reporting bias.

All included trials reported at least one of our outcomes.

For all outcomes specified in the Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6, we judged the evidence to be of very low certainty mainly due to risk of bias and serious imprecision.

Only one trial was solely funded by an university (Erem 2014). The remaining trials did not report funding source or received funding from the pharmaceutical industry. Trials investigating free drugs or devices sponsored by a pharmaceutical company have been shown to produce more favourable results and conclusions than trials receiving funding from other sources (Lundh 2017).

Potential biases in the review process

Due to inclusion of few trials for most of the comparisons, we were unable to perform meta-analyses on all outcomes. For some outcomes, very limited or even no data were available (health-related quality of life, end-stage renal disease, blindness, lactic acidosis, amputation of lower extremity and socioeconomic effects). For the same reason, we were unable to draw funnel plots to assess small-study bias; sensitivity and subgroup analysis could only be performed on a subset of outcomes; and we were not able to explore reasons for heterogeneity in details.

We contacted one or more authors of all the included trials. However, only one author provided additional data which did not substantially change the certainty of the evidence for this trial.

We designed our inclusion criteria to include trials with a minimum duration of 52 weeks because we were interested in long-term, patient-important outcomes. Despite the criteria, many of the included trials only reported few of our predefined primary outcomes.

Two review authors independently performed selection of trials, data extraction and 'Risk of bias' assessments. However, review authors were not blinded as to which trial they were working with, which could potentially have biased the review process.

Agreements and disagreements with other studies or reviews

We checked 16 systematic reviews of RCTs that had metformin monotherapy as an intervention of interest to assess concordance between other results and those of our review (Billington 2015; Boussageon 2012; Buhse 2016; Cai 2016; Cheng 2017; Gu 2014; Hirst 2012; Ida 2017; Liu 2014; Monami 2014; Palmer 2016; Rokkas 2016; Saenz 2005; Salpeter 2003; Zhang 2016; Zintzaras 2014).

Two of the systematic reviews performed network meta-analyses when estimating effect sizes and reported mixed-effect results comprising direct and indirect evidence (Palmer 2016; Zintzaras 2014). The population of interest was exclusively participants

with T2DM in all but two systematic reviews (Billington 2015; Liu 2014), in which participants were healthy or had polycystic ovary syndrome, respectively. Metformin monotherapy was primarily compared with placebo, diet, no treatment or glucose-lowering drugs. The most common outcomes of the systematic reviews were HbA1c, cardiovascular mortality, myocardial infarction, stroke, all-cause mortality and adverse events. Two systematic reviews did not share any outcomes with our review (Billington 2015; Ida 2017). Five systematic reviews did not perform any meta-analyses of metformin monotherapy versus comparator for our outcomes, primarily due to lack of data (Buhse 2016; Cheng 2017; Liu 2014; Rokkas 2016; Zhang 2016). For one systematic review (Hirst 2012), only the citation was identified and could not be investigated any further.

Four systematic reviews showed no substantial difference between metformin and any glucose-lowering drug for all-cause mortality (Boussageon 2012; Palmer 2016), cardiovascular mortality (Boussageon 2012; Palmer 2016), myocardial infarction, heart failure, peripheral revascularisation, amputation (Boussageon 2012), lactic acidosis (Salpeter 2003) or hypoglycaemia (Zintzaras 2014). One systematic review showed no difference between metformin and sulphonylurea for severe hypoglycaemia (Monami 2014). For HbA1c, metformin was favoured versus placebo in three systematic reviews (Cai 2016; Gu 2014; Zintzaras 2014); versus saxagliptin in one systematic review (Zintzaras 2014); not favoured versus DPP-4 inhibitor in one systematic review (Zintzaras 2014); and no substantial difference between metformin and acarbose in one systematic review (Gu 2014).

The majority of the identified systematic reviews suffered from methodological flaws including the following: not reporting or sparsely performing 'Risk of bias' assessment of included trials (Boussageon 2012; Buhse 2016; Cheng 2017; Gu 2014; Ida 2017; Monami 2014; Rokkas 2016; Zhang 2016; Zintzaras 2014); placing language restrictions on trials for inclusion (Billington 2015; Buhse 2016; Cai 2016; Cheng 2017; Ida 2017; Liu 2014; Monami 2014; Rokkas 2016; Zintzaras 2014); and not explicitly searching unpublished data (Billington 2015; Boussageon 2012; Buhse 2016; Cai 2016; Cheng 2017; Gu 2014; Liu 2014; Rokkas 2016; Zhang 2016; Zintzaras 2014).

We exclusively included RCTs of at least 52 weeks because we were primarily interested in long-term, patient-important outcomes, and trials less than 52 weeks rarely report these. Despite this difference between our review and the aforementioned systematic reviews, the results for our outcomes are comparable. However, as mentioned above, these results are limited and not conclusive due to very low-certainty evidence in this review.

To the best of our knowledge, our review is currently the only updated systematic review investigating long-term, patient-important outcomes of metformin monotherapy in RCTs.

The most widely used guidelines recommend metformin as a first-line antidiabetic drug (ADA/EASD 2015). This recommendation may be influenced by the results of the UKPDS trial for the subgroup of overweight and obese participants. However, this trial was of limited size and possibly biased in its reporting of the comparison of sulphonylurea/insulin and metformin because it apparently did not adhere to the predefined statistical analysis plan described in the design article (UKPDS 34 1998).

AUTHORS' CONCLUSIONS

Implications for practice

There is no clear evidence whether metformin monotherapy compared with no intervention, placebo, diet, or glucose-lowering drugs has any benefit or harm for most patient-important outcomes (all-cause mortality, serious adverse events, health-related quality of life, macrovascular and microvascular complications). There were fewer reported severe hypoglycaemic episodes with metformin compared to sulphonylureas. However, the results of our review are limited due to very low-certainty evidence. No trial compared metformin monotherapy with placebo or diet, and no trial reported on blindness, end-stage renal disease, amputation of lower extremity, lactic acidosis, or socioeconomic effects. We identified four ongoing trials and 24 trials awaiting assessment. In total, these trials will include approximately 8193 participants and could have an impact on our results.

Implications for research

It is currently unclear how metformin monotherapy compared with no intervention, placebo, diet or glucose-lowering drugs affects patient-important outcomes. Four ongoing trials with 5824 participants are likely to report one or more of our outcomes of interest and are estimated to be completed between 2018 and 2024. Furthermore, 24 trials with 2369 participants are awaiting assessment. The current evidence suffers from very low-certainty evidence mainly due to risk of bias and serious imprecision. Thus, more large and well-powered randomised controlled trials with low risk of bias, focusing on patient-important outcomes are warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bilezikian 2013

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: women, age between 55 to 80 years, 5 years postmenopausal, T2DM, BMD T-score greater than 2.5 at the total hip, femoral neck, and lumbar spine, prior glucose-lowering intervention

Bilezikian 2013 *(Continued)*

	with diet and exercise alone or monotherapy (non-TZD) for 2 weeks within the past 12 weeks, HbA1c 9.0% if drug-naive and 8.5% if on prior monotherapy **Exclusion criteria**: T1DM, history of diabetic ketoacidosis or uncontrolled hypertension, simultaneous treatment with 2 or more glucose-lowering drugs within the past 12 weeks, previous intervention with estrogens and other bone-active drugs **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** rosiglitazone **Duration of intervention:** 52 weeks[1] **Duration of follow-up:** 52 weeks[1] **Run-in period:** 3 weeks **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication:** BMD, bone turnover markers, calcium and vitamin D status, safety, glycaemic variables, anthropometric measures
Study details	**Trial identifier:** NCT00679939 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding (GSK) **Publication status:** peer-reviewed journal / full article
Stated aim for study	**Quote from publication**: "The aims of this study are to evaluate the effects of RSG on BMD in post-menopausal women with T2DM and to evaluate the potential reversibility of changes in bone mass and turnover on cessation of RSG treatment, thereby providing insight into the clinical significance of the effect of RSG on fracture risk"
Notes	[1]After 52 weeks of metformin vs rosiglitazone all patients received open-label metformin for an additional 24 weeks which was not of relevance to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "This study utilized a computer-generated central randomisation within each geographical region stratified by prior therapy (drug-naive and prior monotherapy) and randomised in a 1:1 ratio to one of two treatment arms..." **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "This study utilized a computer-generated central randomisation within each geographical region stratified by prior therapy (drug-naive and prior monotherapy) and randomised in a 1:1 ratio to one of two treatment arms... Subjects were registered and medication was ordered using an interactive voice response system." **Comment:** method of allocation concealment adequately described

Bilezikian 2013 *(Continued)*

Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "Study medication taken during the double-blind treatment period was blinded to the subjects and the investigator. Blinding was maintained during this phase by use of the double-dummy technique. Blinded study medication was overencapsulated to appear the same." **Comment:** investigator-assessed outcome measurement, adequate blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "The safety population, comprising all subjects who had received at least one dose of drug, was used for analysis of all parameters" "The primary analysis was performed on the observed case dataset. In addition, supportive analyses were prespecified in the statistical analysis plan and performed based on last on-therapy observation..." **Comment:** > 99% of participants included in the analysis, high dropout rate (67.5% to 75.9% of participants completed the study) and not balanced between arms, reasons for missing data similar between arms, inappropriate use of LOCF for handling missing data, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "The safety population, comprising all subjects who had received at least one dose of drug, was used for analysis of all parameters" "The primary analysis was performed on the observed case dataset. In addition, supportive analyses were prespecified in the statistical analysis plan and performed based on last on-therapy observation..."

Bilezikian 2013 *(Continued)*

		Comment: > 99% of participants included in the analysis, high dropout rate (67.5% to 75.9% of participants completed the study) and not balanced between arms, reasons for missing data similar between arms, inappropriate use of LOCF for handling missing data, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "The safety population, comprising all subjects who had received at least one dose of drug, was used for analysis of all parameters" "The primary analysis was performed on the observed case dataset. In addition, supportive analyses were prespecified in the statistical analysis plan and performed based on last on-therapy observation..." **Comment:** > 99% of participants included in the analysis, high dropout rate (67.5% to 75.9% of participants completed the study) and not balanced between intervention groups, reasons for missing data similar between intervention groups, inappropriate use of LOCF for handling missing data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** the study protocol is available. It is clear that intervention failure was measured and analysed; trial report states that outcome was analysed but report no results. Clear that anthropometric variables were measured, since baseline values are reported, but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results.
Other bias	Unclear risk	**Comment:** received funding from a pharmaceutical company

Campbell 1994

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, age between 40 to 69 years, uncontrolled by diet **Exclusion criteria**: not reported **Diagnostic criteria**: FPG > 8 mmol/L on two occasions two weeks apart on diet
Interventions	**Intervention(s):** metformin **Comparator(s):** glipizide **Duration of intervention:** 12 months **Duration of follow-up:** 12 months **Run-in period:** 2 weeks **Number of study centres**: 1
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, lipid profile, anthropometric measures, blood lactate, safety, albuminuria, serum sialic acid
Study details	**Trial identifier:** not reported **Trial terminated early:** no

Campbell 1994 *(Continued)*

Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication:** "This present study is a long term comparison of metformin and the second generation sulphonylurea, glipizide in diet failed type 2 diabetes subjects, unstratified for weight, assessing glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion over a 12 month period."
Notes	Additional information from the FDA document: one in each intervention group withdrew due to adverse events (malignancy), no difference in adverse events between intervention (P = 0.206), trial period and study centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "…subjects were randomised in blocks of four (11) to receive..." **Comment**: method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "…subjects were randomised in blocks of four (11) to receive..." **Comment**: method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "The study was an open, parallel study..." **Comment**: investigator-assessed outcome, no blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "The study was an open, parallel study..." **Comment**: investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication**: "[two] subjects were therefore eliminated from the study before randomisation... The remaining 48 diabetic subjects were randomized... to receive metformin... or glipizide..." "All the 48 patients completed the study period." **Comment**: 100% of participants included in the analysis, no missing data.
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Unclear whether lactic acidosis was measured, since blood lactate was a study outcome; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results. Clear that serious adverse events were measured and analysed; trial report states that outcome was analysed but only gastrointestinal events were reported. Clear that severe hypoglycaemia was measured and analysed; trial report states that outcome was analysed but only reported for the glipizide group.
Other bias	Unclear risk	**Comment:** funding source not reported

Derosa 2003

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, duration > 6 months, no previous oral glucose-lowering drugs, LDL-C > 2.59 mmol/L, HbA1c > 7.0% **Exclusion criteria**: hypertension, coronary heart disease, smoking, abnormal renal function, taking drugs likely to interact with repaglinide or metformin or affect glycaemic control **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** repaglinide **Duration of intervention:** 14 months[1] **Duration of follow-up:** 14 months **Run-in period:** 4 weeks placebo washout period to eliminate metabolic effects of previous non-hypoglycaemic drug therapies **Number of study centres**: 1
Outcomes	**Reported outcome(s) in full text of publication:** safety, anthropometric measures, glycaemic variables, lipid profile, endothelial function, haematological variables
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "The aim of the present study was to compare glycaemic control and cardiovascular risk factors in type 2 diabetic patients who had not previously taken oral hypoglycaemic agent during monotherapy with either repaglinide or metformin."
Notes	[1]8-week titration period followed by 12 months treatment

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomly allocated..." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomly allocated..." **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias)	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding

Derosa 2003 *(Continued)*
serious adverse events

Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Comment:** 100% of participants included in the analysis, moderate to high dropout rate (87.5% to 94.6% of participants completed the study) and not balanced between arms, reasons for missing data not similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Comment:** 100% of participants included in the analysis, moderate to high dropout rate (87.5% to 94.6% of participants completed the study) and not balanced between arms, reasons for missing data not similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Anthropometric measures and glycaemic control (HbA1c) reported in an inadequate format that could not be used in our meta-analysis, because the results of the study consisted of multiple errors
Other bias	Unclear risk	**Comment:** funding source not reported

Derosa 2004

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, duration < 6 months, normotensive, non-smokers, no CAD, normal renal function **Exclusion criteria**: abnormal liver and renal function, history of chronic insulin treatment, cardiac disease, diseases that could interfere with compliance and drop-out, known contraindications to SU or biguanides, pregnancy, lactating, intending to get pregnant, in corticosteroid treatment **Diagnostic criteria**: ADA 2001
Interventions	**Intervention(s):** metformin **Comparator(s):** glimepiride

Derosa 2004 *(Continued)*

	Duration of intervention: 60 weeks **Duration of follow-up:** 60 weeks **Run-in period:** not reported **Number of study centres:3**
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric variables, safety, blood pressure, lipid profile, haematological variables
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "The primary objective of the present study was to assess the effects of the OADs glimepiride and metformin on a number of extraglycaemic parameters, including those specifically associated with cardiovascular risk [...] in patients T2DM over a 12-month period. A secondary objective was to compare the efficacy of these two agents on glycaemic control"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "...patients were randomised to receive either glimepiride or metformin." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "...patients were randomised to receive either glimepiride or metformin." **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "...open..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "...open..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...open..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "...open..."

Derosa 2004 *(Continued)*

		Comment: investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "...open..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...open..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "A per protocol analysis was conducted" **Comment:** > 90% of participants included in the analysis, middle to high dropout rate (90% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate use of per protocol method for analysis of results, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "A per protocol analysis was conducted" **Comment:** > 90% of participants included in the analysis, moderate dropout rate (90.1% to 90.4% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate use of per protocol method for analysis of results, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "A per protocol analysis was conducted" **Comment:** > 90% of participants included in the analysis, moderate dropout rate (90.1% to 90.4% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate use of per protocol method for analysis of results, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol not available
Other bias	Unclear risk	**Comment:** funding source not reported

Derosa 2009

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: age above 18 years, T2DM, drug-naive, poor glycaemic control, HbA1c > 6.5%, BMI between 25 to 30 kg/m^2 **Exclusion criteria**: history of ketoacidosis, progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function[2], impaired renal function[3], severe anaemia, serious cardiovascular disease (e.g., NYHA I to IV or a history of myocardial infarction or stroke), cerebrovascular conditions within 6 months before study enrolment, women who were pregnant, lactating, or of childbearing potential and not on contraceptive precautions

Derosa 2009 *(Continued)*

	Diagnostic criteria: EASD 2007
Interventions	**Intervention(s):** metformin **Comparator(s)** [1] **:** pioglitazone **Duration of intervention:** 12 months **Duration of follow-up:** 12 months **Run-in period:** 3 months in which metformin was titrated from 1000 mg/day to 3000 mg/day and pioglitazone from 15 mg/day to 45 mg/day **Number of study centres**: 3
Outcomes	**Reported outcome(s) in full text of publication:** anthropometric variables, glycaemic measures, safety
Study details	**Trial identifier:** — **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal
Stated aim for study	**Quote from publication**: "The aim of this study was to directly compare the long term effect of 4 antidiabetic treatment protocols on insulin resistance evaluated by euglycemic hyperinsulinemic clamp in type 2 diabetes mellitus patients. In particular, we aimed to evaluate if the combination of 2 insulin-sensitizing agents (pioglitazone and metformin) could significantly improve the insulin resistance when compared with single agent–based protocols and with a protocol including an insulin secretagogue (glimepiride)."
Notes	[1]Participants were also allocated to other comparators which were not of interest to this review [2]Defined as plasma aminotransferase and/or γ-glutamyltransferase level higher than the upper limit of normal for age and sex [3]Defined as serum creatinine level higher than the upper limit of normal for age and sex

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician" **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency" **Comment:** method of allocation concealment inadequately described. It remains unclear whether envelopes were sequentially numbered, opaque and sealed

Derosa 2009 *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Serious adverse events and severe hypoglycaemia reported in an inadequate format that could not be used in our meta-analysis, since only events leading to discontinuation are mentioned. Glycaemic control and anthropometric measures reported in an inadequate format that could not be used in our meta-analysis due to missing information of participants included in the analysis
Other bias	Unclear risk	**Comment:** funding source not reported

Erem 2014

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: age between 30 to 70 years, FPG ≥ 140 mg/dL or HbA1c ≥ 8% or ((FPG between 126 mg/dL to 139 mg/dL or HbA1c between 7% to 8 %) and HOMA-IR > 3) **Exclusion criteria**: T1DM, ketoacidosis, ketonuria, renal function impairment (serum creatinine > 1.4 mg/dL for women and > 1.5 mg/dL for men), liver disease, impairment liver function (AST or ALT ≥ 2 × the upper limit of the normal range)), NYHA Cardiac Status Class III or IV congestive heart failure, history of lactic acidosis, malignancy, chronic inflammatory diseases, acute malabsorption, chronic pancreatitis, familial polyposis coli, active infection, pregnancy, hoping to conceive, breastfeeding, chronic obstructive pulmonary disease, angina pectoris, myocardial infarction, documented cerebrovascular disease, stroke, peripheral vascular disease, rheumatic disease, substance abuse, allergy to SUs, biguanides or TZDs, thyroid disease, or corticosteroid treatment **Diagnostic criteria**: ADA 2010
Interventions	**Intervention(s):** metformin **Comparator(s):** gliclazide, pioglitazone **Duration of intervention:** 12 months **Duration of follow-up:** 12 months **Run-in period:** none **Number of study centres**: 1
Outcomes	**Reported outcome(s) in full text of publication:** safety, anthropometric measures, glycaemic variables, lipid profile, endothelial function, haematological variables, inflammation markers, blood pressure
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** non-commercial funding (University) **Publication status:** peer-reviewed journal / full article
Stated aim for study	**Quote from publication**: "The main objective of the present study was to evaluate and compare the effects of gliclazide-MR, MET and PIO monotherapies on glycemic control and conventional/non-conven-

Erem 2014 *(Continued)*

	tional cardiovascular risk factors including fibrinolysis, inflammation and endothelial functions in patients with newly diagnosed T2DM"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomized..." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomized..." **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	**Quote from publication:** "... open-label..."

Erem 2014 *(Continued)*

serious adverse events		**Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... open-label..." **Comment:** investigator-assessed outcome. No blinding, however, outcome not judged to be influenced by a lack of blinding.
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "... 60 patients with T2DM were initially recruited. Total 57 patients completed the study" **Comment:** 95% of participants included in the analysis, low dropout rate (95% of participants completed the study) and balanced between arms, reasons for missing data not described, inappropriate exclusion of participants not finishing trial, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "... 60 patients with T2DM were initially recruited. Total 57 patients completed the study" **Comment:** 95% of participants included in the analysis, low dropout rate (95% of participants completed the study) and balanced between arms, reasons for missing data not described, inappropriate exclusion of participants not finishing trial, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) non-fatal myocardial infarction	High risk	**Quote from publication:** "... 60 patients with T2DM were initially recruited. Total 57 patients completed the study" **Comment:** 95% of participants included in the analysis, low dropout rate (95% of participants completed the study) and balanced between arms, reasons for missing data not described, inappropriate exclusion of participants not finishing trial, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "... 60 patients with T2DM were initially recruited. Total 57 patients completed the study" **Comment:** 95% of participants included in the analysis, low dropout rate (95% of participants completed the study) and balanced between arms, reasons for missing data not described, inappropriate exclusion of participants not finishing trial, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "... 60 patients with T2DM were initially recruited. Total 57 patients completed the study" **Comment:** 95% of participants included in the analysis, low dropout rate (95% of participants completed the study) and balanced between arms, reasons for missing data not described, inappropriate exclusion of participants not finishing trial, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol not available
Other bias	Low risk	**Quote from publication:** "This study was supported by a research grant from the Karadeniz Technical University... We, the authors, have nothing to declare regarding the study drugs and producing companies... The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work"

Erem 2014 *(Continued)*

Comment: low risk of funding bias

Kahn 2006

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM within the last three years, age between 30 to 75 years, FPG between 7 mmol/L to 13 mmol/L at screening and between 7 mmol/L to 10 mmol/L at randomisation, previously only managed with diet/exercise except for the following conditions: prior insulin use for gestational diabetes, short-term (≤ 1 months) insulin use to maintain glycaemic control for hospitalisation, medical procedure, or intervention, and ≤ 1 month use of any oral hypoglycaemic agent at least 2 months before screening **Exclusion criteria**: clinical significant hepatic disease, alanine aminotransferase ≥ 2.5 times the upper limit of the normal reference range, renal impairment indicated by serum creatinine concentration, anaemia, history of lactate acidosis, unstable or severe angina, congestive heart failure, uncontrolled hypertension, any chronic disease requiring continuous intermittent treatment with corticosteroids, any associated condition that could preclude completion of the study, active drug or alcohol abuse within the last 6 months, patients with variation in body weight ≥ 5% during the run-in period were excluded **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** rosiglitazone, glyburide **Duration of intervention:** time to monotherapy failure. Median duration was 4.0 years for metformin and rosiglitazone and 3.3 years for glyburide **Duration of follow-up:** same as intervention period **Run-in period:** 4 week placebo run-in **Number of study centres**: 488
Outcomes	**Reported outcome(s) in full text of publication:** safety, anthropometric variables, glycaemic variables, health-related quality of life, liver function, haematological variables, blood pressure, lipid profile
Study details	**Trial identifier:** NCT00279045 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding (GSK) **Publication status:** peer-reviewed journal / full article
Stated aim for study	**Quote from publication**: "... to evaluate the durability of glycemic control in patients receiving monotherapy with a thiazolidinedione, rosiglitazone (Avandia, GlaxoSmithKline); a biguanide, metformin (Glucophage, Bristol-Myers Squibb); or a sulfonylurea, glyburide (Micronase, Pfizer)"
Notes	
Risk of bias	

Kahn 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six." **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six." **Comment:** method of allocation concealment adequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding

Kahn 2006 *(Continued)*

Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double-blind..." "All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day" **Comment:** investigator-assessed outcome measurement, adequate blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "... exclusion of 9 patients who did not receive a study drug..." "Site investigators were also asked to report deaths considered to be related to a study drug that occurred after the treatment period" **Comment:** > 99% of participants included in the analysis, high dropout rate (55.8% to 62.1% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of participants after randomisation, however, balanced between arms, method of handling missing data not described, mortality status has been investigated at the of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "... exclusion of 9 patients who did not receive a study drug..." "Site investigators were also asked to report deaths considered to be related to a study drug that occurred after the treatment period" **Comment:** > 99% of participants included in the analysis, high dropout rate (55.8% to 62.1% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of participants after randomisation, however, balanced between arms, method of handling missing data not described, mortality status has been investigated at the of the study
Incomplete outcome data (attrition bias) non-fatal myocardial infarction	High risk	**Quote from publication:** "... exclusion of 9 patients who did not receive a study drug..." **Comment:** > 99% of participants included in the analysis, high dropout rate (55.8% to62.1% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of participants after randomisation, however, balanced between arms, method of handling missing data not described, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "... exclusion of 9 patients who did not receive a study drug..." **Comment:** > 99% of participants included in the analysis, high dropout rate (55.8% to 62.1% of participants completed the study) but balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of participants after randomisation, however, balanced between arms, method of handling missing data not described, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "... exclusion of 9 patients who did not receive a study drug..." **Comment:** > 99% of participants included in the analysis, high dropout rate (55.8% to 62.1% of participants completed the study) but balanced between

Kahn 2006 *(Continued)*

		arms, reasons for missing data similar between arms, inappropriate exclusion of participants after randomisation, however, balanced between arms, method of handling missing data not described, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment**: study protocol available. Clear that health-related quality of life was measured and analysed; trial report states that outcome was analysed but report no results
Other bias	Unclear risk	**Comment**: received funding from a pharmaceutical company

Kiyici 2009

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, age between 30 to 65 years, HbA1c < 8% and BMI < 40 kg/m^2 **Exclusion criteria**: use of hypoglycaemic agents, cardiovascular, gastrointestinal, hepatic, renal, rheumatological, neoplastic, infectious and other endocrine diseases (except T2DM and hyperlipidaemia), micro- and macrovascular complications of T2DM, smoker, previous history of substance abuse **Diagnostic criteria**: ADA 2006
Interventions	**Intervention(s):** metformin **Comparator(s):** rosiglitazone, no intervention **Duration of intervention:** 52 weeks **Duration of follow-up:** 52 weeks **Run-in period:** none **Number of study centres**: 1
Outcomes	**Reported outcome(s) in full text of publication:** safety, glycaemic variables, anthropometric measures, lipid profile, arterial stiffness
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "...to investigate the long-term effects of metformin and rosiglitazone monotherapy with medical nutrition treatment (MNT) and of MNT alone on SAEI, LAEI, and serum MCP-1 and MMP-9 levels in drug-naive type 2 diabetic patients"
Notes	

Kiyici 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomized..." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "... patients were randomized..." **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "... open-labeled..." **Comment:** investigator-assessed outcome measurement. No blinding, however, outcome not judged to be influenced by a lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "All patients completed the study" **Comment:** 100% of participants included in the analysis, all participants completed the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "All patients completed the study" **Comment:** 100% of participants included in the analysis, all participants completed the study
Incomplete outcome data (attrition bias) serious adverse events	Low risk	**Quote from publication:** "All patients completed the study. No serious adverse effect was seen during the study period" **Comment:** 100% of participants included in the analysis, all participants completed the study
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available

Kiyici 2009 *(Continued)*

Other bias	Unclear risk	**Comment:** funding source not reported

Onuchin 2010

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: female, age above 55 years, duration of T2DM > 3 years, inadequately controlled for more than a year, abdominal obesity, arterial hypertension **Exclusion criteria**: thyroid disease, AMI during study, chronic obstructive pulmonary disease, liver cirrhosis **Diagnostic criteria**: WHO 1999
Interventions	**Intervention(s):** metformin **Comparator(s)** [1] **:** insulin **Duration of intervention:** 12 months **Duration of follow-up:** 12 months **Run-in period:** none **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, health-related quality of life, lipid profile, albuminuria, blood pressure, cardiac function, risk of developing cardiac adverse events, depression
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: Russian **Funding:** not reported **Publication status:** full article
Stated aim for study	**Quote from publication**: "[The aim of the study was a comparative evaluation of the efficacy of various variants of glucose-lowering drugs in patients with type 2 diabetes mellitus inadequately controlled for more than 1 year]"
Notes	[1]There were 2 more comparators that were not of interest to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "[Patients were randomised by random number method]..." **Comment:** method of random sequence generation inadequately described

Onuchin 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "[Patients were randomised by random number method]..." **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) health-related quality of life	High risk	**Quote from publication:** "[An open prospective study]... " **Comment:** self-reported outcome measurement. No blinding and outcome judged likely to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) health-related quality of life	High risk	**Quote from publication:** "[An open prospective study]... " **Comment:** self-reported outcome measurement. No blinding and outcome judged likely to be influenced by a lack of blinding.
Incomplete outcome data (attrition bias) health-related quality of life	Unclear risk	**Comment:** 100% of participants included in the analysis, however, dropout rate not reported and unclear whether there were missing data and how they were handled
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality and serious adverse events were measured but were not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Unclear whether severe hypoglycaemia was measured, since hypoglycaemia was reported in the trial; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results
Other bias	Unclear risk	**Comment:** funding source not reported

Pfützner 2011

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: age between 18 to 77 years, T2DM, HbA1c between 8% to 12% at screening, fasting C-peptide concentration ≥ 1.0 ng/mL and BMI ≤ 40 kg/m^2, never having received medical treatment for T2DM or having received medical treatment for T2DM for a total period of < 1 month since original diagnosis and not having received glucose-lowering intervention for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening **Exclusion criteria**: poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, insulin therapy within 1 year of screening, cardiovascular event within 6 months before study entry or NYHA III/IV congestive heart failure and/or known left ventricular ejection fraction 40%, significant renal, liver or psychiatric history, history of alcohol or drug abuse within the previous year, treatment with potent CYP3A4 inhibitors or inducers, immuno compromised individuals, active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or haematological screening tests **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s)** [1] **:** saxagliptin **Duration of intervention:** 76 weeks

Pfützner 2011 *(Continued)*

	Duration of follow-up: 76 weeks **Run-in period:** 1-week, single-blind, dietary and exercise placebo lead-in period **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety
Study details	**Trial identifier:** NCT00327015 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding (Bristol-Myers Squibb and AstraZeneca) **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "The present study assessed the long-term efficacy and safety up to week 76 (including the 24-week short-term period and a 52-week extension) of saxagliptin, given in combination with metformin as initial therapy compared with saxagliptin or metformin alone for the treatment of hyperglycaemia in treatment-naïve patients"
Notes	[1]The study had more comparator groups that were not of interest of this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "At screening, an interactive voice response system (IVRS) assigned each patient a unique numeric identifier used throughout the study. Following the lead-in period, eligible patients were randomized (1 : 1 : 1: 1) by IVRS using a blocked randomization schedule (block size 4)" **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "At screening, an interactive voice response system (IVRS) assigned each patient a unique numeric identifier used throughout the study. Following the lead-in period, eligible patients were randomized (1 : 1 : 1: 1) by IVRS using a blocked randomization schedule (block size 4)" **Comment:** method of allocation concealment adequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of participants and personnel inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of participants and personnel inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of participants and personnel inadequately described, however, outcome not judged to be influenced by a lack of blinding.

Pfützner 2011 *(Continued)*

Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of participants and personnel inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of outcome assessment inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of outcome assessment inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of outcome assessment inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double blind..." **Comment:** investigator-assessed outcome measurement, method of blinding of outcome assessment inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "Safety parameters were evaluated in all patients who received at least one dose of double-blind treatment, regardless of rescue therapy" **Comment:** 100% of participants included in the analysis, high dropout rate (62.6% to 66.8% of participants completed the study) and not balanced between arms, reasons for missing data inadequately described, unclear how missing data were handled, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "Safety parameters were evaluated in all patients who received at least one dose of double-blind treatment, regardless of rescue therapy" **Comment:** 100% of participants included in the analysis, high dropout rate (62.6 to 66.8% of participants completed the study) and not balanced between arms, reasons for missing data inadequately described, unclear how missing data were handled, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "Safety parameters were evaluated in all patients who received at least one dose of double-blind treatment, regardless of rescue therapy" **Comment:** 100% of participants included in the analysis, high dropout rate (62.6% to 66.8% of participants completed the study) and not balanced between arms, reasons for missing data inadequately described, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate

Pfützner 2011 *(Continued)*

Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "Safety parameters were evaluated in all patients who received at least one dose of double-blind treatment, regardless of rescue therapy" **Comment:** 100% of the randomised participants included in the analysis, high dropout rate (62.6% to 66.8% of participants completed the study) and not balanced between arms, reasons for missing data inadequately described, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol available. Anthropometric measures reported in an inadequate format that could not be used in our meta-analysis, since body weight only reported with a mean and BMI only reported at baseline
Other bias	Unclear risk	**Comment:** received funding from a pharmaceutical company

Rahman 2011

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, duration of T2DM ≤ 4 years, controlled with diet or exercise **Exclusion criteria**: diabetic complications **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** glimepiride **Duration of intervention:** 52 weeks **Duration of follow-up:** 52 weeks **Run-in period:** 4 weeks in which participants received advice on diet and exercise to obtain FPG between 126 mg/dL to 240 mg/dL **Number of study centres**: 1
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, blood pressure, lipid profile
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal / full article
Stated aim for study	**Quote from publication**: "...to investigate SSA levels in patients following rosiglitazone and glimepiride monotherapy"

Rahman 2011 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "...patients [...] were randomly assigned..." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "..." **Comment:** method of allocation concealment inadequately described
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality and serious adverse events were measured but were not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results
Other bias	Unclear risk	**Comment:** funding source not reported

Schernthaner 2004

Study characteristics

Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: age between 35 - 75 years, T2DM inadequately treated with diet alone, HbA1c between 7.5% - 11% with stable or worsening glycaemic control for at least 3 months **Exclusion criteria**: use of glucose-lowering intervention and specific contraindications to either drug, corticosteroids and-blockers were permitted if treatment commenced at least 4 weeks before screening, antihypertensive agents, except thiazides, were allowed dependent on clinical need. Lipid-lowering agents were also permitted **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone **Duration of intervention:** 52 weeks **Duration of follow-up:** 52 weeks **Run-in period:** none **Number of study centres**: 167
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety, lipid profile
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English

Schernthaner 2004 *(Continued)*

Funding: not reported

Publication status: peer-reviewed journal / full article

Stated aim for study	**Quote from publication**: "We have compared the effects of pioglitazone with metformin on metabolic variables in type 2 diabetes patients naive to oral hypoglycemic therapy. To determine any additional benefits, we also evaluated the effects on lipid profiles, hyperinsulinemia, and glucose disposal during oral glucose tolerance tests (OGTT)."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "A computer-generated list was administered centrally via a telephone randomization and resupply service." **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Patients were randomized centrally using block randomization. A computer-generated list was administered centrally via a telephone randomization and resupply service." **Comment:** method of allocation concealment adequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind..." "The study medication was identified by pack numbers." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind..." "The study medication was identified by pack numbers." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind..." "The study medication was identified by pack numbers." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind..." "The study medication was identified by pack numbers." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Comment:** > 99% of participants included in the analysis, high dropout rate (83.4% of randomised participants completed the study) and balanced between arms, reasons for missing data similar between arms, population used for the analysis was not defined, unclear how missing data were handled, it is assumed that mortality status has been investigated in death registers at the end of the study.
Incomplete outcome data (attrition bias) serious adverse events	Low risk	**Comment:** > 99% of participants included in the analysis, high dropout rate (83.4% of randomised participants completed the study) and balanced between arms, reasons for missing data similar between arms, population used for the analysis was not defined, unclear how missing data were handled,

Schernthaner 2004 *(Continued)*

		the proportion of missing outcomes compared with observed event risk not enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Anthropometric measures reported in an inadequate format that could not be used in our meta-analysis, since BMI was clearly measured but not reported and body weight only reported with a mean.Clearly that serious adverse events were collected, but reported in a format unsuitable for meta-analysis.
Other bias	Unclear risk	**Comment:** funding source not reported.

