*Draft Comparative Effectiveness Review*

# Comparative Effectiveness and Safety of Diabetes Medications for Adults with Type 2 Diabetes

**Prepared for:**
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Note Regarding Drugs Recently Approved by the U.S. Food and Drug Administration:

The final report will incorporate drugs that were recently approved by the U.S. Food and Drug Administration and amended to the protocol after the initial literature search. The search will be updated to include all FDA-approved drugs and indications, as of March 31, 2010. This will include the DPP-IV inhibitor saxagliptin, which was FDA-approved in July 2009. Thus there will be two included DPP-IV inhibitors: sitagliptin and saxaglitpin. The GLP-1 agonist, liraglutide, was just FDA approved in January 2010, for both mono- and combination therapy and both indications will be included. In addition, the GLP-1 agonist exenatide was approved for the indication of monotherapy, in addition to combination therapy, which had already been included in the protocol.

**None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.**

# Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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# Comparative Effectiveness of Diabetes Medications for Adults with Type 2 Diabetes

## *Executive Summary*

### Background

Type 2 diabetes is a common chronic illness, characterized by insulin resistance, and eventually decreased insulin secretion by pancreatic β cells, leading to chronic hyperglycemia and associated long-term disease complications. In the United States, the prevalence of diabetes increased from 5.1% in 1988 to 1994 to 6.5% in 1999 to 2002. Like many chronic illnesses, diabetes disproportionately affects older people. Because of its association with obesity, diabetes prevalence is higher among racial and ethnic minority populations. The annual economic burden of diabetes is estimated to be $132 billion and is increasing, mostly attributable to costly complications of the disease.

Long-term complications of diabetes include microvascular disease, such as retinopathy and blindness, neuropathy, nephropathy and end stage kidney disease. In addition, the death rate from cardiovascular disease in adults with type 2 diabetes is increased 2- to 4-fold, compared with adults without diabetes. Management of hyperglycemia using diet and pharmacologic therapy is the cornerstone of treatment for type 2 diabetes. Results from randomized controlled trials (RCTs) have demonstrated that the risk of microvascular complications, particularly retinopathy, can be reduced by improved glycemic control in patients with type 2 diabetes. However, the effect of tight glycemic control on cardiovascular disease has been inconclusive. In addition to questions about optimal glycemic control, recent studies have addressed concerns about excess cardiovascular risk associated with specific oral hypoglycemic agents, specifically the risk of rosiglitazone on ischemic heart disease and congestive heart failure.

Since 1995 the market for new pharmacotherapy options for diabetes has greatly expanded, and currently there are eleven classes of diabetes medications, including sulfonylureas, meglitinides, incretins, biguanides, amylin analogues, thiazolidinediones, bromocriptine, colesevalam, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and both long- and short-acting insulins. In addition to the increasing number of available medication choices for diabetes, patients are increasing the number of classes of diabetes medications they are taking at the same time. In 2005 to 2006, 35% of all patients with diabetes were taking two classes of antidiabetes medications and 14% were taking three or more classes, compared to only 6% taking three or more classes in 1999 to 2000.

In 2007, the Agency for Healthcare Research and Quality (AHRQ) published its first systematic review on the comparative effectiveness of oral hypoglycemic medications for type 2 diabetes. The review was unique because it included comparisons of all oral diabetes medications. It also had a broad scope, including intermediate outcomes like glycemic control and clinical outcomes like cardiovascular disease and nephropathy, as well as adverse events. The review of 216 studies concluded that most oral diabetes medications had a similar effect on reducing hemoglobin A1C (HgbA1c), most drugs except for metformin and acarbose caused increases in body weight, and only metformin decreased low density lipoprotein (LDL) cholesterol. There were too few studies to determine the differential effects of the oral diabetes medications on all cause mortality, cardiovascular mortality and morbidity, and microvascular

complications. The sulfonylurea class was associated with an increased risk of hypoglycemia, metformin with gastrointestinal problems, and the thiazolidinediones with heart failure.

In the years following completion of that review, numerous studies were published on the comparative effectiveness of diabetes medications. The previous report was completed at about the time that controversy erupted concerning the safety of rosiglitazone. Additional evidence about rosiglitazone has been published since then. Two new medication classes were approved recently by the Food and Drug Administration (FDA). The incretin mimetic, exenatide, was approved in 2005, and the DPP-4 inhibitor, sitagliptin, was approved in 2006. Although exenatide is an injectable medication, our clinical advisors indicated that it was important to include exenatide in a review of the oral medications that are alternatives to insulin therapy. Our clinical advisors also indicated a need for a review of the comparative effectiveness and safety of combinations of medications that must be considered for patients with type 2 diabetes that cannot be controlled with monotherapy, including combination of an oral medication with insulin. Accordingly, AHRQ requested this update to integrate additional evidence about the comparative effectiveness and safety of oral medications for adults with type 2 diabetes.

We decided to build upon the previous evidence report by focusing on the most important issues without seeking to replicate all parts of the previous report. Thus, the current evidence report focuses on the head-to-head comparisons of medications that should be of greatest relevance to clinicians and their patients. Readers should refer to the original evidence report if they want more information about placebo-controlled trials of the medications. For the head-to-head comparisons, we conducted a comprehensive literature search that included all literature that had been searched for the first report. We expanded the scope of the review by including a few additional outcomes that were relevant to the comparisons of interest. We also included comparisons with combinations of medications. As part of the revised scope of work, we applied slightly different exclusion criteria. Therefore, this report represents both an update and an expansion of our previous comprehensive review of the evidence comparing the effectiveness and safety of oral medications used to treat type 2 diabetes.

The report addresses the following key questions for the priority medication comparisons presented in Table A:

Key Question 1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see list of comparisons) for the intermediate outcomes of glycemic control (in terms of HgbA1c), weight, or lipids?

Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options (see list of comparisons) in terms of the following long-term clinical outcomes?

1. All-cause mortality
2. Cardiovascular mortality
3. Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke)
4. Retinopathy
5. Nephropathy
6. Neuropathy

Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options (see list of comparisons) in terms of the following adverse events and side-effects?

1. Hypoglycemia
2. Liver injury
3. Congestive heart failure
4. Severe lactic acidosis
5. Cancer
6. Severe allergic reactions
7. Hip and non-hip fractures
8. Pancreatitis
9. Cholecystitis
10. Macular edema or decreased vision
11. Gastrointestinal (GI) side effects

Key Question 4: Do safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular, and cerebrovascular outcomes?

**Table A. Priority medication comparisons included for each of the key questions**

| | Main intervention | Comparisons |
|---|---|---|
| **Monotherapy as main intervention** | Metformin | • Thiazolidinedione<br>• Sulfonylurea<br>• Sitagliptin<br>• Meglitinides<br>• Combination of metformin plus thiazolidinedione<br>• Combination of metformin plus sulfonylurea<br>• Combination of metformin plus sitagliptin<br>• Combination of metformin plus meglitinides |
| | Thiazolidinedione | • Different thiazolidinedione<br>• Sulfonylurea<br>• Sitagliptin<br>• Meglitinides |
| | Sulfonylurea | • Sitagliptin<br>• Meglitinides |
| | Sitagliptin | • Meglitinides |
| **Combination therapy as main intervention** | Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) | • Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) |
| | Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) | • Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or sitagliptin) |

## Conclusions (see Table B)

Summary Table B presents the main conclusions and strength of evidence from published evidence regarding the comparative effectiveness and safety of diabetes medications, organized by key question and outcome.

Below we provide additional summary information for selected comparisons of interest by key question, with a description of key factors that influenced our grading of the strength of evidence, any important exceptions, and implications.

## Key Question 1: Intermediate Outcomes

Intermediate clinical outcomes were the most frequently evaluated outcomes. We identified 104 relevant articles (101 studies) with data from RCTs that addressed either HgbA1c, body weight, or lipids. Fifty-three had also been also included in the 2007 Comparative Effectiveness Review (CER).

**HgbA1c.** We found that most oral diabetes medications (metformin, thiazolidinediones, sulfonylureas, and repaglinide) reduced HgbA1c to a similar degree - by about 1 absolute percentage point compared with baseline after 3 or more months of treatment. Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, and metformin plus sitagliptin) were generally more effective at reducing HgbA1c compared with metformin monotherapy - by about 1 absolute percentage point. Most combinations of metformin, sulfonylureas and thiazolidinediones had similar efficacy in lowering HgbA1c.

**Weight.** Oral diabetes medications varied in their effects on body weight. Compared with either thiazolidinediones or sulfonylureas, metformin was consistently associated with weight maintenance or decreased weight, with a mean difference of about 2.6 kg, in trials that lasted greater than 3-months but generally less than one year. Although placebo controlled trials of metformin were excluded from this review, we know from the 2007 evidence report that metformin was associated with weight neutrality when compared with placebo.

**Lipids.** Effects on lipid levels varied across medication type, but most effects were small to moderate, in studies that generally lasted between 3 and 12 months. Metformin decreased triglycerides (TG) and LDL, relative to sulfonylureas and rosiglitazone. Pioglitazone increased LDL and decreased TG relative to metformin. The combination of rosiglitazone and metformin increased LDL, high density lipoproteins (HDL), and TG compared with metformin monotherapy or the combination of metformin and a sulfonylurea. The addition of pioglitazone to metformin also increased HDL and decreased TG compared with the combination of metformin and a sulfonylurea. We found that the addition of sitagliptin to metformin decreased TG relative to metformin monotherapy. Placebo controlled trials included in the 2007 evidence report were generally consistent with the results from the comparisons included in this report.

## Key Question 2: Macrovascular and Microvascular Long-Term Complications of Diabetes

Although we identified 28 new studies in addition to the 25 studies included in the 2007 evidence report, the new studies were generally of short duration (less than one year) and had few long-term events, like deaths and cardiovascular disease, making any estimates of risk difference very imprecise. Therefore, most comparisons for this key question had low strength of evidence. Metformin was associated with slightly lower all-cause mortality, cardiovascular disease mortality, and cardiovascular disease morbidity compared with sulfonylureas. However, the evidence was limited by inconsistency between the trials and observational studies, and overall low precision of the results due to the rarity of events. Data from the 2007 evidence

report also showed that treatment with metformin was associated with a decreased risk of cardiovascular mortality compared with any other oral diabetes agent or placebo, although the results for all-cause mortality and cardiovascular morbidity were not significant.

For these long-term macrovascular outcomes, no studies addressed several comparisons, including comparisons of the new medications: sitagliptin and exenatide. Few studies included insulin added to oral medications or compared other two-drug combination therapies.

Few studies addressed microvascular outcomes of nephropathy, retinopathy, and neuropathy. We found moderate strength of evidence that pioglitazone is better at reducing short-term nephropathy compared with metformin, based on two short-duration RCTs. Only three comparisons were included for the outcome of neuropathy, but studies were limited by low sample sizes and poorly defined outcomes. We did not identify any studies for the outcome of retinopathy.

## Key Question 3: Adverse Events and Side Effects

One hundred and three studies applied to this Key Question.

**Hypoglycemia.** Hypoglycemia episodes were three to seven times more frequent in people taking sulfonylureas compared with metformin and thiazolidinediones. Combination therapies that included a sulfonylurea plus metformin also had excess hypoglycemia risk compared with metformin plus a thiazolidinedione.

**Congestive heart failure.** Based on a single RCT with moderate risk of bias, we found low strength of evidence that compared with a combination of metformin plus a sulfonylurea, the risk of congestive heart failure (CHF) doubled with treatment with combination therapy containing rosiglitazone. We also found higher risk of CHF with thiazolidinedione monotherapy compared with sulfonylurea monotherapy.

**Gastrointestinal side effects.** Metformin was associated with higher risk of gastrointestinal side effects than all other medications, and this was observed when used as monotherapy or as part of combination therapy.

**Other adverse events.** We found reports of four types of adverse events that were not addressed in our previous evidence report: macular edema, cholecystitis, pancreatitis, and fractures. Except for fractures, the majority of the evidence was graded as low strength because few studies and few events limited the assessment of consistency and precision of the results. We did find high strength of evidence showing that thiazolidinediones, either in combination with another medication or as monotherapy, were associated with a 1.5 times higher risk of bone fractures compared with metformin alone or in combination with sulfonylurea.

We also found little evidence about liver injury and cancer, outcomes included in the 2007 evidence report. However, moderate strength of evidence showed no increased risk of lactic acidosis for metformin compared to a sulfonylurea or a combination of metformin and sulfonylurea, consistent with other reviews.

## Key Question 4: Differences in Subgroups

Twenty-five studies applied to Key Question 4. We found that women taking rosiglitazone either as monotherapy or in combination, compared with those taking metformin alone or in combination with sulfonylureas were at higher risk for bone fractures, compared with men.

However, for the majority of comparisons, studies did not have sufficient power to conduct subgroup analyses, and few studies occurred exclusively in a sub-population.

## Remaining Issues

In this review, we synthesized current literature about the comparative effectiveness and safety of oral diabetes medications when used alone and in two-drug combinations. We identified some deficiencies in the published literature that need to be addressed by future research to meet the decision making needs of patients, physicians, and policy makers. We organized these deficiencies and recommendations using the PICOTS format for specifying research questions: patient populations, interventions, comparators, outcome measures of interest, timing, and settings.

### Populations

Studies often employed narrow inclusion criteria, enrolling patients at lowest risk for complications, and commonly used run-in periods to avoid enrolling patients with adverse effects or poor adherence, which may limit applicability. We identified the following research gaps related to targeted patient populations:

1. The literature is deficient in studies enrolling people with varying levels of underlying cardiovascular risk.
2. Results reported in subgroups of the population were rare, especially the elderly and people with multiple comorbid conditions, such as underlying chronic kidney disease.

### Interventions and Comparators

We identified the following gaps in the literature where future studies could address additional medication comparisons to support clinicians in decision making.

1. The published literature is deficient in studies of the comparative effectiveness of two-drug combinations, focused either on their effectiveness or the safety and thus, information about positive and negative interactions between two medications is limited.
2. The comparative effectiveness literature is sparse on monotherapy and combination therapy comparisons of nateglinide, exenatide, or sitagliptin with other first line diabetes medications.
3. Few studies use comparisons with a basal or premixed insulin added to metformin or thiazolidinediones.

### Outcomes of Interest

Overall, few studies contained sufficient data on event rates for major clinically important adverse events and long-term complications of diabetes.

1. We identified few published studies on long-term clinical outcomes such as cardiovascular disease, stroke, nephropathy, and neuropathy.
2. Few studies used standard measures for diabetic nephropathy and kidney function, such as estimated glomerular filtration rate (GFR), or clinical outcomes like time to dialysis, as outcomes in the comparison of these medications.
3. Few studies reported the outcome of neuropathy and among those that did, the outcomes were poorly defined.
4. We identified few observational studies that examined macular edema, cancer and fractures for thiazolidinediones and other medications.

We identified several key deficiencies in study timing and duration of followup.

1. The literature is relatively deficient in studies of the short-term benefits, if any, of the addition of insulin to oral agents, and the long-term effects on mortality and cardiovascular disease, from the addition of insulin to a regimen relative to the addition of another oral agent.
2. Few studies on harms lasted greater than 2 years, a shorter duration of exposure than typically seen in clinical practice, where these drugs may be prescribed for decades. Some adverse effects, like congestive heart failure, may take years to develop, and others like fractures, may be due to cumulative exposure.

## Setting

Study settings are relevant to understanding the applicability of the findings to the general U.S. population of patients with diabetes.

1. Few trials reported the study setting or source for participant recruitment, such as an outpatient clinical or subspecialty clinical setting, which is relevant because the majority of patients with diabetes are cared for by primary care physicians.

We also identified methodological problems and made recommendations to consider for future research:

1. We recommend studies consistently report between-group comparisons of changes from baseline, as well as measures of dispersion such as standard errors, to improve interpretation of the significance of their findings.
2. We recommend improved adverse event and long-term outcome reporting, with pre-defined outcomes and definitions, and a description of methods for ascertainment.
3. We recommend trials report the steps taken to ensure randomization and allocation concealment.
4. We recommend that observational studies of the comparative effectiveness and safety of oral diabetes medications report details of the treatment type, dose, timing, and duration of use of the medication, when available.
5. We recommend that studies consistently report the number of deaths in each study arm, even if none occurred.

**Table B. Evidence of the comparative effectiveness and safety of diabetes medications as monotherapy and combination therapy on intermediate endpoints, mortality, microvascular outcomes, macrovascular outcomes and adverse events**

| Outcome | Level of Evidence* | Conclusions |
|---|---|---|
| Key Question 1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of treatment options for the intermediate outcomes of glycemic control (in terms of HgbA1c), weight, or lipids? | | |
| HgbA1c | High | Metformin compared with second-generation sulfonylureas showed similar changes in HgbA1c, with a pooled mean absolute difference of 0.07% (95% CI -0.12% to 0.26%) for studies lasting greater than 3 months but usually less than 1 year duration. |
| | High | Combination therapies were better at reducing HgbA1c than monotherapy regimens by an absolute difference of about 1%. In comparisons of metformin versus metformin plus thiazolidinediones and metformin versus metformin plus sulfonylureas, the combination therapy was favored for HgbA1c reduction. |
| | Moderate | Comparisons of metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone showed similar reductions in HgbA1c, with trials lasting one year or less. |
| | Moderate | Metformin plus sitagliptin was favored over metformin alone for HgbA1c reduction. |
| | Moderate | Combination metformin plus thiazolidinedione had similar efficacy in reducing HgbA1c as the combination of metformin plus sulfonylurea. |
| | Low | Combinations of metformin plus repaglinide versus metformin plus thiazolidinedione, metformin plus sitagliptin versus metformin plus thiazolidinedione, and metformin plus sulfonylurea versus metformin plus sitagliptin showed similar efficacy in reduction of HgbA1c. |
| | Low | Combination of pioglitazone plus sulfonylurea was minimally favored over metformin plus pioglitazone by an absolute difference of 0.03%. |
| | Low | Combination of metformin plus a premixed insulin analogue was minimally favored over metformin plus a basal insulin by an absolute difference of 0.30-0.43%. |
| | Insufficient | No studies addressed several comparisons, including sitagliptin versus a thiazolidinedione, sitagliptin versus a meglitinides, all comparisons with exenatide, and combination therapy with some meglitinides. |
| Body weight | High | Metformin maintained or decreased weight when compared with thiazolidinediones with a difference of about 2.6 kg. |
| | High | Metformin maintained or decreased weight when compared with sulfonylureas, with a difference of about 2.7 kg. |
| | High | Sulfonylureas had similar effects on body weight as the meglitinides. |
| | High | Metformin monotherapy had a more favorable effect on weight compared with the combinations of metformin plus a thiazolidinedione (between-group difference of about 2.2 kg) or metformin plus a sulfonylurea (between-group difference of about 2.3 kg). |
| | Moderate | Metformin plus sulfonylurea had a more favorable effect on weight compared with both the combinations of a thiazolidinedione plus sulfonylurea (between-group difference of about 3.2 kg) and metformin plus a thiazolidinedione (between-group difference of about 0.9 kg). |
| | Low | Few studies addressed monotherapy and combination therapy comparisons with sitagliptin, meglitinides, premixed insulin analogues, and basal insulin preparations, and available results were imprecise. |
| | Insufficient | No studies addressed several comparisons including sitagliptin versus a thiazolidinedione, sitagliptin versus meglitinides, metformin plus a thiazolidinedione versus a thiazolidinedione plus a sulfonylurea, and all comparisons with exenatide. |

**Table B. Evidence of the comparative effectiveness and safety of diabetes medications as monotherapy and combination therapy on intermediate endpoints, mortality, microvascular, macrovascular outcomes and adverse events (continued)**

| Outcome | Level of Evidence* | Conclusions |
|---|---|---|
| LDL cholesterol | High | Metformin decreased LDL cholesterol compared to pioglitazone, which increased LDL cholesterol, with pooled between-group difference in LDL of about -14 mg/dL. |
| | High | Metformin decreased LDL by about 10 mg/dL compared to second-generation sulfonylureas which generally had little effect on LDL. |
| | High | Addition of rosiglitazone to metformin increased LDL compared to metformin monotherapy by about 14.5 mg/dL. |
| | Moderate | Metformin decreased LDL cholesterol compared to rosiglitazone, which increased LDL cholesterol, with pooled between-group difference in LDL of about -14 mg/dL. |
| | Moderate | Combination of metformin and a second-generation sulfonylurea decreased LDL more than the combination of metformin and rosiglitazone by about 13.5 mg/dL. |
| | Low | Few studies addressed comparisons with sitagliptin or meglitinides as monotherapy and in combination with other medications, and available results were generally imprecise. |
| | Insufficient | No studies addressed several comparisons, including sitagliptin versus a thiazolidinedione, sitagliptin versus a meglitinides, comparisons with premixed insulin analogues or basal insulin preparations combined with oral medications, and all comparisons with exenatide. |
| HDL cholesterol | High | Pioglitazone increased HDL cholesterol more than metformin by about 3.2 mg/dL. |
| | High | Second generation sulfonylureas were similar to metformin in terms of changes in HDL cholesterol. |
| | High | Addition of rosiglitazone to metformin increased HDL cholesterol relative to metformin monotherapy by about 2.8 mg/dL. |
| | Moderate | Rosiglitazone was similar to metformin in terms of changes in HDL cholesterol. |
| | Moderate | Addition of rosiglitazone or pioglitazone to metformin increased HDL cholesterol relative to the combination of metformin and a second-generation sulfonylurea by about 2.7 mg/dL for rosiglitazone addition and about 5 mg/dL for pioglitazone addition. |
| | Low | Few studies addressed comparisons with sitagliptin or meglitinides as monotherapy and in combination with other medications and available results were often imprecise. |
| | Insufficient | No studies addressed several comparisons, including sitagliptin versus a thiazolidinedione, sitagliptin versus a meglitinides, comparisons with premixed insulin analogues or basal insulin preparations combined with oral medications, and all comparisons with exenatide. |
| Triglyceride | High | Pioglitazone decreased TG compared to metformin by about 27.2 mg/dL. |
| | High | Metformin monotherapy decreased TG relative to the addition of rosiglitazone to metformin by about 14.5 mg/dL. |
| | Moderate | Metformin decreased TG by about 30.1 mg/dL relative to rosiglitazone, which increased TG. |
| | Moderate | Metformin decreased TG relative to second-generation sulfonylureas by about 8.6 mg/dL. |
| | Moderate | Addition of rosiglitazone to metformin did not affect TG relative to the addition of a second-generation sulfonylurea to metformin. The addition of pioglitazone to metformin decreased TG relative to the addition of a second-generation sulfonylurea to metformin by about 15 mg/dL. |
| | Low | Few studies addressed comparisons of metformin versus sitagliptin or meglitinides and available results were often imprecise. |
| | Insufficient | No studies addressed several comparisons, including sitagliptin versus a thiazolidinedione, sitagliptin versus meglitinides, comparisons with premixed insulin analogues or basal insulin preparations combined with oral medications, and all comparisons with exenatide. |

**Table B. Evidence of the comparative effectiveness and safety of diabetes medications as monotherapy and combination therapy on intermediate endpoints, mortality, microvascular, macrovascular outcomes and adverse events (continued)**

| Outcome | Level of Evidence* | Conclusions |
|---|---|---|
| Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, and neuropathy? | | |
| All-cause mortality | Low | Metformin was associated with slightly lower risk of all-cause mortality compared with a sulfonylurea, but results between trials and observational studies were inconsistent and had moderate risk of bias. |
| | Low | Many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results. |
| | Insufficient | No studies addressed several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, comparisons with a basal insulin preparation, comparisons with exenatide, and the majority of combination therapy comparisons. |
| Cardiovascular disease mortality | Low | Metformin was associated with slightly lower risk of cardiovascular mortality compared with a sulfonylurea, but results were imprecise and had moderate risk of bias. |
| | Low | Risk of cardiovascular mortality was similar between metformin and thiazolidinediones, but results were imprecise and had moderate risk of bias. |
| | Insufficient | No studies addressed several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. |
| Cardiovascular and cerebrovascular morbidity (nonfatal myocardial infarction and stroke) | Low | Metformin was associated with slightly lower risk of cardiovascular morbidity compared with a sulfonylurea, but results were very imprecise. . |
| | Low | Risk of cardiovascular morbidity was similar between metformin and thiazolidinediones, bur results were very imprecise. |
| | Insufficient | No studies addressed several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons. |
| Microvascular outcomes (retinopathy, nephropathy, neuropathy) | Moderate | Pioglitazone had a more favorable effect compared with metformin in reducing the urinary albumin-to-creatinine ratio, likely indicating less nephropathy. |
| | Low | Three other comparisons were included for the outcome of nephropathy, but studies were at moderate to high risk for bias, provided imprecise results or used surrogate outcomes with indirect evidence. |
| | Low | Three comparisons were included for the outcome of neuropathy, but studies were at high risk for bias, had low sample sizes and poorly defined outcomes. |
| | Insufficient | We found insufficient evidence for the outcome of retinopathy. |

**Table B. Evidence of the comparative effectiveness and safety of diabetes medications as monotherapy and combination therapy on intermediate endpoints, mortality, microvascular, macrovascular outcomes and adverse events (continued)**

| Outcome | Level of Evidence* | Conclusions |
|---|---|---|
| Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options in terms of the adverse events and side effects? | | |
| Hypoglycemia | High | Risk of hypoglycemia with sulfonylureas was almost 3 times higher than risk with metformin. |
| | High | Risk of hypoglycemia with sulfonylureas was about 7 times the risk with thiazolidinediones. |
| | High | Risk of hypoglycemia with metformin plus sulfonylurea was about 6 times higher than the risk with metformin plus thiazolidinediones. |
| | Moderate | Risk of hypoglycemia was similar between metformin and thiazolidinediones. |
| | Moderate | Risk of hypoglycemia with metformin plus sulfonylurea exceeded the risk with metformin alone (range of RR was 0.6 to 9.3). |
| | Moderate | Risk of hypoglycemia was modestly higher for meglitinides over metformin (RR 1.74). |
| | Moderate | Risk of hypoglycemia was 1.5 times higher for metformin plus a thiazolidinedione over metformin alone. |
| | Moderate | Metformin combined with sitagliptin has approximately an equivalent risk of hypoglycemia as metformin alone. |
| | Low | Few studies addressed metformin versus sitagliptin or versus a meglitinides, or included metformin plus a basal insulin as a comparator, and available results had high risk of bias or were very imprecise. |
| | Insufficient | No studies addressed combination therapy with exenatide. |
| Gastrointestinal side effects | High | Metformin doubled GI adverse event rates, most commonly diarrhea, nausea, and vomiting, compared with thiazolidinediones. |
| | Moderate | Metformin doubled GI adverse event rates compared with second-generation sulfonylureas. |
| | Low | Few studies addressed comparisons with sitagliptin, meglitinides, or combination therapy, and available results had moderate risk of bias or were very imprecise. |
| | Insufficient | No studies addressed combination therapy with exenatide. |
| Congestive heart failure | Moderate | Risk of CHF is higher for thiazolidinediones when compared to sulfonylureas. |
| | Low | Risk of CHF is doubled for combination therapy with a thiazolidinedione compared to a combination of metformin plus a sulfonylurea. |
| | Insufficient | No studies addressed several comparisons, including most sitagliptin comparisons and the majority of combination therapy comparisons. |
| Cholecystitis and pancreatitis | Low | Two comparisons were included for the outcome of cholecystitis and one comparison was included for the outcome of pancreatitis, with unclear conclusions |
| Lactic acidosis | Moderate | Risk of lactic acidosis was similar between metformin and sulfonylurea alone or a combination with metformin. |
| Cancer | Low | Few studies addressed metformin versus meglitinides, thiazolidinediones versus sulfonylureas, metformin versus metformin plus sitagliptin and available results were imprecise with high risk of bias. |
| Liver injury | Moderate | Risk of liver injury was similar between thiazolidinediones and sulfonylureas. |
| Fractures | High | Risk of fracture was 1.5 times higher in thiazolidinedione compared with metformin, with highest risk among women compared with men. |
| | High | Risk of fracture was 1.5 times higher in a combination therapy with thiazolidinedione compared with metformin plus sulfonylurea, with the highest risk among women compared with men. |

GI = gastrointestinal; HDL = high density lipoprotein; HgbA1c = hemoglobin A1c; kg = kilograms; LDL = low density lipoproteins; mg/dL = milligrams per deciliter; RCT = randomized controlled trial; RR = relative risk; TG = triglycerides

# Introduction

## Background

Type 2 diabetes is a common chronic illness, with an increasing prevalence that parallels the rise in obesity rates. Type 2 diabetes is characterized by insulin resistance, which is worsened by obesity and physical inactivity. Over time, the pancreatic β cells lose their ability to maintain the high insulin levels needed to counter liver and muscle insulin resistance and β cell failure occurs.[1] The natural history of type 2 diabetes has been described in several populations.[1]

In the United States, the prevalence of diabetes has increased from 5.1% in 1988 to 1994 to 6.5% in 1999 to 2002.[2] Like many chronic illnesses, diabetes disproportionately affects older people, and its prevalence is higher among racial and ethnic minority populations.[3] The annual economic burden of diabetes is estimated to be 132-billion dollars[4] and is increasing, mostly attributable to costly complications of the disease.[5]

Complications of long-standing diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy and end stage kidney disease. In addition, there is a two- to four-fold increased death rate from cardiovascular disease in adults with type 2 diabetes compared to adults without diabetes. Management of hyperglycemia using diet and pharmacologic therapy is the cornerstone of treatment for type 2 diabetes, along with management of co-existing lipid abnormalities and hypertension. Results from randomized controlled trials (RCTs) have demonstrated that the risk of microvascular complications, particularly retinopathy, can be reduced with good glycemic control in patients with type 2 diabetes.[6-8] However, the impact of tight glycemic control on cardiovascular disease has been inconclusive.[8-10]

Early data from the United Kingdom Prospective Diabetes Study (UKPDS) suggested a protective effect of improved glucose control on cardiovascular disease morbidity and mortality. In particular, treatment with metformin compared with sulfonylureas and insulin resulted in greater cardiovascular benefit.[7] However, in the last two years, several major trials have found no benefit from intensive glycemic control.[11 12] In fact, the Action to Control Cardiovascular Disease in Diabetes (ACCORD) study identified an increased risk for death from cardiovascular causes and higher total mortality among those participants treated with an intensive glucose control strategy.[12] There have been concerns, too, about specific oral hypoglycemic agents and cardiovascular disease risk, specifically rosiglitazone, from the thiazolidinedione class, and ischemic heart disease and congestive heart failure.[13 14] National trends in the treatment of diabetes have reflected the public's concern about this drug, with a 63% decrease in rosiglitazone use between 2004 and 2007.[15]

Prior to 1995, the only drugs for treating diabetes were sulfonylureas and insulin. Since 1995 there has been an explosion in new pharmacotherapy options and currently there are eleven classes of diabetes medications, including sulfonylureas, meglitinides, incretins, biguanides, amylin analogues, TZDs, bromocriptine, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, colesevalam, and both long- and short-acting insulins (Table 1).[15] The newer agents are more costly than the older medications, and some are only approved as adjunctive therapies.

**Table 1. Characteristics of medications included in this report**

| Drug | Trade name | Dosing | Cost in US dollars* |
|---|---|---|---|
| **ORAL AGENTS** | | | |
| **Biguanides** | | | |
| Metformin | Glucophage, Glucophage XR | 500 to 2550 mg divided doses (qd to tid)<br>max dose: 2550 mg; 2000 mg for XR | Tablets (Metformin HCl)<br>500 mg (60): $33.99<br>850 mg (60): $51.99<br>1000 mg (60): $55.99<br>Tablet, 24-hour (Metformin HCl)<br>500 mg (60): $39.99 |
| **Thiazolidinediones** | | | |
| Pioglitazone | Actos | 15 to 30 mg qd<br>max dose: 45 mg qd | 15 mg (30): $102.55<br>30 mg (30): $162.99<br>45 mg (30): $179.99 |
| Rosiglitazone | Avandia | 4 to 8 mg qd or 2 to 4 mg bid<br>max dose: 8 mg qd or 4 mg qd with insulin or sulfonylurea | 2 mg (60): $133.31<br>4 mg (30): $105.53<br>8 mg (30): $175.08 |
| **Sulfonylureas** | | | |
| Glimepiride | Amaryl | 1 to 8 mg qd<br>max dose: 8 mg qd | 1 mg (30): $9.99<br>2 mg (30): $13.99<br>4 mg (30): $14.99 |
| Glipizide | Glucotrol, Glucotrol XL or GITS | 5 to 15 mg qd or 5 to 20 mg bid<br>max dose: 20 mg bid, 20 mg qd for XL | Tablet, 24-hour<br>2.5 mg (30): $10.99<br>5 mg (30): $10.99<br>10 mg (30): $19.99<br>Tablets<br>5 mg (60): $9.99<br>10 mg (60): $10.99 |
| Glyburide | Micronase, Diabeta, Glynase Prestab | 2.5-20 mg qd or bid<br>max dose: 20 mg qd | Tablets<br>1.25 mg (30): $7.99<br>2.5 mg (30): $7.99<br>5 mg (30): $7.99 |
| **Dipeptidyl peptidase-4 inhibitors** | | | |
| Sitagliptin | Januvia | 25 to 100 mg qd<br>recommended dose is 100 mg qd | 100 mg (30): $193.58 |
| **Meglitinides** | | | |
| Repaglinide | Prandin | 0.5 to 4 mg before meals<br>max dose:16 mg | 0.5 mg (90): $104.77<br>1 mg (90): $111.10<br>2 mg (90): $111.10 |
| Nateglinide | Starlix | 60 to 120 mg before meals | 60 mg (30): $39.51<br>120 mg (30): $43.20 |
| **NON-INSULIN INJECTABLE AGENT** | | | |
| Exenatide injection | Byetta | 5-10 mcg injected SC bid | 5 mcg/0.02 mL solution 1.2 mL pen: $245.03<br>10 mcg/0.04 mL solution 2.4 mL pen: $271.44 |
| **INSULIN** | | | |
| **Long- or intermediate-acting insulin** | | | |
| NPH insulin | Humulin N<br>Novolin N | NA | Humulin N: 100 unit/mL suspension 10 mL vial: $54.00<br>Novolin N: 100 unit/mL suspension 10 mL vial: $57.81 |
| Insulin detemir | Levemir | NA | 100 unit/mL solution 10 mL vial: $102.82 |
| Insulin glargine | Lantus | 1-80 units daily | 100 unit/mL solution 10 mL vial: $103.59 |

**Table 1. Characteristics of medications included in this report (continued)**

| Drug | Trade name | Dosing | Cost in US dollars* |
|---|---|---|---|
| **Premixed insulin** | | | |
| 50% NPH: 50% Regular | Humulin 50/50 | NA | 10 mL vial: $54.00 |
| 70% NPH: 30% Regular | Humulin 70/30<br>Novolin 70/30 | NA | Humulin: 10 mL vial: $54.00<br>Novolin: 10 mL vial: $57.81 |
| 50% lispro protamine suspension: 50% lispro | Humalog Mix 50/50 | NA | Pen: $199.99 |
| 75% lispro protamine suspension: 25% lispro | Humalog Mix 75/25 | NA | 10 mL vial: $110.75 |
| 70% aspart protamine suspension: 30% aspart | NovoLog Mix 70/30 | NA | 10 mL vial: $109.70 |

bid = twice daily; GITS = gastrointestinal therapeutic system; HCl = hydrogen chloride; max = maximum; mcg = micrograms; mg = milligram; mL = milliliter; NA = not applicable; NPH = neutral protamine Hagedord; qd = once daily; SC = subcutaneous; tid = three-times daily; US = United States; XL = extended release; XR = extended release
Used Micromedix: http://www.thomsonhc.com/hcs/librarian for pharmaceutical information.
*Information provided includes dose, pill count, and cost in US dollars (drugstore.com)

With the increasing number of available medication choices for diabetes, patients are being managed with a greater number of classes of medications in combination. In 2005 to 2006, 35.3% of all patients with diabetes were taking 2 classes of anti-diabetes medications and 14.2% were taking three or more classes, compared to only 5.6% percent taking three or more classes in 1999 to 2000.[16] Some experts advocate earlier use of combination therapies to prevent the progressive β cell failure associated with diabetes, but the evidence for this protection is still not clear.[1] With newer insulin products on the market since 2001, use of insulin has started to increase. Long-acting insulin glargine and the ultra-short-acting insulin lispro are the most commonly used individual insulin therapies in 2007.[15]

## Rationale for Update of Review on Comparative Effectiveness of Diabetes Medications

In 2007, the Agency for Healthcare Research and Quality (AHRQ) published its first systematic review on the comparative effectiveness of oral hypoglycemic medications for type 2 diabetes.[17] This comprehensive review was unique because it included comparisons of all oral diabetes medications. It also had a broad scope, including both intermediate outcomes like glycemic control and clinical outcomes like cardiovascular disease and nephropathy, as well as adverse events. This review of 216 studies concluded that most oral diabetes medications had a similar effect on reducing hemoglobin A1C (HgbA1c), most drugs except for metformin and acarbose caused increases in body weight, and only metformin decreased low density lipoprotein (LDL) cholesterol. There were too few studies to support any conclusions about differential effects of the oral diabetes medications on all cause mortality, cardiovascular mortality and morbidity, and microvascular complications. The sulfonylurea class was shown to be associated

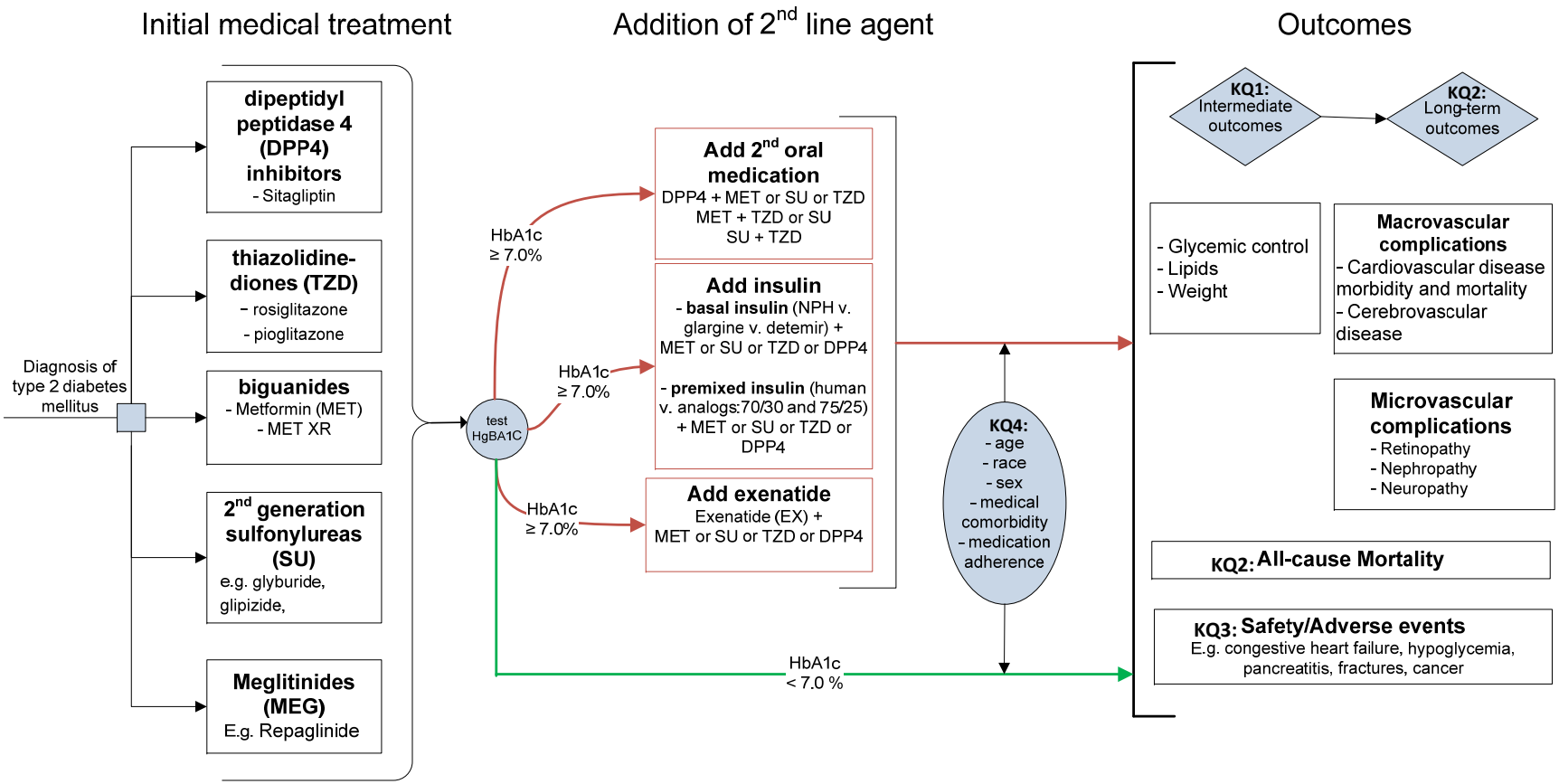
with an increased risk of hypoglycemia, metformin with gastrointestinal problems, and the thiazolidinediones with heart failure.

In the two years following publication of that review, there was sufficient change in the evidence base that an update to address research gaps and integrate newer evidence was needed. Since the first review, two new medication classes were approved by the Food and Drug Administration (FDA). The injectable incretin mimetic, exenatide, was FDA-approved in 2005, and the DPP-4 inhibitor, sitagliptin, was approved in 2006. Additionally, an update of the review was needed to include evidence about combinations of medications, including combinations of an oral medication with insulin therapy. Accordingly, AHRQ requested this update to the previously published work to amalgamate and update the previously published work.

## Conceptual Model

Our conceptual model describes the decisions that patients and their providers face when managing type 2 diabetes pharmacologically. When beginning medical treatment, patients usually begin with one of five drugs classes, which have all been FDA-approved for monotherapy. These include DPP4-inhibitors, TZD's, sulfonylureas, biguanides, and meglitinides. Clinical guidelines recommend monitoring the HgbA1c to make determinations about dose titration and adding other agents, with a HgbA1c ≥ 7.0% prompting the need to make a change to improve glycemic control.[18] If the HgbA1c is ≥ 7.0%, clinicians typically add an additional oral hypoglycemic medication, or may add insulin or exenatide. Both intermediate- and long-term outcomes are monitored as indicators of effectiveness. Intermediate outcomes include HgbA1c, weight, and lipids. In addition, clinicians monitor short-term and long-term safety and adverse effects of the drug.

**Figure 1. Conceptual model**




HgbA1c = hemoglobin A1c; KQ = Key Question; NPH = neutral protamine Hagedorn

# Scope and Key Questions

This Comparative Effectiveness Review was commissioned by AHRQ to update the Comparative Effectiveness Review on "The Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes".[17] Because of the rapid advances in the field of diabetes, with new medications on the market and the increasing use of medications in combination, AHRQ recognized the need to conduct an updated review and synthesis. We conducted a topic refinement process to identify the evidence gaps specified in the prior report, to assess the utility and impact of the Report in subsequent guideline development, and to refine the key questions for the Update. Based on this process, there are several notable distinctions from the 2007 Report, which include:

1. A focus on priority head-to-head drug comparisons, identified *a priori* as clinically relevant comparisons for which there were evidence gaps
2. The inclusion of two newly FDA-approved medications: exenatide and sitagliptin
3. The inclusion of comparisons of two-drug combinations with a focus on:
    a. Metformin and thiazolidinediones in combination with another medication
    b. Basal and premixed insulin therapy in combination with an oral medication
4. The addition of safety outcomes, including fractures and macular edema.

## Key Questions

We addressed the following key questions:

Key Question 1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see list of comparisons) for the intermediate outcomes of glycemic control (in terms of HgbA1c), weight, or lipids?

Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see list of comparisons) in terms of the following long-term clinical outcomes?

- All-cause mortality
- Cardiovascular mortality
- Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke)
- Retinopathy
- Nephropathy
- Neuropathy

Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the following treatment options (see list of comparisons) in terms of the following adverse events and side effects?

- Hypoglycemia
- Liver injury
- Congestive heart failure
- Severe lactic acidosis
- Cancer
- Severe allergic reactions

- Hip and non-hip fractures
- Pancreatitis
- Cholecystitis
- Macular edema or decreased vision
- Gastrointestinal (GI) side effects

Key Question 4: Do safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular and cerebrovascular outcomes?

**Table 2. Priority medication comparisons included for each of the key questions**

| | Main intervention | Comparisons |
|---|---|---|
| **Monotherapy as main intervention** | Metformin | • Thiazolidinedione<br>• Sulfonylurea<br>• Sitagliptin<br>• Meglitinides<br>• Combination of metformin plus thiazolidinedione<br>• Combination of metformin plus sulfonylurea<br>• Combination of metformin plus sitagliptin<br>• Combination of metformin plus meglitinides |
| | Thiazolidinedione | • Different thiazolidinedione<br>• Sulfonylurea<br>• Sitagliptin<br>• Meglitinides |
| | Sulfonylurea | • Sitagliptin<br>• Meglitinides |
| | Sitagliptin | • Meglitinides |
| **Combination therapy as main intervention** | Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) | • Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) |
| | Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or sitagliptin or exenatide or a basal insulin or a premixed insulin) | • Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or sitagliptin) |

1

# Methods

AHRQ requested an update to the comparative effectiveness review (CER), "Comparative Effectiveness and Safety of Oral Diabetes Medications For Adults with Type 2 Diabetes." In addition, AHRQ requested that the scope be broadened to include a review of the comparative effectiveness and safety of combinations of medications for diabetes treatment. Our Evidence-based Practice Center (EPC) established a team and a work plan to develop the evidence report. The project involved recruiting technical experts, formulating and refining the questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

## Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of internal and external technical experts and key informants to give input on key steps including the selection and refinement of the questions to be examined. The panel included internal technical experts from the Johns Hopkins University having expertise in various aspects of the efficacy and/or safety of oral diabetes medications, and external experts who have expertise in diabetes research (Appendix A).

To understand some of the pressing issues concerning the use of oral diabetes medications, we analyzed the recommendations in published guidelines on the treatment of type 2 diabetes. We conducted a search of PubMed and the National Guideline Clearinghouse for all guidelines concerning oral diabetes medications published since completion of the 2007 CER. Two investigators reviewed each guideline for inclusion in this process. Guidelines needed to have been written in English, published after July 2007, and included recommendations on the medical management of type 2 diabetes in non-pregnant adults. Additionally the guideline had to have been sponsored by or authorized by an organization in the United States, United Kingdom, or Canada, and met the criteria for a guideline.[19] For each included guideline, two reviewers abstracted the recommendations on medical management and whether the recommendations agreed with the key findings from the 2007 CER.

With the technical experts and representatives of AHRQ and the Scientific Resources Center, and with our understanding of the gaps in existing guidelines, we developed the Key Questions that are presented in the Scope and Key Questions section of the Introduction. The final Key Questions focus on the differences among oral diabetes medications, used as monotherapy and used in combination, in their ability to affect intermediate outcomes, long-term clinical outcomes, and their adverse effects.

## Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to June 2009), EMBASE® (1974 to June 2009), and the Cochrane Central Register of Controlled Trials (1966 to June 2009). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. Our search strategy was similar to the one

used for the initial 2007 CER,[17] but it included terms for the additional medications included in this review (Appendix B).

In addition, we received the following material from the Scientific Resource Center:

- Medical reviews of rosiglitazone, pioglitazone, sitagliptin, glyburide and metformin, combination of metformin and glipizide, combination of metformin and sitagliptin, insulin detemir, exenatide and postmarketing drug safety information on pioglitazone and insulin glargine from the FDA website,
- The Scientific Discussion sections of the European Public Assessment Reports for rosiglitazone, pioglitazone, sitagliptin, combination rosiglitazone and metformin, exenatide, insulin detemir, and insulin glargine,
- Health Canada Product Monographs for rosiglitazone, pioglitazone, sitagliptin, combination rosiglitazone and metformin, insulin glargine, and insulin detemir,
- Public registries of clinical trials, such as Clinical Study Results website (www.clinicalstudyresults.org) and ClinicalTrials.gov (www.clinicaltrials.gov).

We hand searched 15 journals that most likely to publish articles on this topic (see Appendix C) by scanning the table of contents of each issue for relevant citations from February 2009 through September 2009. We also reviewed the reference lists of each included article and relevant review articles.

The results of the searches were downloaded and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in both ProCite®. From ProCite, the articles were uploaded to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a web-based software package developed for systematic review data management. This database was used to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

## Study Selection

Two independent reviewers conducted title scans in parallel. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible. If they disagreed, the article was promoted to the next level (Appendix D, Title Review Form). The title review was designed to capture as many studies as possible that reported on the efficacy or safety of oral diabetes medications. These titles were promoted to the abstract review phase.

The abstract review phase was designed to identify studies reporting on the effects of oral diabetes medications on intermediate outcomes, long-term clinical outcomes, or adverse events and side effects (Appendix D, Abstract Review Form). Abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 3). Differences between investigators regarding abstract inclusion or exclusion were resolved through consensus adjudication.

Articles promoted on the basis of abstract review underwent another independent parallel review to determine if they should be included for data abstraction (Appendix D, Article Review Form). Differences regarding article inclusion were resolved through consensus adjudication. During both the abstract review and article review, reviewers indicated if there was a monotherapy comparison or a combination comparison of interest. For studies that were

**Table 3. Inclusion and exclusion criteria**

| | |
|---|---|
| **Population and condition of interest** | ☐ All studies included patients with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes. We excluded studies that evaluated only patients with type I diabetes, impaired glucose tolerance, metabolic syndrome, maturity onset diabetes of youth, and gestational diabetes.<br>☐ All studies included human subjects.<br>☐ We excluded studies if they included only pregnant women or only subjects less than or equal to 18 years of age. |
| **Interventions** | ☐ All studies must have evaluated an oral diabetes medication or drug combination of interest.<br>○ Biguanides (metformin)<br>○ Thiazolidinediones (rosiglitazone, pioglitazone)<br>○ Second-generatoin sulfonylureas (glyburide, glibenclamide, glipizide, glimepiride)<br>○ Dipeptidyl peptidase-4 inhibitor (sitagliptin)<br>○ Meglitinides(repaglinide, nateglinide)<br>○ Combination of metformin plus a thiazolidinedione<br>○ Combination of metformin plus a sulfonylurea<br>○ Combination of metformin plus sitagliptin<br>○ Combination of metformin plus a meglitinide<br>○ Combination of metformin plus exenatide<br>○ Combination of metformin plus a basal insulin (insulin glargine, insulin detemir, NPH insulin)<br>○ Combination of metformin plus a premixed insulin (NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30)<br>○ Combination of a thiazolidinedione and a sulfonylurea<br>○ Combination of a thiazolidinedione and a meglitinide<br>☐ We excluded studies that did not specify the adjunctive medications, such as those stating use of “any oral hypoglycemic” or if the study listed possible medications without stratification of the results by treatment. |
| **Comparisons of interest** | ☐ We excluded studies that did not have a comparison group.<br>☐ Table 2 presents the diabetes medication comparisons of interest. We excluded studies that did not have one of these comparisons. |
| **Outcomes** | ☐ We excluded studies that did not apply to the key questions.<br>☐ For Key Question 1, we included the following outcomes: HgbA1c, weight, and serum lipid levels (HDL, LDL, TG).<br>○ We did not include data on total cholesterol or other measures of glycemic variability.<br>☐ For Key Question 2, we included the following outcomes: all-cause mortality, cardiovascular disease mortality, cardiovascular and cerebrovascular disease morbidity, retinopathy, neuropathy, and nephropathy.<br>○ We excluded biologic markers of outcomes, such as vascular endothelial function or carotid intima medial thickness.<br>☐ For Key Question 3, we included the following outcomes: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and non-hip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and GI side effects. |
| **Type of study** | ☐ We excluded articles not written in English, studies less than 3 months in duration, studies with less than 40 total subjects, articles with no original data (editorials, comments, letters).<br>☐ For Key Question 1, we included only RCTs.<br>☐ For Key Questions 2 and 3, we included only RCTs, non-RCTs, cohort studies with a comparison group, and case-control studies.<br>☐ We included crossover studies for the outcomes of hypoglycemia, liver injury, and GI side effects regardless of the duration of the washout period. For all other outcomes, we included crossover studies only if the duration of the washout period was greater than 1 month. |

GI = gastrointestinal; HDL = high density lipoprotein; HgbA1c = hemoglobin A1c; LDL = low density lipoprotein; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; TG = triglycerides

excluded because they did not involve a comparison of interest, reviewers still noted the comparison (see Appendix E for a list of the comparisons that were tallied).