Schweizer 2007

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, HbA1c between 7.5% to 11.0% at the screening visit while receiving no drug treatment (no oral glucose-lowering interventions for at least 12 weeks prior to screening and no oral glucose-lowering agents for more than three consecutive months at any time in the past were considered to be drug naive, age between 18 to 78 years, FPG < 15 mmol/L **Exclusion criteria**: T1DM or secondary forms of diabetes, acute metabolic diabetic complications within the past 6 months, congestive heart failure requiring pharmacological treatment, or myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months, liver disease such as cirrhosis or chronic active hepatitis, renal disease or renal dysfunction suggested by elevated serum creatinine levels, in accordance with prescribing guidelines for metformin. Any of the following laboratory abnormalities were also excluded: ALT or AST greater than three times the upper limit of normal, direct bilirubin greater than 1.3 times the upper limit of normal, clinically significant abnormal TSH or fasting triglycerides > 7.9 mmol/L **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** vildagliptin **Duration of intervention:** 104 weeks **Duration of follow-up:** 104 weeks **Run-in period:** none **Number of study centres**: 183
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety, haematological variables, biochemistry, blood pressure, lipid profile
Study details	**Trial identifier:** NCT00099866, NCT00138567 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding (Novartis) **Publication status:** peer-reviewed journal / full article

Schweizer 2007 *(Continued)*

Stated aim for study	**Quote from publication**: "..to assess the efficacy and tolerability of vildagliptin monotherapy (100 mg daily) over 1 year in drug-naïve patients with Type 2 DM. Metformin (titrated to 2000 mg daily) was used as an active control"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Eligible patients were randomized..." **Comment:** method of random sequence generation inadequately described in the publication. However, a co-author provided additional information about the study per request: randomisation was by computer and was unknown to the investigators.
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Eligible patients were randomized..." **Comment:** method of allocation concealment inadequately described in the publication. However, a co-author provided additional information about the study per request: randomisation was by computer and was unknown to the investigators.
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...double-blind..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.

Schweizer 2007 *(Continued)*

Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "The safety population consisted of all patients who received at least one dose of study medication and who had at least one post-baseline safety assessment (n=771)" "The extension safety population consisted of all patients who received at least one dose of extension study drug and had at least one post-week 52 safety assessment. Events that occurred after the start of rescue medication were not included in the primary analysis of safety" **Comment:** > 98% of participants included in the analysis, high drop out rate (49.4% to 55.9% of participants completed the full 104 -week study), and not balanced between arms, reasons for missing data not similar between arms in the first 52 weeks of study (discontinuation due to adverse events higher in metformin group than in vildagliptin group), unclear whether similar in the extension period, inadequate extension population used for analysis since only events prior to initiation of rescue were included in the analysis, inappropriate handling of missing data using LOCF as stated by a co-author of the study per request, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "The safety population consisted of all patients who received at least one dose of study medication and who had at least one post-baseline safety assessment (n=771)" "The extension safety population consisted of all patients who received at least one dose of extension study drug and had at least one post-week 52 safety assessment. Events that occurred after the start of rescue medication were not included in the primary analysis of safety" **Comment:** > 98% of participants included in the analysis, high dropout rate (71.9% to 75.2% of participants completed the first 52 weeks of intervention), and not balanced between arms, reasons for missing data not similar between arms in the first 52 weeks of study, inappropriate handling of missing data using lLOCF as stated by a co-author of the study per request, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "The safety population consisted of all patients who received at least one dose of study medication and who had at least one post-baseline safety assessment (n=771)" "The extension safety population consisted of all patients who received at least one dose of extension study drug and had at least one post-week 52 safety assessment. Events that occurred after the start of rescue medication were not included in the primary analysis of safety" **Comment:** > 98% of participants included in the analysis, high dropout rate (71.9% to 75.2% of participants completed the first 52 weeks of intervention), and not balanced between arms, reasons for missing data not similar between arms in the first 52 weeks of study, inappropriate handling of missing data using LOCF as stated by a co-author of the study per request, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol available. Unclear whether non-fatal myocardial infarction was measured, since myocardial infarction was reported; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results. Body weight and glycaemic variables reported in an inadequate format that could not be used in our meta-analysis, since unclear how many participants were included in the analyses from the extension period. Clear that intervention failure was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Serious adverse

Schweizer 2007 *(Continued)*

		events and severe hypoglycaemia reported in an inadequate format that could not be used in our meta-analysis, since the results only included participants entering the extension period and thus, it was unclear whether the participants with the outcomes in the initial study were being added to the results from the extension period.
Other bias	High risk	**Quote:** "AS is an employee and stockholder of Novartis Pharma AG. AC, JF and SD are employees and stockholders of Novartis Pharmaceuticals. The concept, design, data analysis and write-up of this study were by Novartis, with the editorial assistance of Beth Dunning Lower, a subcontractor of Novartis" **Comment:** All authors are employees and stockholders of the pharmaceutical company Novartis Pharmaceuticals that funded the study and did the concept, design, data analysis and write-up.

Teupe 1991

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, FPG between 120 mg/100 mL to 180 mg/100 mL, early post-prandial value between 180 mg/100 mL to 250 mg/100 mL, 14 days hospitalised treatment with diet alone and intensive diet-orientated training. **Exclusion criteria**: age above 70 years, creatinine > 1.2 mg/100 mL, liver cirrhosis, ischaemic or wasting disease, acute severe diseases. **Diagnostic criteria**: not reported **Setting:** hospital/outpatient[1]
Interventions	**Intervention(s):** metformin **Comparator(s):** no intervention **Duration of intervention:** 2 years **Duration of follow-up:** 2 years **Run-in period:** none **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication**: glycaemic variables, safety, blood pressure, anthropometric measures, lipid profile, haematological variables, biochemistry, lipid profiles, electrocardiography
Study details	**Trial identifier:** - **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal/full article

Teupe 1991 *(Continued)*

Stated aim for study	**Quote from publication**: "Primary aim of this study was to evaluate of whether the addition of metformin to a supervised diet could reduce the frequency of treatment failures of the diet alone"
Notes	[1]Participants were recruited from hospitals and then followed for 1-2 years as outpatients. If participants had persistent elevated HbA1c levels, they were readmitted to the hospital for at least 5 days in which treatment continued.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "... randomly allocated..." **Comment:** method of random sequence generation inadequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "... randomly allocated..." **Comment:** method of allocation concealment inadequately described
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality and serious adverse events were measured but were not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Unclear whether lactic acidosis was measured, since blood lactate was a study outcome; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results
Other bias	Unclear risk	**Comment:** funding source not reported

UKPDS 34 1998

Study characteristics

Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: newly-diagnosed T2DM patients, age between 25 to 65 years inclusive, FPG > 6 mmol/L on two mornings, 1 to3 weeks apart, > 120% of ideal bodyweight. After 3 months dietary run-in period FPG was between 6.1 mmol/L to 14.9 mmol/L **Exclusion criteria**: ketonuria > 3 mmol/L, history of myocardial infarction in the previous year, current angina or heart failure, more than one major vascular episode, serum creatinine > 175 µmol/L, severe retinopathy requiring photocoagulation, malignant hypertension, an uncorrected endocrine abnormality, an occupation which would not allow randomisation to insulin therapy (e.g. heavy goods vehicle driver), severe concurrent illness likely to limit life (e.g. cancer) or requiring extensive systemic treatment (e.g. ulcerative colitis), inadequate comprehension to allow co-operation **Diagnostic criteria**: FPG > 6 mmol/L on two occasions
Interventions	**Intervention(s):** metformin **Comparator(s):** glibenclamide, insulin **Duration of intervention:** 10.7 years **Duration of follow-up:** 10.7 years **Run-in period:** 3 months

UKPDS 34 1998 *(Continued)*

	Number of study centres: 15
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, safety
Study details	**Trial identifier:** — **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding and non-commercial funding **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage."
Notes	We have not included data from the conventional intervention arm in the UKPDS, as it had another glycaemic target. We have not included the chlorpropamide intervention arm, as this drug is no longer used in clinical practice

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication**: "Randomisation was by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes which were opened in sequence." **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication**: "Randomisation was by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes which were opened in sequence." **Comment:** method of allocation concealment adequately described
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "The trial was open once patients were randomised" **Comment**: self-reported outcome measurement, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "Members of the UKPDS end-point committee, who were unaware of assignments to study groups, adjudicated outcomes.." **Comment:** adjudicated outcome measurement, adequate blinding
Selective reporting (reporting bias)	High risk	**Quote from publication:** "The response to metformin therapy in the obese subjects is assessed by comparison with those allocated to diet policy and to sulphonylurea therapy." **Comment:** the publications only report a few outcomes for the comparison metformin versus sulphonylurea, and not for all outcomes as prespecified
Other bias	Unclear risk	**Comment:** received funding from pharmaceutical company. Factorial design (randomisation to blood pressure control) - no test of interaction

Umpierrez 2014

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: age above 18 years, T2DM, duration between 3 months to 5 years inclusive, HbA1c between 6.5% to 9.5% inclusive, diet and exercise alone or on one oral glucose-lowering drug for more than or equal to 3 months prior to screening. Individuals who were receiving glucose-lowering drugs were only eligible if they were taking ≤ 50% of the approved maximum daily dose per respective labels in participating countries **Exclusion criteria**: previously taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening or had ever received chronic insulin therapy **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** dulaglutide (1.5 mg/week), dulaglutide (0.75 mg/week) **Duration of intervention:** 52 weeks **Duration of follow-up:** 56 weeks **Run-in period:** 2 weeks without any glucose-lowering drugs **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety, blood pressure
Study details	**Trial identifier:** NCT01126580 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding (Eli Lilly and Company) **Publication status:** peer-reviewed journal full article
Stated aim for study	**Quote from publication:** "[...] to evaluate the efficacy and safety of monotherapy with once-weekly dulaglutide compared with daily metformin in patients with early stage type 2 diabetes over a period of 52 weeks."
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Randomization occurred, stratified by country and prior OAM use, according to a computer-generated random sequence using an interactive voice response system" **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "Randomization occurred, stratified by country and prior OAM use, according to a computer-generated random sequence using an interactive voice response system" **Comment:** method of allocation concealment adequately described

Umpierrez 2014 *(Continued)*

Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, adequate blinding
Blinding of participants and personnel (performance bias) non-fatal stroke	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, adequate blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, adequate blinding
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, adequate blinding

Umpierrez 2014 *(Continued)*

Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." **Comment:** investigator-assessed outcome, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) non fatal stroke	Low risk	**Quote from publication:** "...double-blind, double-dummy (both injectable and oral placebo)..." "Deaths and nonfatal cardiovascular adverse events (AEs) were adjudicated by an external committee of physicians with cardiology expertise" **Comment:** adjudicated-assessed outcome, adequate blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment." "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% to 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inappropriate use of LOCF for handling missing data, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment." "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% - 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inappropriate use of LOCF for handling missing data, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) non-fatal myocardial infarction	High risk	**Quote from publication:** "The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment." "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% to 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inappropriate use of LOCF for handling missing data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) non-fatal stroke	High risk	**Quote from publication:** "The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment." "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% to 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inappropriate use

Umpierrez 2014 *(Continued)*

		of LOCF for handling missing data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment." "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% - 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inappropriate use of LOCF for handling missing data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "For the assessment of efficacy and hypoglycemia, only data obtained prior to rescue medication were used" "The last observation was carried forward (LOCF) for missing data" **Comment:** 100% of participants included in the analysis, high drop out rate (79.5% to 81.8% of participants completed the study) but balanced between arms, reasons for missing data not similar between arms, inadequate population used for analysis since only data prior to rescue medication were used, inappropriate use of LOCF for handling missing data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol available. All prespecified outcomes of interest to this review reported adequately
Other bias	Unclear risk	**Quote:** "G.U. has received research funding for investigator-initiated studies from Sanofi, Merck, Novo Nordisk, and Boehringer Ingelheim. S.T.P. has received honoraria for lectures and research funding from Eli Lilly and Company. L.S. and V.P. are employees of Eli Lilly and Company. V.P. is a stock/shareholder at Eli Lilly and Company." **Comment:** risk of funding bias

Williams-Herman 2010

Study characteristics	
Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, age between 18 – 78 **Exclusion criteria**: T1DM, unstable cardiac disease, significant renal impairment (estimated creatinine clearance < 60 mL/min), or elevated (more than twofold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin (1000 mg/day), metformin (2000 mg/day) **Comparator(s)** [1] **:** sitagliptin **Duration of intervention:** 104 weeks

Williams-Herman 2010 *(Continued)*

	Duration of follow-up: 104 weeks **Run-in period:** participants with HbA1c between 7.5% to 11% and not on any glucose-lowering agents for 8 weeks were eligible to directly enter a 2-week, single-blind, placebo run-in period. Participants with HbA1c > 11% and not on any glucose-lowering drug entered a diet and exercise run-in period of up to 6 weeks, and people on an glucose-lowering drug with HbA1c between 7% to 10.5% had the agent(s) discontinued and entered a wash-off period of 6 to 10 weeks (8 to 12 weeks for those on thiazolidinediones). After the wash-off/run-in period, participants with HbA1c between 7.5% to 11% entered a 2-week, single-blind, placebo run-in period. All participants with adequate compliance (≥ 75% as assessed by tablet counts) during the placebo run-in period had baseline assessments and were randomised. Participants who met non-glycaemic eligibility criteria but who had HbA1c > 11% or a fasting glucose value > 280 mg/dL after the run-in period were not randomised **Number of study centres**: 140 in base study and 117 in extension study
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety, lipid profile
Study details	**Trial identifier:** NCT00103857 **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** commercial funding Merck & Co., Inc., Whitehouse Station, NJ **Publication status:** peer-reviewed journal/full article
Stated aim for study	**Quote from publication**: "To evaluate the longer term efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy..."
Notes	[1]There were more comparators in this study which were not of interest to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Patients then had baseline assessments and were randomized to one of six treatments using a computer-generated allocation schedule" **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "Patients then had baseline assessments and were randomized to one of six treatments using a computer-generated allocation schedule" **Comment:** method of allocation concealment inadequately described
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding

Williams-Herman 2010 *(Continued)*

Blinding of participants and personnel (performance bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) non-fatal stroke	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) cardiovascular mortality	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..."

Williams-Herman 2010 *(Continued)*

		Comment: investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) severe hypoglycaemia	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) non fatal stroke	Low risk	**Quote from publication:** "... double-blind, double-dummy..." "Laboratory measurements and ECGs were analysed at central laboratories... by technicians blinded to treatment group..." **Comment:** investigator-assessed outcome measurement, blinding inadequately described, however, outcome not judged to be influenced by a lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100**%** of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not balanced between arms, reasons for missing data balanced between arms, unclear how missing data were handled, it is assumed that mortality status has been investigated in death registers at the end of the study
Incomplete outcome data (attrition bias) cardiovascular mortality	Low risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100**%** of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not balanced between arms, reasons for missing data balanced between arms, unclear how missing data were handled, it is assumed that mortality status has been investigated in death registers at the end of the study and none of the reported deaths were of cardiovascular nature
Incomplete outcome data (attrition bias) non-fatal myocardial infarction	High risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100% of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not

Williams-Herman 2010 *(Continued)*

		balanced between arms, reasons for missing data similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) non-fatal stroke	High risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100% of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not balanced between arms, reasons for missing data similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) serious adverse events	High risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100% of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not balanced between arms, reasons for missing data similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) severe hypoglycaemia	High risk	**Quote from publication:** "The population for the safety analysis included all randomized patients... who received at least one dose of blinded study medication during the 104-week treatment period... All serious adverse experiences and reported deaths are summarised herein regardless of initiation of glycaemic rescue therapy." **Comment:** 100% of randomised participants included in the analysis, high dropout rate (36.3% to 52.2% of participants completed the study) and not balanced between arms, reasons for missing data similar between arms, unclear how missing data were handled, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol available. Several differences in study results between the main publication after 104 weeks of intervention and the trial in the trial registry. Intervention failure reported in an inadequate format that could not be used in our meta-analysis, since it was unclear which population was used to calculate the risk of intervention failure.
Other bias	Unclear risk	**Quote:** "The study was funded by Merck & Co., Inc., Whitehouse Station" **Comment:** received funding from a pharmaceutical company

Yamanouchi 2005

Study characteristics

Yamanouchi 2005 *(Continued)*

Methods	**Study design:** parallel RCT
Participants	**Inclusion criteria**: T2DM, never used antidiabetic drugs, HbA1c ≥ 7.0% and FPG ≥ 7.78 mmol/L at the end of a 1-month observation period **Exclusion criteria**: unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, liver dysfunction (aspartate aminotransferase, alanine aminotransferase > 1.5 × upper limit of normal) impaired kidney function (serum creatinine > 133 µmol/L), anaemia, myocardial infarction, angina, congestive heart failure, or a documented cerebrovascular accident **Diagnostic criteria**: not reported
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone, glimepiride **Duration of intervention:** 52 weeks **Duration of follow-up:** 52 weeks **Run-in period:** 1 month **Number of study centres**: not reported
Outcomes	**Reported outcome(s) in full text of publication:** glycaemic variables, anthropometric measures, safety, lipid profile, haematological variables, biochemistry, blood pressure
Study details	**Trial identifier:** not reported **Trial terminated early:** no
Publication details	**Language of publication**: English **Funding:** not reported **Publication status:** peer-reviewed journal / full article
Stated aim for study	**Quote from publication**: "In this study, we compared changes in major metabolites for 12 months when TZD, biguanide, or glimepiride were used in drug-naive Japanese patients with Type 2 diabetes."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Random assignment was determined by the biostatistician, who provided sealed sequentially numbered envelopes opened only at the time of randomization." **Comment:** method of random sequence generation adequately described
Allocation concealment (selection bias)	Unclear risk	**Quote from publication:** "Random assignment was determined by the biostatistician, who provided sealed sequentially numbered envelopes opened only at the time of randomization." **Comment:** method of allocation concealment inadequately described. It remains unclear whether envelopes were opaque

Yamanouchi 2005 *(Continued)*

Blinding of participants and personnel (performance bias) non-fatal myocardial infarction	Low risk	**Comment:** investigator-assessed outcome, blinding not described, however, outcome not judged to be influenced by a lack of blinding
Blinding of participants and personnel (performance bias) non-fatal stroke	Low risk	**Comment:** investigator-assessed outcome, blinding not described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction	Low risk	**Comment:** investigator-assessed outcome, blinding not described, however, outcome not judged to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) non fatal stroke	Low risk	**Comment:** investigator-assessed outcome, blinding not described, however, outcome not judged to be influenced by a lack of blinding
Incomplete outcome data (attrition bias) non-fatal myocardial infarction	High risk	**Quote from publication:** "All these withdrawals occurred within the first 3 months of the study, and were excluded from the final data analysis." **Comment:** 93% of participants included in the analysis, moderate dropout rate (91.9% to 94.9% of participants completed the study) and balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of withdrawals from analysis, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) non-fatal stroke	High risk	**Quote from publication:** "All these withdrawals occurred within the first 3 months of the study, and were excluded from the final data analysis." **Comment:** 93% of participants included in the analysis, moderate dropout rate (91.9% to 94.9% of participants completed the study) and balanced between arms, reasons for missing data similar between arms, inappropriate exclusion of withdrawals from analysis, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	High risk	**Comment:** study protocol not available. Clear that all-cause mortality and serious adverse events were measured but were not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results. Unclear whether severe hypoglycaemia was measured, since mild hypoglycaemia was reported in the trial; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results
Other bias	Unclear risk	**Comment:** funding source not reported

ADA: American Diabetes Association; **ALT**: alanine transaminase; **AMI**: acute myocardial infarction; **AST**: aspartate transaminase; **BMD**: bone mineral density; **BMI**: body mass index; **CAD**: coronary artery disease; **CYP3A4**: Cytochrome P450 3A4; **DXA**: Dual-energy X-ray absorptiometry; **EASD**: the European Association for the Study of Diabetes; **ECG**: electrocardiogram; **ESC**: European Society of Cardiology; **FDA:** Food and Drug Administration; **FPG**: fasting plasma glucose; **FPI**: fasting plasma insulin; **GLP-1**: glucagon-like peptide 1; **GSK**: GlaxoSmithKline; **HbA1c**: glycosylated haemoglobin A1c; **HDL-C**: high density lipoprotein cholesterol; **HOMA-IR**: homeostatic model assessment for insulin resistance; **IR**: immediate release; **IVRS**: interactive voice response system; **LAEI**: large artery elasticity index; **LDL-C**: low-density lipoprotein cholesterol; **LOCF**: last observation carried forward; **MCP-1**: monocyte chemoattractant protein 1; **MET**: metformin; **MMP-9**: matrix metalloproteinase 9; **MNT**: medical nutrition treatment; **MR**: modified release; **NYHA**: New York Heart Association; **OGTT**: oral glucose tolerance test; **PIO**: pioglitazone;**PPG**: post-prandial glucose;**PPI**: post-prandial insulin; **RCT**: randomised controlled trial; **SAEI**:

small artery elasticity index; **SSA**: serum sialic acid; **SU**: sulphonylurea; **T1DM**: type 1 diabetes mellitus; **T2DM**: type 2 diabetes mellitus; **TC**: total cholesterol; **TG**: triglycerides; **TSH**: thyroid stimulating hormone; **TZD**; thiazolidinediones; **UKPDS**: United Kingdom Prospective Diabetes Study; **WHO**: World Health Organization.

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

Study	Reason for exclusion
Anderson 2016	Review
Anonymous 2014	Not a randomised controlled trial
Australian Prescriber 2013	Not a randomised controlled trial
Australian Prescriber 2014	Not a randomised controlled trial
Bailey 2015	Non-concomitant interventions
Belcher 2004	Review
Belcher 2005a	Review
Belcher 2005b	Review
Billington 2015	Systematic review/meta-analysis
Borges 2011	Comparator arm included metformin
Boussageon 2012	Systematic review/meta-analysis
Boussageon 2016	Review
Bruce 2006	Intervention 20 weeks
Buhse 2016	Systematic review/meta-analysis
Cai 2016	Systematic review/meta-analysis
Ceriello 2005	Review
Chanson 2014	Review
Chen 2016	Randomisation of participants to comparator comprising multiple glucose-lowering interventions reported as one
Cheng 2017	Systematic review/meta-analysis
ChiCTR-IOR-16009296	Intervention 4 months
ChiCTR-IPR-16008578	Intervention 24 weeks
ChiCTR-IPR-17010825	Intervention 24 weeks
ChiCTR-IPR-17011120	Inclusion only of participants with intercurrent polycystic ovarian syndrome
ChiCTR-TRC-08000231	Intervention 48 weeks

Study	Reason for exclusion
ChiCTR-TRC-11001613	Inclusion only of participants with chronic heart failure in addition to T2DM
ChiCTR-TRC-11001808	Intervention 24 weeks
ChiCTR-TRC-12002320	Intervention 12 weeks
ChiCTR-TRC-12002505	Intervention 3 months
ChiCTR-TRC-13003368	Intervention 12 weeks
ChiCTR-TRC-14004660	Inclusion only of participants with intercurrent non-alcoholic fatty liver disease in addition to T2DM
Clarke 1968	Randomisation of participants to first-generation sulphonylurea
Clarke 1977	Randomisation of participants to first-generation sulphonylurea
Clarke 2001	The glycaemic target was different between the metformin arm and conventional therapy. The sulphonylurea- and insulin arm had the same glycaemic target as the metformin arm, but data were not reported
Coleman 2015	Review
Cooper 2015	Review
Cryer 2005	Study drug used in the comparator arm determined by study investigators
Dalzell 1986	Randomisation of participants to first-generation sulphonylurea
EUCTR2005-001027-11-GB	Intervention less than 52 weeks due to premature termination
EUCTR2007-006665-33-DK	Intervention less than 52 weeks
EUCTR2012-001390-88-CZ	Intervention 3 months
Ferrannini 2013	Non-concomitant comparator
Gallo 2014	Intervention 48 weeks
Garcia 2014	No participants randomised to metformin monotherapy
Gu 2014	Systematic review/meta-analysis
Haak 2013	No participants randomised to metformin monotherapy
Heitmann 2016	Review
Hirst 2012	Systematic review/meta-analysis
Holden 2014	Review
Hong 2013	Inclusion of participants with coronary artery disease in addition to T2DM
Hou 2017	Systematic review/meta-analysis

Study	Reason for exclusion
Hwang 2015	Systematic review/meta-analysis
Ida 2017	Systematic review/meta-analysis
ISRCTN75451837	Not a randomised controlled trial
JPRN-UMIN000004367	Participants continued prior glucose-lowering drugs
JPRN-UMIN000005327	Participants continued prior glucose-lowering drugs
JPRN-UMIN000011063	Intervention 12 weeks
Kakorin 2016	Review
Kanazawa 2009	Participants continued prior glucose-lowering drugs
Lambadiari 2018	Intervention 6 months
Lester 2005	Not a randomised controlled trial
Liakos 2014	Systematic review/meta-analysis
Liu 2014	Systematic review/meta-analysis
Liu 2014a	Systematic review/meta-analysis
Liu 2017	Systematic review/meta-analysis
MacConell 2015	Post-hoc analysis
Mei 2014	Systematic review/meta-analysis
MET/D/86/BERGI 1994	Study never published. Unknown design
Mo 2019	Intervention 48 weeks
Monami 2014	Systematic review meta-analysis
NCT00214591	Tesaglitazar in developmental phase
NCT00282945	Intervention 6 months
NCT00308373	Intervention 4 months
NCT00373178	Intervention 14 weeks
NCT00396851	Withdrawn due to lack of funding
NCT00399204	Withdrawn due to lack of funding
NCT00481663	Non-concomitant interventions
NCT00543361	Comparator is not an approved drug (MK0767)
NCT00754689	Comparator is not a recognised drug (rimonabant)

Study	Reason for exclusion
NCT01087567	Intervention 6 months
NCT01099618	Inclusion only of participants with diabetic ketoacidosis in addition to T2DM
NCT01217073	No randomisation to metformin
NCT01700075	Participants with T2DM not included
NCT01958671	Metformin intervention does not last for 52 weeks
NCT02234440	Inclusion only of participants with intercurrent non-alcoholic steatohepatitis
NCT02409238	Participants with T2DM not included
NCT02587741	Metformin in all interventions
NCT02694289	Withdrawn due to failure to enrol participants
Palmer 2016	Systematic review/meta-analysis
Polzer 2015	Intervention 16 weeks
Prescrire International 2014	Review
Prescrire International 2015	Review
Rokkas 2016	Systematic review/meta-analysis
Rosenstock 2013	Non-concomitant intervention
Rutter 2010	Study drug used in the comparator arm determined by study investigators
Salpeter 2003	Systematic review/meta-analysis
Sazia 2015	Intervention of 3 months
Scheen 2016	Not a randomised controlled trial
Scheen 2017	Not a randomised controlled trial
The Medical Letter 2015	Not a randomised controlled trial
UKPDS 24	Data reported after 6 years of follow-up where approximately 70% of the participants in each intervention arm received combination therapy
UKPDS 72	Comparator arm had a different glycaemic target from the one in the intervention arm
Unnikrishnan 2016	Review
Yang 2014	Intervention 48 weeks
Zhang 2015	Systematic review/meta-analysis
Zhang 2016	Systematic review/meta-analysis

Study	Reason for exclusion
Zhou 2017	Systematic review/meta-analysis
Zintzaras 2014	Systematic review/meta-analysis

T2DM: type 2 diabetes mellitus.

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

ChiCTR-IOR-16007720

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: — **Masking**: — **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 30 participants of interest to this review **Inclusion criteria**: T2DM WHO 1999, newly T2DM, aged 30 to 65 years, with HbA1c < 9% and glucose-lowering drug-naive. **Exclusion criteria**: FBD, IBD or other gastrointestinal disorders, medications or surgery influential to gastrointestinal tract, acute infection, taking antibiotics or glucocorticoids lately, with complications of DKA, lactic acidosis or hyperosmolar and hyperglycaemic state, abnormal kidney function and creatinine > 130 umol/L, serious cardiovascular diseases (e.g.. heart failure, unstable angina, AMI and uncontrolled hypertension), ALT and/or AST > 2.5 * UNL and/or total biliary > 2.5 * UNL, women during pregnancy or lactation, and those who are unwilling to avoid conception
Interventions	**Intervention(s)**: metformin **Comparator(s)**: gliclazide
Outcomes	**Primary outcome(s)**: — **Secondary outcome(s)**: — **Other outcome(s)**: —
Study details	**Trial identifier**: ChiCTR-IOR-16007720
Publication details	**Language of protocol**: Chinese / English **Funding**: other (journal) **Publication status**: unclear if published
Stated aim of study	**Quote:** "To compare the effects of metformin and gliclazide on gut microbiota in type 2 diabetics by using high-throughput sequencing techniques. To compare the effects of metformin and gliclazide on serum endotoxin in type 2 diabetics"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

ChiCTR-IOR-17011477

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 60 participants **Inclusion criteria**: T2DM, drug-naive, HbA1c between 7% to 10%, BMI < 30 kg/m^2, weight fluctuation before screening < 10% and at least 3 months stable **Exclusion criteria**: acute complications of type 1 diabetes or diabetes, due to pancreatic injury caused by diabetes or secondary diabetes, fractures, osteoporosis disease, currently taking anti osteoporosis drugs or drugs that can cause secondary osteoporosis, liver or kidney damage, history of pancreatitis, severe cardiovascular disease, immune system, blood system or endocrine system disease, alcoholism, allergic to drug, use of other drugs and drug interactions.
Interventions	**Intervention(s)**: metformin **Comparator(s)**: saxagliptin
Outcomes	**Primary outcome(s)**: FPG, bone gamma-carboxyglutamic acid-containing protein, total procollagen type N-terminal propeptide, CRP **Secondary outcome(s)**: — **Other outcome(s)**: —
Study details	**Trial identifier**: ChiCTR-IOR-17011477
Publication details	**Language of protocol**: Chinese / English **Funding**: non-commercial (research department) **Publication status**: unclear if published
Stated aim of study	—
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR-IPR-16009666

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: —

ChiCTR-IPR-16009666 *(Continued)*

	Primary purpose: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 100 participants **Inclusion criteria**: FPG ≥ 11.1 mmol/L and/or HbA1c ≥ 9.0%, BMI ≥ 24 kg/m2, duration of T2DM 0 - 12 months, not accepted any oral glucose-lowering drugs. **Exclusion criteria**: acute diabetes complications, concurrent infection, combined liver and kidney impairment, combined cardiac insufficiency.
Interventions	**Intervention(s)**: metformin **Comparator(s)**: liraglutide
Outcomes	**Primary outcome(s)**: FPG, 2h-PPG, HbA1c, FC-P, 2-h C-P, HOMA-β **Secondary outcome(s)**: BMI, gastrointestinal adverse events **Other outcome(s)**: —
Study details	**Trial identifier**: ChiCTR-IPR-16009666
Publication details	**Language of protocol**: Chinese / English **Funding**: non-commercial (hospital) **Publication status**: unclear if published
Stated aim of study	**Quote:** "To observe the efficacy of liraglutide on inducing long-term clinical remission in newly diagnosed type 2 diabetes after intensive treatment"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR-IPR-17010811

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 24 participants of interest to this review **Inclusion criteria**: age between 30 and 75 years, T2DM, hyperglucagonaemia, oral hypoglycemic drugs, the general HbA1c <= 10%, the entire study period does not adjust the amount of antidiabetic drug usage. **Exclusion criteria**: poor blood pressure control: SBP > 180 mmHg, DBP > 100 mmHg, other diseases affecting the metabolism of glycolipid: hyperthyroidism, hypothyroidism, Cushing's syndrome, heart failure (NYHA classification: III - IV), ALT and / or AST > 3 times ULN, or active liver disease, PLT < 60 * 10^9/L, Hb < 100 g/L, chronic renal disease or severe renal impairment, definition

ChiCTR-IPR-17010811 *(Continued)*

	of serum creatinine > 135 mmol/L (1.5 mg/dL (male), and 110 mmol/L (1.3 mg/dL) (female), 2 years had malignant tumors, patients with bleeding tendency, recent gastrointestinal bleeding, anticoagulant therapy, have been pregnant or plan to be pregnant in the near future, known to metformin, aspirin drug allergy, 30 days participated in other drug clinical trials, there are other circumstances that can not participate in the intervention of the followers, the investigators considered the participants to be affected by the outcome of the assessment of the disease or not suitable for inclusion.
Interventions	**Intervention(s)**: metformin **Comparator(s)**: placebo
Outcomes	**Primary outcome(s)**: blood parameters **Secondary outcome(s)**: — **Other outcome(s)**: —
Study details	**Trial identifier**: ChiCTR-IPR-17010811
Publication details	**Language of protocol**: Chinese / English **Funding**: non-commercial (university) **Publication status**: unclear if published
Stated aim of study	**Quote:** "To determine the hypothesis whether hyperglucagonaemia causes metformin resistance and aspirin is able to improve metformin resistance as observed in our animal experiment."
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR-TCH-10001013

Methods	**Type of trial:** efficacy and safety trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** — P**rimary purpose:** treatment and prevention
Participants	**Condition:** T2DM and cognitive impairment **Enrollment:** estimated 120 participants of interest to this review **Inclusion criteria:** T2DM, mild to moderate cognitive impairment as defined by a MMSE score ≤ 26 at screening, Hachinski ischaemia score ≤ 4 at screening, brain CT or MRI scan and neurological exam performed at screening, showing no evidence of any focal neurological changes (i.e. hemiplegia, hemidysaesthesia, aphasia). **Exclusion criteria:** history of significant psychiatric illness such as schizophrenia or bipolar affective disorder, major depressive disorder (according to DSM-IV) in the past year, or current active depression requiring initiation of treatment, history or evidence of any other CNS disorder that could be interpreted as a cause of dementia: e.g. cerebrovascular disease (stroke, haemorrhage), structural abnormality, epilepsy, head injuries, infectious or inflammatory/demyelinating CNS conditions, Parkinson's disease, evidence of the following disorders: current vitamin B12 deficiency, malignancy, positive syphilis serology, or active thyroid dysfunction (particularly that suggestive of hypothyroidism), clinically significant anaemia (i.e. Hb < 11 g/dL for males or < 10 g/dL for females) which would prevent accurate assessment of HbA1c, current or recent drug or alcohol abuse or dependence (defined by DSM-IV criteria for substance-related disorders), or recent or remote history of the same if that could be a contributing factor to the dementia, heart rate ≤ 50 beats/min or ≥ 110 beats/min, history of cardiovascular event within the last 4 months (i.e. acute coronary syn-

ChiCTR-TCH-10001013 *(Continued)*

	drome (myocardial infarction, unstable angina) or significant arrhythmia, intervention, percutaneous coronary intervention, or major intervention (e.g. cardiac surgery or angiography plus stenting), SBP ≥ 180 or < 90 mmHg at the time of screening, history or clinical/investigational evidence of congestive heart failure defined by the New York Heart Association criteria (Class Ⅱ to IV cardiac status), abnormal kidney function tests (> 1.5 the upper limit of normal (UNL)), ALT, AST, or alkaline phosphatase values > 2.5 times the ULN, total bilirubin values > 1.5 times the ULN, or history of severe hepatobiliary disease (e.g. hepatitis B or cirrhosis, Child-Pugh Class B/C), asthma and chronic obstructive pulmonary disease, history or presence of gastro-intestinal, or other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, or any other clinically relevant abnormality, medical or psychiatric condition, T2DM being treated with other than PPARγ agonist (e.g. rosiglitazone), or an insulin secretagogue (e.g. a sulphonylurea), a history of allergic reaction to pioglitazone and metformin, unable to comply with procedures for cognitive and other testing.
Interventions	**Intervention(s):** metformin **Comparator(s):** exenatide, insulin, pioglitazone and insulin
Outcomes	**Primary outcome(s):** evaluation of cognition **Secondary outcome(s):** risk of stroke **Other outcome(s):** biochemical indices
Study details	**Trial identifier:** ChiCTR-TCH-10001013
Publication details	**Language of protocol:** Chinese / English **Funding:** non-commercial (educational program) **Publication status:** unclear if published
Stated aim of study	**Quote:** "To evaluate the efficacy and safety of Pioglitazone and/or Metformin as Treatment for Cognitive Impairments and Risk of Stroke in Patients with Type 2 Diabetes."
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR-TRC-11001331

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** single blinding (participants) **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 90 participants **Inclusion criteria:** aged 18 to 75 years old, newly diagnosed type 2 diabetes or poor controlled glycaemia with metformin alone or other one kind antidiabetic diabetes drug, HbA1c between 7% - 10%, BMI < 35. **Exclusion criteria:** impaired hepatic function with ALT higher than 3 X ULN, impaired renal function with serum creatinine higher than 1.5 mg/dL, myocardial infarction, stroke or TIA within 6 months prior to informed consent, use of insulin, rosiglitazone or pioglitazone, or GLP-1 analogue within 3 months prior to informed consent.
Interventions	**Intervention(s):** metformin (1500 mg/day) **Comparator(s):** DPP-IV inhibitor (5 mg/day)
Outcomes	**Primary outcome(s):** adipocytokines, inflammation markers, vascular endothelial function **Secondary outcome(s):** —