The inclusion and exclusion criteria for this review differed from the initial CER. First, this review includes interventions that were excluded from the initial CER: sitagliptin, combination metformin plus sitagliptin, combination metformin plus a meglitinide, combination metformin

plus exenatide, combination of metformin plus a basal insulin, combination of metformin plus a premixed insulin, and combination thiazolidinedione plus a meglitinide. This review includes studies with unambigous medication combinations but not studies in which participants were treated with unspecified adjunctive diabetes medications. Second, this review includes outcomes that were not included in the initial CER: fractures, cholecystitis, and macular edema. We did not update the initial CER on the outcomes of blood pressure, body mass index, 2-hour postprandial glucose, peripheral arterial disease, amputations, quality of life, functional status, anemia, thrombocytopenia, leucopenia, hypervolemia, and withdrawals due to adverse events.

## Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis. If reviewers determined that an article addressed both efficacy and safety, multiple data abstraction forms were used.

Each article underwent double review by study investigators for data abstraction and assessment of study quality. The second reviewer confirmed the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer re-reviewed a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Reviewers were not masked to the articles' authors, institution, or journal.[20] In most instances, data were directly abstracted from the article. If possible, relevant data were also abstracted from figures. Differences in opinion were resolved through consensus adjudication. For assessments of study quality, each reviewer independently judged study quality and rated items on quality assessment forms (Appendix D, Data Abstraction Review Forms).

For all articles, reviewers extracted information on general study characteristics (e.g., study design, study period and followup), study participants (e.g., age, gender, race, weight/body mass index, HgbA1c levels, and duration of diabetes), eligibility criteria, interventions (e.g., initial, maximum, and mean doses, frequency of use, and duration of use), outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability (Appendix D, Data Abstraction Review Forms).

All information from the article review process was entered into the DistillerSR database by the individual completing the review. Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain and clean the data, as well as to create detailed evidence tables and summary tables.

## Quality Assessment

Article quality was assessed differently for RCTs and observational studies. For RCTs the dual, independent review of article quality was based on the Jadad criteria: (1) appropriateness of the randomization scheme, (2) appropriateness of the blinding, and (3) description of withdrawals and drop-outs.[21] For the updated review, we also included a question to evaluate the overall quality of the study, as suggested by the Guide for Conducting Comparative Effectiveness Reviews.[22]

We developed a quality assessment tool for observational studies based on the recommendations in the Guide for Conducting Comparative Effectiveness Reviews[22] and quality forms previously developed by our Evidence-based Practice Center.[23] The quality assessment included items about the study setting, inclusion and exclusion criteria, key characteristics of enrolled subjects, details about the treatments, details about the outcomes and how they were measured, statistical analysis, losses to followup, and the overall study quality. For both the RCTs and the observational studies, the overall study quality was assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a formal randomized controlled design; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[22]

In the initial 2007 CER, we did not assess the quality of observational studies or non-randomized trials.

We had high consistency between the primary and secondary reviewer; therefore, we report only the second reviewers' quality scores (the second reviewers generally had more research experience than the primary reviewers). We used our study quality assessment to help us understand differences in results between studies.

## Applicability

Throughout the report, we discuss the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings are typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting (conceived as outpatient treatment by internists, family physicians, and endocrinologists).

## Data Analysis and Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least 3 trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose).

We recorded the mean difference between groups along with its measure of dispersion. If this was not reported, we calculated the point estimate using the mean difference from baseline for each group. If the mean difference from baseline was not reported, we calculated this from the

baseline and final values for each group. If no measure of dispersion was reported for the between-group difference, we calculated it using the sum of the variances for the mean difference from baseline for each group. If there were no measures of dispersion for the mean difference from baseline for each group, we calculated the variance using the standard deviation of the baseline and final values, assuming a correlation between baseline and final values of 0.5. If data were only presented in graphical form, we abstracted data from the graphs. For trials that had more than one dosing arm, we chose the arm that was most consistent with dosing in the other trials. When more than one followup interval was reported, we used the data from the followup most similar to the other trials. We reported the rest of the results descriptively. When data were not sufficient to combine in a meta-analysis, we summarized the outcomes by reporting the ranges of values for mean differences from baseline or mean differences between groups (when possible).

For Key Questions 2 and 3, we were unable to conduct meta-analyses on most of the outcomes due to methodologic diversity among the trials such as differences in definitions of selected outcomes or lack of sufficient numbers of trials to combine. When there were sufficient data (at least 3 trials) and the studies were considered to be similar with respect to important variables (population characteristics, drug comparisons, drug dosage, definition of outcome, and followup time), we performed meta-analyses.

For the outcome of hypoglycemia, we needed to generate categories for the outcomes to match those in the 2007 CER. The studies included in the 2007 CER had hypoglycemia outcomes categorized as total, serious, and those which led to withdrawal from the study. In order to pool these with the new studies, we categorized those outcomes as: a) serious hypoglycemia or hypoglycemia leading to withdrawal from the study, and b) all other. These were then combined with events categorized as: a) severe hypoglycemia and b) mild or moderate hypoglycemia, which were the categories for the newly abstracted studies. In previously included studies from the 2007 CER, the hypoglycemia outcomes were reported as the number of people with hypoglycemic episodes (not the number of events). Therefore, in integrating the previously and newly identified studies, we pooled the number of people with events. The number of events is reported descriptively when available. Several studies reported only the rates of events per time of follow-up; these too are described in the text. The count of individuals upon enrollment was used as the denominator for the prevalence of hypoglycemic events. For trials not amenable to pooling, the Mantel-Haenszel risk ratios were calculated with 95% confidence intervals surrounding the estimate (STATA (Intercooled, version 9.2, StataCorp, College Station, TX).

For trials amenable to pooling, we calculated pooled effect estimates of the relative risk between trial arms from the RCTs, with each study weighted by the inverse of the study variance, using a random effects model with the DerSimonian and Laird formula for calculating between-study variance.[24] Heterogeneity among the trials in all the meta-analyses was tested using a standard chi-squared test using a significance level of alpha less than or equal to 0.10. We also examined heterogeneity among studies with an $I^2$ statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[25] A value greater than 50% may be considered to have substantial variability. If heterogeneity was found, we attempted to determine potential reasons by conducting metaregression using study level characteristics such as baseline values, study duration, and dose ratio (dose ratio of drug 1 divided by dose ratio of drug 2). The dose ratio for each drug was calculated as the dose given in the study divided by the maximum approved dose of drug. We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate.

Because statistically significant findings are more likely to be published than studies without statistically significant results (publication bias), we examined whether there was evidence that smaller, negative studies appeared to be missing from the literature. We therefore conducted formal tests for publication bias using Begg's[26] and Eggers tests[27] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes where meta-analyses were conducted for Key Question 1. All meta-analyses were conducted using STATA (Intercooled, version 9.2, StataCorp, College Station, TX).

Unadjusted odds ratios were calculated in instances when the total number of deaths was reported for each arm, the total number of participants was reported for each arm, and when measures of association were either not calculated at all or when a comparator which was not of interest was used as the reference group. These unadjusted odds ratios and confidence intervals were calculated using SAS 9.1.3 using the PROC FREQ command.

## Data Entry and Quality Control

After a second reviewer reviewed the data that had been entered into DistillerSR, adjudicated data were re-submitted into web-based data collection forms by the second reviewer. Second reviewers were generally more experienced members of the research team. In addition, two additional investigators audited a random sample of the reviews to identify problems with data abstraction. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

## Rating the Body of Evidence

At the completion of our review, we graded the quantity, quality and consistency of the best available evidence addressing Key Questions 1, 2 and 3 by adapting an evidence grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.[22] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome. We assessed the strength of the study designs with RCTs considered best, followed by non-RCTs, and observational studies. We also assessed the quality and consistency of the best available evidence, including assessment of limitations to individual study quality (using individual quality scores), consistency, directness, precision, and the magnitude of the effect.

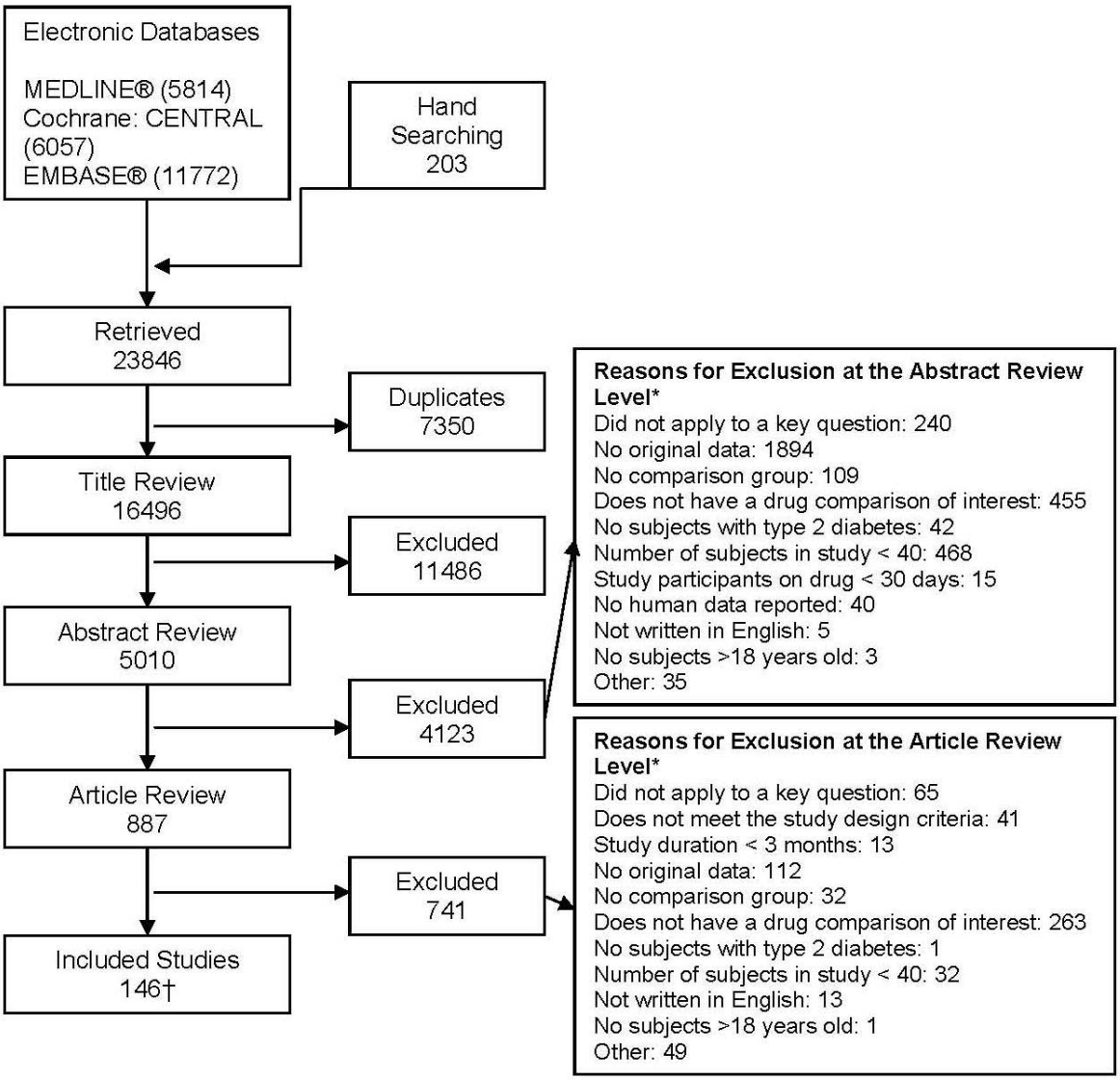
We classified evidence bodies pertaining to Key Questions 1, 2 and 3, into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (evidence is unavailable).

# Results

## Search Results

A summary of the search results is presented in Figure 2. From the search, we retrieved 16,496 unique citations. After a review of the titles and abstracts, 887 were deemed eligible for further review, and the full articles were retrieved. A total of 146 articles were included in this review.

**Figure 2. Summary of the literature search (number of articles)**




* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
†71 studies were included in the 2007 review
CENTRAL = Central Register of Controlled Trials

# Key Question 1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options (see list of comparisons) for the intermediate outcomes of glycemic control (in terms of HgbA1c), weight, or lipids?

## Key Points and Evidence Grades

**HgbA1c.**

- As monotherapy, most oral diabetes medications had similar efficacy in achieving reductions in HgbA1c, with absolute reduction of HgbA1c by around 1% as compared with baseline values. The strength of evidence was graded high for metformin versus sulfonylurea, and graded moderate for the following comparisons: metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone.
- All combination therapies were better at reducing HgbA1c than monotherapy regimens, with an absolute between group difference of about 1%. The strength of evidence was graded high for metformin versus metformin plus thiazolidinediones, and metformin versus metformin plus sulfonylureas, and graded moderate for metformin versus metformin plus sitagliptin.
- There was moderate evidence showing that the combination of metformin plus thiazolidinedione had similar efficacy in reducing HgbA1c as the combination of metformin plus sulfonylurea.
- Five other combination comparisons were graded as low evidence, making it difficult to draw firm conclusions; however, they generally showed similar efficacy in reducing HgbA1c.
    - Three of these combinations showed similar efficacy in reducing HgbA1c: metformin plus repaglinide versus metformin plus thiazolidinedione, metformin plus sitagliptin versus metformin plus thiazolidinedione, and metformin plus sulfonylurea versus metformin plus sitagliptin.
    - Two of these comparisons favored one combination over another minimally ranging from 0.03% to 0.09%: metformin plus sulfonylurea versus thiazolidinediones plus sulfonylurea, and thiazolidinediones plus sulfonylureas versus metformin plus thiazolidinediones

**Weight.**

- When compared with thiazolinediones, metformin maintained or decreased weight with between-group difference of -2.6 kg, 95% CI -4.1 kg to -1.2 kg). The strength of evidence was graded high favoring metformin.
- When compared with sulfonylureas, metformin maintained or decreased weight (between-group difference of -2.7 kg, 95% CI -3.5 kg to -1.9 kg). The strength of evidence was graded high favoring metformin.
- Sulfonylureas had similar effects on body weight as the meglitinides when used as monotherapy, with a high evidence grade.

- Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg, 95% CI -0.6 kg to -1.9 kg). While this was graded as low evidence for the monotherapy comparisons, it was strengthened by the combination comparisons below which favor metformin plus sulfonylurea over metformin plus a thiazolidinedione (between-group difference of -0.9 kg, 95% CI -0.4 kg to -1.3 kg) with a moderate grade of evidence.
- Metformin monotherapy had a more favorable effect on weight compared with the combination of metformin plus a thiazolidinedione (between-group difference of -2.2 kg, 95% CI -2.6 kg to -1.9 kg) or metformin plus a sulfonylurea (between-group difference of -2.3 kg, 95% CI -3.3 kg to -1.2 kg). The strength of evidence was graded high for these comparisons.
- Metformin plus sulfonylurea had a more favorable effect on weight compared with both the combination of a thiazolidinedione plus sulfonylurea (between-group difference of -3.2 kg, 95% CI –5.2 kg to -1.1 kg) and the combination of metformin plus a thiazolidinedione (between-group difference of -0.9 kg, 95% CI -0.4 kg to -1.3 kg). Both comparisons had moderate strength of evidence.
- No between-group differences in weight exceeded 5 kg, even in the few longer term trials.

**Low density lipoproteins.**

- There was moderate to high strength of evidence that rosiglitazone and pioglitazone increased LDL cholesterol while metformin decreased LDL cholesterol. The pooled between-group differences comparing metformin to rosiglitazone and pioglitazone were -14.0 mg/dL (95% CI -26.5 mg/dL to -1.5 mg/dL) and -14.2 mg/dL (95% CI -15.3 mg/dL to -13.1 mg/dL), respectively.
- Metformin decreased LDL by about 10 mg/dL compared to second-generation sulfonylureas which generally had little effect on LDL, with high strength of evidence.
- The addition of rosiglitazone to metformin increased LDL compared to metformin monotherapy (pooled between-group difference 14.5 mg/dL, 95% CI 13.3 mg/dL to 15.7 mg/dL) with high strength of evidence.
- There was moderate strength of evidence that the combination of metformin and a second-generation sulfonylurea decreased LDL more than the combination of metformin and rosiglitazone (pooled between-group difference -13.5 mg/dL, 95% CI -17.9 mg/dL to -9.1 mg/dL).

**High density lipoproteins.**

- The strength of the evidence was high that pioglitazone increased HDL cholesterol more than metformin (pooled between-group difference 3.2 mg/dL, 95% CI 2.1 mg/dL to 5.7 mg/dL).
- Neither rosiglitazone nor second-generation sulfonylureas had an effect on HDL cholesterol relative to metformin, with moderate to high strength of evidence.
- The addition of rosiglitazone to metformin increased HDL cholesterol relative to metformin monotherapy (pooled between-group difference 2.8 mg/dL, 95% CI 2.2 mg/dL to 3.5 mg/dL) with high strength of evidence.
- The addition of rosiglitazone or pioglitazone to metformin increased HDL cholesterol relative to the combination of metformin and a second-generation sulfonylurea. The

pooled between-group difference for the combination of metformin and rosiglitazone compared to the combination of metformin and a second-generation sulfonylurea was 2.7 mg/dL (95% CI 1.4 mg/dL to 4.1 mg/dL). The addition of pioglitazone to metformin increased HDL by about 5 mg/dL compared to the addition of a second-generation sulfonylurea to metformin. The strength of evidence was graded as moderate for these comparisons.

**Triglycerides.**

- There was moderate strength of evidence to conclude that metformin decreased TG relative to rosiglitazone which increased TG (pooled between-group difference -30.1 mg/dL, 95% CI -52.8 mg/dL to -7.3 mg/dL).
- There was high strength of evidence that pioglitazone decreased TG compared to metformin (pooled between-group difference -27.2 mg/dL, 95% CI -30.1 mg/dL to -24.4 mg/dL).
- Metformin decreased TG relative to second-generation sulfonylureas (pooled between-group difference -8.6 mg/dL, 95% CI -15.6 mg/dL to -1.6 mg/dL). There was moderate strength of evidence for this comparison.
- There was high strength of evidence that metformin monotherapy decreased TG relative to the addition of rosiglitazone to metformin (pooled between-group difference -14.5 mg/dL, 95% CI -15.7 mg/dL to -13.3 mg/dL).
- The addition of rosiglitazone to metformin did not affect TG relative to the addition of a second-generation sulfonylurea to metformin. However, the addition of pioglitazone to metformin decreased TG relative to the addition of a second-generation sulfonylurea to metformin by about 15 mg/dL. There was moderate strength of evidence for these comparisons.

See Table 4 for the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix G, Table 1.

## Study Design and Population Characteristics

One hundred and one RCTs reported in 104 articles evaluated intermediate clinical outcomes for adults with type 2 diabetes, and met our inclusion criteria (Appendix G, Tables 2 and 3). Eighty-nine, 64, and 58 of these RCTs reported HgbA1c, weight, and lipid outcomes respectively. All trials were parallel arm RCTs except one which used a crossover design.[28] About half the trials answering Key Question 1 occurred partly or exclusively in the United States (US) (n = 26), Italy (n = 12), and/or were multi-national (n = 22); the rest of the trials occurred in developed or newly industrialized countries. These RCTs lasted from 12 weeks to 9 years; however, most studies lasted less than a year and only three studies lasted more than 2 years (UKPDS, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), and A Diabetes Outcome Progression Trial (ADOPT)).[14 29 30] Only five studies reported receiving no pharmaceutical support,[31-35] while about a quarter of RCTs (n = 28) did not describe whether or not they received pharmaceutical support.

Study participants were mainly middle-aged, overweight or obese adults who had diabetes between 3 to 6 years duration. The exclusion criteria were generally similar for most trials: significant renal, cardiovascular, and hepatic disease. About half the trials (58%) excluded older

**Table 4. Key findings and strength of the evidence comparing diabetes medications as monotherapy or combination therapy for intermediate outcomes**

| Comparison | HgbA1c | Weight/BMI | LDL | HDL | TG |
|---|---|---|---|---|---|
| | | **MONOTHERAPY COMPARISONS** | | | |
| **Metformin versus** | | | | | |
| TZD | Moderate; Neither favored | High; Favored Met | Moderate; Favored Met‡<br>High; Favored Met§ | Moderate; Neither favored‡<br>High; Favored pio§ | Moderate; Favored met‡<br>High; Favored pio§ |
| SU | High; Neither favored | High; Favored Met | High; Favored Met | High; Neither favored | Moderate; Favored Met |
| Sitagliptin | Low; Favored Met | Low; Unclear | Low; Unclear | Low; Unclear | Low; Unclear |
| Meglitinides | Low; Neither favored*<br>Low; Favored Met† | Low; Unclear | Low; Unclear | Low; Unclear | Low; Unclear |
| Metformin + TZD | High; Favored Met+TZD | High; Favored Met | High; Favored Met‡<br>Low; Unclear§ | High; Favored Met+Rosi‡<br>Low; Favored Met+Pio§ | High; Favored Met‡<br>Low; Unclear§ |
| Metformin + SU | High; Favored Met+SU | High; Favored Met | Low; Neither favored | Low; Neither favored | Low; Neither favored |
| Metformin + sitagliptin | Moderate; Favored Met+Sita | Low; Favored Met | Low; Unclear | Low; Neither favored | Low; Favored Met+Sita |
| Metformin + meglitinides | Low; Favored Met+Meg | Low; Favored Met | Low; Unclear | Low; Neither favored | Low; Favored Met+Meg |
| **TZD versus** | | | | | |
| TZD | Moderate; Neither favored | Low; Neither favored | Low; Favored pio | Low; Favored pio | Low; Favored pio |
| SU | Moderate; Neither favored | Low; Favored SU | Low; Favored SU‡§ | Low; Favored rosi‡<br>Low; Favored pio§ | Low; Unclear‡<br>Low; Neither favored§ |
| Sitagliptin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Meglitinides | Low; Unclear | Low; Unclear | Low; Unclear‡§ | Low; Unclear‡§ | Low; Unclear‡§ |
| **SU versus** | | | | | |
| Sitagliptin | Low: Neither favored | Low; Unclear | Low; Neither favored | Low; Neither favored | Low; Neither favored |
| Meglitinides | High; Neither favored*<br>Low; Neither favored† comparison | High; Neither favored | Low; Neither favored | High; Neither favored | Low; Neither favored |
| **Sitagliptin versus** | | | | | |
| Meglitinides | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |

**Table 4. Strength of the evidence and conclusion comparing diabetes medications as monotherapy or combination therapy for intermediate outcomes (continued)**

| Comparison | HgbA1c | Weight/BMI | LDL | HDL | TG |
|---|---|---|---|---|---|
| | | | **COMBINATION COMPARISONS** | | |
| **Metformin + TZD versus** | | | | | |
| Metformin + SU | Moderate; Neither favored | Moderate; Favored Met + SU | Moderate; Favored Met+SU‡<br>Low; Favored Met+SU§ | Moderate; Favored Met+TZD‡§ | Moderate; Neither favored‡<br>Moderate; Favored Met+Pio§ |
| Metformin + meglitinides | Low; Neither favored*<br>Insufficient† | Low; Unclear | Low; Favored Met+Meg‡<br>Insufficient§ | Low; Favored Met+Rosi‡<br>Insufficient§ | Low; Neither favored‡<br>Insufficient§ |
| Metformin + sitagliptin | Low; Neither favored | Low; Unclear | Insufficient‡§ | Low; Favored Met+Rosi‡<br>Insufficient§ | Low; Favored Met+Sita‡<br>Insufficient§ |
| TZD + SU | Low; Favored TZD+SU | Insufficient | Insufficient‡<br>Low; Neither favored§ | Insufficient‡<br>Low; Favored Met+Pio§ | Insufficient‡<br>Low; Favored Met+Pio§ |
| **Met + SU versus** | | | | | |
| Metformin + meglitinides | Insufficient*<br>Low; Unclear† | Low; Unclear | Low; Unclear | Low; Neither favored | Low; Unclear |
| Metformin + sitagliptin | Low; Neither favored | Low; Favored Met+Sita | Insufficient | Insufficient | Insufficient |
| TZD + SU | Low; Favored Met+SU | Moderate; Favored Met+SU | Low; Unclear‡<br>Low; Favored Met+SU§ | Low; Unclear‡<br>Low; Favored Pio+SU§ | Low; Unclear‡<br>Low; Favored Pio+SU§ |
| Metformin + premixed insulin | Low; Unclear | Low; Favored Met+Basal Insulin | Insufficient | Insufficient | Insufficient |
| **Met + Basal Insulin versus** | | | | | |
| Metformin + premixed insulin | Low: Favored Met+Premixed | Low; Neither favored | Insufficient | Insufficient | Insufficient |

BMI = body mass index; HDL = high density lipoprotein; HgbA1c = hemoglobin A1c; Meg = meglitinides; Met = metformin; LDL = low density lipoprotein; Pio = pioglitazone; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TG = triglycerides; TZD = thiazolidinedione

* For comparisons with repaglinide

† For comparisons with nateglinide

‡ For comparisons with rosiglitazone

§ For comparisons with pioglitazone

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

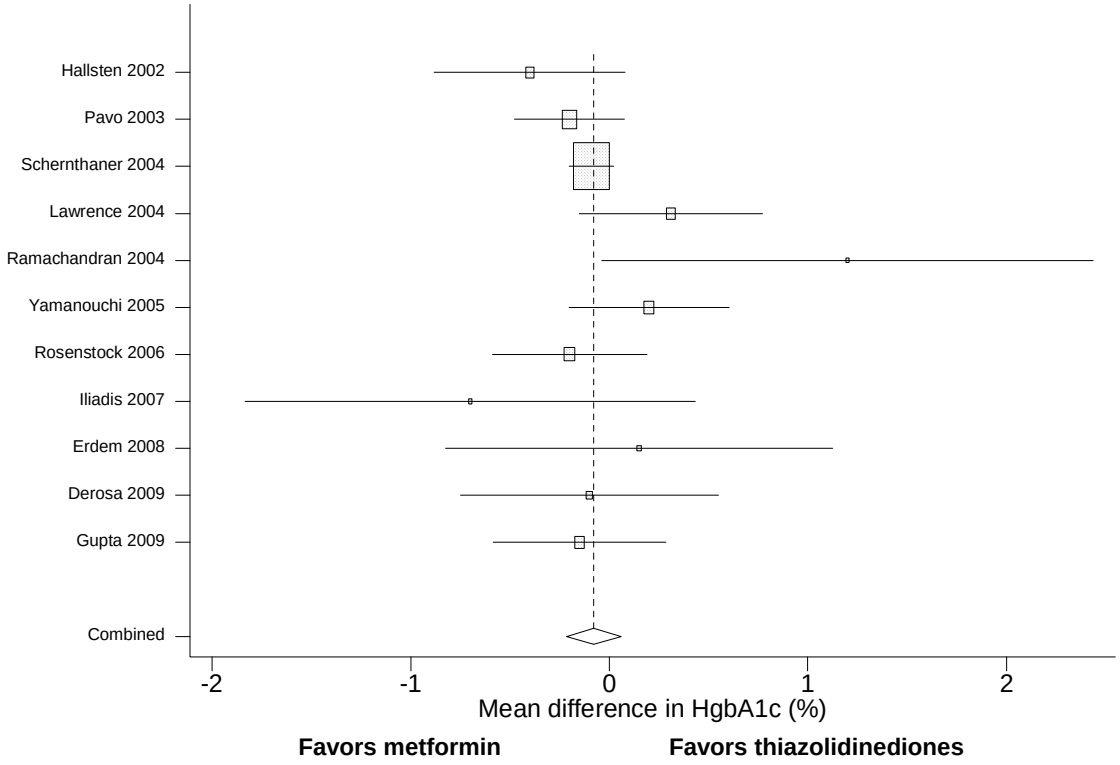
All other comparisons and intermediate outcomes were graded as insufficient since there were no studies.

subjects (generally over 75 to 80 years old). Almost all the studies reported a diverse gender mix among the participants. About 20% of the RCTs did not report race. When race was reported, most subjects were Caucasian. The mean baseline HgbA1c among study subjects varied from 6 to 12 absolute percentage points, with most subjects having a mean baseline HgbA1c between 7 and 9 absolute percentage points.

## The Evidence about Hemoglobin A1c (Appendix G, Table 4)

**Metformin versus thiazolidinediones.** Eleven RCTs lasting around a year or less directly compared metformin versus thiazolidinedione showing no between-group differences in HgbA1c, with a pooled mean difference of -0.08% (95% CI -0.21% to 0.06%) (Figure 3).[31 36-45] If the study by Iliadis et al was removed from the meta-analysis, the pooled mean difference of -0.09% (95% CI -0.18% to -0.003%) would minimally favor metformin. However, we have no reason to exclude this small comparably-dosed RCT, especially given the unlikely clinical relevance of such a minimal difference. No substantial heterogeneity was noted.

**Figure 3. Mean difference in HgbA1c comparing metformin with thiazolidinediones**



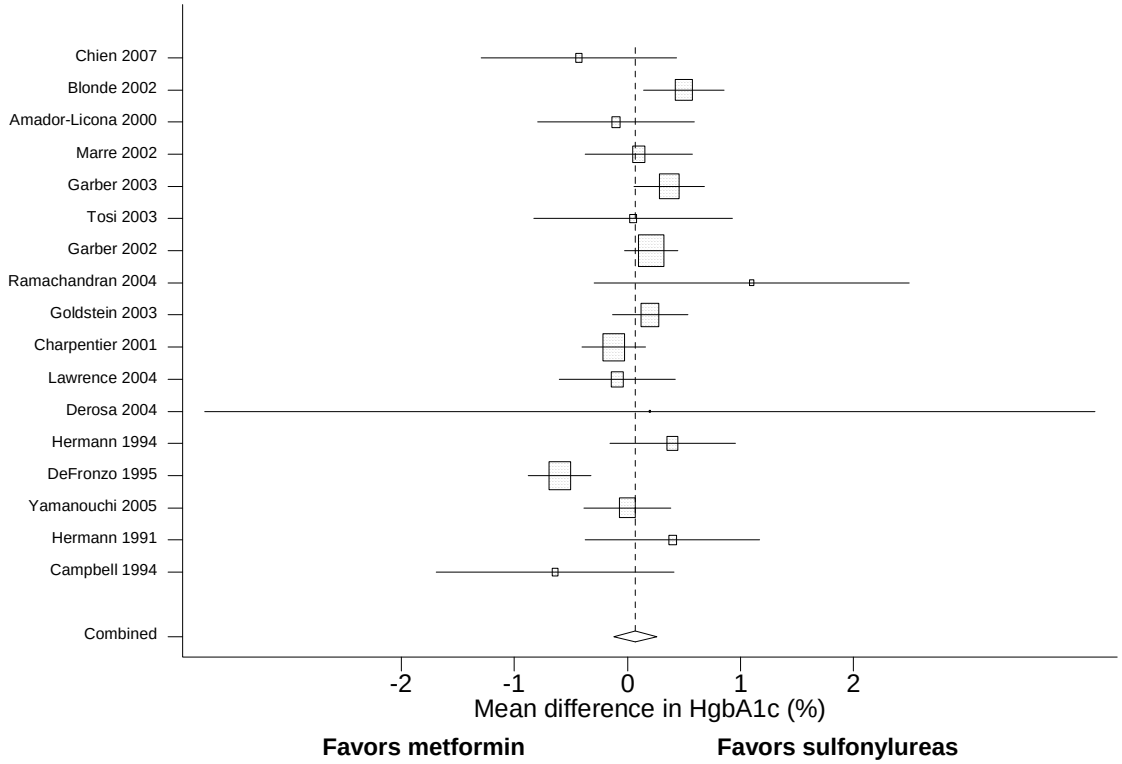

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 12.99 with 10 degrees of freedom (p = 0.22)
I-squared statistic = 23%

We excluded two studies from the meta-analysis, one with a median study duration of 4 years[30] and one which reported median HgbA1c instead of means.[46] The 4-year double-blind RCT (known as the ADOPT study) was designed to compare long-term glycemic control

between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults.[30] While they found a statistically significant difference between groups favoring rosiglitazone (mean difference between groups 0.13%, 95% CI 0.22% to 0.05%), the clinical relevance of this difference is less clear. In fact, cardiac events were similar between rosiglitazone and metformin, with slightly higher absolute events in the rosiglitazone arm. Of note, the HgbA1c decreased in all groups for the first 6 months, and then increased in all groups over the rest of the study. The other short duration RCT excluded from the meta-analysis was consistent with the pooled results, reporting no between-group differences in median HgbA1c.[46]

**Metformin versus sulfonylureas.** We combined 17 studies comparing metformin with a second-generation sulfonylurea and showed similar changes in HgbA1c in both groups, with a pooled mean difference of 0.07% (95% CI -0.12% to 0.26%) (Figure 4).[28 40 41 43 47-59] Removing the one year study by DeFronzo et al changed the results of the meta-analysis, favoring second-generation sulfonylureas slightly with a pooled mean difference of 0.15% (95% CI 0.02% to 0.28%);[58] which may reflect the slightly longer study duration.

**Figure 4. Mean difference in HgbA1c comparing metformin with sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 43.22 with 17 degrees of freedom (p = 0.003)
I-squared statistic = 63%

While most of the point estimates were close to zero, substantial heterogeneity was found. Metaregression suggested that study duration may explain some of the heterogeneity (p = 0.09). Studies lasting less than 6 months seemed to favor sulfonylureas slightly (pooled mean difference of 0.18%, 95% CI 0.01% to 0.34%), while those lasting 6 months to a year showed no between-group differences in medications (pooled mean difference of -0.09%, 95% CI -0.46% to

0.28%). The small possible difference of 0.18% seen with studies lasting less than 6 months has questionable clinical relevance. Baseline HgbA1c and dosing ratio did not explain the heterogeneity.

The two long-term studies excluded from the meta-analysis (ADOPT and UKPDS) lasting greater than 4 years have conflicting results related to glycemic control. ADOPT favored metformin over sulfonylurea after a median followup of 4 years.[30] UKPDS appeared to favor sulfonylurea over metformin in overweight individuals on monotherapy after 9 years of followup, while showing no between-group differences in mean HgbA1c after 10 years of followup for those subjects where other diabetes medications were added to their monotherapy regimen.[7] These differences could be due to different types of sulfonylureas between studies, study duration, or study design components such as double-blind versus open label.

The ADOPT study was excluded from the meta-analysis since the median followup was 4 years compared with the other shorter duration studies lasting less than 1 year.[30] As mentioned previously, this double-blind RCT evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults. The between-group difference between metformin and glyburide favored metformin after 4 years (mean difference between-groups of -0.28%, 95% CI -0.20% to -0.37%). Of note, the glyburide group reduced HgbA1c more than metformin initially, but then the HgbA1c started to rise after about 6 months in all groups. The HgbA1c rose more in the glyburide arm compared with the metformin arm by 1.5 years after treatment was started.

One of the UKPDS studies was included in this report since the article evaluated only those overweight individuals assigned metformin or sulfonylurea who did not have a second medication added over time.[29] They compared the proportion of subjects who achieved a target HgbA1c less than 7% after 9 years of followup between metformin and sulfonylurea, and appeared to favor sulfonylurea slightly (13% versus 21% respectively with non-overlapping confidence intervals). However, only 25% of subjects were able to achieve a target HgbA1c after 9 years on monotherapy alone.

The rest of the UKPDS[60-62] studies were excluded from this section of the report since they were allowed to add other diabetes medications to their initial monotherapy groups, making it impossible to discern comparative drug effects. We describe it here briefly since it is a well known study with the longest followup (up to 10 years). The UKPDS was a multi-center trial conducted in the United Kingdom (UK) comparing different types of treatment for type 2 diabetes. Patients were recruited starting in 1977, and initially put on a diet with 50% carbohydrates, high fiber, reduced calories if obese, and low saturated fat. After 3 months, subjects were randomized to treatment arms or diet based on the fasting plasma glucose. If subjects had very high serum glucose values and symptoms of hyperglycemia prior to the 3-month main randomization, they were randomized to treatment early without a diet arm (the primary diet failure group). Both groups (the main randomization and the primary diet failure groups) were randomized to medications stratified by weight. If subjects were overweight based on ideal body weight, they could be randomized to insulin, chlorpropamide, glibenclamide, metformin, or diet. If they were not overweight, they could be randomized to insulin, diet, chlorpropamide, or glibenclamide. No metformin arm was available if the patient was not overweight. Metformin, glibenclamide, and insulin could be added to any of the groups if a participant was still hyperglycemic based on study protocols. Losses to followup were less than or equal to 5% in both the primary diet failure and main randomization groups.

The 1-year, 3-year, 6-year, and 10-year data all showed similar changes in HgbA1c between groups.[7 60-62] After 10 years, the change in median HgbA1c from baseline was similar in both the metformin and glibenclamide arms for the main randomization group as reported in a figure (+1.3% versus +1.0%).[7] The median HgbA1c results were not broken down by medication type in the primary diet failure group at 10 years. After 6 years, the reported 95% CI for the mean final HgbA1c was 7.1% to 9.4% for metformin and 6.8% to 9.7% for glibenclamide/chlorpropamide in overweight patients in the primary diet failure group.[60] Of note, the main randomization group of UKPDS demonstrated that HgbA1c was reduced within the first few years of the study for patients on either glibenclamide or metformin then began to rise again for all medications.[7]

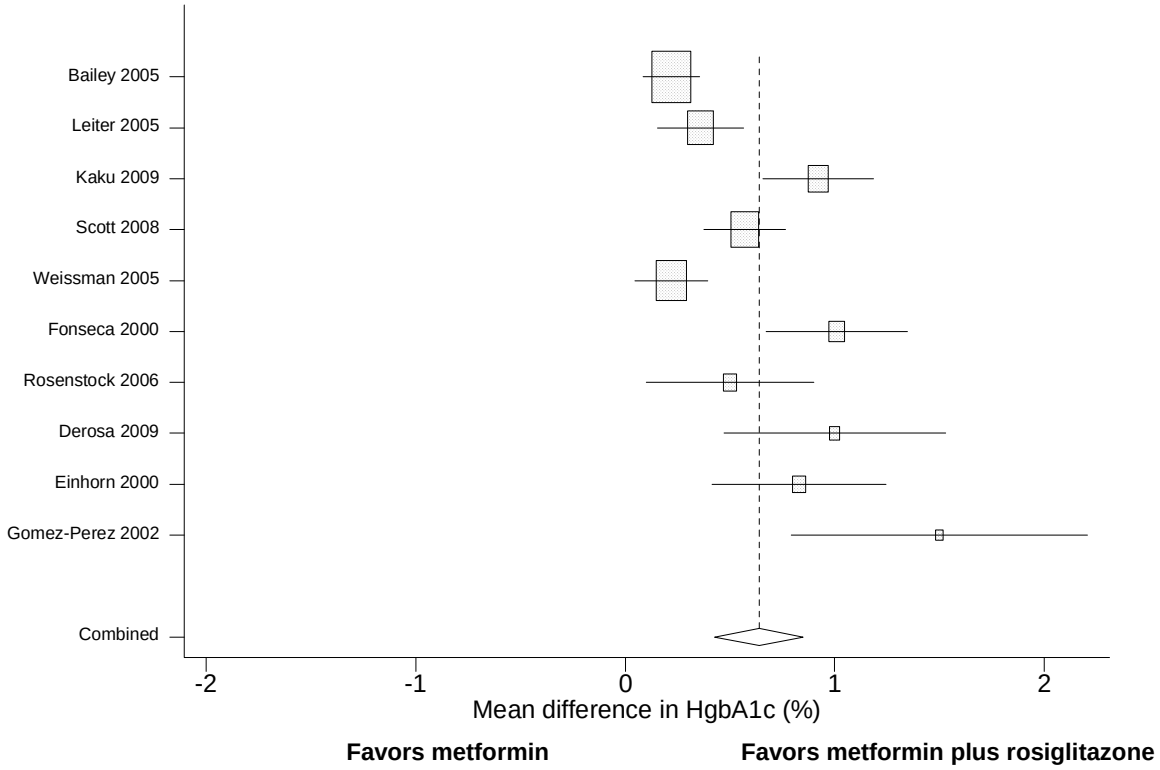
**Metformin versus sitagliptin.** One lower quality study (in two articles) reported between-group differences in HgbA1c favoring high dose metformin (2000 mg a day) over maximum dose sitagliptin (100 mg a day), but they did not report an intention to treat analysis.[63 64] The first article was a 24-week RCT,[64] while the second article was the 30-week continuation study with a higher loss to followup.[63] The between-group difference in HgbA1c of -0.5% favored metformin over sitagliptin at both 24 and 54 weeks of followup. While neither article commented on the significance of the between-group difference, both reported a non-overlapping 95% CI for change in HgbA1c from baseline. The higher dose metformin arms reduced HgbA1c greater than the lower dose arms when compared with maximum dose sitagliptin.

**Metformin versus meglitinides.** Three RCTs (reported in four articles) lasting 3 months to 1 year compared metformin with meglitinides, showing similar effects on HgbA1c.[65-68] One study favored the slightly underdosed metformin arm compared with the nateglinide arm (-0.3% between-group difference).[65] This same study reported in a second article showed no between-group differences in HgbA1c; however, they evaluated only the subset of patients who were treatment naïve.[66] The other two studies evaluated metformin and repaglinide at comparable doses showing non-meaningful between-group differences of 0.1% and 0.05%.[67 68]

**Metformin versus a combination of metformin and thiazolidinediones.** Ten studies compared metformin with the combination of metformin plus a thiazolidinedione (most rosiglitazone except for three studies with pioglitazone),[36 39 69-76]showing a greater improvement in HgbA1c with the combination in all the studies. The pooled mean difference was 0.64% (95% CI 0.43% to 0.85%) (Figure 5). No single study markedly affected the results. Despite the substantial heterogeneity reported, all studies favored the combination arm. Metaregression showed that baseline HgbA1c was a significant source of heterogeneity ($p = 0.02$) while study duration and dosing ratio were not. Studies with higher baseline HgbA1c had greater between-group differences (pooled mean difference of 0.91%, 95% CI 0.63% to 1.18%) than studies with lower baseline HgbA1c (pooled mean difference of 0.44%, 95% CI 0.22% to 0.67%).

**Metformin versus a combination of metformin and sulfonylureas.** Fourteen RCTs (thirteen double-blinded) compared metformin with the combination of metformin plus a second-generation sulfonylurea with all of the studies favoring the combination arm over monotherapy (pooled mean difference of 1.0%, 95% CI 0.75% to 1.25%) (Figure 6).[28 36 47 49-53 56-59 77 78] No single study markedly influenced the results. Metaregression was conducted due to substantial heterogeneity, showing that higher dose combinations had greater between-group effects and lower dose combinations had smaller between-group effects ($p = 0.002$). The study by Blonde et al. showed the greatest between-group differences since this study used a high dose combination and started with the highest baseline HgbA1c compared with other studies.[51] Three

**Figure 5. Mean difference in HgbA1c comparing metformin with combination of metformin and thiazolidinediones**



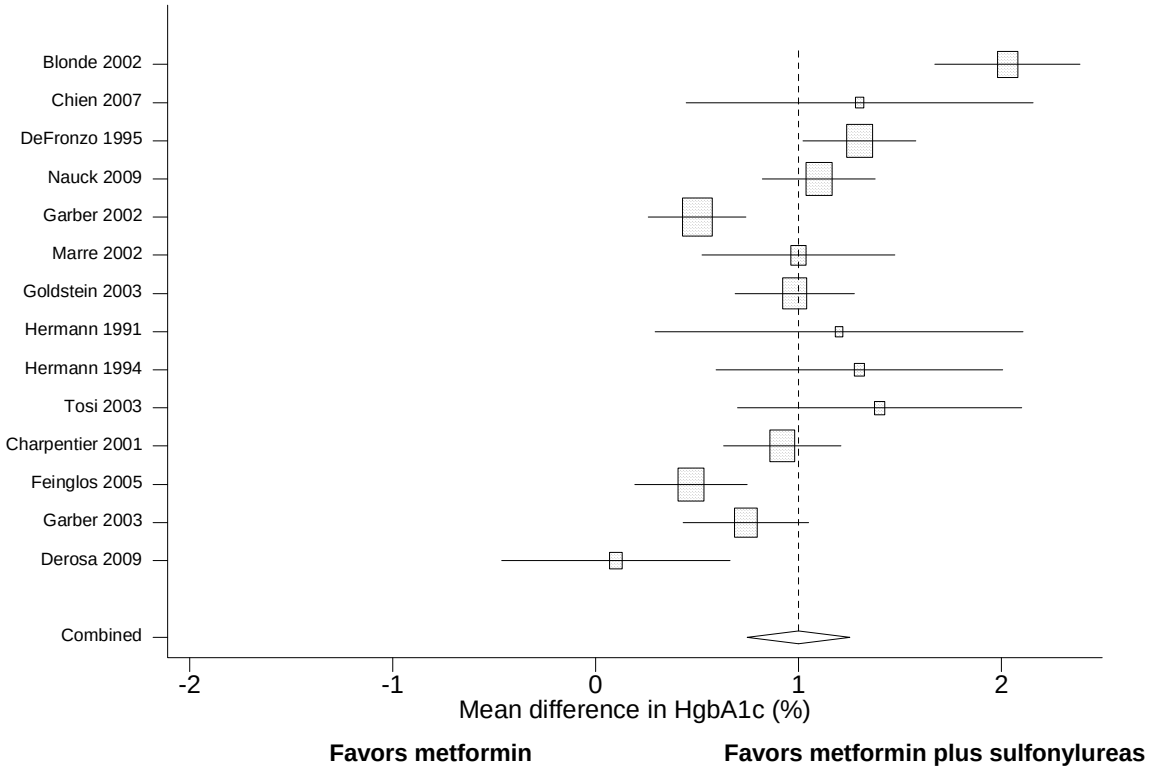

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 58.76 with 9 degrees of freedom (p = 0.0000)
I-squared statistic = 85%

of the six dose-response studies showed a dose-response gradient favoring greater reductions in HgbA1c with a higher dose combination than with a lower dose combination.[51 52 56] One crossover study initially showed a difference between groups at the first crossover and then a negative rebound effect when changing the combination to monotherapy.[28]

**Metformin versus a combination of metformin and sitagliptin.** Four RCTs directly compared metformin with the combination of metformin plus sitagliptin – all favoring the combination arm, with a pooled mean difference of 0.68% (95% CI 0.52% to 0.84%) (Figure 7).[64 71 79 80] No single study markedly influenced the results. Metaregression was conducted due to moderate heterogeneity, although point estimates were extremely similar. Baseline HgbA1c and study duration may have accounted for differences seen in the mild differences in between-group effects ($p < 0.05$); however, this is difficult to state securely given the low number of studies. One RCT was published twice, first with the 24-week RCT results[64] and second as a 30-week continuation[63] to that same study. We included the shorter duration results in the meta-analysis since the study duration was more homogenous with the rest of the studies, plus had less loss to followup.[64] The 54-week results also favored the combination arm over the monotherapy arm, between-group difference of 0.8%.[63] They also showed a small dose-response effect in the combination arms, with the 2000 mg metformin and 100 mg sitagliptin arm reducing HgbA1c

more than the 1000 mg metformin plus 100 mg sitagliptin arm (mean change from baseline -1.8% versus -1.4% respectively).

**Figure 6. Mean difference in HgbA1c comparing metformin with combination of metformin and sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 81.30 with 13 degrees of freedom (p = 0.0000)
I-squared statistic = 84%

**Metformin versus a combination of metformin and meglitinides.** Three RCTs compared metformin with combination of metformin plus meglitinides, all favoring the combination arm (range in between-group differences of -0.5% to -1.08%). We separated out nateglinide from repaglinide combinations since indirect monotherapy comparisons suggest nateglinide has less effect on HgbA1c than repaglinide.[17]

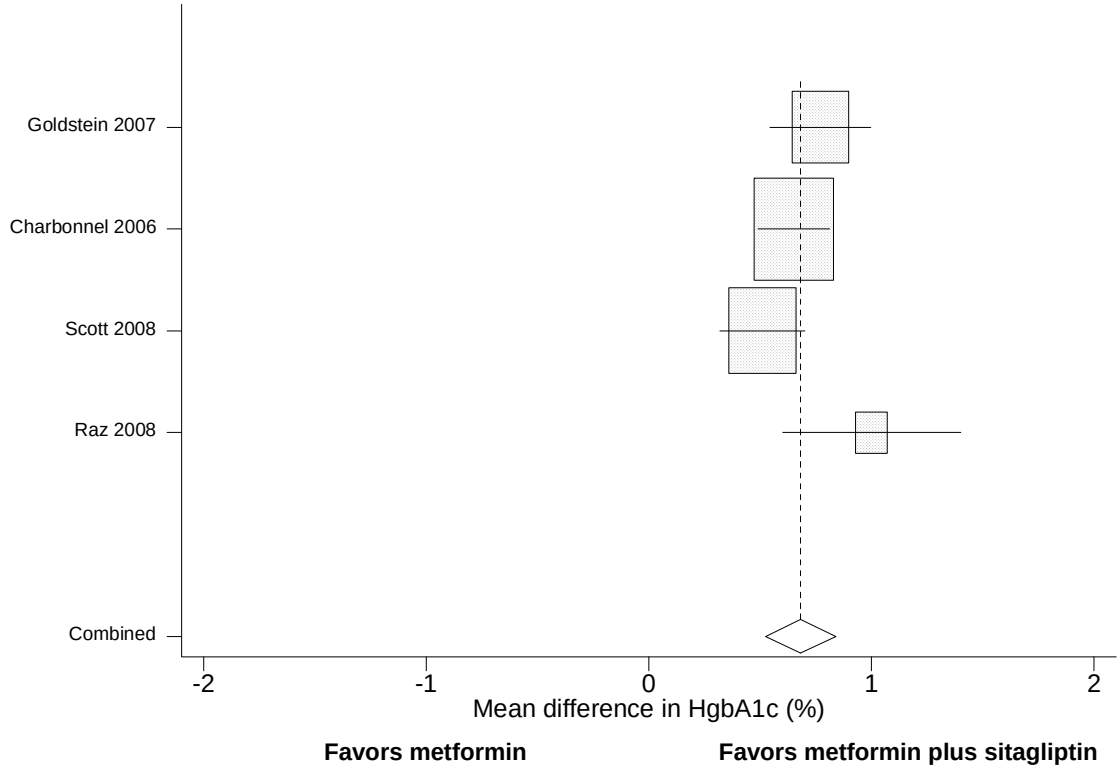
Two similarly dosed 24 week studies reported in three articles compared metformin versus metformin plus nateglinide, showing greater reductions in HgbA1c in the combination arms compared with the monotherapy arms (range in between-group differences of -0.5% to -0.8%).[65 66 81] Only one of these RCTs reported that this between-group difference was also statistically significant,[81] while the other study did not report on the between-group statistical significance in either article.[65 66]

One additional short duration study compared metformin versus metformin plus repaglinide, which also favored the combination therapy over monotherapy (between-group difference of -1.08%, 95% CI -1.84% to -0.33%).[68]

**Rosiglitazone versus pioglitazone.** As noted in the first report,[17] two RCTs compared pioglitazone with rosiglitazone at comparable doses, showing no clinically relevant between-group differences in HgbA1c (range of -0.1% to 0.1%).[82 83]

**Thiazolidinediones versus sulfonylureas.** Both thiazolidinediones (pioglitazone and rosiglitazone) and second-generation sulfonylureas (glibenclamide, glimepiride, and glyburide)

**Figure 7. Mean difference in HgbA1c comparing metformin with combination of metformin and sitagliptin**

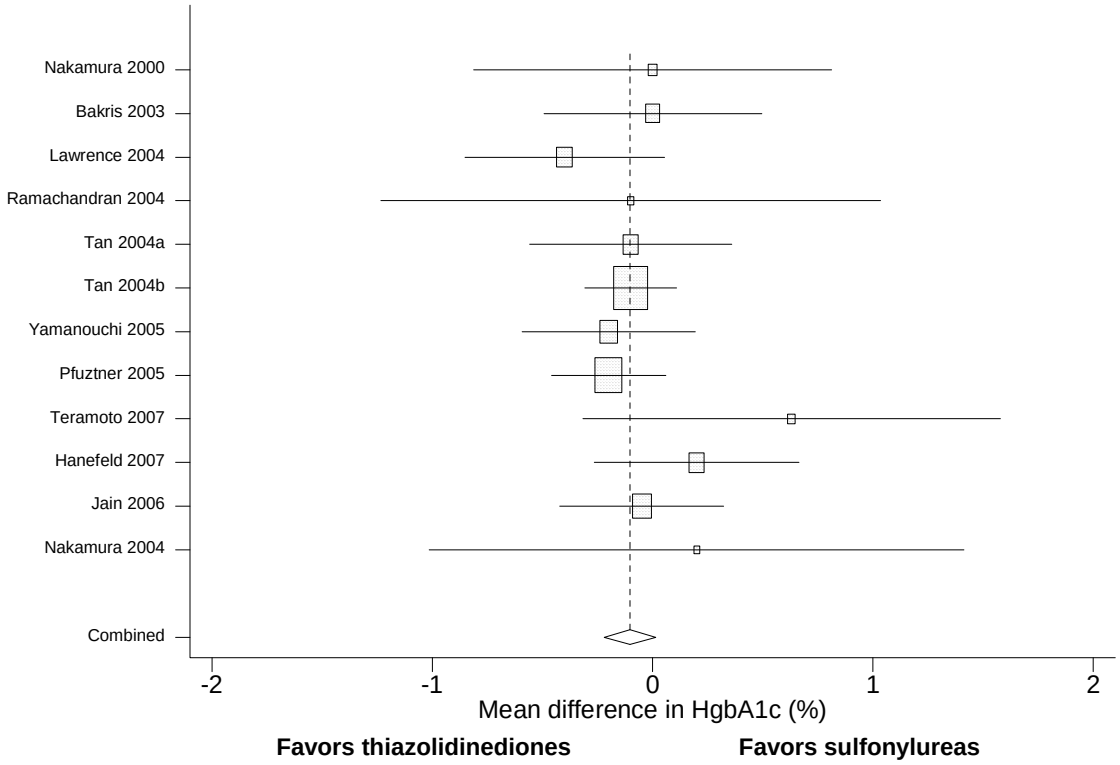



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 6.09 with 3 degrees of freedom (p = 0.11)
I-squared statistic = 51%

had similar effects on HgbA1c, with a pooled mean difference of -0.10% (95% CI -0.22% to 0.01%) (Figure 8).[33 40 41 43 84-91] When we combined the three out of 12 studies with comparable dosing,[43 84 91] the results were similar with a weighted mean difference of -0.10% (95% CI -0.44% to 0.24%). When one of the lower quality studies by Bakris et al[88] was removed from the main meta-analysis, the pooled mean difference favored TZDs slightly, with a pooled mean difference between-groups of -0.12% (95% CI -0.24% to -0.004%). When we excluded Bakris et al along with three other low quality RCTs rated 1 out of 5 on the Jadad quality scale, the pooled mean difference continued to show no difference between-groups. No other single study influenced the results, and no substantial heterogeneity was found. Glipizide was the only second-generation sulfonylurea that was not evaluated in head-to-head trials with the thiazolidinediones.

We excluded the ADOPT study from the meta-analysis due to the longer study duration (median followup of 4 years).[30] As mentioned previously, this double-blind RCT evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults. The between-group difference between rosiglitazone and glyburide favored rosiglitazone after 4 years (mean difference between-groups of -0.42%, 95% CI -0.50% to -0.33%). Of note, glyburide reduced HgbA1c more than rosiglitazone initially. The HgbA1c then rose higher in the glyburide arm compared with the rosiglitazone arm after 1.5 years.

**Figure 8. Mean difference in HgbA1c comparing thiazolidinediones with sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 6.90 with 11 degrees of freedom (p = 0.81)
I-squared statistic = 0%

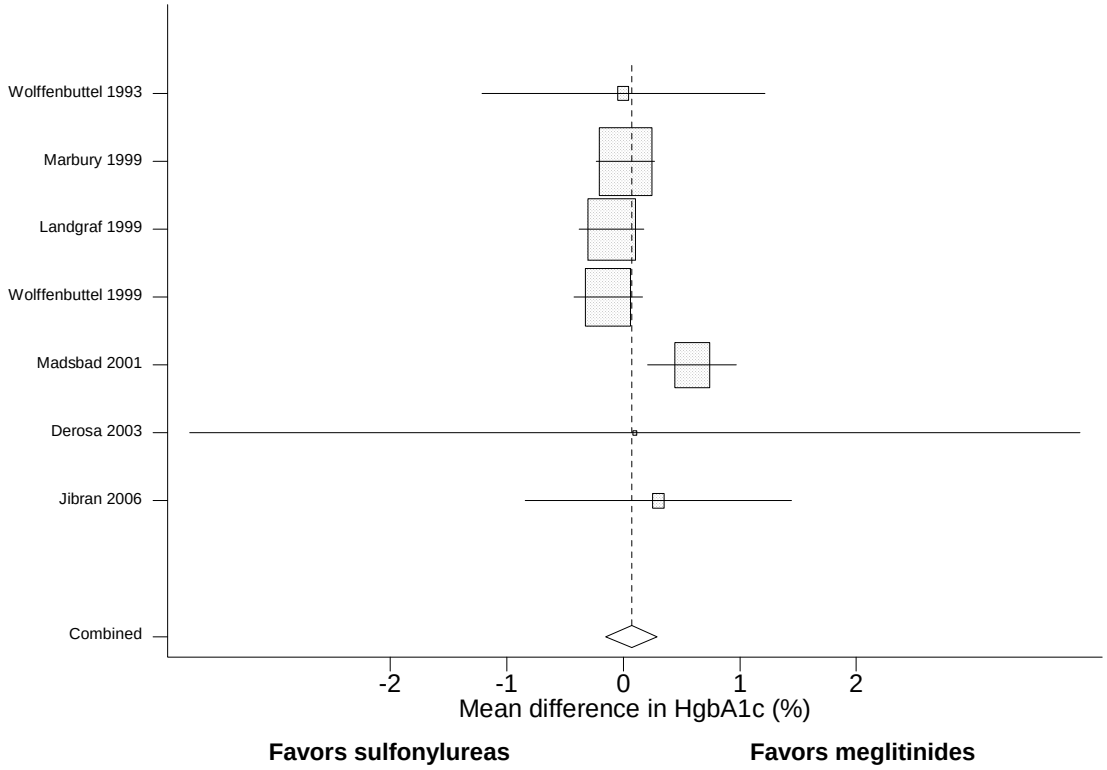
**Thiazolidinediones versus meglitinides.** Two 24-week similar quality head-to-head trials compared thiazolidinediones with repaglinide specifically, and showed no consistent effects favoring one of the medications.[92 93] These inconsistent results may be due to different thiazolidinediones, or different dosing. One study with slightly lower doses of pioglitazone (30 mg fixed dose) versus upward titration of repaglinide to a maximum of 12 mg per day favored repaglinide monotherapy (between-group difference of 0.5%),[93] while the other study with more comparable dosing between rosiglitazone and repaglinide favored rosiglitazone with a between-group difference of 0.39%.[92]

**Sulfonylureas versus sitagliptin.** One double blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[94] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg per day) similarly reduced HgbA1c (-0.77% versus -1.00% respectively), with overlapping confidence intervals for the placebo-subtracted change from baseline in each group. A small absolute dose-response relationship was reported but it was not statistically significant.

**Sulfonylureas versus meglitinides.** Seven RCTs compared a second-generation sulfonylurea with repaglinide, showing a pooled mean difference of 0.07% (95% CI -0.15% to 0.29%) (Figure 9).[95-101] No single study markedly influenced these results nor was there substantial heterogeneity among the studies. There were no differences in results when only evaluating the studies using comparable doses.[96 100 101] One 12-week double-blind RCT compared

submaximally dosed glibenclamide with maximally dosed nateglinide, favoring glibenclamide nonsignificantly over nateglinide by 0.5%.[102] We did not include this study in the meta-analysis due to potential differences in glycemic control between nateglinide and repaglinide.

**Figure 9. Mean difference in HgbA1c comparing sulfonylureas with meglitinides**

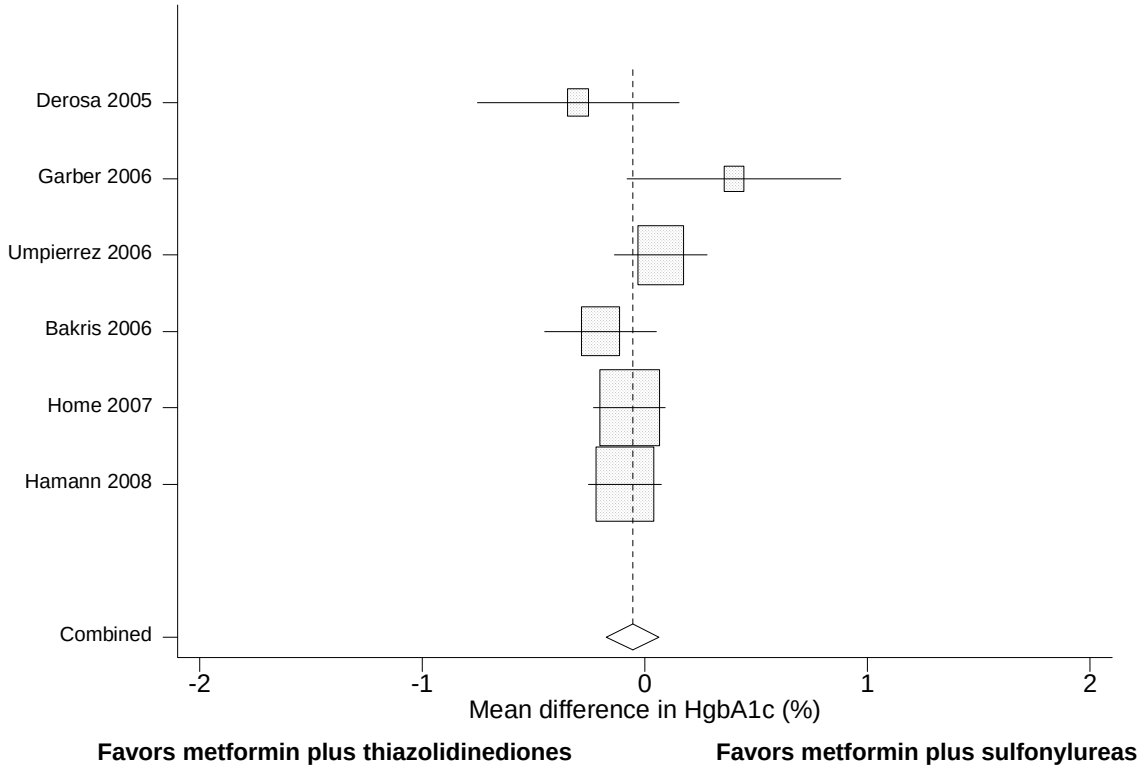



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 10.548 with 6 degrees of freedom (p = 0.10)
I-squared statistic = 43%

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** Six comparably-dosed shorter duration RCTs directly compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea, showing a pooled mean difference in HgbA1c between groups of -0.06% (95% CI -0.17% to 0.06%) (Figure 10).[103-108]No single study markedly influenced the results, and no substantial heterogeneity was found. We excluded two studies due to inconsistent dosing within arms of the study and therefore between them and the rest of the studies.[36 109] Both studies underdosed the metformin in the metformin plus sulfonylurea arms, and found between-group differences in HgbA1c favoring the metformin plus thiazolidinedione arms (-0.3% in both studies). A sensitivity analysis including both these studies in the meta-analysis showed no differences between-groups but increases the heterogeneity between studies markedly.

In the meta-analysis, we included the shorter duration RECORD study since the study duration was more comparable to the other included studies.[104] The RECORD study was a multicenter open label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[14 104] They randomly assigned subjects to addition of rosiglitazone or to a combination of metformin and sulfonylurea, and the

**Figure 10. Mean difference in HgbA1c comparing combination of metformin and thiazolidinediones with combination of metformin and sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 7.45 with 5 degrees of freedom (p = 0.19)
I-squared statistic = 33%

primary endpoint was cardiovascular hospitalization or cardiovascular death. They reported glycemic control at a mean of 18 months and 5.5 years after study start.[14 104] The between-group difference in HgbA1c of -0.07% was small and not significant in the 516 subjects with 18-month followup.[104] In the article reporting on the mean followup of 5.5 years in 2222 subjects, the between-group difference in HgbA1c of -0.29% significantly favored metformin plus rosiglitazone over metformin plus sulfonylurea.[14] However, it is unclear whether these mild differences in glycemic control affect cardiovascular outcomes. While the RECORD study reported cardiovascular outcomes in the rosiglitazone arm versus active control showing no statistically significant differences between groups, they did not break it out further into specific drug combination comparisons.[14]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One double-blind small RCT lasting 18 weeks compared maximum dose metformin plus rosiglitazone with the combination of maximum dose metformin plus sitagliptin showing no between-group differences in HgbA1c (mean difference of -0.06%, 95% CI -0.25% to 0.14%).[71]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One RCT lasting 26 weeks compared metformin plus rosiglitazone twice daily

with the combination of metformin plus repaglinide twice daily and three times daily, showing no significant between-group differences.[110]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two moderately-sized double-blinded RCTs lasting 1-2 years directly compared the combination of metformin plus sulfonylurea with metformin plus nateglinide showing conflicting results.[111 112] These differences may reflect differences in dosing. The first RCT compared the combination of metformin (mean dose 2500 mg) plus glibenclamide (mean dose 12.5 mg) with metformin (mean dose 2500 mg) plus nateglinide (mean dose 300 mg), and significantly favored the slightly higher dosed metformin plus nateglinide combination arm, with a between-group difference of 0.8%.[111] The second RCT showed no significant difference between-groups (between-group difference of -0.3%) despite the higher dosed metformin plus nateglinide arm.[112]

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** One double-blinded moderately-sized RCT compared metformin plus sulfonylurea with the combination of metformin plus sitagliptin showing no between group differences in HgbA1c after 1 year (mean difference of -0.01%, 95% CI -0.09% to 0.08%).[113]

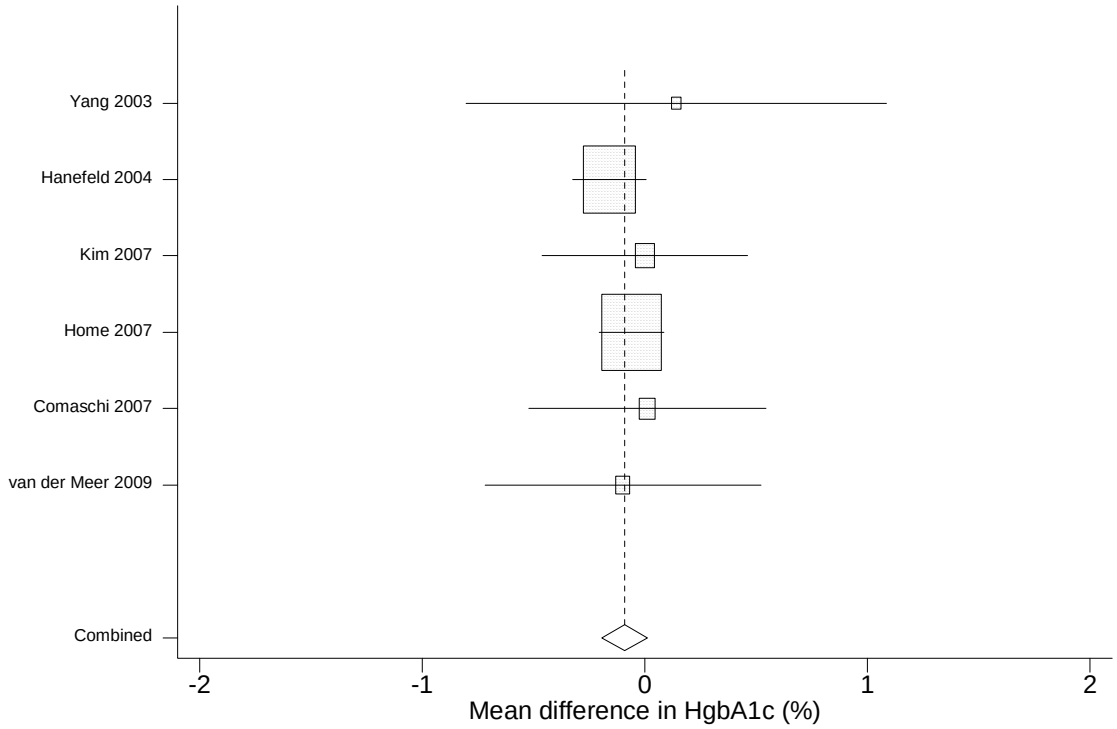
**Combination of metformin and thiazolidinediones versus combination of thiazolidinediones and sulfonylureas.** One small RCT conducted a post hoc analysis comparing the combination of pioglitazone added to either existing metformin or existing sulfonylurea, favoring the pioglitazone plus sulfonylurea combination arm by 0.03% ($p = 0.04$).[109]

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** Six similar RCTs directly compared the combination of metformin and sulfonylurea with the combination of thiazolidinediones and sulfonylurea, showing no between-group differences in HgbA1c (pooled mean difference of -0.09%, 95% CI -0.19% to 0.01%) (Figure 11).[34 104 109 114-116] No one study markedly influenced the results, and these studies showed no significant heterogeneity.

We excluded two articles from the meta-analysis with longer study durations[14 117] since both studies had other articles in the meta-analysis that presented the shorter term glycemic results[104 115] which were more comparable to the other RCTs. The RECORD study was a multicenter open label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[14 104] They randomly assigned subjects to addition of rosiglitazone or to a combination of metformin and sulfonylurea, with a primary endpoint of cardiovascular hospitalization or cardiovascular death. They reported glycemic control at a mean of 18 months and 5.5 years after study start.[14 104] The between-group difference in HgbA1c of -0.06% was small and not significant in the 573 subjects with 18-month followup.[104] In the article reporting on the mean followup of 5.5 years in 2225 subjects, the between-group difference in HgbA1c of 0.26% significantly favored rosiglitazone plus sulfonylurea over metformin plus sulfonylurea.[14] However, it is unclear whether these mild differences in glycemic control affect cardiovascular outcomes. While the RECORD study reported cardiovascular outcomes in the rosiglitazone arm versus active control showing no statistically significant differences between-groups, they did not break it out further into specific drug-drug combination comparisons.[14]

The second RCT excluded was a 2-year followup[117] of the 1-year study[115] presented in the meta-analysis. Both articles presented similar between-group differences in HgbA1c between the combination of thiazolidinedione plus sulfonylurea and metformin plus sulfonylurea (nonsignificant between-group differences of -0.16% and -0.13%).

**Figure 11. Mean difference in HgbA1c comparing combination of metformin and sulfonylureas with combination of thiazolidinediones and sulfonylureas**




**Favors metformin plus sulfonylureas** **Favors thiazolidinediones plus sulfonylureas**

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.37 with 5 degrees of freedom (p = 0.93)
I-squared statistic = 0%

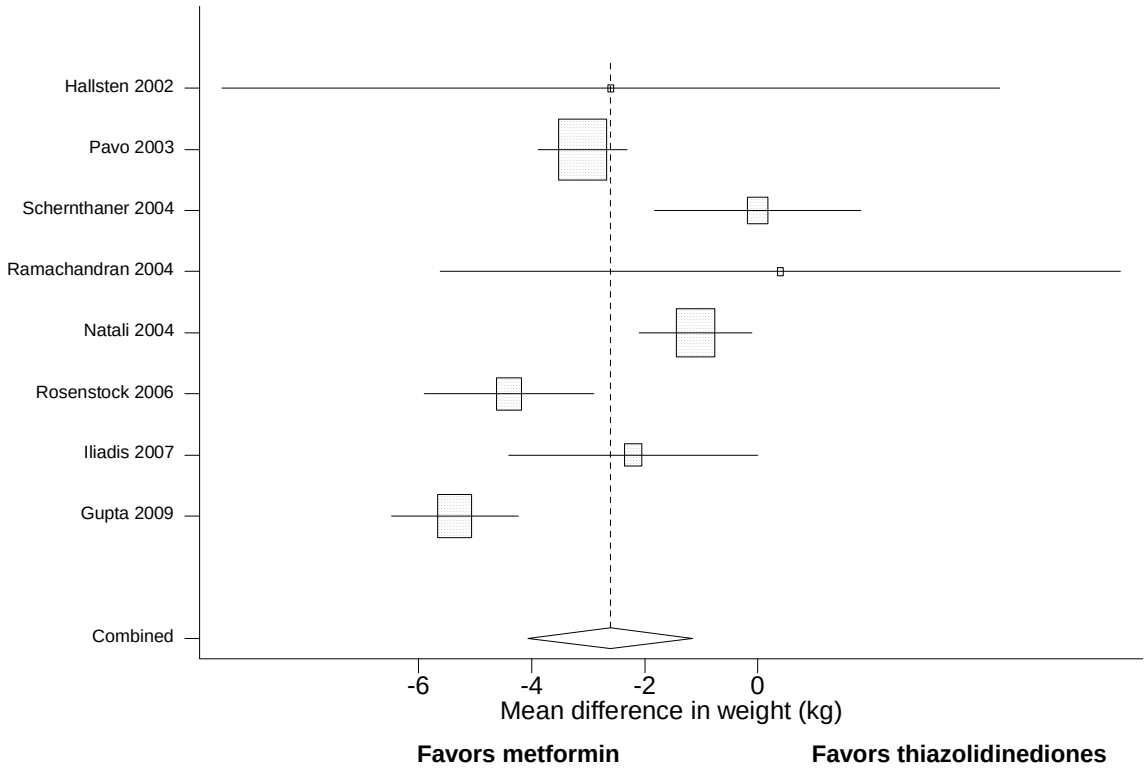
**Combination of metformin and sulfonylureas versus combination of metformin and premixed insulin.** Two 16-week RCTs compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue – insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study, showing different results.[118 119] These differences may have been due to differences in dosing of the medications. The RCT[118] that showed no significant between-group differences in HgbA1c (-0.11%, p = 0.238) reported their mean total dose for each combination arm, while the other RCT which significantly favored the metformin plus premixed insulin analogue (insulin aspart 70/30) arm over the metformin plus sulfonylurea arm (between-group difference of 0.46%, p = 0.027) did not clearly report mean total or maximum doses.[119] Another possible difference may have been the type of premixed insulin analogue.

**Combination of metformin and basal insulin versus combination of metformin and premixed insulin.** Two small to moderate RCTs lasting around 6 months compared metformin plus glargine with the combination of metformin plus premixed insulin analogues- insulin lispro 50/50 or insulin aspart 70/30. Both comparably-dosed RCTs significantly favored the metformin plus premixed insulin analogue arms (range in between-group differences 0.30% to 0.43%).[120 121]

## The Evidence about Weight (Appendix G, Table 4)

**Metformin versus thiazolidinediones.** Eight RCTs lasting around a year or less directly compared metformin versus thiazolidinedione favoring metformin, with a pooled mean between group difference of -2.6 kg (95% CI -4.1 kg to -1.2 kg) (see Figure 12).[37-39 41 42 44 45 122] All the metformin arms had small decreases in weight while the thiazolidinedione arms had mild increases in weight except for two studies.[38 41] No single study markedly influenced the results. There was significant heterogeneity, yet we felt comfortable combining these studies since almost all the point estimates favored metformin. Metaregression suggested that differences in baseline weight between studies (p = 0.07) may have contributed to the heterogeneity. We excluded one study from the meta-analysis which had consistent results favoring metformin, since the median study duration was 4 years.[30] This double-blind RCT (known as the ADOPT study) was designed to compare long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for diabetic adults, where weight was evaluated as a secondary outcome. The between group difference in weight was -6.9 kg (95% CI -6.3 kg to -7.4 kg) favoring metformin.

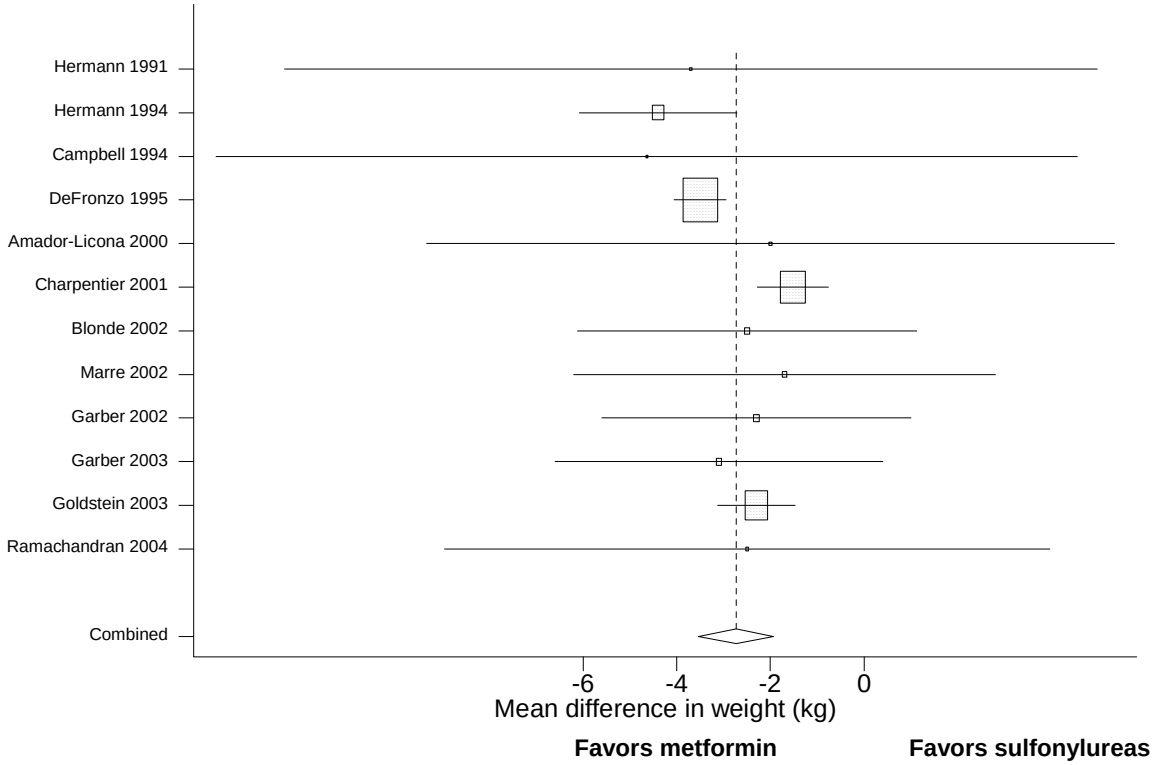
**Figure 12. Mean difference in weight comparing metformin with thiazolidinediones**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 46.51 with 7 degrees of freedom (p = 0.0000)
I-squared statistic = 85%

**Metformin versus sulfonylureas.** We combined 12 studies comparing metformin with a second-generation sulfonylurea, with a pooled mean difference of -2.7 kg (95% CI -3.5 kg to -1.9 kg) favoring metformin (Figure 13).[41 49-59] We stratified the meta-analyses based on study duration (less than 24 weeks and more than 24 weeks) since this may have been a source of the heterogeneity between studies. The longer studies had slightly larger between-group differences in weight. In eight studies with less than 24-weeks duration, studies favored metformin with a pooled between group difference of -1.9 kg (95% CI -2.5 kg to -1.4 kg) (Figure 14).[41 49-54 59] Four studies lasting 24 weeks or longer were combined and favored metformin, with a pooled between group difference of -3.6 kg (95% CI -4.1 kg to -3.1 kg) (Figure 15).[55-58] Heterogeneity tests were not significant once we stratified the meta-analyses by study duration.

**Figure 13. Mean difference in weight comparing metformin with sulfonylureas**

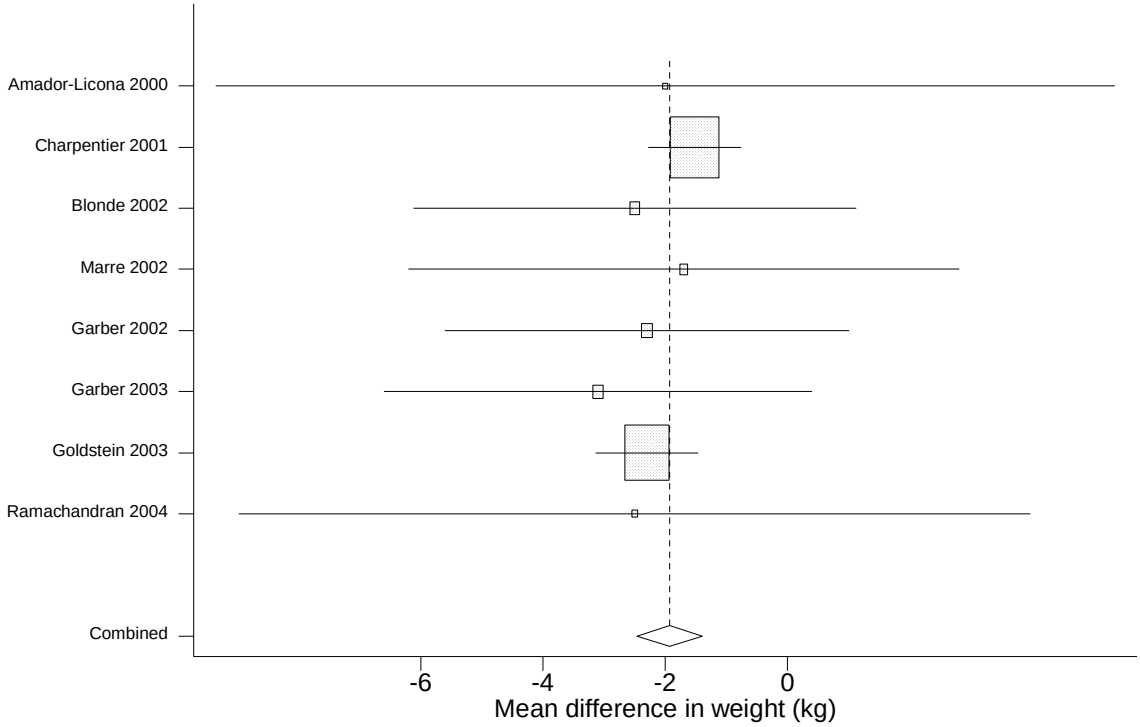



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 22.64 with 11 degrees of freedom (p = 0.02)
I-squared statistic = 51%

The ADOPT study was excluded from the meta-analysis since the median followup was 4 years compared with the other shorter duration studies lasting less than a year, yet showed consistent results favoring metformin over glyburide (mean between-group difference in weight of -2.5 kg; 95% CI -2.0 kg to -3.1 kg).[30] This double-blind RCT evaluated long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults, where weight was a secondary end point. Metformin decreased weight over the study duration while glyburide increased weight in the first year followed by weight maintenance for the rest of the study.

1 The UKPDS,[7 60 62] while consistent with the above meta-analysis, was excluded from this
2 section of the report since they were allowed to add other diabetes medications to their initial

**Figure 14. Mean difference in weight comparing metformin with sulfonylureas among studies less than 24 weeks in duration**




**Favors metformin** **Favors sulfonylureas**

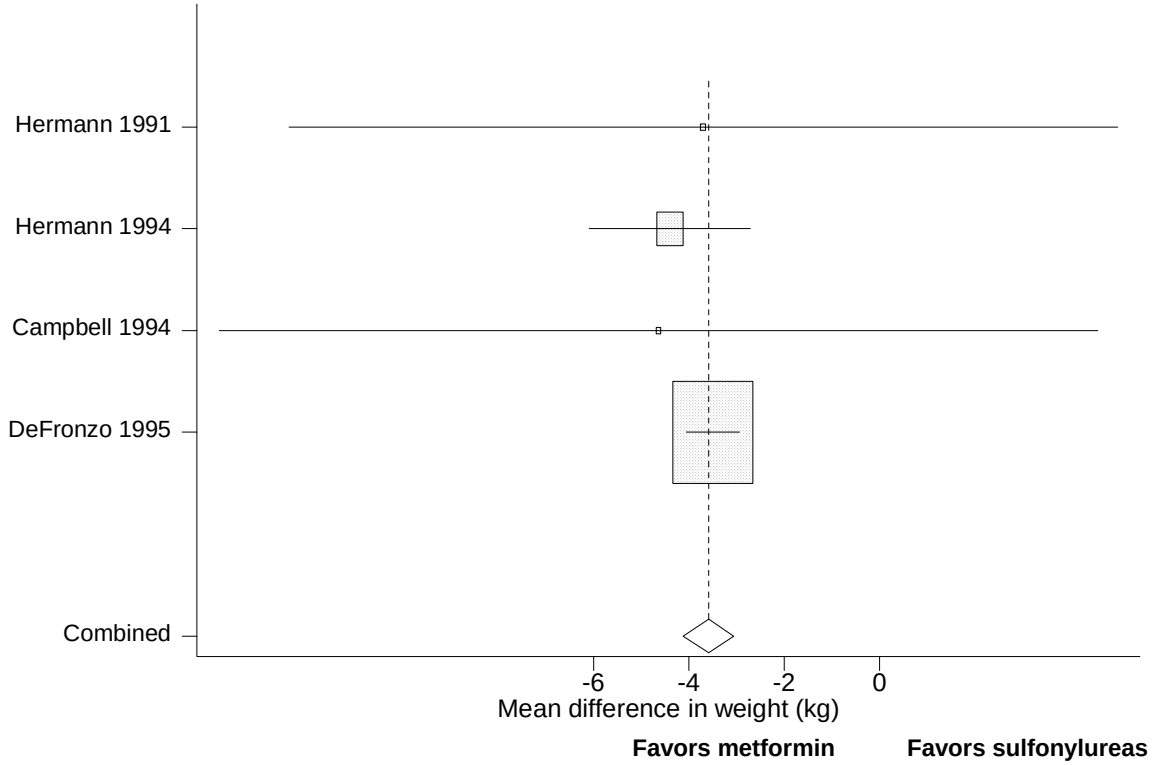
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.51 with 7 degrees of freedom (p = 0.93)
I-squared statistic = 0%

monotherapy groups. We describe it here briefly since it is a well known study with the longest followup (up to 10 years). In the 3-year followup of UKPDS in the obese subjects from the primary diet failure and main randomization groups combined, the between-group difference was -2 kg, favoring metformin.[62] In the 6-year followup in the primary diet failure group only, the between-group difference was -5 kg comparing obese subjects taking metformin with obese and non-obese subjects taking glibenclamide.[60] In the 10-year followup comparing obese subjects on metformin with obese and non-obese subjects on glibenclamide, the between-group difference still favored metformin at -2 kg.[7] None of these papers reported the statistical significance of these differences except as it relates to diet or insulin. Of note, most of the weight gain in the glibenclamide group occurred in the first two years, while metformin maintained weight in the first 2 years and then had some weight gain after that.[7]

**Metformin versus sitagliptin.** One lower quality study (in two articles) comparing metformin with sitagliptin reported that the metformin arms had significant weight loss while the sitagliptin arm had no significant change in weight from baseline.[63 64] The first article was a 24-week RCT,[64] while the second article was the 30-week continuation study with a higher loss to followup.[63] The higher dosed metformin arm had greater weight loss from baseline compared with the lower dose metformin arm.

**Metformin versus meglitinides.** Two small comparably-dosed RCTs lasting about a year compared metformin with repaglinide, suggesting metformin may reduce weight compared with

**Figure 15. Mean difference in weight comparing metformin with sulfonylureas among studies 24 weeks or longer in duration**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.04 with 3 degrees of freedom (p = 0.79)
I-squared statistic = 0%

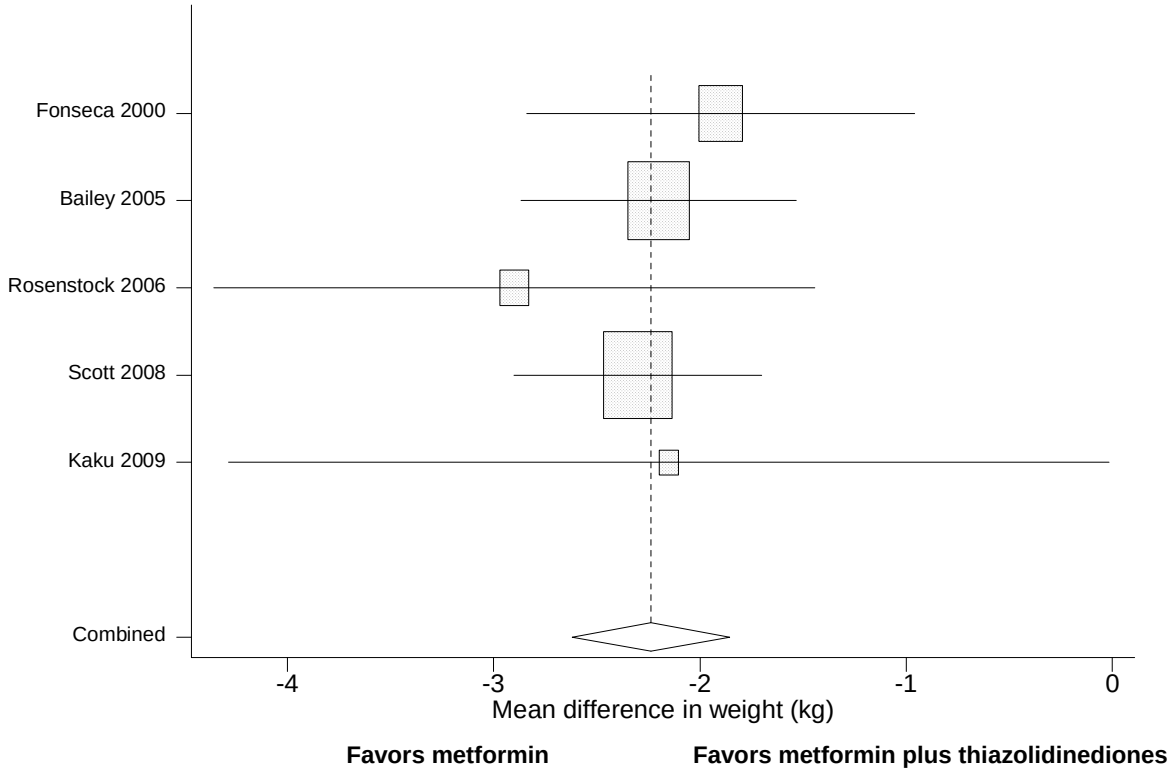
repaglinide (range in between-group differences from -2.0 kg to -3.4 kg).[67 68] One study reported this difference as nonsignificant,[67] and one reported only that there were significant differences from baseline in both arms.[68] The small number of subjects may have precluded the ability to detect significant differences between groups.

**Metformin versus a combination of metformin and thiazolidinediones.** We combined five studies which directly compared metformin monotherapy with the combination of metformin plus a thiazolidinedione (mostly rosiglitazone), showing a pooled mean difference in weight of -2.2 kg (95% CI -2.6 kg to -1.9 kg) favoring metformin (Figure 16).[39 70 71 73 76] There was no significant heterogeneity between studies, and no single study markedly affected the results. All five studies showed that the metformin arms had weight loss while the combination arms had weight gain. One study reported only qualitatively that the metformin arm had relatively no weight change while the combination therapy arm had a significant increase in weight of 1.6 kg reported quantitatively.[69] While consistent with the meta-analysis results, we did not have sufficient quantitative data to include it with the other studies.

**Metformin versus a combination of metformin and sulfonylureas.** Ten RCTs compared metformin with the combination of metformin plus a second-generation sulfonylurea favoring metformin monotherapy, with a pooled mean difference of -2.3 kg (95% CI -3.3 kg to -1.2 kg) (Figure 17).[49 50 52 53 56-59 77 78] No single study markedly influenced the results. While

1 heterogeneity existed, all studies favored the metformin arm over the combination arm with

**Figure 16. Mean difference in weight comparing metformin with combination metformin and thiazolidinediones**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.35 with 4 degrees of freedom (p = 0.85)
I-squared statistic = 0%

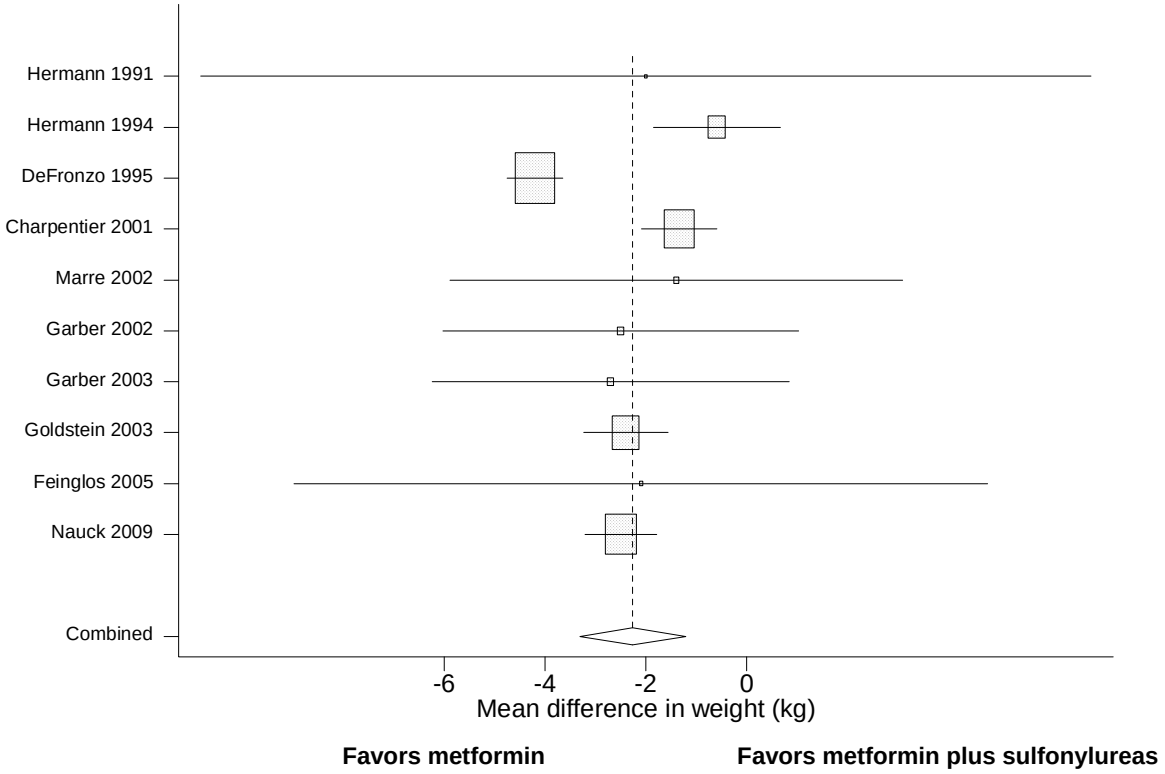
minimal between-group differences among the studies. Studies with lower baseline weight appeared to have somewhat smaller between-group differences than studies with higher baseline weight.

**Metformin versus a combination of metformin and sitagliptin.** Four mainly short duration RCTs (in five articles) directly compared metformin with the combination of metformin plus sitagliptin, all reporting similar weight loss in each study arm (range in between-group differences of -0.4 kg to 0.2 kg).[63 64 71 79 80] The two studies reporting point estimates with measures of variability for each arm showed no significant between-group differences,[63 71] while the rest gave a combination of qualitative and quantitative data consistent with this result but making it impossible to combine in a meta-analysis. One RCT was published twice, first with the 24-week RCT results[64] and second as a 30-week continuation[63] study. The 54-week results report a significant weight loss from baseline in both groups with overlapping confidence intervals or a nonsignificant between-group difference of 0.2 kg.[63] They also showed a small dose-response effect in the combination arms, with the 2000 mg metformin and 100 mg sitagliptin arm reducing weight more than the 1000 mg metformin plus 100 mg sitagliptin arm (mean change from baseline -1.7 kg versus -0.7 kg respectively).

**Metformin versus a combination of metformin and meglitinides.** Two RCTs compared metformin with combination of metformin plus meglitinides; both slightly favoring the

1 monotherapy metformin arms.[68 81] One small 3-month RCT compared metformin (mean dose

**Figure 17. Mean difference in weight comparing metformin with combination metformin and sulfonylureas**



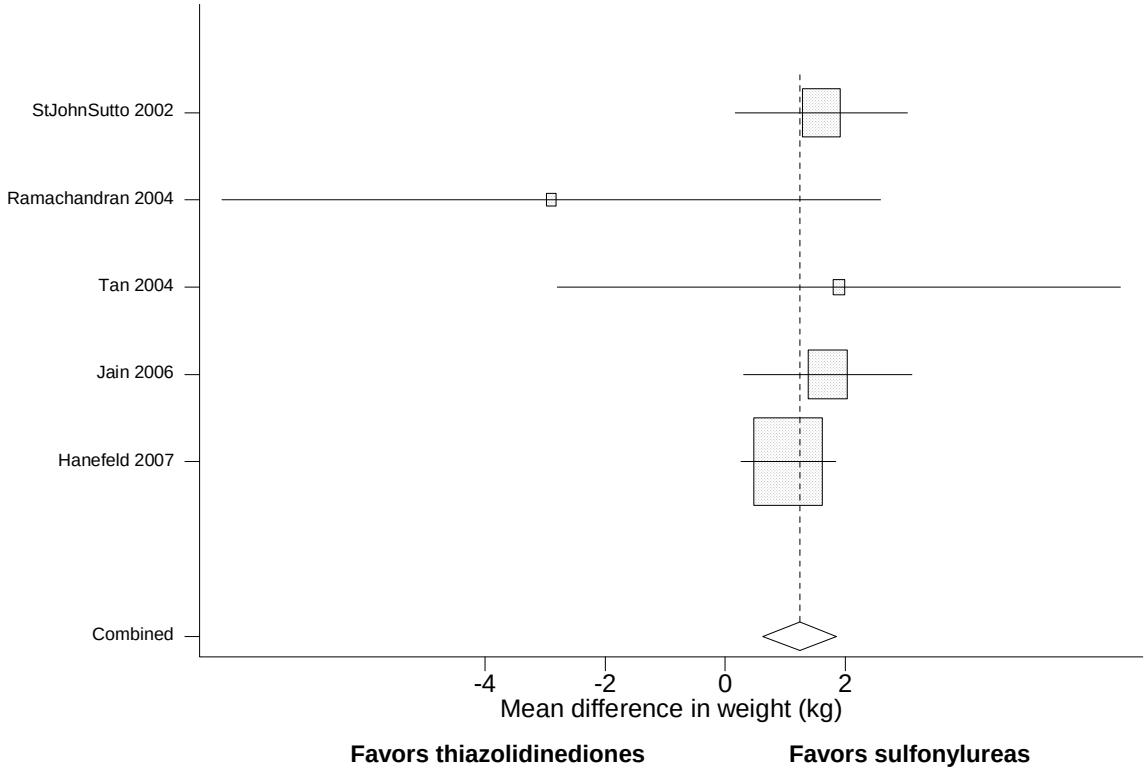

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 52.88 with 9 degrees of freedom (p = 0.0000)
I-squared statistic = 83%

1800 mg) versus metformin (mean dose 1800 mg) plus repaglinide (maximum titrated dose of 4 mg before meals), and reported qualitatively that weight remained stable in the metformin arm while increasing from baseline in the metformin plus repaglinide arm (3.0 kg $\pm$ 0.5 kg, $p < 0.05$).[68] The second 24-week moderately-sized study compared metformin with metformin plus nateglinide at two different doses, showing a statistically significant between-group difference in weight of 0.9 kg favoring metformin monotherapy when compared with the higher dosed metformin plus nateglinide arm (120 mg three times daily). No significant difference was reported when metformin was compared with the metformin plus lower dose nateglinide (60 mg three times daily).[81]

**Rosiglitazone versus pioglitazone.** As noted in the first evidence report,[17] two studies compared the thiazolidinedione pioglitazone with rosiglitazone;[82 83] and none reported a significant between-group difference (range in between-group differences of 0 kg to -0.4 kg). Both studies showed an increase in weight from baseline, ranging from 1.6 kg to 2 kg for both thiazolidinediones.