ChiCTR-TRC-11001331 *(Continued)*

	Other outcome(s): —
Study details	**Trial identifier:** ChiCTR-TRC-11001331
Publication details	**Language of protocol:** Chinese / English **Funding:** non-commercial (government foundation) **Publication status:** unclear if published
Stated aim of study	**Quote:** "To investigate the effects of DPP-Ⅳ inhibitor and/or metformin combination on adipokine, inflammation and vascular endothelial function in type 2 diabetes patients "
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR1800018825

Methods	**Type of trial:** safety and efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** — **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 80 participants **Inclusion criteria:** T2DM, drug-naive, aged between 18 to 70 years old, HbA1c between 6.5% to 13%, with one of atherosclerotic cardiovascular disease (SBP ≥140 bmmHg or DBP ≥ 90 mmHg; older than 50 years old in male or 60 years old in female; LDL-C≥ 2.6 mmol/L or TG ≥ 2.3 mmol/L or HDL-C ≤ 0.88 mmol/L; BMI ≥ 28 kg/m2; urine microalbumin/creatinine > 30; ankle brachial pressure index (ABI) ≤0.9 in either side), there is a fixed residence for at least 5 years, in good ability of memory and activity, be in good mental health and self-reliant, with an informed consent form. **Exclusion criteria:** with positive diabetes antibody (insulin autoantibody, islet cell antibodies, or glutamic acid decarboxylase), or diagnosed type 1 diabetes, with severe diabetes complications, e.g. leg ulcers, severe liver and kidney damage, severe neurological diseases and severe retinopathy, blood pressure≥180/110 mmHg or total cholesterol ≥ 6.2 mmol/L, antibiotics used in the past 3 months for 3 days or more, pregnancy or planning to become pregnant, intemperance (drinking more than 5 times in one week and drinking more than 100 g spirit, 250 g rice wine or 5 bottles of beer), patients diagnosed with severe mental disease in 6 months, received drug therapy aim at the following diseases, e.g. cholecystitis, peptic ulcer, urinary tract infection, acute pyelonephritis, urocystitis or hyperthyreosis, had gastrointestinal surgery, except for appendicitis and hernia surgery, patients with severe liver diseases such as chronic, persistent hepatitis or cirrhosis, or HBsAg positive, or liver dysfunction (serum alanine transaminase and oxaloacetic transaminase 2.5 times than normal), patients with IBD or Cushing syndrome; patients with abnormal pituitary function; patients with severe diseases like cancer, cardiovascular disease, AMI, or stroke etc patients with infectious diseases such as tuberculosis and acquired immune deficiency syndrome etc, physical disability, or other causes of life can not be self-care, can not be clearly recalled, answer the question of the person, anaemia: HbA1c less than 10 g/dL, physical disability or self-care disability or disability of recalling clearly and answering questions caused by any other reasons, without enough time taking part in this project, participating in other research program
Interventions	**Intervention(s):** metformin **Comparator(s):** empagliflozin
Outcomes	**Primary outcome(s):** HbA1c **Secondary outcome(s):** weight, blood pressure, carotid ultrasound, cardiac ultrasound **Other outcome(s):** —
Study details	**Trial identifier:** ChiCTR1800018825

ChiCTR1800018825 *(Continued)*

Publication details	**Language of protocol:** Chinese / English **Funding:** non-commercial (hospital) **Publication status:** unclear if published
Stated aim of study	**Quote:** "to estimate: (1) Clinical efficacy and safety of Empagliflozin in the treatment of patients with new-onset type 2 diabetes and risk factor for atherosclerotic cardiovascular disease; (2) Mechanism of Empagliflozin in the treatment of patients with new-onset type 2 diabetes and risk factor for atherosclerotic cardiovascular disease; (3) Provide a new treatment for patients with new-onset type 2 diabetes and risk factor for atherosclerotic cardiovascular disease;(4) Provide new target and new perspective for individualized treatment of type 2 diabetes mellitus. "
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

ChiCTR1900021632

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 72 participants **Inclusion criteria:** diagnosed within the past 12 months with T2DM, not received oral anti-diabetic drugs or insulin therapy, HbA1c between 7.5% and 10.5%, fasting plasma glucose ≤11.1 mmol/L, BMI between 19 to 30 kg/m2, age ≥ 60 years **Exclusion criteria:** acute diabetic complications, severe chronic diabetic complications, severe abnormal liver and kidney function, severe gastrointestinal disease, severe cardiac disease, chronic obstructive pulmonary disease, uncontrolled hypertension (SBP > 160 mmHg or DBP > 100 mmHg), previous bariatric surgery, a history of bulimia, substance abuse, or the use of any weight loss medications, pregnant women, ready to deliver or lactating, or childbearing women, diagnosed as T2DM more than 12 months.
Interventions	**Intervention(s):** metformin **Comparator(s):** acarbose
Outcomes	**Primary outcome(s):** HbA1c **Secondary outcome(s):** insulin, glucagon **Other outcome(s):** interleukin-6, tumor necrosis factor-alpha
Study details	**Trial identifier:** ChiCTR1900021632
Publication details	**Language of protocol:** Chinese / English **Funding:** other (self-financed) **Publication status:** unclear if published
Stated aim of study	**Quote:** "To compare the effects of acarbose with those of metformin on glycemic control, b-cell function, glucagon levels, body weight in the elderly Chinese with newly diagnosed T2DM "
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

EUCTR2005-000461-18-GB

Methods	**Type of trial:** safety trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** no blinding **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** — **Inclusion criteria:** age 40 - 50 years, diabetes (diagnosed by WHO criteria) **Exclusion criteria:** peri-menopausal symptoms, patient should not be on any medication, unwilling for GP to be informed, polycystic ovarian syndrome (patients must have regular periods, no clinical or biochemical evidence of hyperandrogenism, normal ovaries on ultrasound scanning
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone
Outcomes	**Primary outcome(s):** change in insulin resistance pre and post treatment with metformin or pioglitazone as measured by insulin clamp study and change in endothelial function pre and post treatment as measured by flow-mediated vasodilatation. **Secondary outcome(s):** — **Other outcome(s):** —
Study details	**Trial identifier:** EUCTR2005-000461-18-GB
Publication details	**Language of protocol:** English **Funding:** non-commercial (university) **Publication status:** unclear if published
Stated aim of study	**Quote:** "To compare the cardiovascular risk indices in women with type 2 diabetes with age matched women with PCOS to determine if women with PCOS have the same risk of accelerated atherosclerosis as those with diabetes"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Insufficient information to contact trial authors.

JPRN-UMIN000000689

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM and diabetic nephropathy **Enrollment:** estimated 70 participants **Inclusion criteria:** age between 20 to 75 years, T2DM, diabetic nephropathy (stage II - IV), HbA1c < 9.0% **Exclusion criteria:** participants already taking thiazolidinediones, serious liver functional dysfunction, pregnancy or likelihood of pregnancy, allergy towards thiazolidinediones
Interventions	**Intervention(s):** metformin (750 mg/day) **Comparator(s):** pioglitazone (15 to 30 mg/day)
Outcomes	**Primary outcome(s):** cystatine C, creatinine clearance, albumin excretion rate, creatinine **Secondary outcome(s):** general biochemical tests, HOMA-R, fasting blood insulin, serum resistin, CRP, adiponectin, leptin levels

JPRN-UMIN000000689 *(Continued)*

	Other outcome(s): —
Study details	**Trial identifier:** JPRN-UMIN000000689
Publication details	**Language of protocol:** Japanese /English **Funding:** non-commercial (university) **Publication status:** unpublished
Stated aim of study	**Quote:** "Examination of renal protective effect by pioglitazone on the progression of type 2 diabetic nephropathy by measurement of cystatine C levels"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

JPRN-UMIN000000771

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 40 participants **Inclusion criteria:** T2DM, HbA1c between 6.5% to 9.0% **Exclusion criteria:** treated with insulin, renal dysfunction, history of heart failure and cerebrovascular disease, liver dysfunction, pulmonary dysfunction, pregnancy or lactation, history of side effects by thiazolidinediones or biguanides, judged inappropriate for this study by the physicians
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone
Outcomes	**Primary outcome(s):** Insulin secretion and sensitivity, surrogate markers of atherosclerosis, adipocytokines, and appetite-regulating hormones **Secondary outcome(s):** — **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000000771
Publication details	**Language of protocol:** Japanese / English **Funding:** non-commercial (university) **Publication status:** unpublished
Stated aim of study	**Quote:** "To study multifactorial effects of pioglitazone and metformin on insulin secretion and sensitivity, surrogate markers of atherosclerosis, adipocytokines, and appetite-regulating hormones in Type 2 diabetic patients."
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

JPRN-UMIN000001085

Methods	**Type of trial:** efficacy trial **Allocation:** randomised

JPRN-UMIN000001085 *(Continued)*

	Intervention model: parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 50 participants **Inclusion criteria:** T2DM **Exclusion criteria:** severe renal dysfunction, severe liver dysfunction, heart failure, history of lactic acidosis, severe retinopathy, severe vascular disease with urgent treatment, HbA1c > 9%, blood pressure > 180/100 mmHg
Interventions	**Intervention(s):** metformin (750 mg/day) **Comparator(s):** pioglitazone (15 mg/day)
Outcomes	**Primary outcome(s):** change of carotid arterial elasticity **Secondary outcome(s):** changes of serum markers of atherosclerosis, pulse wave velocity and carotid intima-media thickness **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000001085
Publication details	**Language of protocol:** Japanese / English **Funding:** non-commercial (university) **Publication status:** unpublished
Stated aim of study	**Quote:** "To evaluate the effect of insulin sensitizer treatment on arterial elasticity of diabetic subjects"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

JPRN-UMIN000001891

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 20 participants **Inclusion criteria:** T2DM, on no other glucose-lowering intervention, HbA1c between 6.0% to 10.0%, BMI > 25 kg/m2 **Exclusion criteria:** T1DM, severe liver disease, severe renal disease, severe heart disease, history of myocardial infarction within 6 months, severe pancreatic disease, cancer, severe diabetic neuropathy, severe diabetic retinopathy, history of lactic acidosis, heavy drinkers, pregnant
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone
Outcomes	**Primary outcome(s):** Glucose variability in CGM (area under the glucose curve from pre-meal baseline to baseline, pattern of glucose curve, magnitude of increase in glucose levels and the time to peak glucose levels from baseline after each meal) **Secondary outcome(s):** Pre-meal plasma glucose, 2H-PPG, adverse events, body weight **Other outcome(s):** -

JPRN-UMIN000001891 *(Continued)*

Study details	**Trial identifier:** JPRN-UMIN000001891
Publication details	**Language of protocol:** Japanese / English **Funding:** non-commercial (university) **Publication status:** unpublished
Stated aim of study	**Quote:** "To compare glucose variability in patients given pioglitazone or metformin by using continuous glucose monitoring (CGM)."
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

JPRN-UMIN000002099

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** single blinded (outcome assessors) **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 80 participants **Inclusion criteria:** T2DM **Exclusion criteria:** hepatic or renal dysfunction, nutritional derangements, prior treatment with thiazolidinediones or metformin
Interventions	**Intervention(s):** metformin **Comparator(s):** pioglitazone sulphonylurea or insulin
Outcomes	**Primary outcome(s):** serum pentosidine levels **Secondary outcome(s):** — **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000002099
Publication details	**Language of protocol:** Japanese / English **Funding:** — Publication status: unpublished
Stated aim of study	**Quote:** "The aim of the present study is to investigate the effects of metformin or pioglitazone on serum pentosidine levels"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

JPRN-UMIN000003563

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label

JPRN-UMIN000003563 *(Continued)*

	Primary purpose: treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 200 participants **Inclusion criteria:** treated only with life style modification (or cessation of previous treatment for more than 1 month), obtained documented agreement, age between 20 to 35 years, HbA1c between 6.5% to 8.0% **Exclusion criteria:** T1DM, diabetes by other aetiology, anti-GAD antibody positive (over 1.5 U/mL), allergy towards sitagliptin or metformin, severe liver dysfunction, severe renal dysfunction, severe heart failure, poor prognosis condition (ex: malignancy), pregnancy or breast-feeding woman, metabolic emergency (diabetic ketoacidosis, hyperosmolar hyperglycaemic state), insulin user, psychological disorder, hypoglycaemia unawareness, steroid user, other improper patient
Interventions	**Intervention(s):** metformin (500 - 1500 mg/day) **Comparator(s):** sitagliptin (50 - 100 mg/day)
Outcomes	**Primary outcome(s):** change in C-peptide response index during 3 years **Secondary outcome(s):** duration to monotherapy failure, HbA1c, MAGE obtained from SMBG, new onset or progression of micro, macrovascular complication, HOMA-β, HOMA-R, proinsulin/insulin ratio, adverse event and body weight change **Other outcome(s):** -
Study details	**Trial identifier:** JPRN-UMIN000003563
Publication details	**Language of protocol:** Japanese / English **Funding:** other (non-profit foundation) **Publication status:** unpublished
Stated aim of study	**Quote:** "To compare the effectiveness of beta cell reservation"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted.

JPRN-UMIN000006504

Methods	**Type of trial:** efficacy trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 440 participants **Inclusion criteria:** T2DM, HbA1c over 6.5%, age between 30 to 75 years old, hypertension (blood pressure less than 140/90 mmHg and stable for at least 1 month. The participants include patients who receive antihypertensive medication. LVEF over 50%), did not receive medication with metformin and pioglitazone for 3 months before enrolment, did not receive insulin therapy for 1 year before enrolment, no renal dysfunction (serum creatinine less than 1.3 mg/dL (male), less than 1.2 mg/dL (female)), informed consent of taking part in clinical research **Exclusion criteria:** insulin treatment or secondary diabetes patients, serious hepatic dysfunction/hepatic cirrhosis, unstable angina, AMI, severe CAD patients (Left Main Trunk or triple-vessel disease), chronic atrial fibrillation or pacemaker patients, prior lactic acidosis, severe dysfunction in cardiovascular system, heart failure, myocardial infarction, pulmonary embolism, likely to develop hypoxaemia, heavy drinker, gastrointestinal disorder such as diarrhoea and vomiting that worried dehydration, severe ketosis, diabetic coma or precoma, severe infection, perioperative, severe injury, malnutrition, starvation, debilitation, pituitary insufficiency or adrenal insufficiency pa-

JPRN-UMIN000006504 *(Continued)*

	tients, allergic response towards the medication, pregnant or lactating, intent of becoming pregnant, judged inappropriate for the clinical trial
Interventions	**Intervention(s):** metformin (500 1500 mg/day to 1500 mg/day) **Comparator(s):** other oral glucose-lowering drug and pioglitazone
Outcomes	**Primary outcome(s):** left ventricular mass and diastolic function by echocardiography, blood biomarker of heart failure **Secondary outcome(s):** left ventricular mass by cardiac MRI, electrocardiogram (assessment of autonomic function by R-R variation), exploratory analysis, subgroup analyses **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000006504
Publication details	**Language of protocol:** Japanese / English **Funding:** - **Publication status:** unpublished
Stated aim of study	**Quote:** "To assess beneficial effects on left ventricular hypertrophy and diastolic function by metformin in hypertensive patients with type 2 diabetes mellitus using left ventricular mass index of echocardiography and blood biomarkers of heart failure"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

JPRN-UMIN000010624

Methods	**Type of trial:** efficacy and safety trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM with coronary disease **Enrollment:** estimated 20 participants **Inclusion criteria:** T2DM, HbA1c over 6.9% even after dietary and exercise therapies, CAD, informed consent, age over 20 years **Exclusion criteria:** history of adverse events with vildagliptin or biguanides, treated with glucose-lowering agents, ongoing treatment with insulin, diabetic ketoacidosis or diabetic coma or type 1 diabetes, severe liver dysfunction, moderate or severe renal disorders (creatinine level >= 1.5 mg/dL (men) or >= 1.3 mg/dL (women)), pregnant or lactating, severe illness, judged as ineligible by clinical investigators
Interventions	**Intervention(s):** metformin **Comparator(s):** vildagliptin
Outcomes	**Primary outcome(s):** change in blood glucose, insulin and lipids **Secondary outcome(s):** change in vascular endothelial function **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000010624
Publication details	**Language of protocol:** Japanese / English **Funding:** non-commercial (university) **Publication status:** unpublished

JPRN-UMIN000010624 *(Continued)*

Stated aim of study	**Quote:** "To investigate the effects of vildagliptin and biguanide on postprandial blood glucose and vascular endothelial function in diabetic patients with CAD"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

JPRN-UMIN000014775

Methods	**Type of trial:** efficacy and safety trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Condition:** T2DM **Enrollment:** estimated 30 participants **Inclusion criteria:** T2DM, without severe complications, able to comply to diet and exercise therapy **Exclusion criteria:** contraindications towards ipragliflozin, treated with metformin or GLP-1 analogues, pregnancy
Interventions	**Intervention(s):** metformin **Comparator(s):** ipragliflozin
Outcomes	**Primary outcome(s):** lean body mass **Secondary outcome(s):** body weight, FPG, HbA1c, free fatty acids **Other outcome(s):** —
Study details	**Trial identifier:** JPRN-UMIN000014775
Publication details	**Language of protocol:** Japanese / English **Funding:** non-commercial (university) **Publication status:** unpublished
Stated aim of study	**Quote:** "To evaluate the effect of Ipragliflozin, a new oral hypoglycemic agent, on body composition"
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

Ma 2015

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: —
Participants	**Condition**: T2DM **Enrollment**: 90 participants

Ma 2015 *(Continued)*

	Inclusion criteria: —
	Exclusion criteria: —
Interventions	**Intervention(s)**: metformin (1500 mg/day)
	Comparator(s): pioglitazone (15 mg/day)
Outcomes	**Primary outcome(s)**: —
	Secondary outcome(s): —
	Other outcome(s): blood levels of glucose, insulin and glucagon, insulin sensitivity index, HOMA-IR, HOMA-β, 1-phase index, 2-phase index, insulin secretion sensitivity index
Study details	**Trial identifier**: —
Publication details	**Language of publication**: Chinese / English (abstract)
	Funding: —
	Publication status: full article / peer-reviewed journal
Stated aim of study	**Quote from publication:** "To observe and evaluate the effects of metformin and pioglitazone on blood glucose, insulin, glucagon, β-cell function and insulin resistance among patients with diabetes and metabolic syndrome, so as to discuss the role of pancreatic a cells in pathogenesis of type 2 diabetes mainly caused by insulin resistance and the change of a-cell function after treatment."
Notes	Marked as a study awaiting classification due to publication being in Chinese and a lack of data to assess inclusion. Translators have been contacted. Trial author have been contacted

NCT01303055

Methods	**Type of trial:** efficacy trial
	Allocation: randomised
	Intervention model: parallel assignment
	Masking: none (open-label)
	Primary purpose: treatment
Participants	**Condition**: T2DM
	Enrollment: estimated 80 participants
	Inclusion criteria: T2DM, HbA1c level < 7.9%, no previous oral hypoglycaemic agents or insulin treatments for the past three months
	Exclusion criteria: 75 g OGTT 30-minutes insulin secretion > 100 μU/mL, renal failure with serum creatinine level ≧ 1.2, hepatocirrhosis, proliferative diabetic retinopathy or worse, acute infectious disease, treated with steroids, cancer, pregnant, malfunction of the heart (NYHA classification III-IV), inappropriate participants decided by study physicians
Interventions	**Intervention(s)**: metformin (2250 mg/day)
	Comparator(s): alogliptin (75 mg/day)

NCT01303055 *(Continued)*

Outcomes	**Primary outcome(s)**: beta cell function evaluated from 75 g OGTT **Secondary outcome(s)**: 1,5-AG level **Other outcome(s)**: —
Study details	**Trial identifier**: NCT01303055
Publication details	**Language of publication / protocol**: English **Funding**: non-commercial (university) **Publication status**: unpublished
Stated aim of study	—
Notes	Only the protocol is available. Trial authors have been contacted

NCT01935804

Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: quadruple blinded (participant, care provider, investigator, outcomes assessor) **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 440 participants **Inclusion criteria**: BMD T-score greater than -2.5 at the total hip, femoral neck, and lumbar spine, no prior antidiabetic therapy, drug-naïve with glycosylated haemoglobin A1c (HbA1c) ≥ 7.0 to ≤ 10.0% (53.2 mmol/mol to 88.2 mmol/mol), BMI ≤ 40 kg/m^2, stable body weight for at least 4 months **Exclusion criteria**: Type 1 diabetes mellitus (presence of GAD auto antibodies), history of diabetes or uncontrolled hypertension, treatment with antidiabetic agents including TZDs, chronic diseases known to affect bone, previous treatment with estrogens and other medications known to affect bone, creatinine clearance < 60 mL/min
Interventions	**Intervention(s)**: metformin (850 mg/day) **Comparator(s)**: pioglitazone (30 mg/day)
Outcomes	**Primary outcome(s)**: change in mean percentage change in BMD at various sites by Dual energy X-ray absorptiometry from baseline and at 6, 12 months **Secondary outcome(s)**: bone turnover markers and other biomarkers **Other outcome(s)**: exploratory and safety outcomes, lipid profile, liver and renal function tests, glycaemic control
Study details	**Trial identifier**: NCT01935804
Publication details	**Language of publication / protocol**: English

NCT01935804 *(Continued)*

	Funding: non-commercial (university) **Publication status**: unpublished
Stated aim of study	—
Notes	Only the protocol is available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Trial authors have been contacted

Wang 2005

Methods	**Type of trial:** — **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: —
Participants	**Condition**: T2DM **Enrollment**: — **Inclusion criteria**: — **Exclusion criteria**: —
Interventions	**Intervention(s)**: metformin **Comparator(s)**: acarbose
Outcomes	**Primary outcome(s)**: — **Secondary outcome(s)**: — **Other outcome(s)**: —
Study details	**Trial identifier**: —
Publication details	**Language of publication**: — **Funding**: — **Publication status**: —
Stated aim of study	—
Notes	Only the reference was available. Marked as a study awaiting classification due to a lack of data to assess inclusion. Insufficient information to contact trial authors

Wu 2014

Methods	**Type of trial:** efficacy trial **Allocation**: randomised

Wu 2014 *(Continued)*

	Intervention model: parallel assignment **Masking**: no blinding **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: 93 participants **Inclusion criteria**: T2DM, FPG levels > 7.8 mmol/L and/or 2-h PPG > 10.0 mmol/L. **Exclusion criteria**: T1DM, hypertension, hyperlipidaemia, kidney disease, infection, heart failure, thyroid dysfunction, diabetic ketoacidosis, smoking
Interventions	**Intervention(s)**: metformin (1500 mg/day) **Comparator(s)**: pioglitazone (15 mg/day)
Outcomes	**Primary outcome(s)**: — **Secondary outcome(s)**: — **Other outcome(s)**: glucose, insulin, islet function, vascular endothelial function, plasma endothelin (ET-1), serum nitric oxide (NO), adverse reactions and liver and kidney function
Study details	**Trial identifier**: —
Publication details	**Language of publication**: English **Funding**: — **Publication status**: full article / peer-reviewed journal
Stated aim of study	**Quote from publication:** "... investigating the effects of metformin on vascular endothelial function in patients with type 2 DM (T2DM)"
Notes	Marked as a study awaiting classification due to it being unclear whether participants continued existing glucose-lowering drugs during intervention. Trial authors have been contacted.

Zhang 2009

Methods	**Type of trial:** safety trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: —
Participants	**Condition**: T2DM **Enrollment**: 140 participants **Inclusion criteria**: — **Exclusion criteria**: —
Interventions	**Intervention(s)**: metformin

Zhang 2009 *(Continued)*

	Comparator(s): no intervention
Outcomes	**Primary outcome(s)**: common carotid intima-media thickness **Secondary outcome(s)**: — **Other outcome(s)**: —
Study details	**Trial identifier**: —
Publication details	**Language of publication**: Chinese / English (abstract) **Funding**: — **Publication status**: full article / peer-reviewed journal
Stated aim of study	**Quote from publication:** "To investigate the preventive action of metformin for atherosclerosis (AS) in patients with type 2 diabetes mellitus (T2DM)"
Notes	Marked as a study awaiting classification due to publication being in Chinese and a lack of data to assess inclusion. Translators have been contacted. Trial authors have been contacted.

—: denotes not reported
2hC-P: 2-hour C-peptide; **2h-PPG**: 2-hour post prandial glucose; **ALT**: alanine aminotransferase; **AMI**: acute myocardial infarction; **anti-GAD**: anti glutamate decarboxylase; **AST**: aspartate aminotransferase; **BMD**: bone mineral density; **BMI**: body mass index; **CAD**: coronary artery disease; **CGM**: continuous glucose monitoring; **CNS**: central nervous system; **CRP: C-reactive protein; CT**: computer tomography; **DBP**: diastolic blood pressure; **DKA**: diabetic ketoacidosis; **DPP-IV**: dipeptidyl peptidase-4 inhibitor; **DSM-IV**: Diagnostic and Statistical Manual of Mental Disorders IV; **ET-1**: endothelin 1; **FBD**: functional bowel disorder; **FC-P**: fasting C-peptide; **FPG**: fasting plasma glucose; **GLP-1**: glucagon-like peptide-1 receptor analogue; **GLP-1R**: glucagon-like peptide-1 receptor analogue; **GP**: general practitioner; **HbA1c**: glycosylated haemoglobin A1c; **HDL:** high-density lipoprotein; **HOMA-R / HOMA-IR**: homeostasis model assessment of insulin resistance; **HOMA-β**: homeostasis model assessment of beta cell function; **IBD**: inflammatory bowel disease; **LDL:** low-density lipoprotein; **LVEF**: left ventricle ejection fraction; **MAGE**: mean amplitude of glycaemic excursions; **MMSE**: Mini-Mental State Examination; **MRI**: magnetic resonance imaging; **NO**: nitric oxide; **NYHA**: New York Heart Association; **OGTT**: oral glucose tolerance test; **PCOS**: polycystic ovary syndrome; **PLT**: platelets; **PPARγ**: peroxisome proliferator-activated receptor gamma; post-prandial glucose;**SBP**: systolic blood pressure; **SMBG**: self-monitoring of blood glucose; **T1DM**: type 1 diabetes mellitus; **T2DM**: type 2 diabetes mellitus; **TG**: triglycerides;**TIA**: transient ischaemic attack; **TZD**; thiazolidinediones; **UNL**: upper normal limit; **WHO**: World Health Organization.

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

NCT01001962

Study name	PREHYPD
Methods	**Type of trial:** safety trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: triple (participant, investigator, outcomes assessor) **Primary purpose**: prevention
Participants	**Condition**: T2DM with prehypertension **Enrollment**: estimated 1054 **Inclusion criteria:** age between 45 - 65 years, informed consent, newly diagnosed T2DM, not receiving antihypertensive or diabetes treatment, blood pressure between 130 mmHg to 140 mmHg for systolic blood pressure (prehypertensives), type 2 diabetes, HbA1c between 7.0 mmol/L to 8.0 mmol/L

NCT01001962 *(Continued)*

	Exclusion criteria: known over sensitiveness, chronic renal disease (glomerular filtration rate < 60 mL/min) or end-stage renal disease, heart or respiratory failure, recent myocardial infarction, shock pregnancy or lactation.
Interventions	**Intervention(s)**: metformin (1700 mg/day to 2000 mg/day) **Comparator(s)**: empagliflozin (10 mg/day to 25 mg/day)
Outcomes	**Primary outcome(s)**: new onset of hypertension **Secondary outcome(s)**: 24-hour blood pressure levels, total cardiovascular risk, morbidity cardiovascular, arterial stiffness, central aortic blood pressure, mortality cardiovascular (after 36 months) **Other outcome(s)**: —
Starting date	**Trial start date**: January 2016 **Trial completion date**: January 2020
Contact information	**Responsible party/principal investigator**: Vasilios Kotsis, Prof. Med, Aristotle University Of Thessaloniki
Study identifier	**Trial identifier**: NCT01001962
Official title	Double blind comparison study of JARDIANCE® (Empagliflozin) in prehypertensives Type II Diabetics with metformin
Stated purpose of study	**Quote:** "Primary prevention of new onset of hypertension"
Notes	

NCT01779362

Study name	RISE Adult
Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: quadruple (participant, care provider, investigator, outcomes assessor) **Primary purpose**: treatment
Participants	**Condition**[1]: T2DM **Enrollment**: 267 participants **Inclusion criteria**: fasting plasma glucose 95 mg/dL to 125 mg/dL plus 2-hour glucose ≥ 140 mg/dL on 75 g OGTT plus HbA1c ≤ 7.0%, there is no upper limit for the 2-hour glucose on OGTT, age 20 to 65 years, body mass index (BMI) ≥ 25 kg/m2 but ≤ 50 kg/m2, self-reported diabetes < 1 year in duration, drug-naive (no prior to oral glucose lowering agent(s), insulin or other injectable glucose lowering agents) **Exclusion criteria**: underlying disease likely to limit life span and/or increase risk of intervention or an underlying condition that is likely to limit ability to participate in outcomes assessment, an

NCT01779362 *(Continued)*

	underlying disease that affects glucose metabolism other than type 2 diabetes, taking medications that affect glucose metabolism, or has an underlying condition that is likely to require such medications, active infections, renal disease (serum creatinine > 1.4 mg/dL for men; > 1.3 mg/dL for women) or serum potassium abnormality (< 3.4 or > 5.5 mmol/L), anaemia (haemoglobin < 11 g/dL in women, < 12 g/dL in men) or known coagulopathy, cardiovascular disease, including uncontrolled hypertension, participants must be able to safely tolerate administration of intravenous fluids required during clamp studies, history of conditions that may be precipitated or exacerbated by a study drug:pancreatitis, serum alanine transaminase (ALT) more than 3 times the upper limit of normal, excessive alcohol intake, suboptimally treated thyroid disease, medullary carcinoma of the thyroid or MEN-2 (in participant or a family history), hypertriglyceridaemia (> 400 mg/dL despite treatment). Conditions or behaviours likely to affect the conduct of the RISE Study: unable or unwilling to give informed consent, unable to adequately communicate with clinic staff, another household member is a participant or staff member in RISE, current, recent or anticipated participation in another intervention research project that would interfere with any of the interventions/outcomes in RISE, weight loss of > 5% in past three months for any reason other than postpartum weight loss. Participants taking weight-loss drugs or using preparations taken for intended weight loss are excluded. Likely to move away from participating clinics in next two years, women of childbearing potential who are unwilling to use adequate contraception, current (or anticipated) pregnancy and lactation, major psychiatric disorder that, in the opinion of clinic staff, would impede the conduct of RISE, additional conditions may serve as criteria for exclusion at the discretion of the local site.
Interventions	**Intervention(s)**: metformin (up to 2000 mg/day) **Comparator(s)[2]**: no intervention (placebo)
Outcomes	**Primary outcome(s)**: ß-cell function measured by hyperglycaemic clamp techniques **Secondary outcome(s)**: hyperglycaemic clamp and oral glucose tolerance test (OGTT) measures of ß-cell function and glucose tolerance **Other outcome(s)**: hyperglycaemic clamp and OGTT measures of ß-cell function and glucose tolerance
Starting date	**Trial start date:** April 2013 **Trial completion date:** August 2019
Contact information	**Responsible party/principal investigator**: RISE Study Group
Study identifier	**Trial identifier**: NCT01779362
Official title	Restoring Insulin Secretion adult medication study
Stated purpose of study	**Quote:** "The primary clinical question RISE will address is: Are improvements in ß-cell function following 12 months of active treatment maintained for 3 months following the withdrawal of therapy? Secondary outcomes will assess durability of glucose tolerance following withdrawal of therapy, and whether biomarkers obtained in the fasting state predict parameters of ß-cell function, insulin sensitivity and glucose tolerance and the response to an intervention."
Notes	[1]Some participants only had prediabetes which is not a condition of interest to this review. It is assumed that the results published will contain data for participants exclusively with T2DM. [2]There were other comparators that were not of interest to this review.

NCT02853630

Study name	—
Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: none (open-label) **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: 203 participants **Inclusion criteria**: newly diagnosed type 2 diabetes mellitus patients not receiving any medication for diabetes, HbA1c ranging from 7.0% to ≤ 8.5%, Body Mass Index (BMI) ≥ 19.0 to ≤ 25.0 kg/m2, males and females of age between 20 to 60 years shall be selected, adult participants willing to give informed consent,participant must be available for and willing to attend all evaluation visits, willingness to follow the protocol requirements as evidenced by written informed consent, participant must have access to telephone for calling into the clinical centre as part of test product compliance **Exclusion criteria**: type 1 diabetes, BMI ≤ 18.99 kg/m2 or > 25 kg/m2, presence of severe vascular complications, indications for use of insulin, elevated serum levels of lipase and amylase (> 1.5 upper limit of normal (ULN)), gamma-glutamyltransferase > 2 times ULN at Visit 1, confirmed by repeated measure within 3 working days, urine albumin: creatinine ratio (UACR) > 1800 mg/g (> 203.4 mg/mmol), participants below the age of 20 years and above the age of 60 years, history of any drug abuse in the past 12 months, history of hypersensitivity to study drugs and related drugs or excipients in the formulation, history of allergy to vegetables and or food substances and or any other manifestations suggestive of hypersensitivity reactions, participant who is not willing to participate in the study, clinically significant abnormal laboratory results at screening, participant is being treated for severe active infection of any type, a female participant who is breast-feeding, pregnant, or intends to become pregnant during the study, participant with clinically relevant uncontrolled medical condition (e.g. haematological, renal, hepatic, neurology, cardiac or respiratory), participant has evidence of active malignancy, or prior history of active malignancy that has not been in remission for at least 5 years, participating in a clinical research trial within 30 days prior to screening, donated blood 3 months prior to first study visit and during the study period, individuals who are cognitively impaired and or who are unable to give informed consent, known HIV or Hepatitis B- or C-positive, any other health or mental condition that in the Investigator's opinion may adversely affect the participants ability to complete the study or its measures or that may pose significant risk to the participant
Interventions	**Intervention(s)**: metformin (1000 mg/day to 2500 mg/day) **Comparator(s)**: vildagliptin (100 mg/day)
Outcomes	**Primary outcome(s)**: changes in Insulin secretion rate **Secondary outcome(s)**: changes in HbA1c reduction, changes in C peptide response, changes in Insulin to glucose ratio, changes in Fasting plasma glucose, changes in 2-hour postprandial plasma glucose, changes in Insulin sensitivity, changes in Oral disposition index, percentage of participants reaching HbA1c ≤ 6.5%, percentage of participants reaching HbA1c ≤ 7.0%, number of participants treated related to adverse event **Other outcome(s)**: —
Starting date	**Trial start date:** December 2013 **Trial completion date:** December 2018

NCT02853630 *(Continued)*

Contact information	**Responsible party/principal investigator**: India Diabetes Research Foundation & Dr. A. Ramachandran's Diabetes Hospitals
Study identifier	**Trial identifier**: NCT02853630; CTRI/2014/01/004301
Official title	A multicentric, randomized, open label study on comparison of pancreatic beta cell recovery and preservation in Type 2 Diabetic patients treated with DPP-4 inhibitor (Vildagliptin) and metformin
Stated purpose of study	—
Notes	

NCT03982381

Study name	SMARTEST
Methods	**Type of trial:** efficacy trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: single (outcomes analysis team) **Primary purpose**: treatment
Participants	**Condition**: T2DM **Enrollment**: estimated 4300 **Inclusion criteria:** men and women ≥18 years old, T2DM (according to World Health Organization (WHO) criteria) of less than 4 years duration, BMI 18.5 to 45 kg/m2, drug-naive or oral monotherapy with glucose-lowering drug, accepting NDR participation and other register data collection. **Exclusion criteria**: known or suspected other form of diabetes than type 2, ongoing or more than > 4 weeks in total of any previous treatment with: insulin, GLP-1 receptor agonists, SGLT2 inhibitors or combination of any diabetes medications, medical need to start or intensify any specific glucose-lowering drug treatment, e.g. insulin due to marked hyperglycaemia, HbA1c >70 mmol/mol for patients on monotherapy, > 80 in drug-naive, contraindication to either metformin or dapagliflozin, or any unacceptable risk with either treatment as assessed by the investigator, history or signs of established cardiovascular disease: diagnosis of myocardial infarction, angina pectoris, heart failure, stroke, lower extremity arterial disease, any limb amputation (except due to trauma or malignancy), any serious illness or other condition with short life expectancy (< 4 years), renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m2), any condition, as judged by the investigator, that suggests that the patient will be non-compliant or otherwise unsuitable to study medication or study participation, pregnancy or breastfeeding, women of childbearing potential (including perimenopausal women who have had a menstrual period within 1 year) without adequate anti-conception during any part of the study period, involvement in the planning and/or conduct of the study, ongoing participation in another clinical trial.
Interventions	**Intervention(s)**: metformin (1000 mg/day to 3000 mg/day) **Comparator(s)**: dapagliflozin (10 mg/day)
Outcomes	**Primary outcome(s)**: time to first occurrence of a confirmed composite endpoint of death, myocardial infarction, stroke, heart failure, diabetic nephropathy, retinopathy or foot ulcer **Secondary outcome(s)**: ordinal analysis of components of primary endpoint, time to first occurrence of a confirmed composite endpoint of death, myocardial infarction, stroke, heart failure,

NCT03982381 *(Continued)*	diabetic nephropathy, retinopathy or foot ulcer (ICD10 diagnosis codes) or initiation of insulin treatment, time to first occurrence of a confirmed composite endpoint of non-fatal myocardial infarction, stroke, heart failure, unstable angina or cardiovascular death, time to first occurrence of a confirmed composite endpoint of heart failure or cardiovascular death, death, microvascular events, first of; occurrence or progression of retinopathy, nephropathy, diabetic foot lesions, need for insulin treatment, treatment failure, defined as add-on or switch to another glucose-lowering drug, change in glycemic control, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, albuminuria, blood pressure, body weight and BMI, health care costs, health-related quality of life, health-related quality of life with respect to diabetes treatment satisfaction **Other outcome(s)**: —
Starting date	**Trial start date**: September 2019 **Trial completion date**: September 2024
Contact information	**Responsible party/principal investigator**: Jan Eriksson, MD, Uppsala University Hospital
Study identifier	**Trial identifier**: NCT03982381
Official title	A multicenter, register-based, randomized, controlled trial comparing dapagliflozin with metformin treatment in early stage Type 2 diabetes patients by assessing mortality and macro- and microvascular complications
Stated purpose of study	—
Notes	

—: denotes not reported
ALT: alanine aminotransferase; **BMI**: body mass index; **GLP-1**: glucagon-like peptide 1; **HbA1c**: glycated haemoglobin; **HIV**: human immunodeficiency virus; **ICD 10:** International Classification of Diseases 10th revision; **LDL:** low-density lipoprotein; **MEN-2**: multiple endocrine neoplasia type 2; **OGTT**: oral glucose tolerance test; **UACR**: urine albumin: creatinine ratio; **UNL**: upper normal limit

DATA AND ANALYSES

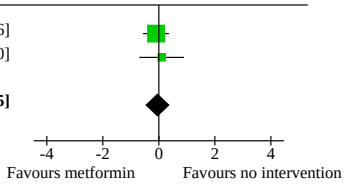
Comparison 1. Metformin vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Glycaemic control: HbA1c	2	85	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.45, 0.35]
1.2 Glycaemic control: HbA1c (subgroup duration of the intervention)	2	85	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.45, 0.35]
1.2.1 Long duration (2 years or more)	1	54	Mean Difference (IV, Random, 95% CI)	0.10 [-0.70, 0.90]
1.2.2 Short duration (less than 2 years)	1	31	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.56, 0.36]

Analysis 1.1. Comparison 1: Metformin vs no intervention, Outcome 1: Glycaemic control: HbA1c

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	No intervention Mean [%]	No intervention SD [%]	No intervention Total	Weight	Mean Difference IV, Random, 95% CI [%]
Kiyici 2009	6.4	0.6	16	6.5	0.71	15	74.7%	-0.10 [-0.56 , 0.36]
Teupe 1991	8.1	1.7	25	8	1.2	29	25.3%	0.10 [-0.70 , 0.90]
Total (95% CI)			**41**			**44**	**100.0%**	**-0.05 [-0.45 , 0.35]**

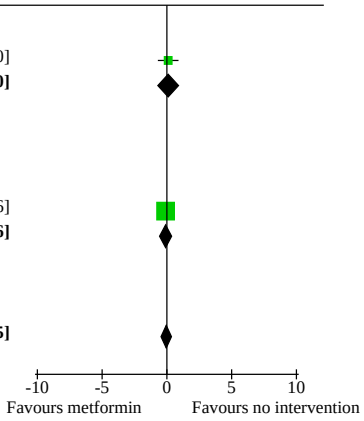
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Metformin vs no intervention, Outcome 2: Glycaemic control: HbA1c (subgroup duration of the intervention)

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Long duration (2 years or more)								
Teupe 1991	8.1	1.7	25	8	1.2	29	25.3%	0.10 [-0.70 , 0.90]
Subtotal (95% CI)			**25**			**29**	**25.3%**	**0.10 [-0.70 , 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.81)								
1.2.2 Short duration (less than 2 years)								
Kiyici 2009	6.4	0.6	16	6.5	0.71	15	74.7%	-0.10 [-0.56 , 0.36]
Subtotal (95% CI)			**16**			**15**	**74.7%**	**-0.10 [-0.56 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
Total (95% CI)			**41**			**44**	**100.0%**	**-0.05 [-0.45 , 0.35]**

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%



Comparison 2. Metformin vs sulphonylurea

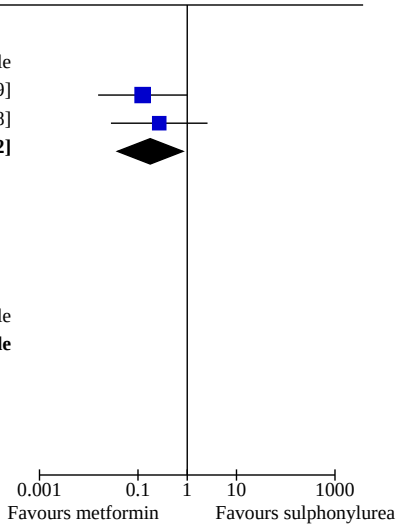
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Severe hypoglycaemia	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 Second-generation sulphonylurea	3	3552	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.82]
2.1.2 Third-generation sulphonylurea	1	148	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Severe hypoglycaemia (Subgroup: duration of intervention	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Long duration (2 years or more)	1	2895	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.99]
2.2.2 Short duration (less than 2 years)	3	805	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Anthropometric measures: BMI	4	461	Mean Difference (IV, Random, 95% CI)	0.55 [0.26, 0.85]
2.3.1 Second-generation sulphonylurea	1	38	Mean Difference (IV, Random, 95% CI)	0.28 [-2.53, 3.09]
2.3.2 Third-generation sulphonylurea	3	423	Mean Difference (IV, Random, 95% CI)	0.56 [0.26, 0.85]
2.4 Anthropometric measures: body weight	4	3185	Mean Difference (IV, Random, 95% CI)	-3.86 [-5.18, -2.53]
2.4.1 Second-generation sulphonylurea	3	2981	Mean Difference (IV, Random, 95% CI)	-4.54 [-5.20, -3.88]
2.4.2 Third-generation sulphonylurea	1	204	Mean Difference (IV, Random, 95% CI)	-2.06 [-3.49, -0.63]
2.5 Anthropometric measures: body weight (duration of intervention)	4	3185	Mean Difference (IV, Random, 95% CI)	-3.86 [-5.18, -2.53]
2.5.1 Long duration (2 years or more)	1	2895	Mean Difference (IV, Random, 95% CI)	-4.50 [-5.31, -3.69]
2.5.2 Short duration (less than 2 years)	3	290	Mean Difference (IV, Random, 95% CI)	-3.49 [-5.81, -1.17]
2.6 Glycaemic control: FPG	7	3878	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.54, 0.07]
2.6.1 Second-generation sulphonylurea	4	3455	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.01, 0.08]
2.6.2 Third-generation sulphonylurea	3	423	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.32, 0.24]
2.7 Glycaemic control: FPG (Subgroup: duration of the intervention)	7	3878	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.54, 0.07]
2.7.1 Long duration (2 years or more)	2	3369	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.83, -0.08]
2.7.2 Short duration (less than 2 years)	5	509	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.52, 0.34]
2.8 Glycaemic control: HbA1c	6	3404	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.02]
2.8.1 Second-generation sulphonylurea	3	2981	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.85, -0.09]
2.8.2 Third-generation sulphonylurea	3	423	Mean Difference (IV, Random, 95% CI)	0.05 [-0.15, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Glycaemic control: HbA1c (Subgroup: duration of the intervention)	6	3404	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.02]
2.9.1 Long duration (2 years or more)	1	2895	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.35, -0.13]
2.9.2 Short duration (less than 2 years)	5	509	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.60, 0.13]
2.10 Intervention failure	3	3590	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]
2.10.1 Second-generation sulphonylurea	2	3514	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.77]
2.10.2 Third-generation sulphonylurea	1	76	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.12, 67.83]
2.11 Intervention failure (Subgroup: duration of the intervention	3	3590	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]
2.11.1 Long duration (2 years or more)	2	3514	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.77]
2.11.2 Short duration (less than 2 years)	1	76	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.12, 67.83]

Analysis 2.1. Comparison 2: Metformin vs sulphonylurea, Outcome 1: Severe hypoglycaemia

Study or Subgroup	Metformin Events	Metformin Total	Sulphonylurea Events	Sulphonylurea Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Second-generation sulphonylurea						
Erem 2014	0	19	0	19		Not estimable
Kahn 2006	1	1454	8	1441	54.1%	0.12 [0.02 , 0.99]
UKPDS 34 1998 (1)	1	342	3	277	45.9%	0.27 [0.03 , 2.58]
Subtotal (95% CI)		**1815**		**1737**	**100.0%**	**0.18 [0.04 , 0.82]**
Total events:	2		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.22 (P = 0.03)						
2.1.2 Third-generation sulphonylurea						
Derosa 2004	0	75	0	73		Not estimable
Subtotal (95% CI)		**75**		**73**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

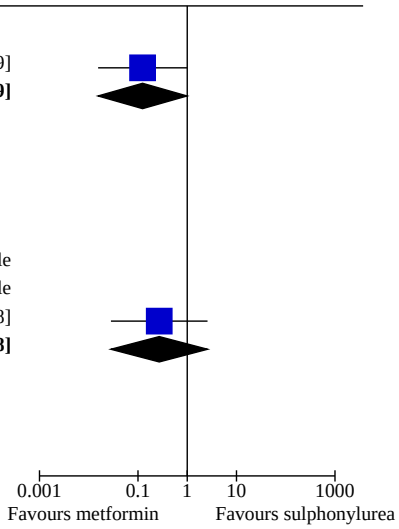


Footnotes

(1) Data after 1 year of follow-up. Not clearly described how many participants included in the analysis.

Analysis 2.2. Comparison 2: Metformin vs sulphonylurea, Outcome 2: Severe hypoglycaemia (Subgroup: duration of intervention

Study or Subgroup	Metformin Events	Metformin Total	Sulphonylurea Events	Sulphonylurea Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Long duration (2 years or more)						
Kahn 2006	1	1454	8	1441	100.0%	0.12 [0.02 , 0.99]
Subtotal (95% CI)		**1454**		**1441**	**100.0%**	**0.12 [0.02 , 0.99]**
Total events:	1		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
2.2.2 Short duration (less than 2 years)						
Derosa 2004	0	75	0	73		Not estimable
Erem 2014	0	19	0	19		Not estimable
UKPDS 34 1998 (1)	1	342	3	277	100.0%	0.27 [0.03 , 2.58]
Subtotal (95% CI)		**436**		**369**	**100.0%**	**0.27 [0.03 , 2.58]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.26)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						

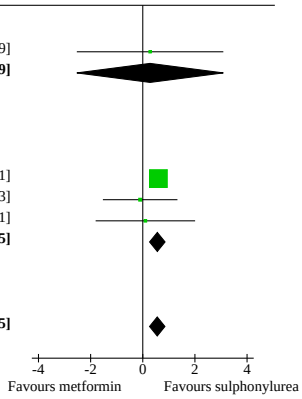


Footnotes

(1) Data after 1 year of follow-up. Not clearly described how many participants included in the analysis.

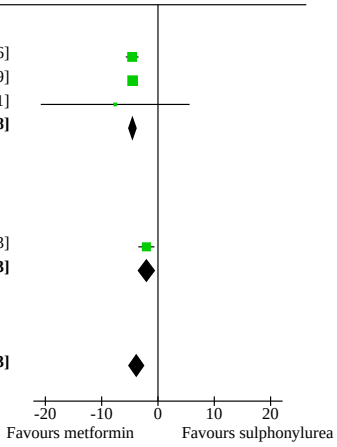
Analysis 2.3. Comparison 2: Metformin vs sulphonylurea, Outcome 3: Anthropometric measures: BMI

Study or Subgroup	Metformin Mean [kg/m2]	Metformin SD [kg/m2]	Metformin Total	Sulphonylurea Mean [kg/m2]	Sulphonylurea SD [kg/m2]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [kg/m2]
2.3.1 Second-generation sulphonylurea								
Erem 2014	31.92	4	19	31.64	4.8	19	1.1%	0.28 [-2.53 , 3.09]
Subtotal (95% CI)			**19**			**19**	**1.1%**	**0.28 [-2.53 , 3.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.85)								
2.3.2 Third-generation sulphonylurea								
Derosa 2004	27.5	0.9	75	26.9	1	73	92.3%	0.60 [0.29 , 0.91]
Rahman 2011	26	5.5	102	26.1	4.9	102	4.2%	-0.10 [-1.53 , 1.33]
Yamanouchi 2005	25.5	4.2	37	25.4	4	34	2.4%	0.10 [-1.81 , 2.01]
Subtotal (95% CI)			**214**			**209**	**98.9%**	**0.56 [0.26 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
Total (95% CI)			**233**			**228**	**100.0%**	**0.55 [0.26 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%								



Analysis 2.4. Comparison 2: Metformin vs sulphonylurea, Outcome 4: Anthropometric measures: body weight

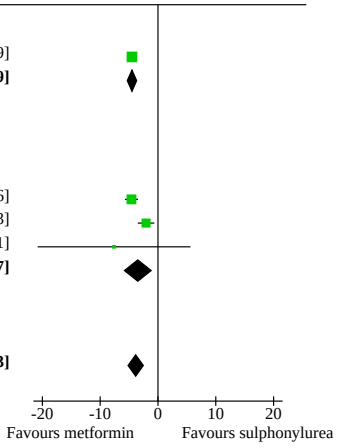
Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Sulphonylurea Mean [kg]	Sulphonylurea SD [kg]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [kg]
2.4.1 Second-generation sulphonylurea								
Campbell 1994 (1)	-1.97	1.5	24	2.62	2.4	24	32.9%	-4.59 [-5.72 , -3.46]
Kahn 2006 (1)	-2.9	10.7	1454	1.6	11.6	1441	37.3%	-4.50 [-5.31 , -3.69]
Erem 2014	83.4	13.3	19	91	26.2	19	1.0%	-7.60 [-20.81 , 5.61]
Subtotal (95% CI)			**1497**			**1484**	**71.2%**	**-4.54 [-5.20 , -3.88]**
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.89); I² = 0%								
Test for overall effect: Z = 13.48 (P < 0.00001)								
2.4.2 Third-generation sulphonylurea								
Rahman 2011	75.9	4.9	102	77.96	5.5	102	28.8%	-2.06 [-3.49 , -0.63]
Subtotal (95% CI)			**102**			**102**	**28.8%**	**-2.06 [-3.49 , -0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.82 (P = 0.005)								
Total (95% CI)			**1599**			**1586**	**100.0%**	**-3.86 [-5.18 , -2.53]**
Heterogeneity: Tau² = 1.06; Chi² = 9.74, df = 3 (P = 0.02); I² = 69%								
Test for overall effect: Z = 5.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.52, df = 1 (P = 0.002), I² = 89.5%								



Footnotes
(1) Not adjusted

Analysis 2.5. Comparison 2: Metformin vs sulphonylurea, Outcome 5: Anthropometric measures: body weight (duration of intervention)

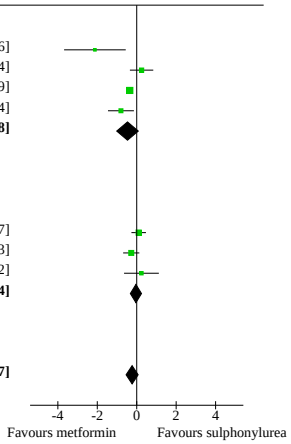
Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Sulphonylurea Mean [kg]	Sulphonylurea SD [kg]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [kg]
2.5.1 Long duration (2 years or more)								
Kahn 2006 (1)	-2.9	10.7	1454	1.6	11.6	1441	37.3%	-4.50 [-5.31 , -3.69]
Subtotal (95% CI)			**1454**			**1441**	**37.3%**	**-4.50 [-5.31 , -3.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.85 (P < 0.00001)								
2.5.2 Short duration (less than 2 years)								
Campbell 1994 (1)	-1.97	1.5	24	2.62	2.4	24	32.9%	-4.59 [-5.72 , -3.46]
Rahman 2011	75.9	4.9	102	77.96	5.5	102	28.8%	-2.06 [-3.49 , -0.63]
Erem 2014	83.4	13.3	19	91	26.2	19	1.0%	-7.60 [-20.81 , 5.61]
Subtotal (95% CI)			**145**			**145**	**62.7%**	**-3.49 [-5.81 , -1.17]**
Heterogeneity: Tau² = 2.45; Chi² = 7.74, df = 2 (P = 0.02); I² = 74%								
Test for overall effect: Z = 2.95 (P = 0.003)								
Total (95% CI)			**1599**			**1586**	**100.0%**	**-3.86 [-5.18 , -2.53]**
Heterogeneity: Tau² = 1.06; Chi² = 9.74, df = 3 (P = 0.02); I² = 69%								
Test for overall effect: Z = 5.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%								



Footnotes
(1) Not adjusted

Analysis 2.6. Comparison 2: Metformin vs sulphonylurea, Outcome 6: Glycaemic control: FPG

Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	Sulphonylurea Mean [mmol/L]	Sulphonylurea SD [mmol/L]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
2.6.1 Second-generation sulphonylurea								
Campbell 1994	7.11	1.28	24	9.23	3.69	24	3.4%	-2.12 [-3.68 , -0.56]
Erem 2014	6.2965	1.0878	19	6.0495	0.7437	19	13.4%	0.25 [-0.35 , 0.84]
Kahn 2006	-0.3	2.2	1454	0.05	2.2	1441	25.2%	-0.35 [-0.51 , -0.19]
UKPDS 34 1998 (1)	7.7	2.1	262	8.5	4.5	212	12.0%	-0.80 [-1.46 , -0.14]
Subtotal (95% CI)			**1759**			**1696**	**54.0%**	**-0.47 [-1.01 , 0.08]**
Heterogeneity: Tau² = 0.20; Chi² = 10.63, df = 3 (P = 0.01); I² = 72%								
Test for overall effect: Z = 1.68 (P = 0.09)								
2.6.2 Third-generation sulphonylurea								
Derosa 2004	6.9	0.8	75	6.8	1.4	73	19.4%	0.10 [-0.27 , 0.47]
Rahman 2011	8.103	1.4874	102	8.3805	1.50405	102	18.2%	-0.28 [-0.69 , 0.13]
Yamanouchi 2005	9.03	2.01	37	8.79	1.78	34	8.3%	0.24 [-0.64 , 1.12]
Subtotal (95% CI)			**214**			**209**	**46.0%**	**-0.04 [-0.32 , 0.24]**
Heterogeneity: Tau² = 0.01; Chi² = 2.23, df = 2 (P = 0.33); I² = 10%								
Test for overall effect: Z = 0.28 (P = 0.78)								
Total (95% CI)			**1973**			**1905**	**100.0%**	**-0.23 [-0.54 , 0.07]**
Heterogeneity: Tau² = 0.09; Chi² = 16.92, df = 6 (P = 0.010); I² = 65%								
Test for overall effect: Z = 1.50 (P = 0.13)								
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 45.9%								

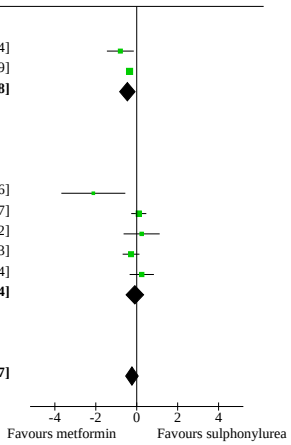


Footnotes

(1) Data after 3 years of follow-up

Analysis 2.7. Comparison 2: Metformin vs sulphonylurea, Outcome 7: Glycaemic control: FPG (Subgroup: duration of the intervention)

Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	Sulphonylurea Mean [mmol/L]	Sulphonylurea SD [mmol/L]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
2.7.1 Long duration (2 years or more)								
UKPDS 34 1998 (1)	7.7	2.1	262	8.5	4.5	212	12.0%	-0.80 [-1.46 , -0.14]
Kahn 2006	-0.3	2.2	1454	0.05	2.2	1441	25.2%	-0.35 [-0.51 , -0.19]
Subtotal (95% CI)			**1716**			**1653**	**37.3%**	**-0.46 [-0.83 , -0.08]**
Heterogeneity: Tau² = 0.04; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 2.38 (P = 0.02)								
2.7.2 Short duration (less than 2 years)								
Campbell 1994	7.11	1.28	24	9.23	3.69	24	3.4%	-2.12 [-3.68 , -0.56]
Derosa 2004	6.9	0.8	75	6.8	1.4	73	19.4%	0.10 [-0.27 , 0.47]
Yamanouchi 2005	9.03	2.01	37	8.79	1.78	34	8.3%	0.24 [-0.64 , 1.12]
Rahman 2011	8.103	1.4874	102	8.3805	1.50405	102	18.2%	-0.28 [-0.69 , 0.13]
Erem 2014	6.2965	1.0878	19	6.0495	0.7437	19	13.4%	0.25 [-0.35 , 0.84]
Subtotal (95% CI)			**257**			**252**	**62.7%**	**-0.09 [-0.52 , 0.34]**
Heterogeneity: Tau² = 0.13; Chi² = 9.93, df = 4 (P = 0.04); I² = 60%								
Test for overall effect: Z = 0.42 (P = 0.67)								
Total (95% CI)			**1973**			**1905**	**100.0%**	**-0.23 [-0.54 , 0.07]**
Heterogeneity: Tau² = 0.09; Chi² = 16.92, df = 6 (P = 0.010); I² = 65%								
Test for overall effect: Z = 1.50 (P = 0.13)								
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.0%								

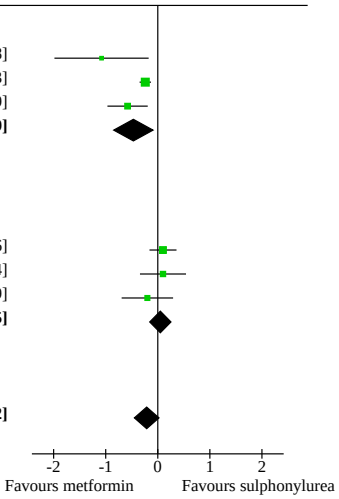


Footnotes

(1) Data after 3 years of follow-up

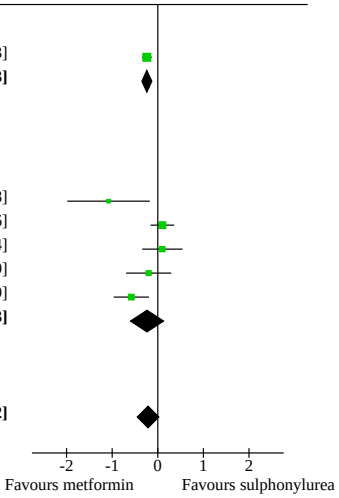
Analysis 2.8. Comparison 2: Metformin vs sulphonylurea, Outcome 8: Glycaemic control: HbA1c

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	Sulphonylurea Mean [%]	Sulphonylurea SD [%]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [%]
2.8.1 Second-generation sulphonylurea								
Campbell 1994	8.64	1.21	24	9.72	1.91	24	5.6%	-1.08 [-1.98 , -0.18]
Kahn 2006	0.06	1.5	1454	0.3	1.5	1441	28.2%	-0.24 [-0.35 , -0.13]
Erem 2014	6.4	0.7	19	6.98	0.5	19	16.6%	-0.58 [-0.97 , -0.19]
Subtotal (95% CI)			**1497**			**1484**	**50.4%**	**-0.47 [-0.85 , -0.09]**
Heterogeneity: Tau² = 0.07; Chi² = 5.82, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 2.43 (P = 0.01)								
2.8.2 Third-generation sulphonylurea								
Derosa 2004	7	0.9	75	6.9	0.7	73	22.0%	0.10 [-0.16 , 0.36]
Yamanouchi 2005	7.8	1	37	7.7	0.9	34	14.6%	0.10 [-0.34 , 0.54]
Rahman 2011	8.3	1.8	102	8.5	1.8	102	13.0%	-0.20 [-0.69 , 0.29]
Subtotal (95% CI)			**214**			**209**	**49.6%**	**0.05 [-0.15 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.56); I² = 0%								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**1711**			**1693**	**100.0%**	**-0.21 [-0.45 , 0.02]**
Heterogeneity: Tau² = 0.05; Chi² = 14.74, df = 5 (P = 0.01); I² = 66%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Test for subgroup differences: Chi² = 5.59, df = 1 (P = 0.02), I² = 82.1%								



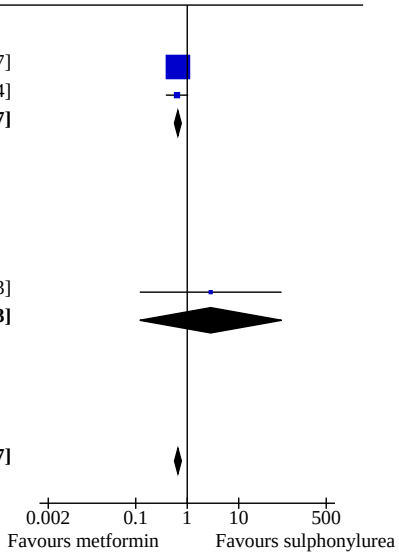
Analysis 2.9. Comparison 2: Metformin vs sulphonylurea, Outcome 9: Glycaemic control: HbA1c (Subgroup: duration of the intervention)

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	Sulphonylurea Mean [%]	Sulphonylurea SD [%]	Sulphonylurea Total	Weight	Mean Difference IV, Random, 95% CI [%]
2.9.1 Long duration (2 years or more)								
Kahn 2006	0.06	1.5	1454	0.3	1.5	1441	28.2%	-0.24 [-0.35 , -0.13]
Subtotal (95% CI)			**1454**			**1441**	**28.2%**	**-0.24 [-0.35 , -0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.30 (P < 0.0001)								
2.9.2 Short duration (less than 2 years)								
Campbell 1994	8.64	1.21	24	9.72	1.91	24	5.6%	-1.08 [-1.98 , -0.18]
Derosa 2004	7	0.9	75	6.9	0.7	73	22.0%	0.10 [-0.16 , 0.36]
Yamanouchi 2005	7.8	1	37	7.7	0.9	34	14.6%	0.10 [-0.34 , 0.54]
Rahman 2011	8.3	1.8	102	8.5	1.8	102	13.0%	-0.20 [-0.69 , 0.29]
Erem 2014	6.4	0.7	19	6.98	0.5	19	16.6%	-0.58 [-0.97 , -0.19]
Subtotal (95% CI)			**257**			**252**	**71.8%**	**-0.24 [-0.60 , 0.13]**
Heterogeneity: Tau² = 0.11; Chi² = 13.57, df = 4 (P = 0.009); I² = 71%								
Test for overall effect: Z = 1.28 (P = 0.20)								
Total (95% CI)			**1711**			**1693**	**100.0%**	**-0.21 [-0.45 , 0.02]**
Heterogeneity: Tau² = 0.05; Chi² = 14.74, df = 5 (P = 0.01); I² = 66%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								



Analysis 2.10. Comparison 2: Metformin vs sulphonylurea, Outcome 10: Intervention failure

Study or Subgroup	Metformin Events	Metformin Total	Sulphonylurea Events	Sulphonylurea Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Second-generation sulphonylurea						
Kahn 2006	207	1454	311	1441	90.5%	0.66 [0.56 , 0.77]
UKPDS 34 1998 (1)	25	342	32	277	9.3%	0.63 [0.38 , 1.04]
Subtotal (95% CI)		**1796**		**1718**	**99.8%**	**0.66 [0.56 , 0.77]**
Total events:	232		343			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
2.10.2 Third-generation sulphonylurea						
Yamanouchi 2005 (2)	1	39	0	37	0.2%	2.85 [0.12 , 67.83]
Subtotal (95% CI)		**39**		**37**	**0.2%**	**2.85 [0.12 , 67.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**1835**		**1755**	**100.0%**	**0.66 [0.57 , 0.77]**
Total events:	233		343			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 5.37 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.36), I² = 0%						



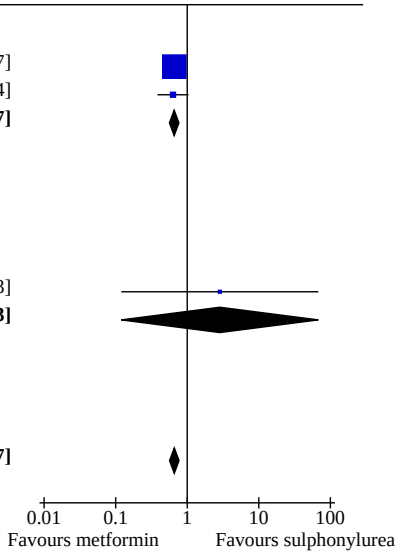
Footnotes

(1) Data after 3 years of follow-up

(2) Results including withdrawals (that were excluded from all other analyses)

Analysis 2.11. Comparison 2: Metformin vs sulphonylurea, Outcome 11: Intervention failure (Subgroup: duration of the intervention

Study or Subgroup	Metformin Events	Metformin Total	Sulphonylurea Events	Sulphonylurea Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Long duration (2 years or more)						
Kahn 2006	207	1454	311	1441	90.5%	0.66 [0.56 , 0.77]
UKPDS 34 1998 (1)	25	342	32	277	9.3%	0.63 [0.38 , 1.04]
Subtotal (95% CI)		**1796**		**1718**	**99.8%**	**0.66 [0.56 , 0.77]**
Total events:	232		343			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
2.11.2 Short duration (less than 2 years)						
Yamanouchi 2005 (2)	1	39	0	37	0.2%	2.85 [0.12 , 67.83]
Subtotal (95% CI)		**39**		**37**	**0.2%**	**2.85 [0.12 , 67.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**1835**		**1755**	**100.0%**	**0.66 [0.57 , 0.77]**
Total events:	233		343			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 5.37 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.36), I² = 0%						



Footnotes

(1) Data after 3 years of follow-up

(2) Results including withdrawals (that were excluded from all other analyses)

Comparison 3. Metformin vs thiazolidinedione

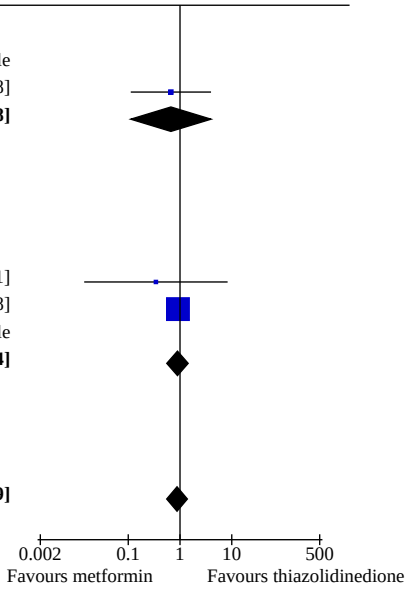
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	5	4402	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.39]
3.1.1 Pioglitazone	2	1232	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.11, 3.98]
3.1.2 Rosiglitazone	3	3170	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.44]
3.2 All-cause mortality (Subgroup: duration of the intervention)	5	4402	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.39]
3.2.1 Long duration (2 years or more)	1	2910	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.56, 1.48]
3.2.2 Short duration (less than 2 years)	4	1492	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.70]
3.3 Serious adverse events	4	3208	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.09]
3.3.1 Pioglitazone	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3.2 Rosiglitazone	3	3170	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.09]
3.4 Serious adverse event (Subgroup: duration of the intervention)s	4	3208	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.09]
3.4.1 Long duration (2 years or more)	1	2910	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.09]
3.4.2 Short duration (less than 2 years)	3	298	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.24]
3.5 Cardiovascular mortality	4	3211	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.21, 2.39]
3.5.1 Pioglitazone	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.5.2 Rosiglitazone	3	3173	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.21, 2.39]
3.6 Cardiovascular mortality Subgroup: duration of the intervention)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6.1 Long duration (2 years or more)	1	2913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.22, 2.98]
3.6.2 Short duration (less than 2 years)	3	298	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.31]
3.7 Anthropometric measures: BMI	3	145	Mean Difference (IV, Random, 95% CI)	-0.39 [-2.34, 1.56]
3.7.1 Pioglitazone	2	110	Mean Difference (IV, Random, 95% CI)	0.10 [-2.82, 3.02]
3.7.2 Rosiglitazone	1	35	Mean Difference (IV, Random, 95% CI)	-1.50 [-4.78, 1.78]
3.8 Anthropometric measures: body weight	2	2948	Mean Difference (IV, Random, 95% CI)	-1.27 [-15.21, 12.67]
3.8.1 Pioglitazone	1	38	Mean Difference (IV, Random, 95% CI)	6.60 [-2.31, 15.51]
3.8.2 Rosiglitazone	1	2910	Mean Difference (IV, Random, 95% CI)	-7.70 [-8.44, -6.96]
3.9 Glycaemic control: FPG	6	4456	Mean Difference (IV, Random, 95% CI)	0.32 [-0.21, 0.84]
3.9.1 Pioglitazone	3	1286	Mean Difference (IV, Random, 95% CI)	0.66 [0.10, 1.22]
3.9.2 Rosiglitazone	3	3170	Mean Difference (IV, Random, 95% CI)	0.12 [-0.61, 0.85]
3.10 Glycaemic control: FPG (Subgroup: duration of the intervention)	6	4456	Mean Difference (IV, Random, 95% CI)	0.32 [-0.21, 0.84]
3.10.1 Long duration (2 years or more)	1	2910	Mean Difference (IV, Random, 95% CI)	0.73 [0.57, 0.89]
3.10.2 Short duration (less than 2 years)	5	1546	Mean Difference (IV, Random, 95% CI)	0.12 [-0.32, 0.56]
3.11 Glycaemic control: FPG (Subgroup: selection bias)	6	4456	Mean Difference (IV, Random, 95% CI)	0.32 [-0.21, 0.84]
3.11.1 Low risk of selection bias	3	4311	Mean Difference (IV, Random, 95% CI)	0.28 [-0.58, 1.13]
3.11.2 Unclear or high risk of selection bias	3	145	Mean Difference (IV, Random, 95% CI)	0.35 [-0.38, 1.08]
3.12 Glycaemic control: HbA1c	6	4456	Mean Difference (IV, Random, 95% CI)	0.01 [-0.18, 0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.12.1 Pioglitazone	3	1286	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
3.12.2 Rosiglitazone	3	3170	Mean Difference (IV, Random, 95% CI)	0.08 [-0.19, 0.34]
3.13 Glycaemic control: HbA1c (Subgroup: duration of the intervention)	6	4456	Mean Difference (IV, Random, 95% CI)	0.01 [-0.18, 0.19]
3.13.1 Long duration (2 years or more)	1	2910	Mean Difference (IV, Random, 95% CI)	0.26 [0.15, 0.37]
3.13.2 Short duration (less than 2 years)	5	1546	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.01]
3.14 Glycaemic control: HbA1c (Subgroup: selection bias)	6	4456	Mean Difference (IV, Random, 95% CI)	0.01 [-0.18, 0.19]
3.14.1 Low risk of selection bias	3	4311	Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.29]
3.14.2 Unclear or high risk of selection bias	3	145	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.29, 0.19]
3.15 Intervention failure	2	2987	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.18, 1.77]
3.15.1 Pioglitazone	1	77	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.02]
3.15.2 Rosiglitazone	1	2910	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.19, 1.77]
3.16 Intervention failure (Subgroup: duration of the intervention	2	2987	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.18, 1.77]
3.16.1 Long duration (2 years or more)	1	2910	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.19, 1.77]
3.16.2 Short duration (less than 2 years)	1	77	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.02]
3.17 Intervention failure (Subgroup: selection bias)	2	2987	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.18, 1.77]
3.17.1 Low risk of selection bias	1	2910	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.19, 1.77]
3.17.2 Unclear or high risk of selection bias	1	77	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.02]