**Thiazolidinediones versus sulfonylureas.** Five studies lasting a year or less compared a thiazolidinedione to a second-generation sulfonylurea showing higher weight gain in the thiazolidinedione arms, with a pooled mean difference of 1.2 kg (95% CI 0.6 kg to 1.9 kg) (Figure 18).[41 84 85 90 123] One study showed a dose response relationship between rosiglitazone and weight; patients treated with rosiglitazone 4 mg gained 1.8 kg and those treated with 8 mg gained

**Figure 18. Mean difference in weight comparing thiazolidinediones with sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.16 with 4 degrees of freedom (p = 0.53)
I-squared statistic = 0%

3.0 kg over 52 weeks compared to the glibenclamide arm which gained 1.9 kg.[84] No single study markedly influenced the results, and no substantial heterogeneity was found.

We excluded the ADOPT study from the meta-analysis due to the longer study duration (median followup of 4 years).[30] As mentioned previously, this double blind RCT evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults, with weight as a secondary outcome. The between-group difference between rosiglitazone and glyburide was consistent with the results of the meta-analysis of the shorter duration studies favoring sulfonylureas after an estimated 5 years of followup (mean difference between-groups of 2.5 kg, 95% CI 2.0 kg to 3.1 kg). Of note, the glyburide arm showed increased weight over the first year when weight began to stabilize while the rosiglitazone arm had continued weight gain over the course of the study.

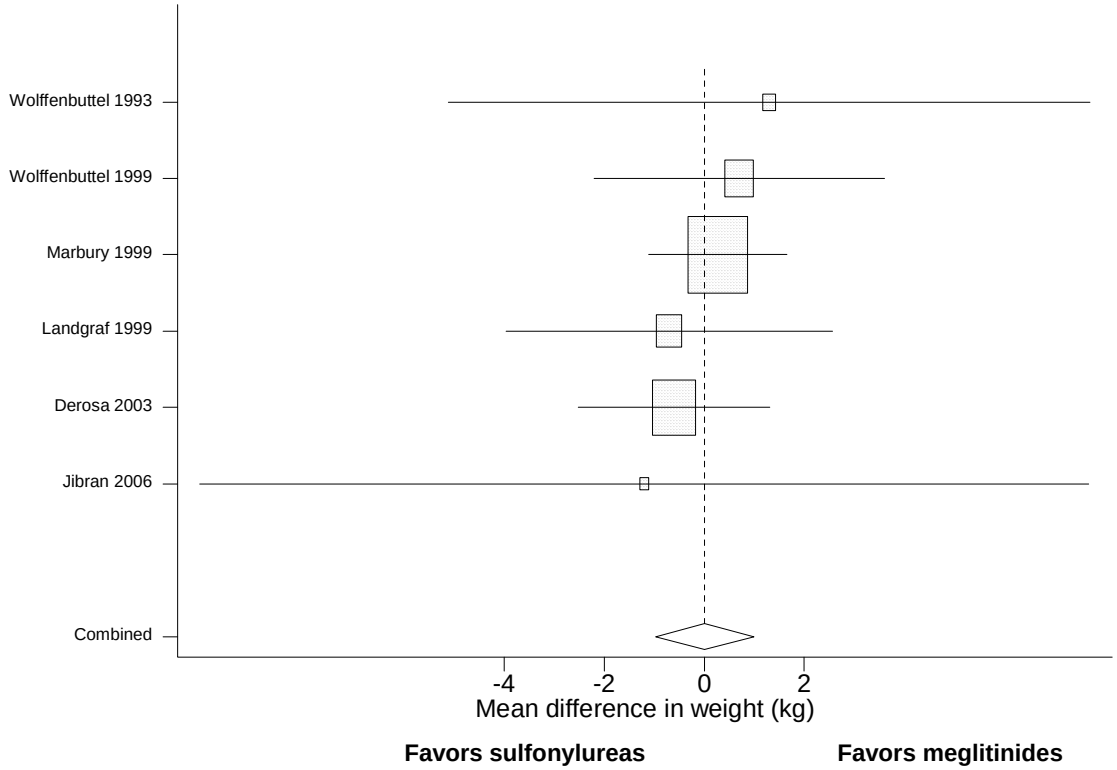
**Thiazolidinediones versus meglitinides.** Two 24-week non-blinded RCTs compared thiazolidinediones with repaglinide specifically, and both reported slightly greater weight gain in the thiazolidinedione groups (range in between-group differences of 0.7 to 1.7 kg, no measures of variability reported).[92 93]

**Sulfonylureas versus sitagliptin.** One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily, showing a potential benefit in weight of sitagliptin over glipizide.[94] After 12 weeks, the high dose sitagliptin arm (100 mg a day) showed a nonsignificant between-group difference comparing sitagliptin

with placebo of 0.4 kg (95% CI -0.2 kg to 0.9 kg) while the glipizide (maximum dose: 20 mg a day) arm showed a significant between-group difference compared with placebo of 1.3 kg (0.8 kg to 1.8 kg). The study did not report the direct between-group differences in weight.

**Sulfonylureas versus meglitinides.** Six RCTs compared weight between a second-generation sulfonylurea and repaglinide showing no differences between groups, with a pooled mean difference of 0.01 kg (95% CI -1.0 kg to 1.0 kg) (Figure 19).[95 96 98-101] Heterogeneity tests were not significant, and no single study markedly influenced this result. Most studies showed no change in weight in both treatment arms.

**Figure 19. Mean difference in weight comparing sulfonylureas with meglitinides**

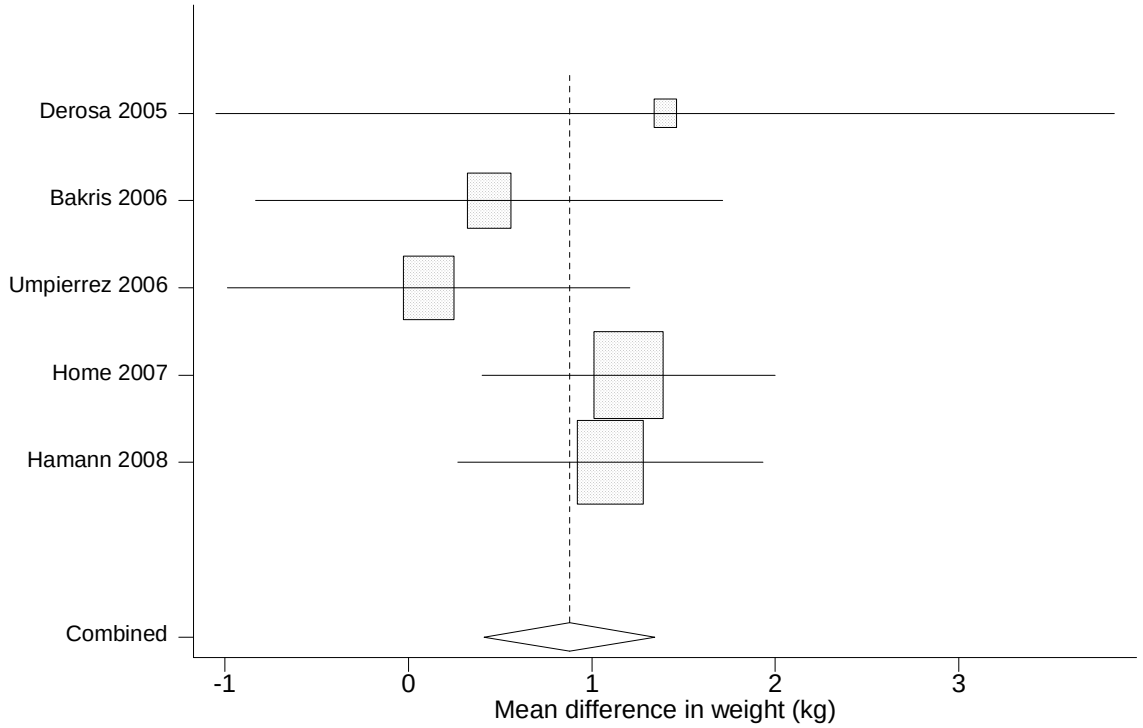



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.15 with 5 degrees of freedom (p = 0.95)
I-squared statistic = 0%

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** We combined five studies that directly compared metformin plus a thiazolidinedione to metformin plus a sulfonylurea favoring the combination of metformin plus sulfonylurea, with a pooled between-group difference of 0.9 kg (95% CI 0.4 kg to 1.3 kg) (Figure 20).[103-106 124] No one study markedly influenced the results, and no substantial heterogeneity was found.

In the meta-analysis, we included the shorter duration RECORD study since the study duration was more comparable to the other included studies.[104] The RECORD study was a multicenter open label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[14 104] Body weight was increased significantly with rosiglitazone plus metformin compared to sulfonylurea plus metformin, with a

**Figure 20. Mean difference in weight comparing combination metformin and thiazolidinediones with combination metformin and sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.41 with 4 degrees of freedom (p = 0.49)
I-squared statistic = 0%

mean difference between-groups of 1.2 kg (95% CI 0.4 kg to 2.0 kg) after 18 months[104] which increased to 3.8 kg after 5 years of followup.[14]

We excluded one short duration RCT from the meta-analysis since the dosing was not comparable to the other studies, which likely explains its conflicting results.[108] This RCT used a lower dose of metformin in the metformin plus sulfonylurea arm compared with a higher dose of metformin in the metformin plus thiazolidinedione arm. Since metformin has been shown to reduce or maintain weight compared with most other monotherapy diabetes medications, a higher dose of metformin in the thiazolidinedione combination arm would bias the results in favor of that combination.

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One RCT with 568 patients lasting 26 weeks compared metformin plus rosiglitazone twice daily with the combination of metformin plus repaglinide twice daily and three times daily; they reported qualitatively no significant between-group differences in weight but did not report any quantitative numbers.[110]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One double-blind small RCT lasting 18 weeks compared maximum dose metformin plus rosiglitazone with the maximum dose of metformin plus sitagliptin, favoring the metformin plus sitagliptin arm (mean between-group difference in weight of 1.9 kg).[71] The

metformin plus rosiglitazone arm had an increase in weight from baseline of 1.5 kg (95% CI 1.0 kg to 1.9 kg) while the metformin plus sitagliptin arm had a decrease in weight from baseline of -0.4 kg (95% CI -0.8 kg to 0.0 kg).

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** One double-blinded moderately-sized RCT compared metformin plus sulfonylurea with the combination of metformin plus sitagliptin, showing body weight was significantly reduced in the metformin plus sitagliptin arm compared with an increase in body weight from baseline in the metformin plus sulfonylurea arm (mean difference between-groups of -2.5 kg, 95% CI -3.1 kg to -2.0 kg).[113]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two moderately-sized double-blinded RCTs lasting 2 years directly compared the combination of metformin plus sulfonylurea with metformin plus nateglinide showing slightly different results.[112 125] One study showed a small but significant between-group difference of -1.2 kg favoring the metformin plus nateglinide arm ($p = 0.01$).[112] The other comparable study did not report quantitative data, only stating no clinically relevant changes in weight were found in either group.[125]

**Combination of metformin and sulfonylureas versus combination of metformin and premixed insulin.** Two short duration RCTS compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue – insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study; both studies nonsignificantly favored the metformin plus sulfonylurea arms (range in between-group differences of -0.7 kg to -0.5 kg).[118 119] None of the study arms decreased weight from baseline.

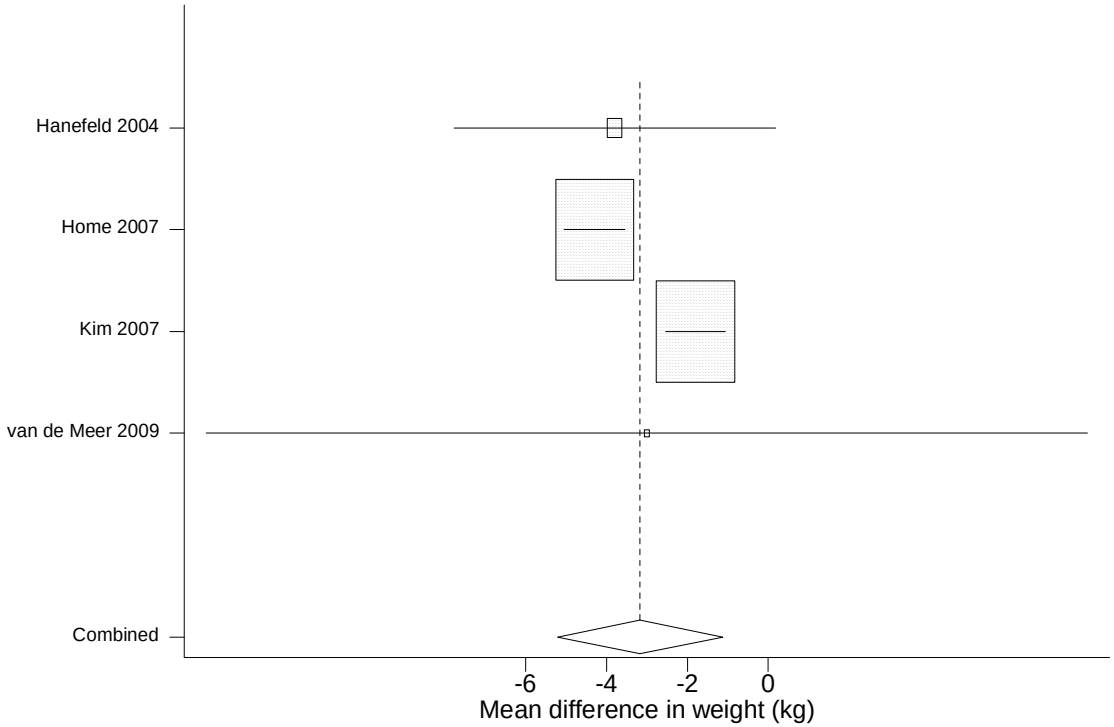
**Combination of metformin and basal insulin versus combination of metformin and premixed insulin.** Two small to moderate RCTs lasting around 6 months compared metformin plus glargine with the combination of metformin plus premixed insulin analogues- insulin lispro 50/50 or insulin aspart 70/30. Both studies favored the metformin plus glargine arms over the metformin plus premixed insulin arms (range in statistically significant between-group differences of -1.4 kg to -2.6 kg).[120 121] One study reported that patients on metformin plus insulin lispro 50/50 gained weight (from 89.1 kg to 90.0 kg; $p < 0.001$), and the patients who received metformin plus insulin glargine experienced weight loss (from 88.1 kg to 87.6 kg; $p = 0.04$) with a significant between-group difference of 1.4 kg ($p < 0.001$).[120] The other study showed that both groups gained weight, yet the metformin plus insulin aspart 70/30 group had a larger weight gain by 2.6 kg compared with the metformin plus insulin glargine group.[121]

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** Four RCTs compared the combination of metformin plus a sulfonylurea with a combination of a thiazolidinedione with a sulfonylurea, favoring the metformin plus sulfonylurea arms with a pooled between-group difference of -3.2 kg (95% CI –5.2 kg to -1.1 kg) (Figure 21).[104 106 115 117] Heterogeneity was significant but all between-group point estimates are in the same direction with minimal differences between studies. No single study markedly influenced these results.

We included only the shorter duration results for the RECORD study[104] in the meta-analysis since all other studies were shorter duration. However, the longer duration results were consistent with the shorter duration studies favoring the metformin plus sulfonylurea arm.[14] The RECORD study was a multicenter open label RCT evaluating 4447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[14 104] They randomly assigned subjects to addition of rosiglitazone or metformin to existing sulfonylurea,

with a primary endpoint of cardiovascular hospitalization or cardiovascular death. These two studies showed a significant increase in weight for the thiazolidinedione plus sulfonylurea arm compared with a slight decrease in weight from baseline in the metformin plus sulfonylurea arm (significant between-group differences of 4.3 kg in the 18 month followup and 5.9 kg in the estimated 5-year followup).

**Figure 21. Mean difference in weight comparing combination metformin and sulfonylureas with combination thiazolidinediones with sulfonylureas**




**Favors metformin plus sulfonylureas** **Favors thiazolidinediones plus sulfonylureas**

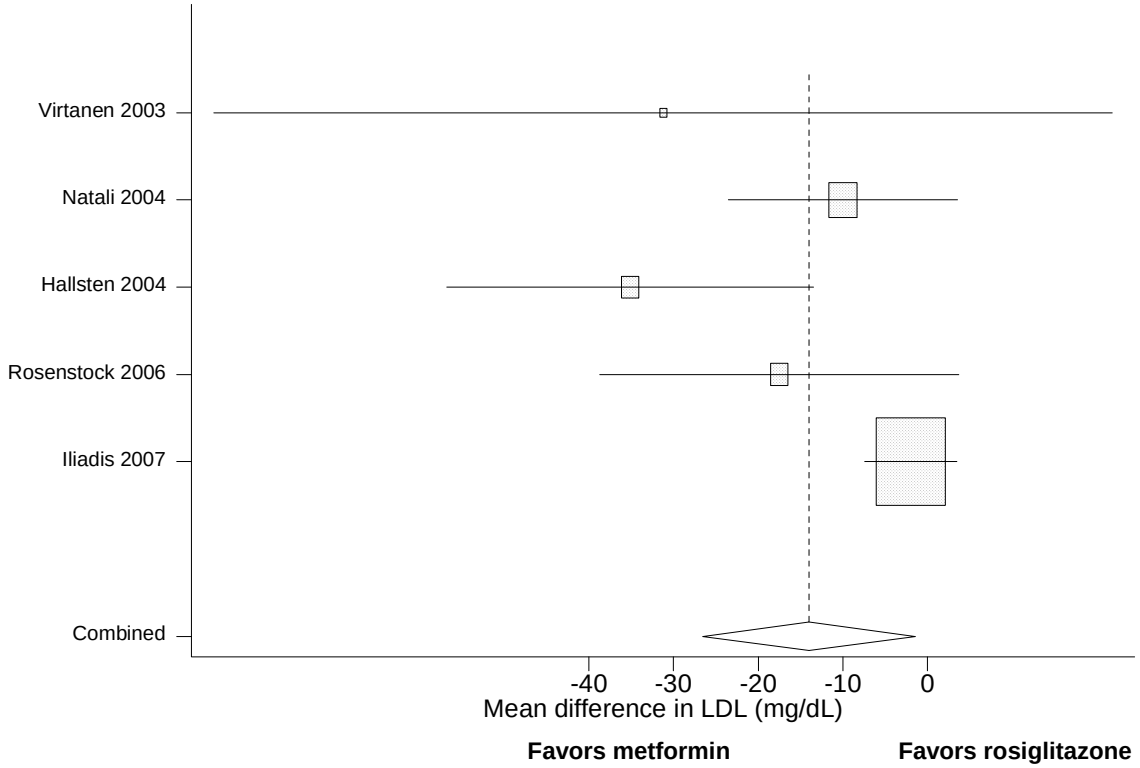
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 21.67 with 3 degrees of freedom (p = 0.0001)
I-squared statistic = 86%

## The Evidence about Low Density Lipoproteins (Appendix G, Table 4)

**Metformin versus rosiglitazone.** Five RCTs compared metformin to rosiglitazone and favored metformin (pooled between-group difference -14.0 mg/dL, 95% CI -26.5 mg/dL to -1.5 mg/dL) (Figure 22).[38 39 122 126 127] Removal of any of three studies resulted in point estimates which still favored metformin but loss of the statistical significance of those pooled between-group differences in LDL.[39 122 126] While there was statistical evidence of heterogeneity, all studies reported between-group differences consistent with the pooled estimate. Another study reported that median LDL decreased by 31.2 mg/dL in the metformin arm and by 15.6 mg/dL in the rosiglitazone arm but was not included the meta-analysis because it reported medians and not means.[46]

**Metformin versus pioglitazone.** Five studies compared metformin to pioglitazone favoring metformin (pooled between-group difference in LDL -14.2 mg/dL (95% CI -15.3 mg/dL to -13.1

**Figure 22. Mean difference in LDL comparing metformin with rosiglitazone**




LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 11.37 with 4 degrees of freedom (p = 0.02)
I-squared statistic = 65%

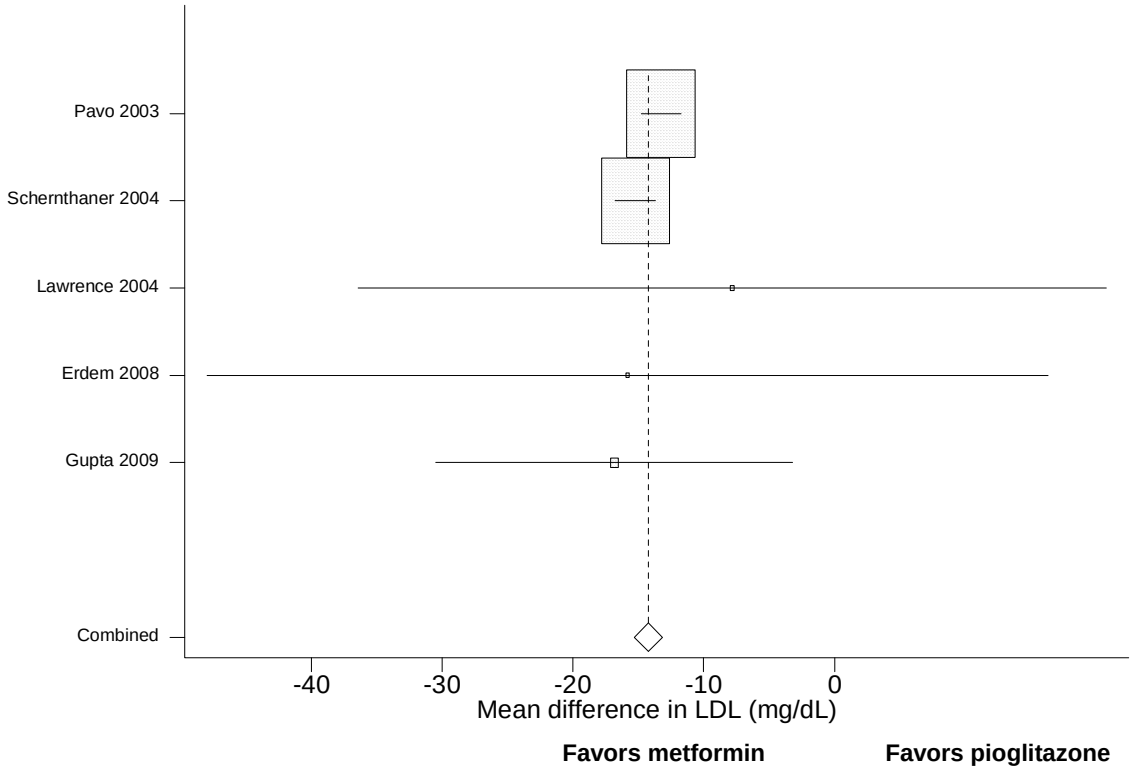
mg/dL) (Figure 23).[31 37 42-44] No one study significantly influenced results, and there was no evidence of heterogeneity.

**Metformin versus sulfonylureas.** Eight RCTs compared metformin with sulfonylureas with a pooled between-group difference in LDL of -10.1 mg/dL (95% CI -13.3 mg/dL to -7.0 mg/dL) which favored metformin (Figure 24).[48-50 52 55 56 58 128] No one study significantly influenced results. While there was statistical evidence of heterogeneity, point estimates from all studies favored metformin. Another study reported no difference in overall lipid levels between groups but did not provide quantitative results.[51]

**Metformin versus sitagliptin.** A single RCT reported no between-group difference in LDL regardless of metformin dose (2000 mg per day or 1000 mg per day) over the course of 24 weeks.[63] The between-group difference in LDL ranged from -5.2 to -4.8 mg/dL at 24 weeks. The significance of the between-group difference was not reported, but the 95% CIs for percentage change in LDL from baseline were overlapping. The results of the 30-week continuation (total of 54 weeks of followup) of this study were consistent with these findings (range of between-group difference in LDL -3.2 mg/dL to -1.4 mg/dL).[63]

**Metformin versus meglitinides.** As seen in the previous report,[17] in a single RCT, the between-group difference in LDL (-3.12 mg/dL) favored metformin over repaglinide, but this difference was not statistically significant ($p > 0.05$).[67]

**Figure 23. Mean difference in LDL comparing metformin with pioglitazone**



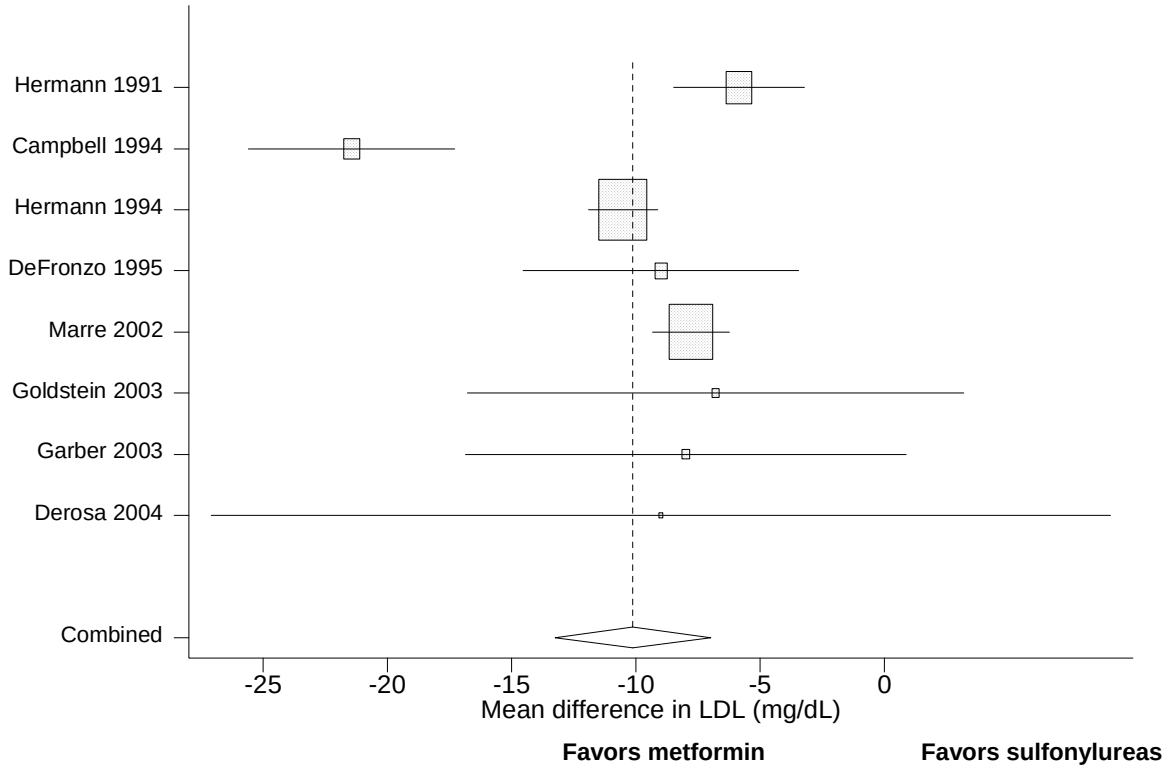

LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.46 with 4 degrees of freedom (p = 0.48)
I-squared statistic = 0%

**Metformin versus a combination of metformin and rosiglitazone.** Seven RCTs favored metformin over the combination of metformin and rosiglitazone (pooled between-group difference in LDL -14.5 mg/dL, 95% CI -15.7 mg/dL to -13.3 mg/dL) (Figure 25).[39 71-74 76 129] No one study significantly affected results, and there was no evidence of statistical heterogeneity.

**Metformin versus a combination of metformin and pioglitazone.** Two RCTs compared metformin to the combination of metformin and pioglitazone (range in between-group differences -2.6 mg/dL to 4.8 mg/dL).[70 75] Statistical significance of between-group differences were not reported.

**Metformin versus a combination of metformin and sulfonylureas.** Six RCTs found no between-group difference in LDL (pooled between-group difference -0.2 mg/dL, 95% CI -5.6 mg/dL to 5.2 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 26).[49 50 52 56 58 128] No one study significantly affected results. Meta-regression revealed study duration as a potential source of heterogeneity. Shorter duration studies (16 to 18 weeks) tended to favor the combination of metformin and a sulfonylurea,[56 58 128] and longer duration studies (24 to 26 weeks) tended to favor metformin.[49 50 52] Another study reported no changes in lipid values between groups but did not provide quantitative results.[51]

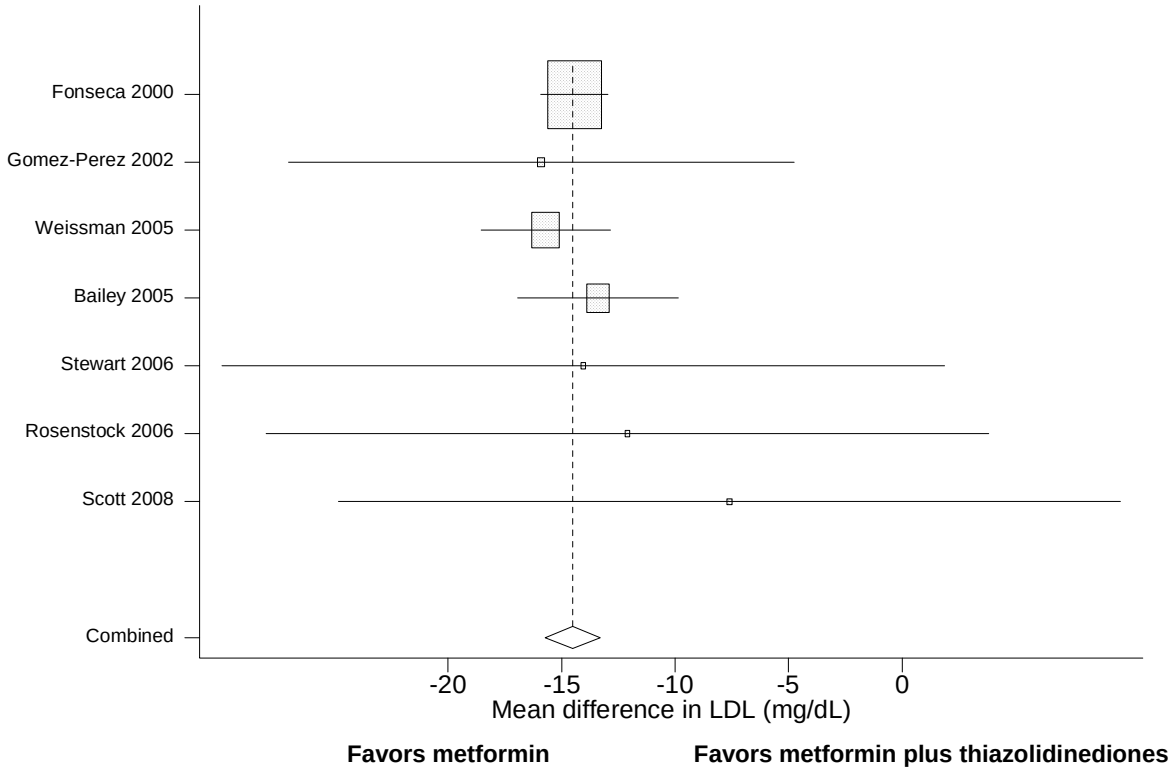
**Figure 24. Mean difference in LDL comparing metformin with sulfonylureas**




LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 46.42 with 7 degrees of freedom (p = 0.0000)
I-squared statistic = 85%

**Metformin versus a combination of metformin and sitagliptin.** Three RCTs found no between-group difference in LDL for metformin compared to the combination of metformin and sitagliptin (pooled between-group difference -0.4 mg/dL, 95% CI -7.3 mg/dL to 6.5 mg/dL) (Figure 27).[63 71 80] There was no statistical evidence of heterogeneity, and no one study significantly influenced results. One study evaluated LDL at 24 weeks and after a continuation (at 54 weeks).[63] We included the shorter duration results in the meta-analysis since the study duration was more homogenous with the rest of the studies and had less loss to followup.[63] The 54-week results were similar to those at 24-weeks; significance of the between-group difference was not reported, but the 95% CIs for percentage change in LDL from baseline were overlapping.[63] There was a possible dose-response relationship with the 2000 mg metformin and 100 mg sitagliptin arm reducing LDL (mean change from baseline -1.1% at 24 weeks and -4.1% at 54 weeks) compared to the 1000 mg metformin plus 100 mg sitagliptin arm (mean change in LDL from baseline 1.4% at 24 weeks and -0.3% at 54 weeks).

**Figure 25. Mean difference in LDL comparing metformin with combination metformin and thiazolidinediones**



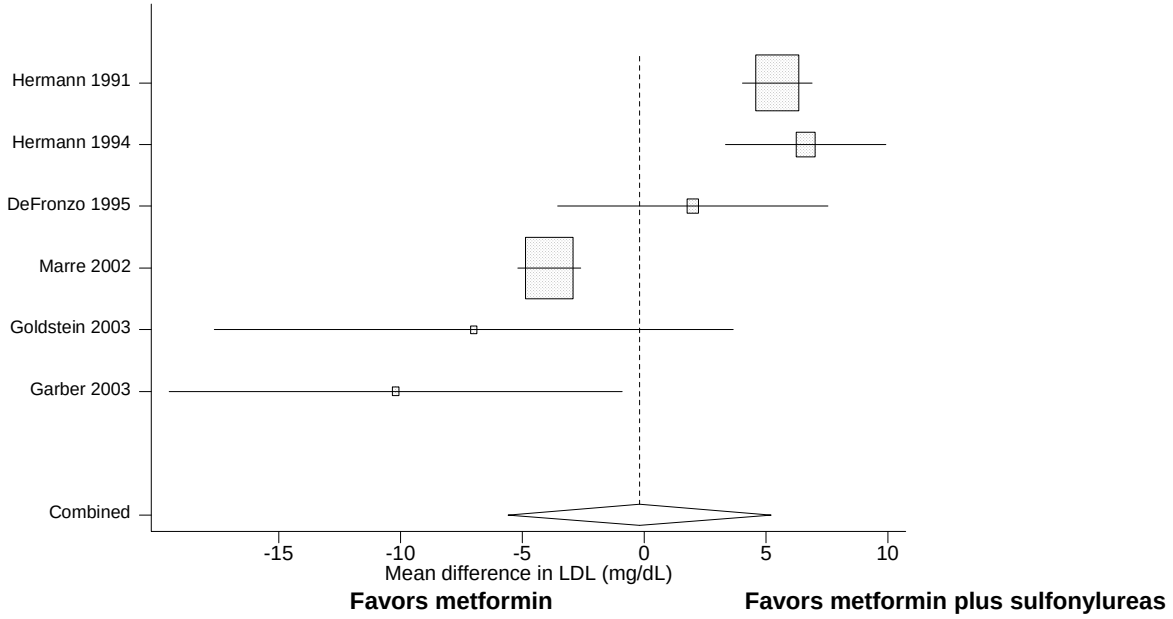

LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.83 with 6 degrees of freedom (p = 0.93)
I-squared statistic = 0%

**Metformin versus a combination of metformin and meglitinides.** A single 24-week RCT directly compared the combination of metformin and nateglinide at two different doses (60 mg and 120 mg) to the combination of metformin and placebo and showed no between-group difference in LDL (0 mg/dL) over the course of the study.[81]

**Rosiglitazone versus pioglitazone.** As seen in the previous report,[17] two RCTs with similarly-dosed pioglitazone and rosiglitazone favored pioglitazone (range in between-group difference in LDL -16 to -9 mg/dL).[82 83] Due to these differences, pioglitazone and rosiglitazone were not combined for comparisons including these thiazolidinediones for the LDL section.

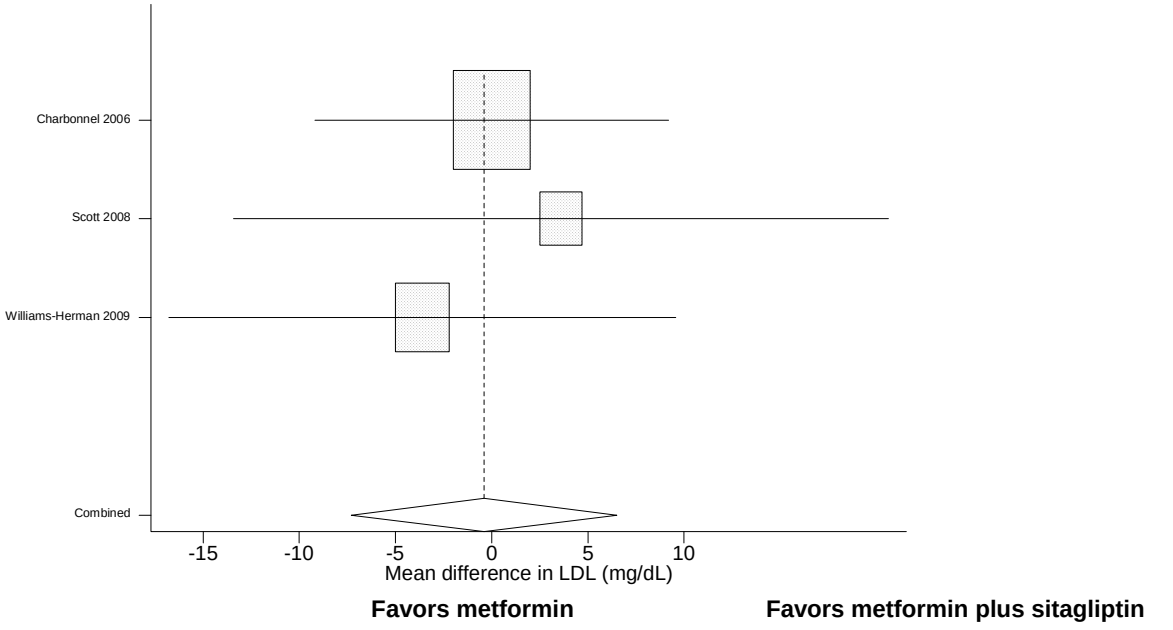
**Rosiglitazone versus sulfonylureas.** Two RCTs compared rosiglitazone to a sulfonylurea, and in both studies, rosiglitazone (8 mg daily) increased median LDL relative to a sulfonylurea (range in median between-group difference 15.2 mg/dL to 19.5 mg/dL).[84 123] Statistical significance of between-group differences were not reported. There was suggestion of a dose-response given that a lower dose rosiglitazone (4 mg daily) was associated with a smaller median between-group difference (11.7 mg/dL) in one study.[84]

**Figure 26. Mean difference in LDL comparing metformin with combination metformin and sulfonylureas**




LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 112.04 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 96%

**Figure 27. Mean difference in LDL comparing metformin to combination metformin and sitagliptin**

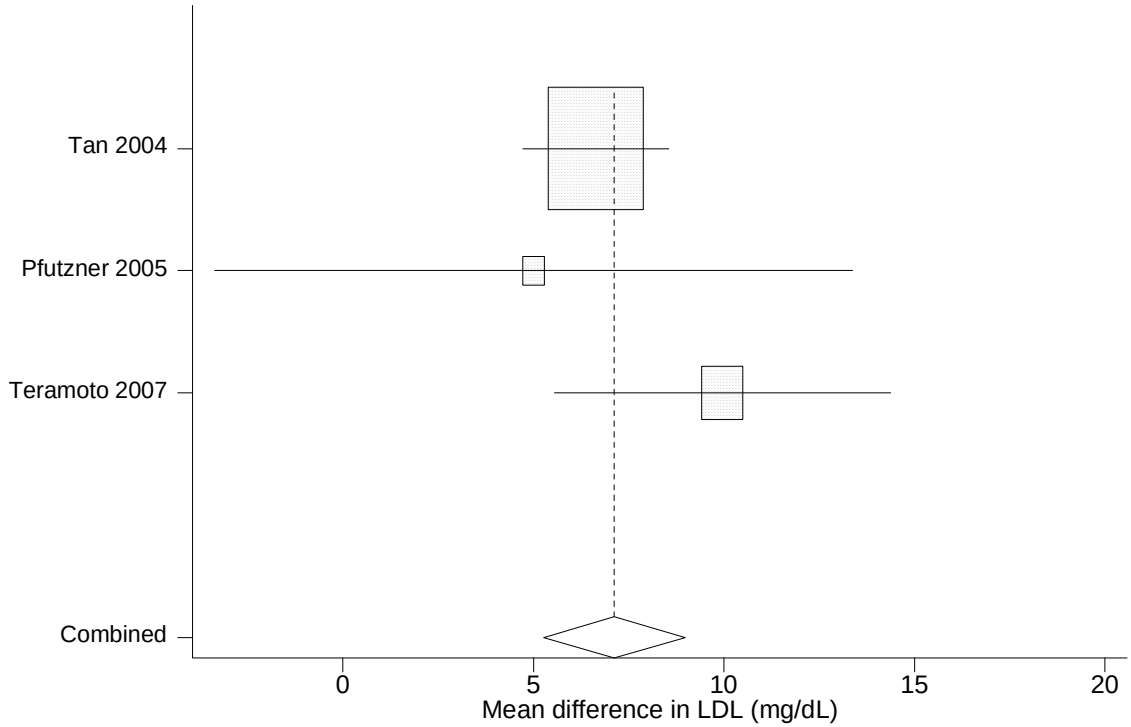



LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.45 with 2 degrees of freedom (p = 0.80)

I-squared statistic = 0%

**Pioglitazone versus sulfonylureas.** Three RCTs compared pioglitazone to a sulfonylurea (pooled between-group difference in LDL 7.1 mg/dL, 95% CI 5.3 mg/dL to 9.0 mg/dL) (Figure 28).[33 89 90] No one study affected results, and there was no significant heterogeneity.

**Figure 28. Mean difference in LDL comparing pioglitazone with sulfonylureas**




**Favors pioglitazone** **Favors sulfonylureas**

LDL = low density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.08 with 2 degrees of freedom (p = 0.35)
I-squared statistic = 4%

**Rosiglitazone versus meglitinides.** As seen in the previous evidence report,[17] a single RCT compared rosiglitazone to repaglinide and found a between-group difference in LDL of 15 mg/dL.[92]

**Pioglitazone versus meglitinides.** As seen in the previous report,[17] a single RCT compared pioglitazone to repaglinide and found a between-group difference in LDL of -16 mg/dL.[93]

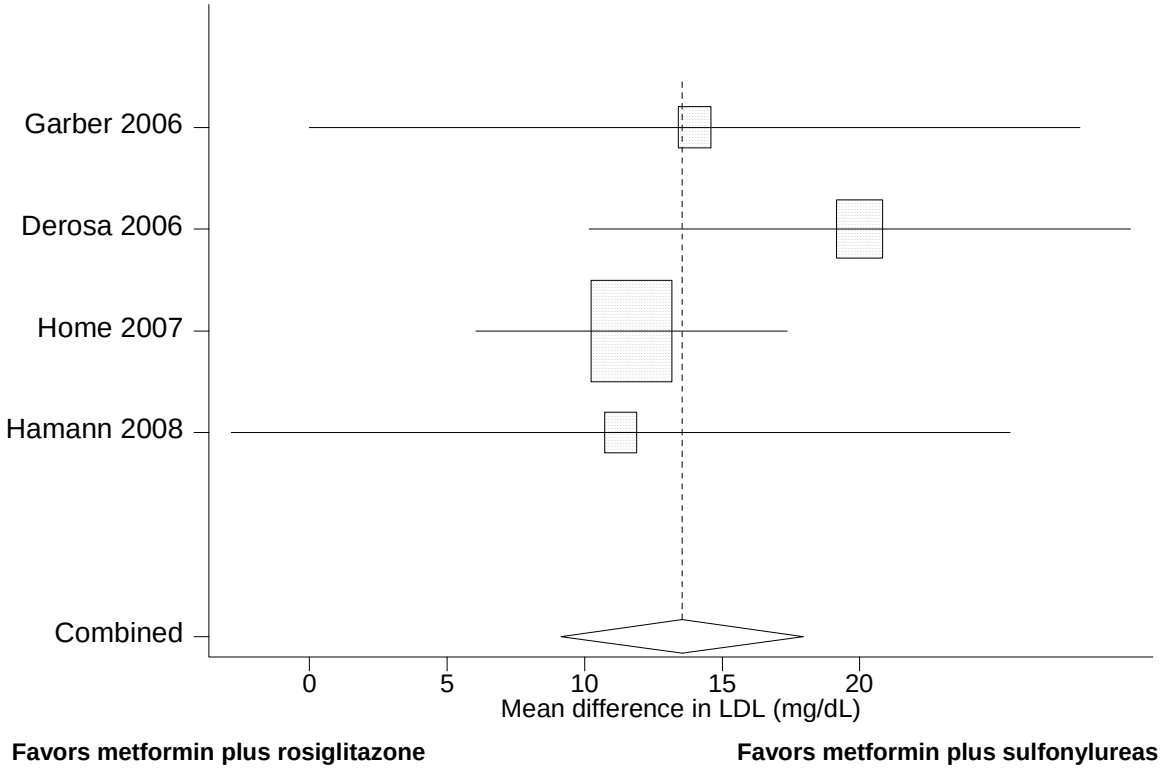
**Sulfonylureas versus sitagliptin.** One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[94] After 12 weeks, both high dose sitagliptin (100 mg a day) and glipizide (maximum dose 20 mg a day) increased LDL (5.5% versus 2.2% respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[94]

**Sulfonylureas versus meglitinides.** As seen in the previous evidence report,[17] two RCTs compared a sulfonylurea with repaglinide and showed no significant between-group differences in LDL (range in between-group differences of -1.5 mg/dL to 1 mg/dL).[96 100] An additional RCT

reported no difference between nateglinide and glibenclamide in LDL, but no quantitative results were provided.[102]

**Combination of metformin and rosiglitazone versus combination of metformin and sulfonylureas.** Four RCTs compared the combination of metformin and rosiglitazone to metformin and a sulfonylurea. The pooled between-group difference in LDL was 13.5 mg/dL (95% CI 9.1 mg/dL to 17.9 mg/dL) comparing metformin and rosiglitazone with metformin and a sulfonylurea (Figure 29).[103 104 108 130] There was no statistical evidence of heterogeneity, and no single study significantly influenced results. We included results from the 18-month analysis of RECORD in the meta-analysis since this duration was more comparable to the other studies included in the meta-analysis.[104] At 5.5 years, the combination of metformin and rosiglitazone decreased LDL less than the combination of metformin and a sulfonylurea (between-group difference 6.6 mg/dL (p = 0.0001).[14]

**Figure 29. Mean difference in LDL comparing combination of metformin and rosiglitazone with combination of metformin and sulfonylureas**




LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.16 with 3 degrees of freedom (p = 0.54)
I-squared statistic = 0%

**Combination of metformin and pioglitazone versus combination of metformin and sulfonylureas.** A single RCT compared the combination of metformin and pioglitazone to the combination of metformin and glimepiride at 26 weeks and reported a between-group difference of 8.5 mg/dL (p = 0.03) favoring the combination of metformin and glimepiride.[106]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One double-blind small RCT lasting 18 weeks compared maximum dose metformin plus rosiglitazone to the combination of maximum dose metformin plus sitagliptin showing a between-group difference in LDL (mean difference of 14.8%, 95% CI 5.7% to 23.9%).[71]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One RCT lasting 26 weeks compared metformin plus rosiglitazone twice daily with the combination of metformin plus repaglinide twice daily and three times daily, showing a significant between-group difference in LDL of 12.2 mg/dL ($p = 0.0002$).[110]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two moderately-sized double-blinded RCTs lasting 1 to 2 years directly compared the combination of metformin plus sulfonylurea with metformin plus nateglinide.[111 112] One study reported that LDL decreased by less than 5% in both groups.[112] The other study reported a decrease in LDL which was greater in the metformin plus sulfonylurea arm compared with the metformin plus nateglinide arm (between group difference -7 mg/dL).[111]

**Combination of metformin and pioglitazone versus combination of pioglitazone and sulfonylureas.** A single RCT found no difference in LDL for pioglitazone added to either metformin or a sulfonylurea ($p = 0.28$) in a post-hoc analysis at 6 months.[131]

**Combination of metformin and sulfonylureas versus combination of rosiglitazone and sulfonylureas.** One RCT lasting only 12 weeks reported less of a decrease in LDL in the metformin plus sulfonylurea arm compared to the rosiglitazone plus sulfonylurea arm (between-group difference 2.7 mg/dL, $p = 0.005$).[34] At 18 months, the RECORD trial reported a between-group difference in LDL of -18.7 mg/dL ($p < 0.001$)[104] and -12.1 mg/dL ($p < 0.0001$) at 5.5 years[104] comparing metformin plus sulfonylurea to rosiglitazone plus sulfonylurea.

**Combination of metformin and sulfonylureas versus combination of pioglitazone and sulfonylureas.** Two RCTs found that the combination of metformin and sulfonylurea decreased LDL relative to the combination of pioglitazone and sulfonylurea. One study reported a median between-group difference of -11.7 mg/dL ($p = 0.11$), and the other a mean between-group difference of -9.4 mg/dL ($p = 0.0002$).[115 116]

## The Evidence about High Density Lipoproteins (Appendix G, Table 4)

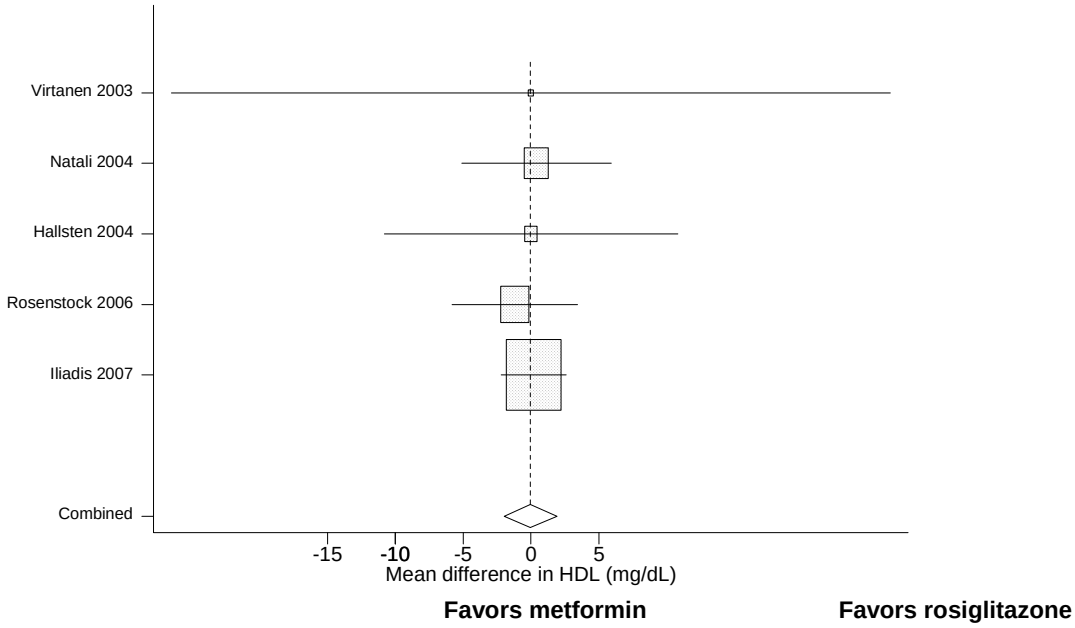
**Metformin versus rosiglitazone.** Five RCTs reported no between-group difference in HDL for metformin compared to rosiglitazone (pooled between-group difference -0.03 mg/dL, 95% CI -2.0 mg/dL to 1.9 mg/dL) (Figure 30).[38 39 126 127 132] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

**Metformin versus pioglitazone.** Seven RCTs favored pioglitazone over metformin with a pooled between-group difference in HDL of -3.2 mg/dL (95% CI -4.3 mg/dL to -2.1 mg/dL) (Figure 31).[31 37 40-44] No one study significantly affected results. While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone.