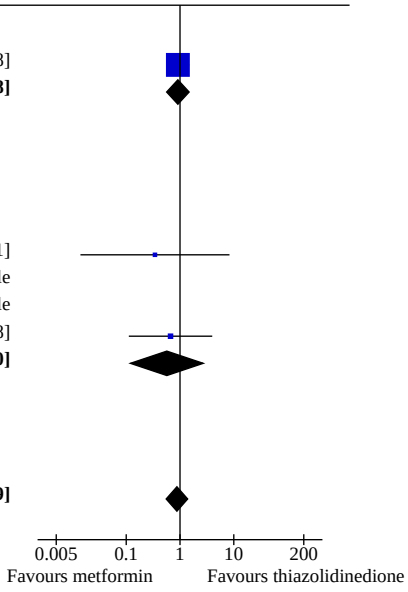
Analysis 3.1. Comparison 3: Metformin vs thiazolidinedione, Outcome 1: All-cause mortality

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Pioglitazone						
Erem 2014	0	19	0	19		Not estimable
Schernthaner 2004	2	597	3	597	6.6%	0.67 [0.11 , 3.98]
Subtotal (95% CI)		**616**		**616**	**6.6%**	**0.67 [0.11 , 3.98]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						
3.1.2 Rosiglitazone						
Bilezikian 2013	0	111	1	114	2.1%	0.34 [0.01 , 8.31]
Kahn 2006	31	1454	34	1456	91.3%	0.91 [0.56 , 1.48]
Kiyici 2009	0	16	0	19		Not estimable
Subtotal (95% CI)		**1581**		**1589**	**93.4%**	**0.89 [0.56 , 1.44]**
Total events:	31		35			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**2197**		**2205**	**100.0%**	**0.88 [0.55 , 1.39]**
Total events:	33		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.76), I² = 0%						



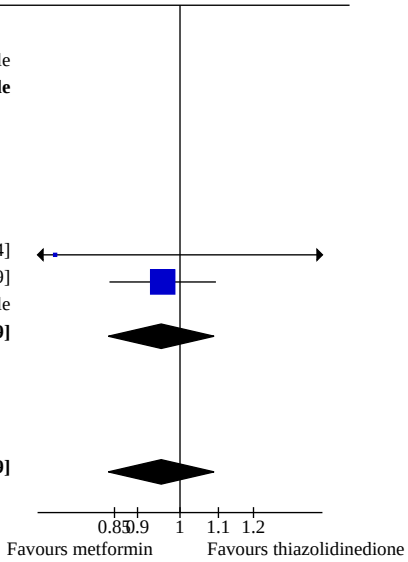
Analysis 3.2. Comparison 3: Metformin vs thiazolidinedione, Outcome 2: All-cause mortality (Subgroup: duration of the intervention)

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Long duration (2 years or more)						
Kahn 2006	31	1454	34	1456	91.3%	0.91 [0.56 , 1.48]
Subtotal (95% CI)		**1454**		**1456**	**91.3%**	**0.91 [0.56 , 1.48]**
Total events:	31		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
3.2.2 Short duration (less than 2 years)						
Bilezikian 2013	0	111	1	114	2.1%	0.34 [0.01 , 8.31]
Erem 2014	0	19	0	19		Not estimable
Kiyici 2009	0	16	0	19		Not estimable
Schernthaner 2004	2	597	3	597	6.6%	0.67 [0.11 , 3.98]
Subtotal (95% CI)		**743**		**749**	**8.7%**	**0.57 [0.12 , 2.70]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**2197**		**2205**	**100.0%**	**0.88 [0.55 , 1.39]**
Total events:	33		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%						



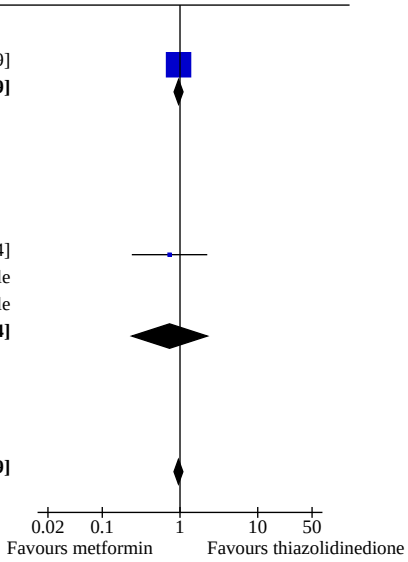
Analysis 3.3. Comparison 3: Metformin vs thiazolidinedione, Outcome 3: Serious adverse events

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Pioglitazone						
Erem 2014	0	19	0	19		Not estimable
Subtotal (95% CI)		**19**		**19**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.2 Rosiglitazone						
Bilezikian 2013	5	111	7	114	1.4%	0.73 [0.24 , 2.24]
Kahn 2006	331	1454	346	1456	98.6%	0.96 [0.84 , 1.09]
Kiyici 2009	0	16	0	19		Not estimable
Subtotal (95% CI)		**1581**		**1589**	**100.0%**	**0.95 [0.84 , 1.09]**
Total events:	336		353			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Total (95% CI)		**1600**		**1608**	**100.0%**	**0.95 [0.84 , 1.09]**
Total events:	336		353			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Not applicable						



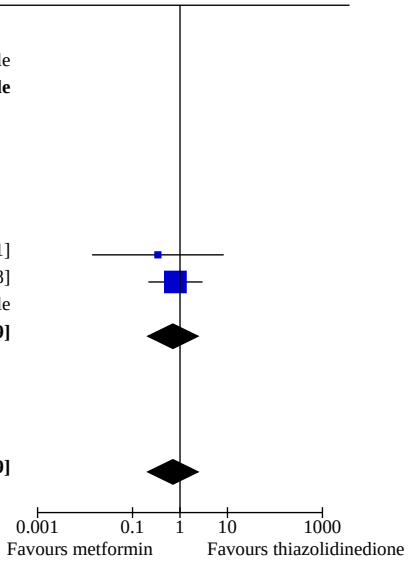
Analysis 3.4. Comparison 3: Metformin vs thiazolidinedione, Outcome 4: Serious adverse event (Subgroup: duration of the intervention)s

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Long duration (2 years or more)						
Kahn 2006	331	1454	346	1456	98.6%	0.96 [0.84 , 1.09]
Subtotal (95% CI)		**1454**		**1456**	**98.6%**	**0.96 [0.84 , 1.09]**
Total events:	331		346			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
3.4.2 Short duration (less than 2 years)						
Bilezikian 2013	5	111	7	114	1.4%	0.73 [0.24 , 2.24]
Erem 2014	0	19	0	19		Not estimable
Kiyici 2009	0	16	0	19		Not estimable
Subtotal (95% CI)		**146**		**152**	**1.4%**	**0.73 [0.24 , 2.24]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**1600**		**1608**	**100.0%**	**0.95 [0.84 , 1.09]**
Total events:	336		353			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						



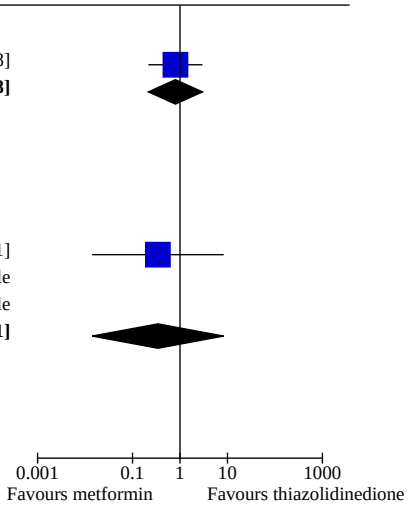
Analysis 3.5. Comparison 3: Metformin vs thiazolidinedione, Outcome 5: Cardiovascular mortality

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Pioglitazone						
Erem 2014	0	19	0	19		Not estimable
Subtotal (95% CI)		**19**		**19**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.2 Rosiglitazone						
Bilezikian 2013	0	111	1	114	14.5%	0.34 [0.01 , 8.31]
Kahn 2006	4	1455	5	1458	85.5%	0.80 [0.22 , 2.98]
Kiyici 2009	0	16	0	19		Not estimable
Subtotal (95% CI)		**1582**		**1591**	**100.0%**	**0.71 [0.21 , 2.39]**
Total events:	4		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**1601**		**1610**	**100.0%**	**0.71 [0.21 , 2.39]**
Total events:	4		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 0.56 (P = 0.58)						
Test for subgroup differences: Not applicable						



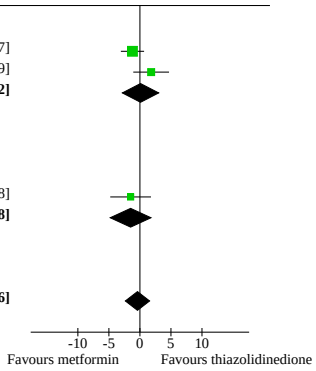
Analysis 3.6. Comparison 3: Metformin vs thiazolidinedione, Outcome 6: Cardiovascular mortality Subgroup: duration of the intervention)

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Long duration (2 years or more)						
Kahn 2006	4	1455	5	1458	100.0%	0.80 [0.22 , 2.98]
Subtotal (95% CI)		**1455**		**1458**	**100.0%**	**0.80 [0.22 , 2.98]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
3.6.2 Short duration (less than 2 years)						
Bilezikian 2013	0	111	1	114	100.0%	0.34 [0.01 , 8.31]
Erem 2014	0	19	0	19		Not estimable
Kiyici 2009	0	16	0	19		Not estimable
Subtotal (95% CI)		**146**		**152**	**100.0%**	**0.34 [0.01 , 8.31]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: $Chi^2 = 0.23$, df = 1 (P = 0.63), $I^2 = 0\%$						



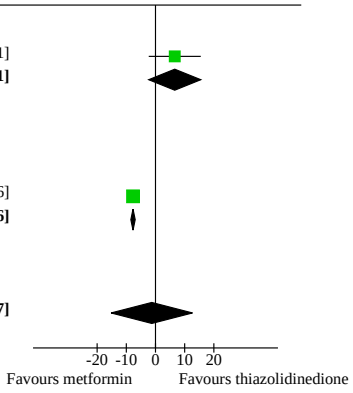
Analysis 3.7. Comparison 3: Metformin vs thiazolidinedione, Outcome 7: Anthropometric measures: BMI

Study or Subgroup	Metformin Mean [kg/m2]	Metformin SD [kg/m2]	Metformin Total	Thiazolidinedione Mean [kg/m2]	Thiazolidinedione SD [kg/m2]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [kg/m2]
3.7.1 Pioglitazone								
Yamanouchi 2005	25.5	4.2	37	26.7	3.9	35	46.2%	-1.20 [-3.07 , 0.67]
Erem 2014	31.92	4	19	30.11	5	19	29.2%	1.81 [-1.07 , 4.69]
Subtotal (95% CI)			**56**			**54**	**75.4%**	**0.10 [-2.82 , 3.02]**
Heterogeneity: Tau² = 3.00; Chi² = 2.95, df = 1 (P = 0.09); I² = 66%								
Test for overall effect: Z = 0.07 (P = 0.95)								
3.7.2 Rosiglitazone								
Kiyici 2009	30.7	3.7	16	32.2	6.08	19	24.6%	-1.50 [-4.78 , 1.78]
Subtotal (95% CI)			**16**			**19**	**24.6%**	**-1.50 [-4.78 , 1.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.90 (P = 0.37)								
Total (95% CI)			**72**			**73**	**100.0%**	**-0.39 [-2.34 , 1.56]**
Heterogeneity: Tau² = 1.23; Chi² = 3.37, df = 2 (P = 0.19); I² = 41%								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.48), I² = 0%								



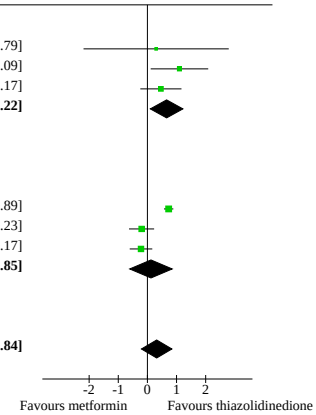
Analysis 3.8. Comparison 3: Metformin vs thiazolidinedione, Outcome 8: Anthropometric measures: body weight

Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Thiazolidinedione Mean [kg]	Thiazolidinedione SD [kg]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [kg]
3.8.1 Pioglitazone								
Erem 2014	83.4	13.3	19	76.8	14.7	19	45.0%	6.60 [-2.31 , 15.51]
Subtotal (95% CI)			**19**			**19**	**45.0%**	**6.60 [-2.31 , 15.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.45 (P = 0.15)								
3.8.2 Rosiglitazone								
Kahn 2006	-2.9	10.7	1454	4.8	9.7	1456	55.0%	-7.70 [-8.44 , -6.96]
Subtotal (95% CI)			**1454**			**1456**	**55.0%**	**-7.70 [-8.44 , -6.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 20.34 (P < 0.00001)								
Total (95% CI)			**1473**			**1475**	**100.0%**	**-1.27 [-15.21 , 12.67]**
Heterogeneity: Tau² = 91.83; Chi² = 9.82, df = 1 (P = 0.002); I² = 90%								
Test for overall effect: Z = 0.18 (P = 0.86)								
Test for subgroup differences: Chi² = 9.82, df = 1 (P = 0.002), I² = 89.8%								



Analysis 3.9. Comparison 3: Metformin vs thiazolidinedione, Outcome 9: Glycaemic control: FPG

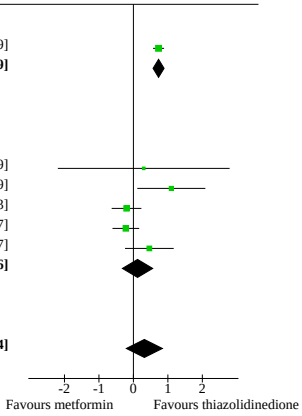
Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	Thiazolidinedione Mean [mmol/L]	Thiazolidinedione SD [mmol/L]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
3.9.1 Pioglitazone								
Schernthaner 2004 (1)	-2.1978	21.802	588	-2.4975	21.802	588	3.7%	0.30 [-2.19 , 2.79]
Yamanouchi 2005	9.03	2.01	37	7.93	2.25	35	13.1%	1.10 [0.11 , 2.09]
Erem 2014	6.2965	1.0878	19	5.83361	1.1322	19	16.9%	0.46 [-0.24 , 1.17]
Subtotal (95% CI)			**644**			**642**	**33.7%**	**0.66 [0.10 , 1.22]**
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.56); I² = 0%								
Test for overall effect: Z = 2.31 (P = 0.02)								
3.9.2 Rosiglitazone								
Kahn 2006	-0.3	2.2	1454	-1.03	2.2	1456	23.9%	0.73 [0.57 , 0.89]
Kiyici 2009	6.4	0.6	16	6.6	0.7	19	20.9%	-0.20 [-0.63 , 0.23]
Bilezikian 2013	6.19	1.31	111	6.41	1.64	114	21.5%	-0.22 [-0.61 , 0.17]
Subtotal (95% CI)			**1581**			**1589**	**66.3%**	**0.12 [-0.61 , 0.85]**
Heterogeneity: Tau² = 0.39; Chi² = 31.36, df = 2 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 0.33 (P = 0.74)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.32 [-0.21 , 0.84]**
Heterogeneity: Tau² = 0.29; Chi² = 32.76, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Chi² = 1.31, df = 1 (P = 0.25), I² = 23.6%								



Footnotes
(1) Adjusted for baseline FPG value

Analysis 3.10. Comparison 3: Metformin vs thiazolidinedione, Outcome 10: Glycaemic control: FPG (Subgroup: duration of the intervention)

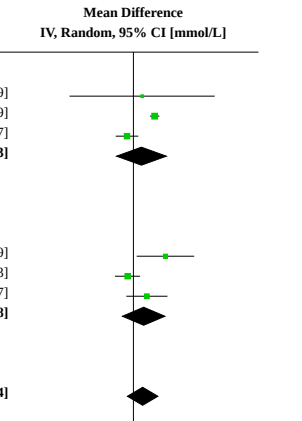
Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	Thiazolidinedione Mean [mmol/L]	Thiazolidinedione SD [mmol/L]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
3.10.1 Long duration (2 years or more)								
Kahn 2006	-0.3	2.2	1454	-1.03	2.2	1456	23.9%	0.73 [0.57 , 0.89]
Subtotal (95% CI)			**1454**			**1456**	**23.9%**	**0.73 [0.57 , 0.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.95 (P < 0.00001)								
3.10.2 Short duration (less than 2 years)								
Schernthaner 2004 (1)	-2.1978	21.802	588	-2.4975	21.802	588	3.7%	0.30 [-2.19 , 2.79]
Yamanouchi 2005	9.03	2.01	37	7.93	2.25	35	13.1%	1.10 [0.11 , 2.09]
Kiyici 2009	6.4	0.6	16	6.6	0.7	19	20.9%	-0.20 [-0.63 , 0.23]
Bilezikian 2013	6.19	1.31	111	6.41	1.64	114	21.5%	-0.22 [-0.61 , 0.17]
Erem 2014	6.2965	1.0878	19	5.83361	1.1322	19	16.9%	0.46 [-0.24 , 1.17]
Subtotal (95% CI)			**771**			**775**	**76.1%**	**0.12 [-0.32 , 0.56]**
Heterogeneity: Tau² = 0.12; Chi² = 8.49, df = 4 (P = 0.08); I² = 53%								
Test for overall effect: Z = 0.54 (P = 0.59)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.32 [-0.21 , 0.84]**
Heterogeneity: Tau² = 0.29; Chi² = 32.76, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Chi² = 6.53, df = 1 (P = 0.01), I² = 84.7%								



Footnotes
(1) Adjusted for baseline FPG value

Analysis 3.11. Comparison 3: Metformin vs thiazolidinedione, Outcome 11: Glycaemic control: FPG (Subgroup: selection bias)

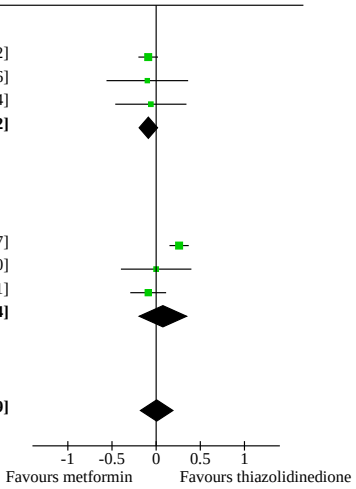
Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	Thiazolidinedione Mean [mmol/L]	Thiazolidinedione SD [mmol/L]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
3.11.1 Low risk of selection bias								
Schernthaner 2004 (1)	-2.1978	21.802	588	-2.4975	21.802	588	3.7%	0.30 [-2.19 , 2.79]
Kahn 2006	-0.3	2.2	1454	-1.03	2.2	1456	23.9%	0.73 [0.57 , 0.89]
Bilezikian 2013	6.19	1.31	111	6.41	1.64	114	21.5%	-0.22 [-0.61 , 0.17]
Subtotal (95% CI)			**2153**			**2158**	**49.1%**	**0.28 [-0.58 , 1.13]**
Heterogeneity: Tau² = 0.40; Chi² = 19.80, df = 2 (P < 0.0001); I² = 90%								
Test for overall effect: Z = 0.63 (P = 0.53)								
3.11.2 Unclear or high risk of selection bias								
Yamanouchi 2005	9.03	2.01	37	7.93	2.25	35	13.1%	1.10 [0.11 , 2.09]
Kiyici 2009	6.4	0.6	16	6.6	0.7	19	20.9%	-0.20 [-0.63 , 0.23]
Erem 2014	6.2965	1.0878	19	5.83361	1.1322	19	16.9%	0.46 [-0.24 , 1.17]
Subtotal (95% CI)			**72**			**73**	**50.9%**	**0.35 [-0.38 , 1.08]**
Heterogeneity: Tau² = 0.29; Chi² = 6.81, df = 2 (P = 0.03); I² = 71%								
Test for overall effect: Z = 0.95 (P = 0.34)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.32 [-0.21 , 0.84]**
Heterogeneity: Tau² = 0.29; Chi² = 32.76, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								



Footnotes
(1) Adjusted for baseline FPG value

Analysis 3.12. Comparison 3: Metformin vs thiazolidinedione, Outcome 12: Glycaemic control: HbA1c

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	Thiazolidinedione Mean [%]	Thiazolidinedione SD [%]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [%]
3.12.1 Pioglitazone								
Schernthaner 2004 (1)	-1.5	0.9699	588	-1.41	0.9699	588	23.6%	-0.09 [-0.20 , 0.02]
Yamanouchi 2005	7.8	1	37	7.9	1	35	9.8%	-0.10 [-0.56 , 0.36]
Erem 2014	6.4	0.7	19	6.46	0.56	19	11.5%	-0.06 [-0.46 , 0.34]
Subtotal (95% CI)			**644**			**642**	**45.0%**	**-0.09 [-0.19 , 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%								
Test for overall effect: Z = 1.67 (P = 0.10)								
3.12.2 Rosiglitazone								
Kahn 2006	0.06	1.5	1454	-0.2	1.5	1456	23.7%	0.26 [0.15 , 0.37]
Kiyici 2009	6.4	0.6	16	6.4	0.6	19	11.7%	0.00 [-0.40 , 0.40]
Bilezikian 2013	6.26	0.81	111	6.35	0.74	114	19.7%	-0.09 [-0.29 , 0.11]
Subtotal (95% CI)			**1581**			**1589**	**55.0%**	**0.08 [-0.19 , 0.34]**
Heterogeneity: Tau² = 0.04; Chi² = 9.62, df = 2 (P = 0.008); I² = 79%								
Test for overall effect: Z = 0.56 (P = 0.58)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.01 [-0.18 , 0.19]**
Heterogeneity: Tau² = 0.03; Chi² = 22.94, df = 5 (P = 0.0003); I² = 78%								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.8%								

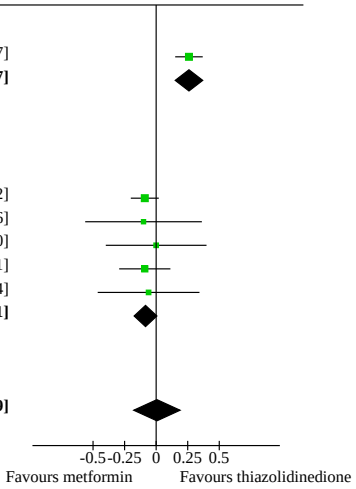


Footnotes

(1) Adjusted for baseline HbA1c value

Analysis 3.13. Comparison 3: Metformin vs thiazolidinedione, Outcome 13: Glycaemic control: HbA1c (Subgroup: duration of the intervention)

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	Thiazolidinedione Mean [%]	Thiazolidinedione SD [%]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [%]
3.13.1 Long duration (2 years or more)								
Kahn 2006	0.06	1.5	1454	-0.2	1.5	1456	23.7%	0.26 [0.15 , 0.37]
Subtotal (95% CI)			**1454**			**1456**	**23.7%**	**0.26 [0.15 , 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.68 (P < 0.00001)								
3.13.2 Short duration (less than 2 years)								
Schernthaner 2004 (1)	-1.5	0.9699	588	-1.41	0.9699	588	23.6%	-0.09 [-0.20 , 0.02]
Yamanouchi 2005	7.8	1	37	7.9	1	35	9.8%	-0.10 [-0.56 , 0.36]
Kiyici 2009	6.4	0.6	16	6.4	0.6	19	11.7%	0.00 [-0.40 , 0.40]
Bilezikian 2013	6.26	0.81	111	6.35	0.74	114	19.7%	-0.09 [-0.29 , 0.11]
Erem 2014	6.4	0.7	19	6.46	0.56	19	11.5%	-0.06 [-0.46 , 0.34]
Subtotal (95% CI)			**771**			**775**	**76.3%**	**-0.08 [-0.17 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 4 (P = 1.00); I² = 0%								
Test for overall effect: Z = 1.83 (P = 0.07)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.01 [-0.18 , 0.19]**
Heterogeneity: Tau² = 0.03; Chi² = 22.94, df = 5 (P = 0.0003); I² = 78%								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Chi² = 22.74, df = 1 (P < 0.00001), I² = 95.6%								

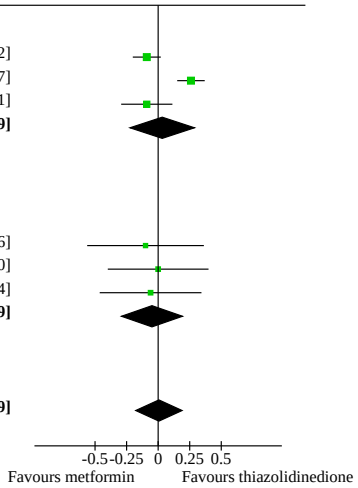


Footnotes

(1) Adjusted for baseline HbA1c value

Analysis 3.14. Comparison 3: Metformin vs thiazolidinedione, Outcome 14: Glycaemic control: HbA1c (Subgroup: selection bias)

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	Thiazolidinedione Mean [%]	Thiazolidinedione SD [%]	Thiazolidinedione Total	Weight	Mean Difference IV, Random, 95% CI [%]
3.14.1 Low risk of selection bias								
Schernthaner 2004 (1)	-1.5	0.9699	588	-1.41	0.9699	588	23.6%	-0.09 [-0.20 , 0.02]
Kahn 2006	0.06	1.5	1454	-0.2	1.5	1456	23.7%	0.26 [0.15 , 0.37]
Bilezikian 2013	6.26	0.81	111	6.35	0.74	114	19.7%	-0.09 [-0.29 , 0.11]
Subtotal (95% CI)			**2153**			**2158**	**67.0%**	**0.03 [-0.22 , 0.29]**
Heterogeneity: Tau² = 0.05; Chi² = 22.05, df = 2 (P < 0.0001); I² = 91%								
Test for overall effect: Z = 0.25 (P = 0.80)								
3.14.2 Unclear or high risk of selection bias								
Yamanouchi 2005	7.8	1	37	7.9	1	35	9.8%	-0.10 [-0.56 , 0.36]
Kiyici 2009	6.4	0.6	16	6.4	0.6	19	11.7%	0.00 [-0.40 , 0.40]
Erem 2014	6.4	0.7	19	6.46	0.56	19	11.5%	-0.06 [-0.46 , 0.34]
Subtotal (95% CI)			**72**			**73**	**33.0%**	**-0.05 [-0.29 , 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.40 (P = 0.69)								
Total (95% CI)			**2225**			**2231**	**100.0%**	**0.01 [-0.18 , 0.19]**
Heterogeneity: Tau² = 0.03; Chi² = 22.94, df = 5 (P = 0.0003); I² = 78%								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%								

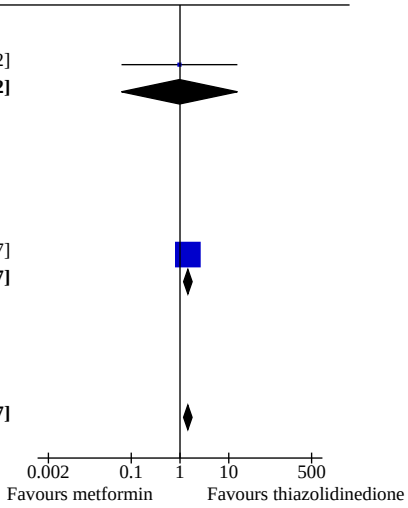


Footnotes

(1) Adjusted for baseline HbA1c value

Analysis 3.15. Comparison 3: Metformin vs thiazolidinedione, Outcome 15: Intervention failure

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.15.1 Pioglitazone						
Yamanouchi 2005 (1)	1	39	1	38	0.5%	0.97 [0.06 , 15.02]
Subtotal (95% CI)		**39**		**38**	**0.5%**	**0.97 [0.06 , 15.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
3.15.2 Rosiglitazone						
Kahn 2006	207	1454	143	1456	99.5%	1.45 [1.19 , 1.77]
Subtotal (95% CI)		**1454**		**1456**	**99.5%**	**1.45 [1.19 , 1.77]**
Total events:	207		143			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.63 (P = 0.0003)						
Total (95% CI)		**1493**		**1494**	**100.0%**	**1.45 [1.18 , 1.77]**
Total events:	208		144			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.62 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

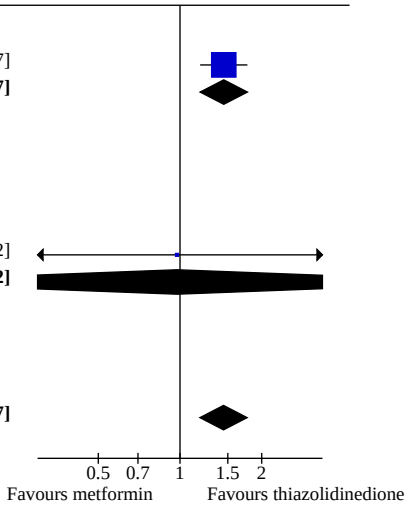


Footnotes

(1) Results including withdrawals (that were excluded from all other analyses)

Analysis 3.16. Comparison 3: Metformin vs thiazolidinedione, Outcome 16: Intervention failure (Subgroup: duration of the intervention

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.16.1 Long duration (2 years or more)						
Kahn 2006	207	1454	143	1456	99.5%	1.45 [1.19 , 1.77]
Subtotal (95% CI)		**1454**		**1456**	**99.5%**	**1.45 [1.19 , 1.77]**
Total events:	207		143			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.63 (P = 0.0003)						
3.16.2 Short duration (less than 2 years)						
Yamanouchi 2005 (1)	1	39	1	38	0.5%	0.97 [0.06 , 15.02]
Subtotal (95% CI)		**39**		**38**	**0.5%**	**0.97 [0.06 , 15.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
Total (95% CI)		**1493**		**1494**	**100.0%**	**1.45 [1.18 , 1.77]**
Total events:	208		144			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.62 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

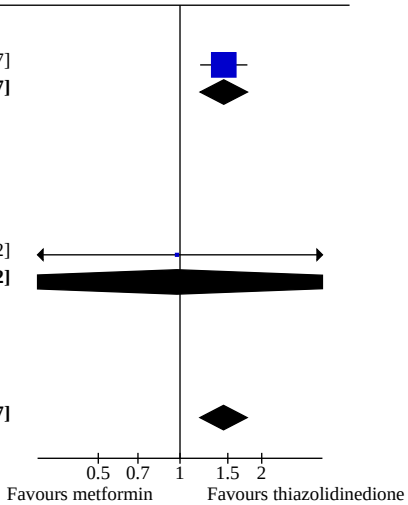


Footnotes

(1) Results including withdrawals (that were excluded from all other analyses)

Analysis 3.17. Comparison 3: Metformin vs thiazolidinedione, Outcome 17: Intervention failure (Subgroup: selection bias)

Study or Subgroup	Metformin Events	Metformin Total	Thiazolidinedione Events	Thiazolidinedione Total	Weight	Risk Ratio M-H, Random, 95% CI
3.17.1 Low risk of selection bias						
Kahn 2006	207	1454	143	1456	99.5%	1.45 [1.19 , 1.77]
Subtotal (95% CI)		**1454**		**1456**	**99.5%**	**1.45 [1.19 , 1.77]**
Total events:	207		143			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.63 (P = 0.0003)						
3.17.2 Unclear or high risk of selection bias						
Yamanouchi 2005 (1)	1	39	1	38	0.5%	0.97 [0.06 , 15.02]
Subtotal (95% CI)		**39**		**38**	**0.5%**	**0.97 [0.06 , 15.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
Total (95% CI)		**1493**		**1494**	**100.0%**	**1.45 [1.18 , 1.77]**
Total events:	208		144			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.62 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



Footnotes

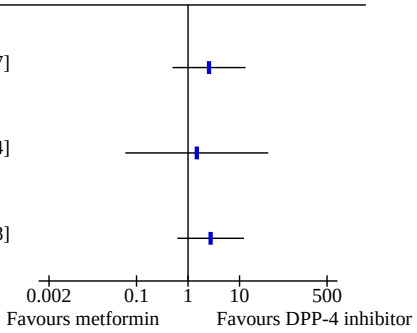
(1) Results including withdrawals (that were excluded from all other analyses)

Comparison 4. Metformin vs dipeptidyl peptidase-4 inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.1 Saxagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.2 Sitagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.3 Vildagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2 Serious adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2.1 Saxagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2.2 Vildagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2.3 Sitagliptin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3 Anthropometric measures: body weight	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.3.1 Vildagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.3.2 Sitagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.3.3 Saxagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4 Glycaemic control: FPG	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.1 Saxagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.2 Vildagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.3 Sitagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5 Glycaemic control: HbA1c	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5.1 Saxagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5.2 Vildagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5.3 Sitagliptin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Metformin vs dipeptidyl peptidase-4 inhibitor, Outcome 1: All-cause mortality

Study or Subgroup	Favours metformin Events	Total	DPP-4 inhibitor Events	Total	Risk Ratio M-H, Random, 95% CI
4.1.1 Saxagliptin					
Pfützner 2011 (1)	5	328	2	335	2.55 [0.50 , 13.07]
4.1.2 Sitagliptin					
Williams-Herman 2010 (2)	1	364	0	179	1.48 [0.06 , 36.14]
4.1.3 Vildagliptin					
Schweizer 2007 (3)	4	252	3	519	2.75 [0.62 , 12.18]



Footnotes

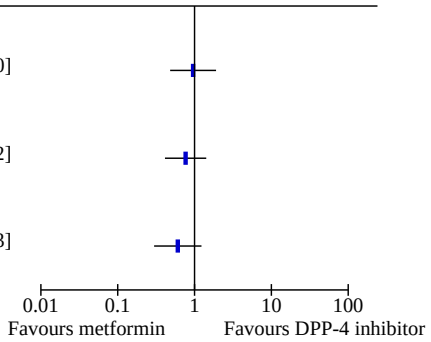
(1) 1 participant in the metformin arm died from sudden death

(2) Results after the 104 weeks of intervention

(3) Calculated using all-cause mortality from the first 52 weeks of intervention summed with all-cause mortality from the extension period. Safety population f

Analysis 4.2. Comparison 4: Metformin vs dipeptidyl peptidase-4 inhibitor, Outcome 2: Serious adverse events

Study or Subgroup	Metformin Events	Total	DPP-4 inhibitor Events	Total	Risk Ratio M-H, Random, 95% CI
4.2.1 Saxagliptin					
Pfützner 2011	15	328	16	335	0.96 [0.48 , 1.90]
4.2.2 Vildagliptin					
Schweizer 2007 (1)	13	252	35	519	0.76 [0.41 , 1.42]
4.2.3 Sitagliptin					
Williams-Herman 2010 (2)	16	364	13	179	0.61 [0.30 , 1.23]



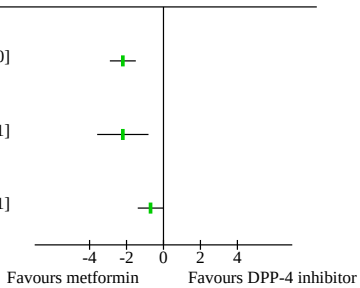
Footnotes

(1) After 52 weeks of intervention.

(2) Results after 104 weeks of intervention. Excluding data after initiation of glycaemic rescue therapy

Analysis 4.3. Comparison 4: Metformin vs dipeptidyl peptidase-4 inhibitor, Outcome 3: Anthropometric measures: body weight

Study or Subgroup	Metformin Mean [kg]	SD [kg]	Total	DPP-4 inhibitor Mean [kg]	SD [kg]	Total	Mean Difference IV, Random, 95% CI [kg]
4.3.1 Vildagliptin							
Schweizer 2007 (1)	-1.9	4.7	249	0.3	4.5	511	-2.20 [-2.90 , -1.50]
4.3.2 Sitagliptin							
Williams-Herman 2010 (2)	-1.7	4.3	140	0.5	4.3	50	-2.20 [-3.59 , -0.81]
4.3.3 Saxagliptin							
Pfützner 2011 (3)	-1	4.6	328	-0.3	4.5	335	-0.70 [-1.39 , -0.01]



Footnotes

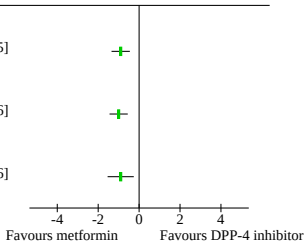
(1) After 52 weeks of intervention. Adjusted for baseline HbA1c value

(2) Results after 104 weeks of intervention. Excluding patients requiring rescue medication in the initial 24 weeks of intervention and or subsequent 30 weeks.