**Metformin versus sulfonylureas.** Eleven studies found no significant change in HDL for metformin compared to a sulfonylurea (pooled between-group difference 0.2 mg/dL, 95% CI -0.4 mg/dL to 0.8 mg/dL) (Figure 32).[40 41 48-50 52 54-56 58 59] No one study significantly affected results. There was no obvious source of the observed heterogeneity on meta-regression. Another study reported no changes in lipid values between groups but did not provide quantitative results.[51]

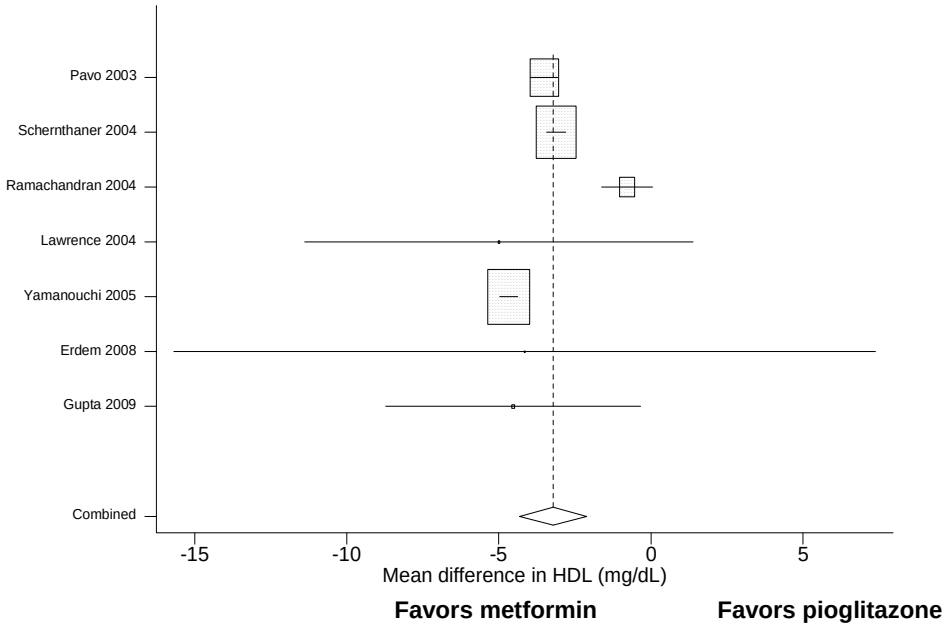
1

**Figure 30. Mean difference in HDL comparing metformin with rosiglitazone**



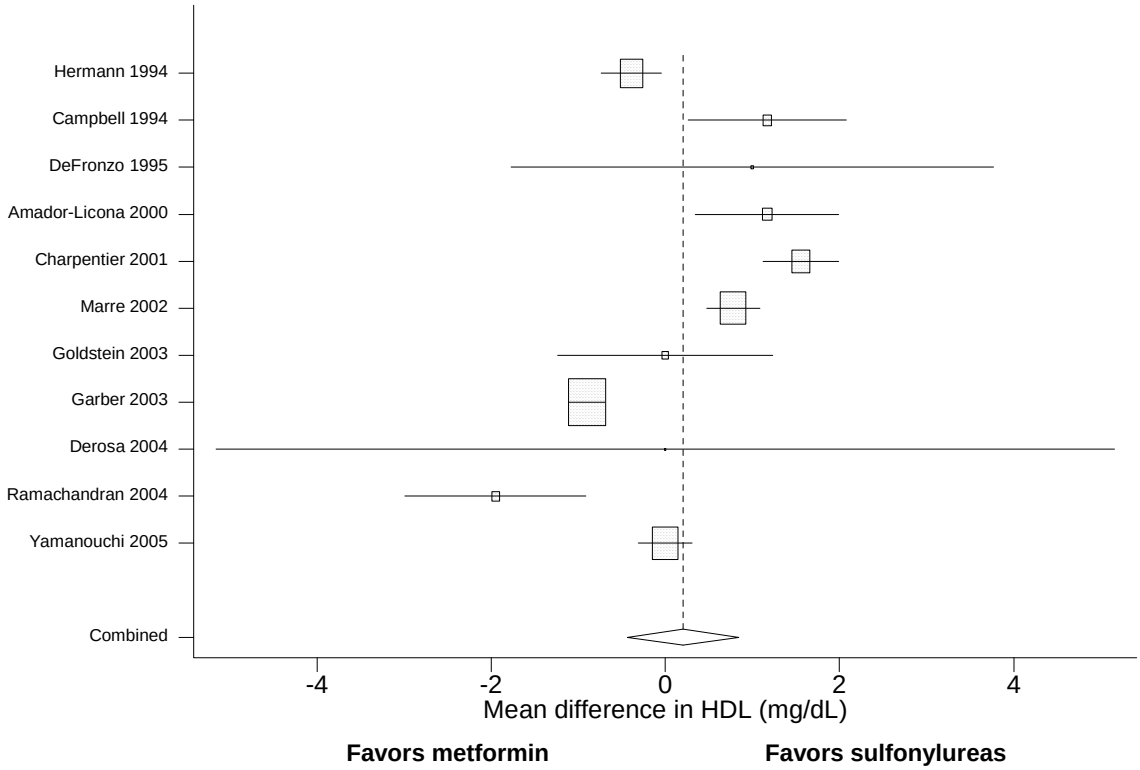

HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.31 with 4 degrees of freedom (p = 0.99)
I-squared statistic = 0%

**Figure 31. Mean difference in HDL comparing metformin with pioglitazone**




HDL = high density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 100.55 with 6 degrees of freedom (p = 0.0000)
I-squared statistic = 94%

**Figure 32. Mean difference in HDL comparing metformin with sulfonylureas**



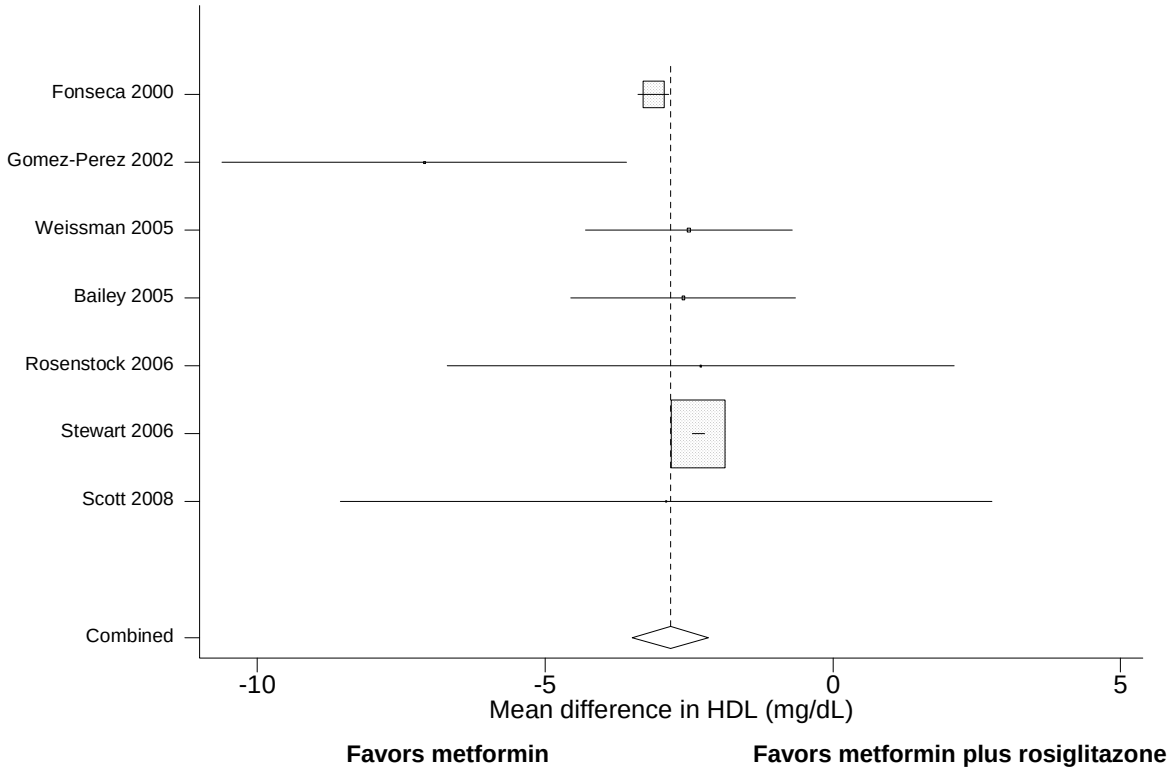

HDL = high density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 175.80 with 10 degrees of freedom (p = 0.0000)
I-squared statistic = 94%

**Metformin versus sitagliptin.** A single RCT reported no between-group difference in HDL regardless of metformin dose (2000 mg per day or 1000 mg per day) over the course of 24 weeks.[63] The between-group difference in HDL ranged from 0.9 mg/dL to 1.8 mg/dL at 24 weeks. Significance of the between-group difference was not reported, but 95% CI for percentage change in HDL from baseline were overlapping. The results of the 30-week continuation (total of 54 weeks of followup) of this study were consistent with these findings (range of between-group difference in HDL 2.3 mg/dL to 3.0 mg/dL).[63]

**Metformin versus meglitinides.** As seen in the previous evidence report,[17] in a single RCT, the between-group difference in HDL (-4.3 mg/dL) favored repaglinide over metformin, but this difference was not statistically significant.[67]

**Metformin versus a combination of metformin and rosiglitazone.** Seven RCTs compared metformin to the combination of metformin and rosiglitazone (pooled between-group difference in HDL -2.8 mg/dL, 95% CI -3.5 mg/dL to -2.2 mg/dL) (Figure 33).[39 71-74 76 129] No one study significantly affected results. While there was evidence of substantial heterogeneity, point estimates from each study were consistent with the pooled results.

**Figure 33. Mean difference in HDL comparing metformin with combination metformin and rosiglitazone**

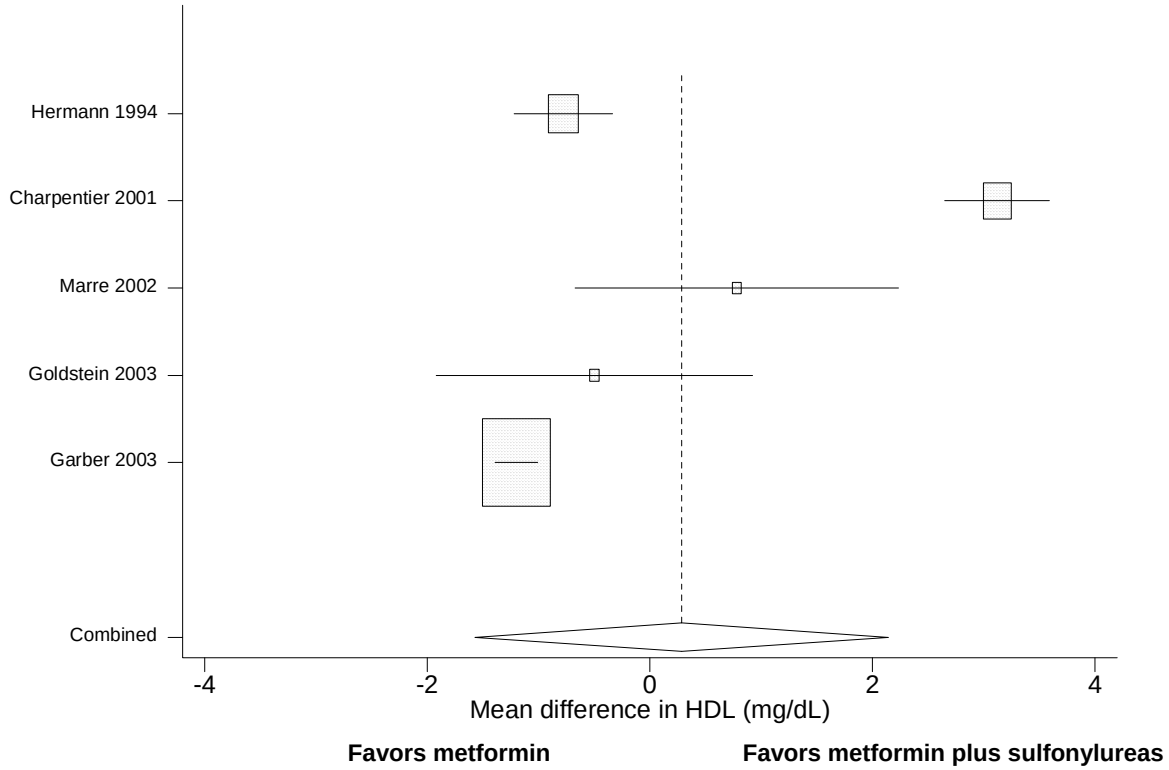



HDL = high density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 34.57 with 6 degrees of freedom (p = 0.0000)
I-squared statistic = 83%

**Metformin versus a combination of metformin and pioglitazone.** Two RCTs favored the combination of metformin and pioglitazone over metformin (range in between-group differences 6.4 to 8.7 mg/dL).[70 75] Statistical significance of between-group differences were not reported.

**Metformin versus a combination of metformin and sulfonylureas.** Five RCTs found no between-group difference in HDL (pooled between-group difference 0.3 mg/dL, 95% CI -1.6 mg/dL to 2.1 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 34).[49 50 52 56 59 77] There was substantial evidence of heterogeneity, and meta-regression suggested medication dose as a potential source of heterogeneity (p = 0.072). In particular, the study with the lowest relative dose of metformin monotherapy compared to the combination of metformin and sulfonylurea reported the largest point estimate (between-group difference 3.1 mg/dL).[59] Removal of this study from the meta-analysis led to a significant pooled between-group difference of -0.75 mg/dL (95% CI -1.3 mg/dL to -0.2 mg/dL).[59] Another study reported no changes in lipid values between groups but did not provide quantitative results.[51]

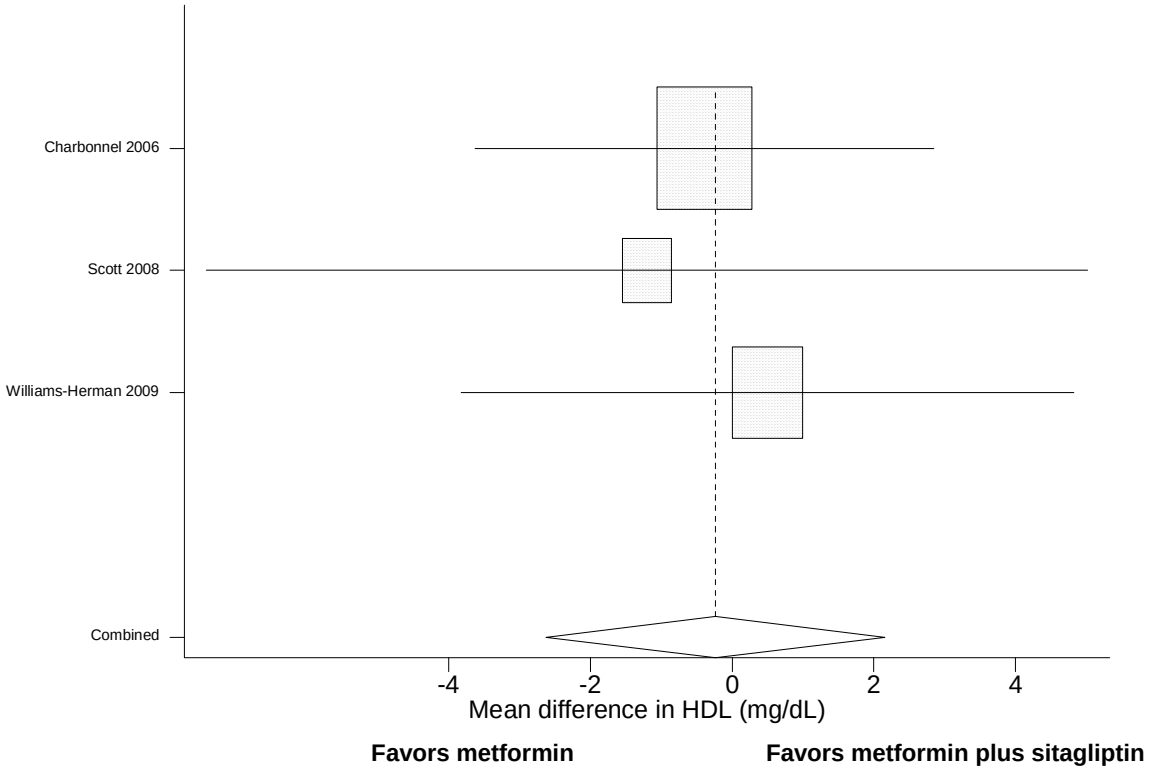
**Figure 34. Mean difference in HDL comparing metformin with combination metformin and sulfonylureas**




HDL = high density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 282.15 with 4 degrees of freedom (p = 0.0000)
I-squared statistic = 99%

**Metformin versus a combination of metformin and sitagliptin.** Three RCTs found no between-group difference in HDL for metformin compared to the combination of metformin and sitagliptin (pooled between-group difference -0.2, 95% CI -2.6 to 2.2) (Figure 35).[63 71 80] There was no statistical evidence of heterogeneity, and no one study significantly influenced results. One study evaluated HDL at 24 weeks and after a continuation (at 54 weeks).[63] We included the shorter duration results in the meta-analysis since the study duration was more homogenous with the rest of the studies and had less loss to followup.[63] The 54-week results were similar to those at 24 weeks; significance of the between-group difference was not reported, but the 95% CIs for percentage change in HDL from baseline were overlapping.[63] There was a possible dose-response relationship with the 2000 mg metformin and 100 mg sitagliptin arm increasing HDL (mean change from baseline 5.8% at 24 weeks and 7.2% at 54 weeks) compared to the 1000 mg metformin plus 100 mg sitagliptin arm (mean change in HDL from baseline 3.6% at 24 weeks and 5.1% at 54 weeks).

**Figure 35. Mean difference in HDL comparing metformin with combination metformin and sitagliptin**




HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.21 with 2 degrees of freedom (p = 0.90)
I-squared statistic = 0%

**Metformin versus a combination of metformin and meglitinides.** A single 24-week RCT directly compared the combination of metformin and nateglinide at two different doses (60 mg and 120 mg) to the combination of metformin and placebo and showed no between-group difference in HDL (0 mg/dL) over the course of the study.[81]

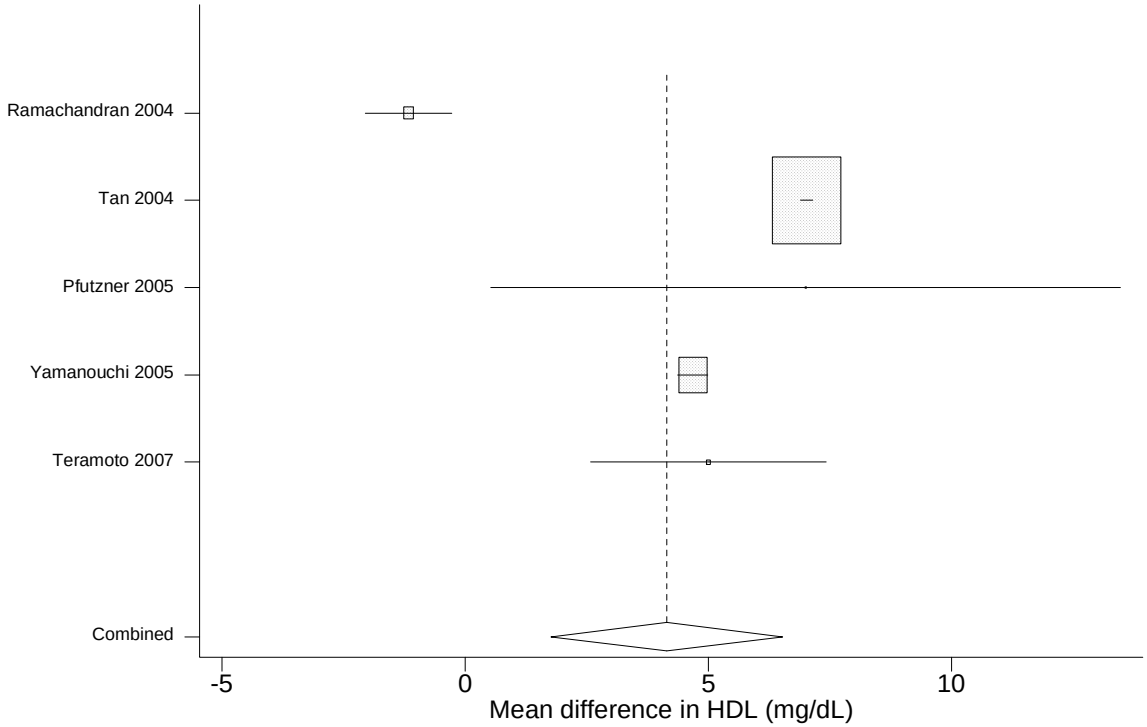
**Rosiglitazone versus pioglitazone.** As seen in the previous report,[17] two RCTs with similarly-dosed pioglitazone and rosiglitazone favored pioglitazone (range in between-group difference in HDL -2.8 mg/dL to -0.5 mg/dL).[82 83] The larger study reported a statistically significant difference between arms.[83] Due to these differences, pioglitazone and rosiglitazone are not combined for comparisons including these thiazolidinediones for the HDL section.

**Rosiglitazone versus sulfonylureas.** Two RCTs compared rosiglitazone to a sulfonylurea, and in both studies, rosiglitazone (8 mg daily) increased median HDL relative to a sulfonylurea (range in median between-group difference 3.5 mg/dL to 7.7 mg/dL).[84 123] The statistical significance of between-group differences was not reported. There was suggestion of a dose-response relationship given that a lower dose rosiglitazone (4 mg daily) was associated with a smaller median between-group difference (1.6 mg/dL) in one study.[84]

**Pioglitazone versus sulfonylureas.** Five RCTs favored pioglitazone over a sulfonylurea (pooled between-group difference in HDL 4.1 mg/dL, 95% CI 1.8 mg/dL to 6.5 mg/dL) (Figure 36).[33 40 41 89 90] Removal of the largest study[90] resulted in a non-significant pooled between-group

difference (3.5 mg/dL, 95% CI -0.5 mg/dL to 7.5 mg/dL). Meta-regression suggested study duration as a potential source of heterogeneity (p = 0.20) with increased study duration associated with an increase in the between-group difference.

**Figure 36. Mean difference in HDL comparing pioglitazone with sulfonylureas**




**Favors pioglitazone** **Favors sulfonylureas**

HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 485.43 with 4 degrees of freedom (p = 0.0000)
I-squared statistic = 99%

**Rosiglitazone versus meglitinides.** As seen in the previous evidence report,[17] a single RCT compared rosiglitazone to repaglinide and found a between-group difference in HDL of 1.3 mg/dL.[92]

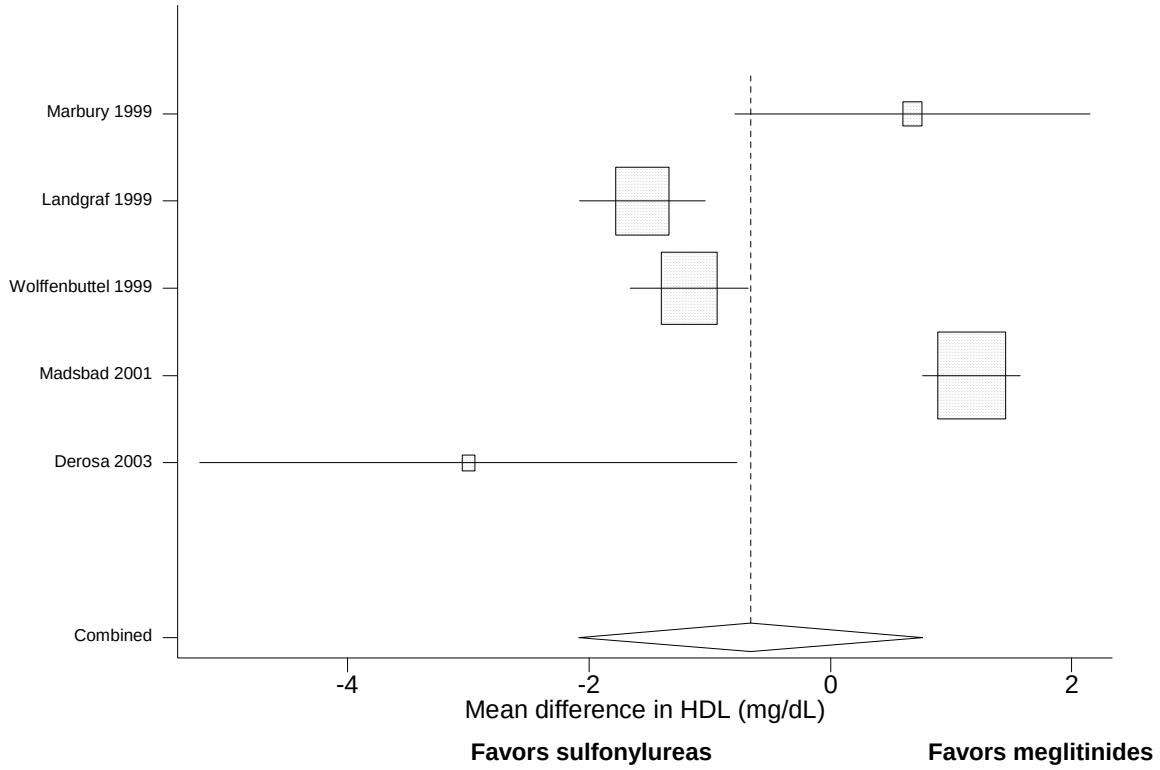
**Pioglitazone versus meglitinides.** As seen in the previous evidence report,[17] a single RCT compared pioglitazone to repaglinide and found a between-group difference in HDL of 7.0 mg/dL.[93]

**Sulfonylureas versus sitagliptin.** One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[94] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg per day) increased HDL (4.6% versus 2.8% respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[94]

**Sulfonylureas versus meglitinides.** Five RCTs compared a sulfonylurea to repaglinide and found no significant difference in HDL (pooled between-group difference -0.7 mg/dL, 95% CI -2.1 mg/dL to 0.8 mg/dL) (Figure 37).[96-100] Removal of one study resulted in a statistically significant pooled between-group difference (-1.2 mg/dL, 95% CI -2.0 mg/dL to -0.4 mg/dL).[97]

This study did not appear to be different from the others and was therefore kept in the meta-analysis. No source of heterogeneity was found on meta-regression. One additional RCT reported no difference between nateglinide and glibenclamide in HDL, but no quantitative results were provided.[102]

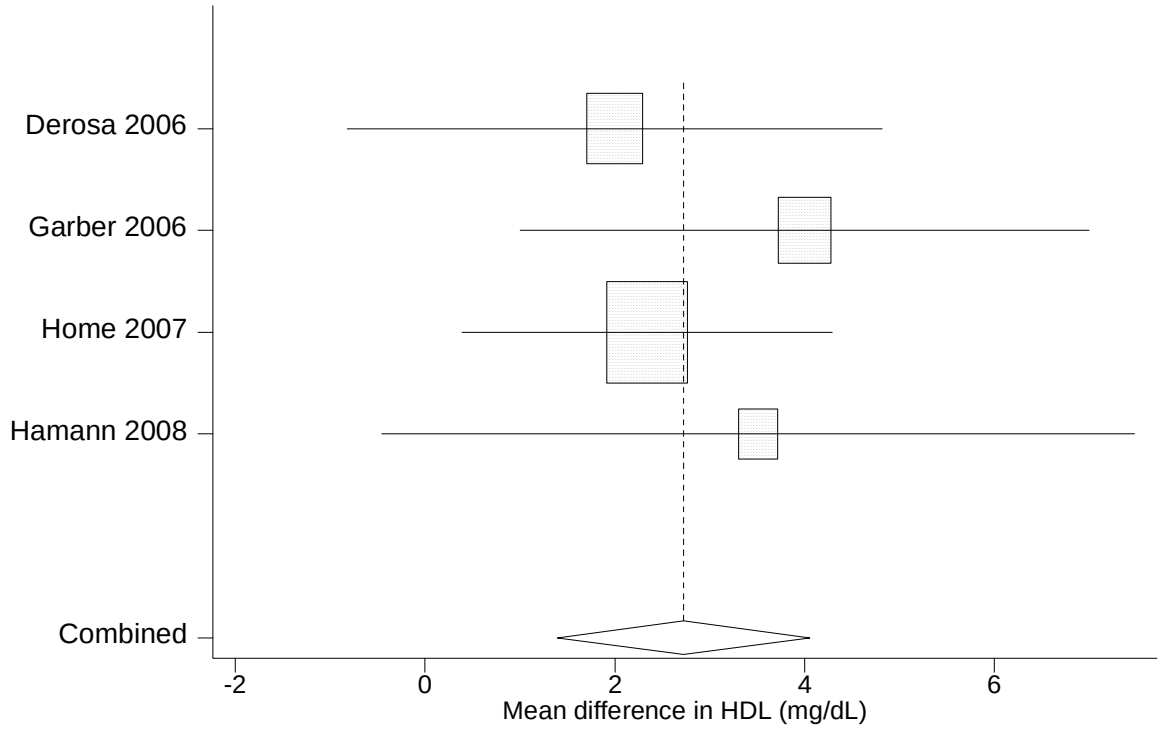
**Figure 37. Mean difference in HDL comparing sulfonylureas with meglitinides**




HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 92.35 with 4 degrees of freedom (p = 0.0000)
I-squared statistic = 96%

**Combination of metformin and rosiglitazone versus combination of metformin and sulfonylureas.** Four RCTs compared the combination of metformin and rosiglitazone with the combination of metformin and a sulfonylurea. The pooled between-group difference in HDL was 2.7 mg/dL (95% CI 1.4 mg/dL to 4.1 mg/dL) comparing combination metformin and rosiglitazone with combination metformin and a sulfonylurea (Figure 38).[103 104 108 130] There was no statistical evidence of heterogeneity, and no one study significantly influenced results. We included results from the 18-month analysis of RECORD in the meta-analysis since this duration was more comparable to the other included studies.[104] At 5.5 years, the combination of metformin and rosiglitazone increased HDL more than the combination of metformin and a sulfonylurea (between-group difference 3.1 mg/dL, $p < 0.0001$).[14]

**Figure 38. Mean difference in HDL comparing combination metformin and rosiglitazone with combination metformin and sulfonylureas**




**Favors metformin plus rosiglitazone** **Favors metformin plus sulfonylureas**

HDL = high density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.25 with 3 degrees of freedom (p = 0.74)
I-squared statistic = 0%

**Combination of metformin and pioglitazone versus combination of metformin and sulfonylureas.** Two RCTs compared the combination of metformin and pioglitazone to metformin and a sulfonylurea.[106 131] In both studies, HDL increased in the metformin and pioglitazone arm and decreased in the metformin and sulfonylurea arm; between-group differences ranged from 5.1 mg/dL ($p < 0.001$) to 5.8 mg/dL ($p = 0.0001$).[106 131]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One double-blind small RCT lasting 18 weeks compared maximum dose metformin plus rosiglitazone to the combination of maximum dose metformin plus sitagliptin showing a significant between-group difference in HDL (mean difference in percentage change from baseline of 4.9%, 95% CI 0.6% to 9.2%).[71]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One RCT lasting 26 weeks compared metformin plus rosiglitazone twice daily with the combination of metformin plus repaglinide twice daily and three times daily, showing a significant between-group difference in HDL of 4.6 mg/dL ($p < 0.0001$).[110]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two moderately-sized double-blinded RCTs lasting 1 to 2 years directly compared the combination of metformin plus sulfonylurea with metformin plus nateglinide.[111 112] One

study reported that HDL increased by approximately 5% in both groups.[112] The other study showed no between-group difference (0 mg/dL) in HDL as well.[111]

**Combination of metformin and sulfonylureas versus combination of metformin and premixed insulin.** A single RCT lasting 4 months compared the combination of metformin and premixed insulin with the combination of metformin and a sulfonylurea, and HDL increased more in the metformin and premixed insulin group relative to the metformin plus sulfonylurea group (between-group difference 2.0 mg/dL), but this difference was not statistically significant.[119]

**Combination of metformin and pioglitazone versus combination of pioglitazone and sulfonylureas.** In a post-hoc analysis in a single RCT, metformin plus pioglitazone increased HDL (2.3 mg/dL, $p = 0.009$) over pioglitazone plus sulfonylurea (0.4 mg/dL, $p = 0.62$) at 6 months.[131]

**Combination of metformin and sulfonylureas versus combination of rosiglitazone and sulfonylureas.** One RCT lasting only 12 weeks reported less of a decrease in HDL in the metformin plus sulfonylurea arm compared to the rosiglitazone plus sulfonylurea arm (between-group difference 2.7 mg/dL, $p = 0.87$).[34] At 18 months, the RECORD trial reported a between-group difference in HDL of -0.4 mg/dL ($p > 0.05$)[104] and -1.6 mg/dL ($p < 0.0001$) at 5.5 years[104] comparing metformin plus sulfonylurea to rosiglitazone plus sulfonylurea.

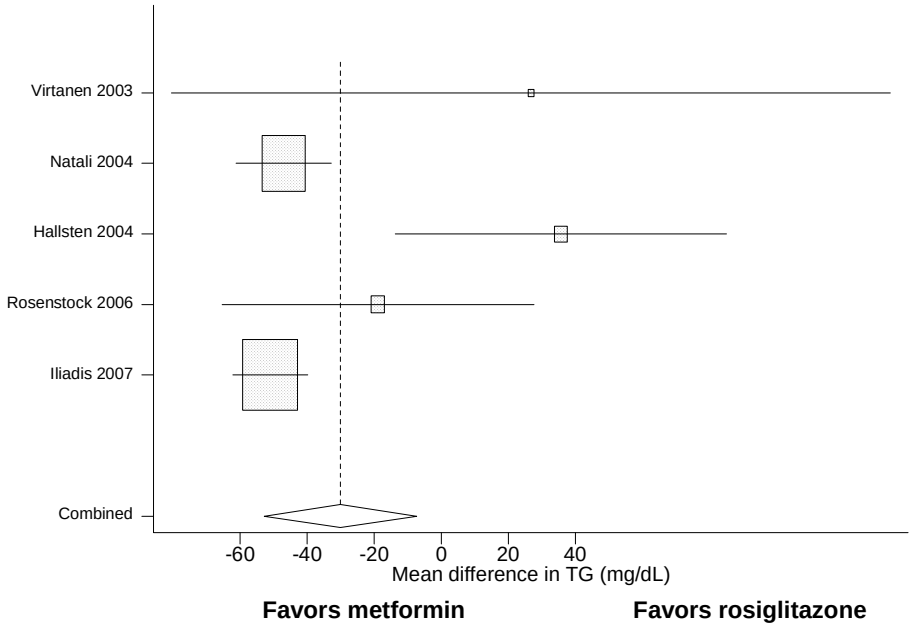
**Combination of metformin and sulfonylureas versus combination of pioglitazone and sulfonylureas.** Three RCTs found that the combination of pioglitazone and sulfonylurea increased HDL relative to the combination of metformin and sulfonylurea.[115 116 131] In one study, the between-group difference in median HDL was 3.1 mg/dL ($p = 0.009$),[116] and two other RCTs found a range of between-group differences of 5.5 mg/dL ($p = 0.20$) to 10.5 mg/dL ($p < 0.0001$).[115 131]

## The Evidence about Triglycerides (Appendix G, Table 4)

**Metformin versus rosiglitazone.** Five RCTs favored metformin over rosiglitazone (pooled between-group difference -30.1 mg/dL, 95% CI -52.8 mg/dL to -7.3 mg/dL) (Figure 39).[38 39 126 127 132] When one study was excluded from the meta-analysis, the point estimate still favored metformin (pooled between-group difference -10.3 mg/dL, but the confidence interval included 0; this may have been because this study was of slightly shorter duration (16 weeks) compared to the other studies.[122] We performed meta-regression because of substantial heterogeneity, and study duration, baseline TG, and dose were not obvious sources of heterogeneity. Another study reported that median TG decreased by 81 mg/dL in the metformin arm and increased by 9.8 mg/dL in the rosiglitazone arm; this study was not included in the meta-analysis because it only provided medians for point estimates.[46]

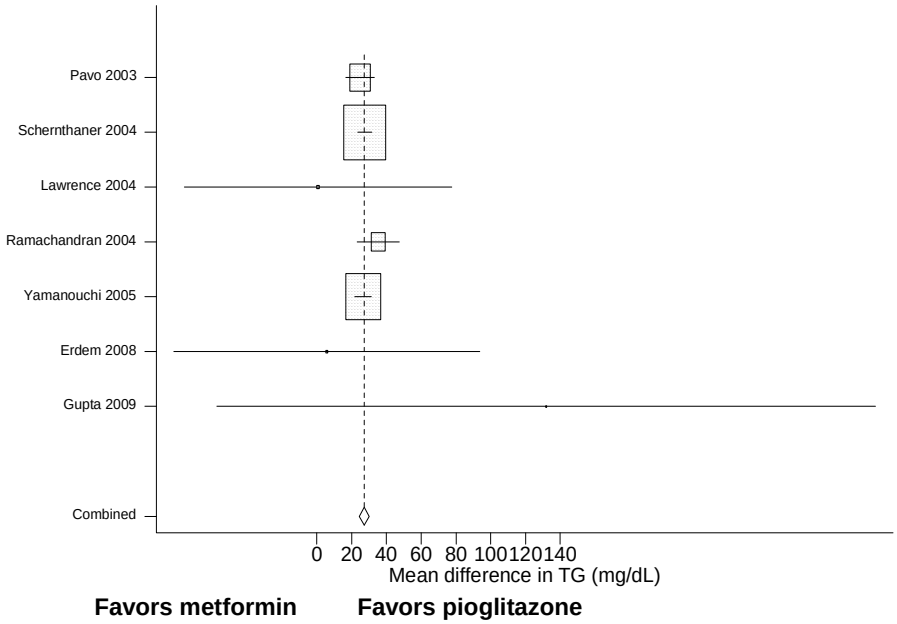
**Metformin versus pioglitazone.** Seven RCTs compared metformin to pioglitazone and found a pooled between-group difference in TG of 27.2 mg/dL (95% CI 24.4 mg/dL to 30.1 mg/dL) (Figure 40).[31 37 40-44] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

**Figure 39. Mean difference in triglycerides comparing metformin to rosiglitazone**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 14.37 with 4 degrees of freedom (p = 0.01)
I-squared statistic = 72%

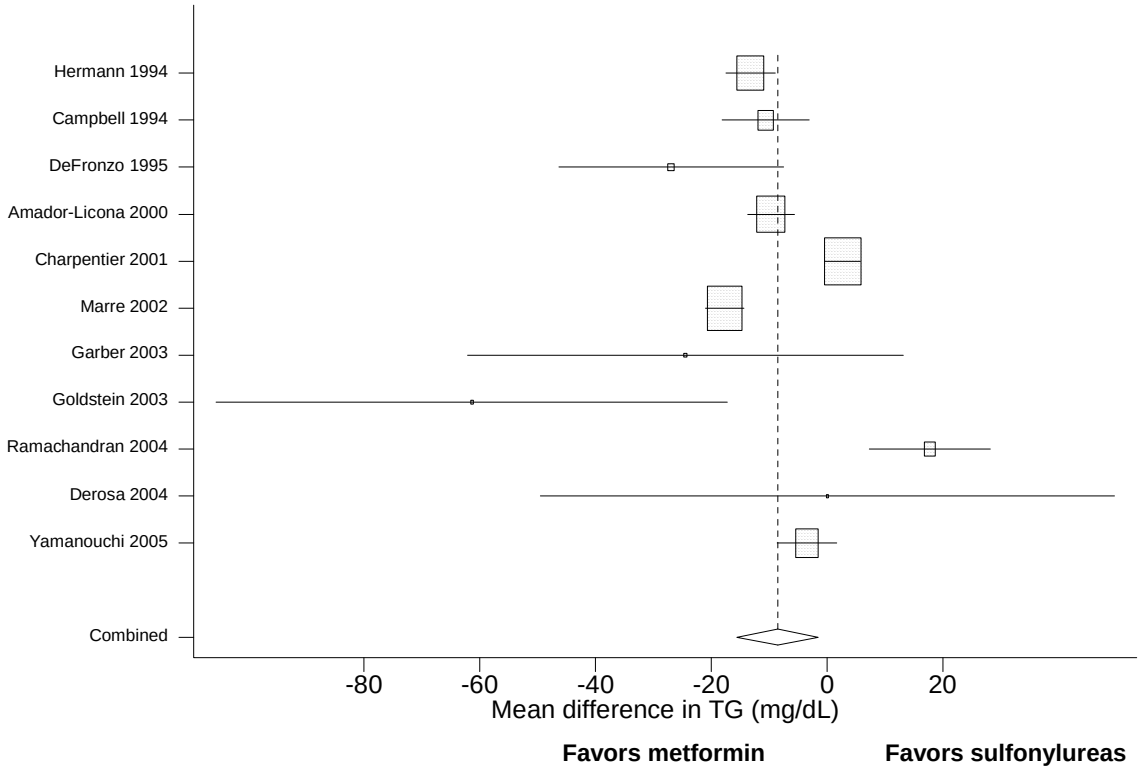
**Figure 40. Mean difference in triglycerides comparing metformin to pioglitazone**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.05 with 6 degrees of freedom (p = 0.67)
I-squared statistic = 0%

**Metformin versus sulfonylureas.** Eleven RCTs favored metformin over sulfonylurea (pooled between-group difference in TG -8.6 mg/dL (95% CI -15.6 mg/dL to -1.6 mg/dL) (Figure 41).[40 41 48-50 52 54-56 58 59] Removal of one study resulted in loss of statistical significance (pooled between-group difference -6.9 mg/dL (95% CI -13.9 mg/dL to 0.1 mg/dL).[52] There was no obvious source of the observed heterogeneity on meta-regression. Another study reported no changes in lipid values between groups but did not provide quantitative results.[51]

**Figure 41. Mean difference in triglycerides comparing metformin to sulfonylureas**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 122.78 with 10 degrees of freedom (p = 0.0000)
I-squared statistic = 92%

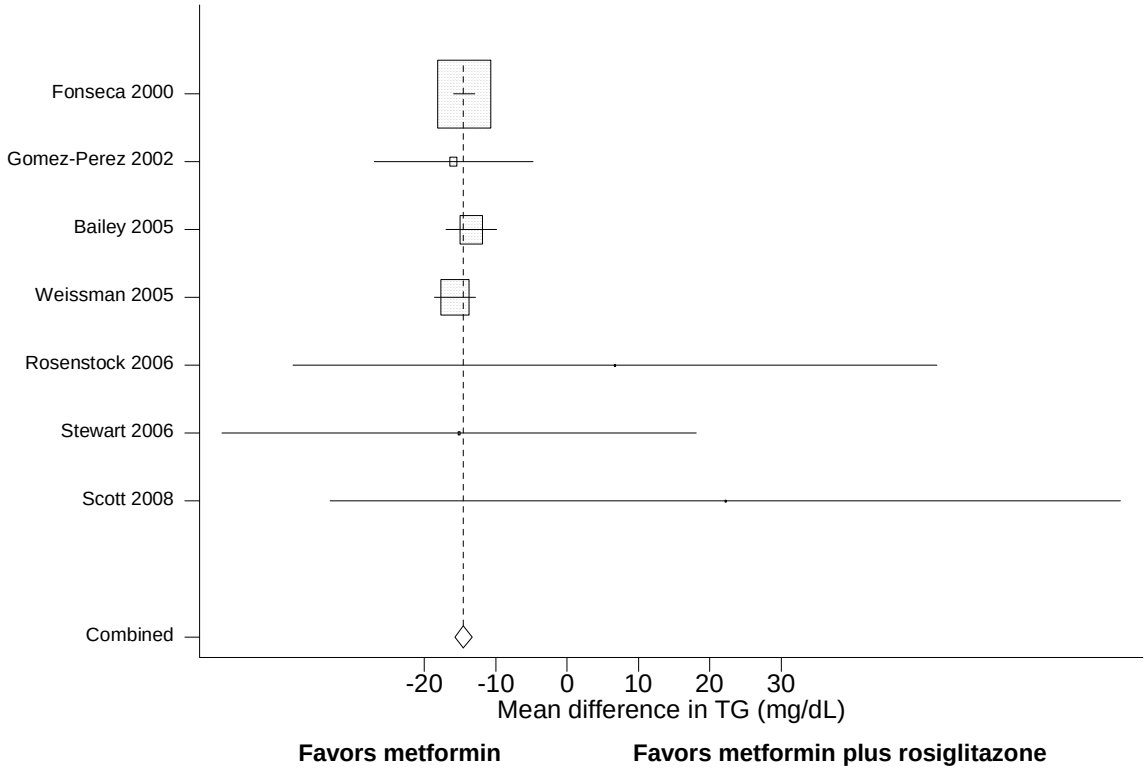
**Metformin versus sitagliptin.** A single RCT reported no between-group difference in triglycerides regardless of metformin dose (2000 mg per day or 1000 mg per day) over the course of 24 weeks.[63] The between-group difference in TG ranged from 1.0 mg/dL to 22 mg/dL at 24 weeks. Significance of the between-group difference was not reported, but the 95% CIs for percentage change in triglycerides from baseline were overlapping. The results of the 30-week continuation (total of 54 weeks of followup) of this study were consistent with these findings (range of between-group difference in triglycerides -9.0 mg/dL to 9.5 mg/dL).[63]

**Metformin versus meglitinides.** As seen in the previous evidence report,[17] in a single RCT, the between-group difference in triglycerides (-8.01 mg/dL) favored metformin over repaglinide, but this difference was not statistically significant.[67]

**Metformin versus a combination of metformin and rosiglitazone.** Seven RCTs compared metformin to the combination of metformin and rosiglitazone (pooled between-group difference

in TG -14.5 mg/dL, 95% CI -15.7 mg/dL to -13.3 mg/dL) (Figure 42).[39 71-74 76 129] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

**Figure 42. Mean difference in triglycerides comparing metformin to combination metformin and rosiglitazone**

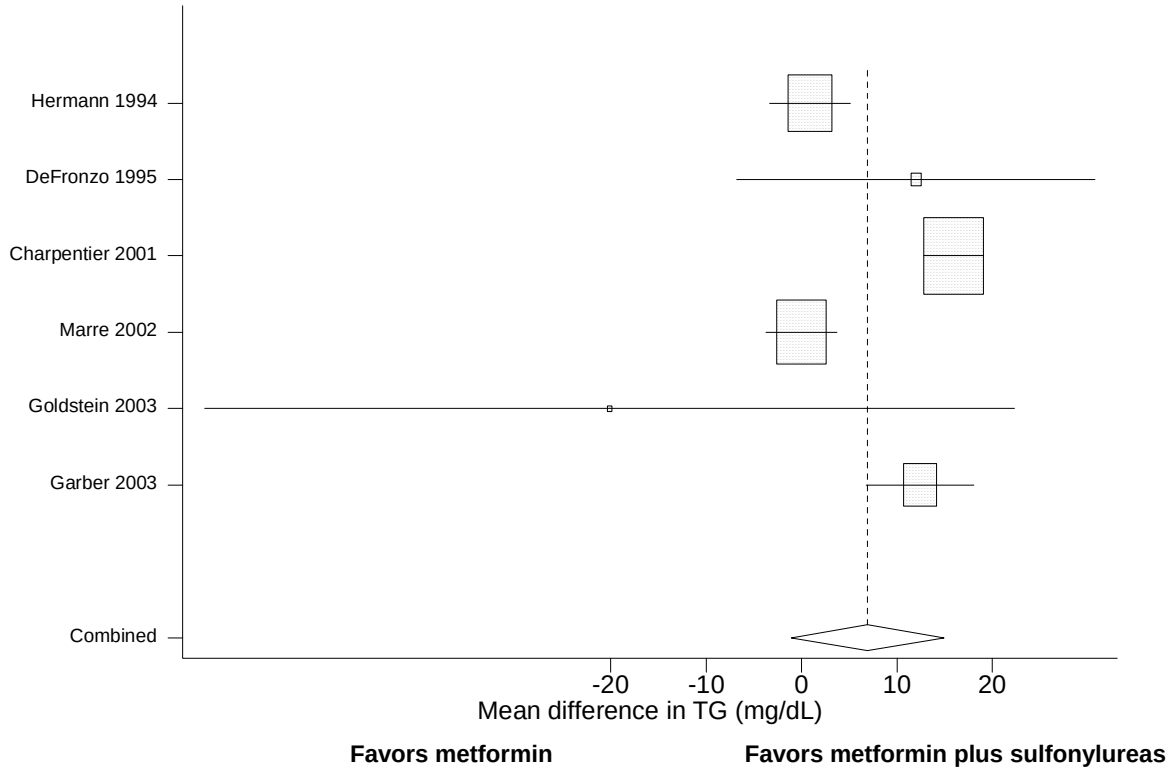



mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.66 with 6 degrees of freedom (p = 0.72)
I-squared statistic = 0%

**Metformin versus a combination of metformin and pioglitazone.** Two RCTs compared metformin to the combination of metformin and pioglitazone (range in between-group differences -6.1 mg/dL to 18.2 mg/dL).[70 75] The statistical significance of between-group differences were not reported.