(3) Standard deviations were imputed by combining the standard deviations from the other trials in the analysis. Results after 76 weeks of intervention.

Analysis 4.4. Comparison 4: Metformin vs dipeptidyl peptidase-4 inhibitor, Outcome 4: Glycaemic control: FPG

Study or Subgroup	Metformin Mean [mmol/L]	Metformin SD [mmol/L]	Metformin Total	DPP-4 inhibitor Mean [mmol/L]	DPP-4 inhibitor SD [mmol/L]	DPP-4 inhibitor Total	Mean Difference IV, Random, 95% CI [mmol/L]
4.4.1 Saxagliptin							
Pfützner 2011 (1)	-2.2	2.8	320	-1.3	3.01	327	-0.90 [-1.35 , -0.45]
4.4.2 Vildagliptin							
Schweizer 2007 (2)	-1.9	3.2	249	-0.9	2.3	511	-1.00 [-1.44 , -0.56]
4.4.3 Sitagliptin							
Williams-Herman 2010 (3)	7.8	2	151	8.7	2	50	-0.90 [-1.54 , -0.26]



Footnotes

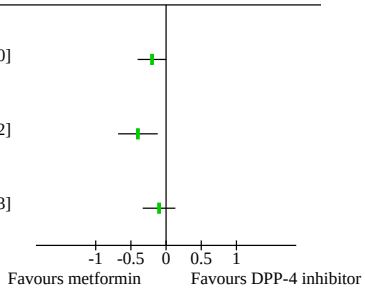
(1) Adjusted for baseline FPG value

(2) After 52 weeks of intervention. Adjusted for baseline HbA1c value

(3) Results after 104 weeks of intervention, excluding patients requiring rescue medication during the initial 24 weeks or subsequent 30 weeks.

Analysis 4.5. Comparison 4: Metformin vs dipeptidyl peptidase-4 inhibitor, Outcome 5: Glycaemic control: HbA1c

Study or Subgroup	Metformin Mean [%]	Metformin SD [%]	Metformin Total	DPP-4 inhibitor Mean [%]	DPP-4 inhibitor SD [%]	DPP-4 inhibitor Total	Mean Difference IV, Random, 95% CI [%]
4.5.1 Saxagliptin							
Pfützner 2011 (1)	-1.8	1.2	308	-1.6	1.4	316	-0.20 [-0.40 , 0.00]
4.5.2 Vildagliptin							
Schweizer 2007 (2)	-1.4	1.6	249	-1	2.3	511	-0.40 [-0.68 , -0.12]
4.5.3 Sitagliptin							
Williams-Herman 2010 (3)	7.3	0.8	151	7.4	0.7	50	-0.10 [-0.33 , 0.13]



Footnotes

(1) Adjusted for baseline HbA1c value

(2) After 52 weeks of intervention. Adjusted for baseline HbA1c value

(3) Results after 104 weeks of intervention. Excluding patients requiring rescue medication in the initial 24 weeks of intervention and or subsequent 30 weeks.

ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (trial design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Randomised (N)	Analysed (N)	Finishing trial (N)	Randomised finishing trial (%)	Follow-up
Bilezikian 2013 (parallel RCT)	I: metformin	"Sample size calculation was based on a 30% dropout rate and a SD of 4% for percentage change from baseline in femoral neck, ensuring that the 95% confidence interval will be the mean +- 0.9% for each treatment group"	316	112	111	85	75.9	52 weeks[a]
	C1: rosiglitazone			114	114	77	67.5	
	total:			**226**	**225**	**162**	**71.7**	
Erem 2014 (parallel RCT)	I: metformin	—	—	20	19	19	95.0	52 weeks
	C1: gliclazide			20	19	19	95.0	
	C2: pioglitazone			20	19	19	95.0	
	total:			**60**	**57**	**57**	**95.0**	
Derosa 2009 (parallel RCT)	I: metformin	"Considering as clinically significant a difference of at least 10% compared with the baseline and an α error of.05, the actual sample size is adequate to obtain a power higher than 0.80 for all variables related to glucose metabolism (HbA1c, FPG, PPG, FPI, PPI, GIR, and TGR)."	—	67	—	60	90.0	15 months
	C1: pioglitazone			69	—	60	87.0	
	total:			**136**	**—**	**120**	**88.2**	
Kahn 2006 (parallel RCT)	I: metformin	"We originally calculated that we would need to enroll 3600 patients to provide the study with a power of 90% to detect a 30% reduction in the risk of treatment failure for rosiglitazone, as compared with metformin and glyburide, at a significance level of P=0.05 (two-sided, adjusted for two comparisons), assuming an event rate of 0.072 per year for metformin or glyburide and a rate of loss to fol-	6676	1455	1454	903	62.1	Median of 4 years (maximum 6.1)
	C1: rosiglitazone			1458	1456	917	62.9	
	C2: glibenclamide			1447	1441	807	55.8	

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

		low-up of 0.064 per year in each group. The protocol was amended in March 2002 to increase the number of patients to 4182 and in February 2004, to extend the follow-up period beyond 4 years, in order to compensate for an overall rate of withdrawal that was greater than anticipated and an overall rate of primary outcome events that was lower than anticipated. The revised power estimate was 83%, assuming a rate of loss to follow-up of 0.128 per year and a hazard rate for treatment failure of 0.035 per year."						
	total:			**4360**	**4351**	**2627**	**60.2**	
Schweizer 2007 (parallel RCT)	I: metformin	"A planned sample size of 660 patients (in 2 : 1 allocation ratio to vildagliptin: metformin) was calculated assuming a 20% drop-out rate, with 90% power and a one-sided significance level of 0.025 to detect non-inferiority of vildagliptin compared with metformin in reducing HbA1c after 52 weeks, with a noninferiority margin of 0.3% and an expected difference between the two treatment groups of 0.0%. Based on health authority feedback, the test of non-inferiority was amended during the course of the study to utilize a non-inferiority margin of 0.4%, which increased the statistical power to 99%"	1606	254 (158)[b]	249 (158)[b]	191 (142)[b]	75.2 (55.9)[b]	104 weeks[c]
	C1: vildagliptin			526 (305)[b]	511 (304)[b]	378 (260)[b]	71.9 (49.4)[b]	
	total:			**780 (463)[b]**	**760 (462)[b]**	**569 (402)[b]**	**73.5 (52.7)[b]**	
Umpierrez 2014 (parallel RCT)	I: metformin	"The study was designed with 90% power to detect noninferiority of dulaglutide 1.5 mg versus metformin on HbA1c change from baseline at the 26-week primary end point with a margin of 0.4%, a SD of 1.3%, and a one-sided a of 0.025, assuming no true difference between treatments. This corresponds to 251 patients per arm, with an assumed dropout rate of 11%. If noninferiority was met, superiority was assessed using a tree-gatekeeping approach in which the type I error rate across all treatment comparisons for change from baseline in HbA1c	—	268	268	213	79.5	52 weeks
	C1: dulaglutide (1.5 mg/week)			269	269	220	81.8	
	C2: dulaglutide (0.75 mg/week)			270	270	218	80.7	

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

		at 26 weeks was strongly controlled at 0.025 (onesided). P values were adjusted so that each can be compared with 0.025 to assess significance while accounting for multiplicity adjustments. The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment."						
	total:			**807**	**807**	**651**	**80.7**	
Kiyici 2009 (parallel RCT)	I: metformin	—	—	16	16	16	100	52 weeks
	C1: rosiglitazone			19	19	19	100	
	C2: no intervention			15	15	15	100	
	total:			**50**	**50**	**50**	**100**	
Pfützner 2011 (parallel RCT)	I: metformin	"...each comparison was performed at the 0.027 alpha level from Dunnett's adjustment so that the overall (family-wise) type I error rate was controlled at the 0.05 significance level." "Based on the primary end-point, the sample size afforded at least 90% power for both the combination comparisons and the individual components based on the min test by Laska and Meisner for normal case."	2936	328	328	219	66.8	76 weeks[d]
	C1: saxagliptin			335	335	209	62.4	
	total:			**663**	**663**	**428**	**64.6**	
Schernthaner 2004 (parallel RCT)	I: metformin	"A noninferiority design was used in this study. Sample size was based on the study objective to disprove the null hypothesis that pioglitazone was inferior to metformin in terms of reduction in HbA1c. Based on a 5% significance level and a statistical power of 90%, a sample size of 450 patients in each treatment group was required."	2145	— (597[e])	597	501	—	52 weeks
	C1: pioglitazone			— (597[e])	597	499	—	

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

	total:			**1199**	**1194**	**1000**	**83.4**	
Yamanouchi 2005 (parallel RCT)	I: metformin	"Our pretrial calculation showed that a two-sided comparison of the pioglitazone vs. the diet-alone group in Japanese patients required at least 30 patients per group to detect a difference in mean HbA1c of at least 1% with 5% significance and 95% power"	—	39	37	37	94.9	52 weeks
	C1: pioglitazone			38	35	35	92.1	
	C2: glimepiride			37	34	34	91.9	
	total:			**114**	**106**	**106**	**93.0**	
Williams-Herman 2010 (parallel RCT)	I: metformin (1000 mg/day)	—	3427	182	—	95	52.2	104 weeks[f]
	I2: metformin (2000 mg/day)			182	—	80	44.0	
	C1: sitagliptin			179	—	65	36.3	
	total:			**543**	**—[g]**	**240**	**44.2**	
Rahman 2011 (parallel RCT)	I: metformin	—	—	102	102	—	—	52 weeks
	C1: glimepiride			102	102	—	—	
	total:			**204**	**204**	**—**	**—**	
Campbell 1994 (parallel RCT)	I: metformin	—	—	24	24	24	100.0	52 weeks
	C1: glipizide			24	24	24	100.0	
	total:			**48**	**48**	**48**	**100.0**	
Derosa 2004 (parallel RCT)	I: metformin	"The power of the study was calculated with a Fisher's exact test, with a 0.050 two-sided significance alpha level and a 90% power; to detect the difference between a glimepiride	—	83	75	75	90.4	60 weeks
	C1: glimepiride			81	73	73	90.1	

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

		group proportion of 0.500 and a metformin group proportion of 0.750 the sample size in each group would be 85."						
	total:			**164**	**148**	**148**	**90.2**	
UKPDS 34 1998 (parallel RCT)	I: metformin	"Table 6 gives the likelihood of detecting a 20 % or 25 % reduction of endpoints by improved plasma glucose and blood pressure control. This reduction has been accepted as being a clinically significant gain, particularly as benefits from treatment are likely to be even greater over a longer period of therapy since complications develop over many years. Power calculations assumed 8 % loss to follow-up and a 4% per annum increased number of events as the cohort ages"	4209	342	342	—	—	10.7 years
	C1: glibenclamide			277	277	—	—	
	C2: insulin			409	409	—	—	
	total:			**1028**	**1028**	**—**	**—**	
Teupe 1991 [h] (parallel RCT)	I: metformin	—	—	50	25	25	50.0	2 years
	C1: no intervention			50	29	29	58.0	
	total:			**100**	**54**	**54**	**54.0**	
Onuchin 2010 (parallel RCT)	I: metformin	—	—	46	46	—	—	12 months
	C1: insulin			45	45	—	—	
	total:			**91**	**91**	**—**	**—**	
Derosa 2003 (parallel RCT)	I: metformin	—	—	56	56	49	87.5	14 months
	C1: repaglinide			56	56	53	94.6	
	total:			**112**	**102**	**102**	**91.1**	
Grand total	**All interventions**			**4041[i]**		**2463[j]**		

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

All com-parator**s**	**6639[i]**	**3732[j]**
All inter-ventions and com-parator**s**	**10,680[i]**	**6195[j]**

—: denotes not reported
[a]After 52 weeks of metformin versus rosiglitazone all participants received open-label metformin for an additional 24 weeks, which was not of interest to this review
[b]Participants also completing the 52-week extension
[c]The trial consisted of a 52-week intervention followed by a 52-week extension period in which participants continued their allocated intervention
[d]The trial consisted of a 24-week intervention followed by a 52-week extension period in which participants continued their allocated intervention
[e]At least 597 participants were randomised to either arm. It is unclear which arm the remaining 5 participants were randomised to
[f]The trial consisted of a 24-week intervention followed by a 30-week extension period followed by an additional 52-week extension period in which participants continued their allocated intervention
[g]Variation in number of participants analysed depending on outcome measure
[h]Results are after 2 years of intervention and follow-up
[i]For Schweizer 2007 numbers outside parentheses were used, for Schernthaner 2004 numbers in parentheses were used
[j]For Rahman 2011, UKPDS 34 1998 and Onuchin 2010 no numbers were available and thus not included in calculation
C: comparator; **I**: intervention; **GIR**: glucose infusion rate; **ITT**: intention-to-treat; **RCT**: randomised controlled trial; **SD**: standard deviation; **HbA1c**: glycosylated haemoglobin A1c; **FPG**: fasting plasma glucose; **FPI**: fasting plasma insulin; **PPG**: post prandial glucose; **PPI**: post prandial insulin.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Register of Studies Online)
1. MESH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES
2. (MODY OR NIDDM OR T2D*):TI,AB,KY
3. (non insulin* depend* OR noninsulin* depend* OR noninsulin?depend* OR non insulin?depend*):TI,AB,KY
4. ((typ? 2 OR typ? II OR typ?2 OR typ?II) ADJ3 diabet*):TI,AB,KY
5. (((late OR adult* OR matur* OR slow OR stabl*) ADJ3 onset) AND diabet*):TI,AB,KY
6. #1 OR #2 OR #3 OR #4 OR #5
7. MESH DESCRIPTOR Metformin
8. metformin*:TI,AB,KY
9. #7 OR #8
10. #6 AND #9
11. 2014 TO 2019:YR
12. #10 AND #11

MEDLINE (OvidSP)
1. exp Diabetes Mellitus, Type 2/
2. (MODY or NIDDM or T2D*).tw.
3. (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.
4. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.
5. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).tw.
6. or/1-5
7. Metformin/
8. metformin*.tw.
9. or/7-8
10. 6 and 9
[11-22: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomi?ed.ab.
14. placebo.ab.
15. drug therapy.fs

(Continued)

16. randomly.ab.

17. trial.ab.

18. groups.ab.

19. or/11-18

20. exp animals/ not humans/

21. 19 not 20

22. 10 and 21

[23: Wong 2006a – systematic reviews filter – SensSpec version]

23. meta analysis.mp,pt. or review.pt. or search*.tw.

24. 10 and 23

25. 22 or 24

26. (2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dc.

27. 25 and 26

28. ..dedup 27

Embase (Ovid SP)

1. non insulin dependent diabetes mellitus/

2. (MODY or NIDDM or T2D*).tw.

3. (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.

4. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.

5. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).tw.

6. or/1-5

7. Metformin/

8. metformin*.tw.

9. or/7-8

10. 6 and 9

[11: Wong 2006b "sound treatment studies" filter – best balance version]

11. random*.tw. or placebo*.mp. or double-blind*.tw.

12. 10 and 11

13. (2014* or 2015* or 2016* or 2017*).dc.

14. 12 and 13

15. conference*.pt.

16. 14 not 15

17. ..dedup 16

(Continued)

ClinicalTrials.gov (Advanced search)

Conditions: diabetes OR diabetic OR diabetics OR "type 2" OR "type II" OR T2D OR T2DM OR NIDDM

Interventions: metformin

Study Type: Interventional Studies

Age Group: Adult, Senior

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (Standard search)

diabet* AND metformin* OR

T2D* AND metformin* OR

NIDDM AND metformin*

Appendix 2. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the study. We considered the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We described for each included study the method used to conceal allocation to interventions prior to assignment and we assessed whether intervention allocation could have been foreseen in advance of or during recruitment or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, Internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014).

Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between studies that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies that we judge as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgements of unclear, low, or high risk of selection bias as specified in Appendix 3.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the study)

(Continued)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to quantity, nature or handling of incomplete outcome data)

For each included study or each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the study reported attrition and exclusions, and we reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the study reported the reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between study arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the study did not address this outcome.
- High risk of bias: reason for missing outcome data were likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by integrating the results of the appendix 'Matrix of study endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting.

- Low risk of bias: the study protocol was available and all the study's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse

(Continued)

effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them into a meta-analysis; the study report failed to include results for a key outcome that we would expect to have been reported for such a study (ORBIT classification).

Other bias

- Low risk of bias: the study appears to be free from other sources of bias.
- Unclear risk of bias: information was insufficient to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the study had a potential source of bias related to the specific study design used; the study was claimed to be fraudulent; or the study had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information[a]

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Ris of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	**Unclear risk** [b]
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[c]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly randomised, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited baseline details, showing balance in some important prognostic variables[c]	**Unclear risk**
		No baseline details	High risk

[a]Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.

(Continued)

[b]Imbalance identified that appears likely to be due to chance.

[c]Details for the remaining important prognostic variables are not reported.

Appendix 4. Description of interventions

Trial ID	Intervention(s) and comparator(s)	Rescue medication
Bilezikian 2013	I: metformin, orally, initially 1000 mg/day and force-titrated to 2000 mg/day, Calcium, orally, 500 mg/day to 1000 mg/day (500 mg to 1000 mg, once a day), vitamin D, orally, at least 400 IU/day (at least 400 IU, once a day). Rosiglitazone placebo	From weeks 8 to 16, participants with mean daily glucose 6.1 mmol/L at the maximum tolerated doses of metformin or rosiglitazone received open-label sulphonylurea. After 4 months of double-blind study medication, participants with HbA1c 7.5% at the maximum dose of medication could up-titrate or add open-label sulphonylurea
	C1: rosiglitazone, orally, initially 4 mg/day and force-titrated to 8 mg/day, Calcium, orally, 500 mg/day to 1000 mg/day (500 mg to 1000 mg, once a day), Vitamin D, orally, at least 400 IU/day (at least 400 IU, once a day). Metformin placebo	
Campbell 1994	I: metformin, orally, initially 1000 mg/day (500 mg, twice a day) and titrated to 3000 mg/day in increments of 500 mg/day if not to target (FPG < 8 mmol/L). Dose was reduced by 500 mg/day if FPG < 4 mmol/L	—
	C1: glipizide, orally, initially 5 mg/day (5 mg, once a day) and titrated to 30 mg/day in increments of 5 mg/day if not to target (FPG < 8 mmol/L). Dose was reduced by 5 mg/day if FPG < 4 mmol/L	
Derosa 2003	I: metformin, orally, initially 1000 mg/day (500 mg, twice a day, after lunch and dinner) and titrated to 1500 mg/day to 2500 mg/day (three times a day, after breakfast, lunch and dinner) if not to target (FPG < 6.7 mmol/L and 2h-PPG < 8.8 mmol/L), diet and exercise	—
	C1: repaglinide, orally, initially 1 mg/day (0.5 mg, twice a day, before lunch and dinner) and titrated to 2 mg/day to 4 mg/day (three times a day, before breakfast, lunch and dinner) if not to target (FPG < 6.7 mmol/L and 2h-PPG < 8.8 mmol/L), diet and exercise	
Derosa 2004	I: metformin, orally, initially 1000 mg/day and titrated to 3000 mg/day (1000 mg, three times a day, after breakfast, lunch and dinner) during the first 8 weeks if not to target (FPG < 120 mg/dL and 2h-PPG < 160 mg/dL), diet and exercise	—
	C1: glimepiride, orally, initially 1 mg/day and titrated to 4 mg/day (2 mg, two times a day, before breakfast and dinner) if not to target (FPG < 120 mg/dL and 2h-PPG < 160 mg/dL), diet and exercise	
Derosa 2009	I: metformin, orally, initially 1000 mg/day in the first month, force-titrated to 2000 mg/day in the second month, and force-titrated to 3000 mg/day in the third month. Continuing this dosage patients entered 12 months of study. Diet and exercise	—

(Continued)

	C1: pioglitazone, orally, initially 15 mg/day in the first month, force-titrated to 30 mg/day in the second month and force-titrated to 45 mg/day in the third month. Continuing this dosage patients entered 12 months of study. Diet and exercise	
Erem 2014	I: metformin, orally, initially 500 mg/day and titrated to 2000 mg/day (1000 mg, twice a day) according to tolerability. Diet and exercise	—
	C1: gliclazide, orally, modified-release, initially 30 mg/day (30 mg, once a day) and titrated to 120 mg/day. Diet and exercise	
	C2: pioglitazone, orally, initially 15 mg/day and titrated to 45 mg/day. Diet and exercise	
Kahn 2006	I: metformin, orally, initially 500 mg/day and titrated to 2000 mg/day (1000 mg, twice a day) if not to target (FPG < 140 mg/dL and no adverse events from medication)	—
	C1: rosiglitazone, orally, initially 4 mg/day titrated to 8 mg/day (4 mg, twice a day) if not to target (FPG < 140 mg/dL and no adverse events from medication)	
	C2: glibenclamide, orally, initially 2.5 mg/day titrated to 15 mg/day (7.5 mg, twice a day) if not to target (FPG < 140 mg/dL and no adverse events from medication)	
Kiyici 2009	I: metformin, orally, 850/mg day. Diet and exercise	—
	C1: rosiglitazone, orally, 4 mg/day. Diet and exercise	
	C2: no intervention. Diet and exercise	
Onuchin 2010	I: metformin, orally, 500 mg/day to 2500 mg/day	—
	C1: insulin (variable dose), p.e. long-acting, 0.2-0.4 IU/1 kg body weight/day (two thirds before breakfast and one third before bedtime) and short-acting before main meals taking into account consumable bread units, 1-1.5 IU/1 unit bread (equal to 10 g carbohydrates)	
Pfützner 2011	I: metformin, orally, initially 1000 mg/day in the first week, titrated to 2000 mg/day in increments of 500 mg/day if not to target (FPG < 110 mg/dL) in weeks 2-5 (taken in two divided doses before breakfast and dinner). Diet and exercise	Patients were eligible for rescue therapy based on progressively strict glycaemic control criteria over 24 weeks if FPG levels were as follows: > 240 mg/dL (week 6); > 220 mg/dL (week 8) and > 200 mg/dL (weeks 12, 16, 20 and 24). Patients who met rescue criteria were entered directly into the long-term extension period, where they were administered open-label pioglitazone 15 mg, which could be up-titrated to 45 mg, in addition to blinded study medication.
	C1: saxagliptin, orally, 10 mg/day (before breakfast). Diet and exercise	

(Continued)

		Patients with HbA1c > 8.0% at week 30, 37 or 50, or > 7.5% at week 63 were similarly rescued with pioglitazone 15 mg once daily, titrated to a maximum of 45 mg once daily according to local or regional policy, in addition to their blinded study medication.
Rahman 2011	I: metformin, orally, initially 500 mg/day and titrated to 2000 mg/day if not to target (FPG < 140 mg/dL) C1: glimepiride, orally, initially 2 mg/day and titrated to 8 mg/day if not to target (FPG < 140 mg/dL)	—
Schernthaner 2004	I: metformin, orally, initially 850 mg/day (850 mg, once a day) force-titrated to 2550 mg/day (850 mg, three times a day) in the first 12 weeks, and dose was increased, maintained or decreased at week 4, 8 and 12 according to tolerability. Diet. Pioglitazone placebo C1: pioglitazone, orally, initially 30 mg/day force-titrated to 45 mg/day in the first 12 weeks, and dose was increased, maintained or decreased at week 4, 8 and 12 according to tolerability. Diet. Metformin placebo	—
Schweizer 2007	I: metformin, orally, titrated to 2000 mg/day (1000 mg, twice a day) C1: vildagliptin, orally, titrated to 100 mg/day (50 mg, twice a day)	Pioglitazone was added to the blinded study drug from the first visit of the extension as rescue medication for patients with confirmed FPG > 10 mmol/L, according to the investigator's clinical judgment and prescribing guidelines[b]
Teupe 1991	I: metformin, orally, maximum of 1700 mg/day. Diet C1: no intervention. Diet	—
UKPDS 34 1998	I: metformin, orally, initially 850 mg/day (850 mg, once a day), titrated to 1700 mg/day (850 mg, twice a day) and titrated to 2550 mg/day (1700 mg in the morning and 850 mg with dinner) according to tolerability. Diet C1: glibenclamide, orally, 2.5 mg/day to 20 mg/day. Diet C2: insulin, sc., initial once daily ultralente insulin or isophane insulin. If the daily dose was more than 14 units or pre-meal or bed-time home blood glucose measurements were more than 7 mmol/L, a short-acting insulin, usually soluble (regular) insulin was added, i.e., basal/bolus regimen. Diet	If the participants allocated to metformin monotherapy developed marked hyperglycaemia, glibenclamide was added with the aim of maintaining fasting plasma glucose below 6.0 mmol/L. If marked hyperglycaemia again developed, the patient was changed to insulin. If participants allocated to sulphonylurea developed fasting plasma glucose concentrations of 6.1–15.0 mmol/L but no symptoms on maximum doses, were then assigned either continuing

(Continued)

		treatment with sulphonylurea alone or addition of metformin to sulphonylurea (according to protocol amendment) Participants allocated to basal insulin regime who could not be adequately controlled were receiving more complex insulin regimens
Umpierrez 2014	I: metformin, orally, titrated to 1500 mg/day to 2000 mg/day in the first 4 weeks depending upon tolerability. Diet and exercise. Dulaglutide placebo	An add-on rescue therapy was allowed for patients who met prespecified criteria for severe, persistent hyperglycaemia
	C1: dulaglutide, sc., 1.5 mg/week (1.5 mg, once a week). Diet and exercise. Metformin placebo	
	C2: dulaglutide, sc., 0.75 mg/week (0.75 mg, once a week). Diet and exercise. Metformin placebo	
Williams-Herman 2010	I: metformin, orally, initially 500 mg/day (500 mg, once a day) titrated to 1000 mg/day (500 mg, twice a day) in increments of 500 mg/week (taken before breakfast and dinner). Participants continued study medication for a total of 54 weeks and were eligible for the 50-week extension if: they completed the 54-week base study, were at least 75% compliant in taking study medication (as assessed by the investigator based on patient interview and tablet count), had not developed a contraindication to study medication or other medical condition that would make participation in the study not in their best interest, and had provided written informed consent. Diet and exercise. Sitagliptin placebo	Participants received rescue glibenclamide if FPG > 270 mg/dL between day 1 and week 6, > 240 mg/dL between weeks 6 and 12, and > 200 mg/dL between weeks 12–24. Between weeks 30 and 50 rescue was initiated if HbA1c > 8.0%. After week 50 rescue was initiated if HbA1c > 7.5 % and continued until end of study
	I2: metformin, orally, initially 500 mg/day (500 mg, once a day) titrated to 2000 mg/day (1000 mg, twice a day) in increments of 500 mg/week (taken before breakfast and dinner). Participants continued study medication for a total of 54 weeks and were eligible for the 50-week extension if: they completed the 54-week base study, were at least 75% compliant in taking study medication (as assessed by the investigator based on patient interview and tablet count), had not developed a contraindication to study medication or other medical condition that would make participation in the study not in their best interest, and had provided written informed consent. Diet and exercise. Sitagliptin placebo	
	C1: sitagliptin, orally, 100 mg/day (50 mg, twice a day) taken before breakfast. Participants continued study medication for a total of 54 weeks and were eligible for the 50-week extension if: they completed the 54-week base study, were at least 75% compliant in taking study medication (as assessed by the investigator based on patient interview and tablet count), had not developed a contraindication to study medication or other medical condition that would make participation in the study not in their best interest, and had provided written informed consent. Diet and exercise. Metformin placebo	
Yamanouchi 2005	I: metformin, orally, 750 mg/day. Diet and exercise	—
	C1: pioglitazone, orally, 30-45 mg/day. Diet and exercise	
	C2: glimepiride, orally, 1–2 mg/day. Diet and exercise	

(Continued)

—: denotes not reported

2h-PPG: 2-hour post-prandial glucose; **C**: comparator; **FPG**: fasting plasma glucose; **HbA1c**: glycated haemoglobin; **I:** intervention; **IU:** international unit; **N/CPS**: no specification of clinical practice setting possible; **pe.**: parenteral administration; **PPG**: post prandial glucose, sc.: subcutaneous administration; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 5. Baseline characteristics (I)

Trial ID	Intervention(s) and comparator(s)	Duration of intervention/duration of follow-up[a]	Description of participants	Trial period	Country	Setting	Ethnic groups (%)	Duration of type 2 diabetes (mean years (SD))
Bilezikian 2013	I: metformin	52 weeks[b]/52 weeks	Postmenopausal women, T2DM, HbA1c > 9.0% if drug-naive and > 8.5% if on prior monotherapy	2008 to 2010	—	Outpatients	White/Caucasian/European: 82 African American/African: 2 American Indian or Alaskan Native: 6 Central/South Asian: 13 South East Asian: 4 Mixed Ethnicity: 3 East Asia: 4	3.9 (—)
	C1: rosiglitazone						White/Caucasian/European: 78 African American/African: 8 American Indian or Alaskan Native: 5 Central/South Asian: 10 South East Asian: 6 Mixed Ethnicity: 2 East Asia: 2	3.3 (—)
Campbell 1994	I: metformin	52 weeks/52 weeks	T2DM, FPG > 8 mmol/L	1985 to 1987	UK	Outpatients	—	2.3 (3.4)
	C1: glipizide							2.8 (3.9)
Derosa 2003	I: metformin	14 months[c]/14 months	T2DM, duration > 6 months, drug-naive, LDL-C > 2.59 mmol/L, HbA1c > 7.0 %	—	Italy	Outpatients	—	5 (2)
	C1: repaglinide							4 (2)

(Continued)

Derosa 2004	I: metformin C1: glimepiride	60 weeks/60 weeks	T2DM, duration < 6 months	—	Italy	Outpatients	—	—
Derosa 2009	I: metformin C1: rosiglitazone	12 months[d]/12 months	White, T2DM, HbA1c > 6.5%, BMI ≥ 25 and < 30 kg/m^2	—	Italy	Outpatients	White: 100	—
Erem 2014	I: metformin C1: gliclazide C2: pioglitazone	52 weeks/52 weeks	T2DM, drug-naive, FPG ≥ 140 mg/dL or HbA1c ≥ 8 %, or FPG between 126 to 139 mg/dL or HbA1c between 7% to 8 % and HOMA-IR > 3	—	—	Outpatients	—	Newly diagnosed
Kahn 2006	I: metformin	Median: 4 years/4 years	T2DM, duration < 3 years, FPG between 7 mmol/L to 10 mmol/L	2000 to 2006	Canada and the USA, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Spain, Sweden and the UK	Outpatients	White: 89 Black: 4 Asian: 2 Hispanic: 4 Other: 1	—
	C1: rosiglitazone	Median: 4 years/4 years					White: 87 Black: 4 Asian: 3 Hispanic: 5 Other: 1	—
	C2: glibenclamide	Median: 3.3 years/3.3 years					White: 89 Black: 4 Asian: 2 Hispanic: 4	—

(Continued)

							Other: 1	
Kiyici 2009	I: metformin C1: rosiglitazone C2: no intervention	52 weeks/52 weeks	T2DM, HbA1c < 8%, BMI < 40 kg/m^2	—	—	Outpatients	—	—
Onuchin 2010	I: metformin C1: insulin	12 months/12 months	T2DM, duration > 3 years, inadequately controlled > 1 year, abdominal obesity, arterial hypertension	—	—	Outpatients	—	7 [3; 14][e] 9 [4; 15][e]
Pfützner 2011	I: metformin	76 weeks[f]/76 weeks	T2DM, HbA1c between 8% to 12%, BMI ≤ 40 kg/m^2	2006 to 2008	—	Outpatients	White: 77 Asian: 16 Black/African American: 1 Other: 6	1.7 (3.1)
	C1: saxagliptin						White: 76 Asian: 17 Black/African American: 2 Other: 5	1.7 (2.8)
Rahman 2011	I: metformin C1: glimepiride	52 weeks/52 weeks	T2DM, duration ≤ 4 years	—	Pakistan	Outpatients	—	—
Schernthaner 2004	I: metformin C1: pioglitazone	52 weeks/52 weeks	T2DM, HbA1c between 7.5% to 11%	—	—	Outpatients	—	3.1 (3.8) 3.4 (4.3)
Schweizer 2007	I: metformin	104 weeks[g]/104 weeks	T2DM, HbA1c between 7.5% to 11.0%, FPG < 15 mmol/L	2004 to 2006	Germany	Outpatients	Caucasian: 70 Hispanic/Latino: 22 Black: 5	1.0 (3.3)[h, i]

(Continued)

							Other: 4	
	C1: vildagliptin						Caucasian: 68 Hispanic/Latino: 20 Black: 8 Other: 4	1.1 (3.6)[h, i]
Teupe 1991	I: metformin	2 years/2 years	T2DM, FPG between 120 mg/100 mL to 180 mg/100 mL, early post-prandial value between 180 mg/100 mL to 250 mg/100 mL	—	Germany	Outpatients[j]	—	8.1 (6.7)
	C1: no intervention							6.4 (4.9)
UKPDS 34 1998	I: metformin	10.7 years/10.7 years	Newly-diagnosed T2DM, > 120% of ideal bodyweight	1977 to 1991	UK	Outpatients	Caucasian: 85 Indian Asian: 4 Afrocaribbean: 10 Other: 1	Newly diagnosed
	C1: glibenclamide						Caucasian: 87 Indian Asian: 4 Afrocaribbean: 8 Other: 1	
	C2: insulin						Caucasian: 88 Indian Asian: 4 Afrocaribbean: 8 Other: 0	
Umpierrez 2014	I: metformin	52 weeks/56 weeks	T2DM, HbA1c between 6.5% to 9.5%	2010 to 2012	USA, Slovakia, Finland, Spain, UK, India, France, Czech Re-	Outpatients	American Indian or Alaska Native: 11 Asian: 8 Native Hawaiian or other Pacific Islander: 1	2.6 (1.8)

(Continued)

					public, Mexico, Canada, Puerto Rico, Argentina, Poland, Brazil, Croatia, Romania, South Africa, Germany, Republic of Korea		Black or African American: 5 White: 75 More than one race: 2	
	C1: dulaglutide (1.5 mg/week)						American Indian or Alaska Native: 11 Asian: 8 Native Hawaiian or other Pacific Islander: 0 Black or African American: 6 White: 75 More than one ethnicity: 1	2.7 (1.5)
	C2: dulaglutide (0.75 mg/week)						American Indian or Alaska Native: 10 Asian: 8 Native Hawaiian or other Pacific Islander: 1 Black or African American: 5 White: 75 More than one ethnicity: 2	2.6 (2.2)
Williams-Herman 2010	I: metformin (1000 mg/day)	104 weeks[k]/104 weeks	T2DM	2005 to 2008	Australia, Chile, Colombia, Costa Rica, Guatemala, Hungary, Lithuania, Malaysia, Mexico, New Zealand, Norway, Peru, Philippines, Russia, South Africa, UK, USA	Outpatients	White: 48 Black: 7 Hispanic: 30 Asian: 8 Other: 8	4.0 (3.9)
	I2: metformin (2000 mg/day)						White: 58 Black: 5 Hispanic: 21 Asian: 6 Other: 10	3.9 (4.0)
	C1: sitagliptin						White: 52 Black: 6	3.7 (4.9)

(Continued)

							Hispanic: 29 Asian: 3 Other: 10	
Yamanouchi 2005	I: metformin C1: pioglitazone C2: glimepiride	52 weeks/52 weeks	T2DM, HbA1c ≥7.0%, FPG ≥ 7.78 mmol/L, BMI between 22 35 kg/m^2 to 35 kg/m^2	—	Japan	Outpatients	—	3.0 (2.5) 3.2 (2.1) 3.3 (2.6)

—: denotes not reported

[a]Follow-up under randomised conditions until end of trial (= duration of intervention + follow-up post-intervention or identical to duration of intervention)

[b]Patients were followed for an additional 24 weeks in which they all received metformin, which was not of interest in this review

[c]The study consisted of an 8 week titration period followed by 12 months of treatment

[d]3 month run-in period prior to 12 months of intervention

[e]Reported as: median [quartile 1; quartile 3]

[f]The study consisted of a 24 week intervention followed by a 52 week extension period in which participants continued their allocated intervention

[g]The study consisted of a 52 week intervention followed by a 52 week extension period in which participants continued their allocated intervention

[h]Reported as: median (interquartile range)

[i]Results from the initial 52 week intervention period

[j]Participants were recruited from hospitals and treated as outpatients. If participants had persistent HbA1C > 10 % they were readmitted to the hospital for further evaluations

[k]The study consisted of a 24 week intervention followed by a 30 week extension period followed by an additional 52 week extension period in which participants continued their allocated intervention

BMI: body mass index; **C**: comparator; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **HOMA-IR**: homeostatic model assessment insulin resistance; **I**: intervention; **IQR**: interquartile range; **SD**: standard deviation; **T2DM**: type 2 diabetes mellitus; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 6. Baseline characteristics (II)

Trial ID	Intervention(s) and comparator(s)	Sex (female %)	Age (mean years (SD))	HbA1c (mean % (SD))	BMI (mean kg/m² (SD))	Comedications/Cointerventions (% of participants)	Comorbidities (% of participants)
Bilezikian 2013	I: metformin	100	64.0 (6.5)	6.8 (0.7)	31.5 (5.8)	Calcium: 100 Vitamin D: 100	—
	C1: rosiglitazone	100	63.6 (6.6)	6.8 (0.7)	31.2 (5.9)	Calcium: 100 Vitamin D: 100	
Campbell 1994	I: metformin	67	57 (10)	11.5 (1.9)	29.6 (5.6)	Diuretic therapy: 16.7 Antihypertensive drugs: 16.7	—
	C1: glipizide	67	57 (9)	11.8 (2.1)	31.2 (6.6)	Diuretic therapy: 12.5 Antihypertensive drugs: 12.5	
Derosa 2003	I: metformin	52	52 (9)	7.4 (0.9)	24.7 (1.2)	Diet and exercise: 100	—
	C1: repaglinide	48	55 (10)	7.6 (0.9)	25.2 (1.1)	Diet and exercise: 100	
Derosa 2004 [a]	I: metformin	49	58 (9)	8.4 (1)	28.1 (1.5)	Diet and exercise: 100	—
	C1: glimepiride	53	56 (10)	8.5 (1.2)	27.6 (1.2)	Diet and exercise: 100	
Derosa 2009	I: metformin	49	55 (5)	9.1 (1.2)	27.2 (1.5)	Diet and exercise: 100	Overweight: 100
	C1: rosiglitazone	54	54 (6)	9.2 (1.3)	27.5 (1.7)	Diet and exercise: 100	Overweight: 100
Erem 2014	I: metformin	68	52.2 (10.5)	7.62 (1.1)	33.6 (4.6)	Diet and exercise: 100	Hypertension: 52.6 Coronary heart disease: 10.5 Hyperlipidemia: 10.5

(Continued)

							Microalbuminuria: 21.1
	C1: gliclazide	63	55.0 (8.7)	8.26 (1.7)	32.7 (3.9)	Diet and exercise: 100	Hypertension: 42.1 Coronary heart disease: 10.5 Hyperlipidemia: 15.8 Microalbuminuria: 15.8
	C2: pioglitazone	74	52.5 (5.2)	8.03 (1.7)	31.3 (4.7)	Diet and exercise: 100	Hypertension: 47.4 Coronary heart disease: 0 Hyperlipidemia: 10.5 Microalbuminuria: 15.8
Kahn 2006	I: metformin	41	57.9 (9.9)	7.4 (0.9)	32.1 (6.1)	—	—
	C1: rosiglitazone	44	56.3 (10.0)	7.4 (0.9)	32.2 (6.7)		
	C2: glibenclamide	42	56.4 (10.2)	7.4 (0.9)	32.2 (6.3)		
Kiyici 2009	I: metformin	—	52.4 (8.3)	6.7 (0.9)	31.6 (3.6)	ACE-inhibitors: 43 Diet and exercise: 100	Hypertension: 43.8
	C1: rosiglitazone		50.7 (6.4)	7.1 (0.9)	31.2 (5.9)	ACE-inhibitors: 26 Diet and exercise: 100	Hypertension: 26.3
	C2: no intervention		52.1 (5.1)	6.4 (0.6)	30.0 (3.2)	ACE-inhibitors: 40 Diet and exercise: 100	Hypertension: 40.0
Onuchin 2010	I: metformin	100	59.4 (9.2)	10.4 (1.6)	32.8 (6.4)	—	Hypertension: 100

(Continued)

							Abdominal obesity: 100
	C1: insulin	100	61.1 (8.5)	11.0 (1.9)	31.1 (7.6)		Hypertension: 100 Abdominal obesity: 100
Pfützner 2011	I: metformin	50	51.8 (10.7)	9.4 (1.3)	30.2 (4.9)	Rescue pioglitazone: 32.0 Diet and exercise: 100	—
	C1: saxagliptin	50	52.1 (10.2)	9.6 (1.3)	30.2 (4.9)	Rescue pioglitazone: 46.3 Diet and exercise: 100	
Rahman 2011	I: metformin	52	51.9 (14.1)	10.5 (2.5)	26.6 (6.2)	—	—
	C1: glimepiride	53	52.0 (15.4)	10.6 (2.9)	26.0 (5.2)		
Schernthaner 2004	I: metformin	42	56 (9.3)	8.7 (1.0)	31.4 (5.2)	Diet: 100	—
	C1: pioglitazone	47	57 (9.4)	8.7 (1.0)	31.2 (4.9)	Diet: 100	
Schweizer 2007	I: metformin	43	53.6 (10.2)	8.7 (1.1)	32.5 (5.7)	Rescue pioglitazone: 27	—[b]
	C1: vildagliptin	47	52.8 (11.7)	8.7 (1.1)	32.4 (5.7)	Rescue pioglitazone: 38	
Teupe 1991	I: metformin	60	51.5 (10.1)	10.0 (1.6)	—	Diet: 100	—
	C1: no intervention	60	56 (7.6)	9.6 (1.3)		Diet: 100	
UKPDS 34 1998	I: metformin	46	53 (8)	7.3 (1.5)	31.6 (4.8)	Diet: 100 Aspirin: 5 Antihypertensive drugs: 51 Lipid-lowering drugs: 1	—
	C1: glibenclamide	46	53 (9)	7.2 (1.7)	31.5 (4.4)	Diet: 100 Aspirin: 3 Antihypertensive drugs: 44	

(Continued)

						Lipid-lowering drugs: 2	
	C2: insulin	45	53 (8)	7.2 (1.5)	31.0 (4.2)	Diet: 100 Aspirin: 12 Antihypertensive drugs: 49 Lipid-lowering drugs: 1	
Umpierrez 2014	I: metformin	55	55.26 (10.1)	7.6 (0.8)	33 (5)	Diet and exercise: 100 Rescue medication: 5.2	—
	C1: dulaglutide (1.5 mg/week)	58	55.51 (10.4)	7.6 (0.9)	34 (6)	Diet and exercise: 100 Rescue medication: 4.5	
	C2: dulaglutide (0.75 mg/week)	56	55.90 (10.7)	7.6 (0.9)	33 (5)	Diet and exercise: 100 Rescue medication: 3.0	
Williams-Herman 2010	I: metformin (1000 mg/day)	51	53.4 (10.2)	8.9 (1.0)	32.1 (6.8)	Rescue glibenclamide: 73	—
	I2: metformin (2000 mg/day)	55	53.2 (9.6)	8.7 (0.9)	32.2 (7.1)	Rescue glibenclamide: 53	
	C1: sitagliptin	48	53.3 (10.2)	8.9 (1.0)	31.2 (5.9)	Rescue glibenclamide: 78	
Yamanouchi 2005	I: metformin	49	54.7 (9.8)	9.9 (0.7)	26.2 (3.8)	Antihypertensive drugs: 46 Diet and exercise: 100	—
	C1: pioglitazone	53	55.2 (9.2)	10.2 (0.8)	25.8 (4.2)	Antihypertensive drugs: 42 Diet and exercise: 100	
	C2: glimepiride	49	55.6 (9.3)	9.8 (0.7)	25.6 (3.5)	Antihypertensive drugs: 49 Diet and exercise: 100	

—: denotes not reported

[a]All baseline values were reported after the 8-week titration period
[b]Study population contained participants at risk of cardiovascular disease

(Continued)

ACE: angiotensin-converting-enzyme; **BMI**: body mass index; **C**: comparator; **HbA1c**: glycosylated haemoglobin A1c; **I**: intervention; **SD**: standard deviation; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 7. Matrix of study endpoints (publications and trial documents)

Trial ID	
Bilezikian 2013	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00679939
	Primary outcome measures: change from baseline in femoral neck BMD via DXA at week 52, change from baseline in femoral neck BMD via DXA at week 76 + 10 days, change in femoral neck BMD via DXA from week 52 +10 Days to Week 76 + 10 days
	Secondary outcome measures: change in BMD in femoral neck, total hip, trochanter, and lumbar spine at week 52, change in BMD in femoral neck, total hip, trochanter, and lumbar spine at week 52 +10 days to week 76 + 10 days, change in BMD in femoral neck, total hip, trochanter, and lumbar spine at week 52 + 30 days to week 76 + 30 days, change in bone specific alkaline phosphatase, procollagen type 1 N-propeptide, C-terminal cross-linking telopeptide of type I collagen, in 25-hydroxyvitamin D, parathyroidea hormone, estradiol, testosterone (total and free), and sex hormone binding globulin at week 52 and week 76
	Other outcome measure: change in free serum estradiol at week 52 and week 76
	Trial results available in trial register: yes
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): change in BMD at the femoral neck by DXA from baseline to week 52 in the rosiglitazone group
	Secondary outcome measure(s): femoral neck, lumbar spine, and total hip BMD as measured by DXA; serum bone-specific alkaline phosphatase, serum procollagen type I N-terminal propeptide and serum C-terminal cross-linking telopeptide of type I collagen; serum calcium, 25-hydroxyvitamin D, parathyroidea hormone and clinical safety
	Other outcome measure(s): change from baseline at prespecified time points in HbA1c, fasting plasma glucose, fasting plasma insulin, and insulin sensitivity measured by the homeostasis model assessment
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): change in bone mineral density at the femoral neck by DXA from baseline to week 52 in the rosiglitazone group
	Secondary outcome measure(s): changes in BMD at the total hip, trochanter, and lumbar spine and to evaluate rosiglitazone effects on bone turnover markers
	Other outcome measure(s): —
Campbell 1994	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —

(Continued)

	Secondary outcome measure(s): —
	Other outcome measure(s): glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion at week 52
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): glycaemic control, body weight, serum lipids, blood lactate and urinary albumin excretion at week 52
Derosa 2003	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): BMI, weight, waist, waist/hip ratio, abdominal circumference, HbA1c, FPG, fasting plasma insulin, total cholesterol, LDL-C, high-density lipoprotein cholesterol, TG, apolipoprotein A-I, apolipoprotein B, lipoprotein(a), plasminogen activator inhibitor-1, fibrinogen, homocysteine, 2h-PPG, 2-h postprandial plasma insulin
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): glycaemic control and cardiovascular risk factors
Derosa 2004	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): HbA1c, FPG, PPG, fasting plasma insulin and postprandial insulin at month 6 and 12
	Secondary outcome measure(s): blood pressure, lipid profile
	Other outcome measure(s): weight, electrocardiogram, adverse experience questioning and laboratory tests
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s):—
	Other outcome measure(s): metabolic parameters

(Continued)

Derosa 2009	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): BMI, HbA1c, FPG, PPG, FPI, and PPI after 3 and after 15 months, adverse events
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): anthropometric and metabolic measurements after 3 and 15 months
Erem 2014	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): anthropometric measures, glycaemic variables, insulin sensitivity measures, lipid profile, coagulation and fibrinolysis measures, inflammation markers, endothelial function and blood pressure measured at baseline at months 3, 6, and 12, and safety and tolerability recorded throughout the study
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): anthropometric measurements, fasting plasma glucose, postprandial plasma glucose, HbA1c, insulin, HOMA-IR, lipid parameters, the markers of coagulation/fibrinolysis, inflammation and endothelial dysfunction at baseline and months 3, 6 and 12
Kahn 2006	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00279045
	Primary outcome measure(s): time from randomisation to monotherapy failure
	Secondary outcome measure(s): comparison of effects of long-term treatment with rosiglitazone, metformin, glibenclamide: - maintenance/restoration of beta-cell function, progression of microalbuminuria, fibrinolytic markers (PAI-1, fibrinogen, CRP)
	Other outcome measure(s): —

(Continued)

	Trial results available in trial register: no
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): time from randomisation to treatment failure **Secondary outcome measure(s)**: time from randomisation to a confirmed FPG of more than 140 mg/dL after at least 6 weeks of treatment at the maximum-tolerated dose of a study drug (for participants who entered the study with a FPG of 140 mg/dL or less) **Other outcome measure(s)**: FPG, HbA1c, weight, and measures of insulin sensitivity and β-cell function
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): time to monotherapy failure **Secondary outcome measure(s)**: FPG, HbA1c, insulin sensitivity and β-cell function **Other outcome measure(s)**: —
Kiyici 2009	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: safety, BMI, waist circumference, percentage body fat, HbA1c, FPG, HOMA-IR, TC, LDL-c, TG, blood pressure, LAEI, SAEI, serum MCP-1, serum MMP-9
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: SAEI, LAEI, serum MCP-1, serum MMP-9 levels measured at baseline and at week 52
Onuchin 2010	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: HbA1c, insulin, C-peptide, HOMA-IR, total cholesterol, triglycerides, HDL-C, LDL-C, albumin excretion in urine, BMI, blood pressure, echocardiography, thickness of carotid arteries via ultrasound, health related quality of life, level of depression, diabetes satisfaction questionnaire

(Continued)

	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): —
Pfützner 2011	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00327015 [d]
	Primary outcome measure(s): change in HbA1c at week 24
	Secondary outcome measure(s): change in FPG at week 24, percentage of participants achieving HbA1c < 7% and ≤ 6.5% at week 24, changes in postprandial glucose area under the curve at week 24, percentage of participants requiring rescue or discontinuation at week 24
	Other outcome measure(s): —
	Trial results available in trial register: yes
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): HbA1c, FPG, vital signs, body weight. Efficacy assessments included change from baseline in HbA1c, FPG, 120-min PPG and PPG-area under the curve; proportion of patients achieving HbA1c < 7.0%; time to rescue therapy for failing to achieve prespecified glycaemic targets or discontinuation; and proportion of patients requiring rescue therapy for failing to achieve prespecified glycaemic targets or discontinuing for insufficient efficacy at weeks 4, 6, 8, 12, 16, 20, 24, 30, 37, 50 and 63. Adverse events, serious adverse events, and discontinuations because of adverse events, and changes from baseline laboratory parameters and vital signs. Hypoglycaemia
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): HbA1c, fasting plasma glucose, 120-min postprandial glucose and PPG-area under the curve
Rahman 2011	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —

(Continued)

	Other outcome measure(s): change in SSA, FPG, HbA1c, BMI and lipid profiles from baseline
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): change in SSA from baseline
Schernthaner 2004	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): FPG, insulin and lipid profiles
	Other outcome measure(s): adverse events, laboratory tests, blood pressure and weight
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): HbA1c, fasting plasma glucose, insulin levels, cholesterol, lipid profiles and urinary albumin/creatinine ratio
Schweizer 2007	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00099866 [e]
	Source: NCT00138567 [f]
	Primary outcome measure [e]: change from baseline in HbA1c at 52 weeks
	Primary outcome measure(s) [f]: safety during 104 weeks of treatment, change from baseline in HbA1c at 104 weeks
	Secondary outcome measure [e]: —
	Secondary outcome measure(s):[f] change in HbA1c between 52 weeks and 104 weeks, change in FPG between 52 weeks and 104 weeks, change from baseline in FPG at 104 weeks, change from baseline in HOMA-β at 104 weeks, change in HOMA-β between 52 weeks and 104 weeks
	Other outcome measure(s): [e, f]: —
	Trial results available in trial register: no
	Endpoints quoted in publication(s)[b,c]
	Schweizer 2007[e]
	Göke 2008[f]
	Primary outcome measure [e]: change from baseline in HbA1c

(Continued)

	Primary outcome measure [f]: mean change in HbA1c from baseline to the end of the extension study **Secondary outcome measure(s)** [e, f]: FPG, fasting plasma lipids and body weight[e, f] **Other outcome measure** [e, f]: —
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure** [e]: HbA1c **Other outcome measure** [f]: efficacy and tolerability
Teupe 1991	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: HbA1c, safety, physical examination, ECG, erythrocyte sedimentation rate, minor blood picture, platelets, Quick-test, ALAT, ASAT, gamma-glutamyl transferase, bilirubin, total protein
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): — **Secondary outcome measure(s)**: — **Other outcome measure(s)**: HbA1c
UKPDS 34 1998	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: design article (UKPDS 34 1998) **Primary outcome measure(s)**: diabetes related outcome measures **Secondary outcome measure(s)**: — **Other outcome measure(s)**: biochemical variables, quality of life, intervention failure, adverse events **Trial results available in trial register**: no
	Endpoints quoted in publication(s)[b,c]
	Source: UKPDS publications (UKPDS 34 1998)[g] **Primary outcome measure(s)**: — **Secondary outcome measure(s)**: —

(Continued)

Other outcome measure(s): biochemical variables, intervention failure, hypoglycaemia

Endpoints quoted in abstract of publication(s)[b,c]

Source: UKPDS publications (UKPDS 34 1998)[g]

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): biochemical variables, intervention failure, hypoglycaemia

Umpierrez 2014

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]

Source: NCT01126580

Primary outcome measure(s): change in HbA1c at 26 weeks

Secondary outcome measure(s): percentage achieving HbA1c less than 7% and less than or equal to 6.5% at 26 and 52 weeks, change from baseline to 26 and 52 weeks in fasting glucose, change from baseline to 26 and 52 weeks in daily mean blood glucose values from the 8-point self-monitored blood glucose profiles, change from baseline to 26 and 52 weeks in Body Weight, change from baseline to 26 and 52 weeks in BMI, change from baseline to 26 and 52 weeks in HOMA, change from baseline to 26 and 52 weeks in the Impact of Weight on Activities of Daily Living Score, Impact of Weight on Self-Perception Score, Diabetes Treatment Satisfaction Questionnaire Score, Status Version Diabetes Treatment Satisfaction Questionnaire Score, Change Version and Diabetes Symptoms Checklist Participant-reported Outcome Score, adverse events at 26 and 52 weeks, change from baseline to 26 and 52 weeks in electrocardiogram parameters, Fridericia Corrected QT Interval and PR interval, change from baseline to 26 and 52 weeks in pulse, blood pressure, cholesterol, pancreatic enzymes and calcitonin, number of participants with treatment emergent anti-LY2189265 antibodies, number of self-reported hypoglycaemic events at 26 and 52 weeks, rate of self-reported hypoglycaemic events at 52 weeks, number of participants with adjudicated pancreatitis at 52 weeks plus 30-day follow up, number of participants with adjudicated cardiovascular events at 52 weeks plus 30-day follow up, measurement of LY2189265 (area under the concentration curve)

Other outcome measure(s): —

Trial results available in trial register: yes

Endpoints quoted in publication(s)[b,c]

Primary outcome measure(s): HbA1c change from baseline at 26 weeks

Secondary outcome measure(s): change in HbA1c at 52 weeks and the following measures at 26 and 52 weeks: percentage of patients achieving HbA1c < 7.0% (< 53 mmol/mol) and < or = 6.5% (< or = 48 mmol/mol), changes in body weight, fasting serum glucose, eight-point self-monitored plasma glucose profiles, and measures of b-cell function, insulin sensitivity, and fasting glucagon

Other outcome measure(s): safety assessments at 26 and 52 weeks and dulaglutide antidrug antibody testing

Endpoints quoted in abstract of publication(s)[b,c]

Primary outcome measure(s): change from baseline glycosylated in HbA1c at 26 weeks

Secondary outcome measure(s): —

Other outcome measure(s): —

(Continued)

Williams-Herman 2010	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00103857
	Primary outcome measure(s): change from baseline in HbA1c at Week 24
	Secondary outcome measure(s): change from baseline in FPG at week 24, change from baseline in 2h-PPG at week 24, change from baseline in HbA1c at week 54, change from baseline in FPG at week 54, change from baseline in 2h-PPG at week 54, change from baseline in HbA1c at week 104, change from baseline in FPG at week 104, change from baseline in 2h-PPG at week 104
	Other outcome measure(s): —
	Trial results available in trial register: yes
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): change from baseline in HbA1c at week 104
	Secondary outcome measure(s): FPG, 2h-PPG, body weight; proportion of participants with an HbA1c < 7% at week 104; proportion of participants with an HbA1c < 7% at both weeks 24 and 104
	Other outcome measure(s): fasting serum insulin, fasting serum proinsulin, proinsulin/insulin ratio, HOMA-β, HOMA-IR, lipids
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s):
	Other outcome measure(s): efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy in patients with T2DM and inadequate glycaemic control at week 104
Yamanouchi 2005	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): HbA1c
	Secondary outcome measure(s): —
	Other outcome measure(s): FPG, 1,5-anhydroglucitol, lipid profile, plasma insulin, haematology and biochemistry
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): fasting plasma glucose, HbA1c, 1,5-anhydroglucitol, cholesterol, weight and safety data

—: denotes not reported

(Continued)

[a]Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers)

[b]Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial)

[c]Primary and secondary outcomes refer to verbatim specifications in publication/records. Other outcome measures refer to all outcomes not specified as primary or secondary outcome measures

[d]Outcome measures from trial register of only 24 weeks of intervention

[e]Initial 52 weeks of intervention

[f]52 week extension

[g]Not reported for the comparisons of interest for this review

2h-PPG: 2 hour post prandial glucose; **ALAT**: alanine-aminotransferase; **ASAT**: aspartate-aminotransferase; **BMD**: bone mineral density; **BMI**: body mass index; **CRP**: C-reactive protein; **DXA**: dual-energy x-ray absorptiometry; **EMA**: European Medicines Agency; **FDA**: Food and Drug Administration (US); **FPG**: fasting plasma glucose; **FPI**: fasting plasma insulin; **HbA1c**: glycated haemoglobin; **HDL-C**: high-density lipoprotein cholesterol; **HOMA-β**: homeostasis model assessment beta cell function;**HOMA-IR**: homeostasis model assessment insulin resistance; **LAEI**: large artery elasticity index; **LDL-C**: low-density lipoprotein cholesterol; **MCP-1:** monocyte chemoattractant protein 1; **MMP-1:** matrix metallopeptidase 9; **mo**: month(s); **NA**: not applicable; **NT**: no trial document available; **PAI-1**: plasminogen activator inhibitor-1; **PPG**: post-prandial glucose; **PPI**: post-prandial insulin; **SAEI**: small artery elasticity index; **SSA**: serum sialic acid; **T2DM**: type 2 diabetes mellitus; **TC**: total cholesterol; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 8. High risk of outcome reporting bias according to ORBIT classification

Trial ID	Outcome	High risk of bias (category A)[a]	High risk of bias (category D)[b]	High risk of bias (category E)[c]	High risk of bias (category G)[d]
Bilezikian 2013	Anthropometric measures	No	No	Yes	No
	Intervention failure	No	Yes	No	No
Campbell 1994	Lactic acidosis	No	No	No	Yes
	Serious adverse events	No	Yes	No	No
	Severe hypoglycaemia	No	Yes	No	No
Derosa 2003	All-cause mortality	No	No	Yes	No
	Anthropometric measures	No	Yes[e]	No	No
	Glycaemic control	No	Yes[e]	No	No
Derosa 2004	ND				
Derosa 2009	All-cause mortality	No	No	Yes	No
	Serious adverse events	No	Yes[e]	No	No
	Severe hypoglycaemia	No	Yes[e]	No	No
	Glycaemic control	No	Yes[e]	No	No

(Continued)

	Anthropometric variables	No	Yes[e]	No	No
Erem 2014	ND				
Kahn 2006	Health-related quality of life	No	Yes	No	No
Kiyici 2009	ND				
Onuchin 2010	All-cause mortality	No	No	Yes	No
	Serious adverse events	No	No	Yes	No
	Severe hypoglycaemia	No	No	No	Yes
Pfützner 2011	Anthropometric measures	No	Yes[e]	Yes	No
Rahman 2011	All-cause mortality	No	No	Yes	No
	Serious adverse events	No	No	Yes	No
Schernthaner 2004	Serious adverse events	No	No	Yes	No
	Anthropometric measures	No	Yes[e]	Yes	No
Schweizer 2007	Non-fatal myocardial infarction	No	No	No	Yes
	Serious adverse events	No	Yes[e, f]	No	No
	Severe hypoglycaemia	No	Yes[e, f]	No	No
	Glycaemic control[g]	No	Yes[e]	No	No
	Anthropometric measures[g]	No	Yes[e]	No	No
	Intervention failure	No	No	Yes	No
Teupe 1991	All-cause mortality	No	No	Yes	No
	Serious adverse events	No	No	Yes	No
	Lactic acidosis	No	No	No	Yes
UKPDS 34 1998	All-cause mortality	No	Yes	No	No
	Serious adverse events	No	Yes	No	No
	Health-related quality of life	No	Yes	No	No
	Cardiovascular mortality	No	Yes	No	No
	Non-fatal myocardial infarction	No	Yes	No	No
	Non-fatal stroke	No	Yes	No	No
	End-stage renal disease	No	Yes	No	No

(Continued)

	Blindness	No	Yes	No	No
Umpierrez 2014	ND				
Williams-Herman 2010	Intervention failure	No	Yes[e]	No	No
Yamanouchi 2005	All-cause mortality	No	No	Yes	No
	Serious adverse events	No	No	Yes	No
	Severe hypoglycaemia	No	No	No	Yes

[a]Clear that outcome was measured and analysed; trial report states that outcome was analysed but reports only that result was not significant
(Classification 'A', table 2, Kirkham 2010)
[b]Clear that outcome was measured and analysed; trial report states that outcome was analysed but report no results
(Classification 'D', table 2, Kirkham 2010)
[c]Clear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported due to non-significant results (Classification 'E', table 2, Kirkham 2010)
[d]Unclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results (Classification 'G', table 2, Kirkham 2010)
[e]Outcome reported in an inadequate format that could not be used in our meta-analysis
[f]Unclear whether participants with the outcomes in the initial 52-week study were being added to the results from the extension period
[g]Outcomes measured in the extension period of 52 weeks

ND: none detected; **ORBIT**: Outcome Reporting Bias In Trials; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 9. Definition of endpoint measurement[a]

Study ID	Endpoints	Definition
Bilezikian 2013	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	ND[b]
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	"Cardiac death" (IO)
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—

(Continued)

	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"From weeks 8 to 16, subjects with mean daily glucose 6.1 mmol/L at the maximum tolerated doses of blinded RSG or MET received open-label sulfonylurea. After 4 months of double-blind study medication, subjects with HbA1c > 7.5% at the maximum dose of medication could up-titrate or add open-label sulfonylurea at the discretion of the investigator." (IO)
Campbell 1994	**All-cause mortality**	ND[b]
	Serious adverse events	ND[b]
	Health-related quality of life	—
	Non serious adverse events	—
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	ND[b]
	Amputation of lower extremity	—
	Congestive heart failure	—

(Continued)

	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Derosa 2003	**All-cause mortality**	ND[b]
	Serious adverse events	"Serious adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	—
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Severe hypoglycaemia" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Derosa 2004	**All-cause mortality**	ND[b]
	Serious adverse events	"Serious adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse experiences" (SO)
	Cardiovascular mortality	—

(Continued)

	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Severe hypoglycaemia" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Derosa 2009	**All-cause mortality**	ND[b]
	Serious adverse events	"All adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	"All adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—

(Continued)

	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Erem 2014	**All-cause mortality**	ND[b]
	Serious adverse events	ND[b]
	Health-related quality of life	—
	Non serious adverse events	"Adverse events and side effects" (SO)
	Cardiovascular mortality	"Cardiovascular death" (IO)
	Non-fatal myocardial infarction	"Myocardial infarction"[c] (IO)
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Hypoglycaemia"[d] (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	"Congestive heart failure" (IO)
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Kahn 2006	**All-cause mortality**	"Deaths from all causes" (IO)
	Serious adverse events	"Any event that was fatal, life threatening, or disabling; resulted in hospitalization or prolonged a hospital stay; was associated with a congenital abnormality, cancer, or a drug overdose (either accidental or intentional); or was regarded by the investigator as serious or suggested any substantial haz-

(Continued)

		ard, contraindication, side effect, or precaution." (IO)
	Health-related quality of life	"Medical Outcomes Study 36-Item Short-Form Health Survey" (SO)
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	"Myocardial infarction… Nonfatal" (IO)
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Hypoglycaemia... Serious Events" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	"Congestive heart failure" (AO)
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"Treatment failure, which was defined as confirmed hyperglycemia (fasting plasma glucose level > 180 mg/dL) on consecutive (IO, AO)
Kiyici 2009	**All-cause mortality**	ND[b]
	Serious adverse events	"Serious adverse effect" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Side effects" (SO)
	Cardiovascular mortality	ND[b]
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—

(Continued)

	Blindness	—
	Severe hypoglycaemia	—
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Onuchin 2010	**All-cause mortality**	ND[b]
	Serious adverse events	ND[b]
	Health-related quality of life	"Medical Outcomes Study 36-2-item Short Form Health Survey" (SF-36v2)" "Total physical health component" "Total mental health component" (SO)
	Non serious adverse events	—
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	ND[b]
	Anthropometric measures	BMI (IO)
	Glycaemic control	HbA1c (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—

(Continued)

	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Pfützner 2011	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	"Serious adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Hypoglycemia" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"Patients were eligible for rescue therapy based on progressively strict glycaemic control criteria over 24 weeks if FPG levels were as follows: > 240 mg/dL (week 6); > 220 mg/dL (week 8) and > 200 mg/dL (weeks 12, 16, 20 and 24). Patients who met rescue criteria were entered directly into the long-term extension period, where they were administered open-label pioglitazone 15 mg, which could be uptitrated to 45 mg, in addition to blinded study medication." (IO)
Rahman 2011	**All-cause mortality**	ND[b]

(Continued)

	Serious adverse events	ND[b]
	Health-related quality of life	—
	Non serious adverse events	—
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Schernthaner 2004	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	"AEs... judged as severe" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—

(Continued)

	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	—
Schweizer 2007	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	"Serious adverse effects" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Severe hypoglycaemia was defined as any episode requiring the assistance of another party" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—

(Continued)

	Intervention failure	In the 52 week extension period: "Pioglitazone was added to the blinded study drug from the first visit of the extension as rescue medication for patients with confirmed fasting plasma glucose > 10 mmol/L, according to the investigator's clinical judgment and prescribing guidelines" (IO)
Teupe 1991	**All-cause mortality**	ND[b]
	Serious adverse events	ND[b]
	Health-related quality of life	—
	Non serious adverse events	"complaints according to a standardized questionnaire (side effects)" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	—
	Non-fatal stroke	—
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	—
	Anthropometric measures	Weight (IO)
	Glycaemic control	HbA1c (IO)
	Lactic acidosis	ND[b]
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"Confirmed therapeutic failure" "HbA1c values exceeding 10 % were re-checked after 4 weeks. If the elevation persisted, the patient was admitted to hospital for at least 5 days to decide whether this was due to non-compliance to diet and/or drug treatment or to secondary failure of therapy" (IO)
UKPDS 34 1998	**All-cause mortality**	ND
	Serious adverse events	"Serious adverse events" (IO)

(Continued)

	Health-related quality of life	—
	Non serious adverse events	—
	Cardiovascular mortality	"Death due to cardiovascular disease is calculated by adding: fatal myocardial infarction, sudden death, fatal stroke, death from peripheral vascular disease" (IO)
	Non-fatal myocardial infarction	"WHO clinical criteria with associated (IO)
	Non-fatal stroke	"Major stroke-stroke with symptoms that persisted for more than one month (ICD 430 to 434.9 and 436)" (IO)
	End-stage renal disease	"Renal failure dialysis and/or plasma creatinine > 250 mmol/1 not ascribable" (IO)
	Blindness	"Blindness" (IO)
	Severe hypoglycaemia	"Major if third-party help or medical intervention was necessary" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	"Major limb complications-requiring amputation of digit or limb for any reason (ICD codes 5.845 to 5.848)" (IO)
	Congestive heart failure	Heart failure (IO)
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"Marked hyperglycaemia again developed" (IO)
Umpierrez 2014	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	"Serious adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	"Fatal CV Event" (AO)
	Non-fatal myocardial infarction	Acute myocardial infarction[e] (AO)

(Continued)

	Non-fatal stroke	Stroke[e](AO)
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Severe hypoglycemia was any episode requiring the assistance of another person to actively administer therapy" (IO)
	Anthropometric measures	BMI; weight (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	Cardiac failure congestive (AO)
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"An add-on re cue therapy was allowed for patients who met prespecified criteria for severe, persistent hyperglycaemia" (IO)
Williams-Herman 2010	**All-cause mortality**	"Deaths" (IO)
	Serious adverse events	"Serious adverse experiences" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse experiences" (SO)
	Cardiovascular mortality	ND[f]
	Non-fatal myocardial infarction	"Acute myocardial infarction"[e] (IO)
	Non-fatal stroke	"Cerebrovascular accident"[e] (IO)
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	"Hypoglycaemia that required assistance (including medical treatment) or exhibited marked severity (i.e. depressed level of consciousness, loss of consciousness or seizure)" (IO)
	Anthropometric measures	BMI; weight (IO)

(Continued)

	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	—
	Cardiac revascularisation	—
	Peripheral revascularisation	—
	Socioeconomic effects	—
	Intervention failure	"Glibenclamide; from week 0 to 6 glycaemic rescue criteria were FPG > 270 mg/dL, from week 6 to 12 FPG > 240 mg/dL, and from week 12 to 24 FPG > 200 mg/dL; from week 30 the criteria was HbA1c > 8.0%; from week 50 the criteria was HbA1c > 7.5%; participants requiring glycaemic rescue during the study continued treatment until discontinuation from or completion of the study" (IO)
Yamanouchi 2005	**All-cause mortality**	ND[b]
	Serious adverse events	"Major adverse events" (IO)
	Health-related quality of life	—
	Non serious adverse events	"Adverse events" (SO)
	Cardiovascular mortality	—
	Non-fatal myocardial infarction	ND[b]
	Non-fatal stroke	ND[b]
	End-stage renal disease	—
	Blindness	—
	Severe hypoglycaemia	ND[b]
	Anthropometric measures	BMI (IO)
	Glycaemic control	HbA1c; FPG (IO)
	Lactic acidosis	—
	Amputation of lower extremity	—
	Congestive heart failure	ND[b]
	Cardiac revascularisation	ND[b]

(Continued)

Peripheral revascularisation	ND[b]
Socioeconomic effects	—
Intervention failure	"Treatment failure" (IO)

[a]In addition to definition of endpoint measurement, description who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement)

[b]We assume the outcome was evaluated but it was not stated explicitly in the full article

[c]There were no myocardial infarctions throughout the study including non-fatal

[d]There were no hypoglycaemic incidents throughout the study including severe hypoglycaemia

[e]Causes of death during the study are known and thus, these events are non-fatal

[f]Causes of death during the study are known and none were cardiovascular.