**Metformin versus a combination of metformin and sulfonylureas.** As seen in the previous evidence report,[17] six RCTs found no between-group difference in TG (pooled between-group difference 6.9 mg/dL, 95% CI -1.1 mg/dL to 14.9 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 43).[49 50 52 56 58 59] Meta-regression did not reveal a source of the observed statistical heterogeneity. Removal of one study from the meta-analysis resulted in a significant pooled between-group difference of 8.9 mg/dL (95% CI 0.2 mg/dL to 17.7 mg/dL).[52] Two studies reported no changes in lipid values between groups but did not provide quantitative results.[51 77]

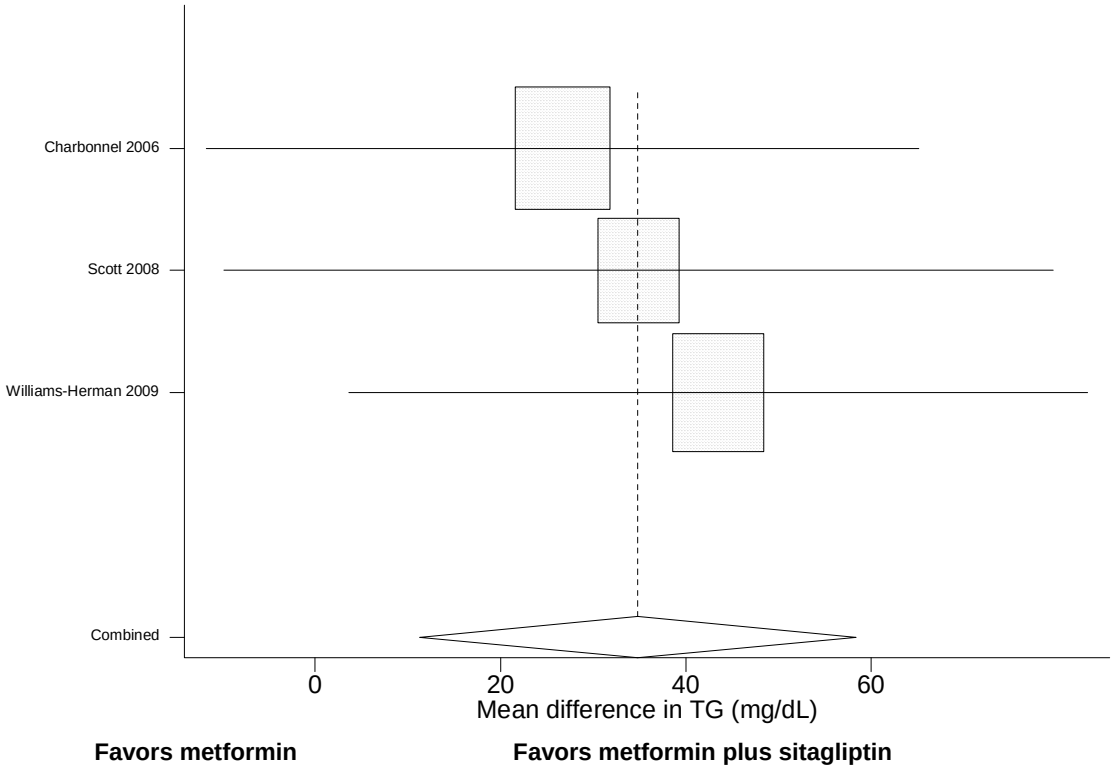
**Figure 43. Mean difference in triglycerides comparing metformin with combination metformin and sulfonylureas**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 57.40 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 91%

**Metformin versus a combination of metformin and sitagliptin.** Three RCTs compared metformin to the combination of metformin and sitagliptin. Compared to the combination which decreased TG, metformin increased TG with a pooled between-group difference of 34.8 mg/dL (95% CI 11.3 mg/dL to 58.3 mg/dL) (Figure 44).[63 71 80] There was no statistical evidence of heterogeneity, and no one study significantly influenced results. One study evaluated TG at 24 weeks and after a continuation (at 54 weeks).[63] We included the shorter duration results in the meta-analysis since the study duration was more homogenous with the rest of the studies and had less loss to followup.[63] The 54-week results were similar to those at 24 weeks.[63] Results suggested a dose-response relationship with the 2000 mg metformin and 100 mg sitagliptin arm decreasing TG (mean change from baseline -10.1% at 24 weeks ($p < 0.05$) and -7.1% at 54 weeks ($p < 0.05$)) compared to the 1000 mg metformin plus 100 mg sitagliptin arm (mean change in TG from baseline -3.7% at 24 weeks ($p > 0.05$) and -4.6% at 54 weeks ($p > 0.05$)).[63]

**Figure 44. Mean difference in triglycerides comparing metformin with combination metformin and sitagliptin**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.35 with 2 degrees of freedom (p = 0.84)
I-squared statistic = 0%

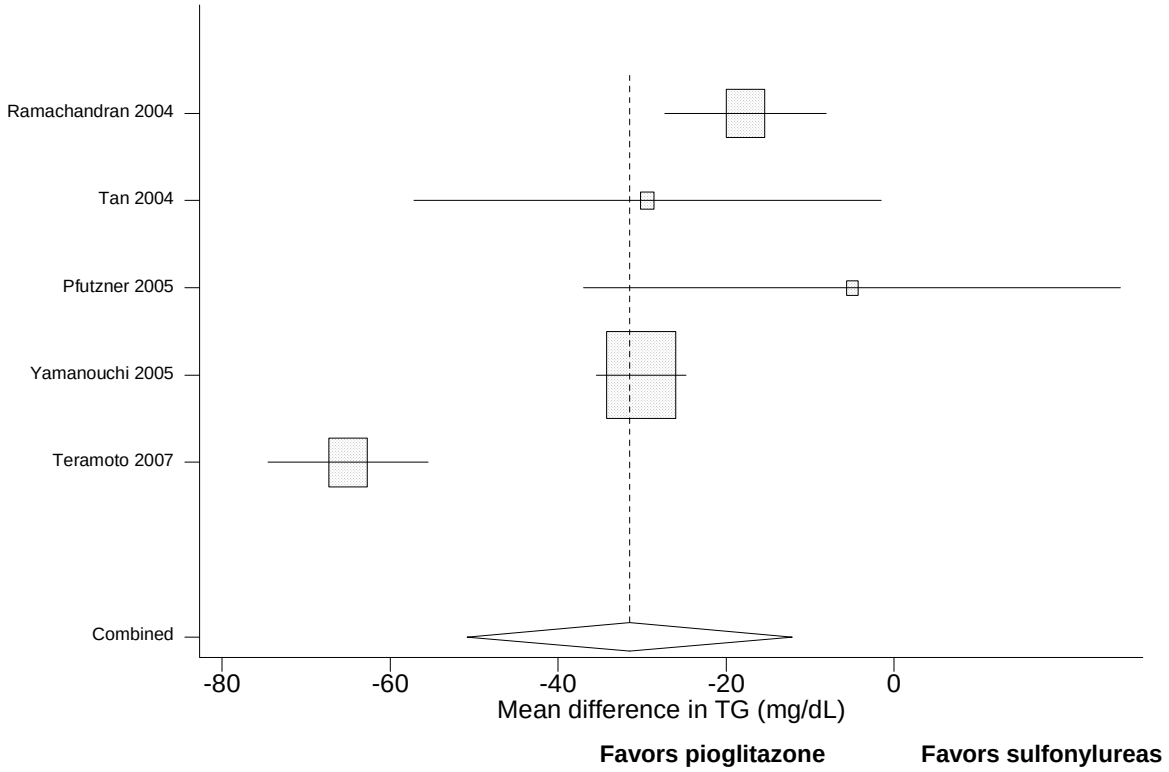
**Metformin versus a combination of metformin and meglitinides.** A single 24-week RCT directly compared the combination of metformin and nateglinide at two different doses (60 mg and 120 mg) to the combination of metformin and placebo and showed a small reduction in triglycerides in the combination arms compared to the monotherapy arm (range in between-group differences in triglycerides -17.8 mg/dL to 8.9 mg/dL). This difference was statistically significant ($p < 0.05$) for the higher-dose nateglinide (120 mg) arm.[81]

**Rosiglitazone versus pioglitazone.** As seen in the previous report,[17] two RCTs with similarly-dosed pioglitazone and rosiglitazone favored pioglitazone (range in between-group difference in triglycerides -58 mg/dL to -28 mg/dL).[82 83] Due to these differences, pioglitazone and rosiglitazone are not combined for comparisons including these thiazolidinediones for the TG section.

**Rosiglitazone versus sulfonylureas.** In one RCT, rosiglitazone (8 mg/day) and a sulfonylurea both decreased TG at 52 weeks (mean between-group difference 11 mg/dL for rosiglitazone relative to sulfonylurea) which was reported to be non-significant.[123] Another RCT found that at 4 mg/day, rosiglitazone decreased TG relative to a sulfonylurea (mean between-group difference -7 mg/dL), but at 8 mg/day rosiglitazone increased TG relative to a sulfonylurea (mean between-group difference 15 mg/dL) at 52 weeks; statistical significance was not reported.[84]

**Pioglitazone versus sulfonylureas.** Five RCTs favored pioglitazone over a sulfonylurea (pooled between-group difference -31.5 mg/dL (95% CI -50.8 mg/dL to -12.1 mg/dL) (Figure 45).[33 40 41 89 90] While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone. When one study was removed from the meta-analysis, the point estimate did not change much (-30.6 mg/dL), but the statistical inference changed with the 95% CI just including 0 (95% CI -62.1 mg/dL to 0.8 mg/dL).[40] This study had a higher dose of pioglitazone and a lower dose of the sulfonylurea.[40]

**Figure 45. Mean difference in triglycerides comparing pioglitazone with sulfonylureas**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 57.25 with 4 degrees of freedom (p = 0.0000)
I-squared statistic = 93%

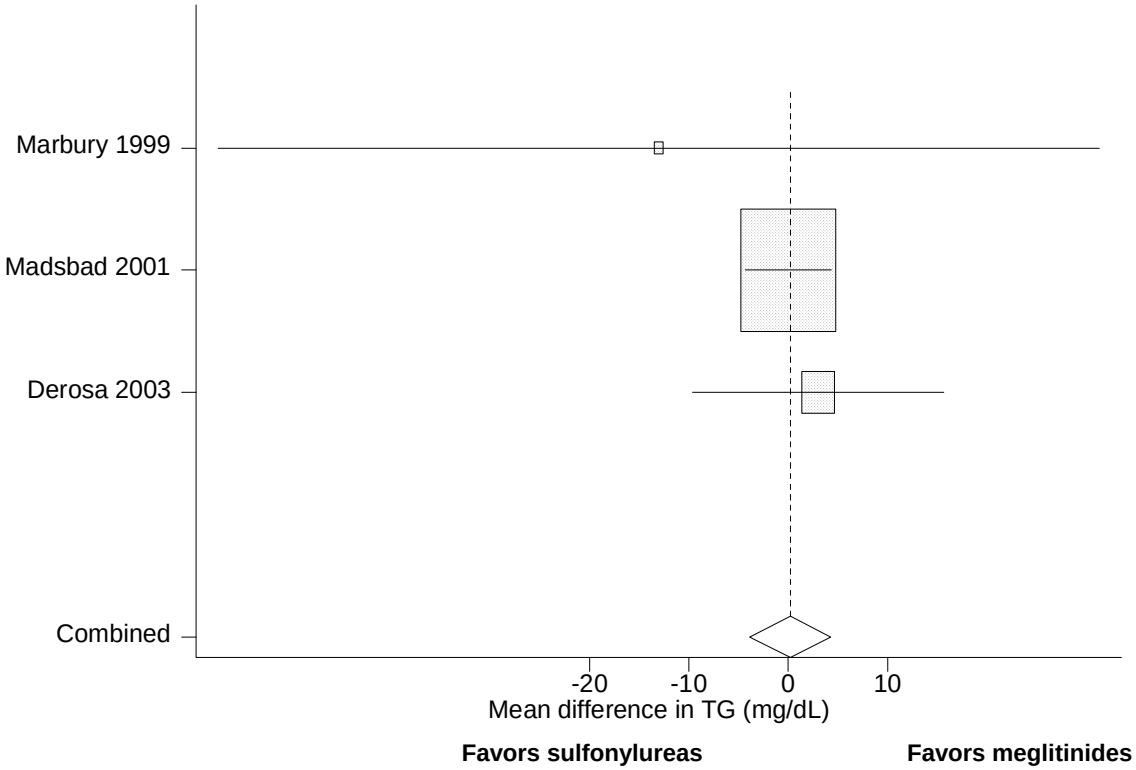
**Rosiglitazone versus meglitinides.** As seen in the previous evidence report,[17] one RCT found that compared to repaglinide, rosiglitazone caused a greater absolute increase in TG (between-group difference 23 mg/dL), but statistical significance was not reported.[92]

**Pioglitazone versus meglitinides**. As seen in the previous evidence report, one RCT found that compared to repaglinide, pioglitazone caused a greater absolute reduction in TG (between-group difference -96 mg/dL), but statistical significance was not reported.[93]

**Sulfonylureas versus sitagliptin.** One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[94] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg a day) increased TG (3.6% versus 7.0% respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[94]

**Sulfonylureas versus meglitinides.** As seen in the previous evidence report,[17] three RCTs compared sulfonylureas with repaglinide and found no difference in TG(pooled estimate of 0.2 mg/dL; 95% CI -3.9 mg/dL to 4.3 mg/dL) (Figure 46).[96 97 100] There was no statistical evidence of heterogeneity, and no one study markedly influenced the results. Two additional RCTs also reported no significant differences in TG between sulfonylureas and meglitinides; one study did not report a measure of variance (e.g., standard error) , and the other study did not provide quantitative results.[99 102]

**Figure 46. Mean difference in triglycerides comparing sulfonylureas with meglitinides**

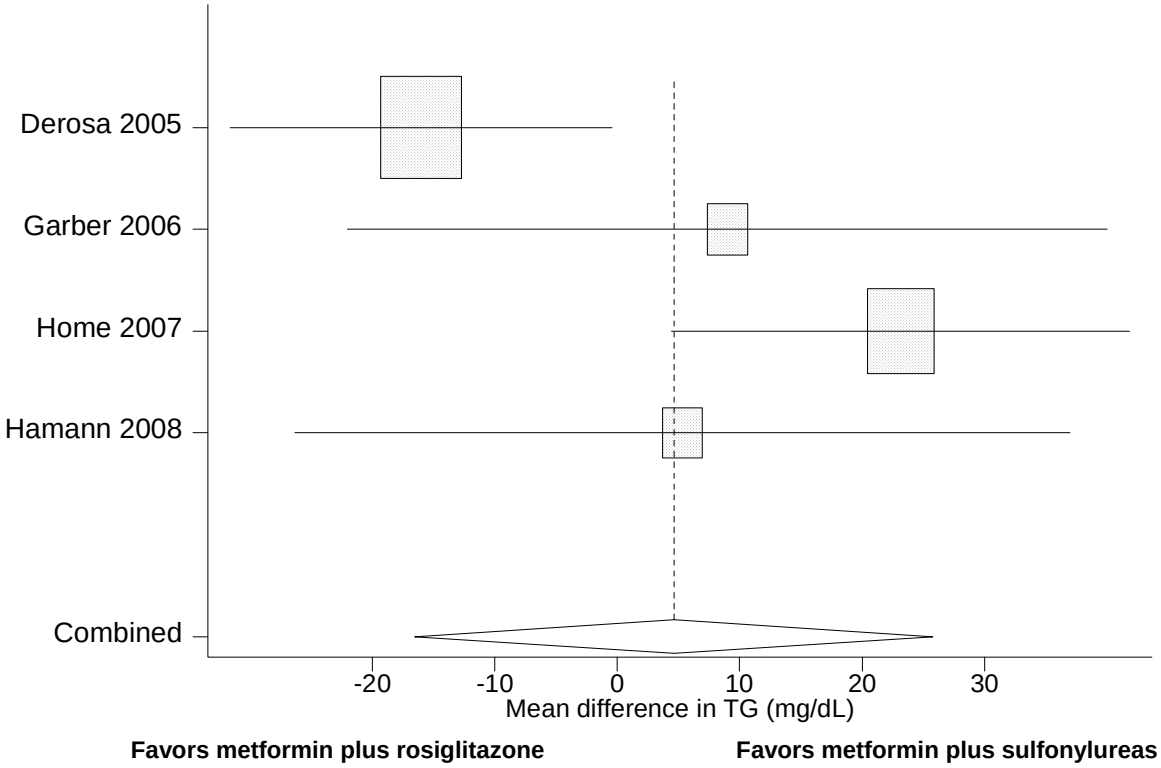



mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.54 with 2 degrees of freedom (p = 0.76)
I-squared statistic = 0%

**Combination of metformin and rosiglitazone versus combination of metformin and sulfonylureas.** Four RCTs compared the combination of metformin and rosiglitazone with the combination of metformin and a sulfonylurea and found a pooled between-group difference in TG of 4.6 mg/dL (95% CI -16.5 mg/dL to 25.8 mg/dL) (Figure 47).[103 104 108 133] Removal of one study[133] from the meta-analysis led to statistical significance of the between-group difference (16.5 mg/dL, 95% CI 2.2 mg/dL to 30.8 mg/dL); this study did not seem different from the other studies in terms of dosing, duration, or baseline TG and was left in the meta-analysis. No source of heterogeneity was found on meta-regression. We included results from the 18-month analysis of RECORD in the meta-analysis since this duration was more comparable to the other included studies.[104] At 5.5 years, the combination of metformin and rosiglitazone decreased TG more than

the combination of metformin and a sulfonylurea (between-group difference -10.7 mg/dL (p = 0.046).[14]

**Figure 47. Mean difference in triglycerides comparing combination metformin and rosiglitazone with combination metformin and sulfonylureas**




mg/dL = milligrams per deciliter; TG = triglycerides
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 10.28 with 3 degrees of freedom (p = 0.02)
I-squared statistic = 71%

**Combination of metformin and pioglitazone versus combination of metformin and sulfonylureas.** Two RCTs compared the combination of metformin and pioglitazone to metformin and a sulfonylurea.[106 131] In both studies, TG decreased in the metformin and pioglitazone arm. TG decreased in the metformin and sulfonylurea arm in one study[106] and increased slightly in another.[131] Between-group differences ranged from -10 mg/dL (p = 0.30) to -24.9 mg/dL (p = 0.045) for the combination of metformin and pioglitazone relative to the combination of metformin and a sulfonylurea.[106 131]

**Combination of metformin and thiazolidinediones versus combination of metformin and repaglinide.** One RCT lasting 26 weeks compared metformin plus rosiglitazone twice daily with the combination of metformin plus repaglinide twice daily and three times daily, showing no significant between-group difference in TG (7.4 mg/dL, p = 0.60).[110]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One double-blind small RCT lasting 18 weeks compared maximum dose metformin plus rosiglitazone to the combination of maximum dose metformin plus sitagliptin

showing a significant between-group difference in TG (mean difference in percentage change from baseline of 17.9%, 95% CI 6.7% to 29.2%).[71]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two moderately-sized double-blinded RCTs lasting 1 to 2 years directly compared the combination of metformin plus sulfonylurea with metformin plus nateglinide.[111 112] One study reported that TG decreased by approximately 10% in both groups.[112] The other study reported a decrease in TG each arm which was greater in the metformin plus sulfonylurea arm compared to the metformin plus nateglinide arm (between group difference -6 mg/dL).

**Combination of metformin and sulfonylureas versus combination of metformin and premixed insulin.** A single RCT lasting 4 months compared the combination of metformin and premixed insulin with the combination of metformin and a sulfonylurea, and TG decreased less in the metformin and premixed insulin group relative to the metformin plus sulfonylurea group (between-group difference 13.3 mg/dL), but this difference was not statistically significant.[119]

**Combination of metformin and pioglitazone versus combination of pioglitazone and sulfonylureas.** On a post-hoc analysis in a single RCT, addition of pioglitazone to a sulfonylurea decreased TG (-28.5 mg/dL, $p = 0.017$) relative to the addition of pioglitazone to metformin (-17.8 mg/dL, $p = 0.07$) at 6 months.[131]

**Combination of metformin and sulfonylurea versus combination of rosiglitazone and sulfonylureas.** One RCT lasting only 12 weeks reported less of a decrease in TG the metformin plus sulfonylurea compared to the rosiglitazone plus sulfonylurea arm (between-group difference 20.5 mg/dL, $p = 0.63$).[34] At 18 months, the RECORD trial reported a between-group difference in HDL of -0.4 mg/dL ($p > 0.05$)[104] and -1.6 mg/dL ($p < 0.0001$) at 5.5 years[14] comparing metformin plus sulfonylurea to rosiglitazone plus sulfonylurea.

**Combination of metformin and sulfonylurea versus combination of pioglitazone and sulfonylureas.** One RCT reported that median TG increased by 17.8 mg/dL ($p = 0.60$) in the metformin plus sulfonylurea group relative to the pioglitazone plus sulfonylurea group at 24 weeks.[116] Another 24-week study reported that mean TG increased by 31.1 mg/dL ($p < 0.05$) in the metformin plus sulfonylurea group relative to the pioglitazone plus sulfonylurea group.[131] A longer RCT (52 weeks) reported that TG decreased in both arms but less so in the metformin plus sulfonylurea arm (between-group difference -12.5 mg/dL, $p = 0.008$).[115]

## Publication Bias

Overall, we did not find strong evidence for publication bias in this literature. Across all analyses of intermediate outcomes, there were only two statistically significant comparisons ($p < 0.05$) by the less conservative Egger's test. Metformin versus rosiglitazone for the TG outcome was one of the comparisons ($p = 0.048$, number of studies (N) = 5). Based on the funnel plot, this comparison was missing one or two large studies with smaller between-group differences and missing a few smaller studies that would have increased effect size slightly. Having these additional studies would have been unlikely to change the conclusions much. The second comparison with significant publication bias was metformin versus metformin plus thiazolidinedione for HgbA1c outcome ($p = 0.004$, number of studies (N) = 10). Few to no small studies with smaller between-group differences were included based on the funnel plot. This may have led to a slight overestimation of effect; however, including these types of studies would likely not have changed the overall conclusion. For all other comparisons, the funnel plots appeared roughly symmetrical and the Begg's and Egger's tests were not significant. In most

cases, the number of studies in each comparison was small and was unlikely to have had high power to detect moderate publication bias.

## Gray Literature

After reviewing the data from the FDA and clinical trials registry, we found this data to be consistent with the published peer-reviewed literature included in this report on the intermediate outcomes.

## Applicability

The applicability of these studies to the question of comparable efficacy and effectiveness of the drugs will depend largely on the comparability of the drug interventions, duration of exposure to the drug, and how similar the trial populations are to the US population with type 2 diabetes. The studies had generally applicable populations, interventions, outcomes, and settings to adults with type 2 diabetes in the US with a few exceptions: less comorbidity, less older populations, less racial diversity, and shorter duration of drug exposure.

Study population differences are the most pronounced threat to applicability for this section. As mentioned under study population characteristics, study participants were mainly middle-aged, overweight or obese adults who had diabetes between 3 to 6 years duration. This is similar to the general US population of type 2 diabetes.[134] However, most of the studies excluded older people over the age of 75 or 80 years and excluded people with significant renal, hepatic, cardiovascular disease, and other significant comorbidity, making these studies less applicable to type 2 diabetic adults with comorbidity and older adults with diabetes. When race was reported, most subjects were Caucasian. These studies are therefore less applicable to people of different races, some of whom have greater diabetes disease burden than Caucasians (i.e., African Americans, Hispanic, and Pima Indians).[2 135 136]

While comparability of interventions could impact applicability, most studies used comparable dosing, frequency, and monitoring to usual care. One possible threat to applicability relates to the duration of drug exposure, especially for glycemic control. All but three studies lasted 2 years or less. Longer exposure to certain diabetes medications may begin to show differences in glycemic control later than most of these trials, especially since insulin sensitivity may allow insulin sensitizers to work longer as monotherapy than non-insulin sensitizers. In usual care, diabetes subjects are kept on medications for over 10 years and are on multiple medications which impacts adherence and side effects. If we were able to determine comparable effectiveness in glycemic control over a longer time frame, we might be able to reduce the number of medications a person takes for a longer period of time after diagnosis (assuming there were differences in glycemic control over longer time frames, and that these differences impacted longer term clinical outcomes).

We had few concerns regarding applicability of the trial settings to usual care. While many trials did not take place exclusively in the US, they did occur in similar settings. About half the trials occurred partly or exclusively in the US (n = 26), Italy (n = 12), and/or were multi-national (n = 22); the rest of the trials occurred in developed or newly industrialized countries. However, few of the trials (about 10%) reported on the setting for recruitment such as outpatient versus inpatient or primary care versus specialty care.

## Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options (see list of comparisons) in terms of the following long-term clinical outcomes?

- **All-cause mortality**
- **Cardiovascular mortality**
- **Cardiovascular and cerebrovascular disease morbidity (e.g., myocardial infarction and stroke)**
- **Retinopathy**
- **Nephropathy**
- **Neuropathy**

### Key Points and Evidence Grades

**All-cause mortality.**

- The majority of comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results.
- Metformin was associated with slightly lower risk of all-cause mortality compared with a sulfonylurea, with low strength of evidence because of inconsistent results and moderate risk of bias.
- We found insufficient evidence for several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, comparisons with a basal insulin preparation, comparisons with exenatide, and the majority of combination therapy comparisons.

**Cardiovascular mortality.**

- Only one RCT had cardiovascular disease mortality as its primary outcome.
- The majority of comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results.
- Metformin was associated with slightly lower risk of cardiovascular mortality compared with a sulfonylurea, with low strength of evidence because of high imprecision and moderate risk of bias.
- Risk of cardiovascular mortality was similar between metformin and thiazolidinediones, with low strength of evidence because of high imprecision and moderate risk of bias.
- We found insufficient evidence for several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons.

**Cardiovascular and cerebrovascular morbidity.**

- Only four studies reported cerebrovascular morbidity outcomes.

- The majority of comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results.
- Metformin was associated with slightly lower risk of cardiovascular morbidity compared with a sulfonylurea, with low strength of evidence because of high degree of imprecision.
- Risk of cardiovascular morbidity was similar between metformin and thiazolidinediones, with low strength of evidence because of high imprecision.
- We found insufficient evidence for several comparisons, including most sitagliptin comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons.

**Retinopathy.**

- We found insufficient evidence for the outcome of retinopathy.

**Nephropathy.**

- There was moderate strength of evidence favoring pioglitazone over metformin for its effects on renal function, over a treatment period of one year. Whether the statistically significant reductions in urinary albumin-to-creatinine ratio translate into lower rates of nephropathy, however, needs to be shown.
- We found low strength of evidence for three comparisons for the outcome of nephropathy: metformin versus sulfonylurea, thiazolidinedione versus sulfonylurea, and metformin plus thiazolidinedione versus metformin plus sulfonylurea. Evidence was graded as low because studies were at moderate to high risk for bias, provided imprecise results, or used surrogate outcomes that provide indirect evidence only.
- For most comparisons addressed in this review, there was insufficient evidence.

**Neuropathy.**

- For most comparisons addressed in this review, there was insufficient evidence.
- We found low strength of evidence for three comparisons for the outcome of neuropathy: metformin versus metformin plus a thiazolidinedione, metformin versus metformin plus sitagliptin, and metformin plus a thiazolidinedione versus metformin plus a sulfonylurea. Evidence was graded as low because studies were at high risk for bias, had low sample sizes, and had poorly defined outcomes. As a consequence, no conclusions regarding the comparative effects of oral diabetes drugs on neuropathy can be drawn.

See Table 5 for the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix G, Table 5.

**Table 5. Key findings and strength of the evidence comparing diabetes medications as monotherapy or combination therapy for long-term clinical outcomes**

| Comparison | All-cause mortality | CVD Mortality | CVD and Cerebrovascular Morbidity | Nephropathy, neuropathy |
|---|---|---|---|---|
| **MONOTHERAPY COMPARISONS** | | | | |
| **Metformin versus** | | | | |
| TZD | Low. Neither favored. | Low. Neither favored. | Low. Neither favored. | Moderate. Favors pioglitazone for nephropathy. |
| SU | Low. Favors Metformin | Low. Favors Metformin. | Low. Favors Metformin. | Low. Conclusion unclear for nephropathy. Insufficient for neuropathy. |
| Sitagliptin | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Meglitinide | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear. | Insufficient. |
| Metformin + TZD | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear for neuropathy. Insufficient for nephropathy. |
| Metformin + SU | Low. Neither favored. | Low. Conclusion unclear. | Low. Favors Metformin. | Insufficient. |
| Metformin + sitagliptin | Insufficient. | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear for neuropathy. Insufficient for nephropathy. |
| Metformin + meglitinide | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear. | Insufficient. |
| **TZD versus** | | | | |
| TZD | Insufficient. | Insufficient. | Insufficient. | |
| SU | Low. Neither favored. | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear for nephropathy. |
| Sitagliptin | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Meglitinide | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| **SU versus** | | | | |
| Sitagliptin | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Meglitinide | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear | Insufficient. |
| **Sitagliptin versus** | | | | |
| Meglitinide | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| **COMBINATION COMPARISONS** | | | | |
| **Metformin + another agent versus** | | | | |
| Metformin + TZD | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear for nephropathy and neuropathy. |
| Metformin + SU | Low. Conclusion unclear. | Low. Conclusion unclear. | Low. Conclusion unclear. | Insufficient. |
| Metformin + meglitinide | Low. Conclusion unclear. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + sitagliptin | Low. Conclusion unclear. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + exenatide | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + basal insulin | Insufficient. | Insufficient. | Low. Conclusion unclear. | Insufficient. |
| Metformin + premixed insulin | Low. Conclusion unclear. | Low. Conclusion unclear. | Insufficient. | Insufficient. |

**Table 5. Key findings and strength of the evidence comparing diabetes medications as monotherapy or combination therapy for long-term clinical outcomes (continued)**

| Comparison | All-cause mortality | CVD Mortality | CVD and Cerebrovascular Morbidity | Nephropathy, neuropathy |
|---|---|---|---|---|
| **TZD + another agent versus** | | | | |
| Metformin + TZD | Insufficient. | Insufficient. | Low. Conclusion unclear. | Insufficient. |
| Metformin + SU | Low. Conclusion unclear. | Insufficient. | Low. Conclusion unclear. | Insufficient. |
| Metformin + meglitinide | Low. Conclusion unclear. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + sitagliptin | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + exenatide | Insufficient. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + basal insulin | Low. Conclusion unclear. | Insufficient. | Insufficient. | Insufficient. |
| Metformin + premixed insulin | Low. Conclusion unclear. | Insufficient. | Low. Conclusion unclear. | Insufficient. |

CVD = cardiovascular disease; SU = sulfonylurea; TZD = thiazolidinedione

Data presented here are strength of the evidence and main conclusion. The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

## Study Design and Population Characteristics

Fifty-three studies reported on the comparative effectiveness of oral diabetes medications on long-term outcomes (Appendix G, Tables 6 and 7). Twenty studies occurred in North America, 15 in multinational Europe, and several were multi-continent studies.

Forty-one studies were RCTs, with the study duration ranging from 12-weeks to 6 years. Only 13 of the RCTs lasted 1 year or more in duration. Only one RCT had a long-term outcome as the primary outcome;[14] the others had intermediate outcomes (see Key Question 1), but then also reported the incidence of one or more long-term outcomes (e.g., mortality), usually as an adverse event. One study used a cross-over design.[137] Twenty-nine RCTs reported support from a pharmaceutical company.

There were 12 cohort studies with duration of followup ranging from 6 months to 8 years, which analyzed data from nine unique cohorts, with four studies coming from the Saskatchewan Health databases.[138-141] Two observational studies reported support from a pharmaceutical company.

Mean age of participants ranged from 48.3 to 74.8 years, with the majority of studies reporting a mean age in the mid-50's. Participants were about 50% female and the majority Caucasian race. Two RCTs reported greater than 25% African American participants,[71 110] and one study that occurred in Mexico reported almost 80% Hispanic participants.[74] Most trials excluded people with co-morbid illnesses, which included renal, cardiovascular, and liver disease.

## The Evidence about All-cause Mortality (Appendix G, Table 8)

There were 36 studies that reported number of deaths by treatment group. Twenty-seven studies were RCTs, and nine studies were observational studies based on data from five unique cohorts. Most of the RCTs were of short duration and had no deaths in at least one of the treatment arms. Twenty-five of the 27 RCTs had support from a pharmaceutical company.

**Metformin versus thiazolidinediones.** Four RCTs compared the effects of metformin versus a thiazolidinedione. A Diabetes Outcome Progression Trial (ADOPT) trial was the largest of these trials and had the longest duration. This study, which recruited participants from 488 different centers in the United States (US), Canada, and Europe, randomized participants to treatments with rosiglitazone, metformin, or glyburide for a median duration of 4.0 years.[30] There were 1454 participants in the metformin arm and 1456 in the rosiglitazone arm, and there was a similar number of deaths in each of these two arms with 31 (2.1%) and 34 (2.3%) deaths during followup respectively. Another trial comparing metformin and rosiglitazone of 32-weeks duration reported no deaths in either arm.[39] The other two trials compared metformin and pioglitazone.[42 43] The larger of these trials which lasted 52 weeks also had a similar number of deaths in each arm: two in the metformin arm and three in the pioglitazone arm.[42]

**Metformin versus sulfonylureas.** Five RCTs and eight observational studies, reporting findings from four unique cohorts, evaluated the effect of metformin versus a sulfonylurea (Table 6).

*Metformin versus sulfonylureas: randomized controlled trials.* Of the RCTs, four trials lasted less than 30 weeks. Described above, the ADOPT trial was the largest and with the longest duration; 1,454 participants were randomized to metformin and 1,441 to glyburide. There were equal number of deaths from any cause, with 31 deaths in each arm.[30] Three smaller trials were

of short duration (16 to 18 weeks) and reported no deaths in either treatment arm[47 49 50] and one 29-week study had a single death in the metformin arm and no deaths in the sulfonylurea arm.[58]

**Table 6. Studies comparing metformin versus sulfonylurea for all-cause mortality**

| Author, year | Number of deaths: metformin *versus* sulfonylurea | Measure of association | Measurement of association (95% CI) (sulfonylurea as reference group) |
|---|---|---|---|
| **Randomized controlled trials** | | | |
| Chien, 2007[47] | 0/17 versus 0/17 | NR | NR |
| Kahn, 2006[30] | 31/1454 versus 31/1441 | NR | NR |
| Garber, 2003[49] | 0/164 versus 0/151 | NR | NR |
| Goldstein, 2003[50] | 0/76 versus 0/84 | NR | NR |
| DeFronzo, 1995[58] | 1/210 versus 0/209 | NR | NR |
| **Cohort studies** | | | |
| Kahler, 2007[142] | 82/2988 versus 1005/19053 | Adjusted OR | 0.87 (0.68 to 1.10) |
| Simpson, 2006[138] | 39.6/1000 person-years versus 61.4/1000 person-years | Unadjusted OR* | 0.55 (0.47 to 0.63) |
| Johnson, 2002[140] | 159/1150 versus 750/3033 | Adjusted OR | 0.60 (0.49 to 0.74) |
| Eurich, 2005[141] | 69/208 versus 404/773 | Adjusted HR | 0.70 (0.54 to 0.91) |
| Evans, 2006[143] | 4.7% versus 17.9% | NR | NR |
| Gulliford, 2004[144] | 144/2232 versus 1030/6620 | Unadjusted OR* | 0.35 (0.29 to 0.42) |
| Fisman, 2001[145] | 25/79 versus 324/953 | Unadjusted OR* | 0.90 (0.56 to 1.47) |
| Fisman, 1999[146] | 20/78 versus 234/1041 | NR | NR |

* Calculated for this report from values published in study
CI = confidence interval; HR = hazard ratio; NR= not reported; OR = odds ratio

*Metformin versus sulfonylureas: observational studies.* Three observational studies[138 140 141] reported all-cause mortality from the cohort based on the Saskatchewan Health registry, which maintains health records for people in the province with prescription drug benefits, and compared metformin versus a sulfonylurea as monotherapy. One study reported an adjusted odds ratio (OR) of all-cause mortality of 0.60 (95% CI 0.49 to 0.74) for those on metformin compared to sulfonylurea monotherapy, adjusted for age, sex, chronic disease score, and nitrate use.[140] Similar results were found in another study and found that higher doses of sulfonylurea were associated with even higher risk of death.[138]

Another study from this cohort examined people with incident heart failure who were then initiated on either sulfonylurea or metformin monotherapy with a mean followup time of 2.5 years.[141] This study reported a higher number of deaths among those on an sulfonylurea alone. In the sulfonylurea group there were 404 deaths out of 773 people (52%) compared to 69 deaths out of 208 people in the metformin group (33%). Adjusted multivariate analyses confirmed these findings, with a lower hazard ratio (HR) of death among those on metformin of 0.70 (95% CI 0.54 to 0.91) compared to those on sulfonylurea monotherapy, after adjusting for age, sex, chronic disease score, medications, and number of physician visits before diagnosis of heart failure.

A Scottish cohort study that followed people receiving care through the United Kingdom (UK) National Health Service in Tayside, Scotland for about 8 years also reported a higher risk of overall mortality among those on sulfonylurea compared with metformin monotherapy, with an adjusted risk ratio of mortality of 1.43 (95% CI 1.15 to 1.77).[143] A cohort from the UK's General Practice Research Database (GPRD), also described a higher rate of death among users of sulfonylurea alone compared with metformin, with a crude mortality rate of 58.6 per 1000 person-years in the sulfonylurea group compared to a crude mortality rate of 25.5 per 1000

person-years in the metformin group with an unadjusted OR of 0.35 (95% CI 0.29 to 0.42) of mortality among those on metformin compared to sulfonylurea.[144] Finally, in a smaller Israeli cohort of people with known coronary artery disease, mortality was similar but slightly higher among those on glyburide compared with metformin.[145]

A large cohort, the Veterans' Health Administrations' Diabetes Epidemiology Cohort, which maintains records on all veterans with diabetes who have received care at the Department of Veterans Affairs (VA) centers since October 1996 showed a higher number of deaths among subjects taking sulfonylureas (1005 deaths of 19,053 people (5.3%)) compared to metformin only (82 deaths out of 2,988 people (2.7%)).[142] The adjusted OR for death for metformin versus sulfonylurea was 0.87 (95% CI 0.68 to 1.10), after adjusting for propensity score plus age, diabetes duration, HgbA1c, creatinine, number of physician visits related to diabetes, and use of medications for dyslipidemia and hypertension.[142]

**Metformin versus meglitinides.** Only one 24-week trial assessed the mortality of participants on metformin compared to a meglitinide and reported 1 death in the metformin arm and no deaths in the nateglinide arm.[65]

**Metformin versus a combination of metformin and thiazolidinediones.** Four RCTs of relatively short duration, ranging from 24 to 32 weeks, and 1 article describing post-hoc pooled data from two different RCTs lasting 6 months each, compared the effects of metformin as monotherapy versus a combination of metformin plus rosiglitazone. Overall, there were very few deaths in these studies. In one RCT, there were no deaths in either arm.[39] For three other RCTs, each reported one death in the combination therapy arm and no deaths in the metformin monotherapy arm.[72 73 76] One death was due to sudden death, one was due to an acute myocardial infarction, and one death was due to unknown causes. In the article that describes data from two RCTs in a post-hoc fashion, there was one death in the combination therapy arm due to fatal myocardial infarction and no deaths in the metformin monotherapy arm.[147]

**Metformin versus a combination of metformin and sulfonylureas.** Four RCTs and four unique cohort studies (published in five articles) assessed the effect of metformin monotherapy versus a combination of metformin plus a sulfonylurea (Table 7). All of these studies had also examined the effect of metformin versus a sulfonylurea, each as monotherapy, and are referred to above. All four RCTs were of short duration, ranging from 16 to 29 weeks. Again, there were few deaths in any of these trials. Two trials reported no deaths[47 50] and one study reported two deaths in the combination arm and no deaths in the metformin monotherapy arm.[49] Another study reported one death in the metformin as monotherapy arm and no deaths in the combination therapy arm.[58]

The Veterans' Health Administrations' Diabetes Epidemiology Cohort and the UK's GPRD cohorts found similar numbers of deaths between the metformin monotherapy group and the combination treatment groups, with only slightly higher rates of death among the combination therapy group. In the VA cohort, which followed people for about 2 years, 3.4% of those in the combination treatment arm died compared to 2.7% in the metformin treatment arm, with an unadjusted OR of death of metformin compared to combination therapy of 0.81 (95% CI 0.63 to 1.02).[142] In the UK GPRD cohort, which followed people for about 6 years, 5.8% of people in the combination treatment groups (reported as those who were treated with metformin first then sulfonylurea combined with those treated with sulfonylurea first then metformin) died compared to 4.6% in the metformin monotherapy group, with an unadjusted OR of mortality of 0.79 (95% CI 0.63 to 1.00) for those on metformin alone compared to those on combination therapy.[144]

**Table 7. Studies comparing metformin with combination of metformin and sulfonylurea for all-cause mortality**

| Author, year | Number of deaths: metformin versus combination of metformin and sulfonylurea | Measure of association | Measurement of association (95% CI) (combination therapy as reference group) |
|---|---|---|---|
| **Randomized controlled trials** | | | |
| Chien, 2007[47] | 0/14 versus 0/42 | NR | NR |
| Garber, 2003[49] | 0/164 versus 2/171 | NR | NR |
| Goldstein, 2003[50] | 0/76 versus 0/87 | NR | NR |
| DeFronzo, 1995[58] | 1/210 versus 0/213 | NR | NR |
| **Cohort studies** | | | |
| Kahler, 2007[142] | 82/2988 versus 468/13820 | Unadjusted OR* | 0.81 (0.63 to 1.02) |
| Gulliford, 2004[144] | 144/3099 versus 159/2735 | Unadjusted OR* | 0.79 (0.63 to 1.00) |
| Johnson, 2002[140] | 159/1150 versus 635/4683 | NR | NR |
| Eurich, 2005[141] | 69/208 versus 263/852 | NR | NR |
| Fisman, 2001[145] | 25/79 versus 111/253 | Unadjusted OR* | 0.59 (0.35 to 1.01) |
| Fisman, 1999[146] | 20/78 versus 84/266 | NR | NR |

* Calculated for this report from values published in study
CI = confidence interval; NR= not reported; OR = odds ratio

Data from the Saskatchewan Health database also showed similar results with no clear difference in mortality rates for metformin as monotherapy compared with metformin plus a sulfonylurea (13.8% versus 13.6%, respectively).[140] Even among the subgroup of people with heart failure, there was a similar rate of death between these 2 treatment groups, 33% for those on metformin alone and 31% for those on the metformin plus sulfonylurea combination therapy.[141]

Unlike the cohorts described above, the Israeli cohort included only people with known heart disease. There was a higher rate of death among those people who were on metformin plus sulfonylurea combination therapy compared with metformin alone, with a mortality rate of 43.9% for those on combination therapy compared to a mortality rate of 31.6% for those on metformin alone, with an unadjusted OR of 0.59 (95% CI 0.35 to 1.01) of mortality for those in metformin compared to combination therapy, over a mean period of 7.7 years.[145]

**Metformin versus a combination of metformin and sitagliptin.** Only one RCT looked at the effect of metformin as monotherapy versus metformin combined with sitagliptin. This was a multinational study of 190 participants over an approximately 30-week period. In this study, there was one death due to a myocardial infarction in the metformin group and no deaths in the combination treatment group.[79]

**Metformin versus a combination of metformin and meglitinides.** Only one RCT looked at the comparison of effects between metformin as monotherapy and metformin combined with a meglitinide agent. This study had one death due to heart disease in the metformin arm and no deaths in the combination arm over a 24-week period.[65]

**Thiazolidinediones versus sulfonylureas.** Four RCTs compared the effect of a thiazolidinedione and a sulfonylurea. The largest and longest duration of these trials was the ADOPT trial which reported a similar number of deaths in the rosiglitazone arm compared to the glyburide arm (2.3% versus 2.2%, respectively).[30] A smaller trial lasting 56 weeks, reported two deaths in the glyburide arm and no deaths in the pioglitazone arm.[85] The other trial reported no deaths in either the thiazolidinedione or sulfonylurea arms.[84]

**Sulfonylureas versus meglitinides.** One RCT compared the effects of a sulfonylurea with a meglitinide. This 1-year US study reported three deaths among the 362 participants randomized to the repaglinide group and one death among the 182 randomized to glyburide.[100]

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** Two RCTs[103 105] directly compared the effect of the combination of metformin plus a thiazolidinedione with the combination of metformin plus a sulfonylurea. One multinational study recruited about 600 participants and randomized them to treatment with metformin plus a sulfonylurea (either glibenclamide or gliclazide) or metformin plus rosiglitazone. This study reported two deaths in each arm over the 52-week treatment period.[103] The second trial was also multinational and randomized participants to treatment with metformin combined with glyburide or metformin with rosiglitazone. This trial had one death due to a fatal myocardial infarction in the metformin plus rosiglitazone combination arm and no deaths in the metformin plus sulfonylurea combination arm.[105]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One US RCT compared the effect of the combination of metformin with a thiazolidinedione (rosiglitazone) versus the combination of metformin with a meglitinide (repaglinide). This study of 26 weeks reported one death in the metformin plus meglitinide combination arm and no deaths in the metformin plus thiazolidinedione combination arm.[110]

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** One multinational RCT compared the effect of the combination of metformin plus a sulfonylurea (glipizide) with the combination of metformin plus sitagliptin. This study, which lasted 52 weeks, randomized 1172 participants to the 2 treatment arms and reported two deaths in the metformin plus sulfonylurea combination arm and one death in the metformin plus sitagliptin combination arm.[113]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** Two US RCTs[112 125] and one Italian cohort study[148] compared the effect of the combination of metformin with a sulfonylurea with the combination of metformin with a meglitinide (nateglinide).

The larger of the RCTs compared metformin plus glyburide versus metformin plus nateglinide over 2 years and reported one death in each arm.[112] Another study of similar duration looked at the effect of the same combinations of medications among a subpopulation of its RCT study population (66 participants that were 65 years of age or older) and reported a single death in the metformin plus sulfonylurea combination arm and no deaths in the metformin plus nateglinide combination arm.[125]

The main purpose of the cohort study that looked at the effect of these combinations of medications was to assess the mortality of people on combinations of secretagogues and biguanides among people with and without ischemic heart disease. Among those with and without ischemic heart disease on a combination of metformin and any sulfonylurea, there were 35 deaths over 6344 person-months. Among those with and without heart disease who were on metformin and repaglinide, there was a slightly lower mortality rate: 5 deaths over 2013 person-months.[148]

**Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones.** One large multinational RCT, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial randomized about 4,450 participants to the following four treatments: combination of metformin plus rosiglitazone, combination of metformin plus sulfonylurea, combination of rosiglitazone plus sulfonylurea, and combination of metformin plus sulfonylurea. For analyses for the outcome of all-cause mortality, the two groups assigned to rosiglitazone were combined and compared to the combination of metformin and sulfonylurea. Over a mean of 5.5 years of treatment and

followup, there were a similar number of deaths in the two groups with 136 deaths out of 2220 in the rosiglitazone group and 157 deaths out of 2227 in the metformin plus sulfonylurea combination group with a HR of mortality of 0.86 (95% CI 0.68 to 1.08) for those on rosiglitazone compared to those not on rosiglitazone.[14]

**Combination of metformin and sulfonylureas versus combination of metformin and biphasic insulin.** Two multinational RCTs compared the effect of the combination of metformin plus a sulfonylurea with the combination of metformin plus a form of biphasic insulin (insulin aspart 70/30 in one study and insulin lispro 75/25 in the other). Both studies reported one death each in the metformin combined with biphasic insulin arms and no deaths in the metformin combined with sulfonylurea arms during the trial period.[119]

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** One RCT directly compared the effect of the combination of metformin plus a sulfonylurea with the combination of a thiazolidinedione plus a sulfonylurea. This study recruited 639 participants from European countries and Canada, who were already on a sulfonylurea, and randomized them to the addition of either metformin or pioglitazone with a mean treatment duration of 11 months. This study reported that there were two deaths in the metformin plus sulfonylurea combination arm and one death in the pioglitazone plus sulfonylurea combination arm.[115]

## The Evidence about Cardiovascular Mortality (Appendix G, Table 8)

Ten trials and four cohort studies contained twelve head-to-head comparisons of interest for the outcome of cardiovascular mortality.

**Metformin versus thiazolidinediones.** The ADOPT trial was a large double-blind RCT involving 4,360 patients followed for a median of 4 years, with patients randomly assigned to metformin, rosiglitazone, or glyburide. There were equal rates of cardiovascular mortality in the metformin and rosiglitazone arms, each with two fatal myocardial infarctions (0.1%).[30] A smaller 24-week RCT of metformin versus pioglitazone did not report any cardiovascular deaths in either arm.[43]

**Metformin versus sulfonylureas.** The ADOPT trial also compared metformin with glyburide, and reported slightly higher incidence of cardiovascular mortality in the glyburide arm versus the metformin arm, with two fatal myocardial infarctions in the metformin arm and three in the sulfonylurea arm (0.2% versus 0.1%), without report of a statistical test.[30]

In addition, four cohort studies compared metformin with a second generation sulfonylurea.[139 140 143 145] Two of these studies were from the Saskatchewan Health databases, a longitudinal cohort of the residents of this Canadian province. They identified over four thousand residents with type 2 diabetes between 1991 and 1999 and grouped them by their first dispensation of an oral diabetes medication. Metformin was associated with lower risk for cardiovascular mortality than any sulfonylurea (HR 0.64, 95% CI 0.49 to 0.84), after adjusting for age, sex, chronic disease score, and nitrate use.[140] This result was confirmed in another analysis in this same cohort after additional adjustment for a calculated propensity score to adjust for between-group differences (HR 0.76, 95% CI 0.58 to 1.00).[139] A different 5-year retrospective cohort study of 5,730 Scottish subjects also reported higher mortality from cardiovascular disease in the second-generation sulfonylurea group versus metformin group, after adjustment for potential confounders, including prior cardiovascular disease-related hospital admission (RR 1.70, 95% CI 1.18 to 2.45).[143]

In contrast, a prospective cohort study of 2,275 Israeli patients with type 2 diabetes and prior coronary artery disease showed slightly higher age-adjusted mortality from coronary artery disease in the metformin versus the glyburide groups (30 per 1000 person-years versus 24.5 per 1000 person-years, respectively).[145]

**Metformin versus meglitinides.** One 24-week RCT with 701 participants reported no cardiovascular deaths in the nateglinide arm and one death in the metformin arm.[65]

**Metformin versus a combination of metformin and thiazolidinediones.** Two large RCTs[73 76] and one study that reported the combined results of two smaller RCTs[147] compared metformin versus metformin with the addition of rosiglitazone. Bailey et al. reported no deaths from cardiovascular disease in the metformin arm. In the metformin plus rosiglitazone arm there was one sudden death in sleep, which may have been sudden cardiac death, and one death related to a myocardial infarction.[73] Fonseca et al. was a trial of 348 participants, with 119 randomized to metformin plus 4 mg per day of rosiglitazone, 113 to metformin plus 8 mg per day of rosiglitazone, and 116 to metformin alone. In this study there was one death due to myocardial infarction in the metformin plus 4 mg per day of rosiglitazone arm and none in the other arms.[76] The study that pooled the results of two RCTs reported one fatal myocardial infarction out of 126 participants in the metformin plus rosiglitazone arms and no events in the 121 participants in the metformin arms.[147] We pooled these three RCTs in a random effects model, which showed a trend toward decreased fatal myocardial infarction risk for metformin monotherapy compared with combination metformin plus rosiglitazone, but with very imprecise estimates (RR 0.47, 95% CI 0.07 to 2.95) (Figure 48).

**Metformin versus a combination of metformin and sulfonylureas.** Two of the cohort studies described above (under comparison of metformin versus sulfonylurea) showed decreased cardiovascular mortality in the group taking metformin alone as compared to subjects taking the combination of metformin and sulfonylurea.[143 145]

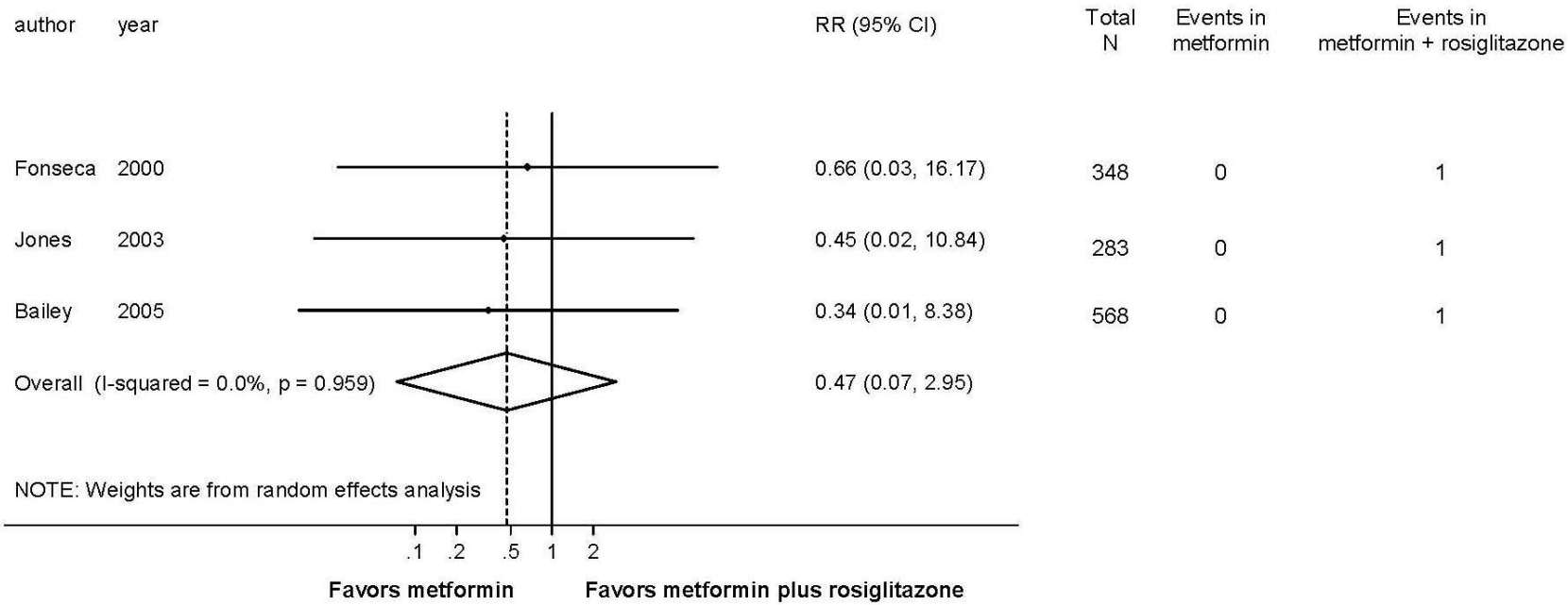
Compared with those on metformin monotherapy, one cohort study reported a risk ratio of 1.94 (95% CI 1.25 to 3.01) in subjects who were started on metformin, with sulfonylurea subsequently added-on and 2.50 (95% CI 1.69 to 3.71) in those started on sulfonylurea with metformin subsequently added-on, but the numbers in these groups were small.[143] Risk ratios were adjusted multiple confounding variables, including sociodemographics, cardiovascular risk factors, prior cardiovascular disease admission and use of cardiovascular medications, making confounding by indication less likely.

A second cohort study examined 2,275 Israeli patients with type 2 diabetes and known prior coronary artery disease. Among subjects on metformin alone, the age-adjusted mortality rate for ischemic heart disease per 1000 person-years was slightly lower compared to the combination of metformin plus sulfonylurea group (30.0 versus 31.2), but these estimates were not adjusted for cardiovascular disease severity.[145]

**Metformin versus a combination of metformin and sitagliptin.** We identified one 30-week RCT in 190 participants on metformin randomized to the addition of sitagliptin or placebo, which reported one fatal myocardial infarction in the metformin plus placebo arm and no cardiovascular deaths in the metformin plus sitagliptin arm.[79]

**Metformin versus a combination of metformin and meglitinides.** Horton et al. (described above under metformin versus meglitinides) also contained a metformin plus nateglinide arm, enabling an additional comparison with metformin alone.[65] In all arms, there was a single death attributed to cardiovascular disease and it occurred in the metformin alone arm.

**Figure 48. Relative risk of fatal myocardial infarction comparing metformin with combination of metformin and rosiglitazone**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
CI = confidence interval; RR = relative risk

**Thiazolidinediones versus sulfonylureas.** The ADOPT trial also contained a comparison of rosiglitazone with glyburide. As described above, there were two myocardial infarctions in the rosiglitazone arm and three myocardial infarctions in the glyburide arm, but no statistical test of this difference.[30]

**Sulfonylureas versus meglitinides.** A 1-year RCT with 576 participants reported one cardiovascular death in the glyburide arm and one in the repaglinide arm.[100]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One 26-week RCT comparing metformin plus rosiglitazone versus metformin plus repaglinide reported one death likely attributable to sudden cardiac death in the metformin plus repaglinide arm.[110]

**Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones.** The RECORD study was an open-label non-inferiority multicenter RCT with 4,447 participants with type 2 diabetes taking either metformin or a sulfonylurea randomly assigned to one of three arms, metformin plus rosiglitazone, sulfonylurea plus rosiglitazone, or metformin plus sulfonylurea, with time to first cardiovascular hospitalization or death as its primary outcome.[14] For analyses of the primary endpoint at a mean of 5.5 years, they combined the two rosiglitazone arms (metformin or sulfonylurea plus rosiglitazone) and compared rosiglitazone with the active control of metformin plus sulfonylurea and showed non-inferiority for cardiovascular mortality (HR 0.84, 95% CI 0.59 to 1.18). Despite the study duration, these were lower than anticipated event rates.

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** One 52-week RCT compared metformin plus the sulfonylurea, glipizide, versus metformin plus sitagliptin.[113] There were two deaths from cardiovascular disease (one from sudden cardiac death and one from myocardial infarction) in the metformin plus glipizide arm and none in the metformin plus sitagliptin arm.

**Combination of metformin and sulfonylureas versus combination of metformin and premixed insulin.** In a 16-week open-label RCT, 341 participants with poorly controlled type 2 diabetes on metformin alone were randomly assigned to metformin plus glibenclamide or metformin plus twice daily insulin aspart 70/30, a premixed insulin analog containing 30% soluble, rapid-acting insulin aspart and 70% intermediate-acting protamine-bound aspart in each injection.[119] There was one death from myocardial infarction in the metformin plus premixed insulin arm and none in the metformin plus glibenclamide arm.

## The Evidence about Cardiovascular and Cerebrovascular Disease Morbidity (Appendix G, Table 8)

Fourteen trials and three cohort studies contained fourteen head-to-head comparisons of interest for the outcome of cardiovascular disease morbidity. We identified only four studies that reported the outcome of cerebrovascular disease morbidity.

**Metformin versus thiazolidinediones.** Three RCTs[30 39 45] and one retrospective cohort study[149] compared metformin versus rosiglitazone and one small 24-week RCT compared metformin versus pioglitazone.[43] Among the RCTs, the ADOPT trial was the largest (total N = 4360 for three study arms) and had the longest duration of treatment (median 4 years). There were minimal differences between the metformin and rosiglitazone arms for non-fatal myocardial infarction and stroke (1.4% versus 1.7% for non-fatal myocardial infarction, 1.3% versus 1.1% for stroke, respectively), without a statistical test.[30]

McAfee et al. was a large retrospective cohort study of over 26,000 from a large insurance company, classified by type of diabetes medication at initiation, with maximum duration of 36-months. There was no difference in the composite outcome of hospitalization for myocardial infarction or coronary revascularization between subjects initiated with metformin compared with rosiglitazone.[149]

**Metformin versus sulfonylureas.** Two RCTs and two cohort studies reported outcomes for metformin versus a second-generation sulfonylurea.[30 56] The ADOPT trial, described above, also contained a glyburide arm. Incidences of non-fatal myocardial infarction and stroke in the glyburide arm were 1.0% and 1.2%, respectively, showing minimal difference compared with the metformin arm reported above.[30]

Both cohort studies described higher risk of cardiovascular disease morbidity for sulfonylurea versus metformin. In the retrospective cohort study from Saskachewan health databases, metformin was associated with a decreased risk of non-fatal cardiovascular hospitalization as compared with unspecified sulfonylurea (HR 0.78, 95% CI 0.63 to 0.97) in the fully adjusted model.[139] McAfee et al. reported a 23% risk reduction of composite outcome of acute myocardial infarction or coronary revascularization for metformin as compared with sulfonylurea monotherapy (HR 0.77, 95% CI 0.62 to 0.96), in a propensity score matched cohort study.[149]

**Metformin versus meglitinides.** Only one 24-week RCT with 701 participants compared metformin with nateglinide and reported low rates of study-related electrocardiogram abnormalities in both arms.[65]

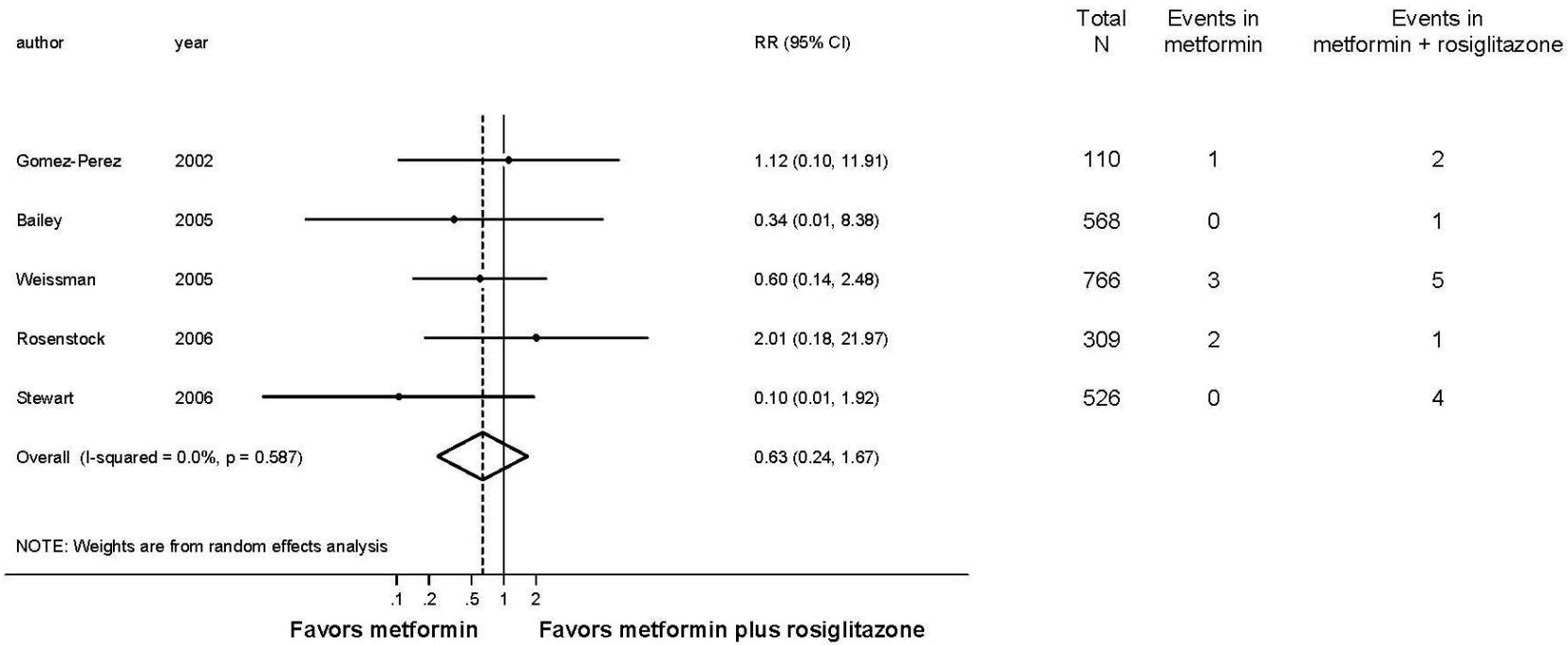
**Metformin versus a combination of metformin and thiazolidinediones.** Six RCTs[39 71-74 129] and one cohort study[149] compared metformin with a combination of metformin plus rosiglitazone and reported the incidence of ischemic cardiac events. The six RCTs were similar in study duration (range 18 to 32 weeks) and used doses of rosiglitazone ranging from 2 mg to 8 mg. Scott et al. reported no cardiovascular events in either the metformin or metformin plus rosiglitazone arms.[71] The five RCTs that had at least one event in each arm were pooled in a meta-analysis.[39 72-74 129] In a random effects model, the pooled relative risk of ischemic cardiac events was 0.63 (95% CI 0.24 to 1.67) for metformin compared with metformin plus thiazolidinedione, which was not statistically significant (Figure 49).

McAfee et al., a large retrospective cohort study, showed minimal difference in incidence rate ratios (IRR) for the composite outcome of hospitalization for myocardial infarction or coronary revascularization between subjects initiated with metformin (IRR 13.90, 95% CI 11.80 to 16.27) compared with metformin plus rosiglitazone (IRR 14.26, 95% CI 9.37 to 20.86).[149]

**Metformin versus a combination of metformin and sulfonylureas.** One RCT[56] and one cohort study[149] assessed this comparison for cardiovascular morbidity. In a 6-month RCT, Hermann et al. reported a 5% versus 14% rate of unspecified cardiovascular adverse events in the metformin versus combination metformin plus sulfonylurea arms, respectively.[56] In a 36-month retrospective cohort study using claims data, the adjusted incidence rates for the composite outcome of hospitalization for myocardial infarction or coronary revascularization between subjects was lower in subjects initiated on metformin compared with metformin plus sulfonylurea (adjusted incidence rate of 13.90 versus 19.44, respectively).[149]

**Metformin versus a combination of metformin and sitagliptin.** One 30-week RCT in 190 participants reported three cases (3.1%) of angina pectoris in the metformin plus sitagliptin arm and none in the metformin alone arm.[79] A shorter 18-week study also reported two coronary

**Figure 49. Relative risk of non-fatal ischemic heart disease comparing metformin with combination of metformin and rosiglitazone**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
CI = confidence interval; RR = relative risk

artery disease events in the metformin plus sitagliptin arm and none in the metformin alone arm.[71]

**Metformin versus a combination of metformin and meglitinides.** Horton et al. (described above under metformin versus meglitinides) also contained an arm of the combination of metformin plus nateglinide arm and reported two study-related electrocardiogram abnormalities in the combination arm and one in the metformin arm.[65]

**Thiazolidinediones versus sulfonylureas.** Two RCTs and one retrospective cohort study compared rosiglitazone with a sulfonylurea[30 123 149] and one RCT compared pioglitazone with a sulfonylurea.[85] The ADOPT trial (described under metformin versus thiazolidinedione) reported minimal differences between the rosiglitazone arms and sulfonylurea arms for non-fatal myocardial infarction and stroke (1.7% versus 1.0% for non-fatal myocardial infarction, 1.3% versus 1.2% for stroke, respectively).[30] A 52-week RCT with 351 participants reported a slightly higher incidence of "cardiac-related" adverse events in the rosiglitazone versus glyburide groups (15.4% versus 12.1%, respectively). These events included mitral insufficiency, tachycardia, myocardial infarction, and palpitations.[123] Another 56-week RCT with 502 participants randomly assigned participants to glyburide or pioglitazone.[85] There were fewer cardiovascular adverse events, defined as coronary artery disease, myocardial infarction, and chest pain, in the pioglitazone arm compared with the glyburide arm (1% versus 3%).[85] One 36-month retrospective cohort study reported a lower adjusted incidence rate for the composite outcome of hospitalization for myocardial infarction or coronary revascularization between subjects on rosiglitazone as compared with sulfonylurea (adjusted incidence rate of 15.71 versus 19.55).[149]

**Sulfonylureas versus meglitinides.** Two 1-year long RCTs compared glyburide with repaglinide.[99 100] One RCT with over 500 participants reported 5% cardiovascular adverse events in the repaglinide arm and 2% in the glyburide arm without a statistical test.[100] The other RCT had 242 participants and stated that cardiac events occurred with similar frequencies between treatment arms.[99]

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** One open-label RCT of 250 participants reported one acute myocardial infarction in the metformin plus pioglitazone arm versus no events on the metformin plus sulfonylurea arm.[109]

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** One 26-week RCT comparing metformin plus rosiglitazone versus metformin plus repaglinide reported one subject with ventricular fibrillation and one with non-cardiac chest pain in the metformin plus rosiglitazone arm, and one transient ischemic attack in the metformin plus repaglinide arm.[110]

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** Another 18 week trial reported no cardiovascular events in the 87 participants in the metformin plus rosiglitazone arm, and two coronary artery disease events in the 94 participants in the metformin plus sitagliptin arm.[71]

**Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones.** The RECORD study, a 5.5 year RCT of 4,447 subjects, combined the two rosiglitazone arms (metformin or sulfonylurea plus rosiglitazone) and compared results with the active control of metformin plus sulfonylurea to assess cardiovascular outcomes. Fatal and non-fatal myocardial infarctions were combined and showed no difference between the two combined rosiglitazone arms and metformin plus sulfonylurea arm (HR 1.14, 95% CI 0.80 to 1.63). Fatal and non-fatal stroke were also combined and showed no difference

between the two combined rosiglitazone arms and metformin plus sulfonylurea (HR 0.72, 95% CI 0.49 to 1.06).[14]

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** There was one myocardial infarction in the metformin plus glipizide arm compared with none in the metformin plus sitagliptin arm in a 52-week RCT with 1172 participants.[113]

**Combination of metformin and a basal insulin versus combination of metformin and premixed insulin.** In a 16-week cross-over study, 105 patients with newly diagnosed type 2 diabetes were randomly assigned to metformin plus insulin lispro 75/25 twice daily versus metformin plus insulin glargine.[137] In addition, there was an 8-week lead-in period when patients received neutral protamine Hagedorn (NPH) at night and the metformin dose was titrated. During the lead-in period, one patient experienced a myocardial infarction, and during treatment with the premixed insulin there was one case of chest pain, but it was not reported whether these events occurred before or after the crossover.[137]

**Combination of metformin and thiazolidinediones versus combination of thiazolidinediones and sulfonylureas.** Rosak et al. was a 6-month observational study of over 22,000 patients in Germany. Fewer myocardial infarctions and strokes occurred in the group with rosiglitazone added onto metformin therapy compared with the rosiglitazone plus sulfonylurea combination (incidence of 0.04% versus 0.11% for myocardial infarction and 0.01% versus 0.18% for stroke, respectively).[150] A limitation of the RECORD study was that it contained separate metformin plus thiazolidinedione and sulfonylurea plus thiazolidinedione arms to make this comparison, but did not report these analyses for cardiovascular disease morbidity.[14]

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** One 52-week trial with 639 participants compared metformin plus a sulfonylurea versus pioglitazone plus a sulfonylurea and reported no difference in the incidence of "cardiac disorders" between the two groups (4.1% versus 3.1% respectively) but no statistical test results were provided.[115]

## The Evidence about Retinopathy

There were no studies included in the report that evaluated the outcome of diabetic retinopathy.

## The Evidence about Nephropathy (Appendix G, Table 8)

For the nephropathy analyses, we included studies where changes in renal function was described for each treatment group, which could have included the number of patients developing nephropathy or changes in urinary albumin-to-creatinine ratio or glomerular filtration rate. There were eight trials reporting on nephropathy as an outcome.[42 54 86-88 105 115 151] In none of the studies was nephropathy a primary outcome. It was either a secondary outcome or reported under adverse effects.

**Metformin versus thiazolidinediones.** Two larger trials (total n = 1176[42] and n = 639[115]) compared the effects of metformin and pioglitazone on renal function. In both trials, the urinary albumin-to-creatinine ratio declined in patients receiving pioglitazone by 15%[115] and 19%,[42] respectively but remained unchanged in patients with metformin with statistically significant differences between groups in both trials.

**Metformin versus sulfonylureas.** One small trial of 3-months duration compared metformin with sulfonylurea (glibenclamide).[54] Microalbuminuria decreased significantly in patients with metformin while it increased with glibenclamide. Also, glomerular filtration rate remained stable in patients receiving metformin while it increased significantly in patients with glibenclamide. However, no formal between group comparisons were reported.

**Thiazolidinediones versus sulfonylureas.** Four small trials compared a thiazolidinedione (pioglitazone or rosiglitazone) with a sulfonylurea.[86-88 151] One trial found significantly lower albuminuria in patients receiving the thiazolidinedione (pioglitazone) compared to glibenclamide.[86]Two other trials also reported reductions in albuminuria with the thiazolidinedione (pioglitazone) but the differences to patients receiving a sulfonylurea were either not significant[151] or not reported.[87] One trial compared 12-month treatment with rosiglitazone and glyburide[88] and found no statistically significant difference in the urinary albumin-to-creatinine ratio. Similarly, there was no difference in the proportion of patients with progression to microalbuminuria.

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** One trial[105] compared metformin plus a thiazolidinedione (rosiglitazone) and metformin plus a sulfonylurea (glyburide) and found a greater reduction of the urinary albumin:creatinine ratio with the combination of metformin plus a thiazolidinedione but the difference to the group with metformin plus a sulfonylurea was not statistically significantly different.

## The Evidence about Neuropathy (Appendix G, Table 8)

For the neuropathy analyses, we included studies where newly developed neuropathy was reported for each treatment group. Three small short-term trials reported on neuropathy as an adverse outcome.[74 79 109] In all three studies neuropathy was reported under adverse effects.

**Metformin versus a combination of metformin and thiazolidinediones.** One trial[74] comparing metformin (n = 34) and metformin plus a thiazolidinedione (rosiglitazone) at 2 different dosages (n = 35 and n = 36, respectively) reported on one withdrawal due to undefined neuropathy in the metformin alone group but did not provide any formal between-group comparison.

**Metformin versus a combination of metformin and sitagliptin.** The other trial[79] reported on the incidence of (undefined) diabetic neuropathy with metformin alone (n = 2, 2.1%) and metformin plus sitagliptin (n = 4, 4.2%) but did not provide a statistical comparison.

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** In a six-month trial[109] neuropathy was not a pre-specified primary or secondary outcome but there was one patient (n = 103) who developed neuropathy in the group with combination metformin plus thiazolidinedione whereas none of the patients with combination metformin plus sulfonylurea (n = 80) developed neuropathy.

## Gray Literature

We found eight unpublished reports from clinicaltrials.gov and the FDA website that reported on long-term clinical outcomes for our comparisons of interest. These results were generally consistent with the results from the published studies included in the review.

**Metformin versus thiazolidinediones.** One unpublished study had 2902 subjects in the rosiglitazone group and 225 subjects in the metformin group, and reported myocardial infarction in nine subjects in the rosiglitazone group and one subject in the metformin group.[152] This study also reported the occurrence of a cerebrovascular disorder in four subjects in the rosiglitazone group and one in the metformin group.

**Metformin versus sulfonylureas.** One unpublished study had 160 subjects in the metformin group and 157 in the sulfonylurea group and reported one death due to myocardial infarction in each arm.[153] Another unpublished study had 225 subjects in the metformin group and 626 subjects in the sulfonylurea group, and reported myocardial infarction in two subjects in the sulfonylurea group and one in the metformin group.[152] An unpublished study had 225 subjects in the metformin group and 626 subjects in the sulfonylurea group, and reported a cerebrovascular disorder in one subject in the metformin group and none in the sulfonylurea group.[152]

**Metformin versus sitagliptin**. One unpublished 54-week RCT, with 364 subjects in the metformin group and 179 subjects in the sitagliptin group, reported myocardial infarction in one subject in the sitagliptin group and none in the metformin group.[154]

**Metformin versus a combination of metformin and sulfonylureas.** One unpublished study had 160 subjects in the metformin arm and 315 subjects on the combination of metformin plus sulfonylurea, and reported one death from myocardial infarction in the metformin group and two deaths in the combination therapy group.[155]

A 24-week double blind active controlled trial, with 521 subjects on metformin plus sulfonylurea and 177 subjects on metformin alone, reported one death in the combination therapy group and none in the metformin group.[156]

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** An unpublished 52-week RCT had 559 subjects in the metformin plus glipizide group and 576 subjects in the metformin plus sitagliptin group, and reported one death in the metformin plus sitagliptin combination group and three in the metformin plus glipizide combination group. There were two myocardial infarctions in the metformin plus glipizide combination group, and none in the metformin plus sitagliptin combination group.[154]

## Applicability

The majority of studies included for Key Question 2 had a short duration limiting their applicability to the assessment of long-term outcomes and complications of diabetes in patients with type 2 diabetes in the US. Among the RCTs, the two with the longest study duration were 6 years[30] and 7.5 years,[14] but the majority were less than 6-months long.

Most trials did not report the source for participant recruitment, such as an outpatient clinical or subspecialty clinical setting, which is relevant because the majority of patients with diabetes are cared for by primary care physicians. In the 22 trials identified since the 2007 Report, three reported recruitment specifically from outpatient primary care settings.[14 110 151] Six studies reported excluding greater than 10% of participants following a run-in period, which may limit their generalizability to outpatient settings with varying degrees of medication adherence.[39 103 105 113 129 137]

Overall, participants were middle-aged, which is fairly representative of the United States population with type 2 diabetes, but most studies excluded people greater than age 74. Participants were about 50% female and the majority was identified as Caucasian. Notably, two RCTs reported greater than 25% African American participants,[71 110] although many studies did

not report any racial-ethnic breakdown of the participants. Two RCTs took place in Mexico,[54 74] although only one reported ethnicity breakdown, with almost 80% Hispanic and about 7% Mestizo participants.[74] Most trials had similar exclusion criteria for comorbid illnesses, which included renal, cardiovascular, and hepatic disease, with the implication that participants were overall less complicated, and thus at lower risk for long-term outcomes of diabetes.

A majority of studies were conducted in the US or multinational Europe, where the practice of medicine related to the treatment of diabetes is fairly similar. The majority of studies received pharmaceutical support.

# Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options (see list of comparisons) in terms of the following adverse events and side effects?

- **Hypoglycemia**
- **Liver injury**
- **Congestive heart failure**
- **Severe lactic acidosis**
- **Cancer**
- **Severe allergic reactions**
- **Hip and non-hip fractures**
- **Pancreatitis**
- **Cholecystitis**
- **Macular edema or decreased vision**
- **Gastrointestinal side effects**

## Key Points and Evidence Grades

**Hypoglycemia.**

- There was high strength of evidence to conclude that the risk of hypoglycemia with sulfonylureas exceeds the risk with metformin with a pooled RR for moderate hypoglycemic events of 2.6 (95% CI 1.3 to 5.4) for sulfonylurea versus metformin.
- There was high strength of evidence to conclude that the risk of hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones with a pooled RR of 6.9 (95% CI 4.2 to 11) for mild to moderate hypoglycemia for sulfonylurea versus thiazolidinediones.
- There was high strength of evidence to conclude that the risk of hypoglycemia with metformin plus sulfonylurea is about 6 times higher than the risk of metformin plus thiazolidinediones.
- Moderate grade evidence showed that the risk of hypoglycemia with metformin is comparable to the risk with thiazolidinediones.

- Moderate grade evidence showed that the risk of hypoglycemia with metformin plus sulfonylurea is higher than the risk with metformin alone.
- Moderate grade evidence showed that the risk of hypoglycemia with sulfonylurea exceeds the risk with sitagliptin.
- Moderate grade evidence showed a modest increase (RR 1.74, 95% CI 1.22 to 2.47) in risk of hypoglycemia with meglitinides over metformin.
- Moderate grade evidence showed a modest increase in risk of hypoglycemia with metformin plus a thiazolidinedione over metformin alone (RR 1.5, 95% CI 1.0 to 2.3).
- Moderate grade evidence showed that metformin with sitagliptin has similar risk of hypoglycemia as metformin alone.
- The evidence about hypoglycemia for the other comparisons had low strength or was insufficient.

**Liver injury.**

- Moderate grade evidence showed that rates of liver injury are similar between thiazolidinediones and sulfonylureas.

**Congestive heart failure.**

- Moderate evidence showed that thiazolidinediones increase the risk of heart failure when compared to sulfonylureas.
- There were no long-term trials that provide a robust assessment of the comparative safety of the newer oral antidiabetic agents, sitagliptin or exenatide, on the risk of heart failure.

**Severe lactic acidosis.**

- Moderate strength of evidence indicated that there is no increased risk of lactic acidosis in metformin users compared to those using a sulfonylurea or a combination of metformin and a sulfonylurea.

**Cancer.**

- The evidence had low strength and did not allow definitive conclusions about the risk of cancer with any of the antidiabetic medication comparisons.

**Severe allergic reactions.**

- No studies addressed the outcome of severe allergic reactions, and therefore insufficient evidence.

**Hip and non-hip fractures.**

- High grade evidence showed that thiazolidinediones, either in combination with another medication or as monotherapy, are associated with a higher risk of bone fractures compared with metformin alone or in combination with sulfonylurea.

**Pancreatitis.**

- The evidence had low strength and did not allow definitive conclusions about the comparative safety of oral antidiabetic agents on the outcome of acute pancreatitis.

**Cholecystitis.**

- The evidence had low strength and did not allow definitive conclusions about the comparative safety of diabetes medications regarding the outcome of cholecystitis.

**Macular edema or decreased vision.**

- The evidence had low strength and did not allow definitive conclusions about the comparative safety of oral antidiabetic agents on the outcome of macular edema.

**Gastrointestinal (GI) side effects.**

- There was high strength of evidence that metformin was associated with more frequent GI adverse events compared with thiazolidinediones.
- There was high strength of evidence that the rates of GI adverse effects were similar between thiazolidinediones and sulfonylureas.
- There was moderate strength of evidence that metformin was associated with more frequent GI adverse events compared with second-generation sulfonylureas.
- There was moderate strength of evidence that metformin monotherapy was associated with more frequent GI adverse events than the combination of metformin plus a second-generation sulfonylurea or metformin plus thiazolidinediones if the metformin component was a lower dose than the metformin monotherapy arm.
- There was moderate strength of evidence that a combination of metformin and sulfonylurea is associated with more frequent GI adverse events compared with a combination of a thiazolidinedione and a sulfonylurea.

See Table 8 for the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix G, Table 9.

**Table 8. Key findings and strength of the evidence comparing diabetes medications as monotherapy or combination therapy for adverse events**

| Comparison | Hypoglycemia | GI adverse events | CHF | Macular edema | Pancreatitis and cholecystitis | Fractures |
|---|---|---|---|---|---|---|
| **MONOTHERAPY COMPARISONS** | | | | | | |
| **Metformin versus** | | | | | | |
| TZD | Moderate; Neither favored | High; Favored TZD | Low; Unclear | Insufficient | Low; Unclear*<br>Insufficient† | High; Favored Met |
| SU | High; Favored Met | Moderate; Favored SU | Moderate; Favored Met | Insufficient | Insufficient | Low; Unclear |
| Sitagliptin | Low; Unclear | Low; Favored sitagliptin | Insufficient | Insufficient | Insufficient | Insufficient |
| Meglitinides | Moderate; Favored Met | Low; Favored meglitinides for diarrhea only | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + TZD | Moderate; Favored Met | Moderate; Favored Met+TZD for diarrhea only | Insufficient | Insufficient | Low; Unclear*<br>Insufficient† | Insufficient |
| Metformin + SU | Moderate; Favored Met | Moderate; Favored Met+TZD when lower dose of Met | Insufficient | Insufficient | Insufficient*<br>Low; Unclear† | Low; Unclear |
| Metformin + sitagliptin | Moderate; Neither favored | Low; Unclear | Insufficient | Insufficient | Insufficient | Low; Unclear |
| Metformin + meglitinides | Low; Favored Met | Low; Unclear | Insufficient | Insufficient | Insufficient | Insufficient |
| **TZD versus** | | | | | | |
| TZD | Low; Favored rosi | Insufficient | Low; Unclear | Insufficient | Insufficient | Insufficient |
| SU | High; Favored TZD | High; Neither favored | Moderate; Favored SU | Insufficient | Insufficient | Low; Neither favored |
| Sitagliptin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Meglitinides | Moderate; Favored TZD | Low; Unclear | Insufficient | Insufficient | Insufficient | Insufficient |
| **SU versus** | | | | | | |
| Sitagliptin | Moderate; Favored sitagliptin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Meglitinides | Low; Favored meglitinides | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| **Sitagliptin versus** | | | | | | |
| Meglitinides | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |

**Table 8. Key findings and strength of the evidence comparing diabetes medications as monotherapy or combination therapy for adverse events (continued)**

| Comparison | Hypoglycemia | GI adverse events | CHF | Macular edema | Pancreatitis and cholecystitis | Fractures |
|---|---|---|---|---|---|---|
| **COMBINATION COMPARISONS** | | | | | | |
| **Metformin + another agent versus** | | | | | | |
| Metformin + TZD | High; Favored Met+TZD | Low; Neither favored | Insufficient | Insufficient | Insufficient | High; Favored Met |
| Metformin + SU | Low; Unclear | Low; Unclear | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + meglitinides | Insufficient | Low; Favored Met+glyburide for dyspepsia | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + sitagliptin | Insufficient | Low; Neither favored | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + exenatide | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + basal insulin | Low; Favored Met+basal insulin | Low; Unclear | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + premixed insulin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| **TZD + another agent versus** | | | | | | |
| Metformin + TZD | Low; Favored Met+TZD | Insufficient | Low; Favored TZD+SU | Insufficient | Insufficient | Insufficient |
| Metformin + SU | Low; Favored TZD+SU | Moderate; Favored TZD combination | High; Favored Met+SU | Insufficient | Insufficient | High; Favored Met+SU |
| Metformin + meglitinides | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + sitagliptin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + exenatide | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + basal insulin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |
| Metformin + premixed insulin | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient | Insufficient |

CHF = congestive heart failure; GI = gastrointestinal; Met = metformin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione

* Key finding and evidence grade for cholecystitis.

† Key finding and evidence grade for pancreatitis.

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

All other comparisons and intermediate outcomes were graded as insufficient since there were no studies.

## Study Design and Population Characteristics

Eight-seven studies are included for KQ3 describing adverse effects during treatment (Appendix G, Tables 10 and 11). We included, 38 articles from the CER published in 2007 that described adverse events for our comparisons of interest and identified an additional 49 studies describing adverse events since completion of that review for this update. The majority of the studies were RCTs. None of the studies was designed explicitly to evaluate adverse events from these medications and medication combinations.

## The Evidence about Hypoglycemia (Appendix G, Table 12)

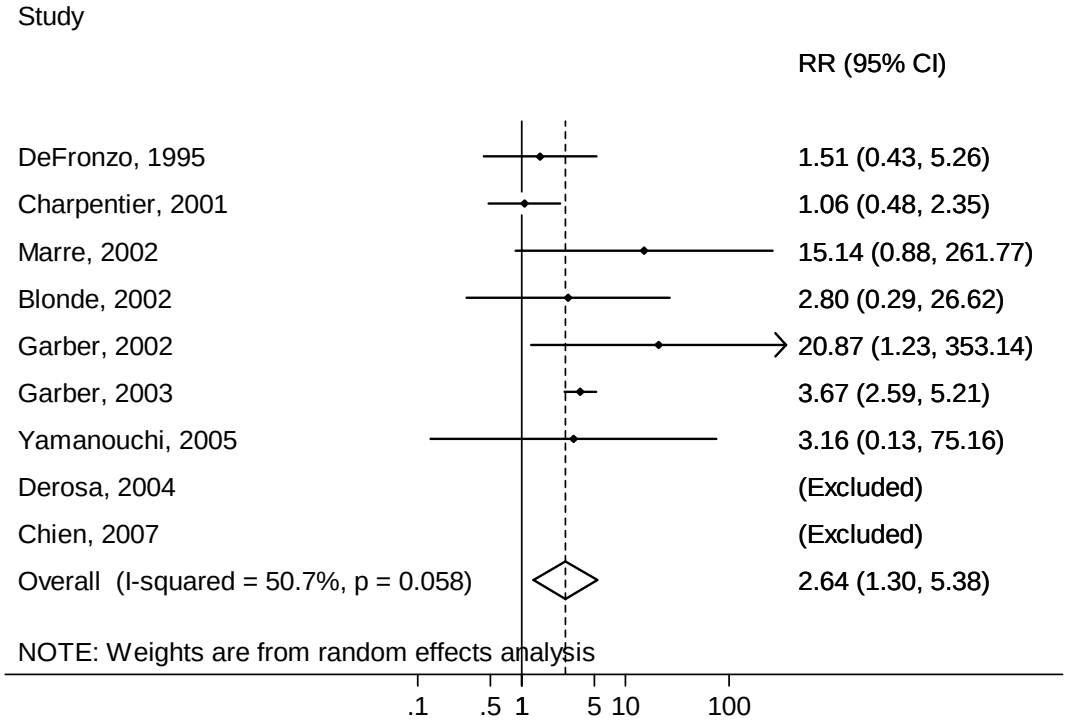
From the 2007 CER[17]we included 29 RCTs,[28 40 48 49 51-53 56 58 59 65 67 72 73 75-77 90 92 93 97-102 108 115 123] and 3 cohort studies that reported hypoglycemia.[157-159] Forty-one of the newly-identified studies reported on hypoglycemia as an adverse event. Of these, 37 were RCTs,[30 36 39 47 63 64 66 68 70 71 78-81 84 85 94 95 103 105 106 109 110 112 113 117-121 125 129 137 147 151 160 161] and four were cohort studies.[150 162-164] The high-quality study from by Home, et al. (RECORD), could not be used to look at adverse events because they did not report the number of affected people stratified by the therapy accompanying the thiazolidinedione (e.g., rosiglitazone plus sulfonylurea or rosiglitazone plus metformin).[14]

**Metformin versus thiazolidinediones.** This comparison was addressed by a single, large trial.[30]The trial was the ADOPT study, a high quality trial comparing metformin, rosiglitazone, and glyburide. There was no significant difference in the number of self-reported hypoglycemic events among individuals receiving rosiglitazone and those receiving metformin (141/1456 versus 167/1454, RR 0.90, 95% CI 0.80 to 1.0) with just a single serious event in each group.[30]

**Metformin versus sulfonylureas.** Nine RCTs were eligible for pooling,[40 47-49 51-53 58 59] although two studies had zero events in both arms.[36 47] There was moderate statistical heterogeneity between these studies with an I-squared of 51%. The pooled RR having at least one mild or moderate hypoglycemic event was 2.6 (95% CI 1.3 to 5.4) with use of sulfonylurea relative to metformin (Figure 50). Only one study reported on severe hypoglycemia and found no significant difference between arms (p = 0.18).[56]

Two additional RCTs could not be pooled, and had results that were similar to those in the pooled analysis (Table 9).[30 161]

**Figure 50. Relative risk of having at least one mild or moderate hypoglycemic event comparing metformin with sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
CI = confidence interval; RR = relative risk

**Table 9. Additional randomized controlled trials comparing metformin with sulfonylurea for hypoglycemia**

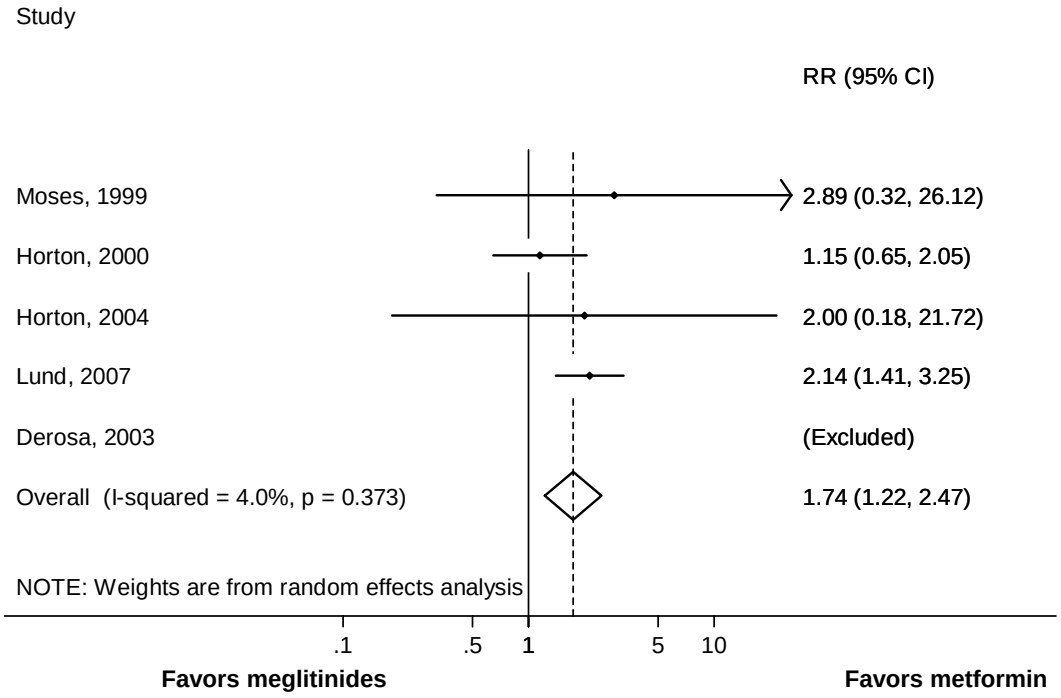
| Author, year | Outcome | Results | Comments |
|---|---|---|---|
| Kahn, 2006[30] | Self-report hypoglycemia, severity unspecified | 168/ 1451 in metformin arm versus 557/1441 events in sulfonylurea arm | High quality trial, Individuals with short duration of disease, HgbA1c = 7.3% at baseline |
| Wright, 2006[161] | Mild to severe (not just transient symptoms) | Mean annual percentage 0.30% in 290 patients in metformin arm versus 1.20% in 1418 patients in sulfonylurea arm | Part of UKPDS study, open-label, HgbA1c 6.9% at baseline, mostly non-obese participants |

HbgA1c = hemoglobin A1c; UKPDS = United Kingdom Prospective Diabetes Study

**Metformin versus sitagliptin.** A single study looked at this comparison for hypoglycemic outcomes.[63] This study was a continuation of that by Goldstein et al.[64] Two of 182 patients randomized to metformin and 2 of 179 randomized to sitagliptin had mild or moderate hypoglycemic symptoms.

**Metformin versus meglitinides.** Five RCTs reported mild or moderate hypoglycemia for this comparison.[65-68 160] One had no events in either arm.[67] There was minimal statistical heterogeneity between these studies (I-squared = 4.0%). The RR for hypoglycemia was 1.7 (95% CI 1.2 to 2.5) for meglitinides compared to metformin (Figure 51). No additional trials or observational studies reported this outcome.

**Figure 51. Relative risk of having at least one mild or moderate hypoglycemic event comparing metformin with meglitinides**

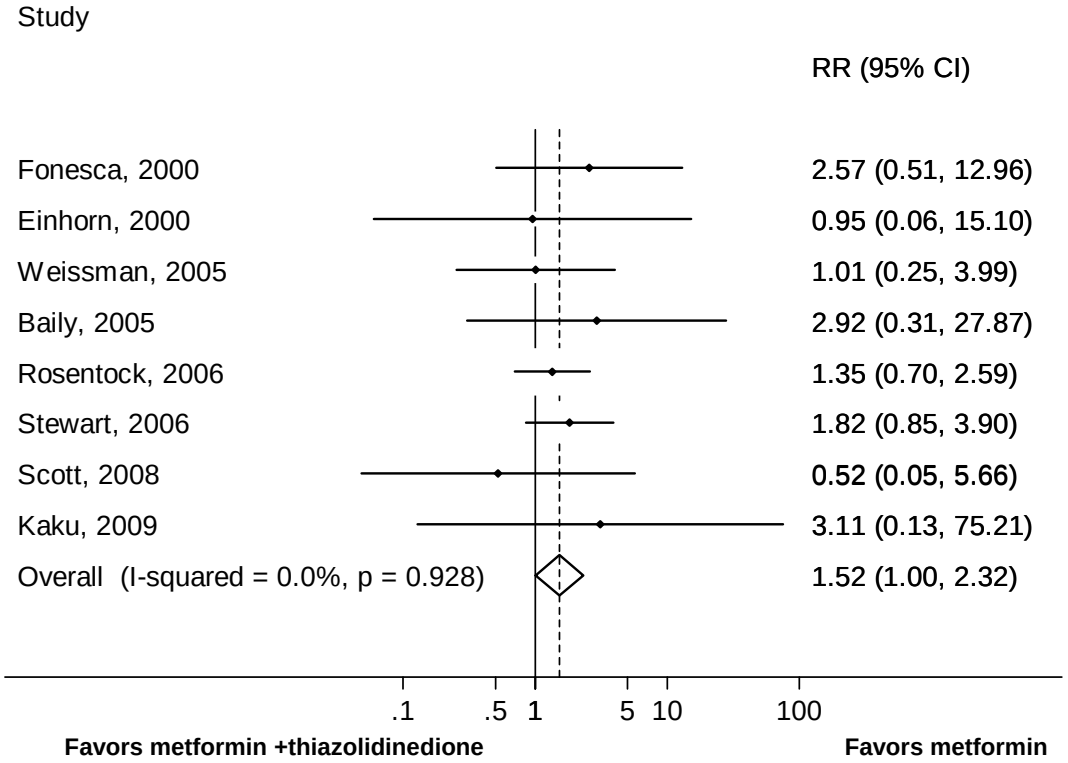



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
CI = confidence interval; RR = relative risk

**Metformin versus a combination of metformin and thiazolidinediones.** Eight RCTs were acceptable for pooling for the outcome of mild or moderate hypoglycemia (Figure 52).[39 70-73 75 76 129] There was minimal statistical heterogeneity. The RR from the fixed effects model was 1.5 (95% CI 1.0 to 2.3) favoring metformin alone for the outcome of hypoglycemia. No additional trials or observational studies reported this outcome.

**Metformin versus a combination of metformin and sulfonylureas.** There were nine RCTs of this comparison (Table 10).[47 49 51 52 56 58 59 77 78] Seven reported mild or moderate hypoglycemia and were pooled, but there was substantial statistical heterogeneity (I-squared of 73%) so this pooled outcome is not reported. Two of the studies had very few events in the metformin alone arm.[51 52]

**Figure 52. Relative risk of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus thiazolidinedione**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the fixed-effects pooled estimate.
CI = confidence interval; RR = relative risk

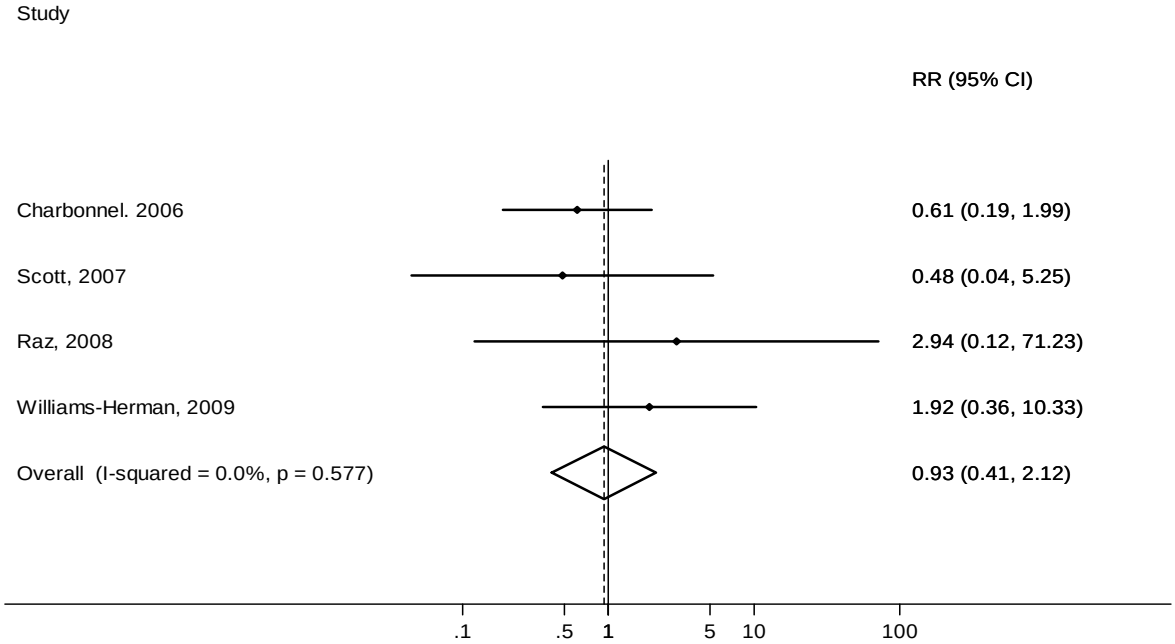
**Table 10. Randomized controlled trials comparing metformin with a combination of metformin and sulfonylurea for hypoglycemia**

| Author, year | Outcome | Results (metformin versus metformin +sulfonylurea) | Comments |
|---|---|---|---|
| Defronzo, 1995[58] | Individuals with mild or moderate hypoglycemia | 4/210 versus 38/213 | RR = 9.3 (95% CI 3.4 to 26) |
| Charpentier, 2001[59] | Individuals with mild or moderate hypoglycemia | 8/75 versus 30/147 | RR = 2 (95% CI 0.9 to 4) |
| Blonde, 2002[51] | Individuals with mild or moderate hypoglycemia | 1/153 versus 22/162 | RR = (95% CI 3 to 152) Definition of hypoglycemia required symptoms with a measured glucose < 60 mg/dl |
| Marre, 2002[52] | Individuals with mild or moderate hypoglycemia | 0/104 versus 12/103 | RR = 25 (95% CI 1.5 to 421) |
| Garber, 2003[49] | Individuals with mild or moderate hypoglycemia | 29/164 versus 59/171 | RR = 2 (95% CI 1.3 to 2.9) |
| Feinglos, 2005[77] | Individuals with mild or moderate hypoglycemia | 2/56 versus 9/56 | RR = 4.5 (95% CI 1.0 to 20) |
| Chien, 2007[47] | Individuals with mild or moderate hypoglycemia | 0/25 versus 0/26 | Most subjects had been on both medications before the trial began. |
| Hermann, 1994[56] | Individuals with severe hypoglycemia | 8 /38 versus 24/72 | RR = 0.6 (95% CI 0.3 to 1.3) |
| Nauk, 2009[78] | Individuals with severe hypoglycemia | 0/122 versus 0/244 | Not a significant difference |

CI = confidence interval; mg/dL = milligrams per deciliter; RR = relative risk

**Metformin versus a combination of metformin and sitagliptin.** Five articles, describing four trials, examined hypoglycemia with this comparison of medications.[63 64 71 79 80] Williams-Herman et al,[63] is an extension of the Goldstein et al trial.[64] There was minimal heterogeneity between these studies. The addition of sitagliptin to metformin does not raise the risk of mild or moderate hypoglycemia (RR = 0.93, 95% CI 0.41 to 2.1) (Figure 53). No additional trials or observational studies reported this outcome.