AEs: adverse events; **BMI**: body mass index; **CV**: cardiovascular; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **ICD**: International Classification of Diseases and Related Health Problems; **ND**: not defined; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 10. Adverse events (I)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Deaths (N)	Deaths (% of participants)	Participants with at least one adverse event (N)	Participants with at least one adverse event (%)	Participants with at least one severe/serious adverse event (N)	Participants with at least one severe/serious adverse event (%)
Bilezikian 2013	I: metformin	111	0	0	72	64.9	5	4.5
	C1: rosiglitazone	114	1	0.9	82	71.9	7	6.1
Campbell 1994	I: metformin	24	0	0	—	—	—	—
	C1: glipizide	24	0	0	—	—	—	—
Derosa 2003	I: metformin	56	—	—	—	—	0	0
	C1: repaglinide	56	—	—	—	—	0	0
Derosa 2004	I: metformin	75	0	0	2	2.7	0	0
	C1: glimepiride	73	0	0	0	0	0	0
Derosa 2009	I: metformin	67	—	—	—	—	—	—
	C1: rosiglitazone	69	—	—	—	—	—	—
Erem 2014	I: metformin	19	0	0	0	0	0	0
	C1: gliclazide	19	0	0	0	0	0	0
	C2: pioglitazone	19	0	0	0	0	0	0
Kahn 2006	I: metformin	1454	31	2.1	1010	69.5	331	22.8
	C1: rosiglitazone	1456	34	2.3	992	68.1	346	23.8
	C2: glibenclamide	1441	31	2.2	1013	70.3	308	21.4
Kiyici 2009	I: metformin	16	0	0	—	—	0	0

(Continued)

	C1: rosiglitazone	19	0	0	—	—	0	0
	C2: no intervention	15	0	0	—	—	0	0
Onuchin 2010	I: metformin	46	—	—	—	—	—	—
	C1: insulin	45	—	—	—	—	—	—
Pfützner 2011	I: metformin	328	5	1.5	224	68.3	15	4.6
	C1: saxagliptin	335	2	0.6	222	66.3	16	4.8
Rahman 2011	I: metformin	102	—	—	—	—	—	—
	C1: glimepiride	102	—	—	—	—	—	—
Schernthaner 2004	I: metformin	597	2	0.3	346	58.0	-[a]	-[a]
	C1: pioglitazone	597	3	0.5	316	52.9	-[a]	-[a]
Schweizer 2007	I: metformin	252[b]	2[b]	1.2	190[b]	75.4	13[b]	5.2
	C1: vildagliptin	519[b]	2[b]	0.6	364[b]	70.1	35[b]	6.7
Teupe 1991	I: metformin	50	—	—	—	—	—	—
	C1: no intervention	50	—	—	—	—	—	—
UKPDS 34 1998	I: metformin	342	—	—	—	—	—	—
	C1: glibenclamide	277	—	—	—	—	—	—
	C2: insulin	409	—	—	—	—	—	—
Umpierrez 2014	I: metformin	268	0	0	170	63.4	16	6.0
	C1: dulaglutide (1.5 mg/week)	269	0	0	177	65.8	15	5.6
	C2: dulaglutide (0.75 mg/week)	270	0	0	178	65.9	20	7.4
Williams-Herman 2010	I: metformin (1000 mg/day)	182	1[c]	0.5	74[d]	40.7	7[d]	5.5

(Continued)

	I2: metformin (2000 mg/day)	182	0[c]	0	99[d]	54.4	9[d]	7.7
	C1: sitagliptin	179	0[c]	0	71[d]	39.7	13[d]	8.4
Yamanouchi 2005	I: metformin	39	—	—	0	0	0	0
	C1: pioglitazone	38	—	—	4	10.5	0	0
	C2: glimepiride	37	—	—	1	2.7	0	0

—: denotes not reported

[a]7.4% and 4.9% of adverse events in the metformin and pioglitazone group, respectively, were judged to be serious adverse events

[b]From the initial 52 weeks of intervention

[c]From full article. Triasl register reports 0 deaths in all intervention groups

[d]From full article. Trials register reports 10, 14 and 15 serious adverse events for metformin 1000 mg/day, 2000 mg/day and sitagliptin 100 mg/day, respectively

C: comparator; **I**: intervention; **N**: number of participants; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 11. Adverse events (II)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants discontinuing trial due to an adverse event (N)	Participants discontinuing trial due to an adverse event (%)	Participants with at least one hospitalisation (N)	Participants with at least one hospitalisation (%)	Participants with at least one outpatient treatment (N)	Participants with at least one outpatient treatment (%)
Bilezikian 2013	I: metformin	111	12	10.8	—	—	—	—
	C1: rosiglitazone	114	14	12.3	—	—	—	—
Campbell 1994	I: metformin	24	1	4.2	—	—	—	—
	C1: glipizide	24	1	4.2	—	—	—	—
Derosa 2003	I: metformin	56	2	3.6	—	—	—	—
	C1: repaglinide	56	0	0	—	—	—	—
Derosa 2004	I: metformin	83[a]	2	2.4	—	—	—	—
	C1: glimepiride	81[a]	0	0	—	—	—	—
Derosa 2009	I: metformin	67	5	7.5	—	—	—	—
	C1: rosiglitazone	69	3	4.3	—	—	—	—
Erem 2014	I: metformin	19	—	—	—	—	—	—
	C1: gliclazide	19	—	—	—	—	—	—
	C2: pioglitazone	19	—	—	—	—	—	—
Kahn 2006	I: metformin	1454	178	12.2	172	11.8	—	—
	C1: rosiglitazone	1456	169	11.6	169	11.6	—	—
	C2: glibenclamide	1441	215	14.9	150	10.4	—	—
Kiyici 2009	I: metformin	16	0	0	—	—	—	—

(Continued)

	C1: rosiglitazone	19	0	0	—	—	—	—
	C2: no intervention	15	0	0	—	—	—	—
Onuchin 2010	I: metformin	46	—	—	—	—	—	—
	C1: insulin	45	—	—	—	—	—	—
Pfützner 2011	I: metformin	328	16	4.9	—	—	—	—
	C1: saxagliptin	335	14	4.2	—	—	—	—
Rahman 2011	I: metformin	102	—	—	—	—	—	—
	C1: glimepiride	102	—	—	—	—	—	—
Schernthaner 2004	I: metformin	597	39	6.5	—	—	—	—
	C1: pioglitazone	597	42	7.0	—	—	—	—
Schweizer 2007	I: metformin	252[b]	18[b]	7.1	—	—	—	—
	C1: vildagliptin	519[b]	22[b]	4.2	—	—	—	—
Teupe 1991	I: metformin	50	—	—	—	—	—	—
	C1: no intervention	50	—	—	—	—	—	—
UKPDS 34 1998	I: metformin	342	—	—	—	—	—	—
	C1: glibenclamide	277	—	—	—	—	—	—
	C2: insulin	409	—	—	—	—	—	—
Umpierrez 2014	I: metformin	268	24	9.0	—	—	—	—
	C1: dulaglutide (1.5 mg/week)	269	24	8.9	—	—	—	—
	C2: dulaglutide (0.75 mg/week)	270	25	9.3	—	—	—	—
Williams-Herman 2010	I: metformin (1000 mg/day)	182	8	4.4	—	—	—	—

(Continued)

	I2: metformin (2000 mg/day)	182	7	3.8	—	—	—	—
	C1: sitagliptin	179	5	2.8	—	—	—	—
Yamanouchi 2005	I: metformin	39	0	0	—	—	—	—
	C1: pioglitazone	38	2	5.3	—	—	—	—
	C2: glimepiride	37	0	0	—	—	—	—

—: denotes not reported

[a]We did not use the per-protocol population, since it excluded participants discontinuing the trial due to an adverse event
[b]From the initial 52 weeks of intervention

C: comparator; **I**: intervention; **N**: number of participants; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 12. Adverse events (III)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse events (N)	Participants with at least one specific adverse event (%)
Bilezikian 2013	I: metformin	111	Peripheral oedema	0	0.0
			Weight increased	1	0.9
			Dyspepsia	6	5.4
			Back pain	1	0.9
			Fatigue	1	0.9
			Headache	0	0.0
			Overweight	0	0.0
			Diarrhoea	12	1.8
			Nausea	2	1.8
	C1: rosiglitazone	114	Peripheral oedema	12	10.5
			Weight increased	9	7.9
			Dyspepsia	2	1.8
			Back pain	2	1.8
			Fatigue	2	1.8
			Headache	2	1.8
			Overweight	2	0.9
			Diarrhoea	1	0.9
			Nausea	1	
Campbell 1994	I: metformin	24	—	—	—
	C1: glipizide	24	—	—	—
Derosa 2003	I: metformin	56	Mild hypoglycaemia	0	0
			Severe hypoglycaemia	0	0
			Nausea and diarrhoea	2	3.6
	C1: repaglinide	56	Mild hypoglycaemia	0	0
			Severe hypoglycaemia	0	0
			Nausea and diarrhoea	0	0
Derosa 2004	I: metformin	83	Diarrhoea	2	2.4

(Continued)

			Nausea	2	2.4
	C1: glimepiride	81	Diarrhoea	0	0
			Nausea	0	0
Derosa 2009	I: metformin	67	Excessive body weight increase	0	0
			Nausea	1	1.5
			Gastroinstentinal events	4	6.0
			Hypoglycemia	0	0
	C1: rosiglitazone	69	Excessive body weight increase	3	4.3
			Nausea	0	0
			Gastrointestinal events	0	0
			Hypoglycemia	0	0
Erem 2014	I: metformin	19	—	—	—
	C1: gliclazide	19	—	—	—
	C2: pioglitazone	19	—	—	—
Kahn 2006	I: metformin	1454	Cardiovascular disease	46 (12)[a]	3.2 (0.8)[a]
			Fatal myocardial infarction	2 (0)	0.1 (0)
			Nonfatal myocardial infarction	18 (3)	1.2 (0.2)
			Congestive heart failure	12 (7)	0.8 (0.5)
			Stroke	17 (2)	1.2 (0.1)
			Peripheral vascular disease	6 (21)	0.4 (1.4)
			Gastrointestinal events 8	7 (550)	0.5 (37.8)
			Nausea	0 (170)	0.0 (11.7)
			Vomiting	1 (83)	0.1 (5.7)
			Diarrhoea	1 (344)	0.1 (23.7)
			Abdominal discomfort	6 (218)	0.4 (15.0)
			Hypoglycaemia	1 (167)	0.1 (11.5)
			Weight gain	0 (18)	0 (1.2)
			Oedema	0 (104)	0 (7.2)
	C1: rosiglitazone	1456	Cardiovascular disease	49 (13)[a]	3.4 (0.9)[a]
			Fatal myocardial infarction	2 (0)	0.1 (0)
			Nonfatal myocardial infarction	22 (3)	1.5 (0.2)
			Congestive heart failure	12 (10)	0.8 (0.7)
			Stroke	13 (3)	0.9 (0.2)
			Peripheral vascular disease	7 (29)	0.5 (2.0)
			Gastrointestinal events	8 (327)	0.5 (22.5)
			Nausea	2 (110)	0.1 (7.6)
			Vomiting	0 (58)	0 (4.0)
			Diarrhoea	1 (128)	0.1 (8.8)
			Abdominal discomfort	5 (156)	0.3 (10.7)
			Hypoglycaemia	1 (141)	0.1 (9.7)
			Weight gain	3 (97)	0.2 (6.7)
			Oedema	2 (203)	0.1 (13.9)
	C2: glibenclamide	1441	Cardiovascular disease	26 (15)[a]	1.8 (1.0)[a]
			Fatal myocardial infarction	3 (0)	0.2 (0)

(Continued)

			Nonfatal myocardial infarction	11 (4)	0.8 (0.3)
			Congestive heart failure	3 (6)	0.2 (0.4)
			Stroke		0.8 (0.3)
			Peripheral vascular disease	12 (5)	0.3 (1.9)
			Gastrointestinal events	4 (27)	0.2 (21.7)
			Nausea	3 (313)	0.0 (6.9)
			Vomiting	0 (99)	0.0 (3.1)
			Diarrhoea	0 (45)	0.0 (9.9)
			Abdominal discomfort	0 (142)	0.2 (11.1)
			Hypoglycaemia	3 (160)	0.6 (38.1)
			Weight gain	8 (549)	0.0 (3.3)
			Oedema	0 (47)	0.1 (8.4)
				2 (121)	
Kiyici 2009	I: metformin	16	—	—	—
	C1: rosiglitazone	19	—	—	—
	C2: no intervention	15	—	—	—
Onuchin 2010	I: metformin	46	Hypoglycaemia	—	—
	C1: insulin	45			
Pfützner 2011	I: metformin	328	Nasopharyngitis	19	5.8
			Urinary tract infection		
			Influenza	25	7.6
			Upper respiratory tract infection		
			Diarrhoea	19	5.8
			Headache		
			Back pain	10	3.0
			Hypertension		
				30	9.1
			Reported hypoglycaemia	18	5.5
			Confirmed hypoglycaemia	11	3.4
			Sudden death	17	5.2
			Cardiac arrest	20	6.1
			Cardiac failure	2	0.6
			Coronary artery arteriosclerosis	0	0.0
			Ischaemic stroke	1	0.3
			Acute myocardial infarction,	1	0.3
			Cerebrovascular accident	0	0.0
			Pancreatic neoplasm/sepsis	0	0.0
			Gastrointestinal AEs	1	0.3
			Skin-related AEs	1	0.3
			Lymphopenia	1	0.3
				76	23.2

(Continued)

				16	4.9
				1	0.3
	C1: saxagliptin	335	Nasopharyngitis	24	7.2
			Urinary tract infection Influenza	23	6.9
			Upper respiratory tract infection	17	5.1
			Diarrhoea Headache	14	4.2
			Back pain Hypertension	12	3.6
			Reported hypoglycaemia	31	9.3
			Confirmed hypoglycaemia	12	3.6
			Sudden death	19	5.7
			Cardiac arrest	7	2.1
			Coronary artery arteriosclerosis	0	0.0
			Ischaemic stroke	0	0.0
			Acute myocardial infarction,	0	0.0
			Cerebrovascular accident	1	0.3
			Pancreatic neoplasm/sepsis	1	0.3
			Gastrointestinal AEs	0	0.0
			Skin-related AEs	0	0.0
			Lymphopenia	0	0.0
				5	16.7
				2	6.9
				7	2.1
Rahman 2011	I: metformin	102	—	—	—
	C1: glimepiride	102	—	—	—
Schernthaner 2004	I: metformin	597	Diarrhoea NOS	66	11.1
			Nausea	25	4.2
			Oedema peripheral	10	1.7
			Oedema NOS	1	0.2
			Fatigue	12	2.0
			Bronchitis NOS	14	2.3
			Influenza	22	3.7
			Nasopharyngitis	19	3.2
			Arthralgia	12	2.0

(Continued)

			Back pain	17	2.8
			Dizziness	11	1.8
			Headache NOS	14	2.3
			Pharyngitis	9	1.5
			Hypertension NOS	17	2.8
			Liver function tests	9	1.5
			Weight gain	0	0
	C1: pioglitazone	597	Diarrhoea NOS	19	3.2
			Nausea	14	2.3
			Edema peripheral	27	4.5
			Edema NOS	13	2.2
			Fatigue	8	1.3
			Bronchitis NOS	11	1.8
			Influenza	14	2.4
			Nasopharyngitis	25	4.2
			Arthralgia	9	1.5
			Back pain	14	2.3
			Dizziness	14	2.3
			Headache NOS	26	4.4
			Pharyngitis	15	2.5
			Hypertension NOS	15	2.5
			Liver function tests	0	0
			Weight gain	6	1.0
Schweizer 2007 [b]	I: metformin	252	Headache	18	7.1
			Nasopharyngitis	24	9.5
			Diarrhoea	66	26.2
			Back pain	9	3.6
			Upper respiratory tract infection	15	6.0
			Dizziness	15	6.0
			Nausea	26	10.3
			Abdominal pain	18	7.1
			Any GI event	110	43.7
			Constipation	5	2.0
			Dyspepsia	12	4.8
			Flatulence		4.0
			Vomiting		4.4

(Continued)

				10	
				11	
	C1: vildagliptin	529	Headache	52	10.0
			Nasopharyngitis	50	9.6
				31	
			Diarrhoea	27	6.0
			Back pain	27	
			Upper respiratory tract infection	25	5.2
			Dizziness	17	
			Nausea	12	5.2
			Abdominal pain		
				113	4.8
			Any GI event		
			Constipation	25	3.3
			Dyspepsia		
			Flatulence	6	2.3
			Vomiting		
				5	21.8
				11	4.8
					1.2
					1.0
					2.1
Teupe 1991	I: metformin	50	Diarrhoea	—	—
	C1: no intervention	50			
UKPDS 34 1998	I: metformin	342	—	—	—
	C1: glibenclamide	277	—	—	—
	C2: insulin	409	—	—	—
Umpierrez 2014	I: metformin	268	Nausea	43	16.0
			Diarrhoea	37	13.8
			Vomiting	13	4.9
			Decreased appetite	12	4.5
			Constipation	3	1.1
			Nasopharyngitis	28	10.4
			URTI	8	3.0
			Headache	20	7.5
	C1: dulaglutide (1.5 mg/week)	269	Nausea	53	19.7
			Diarrhoea	30	11.2
			Vomiting	26	9.7
			Decreased appetite	18	6.7

(Continued)

			Constipation	18	6.7
			Nasopharyngitis	14	5.2
			URTI	16	5.9
			Headache	10	3.7
	C2: dulaglutide (0.75 mg/week)	270	Nausea	31	11.5
			Diarrhoea	21	7.8
			Vomiting	20	7.4
			Decreased appetite	12	4.4
			Constipation	13	4.8
			Nasopharyngitis	8	3.0
			URTI	15	5.6
			Headache	14	5.2
Williams-Herman 2010 [c]	I: metformin (1000 mg/day)	182	Hypoglycaemia	3	1.6
			All gastrointestinal AEs	38	20.9
			Diarrhoea	14	7.7
			Nausea	6	3.3
			Abdominal pain	7	3.8
			Vomiting	0	0
	I2: metformin (2000 mg/day)	182	Hypoglycaemia	4	2.2
			All gastrointestinal AEs	60	33.0
			Diarrhoea	23	12.6
			Nausea	19	10.4
			Abdominal pain	12	6.6
			Vomiting	8	4.4
	C1: sitagliptin	179	Hypoglycaemia	2	1.1
			All gastrointestinal AEs	37	20.7
			Diarrhoea	8	4.5
			Nausea	2	1.1
			Abdominal pain	9	5.0
			Vomiting	1	0.6
Yamanouchi 2005	I: metformin	39	Peripheral oedema	0	0
			Transient hypoglycaemia	0	0

(Continued)

C1: pioglitazone	38	Peripheral oedema	4	10.5
		Transient hypoglycaemia	0	0
C2: glimepiride	37	Peripheral oedema	0	0
		Transient hypoglycaemia	1	2.7

—: denotes not reported

[a]Results reported as: serious adverse events (adverse events)
[b]All results are from the initial 52 week intervention period
[c]Results after 104 weeks of intervention

AEs: adverse events; **C**: comparator; **GI**: gastrointestinal; **I**: intervention, **N**: number of participants; **NOS**: not otherwise specified; **UKPDS**: United Kingdom Prospective Diabetes Study; **URT**I: upper respiratory tract infections.

Appendix 13. Adverse events (IV)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with at least one hypoglycaemic episode (N)	Participants with at least one hypoglycaemic episode (%)	Participants with at least one nocturnal hypoglycaemic episode (N)	Participants with at least one nocturnal hypoglycaemic episode (% participants)	Participants with at least one severe/serious hypoglycaemic episode (N)	Participants with at least one severe/serious hypoglycaemic episode (%)
Bilezikian 2013	I: metformin	111	16	14.4	—	—	—	—
	C1: rosiglitazone	114	16	14.0	—	—	—	—
Campbell 1994	I: metformin	24	—	—	—	—	—	—
	C1: glipizide	24	0	0	—	—	0	0
Derosa 2003	I: metformin	56	0	0	—	—	0	0
	C1: repaglinide	56	0	0	—	—	0	0
Derosa 2004	I: metformin	83[a]	0	0	—	—	0	0
	C1: glimepiride	81[a]	0	0	—	—	0	0
Derosa 2009	I: metformin	67	—	—	—	—	—	—
	C1: rosiglitazone	69	—	—	—	—	—	—
Erem 2014	I: metformin	19	0	0	—	—	0	0
	C1: gliclazide	19	0	0	—	—	0	0
	C2: pioglitazone	19	0	0	—	—	0	0
Kahn 2006	I: metformin	1454	167	11.5	—	—	1	0.1
	C1: rosiglitazone	1456	141	9.7	—	—	1	0.1
	C2: glibenclamide	1441	549	38.1	—	—	8	0.6

(Continued)

Kiyici 2009	I: metformin	16	—	—	—	—	0	0
	C1: rosiglitazone	19	—	—	—	—	0	0
	C2: no intervention	15	—	—	—	—	0	0
Onuchin 2010	I: metformin	46	.[b]	—	—	—	—	—
	C1: insulin	45	.[b]	—	—	—	—	—
Pfützner 2011	I: metformin	328	20	6.1	—	—	0	0
	C1: saxagliptin	335	7	2.1	—	—	0	0
Rahman 2011	I: metformin	102	—	—	—	—	—	—
	C1: glimepiride	102	—	—	—	—	—	—
Schernthaner 2004	I: metformin	597	—	—	—	—	—	—
	C1: pioglitazone	597	—	—	—	—	—	—
Schweizer 2007[c]	I: metformin	252	1	0.4	—	—	0	0
	C1: vildagliptin	519	3	0.6	—	—	0	0
Teupe 1991	I: metformin	50	—	—	—	—	—	—
	C1: no intervention	50	—	—	—	—	—	—
UKPDS 34 1998[c]	I: metformin	—	16	—	—	—	1	—
	C1: glibenclamide	—	52	—	—	—	1	—
	C2: insulin	—	56	—	—	—	3	—
Umpierrez 2014	I: metformin	268	34	12.7	—	—	0	0
	C1: dulaglutide (1.5 mg/week)	269	33	12.3	—	—	0	0
	C2: dulaglutide (0.75 mg/week)	270	30	11.1	—	—	0	0

(Continued)

Williams-Herman 2010	I: metformin (1000 mg/day)	182	3	1.6	—	—	2	1.1
	I2: metformin (2000 mg/day)	182	4	2.2	—	—	0	0
	C1: sitagliptin	179	2	1.1	—	—	0	0
Yamanouchi 2005	I: metformin	39	0	0	—	—	0	0
	C1: pioglitazone	38	0	0	—	—	0	0
	C2: glimepiride	37	1	2.7	—	—	0	0

—: denotes not reported

[a]We did not use the per-protocol population, since it excluded participants that did not finish the trial.

[b]In the metformin arm hypoglycaemia occurred less than once a week, while in the insulin arm they occurred several times a week and/or day for 48% of participants

[c]All results are from the initial 52 week intervention period

C: comparator; **I**: intervention; **N**: number of participants; **UKPDS**: United Kingdom Prospective Diabetes Study.

Appendix 14. Survey of trial investigators providing information

Trial ID	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Bilezikian 2013	18 February 2018	No answer	NA	NA
Campbell 1994	25 August 2018	No answer	NA	NA
ChiCTR-IOR-16007720	11 January 2018	No answer	NA	NA
ChiCTR-IOR-16009296	11 January 2018	12 January 2018	11 January We asked authors to provide basic information about their study in order to assess inclusion	12 February 2018 The study had an intervention of 4 months and was therefore excluded
ChiCTR-IOR-17011477	21 February 2020	No answer	NA	NA
ChiCTR-IPR-16009666	11 January 2018	No answer	NA	NA
ChiCTR-IPR-17010811	11 January 2018	No answer	NA	NA
ChiCTR-IPR-17010825	11 January 2018	No answer	NA	NA
ChiCTR-TCH-10001013	11 January 2018	No answer	NA	NA
ChiCTR-TRC-11001331	11 January 2018	No answer	NA	NA
ChiCTR-TRC-12002505	11 January 2018	12 January 2018	11 January We asked authors to provide basic information about their study in order to assess inclusion	12 January 2018 The study had an intervention of 3 months and was therefore excluded
ChiCTR1800018825	21 February 2020	No answer	NA	NA
ChiCTR1900021632	21 February 2020	No answer	NA	NA
Derosa 2003	20 March 2019	NA[a]	NA	NA
Derosa 2004	20 February 2018	20 February 2018	NA[a]	NA
Derosa 2009	18 February 2018	20 February 2018	NA[a]	NA
Erem 2014	1 September 2018	No answer	NA	NA
EUC-TR2005-000461-18-GB	No contact information was found	NA	NA	NA
JPRN-UMIN000000689	11 January 2018	No answer	NA	NA

(Continued)

JPRN-UMIN000000771	11 January 2018	No answer	NA	NA
JPRN-UMIN000001085	11 January 2018	No answer	NA	NA
JPRN-UMIN000001891	15 January 2018	No answer	NA	NA
JPRN-UMIN000002099	15 January 2018	No answer	NA	NA
JPRN-UMIN000003563	15 January 2018	No answer	NA	NA
JPRN-UMIN000004367	12 January 2018	No answer	NA	NA
JPRN-UMIN000006504	15 January 2018	No answer	NA	NA
JPRN-UMIN000010624	15 January 2018	No answer	NA	NA
JPRN-UMIN000014775	15 January 2018	No answer	NA	NA
Kahn 2006	18 February 2018	No answer	NA	NA
Kanazawa 2009	15 January 2018	No answer	NA	NA
Kiyici 2009	20 February 2018	No answer	NA	NA
Ma 2015	15 January 2018	No answer	NA	NA
Mo 2019	22 February 2020	23 February 2020	22 February 2020 We asked authors to provide information about the duration of interventions in order to assess inclusion	23 February 2020 The study had an intervention of 3 months and was therefore excluded
NCT01303055	11 January 2018	No answer	NA	NA
NCT01935804	4 March 2018	No answer	NA	NA
Onuchin 2010	12 September 2018	No answer	NA	NA
Pfützner 2011	20 February 2018	No answer	NA	NA
Rahman 2011	20 February 2018	No answer	NA	NA
Schernthaner 2004	20 February 2018	No answer	NA	NA
Schweizer 2007	18 February 2018	22 February 2018	26 June 2019 Co-author was asked about random sequence generation, allocation concealment, methods of handling missing data, country in which trial was performed, comorbidites of participants and to provide additional data	7 July 2019 Co-author responded that: randomisation was by computer and unknown to investigators; data were reported as last-observation-carried-forward; participants were from several countries with a majority from Ger-

(Continued)

			on and correct extracted outcomes.	many; population was enriched with participants with cardiovascular risk.
Teupe 1991	No contact information was found	NA	NA	NA
Umpierrez 2014	18 February 2018	No answer	NA	NA
Williams-Herman 2010	No contact information was found	NA	NA	NA
Wu 2014	20 February 2018	No answer	NA	NA
Yamanouchi 2005	20 February 2018	No answer	NA	NA
UKPDS 34 1998	Trial authors have previously been asked when working on another review that they are not able to provide additional data	NA	NA	NA
Zhang 2009	7 March 2019	No answer	NA	NA

[a]After authors replied, we asked them to confirm that they wanted to provide additional information about their study but they did not answer.

NA: not applicable; **UKPDS**: United Kingdom Prospective Diabetes Study

Appendix 15. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus insulin

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	NA	NA	Unclear	NA	NA	NA	NA
	Was allocation concealment used (i.e. no potential for selection bias)?			Unclear				
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?			No (↓)				
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?			No (↓)				
	Was an objective outcome used?			No (↓)				
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]			Yes				
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?			Yes				
	No other biases reported (i.e. no potential of other bias)?			No (↓)				
	Did the trials end up as scheduled (i.e. not stopped early)?			No (↓)				
Inconsistency[b]	Point estimates did not vary widely?			NA				
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point							

(Continued)

	estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	
	Was the direction of effect consistent?	
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?	
	Was the test for heterogeneity statistically significant (P < 0.1)?	
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes
	Was the outcome timeframe sufficient?	Sufficient
	Were the conclusions based on direct comparisons?	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: <100 participants)?[e]	Low (↓)
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Not applicable

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes
	Was grey literature searched?	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes
	There was no industry influence on studies included in the review?	No (↓)
	There was no evidence of funnel plot asymmetry?	NA
	There was no discrepancy in findings between published and unpublished trials?	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 16. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus sulphonylureas

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	NA	Yes	Yes	Yes	NA
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes	Yes		Yes	Yes	Yes	
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was an objective outcome used?	Yes	Yes		Yes	Yes	Yes	
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	Unclear		Yes	No (↓)	No (↓)	
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Unclear		Yes	Unclear	Unclear	
	No other biases reported (i.e. no potential of other bias)?	No (↓)	No (↓)		No (↓)	No (↓)	No (↓)	
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes		Yes	Yes	Yes	
Inconsistency[b]	Point estimates did not vary widely?	Yes	NA		NA	Yes	NA	
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point	Some				Some		

(Continued)

	estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?					
	Was the direction of effect consistent?	Yes			Yes	
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?	Moderate			Moderate	
	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant			Not statistically significant	
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	NA	NA	Yes	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: <100 participants)?[e]	High	High	High	High	Intermediate
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	Yes	Yes	Yes	Yes

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 17. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus thiazolidinediones

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	NA	Yes	Yes	NA	NA
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes	Yes		Yes	Yes		
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes		
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes		
	Was an objective outcome used?	Yes	Yes		Yes	Yes		
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	No (↓)		Yes	Yes		
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Unclear	Unclear		Unclear	Yes		
	No other biases reported (i.e. no potential of other bias)?	No (↓)	No (↓)		No (↓)	No (↓)		
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes		Yes	Yes		
Inconsistency[b]	Point estimates did not vary widely?	Yes	Yes		Yes	NA		
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point	Substantial	Substantial		Substantial			

(Continued)

	estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?				
	Was the direction of effect consistent?	Yes	Yes	Yes	
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?	Low	Low	Low	
	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant	Not statistically significant	Not statistically significant	
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable / Applicable / Poorly applicable (↓)	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes / No (↓)	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	Yes	Yes	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	High	High	High	High
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)

(Continued)

	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	Yes	Yes	Yes
Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	Unclear	Unclear	Unclear	Unclear
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 18. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus dipeptidyl peptidase inhibitor 4 inhibitors

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	NA	Unclear	Low	Low	NA
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear		Unclear	Unclear	Unclear	
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was an objective outcome used?	Yes	Yes		Yes	Yes	Yes	
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	Yes		Yes	Unclear	Unclear	
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes		Yes	Yes	Yes	
	No other biases reported (i.e. no potential of other bias)?	No (↓)	No (↓)		No (↓)	No (↓)	No (↓)	
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes		Yes	Yes	Yes	
Inconsistency[b]	Point estimates did not vary widely?	NA	NA		NA	NA	NA	
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-							

(Continued)

	lap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?					
	Was the direction of effect consistent?					
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?					
	Was the test for heterogeneity statistically significant (P < 0.1)?					
Indirectness	Were the populations in included studies applicable to the decision context?	NA	NA	NA	NA	NA
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	NA	NA	NA	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	High	High	High	High	High
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	Yes	Yes	Yes	Yes

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 19. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus glucagon like peptide 1 analogues

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	NA	Yes	Yes	Yes	NA
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes	Yes		Yes	Yes	Yes	
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes	Yes	
	Was an objective outcome used?	Yes	Yes		Yes	Yes	Yes	
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	Unclear		Yes	Unclear	Unclear	
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes		Yes	Yes	Yes	
	No other biases reported (i.e. no potential of other bias)?	Yes	No (↓)		Yes	No (↓)	No (↓)	
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes		Yes	Yes	Yes	
Inconsistency[b]	Point estimates did not vary widely?	NA	NA		NA	NA	NA	
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-							

(Continued)

	lap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?					
	Was the direction of effect consistent?					
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?					
	Was the test for heterogeneity statistically significant (P < 0.1)?					
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	NA	NA	NA	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	High	High	High	High	High
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	Yes	Yes	Yes	Yes

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	NA	NA	NA	NA	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 20. Checklist to aid consistency and reproducibility of GRADE assessments: metformin monotherapy versus meglitinides

Items		(1) All-cause mortality	(2) Serious adverse events	(3) Health-related quality of life	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction	(6) Non-fatal stroke	(7) End-stage renal disease
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	NA	Unclear	NA	NA	NA	NA	NA
	Was allocation concealment used (i.e. no potential for selection bias)?		Unclear					
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?		Yes					
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?		Yes					
	Was an objective outcome used?		Yes					
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]		Yes					
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?		No (↓)					
	No other biases reported (i.e. no potential of other bias)?		No (↓)					
	Did the trials end up as scheduled (i.e. not stopped early)?		Yes					
Inconsistency[b]	Point estimates did not vary widely?		NA					
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point		NA					

(Continued)

	estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	
	Was the direction of effect consistent?	NA
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?	NA
	Was the test for heterogeneity statistically significant (P < 0.1)?	NA
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes
	Was the outcome timeframe sufficient?	Sufficient
	Were the conclusions based on direct comparisons?	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: <100 participants)?[e]	Low (↓)
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	NA

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes
	Was grey literature searched?	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes
	There was no industry influence on studies included in the review?	Unclear
	There was no evidence of funnel plot asymmetry?	NA
	There was no discrepancy in findings between published and unpublished trials?	NA

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials
[e]Depends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation;**NA**: not applicable.

Appendix 21. Health-related quality of life: instruments

Instrument	Dimensions (subscales) (no. of items)	Validated instrument	Answer options	Scores	Minimum score Maximum score	Weighting of scores	Direction of scales	Minimal important difference
SF-36 v2 (G) employed in Onuchin 2010	Physical functioning (PF) (10) Role-physical (RP) (4) Bodily pain (BP) General health (GH) (5) Vitality (VT) (4) Social functioning (SF) (2) Role-emotional (RE) (3) Mental health (MH) (5)	Yes	3-, 5- and 6-point Likert-scale	Scores for dimensions Physical component summary (PCS) Mental component summary (MCS)	Minimum scores: scores for dimensions/PCS/MCS: norm-based scale Maximum scores: scores for dimensions/PCS/MCS: norm-based scale	No	Higher values mean better assessment	PCS: 2-3 points MCS: 3 points Dimensions: PF/BP/VT: 2 points, if score <40; 3 points, if score ≥ 40 RP: 2 points SF/MH: 3 points RE: 4 points

G: generic; **S**: specific; **SF**: short-form health survey

HISTORY

Protocol first published: Issue 1, 2018
Review first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

Filip Gnesin (FG): acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, writing draft and future review updates.

Anne Cathrine Baun Thuesen (AT): trial selection, data extraction, review of drafts and future review updates.

Lise Katrine Aronsen Kähler (LK): trial selection, data extraction, review of drafts and future review updates.

Sten Madsbad (SM): review of drafts and future review updates.

Bianca Hemmingsen (BH): acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

DECLARATIONS OF INTEREST

Filip Gnesin (FG): none known.

Lise Katrine Aronsen Kähler (LK): none known.

Anne Cathrine Thuesen (AT): has previously been employed by a subsidiary company of Novo Nordisk.

Sten Madsbad (SM): Advisory Boards: Novartis Pharma, Novo Nordisk, Merck Sharp & Dome, Sanofi-Aventis, AstraZeneca, Johnson & Johnson, Astra-Zeneca, Boehringer-Ingelheim, E. Lilly, Intarcia Therapeutics, Bristol-Meyer Squibb. Fee for lectures: Novo Nordisk, Merck, Sharp & Dome, Astra-Zeneca, Sanofi-Aventis, Novartis Pharma, E. Lilly, Bristol-Meyer Squibb, Boeringer-Ingelheim, E.Lilly. Grants for research: Novo Nordisk.

Bianca Hemmingsen (BH): none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We chose not to perform Trial Sequential Analysis (TSA), due to a statement by the Cochrane Scientific Committee (CSC) recommending against the use of sequential methods for updated meta-analyses in most circumstances within the Cochrane context, issued after publication of our protocol.

We did not compare metformin monotherapy with combination therapies or to first-generation sulphonylureas.

We did not compare metformin monotherapy with unapproved therapies for type 2 diabetes mellitus.

We excluded studies having type 2 diabetes mellitus and another medical condition as inclusion criteria (e.g. liver failure), however, conditions often present in people with type 2 diabetes mellitus, e.g. hyperlipidaemia and hypertension were not exclusion criteria.

NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

Carbamates [adverse effects] [therapeutic use]; Cardiovascular Diseases [mortality]; Cause of Death; Diabetes Mellitus, Type 2 [*drug therapy] [mortality]; Dipeptidyl-Peptidase IV Inhibitors [adverse effects] [therapeutic use]; Glucagon-Like Peptide 1 [analogs & derivatives]; Hypoglycemic Agents [adverse effects] [*therapeutic use]; Insulin [therapeutic use]; Metformin [adverse effects] [*therapeutic use]; Myocardial Infarction [epidemiology]; Piperidines [adverse effects] [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Stroke [epidemiology]; Sulfonylurea Compounds [adverse effects] [therapeutic use]

MeSH check words

Adult; Humans