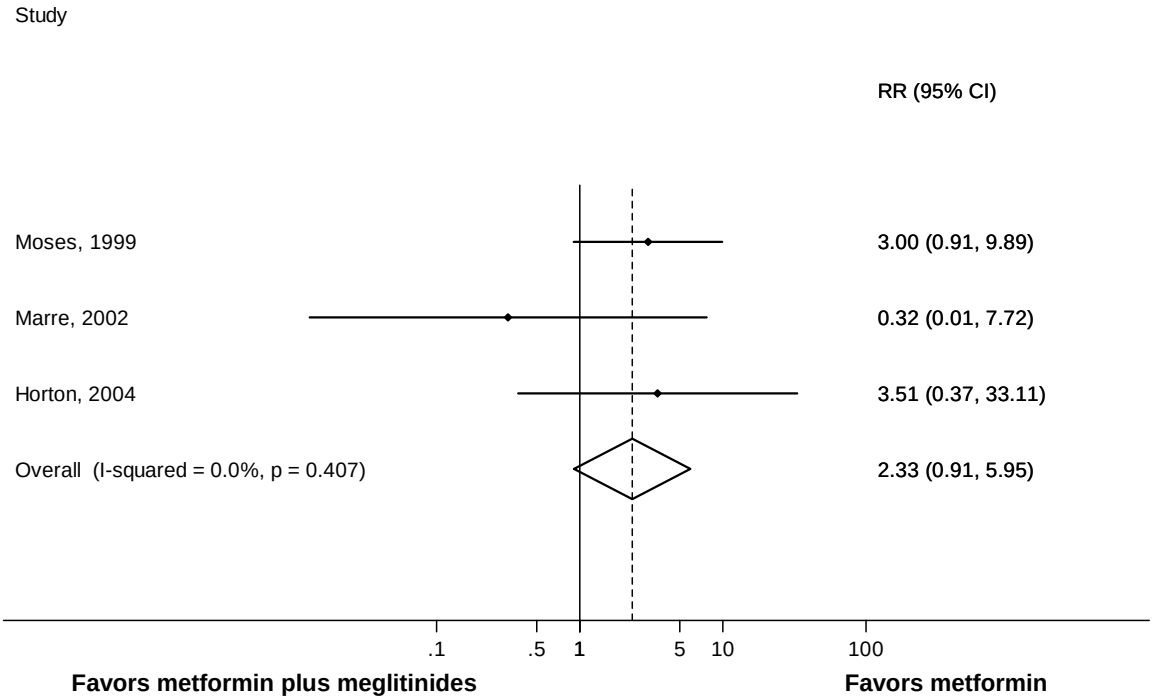
**Figure 53. Relative risk of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus sitagliptin**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the fixed-effects pooled estimate.
CI = confidence interval; RR = relative risk

**Metformin versus a combination of metformin and meglitinides.** Three studies reported mild or moderate hypoglycemia for this comparison.[66 81] There was minimal statistical heterogeneity between the studies. One high quality study had very few affected individuals and used a low dose of nateglinide.[81] Results are unclear but suggest possibly an increased risk of hypoglycemia with the combination (Figure 54). No additional trials or observational studies reported this outcome.

**Figure 54. Relative risk of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus meglitinides**



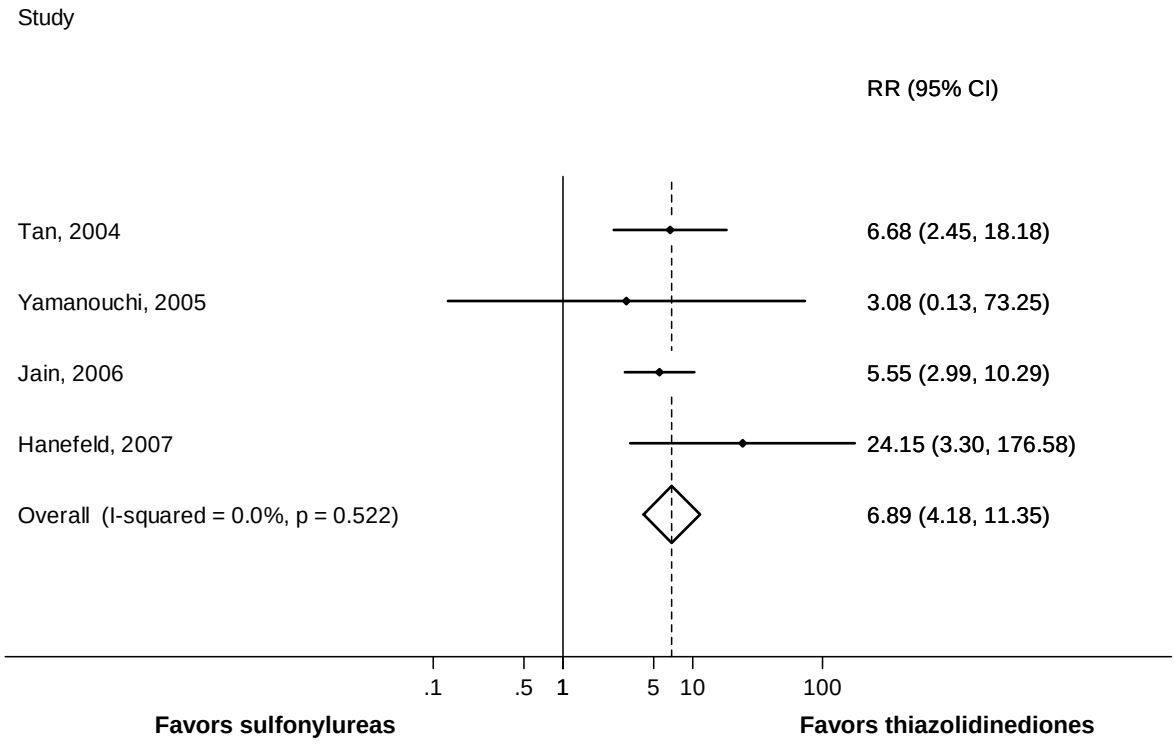

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the fixed-effects pooled estimate.
CI = confidence interval; RR = relative risk

**Rosiglitazone versus pioglitazone.** This was addressed by a single, retrospective cohort study.[164] The subjects had poor glycemic control at cohort entry with a mean HgbA1c of 9.5% in the rosiglitazone group and 9.6% in the pioglitazone group. The prevalence of hypoglycemia did not differ significantly between groups (11 out of 96 in the rosiglitazone-treated group and 18 out of 106 in the pioglitazone group).

**Thiazolidinediones versus sulfonylureas.** Eight studies examined hypoglycemic outcomes for this comparison.[30 40 84 85 90 123 151 162] Two looked at counts of events rather than individuals,[30 151] and one described only the severe events in both arms.[123] The pooled results for mild or moderate hypoglycemia for the four studies reporting affected individuals showed a higher risk of hypoglycemia among those on a sulfonylurea than on any thiazolidinedione (RR = 6.9, 95% CI 4.2 to 11) (Figure 55).

However, a very large multi-continent RCT (ADOPT) reported no significant difference in the number of events in each group (1341 out of 1456 in the group on pioglitazone and 1338 out of 1441 in the sulfonylurea group (p = 0.44).[30] This high number of events suggests that even very minor events were included in this count. One additional trial reported two events of hypoglycemia in the pioglitazone arm among 22 randomized participants and one event among 22 randomized participants receiving sulfonylurea (glipizide).[151] A cohort study evaluating a population over age 65 years reported that 2.6% of recipients of sulfonylurea reported hypoglycemia and 2.2% of thiazolidinedione recipients, which are not significantly different percentages.[162]

**Figure 55. Relative risk of having at least one mild or moderate hypoglycemic event comparing thiazolidinediones with sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the fixed-effects pooled estimate.
CI = confidence interval; RR = relative risk

There were very few patients affected by severe hypoglycemia. Only a single individual treated with a thiazolidinedione in the four studies reporting this outcome had an event (this was in the ADOPT trial[30]); 0 to 3% of the sulfonylurea-treated patients had severe events.[30 40 84 123]

**Thiazolidinediones versus meglitinides.** Two RCTs reported hypoglycemic outcomes for this comparison (Table 11).[92 93]

**Table 11. Randomized controlled trials comparing thiazolidinediones with meglitinides for hypoglycemia**

| Author, year | Outcome | Results (thiazolidinediones versus meglitinides) | RR and comments |
|---|---|---|---|
| Jovanovic, 2004[93] | Individuals with mild or moderate hypoglycemia | 4/62 versus 8/61 | RR = 1.2 (95% CI 0.8 to 1.8) |
| Raskin, 2004[92] | Individuals with mild or moderate hypoglycemia | 1/62 versus 4/63 | RR = 1.6 (95% CI 1.0 to 2.6) |
| | Severe Hypoglycemia | None | |

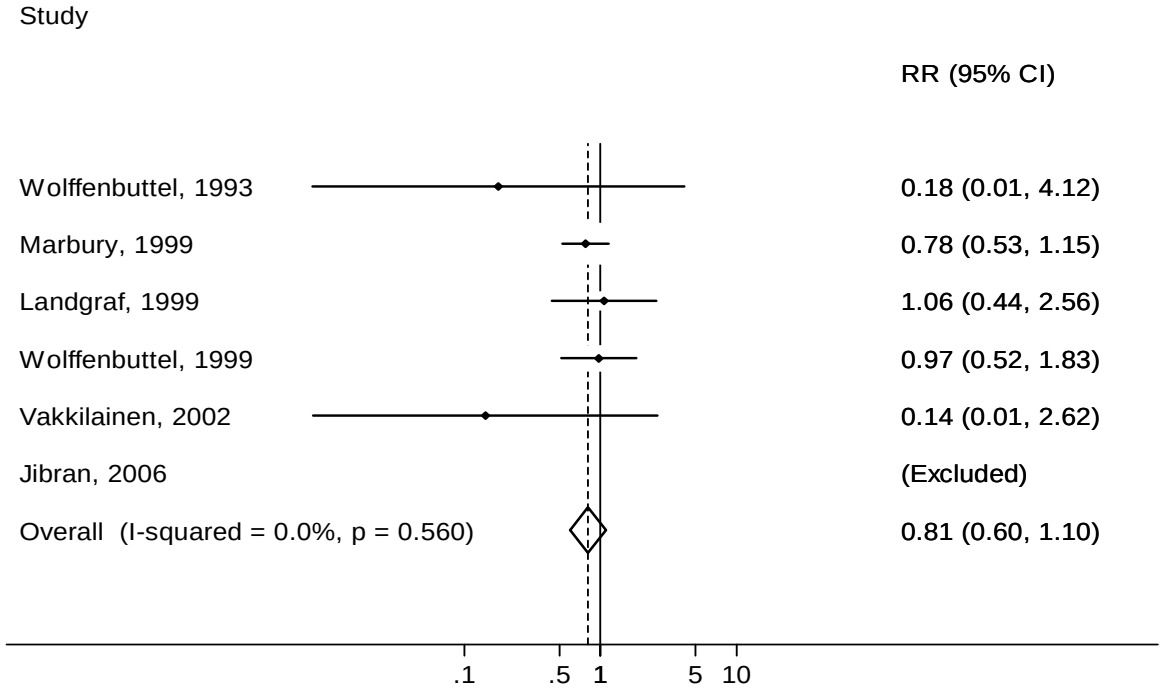
CI = confidence interval; RR = relative risk

**Sulfonylureas versus sitagliptin.** A single high quality RCT examined hypoglycemia with this comparison.[94] Subjects had a mean HgbA1c of 7.9% upon enrollment. Twenty-one of 123 patients treated with a sulfonylurea had mild or moderate hypoglycemia while none did among the 122 patients treated with sitagliptin.

**Sulfonylureas versus meglitinides.** Eight studies reported hypoglycemia with this comparison.[95 97-102 165] One looked only at severe events,[97] and one trial focused on the

comparison while patients were fasting in observance of Ramadan.[165] The other six had similar outcomes and were amenable to pooling. Fewer patients receiving meglitinides had hypoglycemia than those receiving sulfonylurea although the pooled risk ratio was not statistically significant (RR = 0.8, 95% CI 0.6 to 1.1) (Figure 56).

**Figure 56. Relative risk of having at least one mild or moderate hypoglycemic event comparing sulfonylureas with meglitinides**

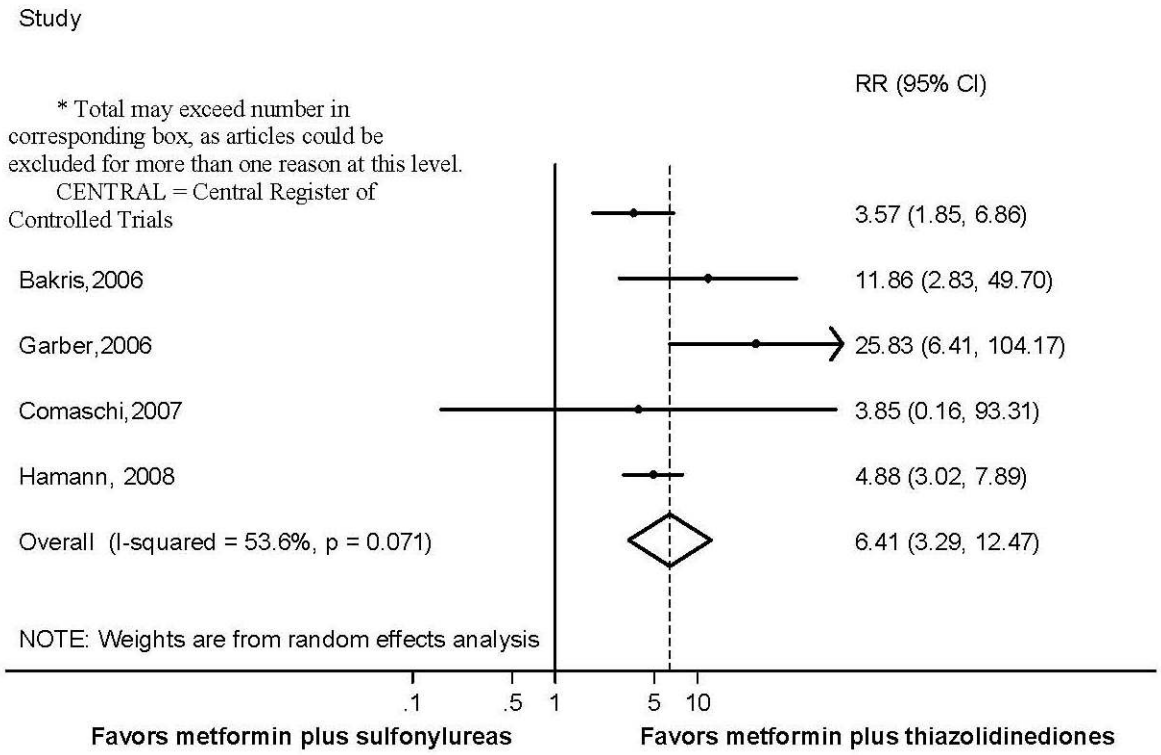



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the fixed-effects pooled estimate.
CI = confidence interval; RR = relative risk

In the trial by Madsbad et al, there were no severe hypoglycemic events in either treatment group.[97] The high quality trial by Mafauzy et al randomized patients to repaglinide or glibenclamide during the period of Ramadan which is observed by daylight fasting.[165] The number of hypoglycemic events with midday blood glucose less than 81 mg/dL was significantly lower in the meglitinide group (2.8%) than in the sulfonylurea group (7.9%) ($p < 0.001$).

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** Six trials examined hypoglycemic outcomes,[36 103 105 106 108 109] as did one non-randomized interventional study.[163] One of the trials examined only severe hypoglycemia as an outcome.[36] Among those reporting mild or moderate hypoglycemia, there was some heterogeneity between studies although not enough to preclude pooling (Figure 57). The trial by Hamann et al was designed so that patients were withdrawn from the study if they did not reach an efficacy target after 8 weeks of treatment.[103] The rates of hypoglycemia were high as medications were titrated up to efficacy, although the relative risk of hypoglycemia in the two arms was comparable to the other studies.

**Figure 57. Relative risk of having at least one mild or moderate hypoglycemic event comparing combination metformin and thiazolidinediones with combination metformin and sulfonylureas**




Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
CI = confidence interval; RR = relative risk

In the studies that reported severe hypoglycemia, the rates were higher in the combination of metformin and sulfonylurea arms than the combination of metformin and thiazolidinedione arms. In Garber et al, 7 of 159 patients had severe hypoglycemic events in the metformin with sulfonylurea arm and none in the metformin with thiazolidinedione group.[108] This study included patients with high HgbA1c upon enrollment and had a higher proportion of Asian patients than most studies (12% Asian). The smaller study reported that a single patient was withdrawn from the metformin with sulfonylurea arm because of hypoglycemia.[36]

One non-randomized trial compared addition of pioglitazone with addition of glibenclamide in patients taking metformin, with a mean followup of 42 months.[163] More patients receiving glibenclamide had hypoglycemic events than those who received pioglitazone (34 out of 250 compared to 5 out of 250, respectively).

**Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides.** A single RCT reported hypoglycemia for this comparison.[110] This study compared meglitinide plus metformin to two different intensities of metformin plus thiazolidinedione (twice-daily or three-times-daily dosing). The combination of metformin plus meglitinide was associated with more hypoglycemia than the combination of metformin plus

thiazolidinedione. In the repaglinide plus metformin twice-daily group, eight of 187 randomized participants had 162 events and in the rosiglitazone plus metformin twice-daily group, one of the 187 randomized participants had 11 events (RR = 1.8, 95% CI 1.4 to 2.3 comparing the number of affected participants). There were no episodes of severe hypoglycemia in either group.

**Combination of metformin and sulfonylureas versus combination of metformin and another agent.** Five trials examined hypoglycemia for metformin plus sulfonylurea compared to metformin plus another drug (Table 12).[112 113 118 119 125]

**Table 12. Randomized controlled trials comparing combination of metformin and sulfonylurea with combination metformin and another agent for hypoglycemia**

| Author, year | Comparison | Outcome | Results | RR and comments |
|---|---|---|---|---|
| Gerich, 2005[112] | Metformin + sulfonylurea versus metformin + meglitinides | Mild or moderate | 38/209 versus 18/219 | RR = 2.2 (95% CI 1.3 to 3.8) |
| | | Severe | 2/209 versus 0/219 | No significant difference |
| Schwarz, 2008[125] | Metformin + sulfonylurea versus metformin + meglitinides | Severe | 1/40 versus 0/35 | No significant difference |
| Nauck, 2007[113] | Metformin + sulfonylurea versus metformin + sitagliptin | Severe | 7/584 versus 1/588 | RR = 7.0 (95% CI 0.9 to 57) |
| Malone, 2003[118] | Metformin + sulfonylurea versus metformin + insulin | Nocturnal; Severe | (N=597 in trial) Greater number of participants with nocturnal hypoglycemia (p < 0.01) with metformin plus sulfonylurea than metformin plus insulin. Comparable number with severe hypoglycemia (p = 1.0) | |
| Kvapil, 2006[119] | Metformin + sulfonylurea versus metformin + insulin | Mild or moderate | 9/114 versus 13/108 | RR = 0.7 (95% CI 0.3 to 1.5) |

CI = confidence interval; RR = relative risk

**Combination of metformin and a basal insulin versus combination of metformin and another insulin.** Three trials examined the comparison of metformin plus insulin glargine to metformin plus another insulin preparation (Table 13).[120 121 137]

**Table 13. Randomized controlled trials comparing combination of metformin and a basal insulin with combination of metformin and another insulin for hypoglycemia**

| Author, year | Comparison | Outcome | Results | RR and comments |
|---|---|---|---|---|
| Raskin, 2007[121] | Metformin + glargine versus metformin + aspart 70/30 | Mild or moderate | 11/78 versus 33/79 (23 versus 121 events) | RR = 0.34 (95% CI 0.2 to 0.6) |
| Robbins, 2007[120] | Metformin + glargine versus metformin + lispro 50/50 | Mild or moderate | 75/158 versus 79/157 | RR = 0.94 (95% CI 0.8 to 1) |
| | | Severe | 2/158 versus 3/157 | RR = 0.66 (95% CI 0.1 to 4) |

| | | | | |
|---|---|---|---|---|
| Malone, 2004[137] | Metformin + glargine versus metformin + lispro 75/25 | Mild or moderate | 40/101 versus 57/100 (87 versus 181 events) | RR = 0.69 (95% CI 0.5 to 0.9), both arms of cross-over pooled |
| | | Severe | 0/95 versus 0/95 | |

CI = confidence interval; RR = relative risk

**Combination of metformin and thiazolidinediones versus combination of thiazolidinediones and sulfonylureas.** A single large cohort study examined this comparison.[150] This prospective cohort study enrolled 22,808 patients in Germany who were treated with rosiglitazone and observed their outcomes as their own clinicians prescribed additional medications. Hypoglycemic events occurred at a rate of 0.05 per 100 person-years of followup in the metformin plus thiazolidinedione group and 0.47 per 100 person-years of followup in the thiazolidinedione plus sulfonylurea group.

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** A single study compared metformin plus sulfonylurea to a thiazolidinedione plus sulfonylurea.[117] This was the longer term followup on the patients enrolled in the study first reported by Hanefeld et al.[115] There was a 10% withdrawal rate from adverse events and an 8% withdrawal rate for lack of efficacy. Fifty of 224 subjects receiving metformin plus sulfonylurea had mild or moderate hypoglycemic symptoms while 36 of 217 receiving thiazolidinedione plus sulfonylurea had symptoms (RR 1.3, 95% CI 0.9 to 2).

## The Evidence about Liver Injury (Appendix G, Table 12)

**Metformin versus thiazolidinediones.** A single cohort study assessed liver injury with metformin as compared with pioglitazone, using propensity scores to match subjects based on disease severity.[166] The incidence of liver failure or hepatitis was defined using claims data. For the 1847 subjects in each group for the metformin versus pioglitazone comparison, the rate of liver failure or hepatitis was 0.8% and 0.4%, respectively, which was not statistically significant in Cox proportional hazard models.

**Metformin versus sulfonylureas.** The ADOPT study, a large 6-year parallel arm RCT, compared metformin with glyburide, with over 1,200 subjects in each arm.[30] The average age in the metformin group was 57.9 (SD 9.9). Average age in the glyburide group was 56.4 (SD 10.4). The percentage of individuals with liver injury was 1.1% among the 1341 individuals in the metformin group and 0.8% among the individuals in the glyburide group. Mean alanine aminotransferase (ALT) levels were slightly higher in the glyburide group (27.2 international units (IU)/liter; 95% CI 26.3 IU/liter to 28.1 IU/liter) compared to the metformin group (24.9 IU/liter; 95% CI 24.1 IU/liter to 25.8 IU/liter), but the clinical significance of this slight difference is not clear and there was no statistical test performed.

**Rosiglitazone versus pioglitazone.** This comparison was addressed by a single, cohort study conducted in the US using a pharmacy database.[166] As mentioned above, the diagnosis of liver failure or hepatitis was based on claims data. There was no difference in the incidence of liver injury between the two treatment groups. The incidence of hepatitis was 0.4% among the 1847 people treated with rosiglitazone and 0.5% among the 1847 treated with pioglitazone.

**Thiazolidinediones versus sulfonylureas.** This comparison was addressed with the ADOPT study, described above, which compared rosiglitazone with glyburide.[30] The average age of participants in the rosiglitazone and glyburide groups was 57.9 (SD 9.9) and 56.4 (SD 10.4), respectively. The outcome of liver injury was based on elevated liver enzymes. There were no

cases of liver injury among the 1,388 people treated with rosiglitazone or the 1,331 people treated with glyburide. The cohort study discussed above also compared pioglitazone versus any sulfonylurea and assessed rates of liver failure and hepatitis.[166] The incidence of hepatitis, defined with claims data, was 0.6% among the 1474 individuals treated with pioglitazone and 1% in the 1474 individuals treated with any sulfonylurea, which was not significant.

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** One RCT examined liver injury as an adverse event for this comparison.[107] Liver injury was defined as an ALT or aspartate aminotransferase (AST) value more than 3 times the upper limit of normal. There were no cases of liver injury reported in the 48 patients in the combination metformin plus rosiglitazone arm and none in the 47 patients in the combination metformin plus glimepiride arm.

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** A single parallel arm 12-week RCT in 198 participants, conducted in China, examined this comparison.[114] Individuals with poor glucose control were randomized to receive metformin plus an sulfonylurea or rosiglitazone plus a sulfonylurea. There were no cases of liver injury reported in either group in this short trial.

## The Evidence about Congestive Heart Failure (Appendix G, Table 12)

Six trials[30 69 116 123 137 151] and 7 observational studies[150 158 162 164 167-169] reported on the outcome of heart failure for our comparisons of interest.

**Metformin versus thiazolidinediones.** Three trials[30 69 116] and one observational study[162] examined heart failure for this comparison (Table 14). The ADOPT study, a large 6-year parallel arm RCT, compared metformin with rosiglitazone, with over 1,400 subjects in each arm. There was no difference between the incidence of investigator reported heart failure in these two arms.

Low grade evidence showed that thiazolidinediones increase the risk of heart failure when compared to metformin.

**Table 14. Studies comparing metformin with thiazolidinediones for heart failure events**

| Author, year | Study design | Heart failure incidence |
|---|---|---|
| Kahn, 2006[30] | RCT | 19/1454 versus 22/1456 |
| Leiter, 2005[69] | RCT | 0/78 versus 3/405 |
| Van der Meer, 2009[116] | RCT | No events reported in either arm |
| Asche, 2008[162] | Observational study | 0/2326 versus 19/889 |

RCT = randomized controlled trial

**Metformin versus sulfonylureas.** Three observational studies described heart failure events.[158 167 168] A retrospective cohort study from Canada reported a higher rate of heart failure with sulfonylurea compared to metformin (adjusted HR 1.2, 95% CI 1.0 to 1.5). The risk of heart failure associated with sulfonylureas was dose-responsive with increasing risk with higher doses.[168] Another retrospective cohort study of nearly 30,000 patients using the General Practitioner Research Database in the UK reported a higher incidence of heart failure with sulfonylurea monotherapy (27/1000 person-years) compared to metformin monotherapy (19/1000 person-years).[158] A short observational study of around 10 months reported a lower risk of incident heart failure hospitalization among metformin users (HR 0.7, 95% CI 0.5 to 1.0, p = 0.05) compared to sulfonylurea users.[167]

**Rosiglitazone versus pioglitazone.** One prospective observational study in Australia reported nearly similar rates of pulmonary edema when pioglitazone (2/107) was compared to rosiglitazone (3/96).[164]

**Thiazolidinediones versus sulfonylureas.** Three trials[30 123 151] and three observational studies[162 167 168] examined outcomes for this comparison (Table 15). Low grade evidence showed that thiazolidinediones increase the risk of heart failure when compared to sulfonylureas.

**Table 15. Studies comparing thiazolidinediones with sulfonylureas for heart failure events**

| Author, year | Study design | Heart failure incidence |
|---|---|---|
| Kahn, 2006[30] | RCT | 22/1456 versus 9/1441 (Statistically significant) |
| Agarwal, 2005[151] | RCT | 2/100 versus 2/100 |
| St John Sutton, 2002[123] | RCT | 1/63 versus 0/66; also reported 5 patients with cardiomegaly on thiazolidinedione and 2 on sulfonylurea |
| McAllister, 2008[168] | Retrospective cohort | HR = 1.3 (95% CI 0.9 to 1.9) |
| Asche, 2008[162] | Observational study | 19/889 and 0/2223 |
| Karter, 2005[167] | Observational study | HR = 1.3 (95% CI 0.85 to 1.92) for incident hospitalization for heart failure |

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial

**Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones.** The RECORD trial was a long-term noninferiority trial designed to assess cardiovascular outcomes with rosiglitazone. Low grade evidence from the RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure in comparison to combination of sulfonylurea and metformin (61/2220 versus 29/2227, RR 2.1, 95% CI 1.35 to 3.27)[14]

**Combination of metformin and a basal insulin versus combination of metformin and another insulin.** In an RCT that compared a combination of insulin glargine daily plus metformin with combination of insulin lispro 75/25 plus metformin, hospitalization due to heart failure was reported in a single patient on the insulin lispro 75/25 and metformin combination.[137]

**Combination of metformin and thiazolidinediones versus combination of thiazolidinediones and sulfonylureas.** A 6-month observational study from Germany reported rates of heart failure that were higher with a thiazolidinedione and sulfonylurea (0.47/100 person-years) relative to a thiazolidinedione and metformin combination (0.13/100 person-years).[150]

## The Evidence for Lactic Acidosis (Appendix G, Table 12)

We identified two double blind RCTs comparing the rates of lactic acidosis between metformin, second-generation sulfonylurea, and metformin in combination with a second-generation sulfonylurea.[50 51] Both the trials were conducted in the US and lasted only 16 to 18 weeks. The average age of individuals participating in both these trials was greater than 50 years and individuals with significant renal or liver diseases were excluded. There were no cases of lactic acidosis reported in any of the treatment arms in either of the two trials.

## The Evidence about Cancer (Appendix G, Table 12)

We found three RCTs which evaluated cancer outcomes.[79 85 160] The first trial was a 56-week, multi-center trial in the US and Puerto Rico conducted among 502 individuals randomly assigned to pioglitazone or glyburide.[85] Two events of stage IV colon cancer (0.8%) were reported in the sulfonylurea group while none were reported in the thiazolidinedione group. The second trial was a 30-week trial conducted among 190 individuals randomly assigned to sitagliptin or placebo as an add-on to ongoing metformin therapy.[79] Three cases of cancer were reported in the metformin only group while none were reported in the combination metformin and sitagliptin group.

Additionally, we identified a single cross-over RCT reporting cancer outcomes that compared metformin to meglitinides.[160] The study was conducted in 96 individuals with two 4-month treatment periods with a 1-month washout period in between. Two cancers (one cancer of the vocal plicae and one lung cancer) were reported in patients on metformin, while none were reported among patients on meglitinides.

## The Evidence about Severe Allergic Reactions

There were no studies included in the report that evaluated the outcome of severe allergic reactions.

## The Evidence about Hip and Non-Hip Fractures (Appendix G, Table 12)

**Metformin versus thiazolidinediones.** The ADOPT study was a large RCT comparing rosiglitazone, metformin, and glyburide for a median of 4 years duration. They reported a separate analysis examining time to first fracture, rates of occurrence, and fracture site. The estimated hazard ratio for risk of fracture with metformin versus rosiglitazone was 1.57 (95% CI 1.13 to 2.17). They also included a subgroup analysis to examine fracture risk by sex (see Key Question 4). Among the 1840 women, there were 111 fractures, 60 (0.3%) in the rosiglitazone arm, 30 (5.1%) in the metformin arm, and 21 (3.5%) in the glyburide arm. This represented an increased HR for risk of fracture for rosiglitazone versus metformin (HR 1.81, 95% CI 1.17 to 2.80, p = 0.008) among women. There was no excess risk among men.[170]

**Metformin versus sulfonylureas.** Two RCTs reported fractures for this comparison.[47 170] In the ADOPT sub-analysis described above,[170] there were slightly more fractures in the metformin arm (59 out of 1454, 4.1%) compared with the glyburide arm (49 out of 1441, 3.4%) but no statistical test was performed. A small 16-week trial, conducted in Taiwan, compared glyburide (N = 17) and metformin (N = 17) as monotherapy and in combination. This study reported one fracture of the right metacarpal bone of the hand in a single subject in the glyburide arm.[47]

**Metformin versus a combination of metformin and sulfonylureas.** The above 16-week trial only reported a single fracture in the glyburide monotherapy group as compared to no fractures in the two combination metformin plus glyburide groups (N = 42).[47]

**Metformin versus a combination of metformin and sitagliptin.** One 30-week multi-continent, parallel arm RCT randomized 190 subjects to metformin or metformin plus sitagliptin.[79] They reported one case of osteoporotic limb fracture among the 94 individuals in the metformin group and no fractures in the metformin plus sitagliptin group.

**Thiazolidinediones versus sulfonylureas.** This comparison was assessed by two RCTs.[85 170] In the ADOPT sub-analysis on fracture risk, there was an increased HR (2.13, 95% CI 1.30 to

3.51) for rosiglitazone as compared with glyburide.[170] A second trial randomized subjects to pioglitazone or glyburide.[85]There were no reported cases of ankle fracture among the 251 individuals in the pioglitazone arm. There were 2 ankle fractures (incidence of 0.2%) among the 251 participants in the glyburide group, without a statistical test.

**Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones.** The RECORD study was an open-label non-inferiority multicenter RCT with 4,447 participants with type 2 diabetes taking either metformin or a sulfonylurea randomly assigned to one of three arms, metformin plus rosiglitazone, sulfonylurea plus rosiglitazone, or metformin plus sulfonylurea.[14] The incidence of participant-reported bone fractures was higher in the combined metformin plus rosiglitazone and sulfonylurea plus rosiglitazone arms, with 49 events out of 2220 participants (2.3%) versus 36 out of 2227 participants (1.6%) in the metformin plus sulfonylurea arms. The risk ratio was 1.57 (95% CI 1.26 to 1.97, $p < 0.0001$) for the rosiglitazone combination therapy arms compared with the combination metformin plus sulfonylurea arms. Consistent with the ADOPT trial reporting metformin versus rosiglitazone monotherapy, the RR was higher for women compared with men (RR 1.82, 95% CI: 1.37 to 2.41 versus 1.23, 95% CI: 0.85 to 1.77). The fractures occurred predominantly in the upper limb, distal lower limb, and not hip or femur fractures.[14]

## The Evidence about Acute Pancreatitis (Appendix G, Table 12)

We identified only one trial that reported on the rates of acute pancreatitis with the specific drug comparisons. The LEAD 2 trial reported one patient with pancreatitis in the metformin plus glimepiride arm compared to none in the metformin arm.[78]

## The Evidence about Cholecystitis (Appendix G, Table 12)

Two RCTs reported on the outcome of cholecystitis.[44 73] One trial identified a single participant with cholecystitis among 105 treated with a thiazolidinedione; none of the 100 patients treated with metformin suffered from cholecystitis.[44] In the other RCT, one patient had cholecystitis of 280 in the combination metformin plus thiazolidinedione arm compared to none of 288 treated with thiazolidinedione alone.[73]

## The Evidence about Macular Edema (Appendix G, Table 12)

In one trial, macular edema was reported in two subjects with metformin plus thiazolidinedione compared to none in the metformin plus meglitinide arm.[110]

## The Evidence about Gastrointestinal Effects (Appendix G, Table 12)

Forty-one studies examined GI adverse events, which included nausea, abdominal pain, diarrhea or a composite outcome. We included 21 studies[28 42 44 48-51 53 54 56 58 59 65 67 72-74 93 108 115 133] from the 2007 CER[17] and identified 20 additional studies[30 39 47 63 66 70 71 79 80 84 85 103 106 113 117 120 125 129 160 162] for the update that reported GI adverse events for comparisons of interest.

**Metformin versus thiazolidinediones.** Four RCTs compared GI adverse events between metformin and either rosiglitazone or pioglitazone (Table 16).[30 39 42 44] GI adverse events rates were consistently higher in the metformin arm compared with a thiazolidinedione.

**Metformin versus sulfonylureas.** Eleven RCTs examined GI adverse events between metformin and a second-generation sulfonylurea.[30 47-51 53 54 56 58 59] GI adverse events rates were consistently higher in the metformin arm compared with a sulfonylurea (Table 17).

**Table 16. Randomized controlled trials comparing metformin with thiazolidinediones for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin versus thiazolidinediones) |
|---|---|---|
| Kahn, 2006[30] | Combined GI events | 38% (557/1454) versus 23% (335/1456) |
| | Nausea | 11.7% (170/1454) versus 7.7% (112/1456) |
| | Vomiting | 5.8%(84/1454) versus 4% (58/1456) |
| | Diarrhea | 23.7%(345/1454) versus 8.9% (129/1456) |
| | Abdominal discomfort | 15.4%(224/1454) versus 11.1% (161/1456) |
| Rosenstock, 2006[39] | Nausea/vomiting | 13% (20/154) versus 8% (13/159) |
| | Diarrhea | 21% (32/154) versus 7% (11/159) |
| | Dyspepsia | 8% (12/154) versus 9% (14/159) |
| Schernthaner, 2004[42] | | |
| | Diarrhea | 11.1% (66/597) versus 3.2% (19/597) |
| | Nausea | 4.2% (25/597) versus 2.3% (14/597) |
| Pavo, 2003[44] | Diarrhea | 16% (16/100) versus 3% (4/105) |

GI = gastrointestinal

**Table 17. Randomized controlled trials comparing metformin with sulfonylureas for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin versus sulfonylureas) |
|---|---|---|
| Chien, 2007[47] | Combined GI events | 32% (8/25) versus 13% (3/23) |
| Kahn, 2006[30] | Combined GI events | 38% (557/1454) versus 22% (316/1441) |
| | | 11.7% (170/1454) versus 6.9% (99/1441) |
| | Nausea | 5.8% (84/1454) versus 3.1% (45/1441) |
| | | 23.7% (345/1454) versus 9.9% (142/1441) |
| | Vomiting | 15.4% (224/1454) versus 11.3% (163/1441) |
| | Diarrhea | |
| | Abdominal discomfort | |
| Garber, 2003[49] | Nausea/Vomiting | 10.4% (17/164) versus 6.6% (10/151) |
| | Abdominal pain | 6.1% (10/164) versus 4% (6/151) |
| | Diarrhea | 18% (30/164) versus 5.3% (18/151) |
| Blonde, 2002[51] | Nausea and vomiting | 12.4% (19/153) versus 5.5% (9/164) |
| | Dyspepsia/Heartburn | 4.6% (7/153) versus 3% (5/164) |
| | Flatulence | 2% (3/153) versus 0% (0/164) |
| Hermann, 1994[56] | Any GI outcome | 63% (24/38) versus 32% (11/34) |
| | Abdominal pain | 18% (7/38) versus 6% (2/34) |
| | Diarrhea | 50% (19/38) versus 0 (0/34) |
| | Nausea | 24% (9/38) versus 9% (3/34) |
| | Withdrawal for GI symptoms | 14% versus 0% |
| Goldstein, 2003[50] | Diarrhea | 17.3% (13/75) versus 13.1% (11/84) |
| Derosa, 2004[48] | Nausea and diarrhea | 2.4% (2/75) versus 0% (0/73) |
| Charpentier, 2001[59] | Diarrhea | 7% (5/75) versus 1% (1/150) |
| DeFronzo, 1995[58] | Nausea and diarrhea | 1.4% (3/210) versus 1.0% (2/209) |
| Amador-Licona, 2000[54] | Diarrhea and abdominal pain | 14.3% (4/28) for metformin; event rates are not reported for sulfonylurea |
| Garber, 2002[53] | | metformin (n = 159); glyburide (n = 160) |
| | Any GI outcome | 43% versus 24% |
| | Diarrhea | 15.1% versus 4.4% |
| | Nausea/Vomiting | 6.3% versus 0.6% |
| | Abdominal pain | 5% versus 3.1% |
| | Dyspepsia | 5% versus 2.5% |

GI = gastrointestinal

One retrospective cohort study compared the risk of adverse events associated with the use of metformin, sulfonylureas, and thiazolidinediones among geriatric patients in a outpatient settings.[162] Consistent with the results from the trials, this cohort reported higher GI adverse events with the use of metformin. However, the incidence of metformin-associated diarrhea in

this study was much lower than in the clinical trials and the authors suggested that it may be a result of pre-therapy screening or effective patient self-management.

**Metformin versus sitagliptin.** A single RCT compared metformin and sitagliptin and assessed the incidence of total GI adverse events, including abdominal pain, diarrhea, nausea, and vomiting.[63] Compared with the arm with highest dose of metformin, there were fewer events for sitagliptin arm overall (31% versus 20%), as well as for specific GI events, diarrhea (12% versus 4%), nausea (10% versus 1%), and vomiting (3% versus 1%). There was no reported difference between groups for abdominal pain.

**Metformin versus meglitinides.** Four RCTs compared GI adverse events between metformin and a meglitinide (Table 18).[65-67 160] Composite GI adverse events rates were generally higher in the metformin arm compared with a meglitinide, but one trial[66] reported higher diarrhea rates, but similar rates for abdominal pain and dyspepsia.

**Table 18. Randomized controlled trials comparing metformin with meglitinides for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin versus meglitinides) |
|---|---|---|
| Lund, 2007[160] | Combined GI events | 70% (65/83) versus 47% (47/82) |
| Horton, 2004[66] | Diarrhea | 20.2% (21/104) versus 3.8% (4/104) |
| | Abdominal pain | 6.7% (7/104) versus 6.7% (7/104) |
| | Dyspepsia | 7.7% (8/104) versus 9.6% (10/104) |
| Derosa, 2003[67] | Withdrawal for GI symptoms | 3.6% (2/56) versus 0% (0/56) |
| Horton, 2000[65] | Withdrawal for GI symptoms | 3.4% (6/178) versus 0.6% (1/179) |

GI = gastrointestinal

**Metformin versus a combination of metformin and thiazolidinediones.** Seven RCTs compared the rates GI adverse events between metformin and a combination of metformin and a thiazolidinedione, showing similar rates between the two groups(Table 19).[39 70-74 129] Where there are lower rates of diarrhea in the combination arm, the a lower dose of metformin was administered when used in combination than when used as monotherapy.

**Table 19. Randomized controlled trials comparing metformin with a combination of metformin and thiazolidinediones for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin versus metformin plus thiazolidinediones) |
|---|---|---|
| Kaku, 2009[70] | Constipation & Abdominal Pain | 2.3% (2/86) versus 2.4% (2/83) |
| Scott, 2008[71] | Combined GI events | 9% (8/91) versus 7% (6/87) |
| Rosenstock, 2006[39] | Diarrhea | 51% (79/154) versus 47% (73/155) (Minimal difference in rates of nausea, vomiting and dyspepsia) |
| Stewart, 2006[129] | Diarrhea | 18% (49/272) versus 8% (20/254) |
| Bailey, 2005[73] | Withdrawal due to GI events | 5.4% (15/280) versus 3% (9/288) |
| Weissman, 2005[72] | Withdrawal due to GI events | 6.8% (26/384) versus 3.1% (12/382) |
| | Combined GI events | OR 1.6 (95% CI 1.2 to 2.2) |
| Gomez-Perez, 2002[74] | Combined GI events | 15.4% (5/35) versus 16.8% (6/35) for low dose combination and 16.8% (6/36) for high dose combination |

CI = confidence interval; GI = gastrointestinal; OR = odds ratio

**Metformin versus a combination of metformin and sulfonylureas.** Nine RCTs examined GI adverse events between metformin and metformin plus a second-generation sulfonylurea.[28 47 49-51 53 56 58 59] One RCT compared subjects with GI adverse events between metformin and a

combination of metformin plus glyburide and favored the combination arm.[47] It reported an incidence of 32% for metformin alone versus 7.69% in the metformin/lowest dose glyburide combination (p = 0.021).[47] The combination arm had a lower dose of metformin than the metformin monotherapy arm, which may account for this difference. Six studies that were included from the 2007 CER[17] compared GI events between metformin versus metformin plus glyburide or glibenclamide.[28 49 51 53 56 58] Two studies did not significantly favor either arm;[50 58] the others found fewer events in the combination arm for at least one GI adverse event, most commonly diarrhea.[28 49 51 53 56 59] In general, the combination arm was favored if the doses of metformin in the combination was lower than in the monotherapy arm.

**Metformin versus a combination of metformin and sitagliptin.** Four RCTs compared the incidence of GI adverse events between metformin and metformin plus sitagliptin and there was no clear difference between the two groups (Table 20).[63 71 79 80]

**Table 20. Randomized controlled trials comparing metformin with a combination of metformin and sitagliptin for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin versus sitagliptin) |
|---|---|---|
| Williams-Herman, 2009[63] | Combined GI events | 31% (57/182) versus 29% (53/182) (no difference) |
| | Dairrhea | 7% versus 13% (high dose combination) and 9% (low dose combination) |
| | Abdominal Pain | 4% versus 3% (high dose combination) and 4% (low dose combination) |
| | Vomitting | 0% versus 2% (high dose combination) and 4% (low dose combination) |
| Scott, 2008[71] | Combined GI events | 9% (8/91) versus 1% (1/94) |
| Raz, 2008[79] | Abdominal Pain | 7.4% (7/94) versus 10.4% (10/96) |
| | Gastritis | 3.2% (3/94) versus 2.1% (2/96) |
| | Upper GI Hemorrhage | 1 case in metformin versus 0 in combination group |
| Charbonnel, 2006[80] | Combined GI events | 10.5% (25/237) versus 11.9% (55/464) (no difference) |

GI = gastrointestinal

**Metformin versus a combination of metformin and meglitinides.** One RCT compared diarrhea, abdominal pain, dyspepsia, and nausea between metformin and metformin plus nateglinide.[66] The incidence of diarrhea and dyspepsia were similar between the treatment groups, but the incidence of abdominal pain was 6.7% in the metformin arm compared with 12.4% in the combination arm.

**Thiazolidinediones versus sulfonylureas.** Three RCTs compared diarrhea between pioglitazone or rosiglitazone and either glyburide or its chemical equivalent, glibenclamide and showed no consistent difference between the groups (Table 21).[30 84 85]

**Thiazolidinediones versus meglitinides.** A single RCT compared diarrhea incidence between pioglitazone and repaglinide and reported slightly fewer events in the pioglitazone arm (3% versus 5%).[93]

**Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas.** Four RCTs examined GI adverse events between metformin plus a thiazolidinedione and metformin plus a sulfonylurea with inconsistent results (Table 22).[103 106 108 133]

**Table 21. Randomized controlled trials comparing thiazolidinediones with sulfonylureas for gastrointestinal effects**

| Author, year | Outcome | Event rates (thiazolidinediones versus sulfonylureas) |
|---|---|---|
| Jain, 2006[85] | Diarrhea | 6.0% (15/251) versus 6.4% (16/251) (no difference) |
| Hanefeld, 2007[84] | Combined GI events | 5.5% versus 3.4% (no difference) (4mg dose of rosiglitazone) |
| Kahn, 2006[30] | Any GI outcome | 23% (335/1456) versus 21.9% (316/1441) |
| | Nausea | 8% (112/1456) versus 7% (99/1441) |
| | Vomiting | 4% (58/1456) versus 3% (45/1441) |
| | Diarrhea | 9% (129/1456) versus 10% (142/1441) |
| | Abdominal discomfort | 11% (161/1456) versus 11% (163/1441) |

GI = gastrointestinal; mg = milligram

**Table 22. Randomized controlled trials comparing a combination of metformin and thiazolidinediones with a combination of metformin and sulfonylureas for gastrointestinal effects**

| Author, year | Outcome | Event rates (metformin plus thiazolidinedione versus metformin plus sulfonylurea) |
|---|---|---|
| Umpierrez, 2006[106] | Diarrhea | 4.7% (5/104) versus 6% (6/96) (no difference) |
| Hamann, 2008[103] | Combined GI events | 13% (38/294) versus 18% (54/301) |
| Derosa, 2005[133] | Flatulence | 4.2% (2/48) versus 2.1% (1/47) |
| Garber, 2006[108] | Combined GI events | 10% (16/155) versus 11% (18/159) (no difference) |
| | Diarrhea | 3% (5/155) versus 6% (10/159) |
| | Abdominal Pain | 4% (6/155) versus 6% (10/159) |

GI = gastrointestinal

**Combination of metformin and thiazolidinediones versus combination of metformin and sitagliptin.** One RCT compared GI adverse events in the combination of metformin plus rosiglitazone versus the combination metformin plus sitagliptin and did not favor either arm for total GI events or for the specific events of diarrhea, nausea, abdominal pain, and vomiting.[71]

**Combination of metformin and sulfonylureas versus combination of metformin and sitagliptin.** One RCT compared diarrhea, abdominal pain, nausea, and vomiting between metformin with glipizide and metformin with sitagliptin and did not favor either arm.[113]

**Combination of metformin and sulfonylureas versus combination of metformin and meglitinides.** One RCT compared diarrhea and constipation between metformin with glyburide and metformin with nateglinide and did not show an overall difference between arms, but did report more dyspepsia in the metformin with glyburide arm (13% versus 3%).[125]

**Combination of metformin and a basal insulin versus combination of metformin and another insulin.** One RCT compared diarrhea incidence between metformin in a combination regimen with either insulin glargine or lispro and neither arm was favored.[120]

**Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas.** Two RCTs compared GI adverse events between a combination of metformin and a sulfonylurea versus a combination of a thiazolidinedione and a sulfonylurea.[115][117] One RCT compared diarrhea incidence and reported a higher incidence of diarrhea in the metformin combination arm (14.4% versus 3.4%). A second RCT had consistent results, favoring the thiazolidinedione combination arm compared with the metformin combination arm. It reported higher rates of diarrhea and withdrawals due to diarrhea in the metformin combination arm (diarrhea: 12% in the metformin combination arm versus 3% in the thiazolidinedione combination arm; withdrawals: 23% in the metformin combination arm versus 12% in the thiazolidinedione combination arm, respectively).[115]

## Gray Literature

**Metformin versus sulfonylureas.** One study evalauted the safety profile of metformin vs. sulfonylurea.[156] The study reported a higher incidence of GI adverse drug effects in the metformin group (20.3%) compared to the sulfonylurea groups (12.9%). Hypoglycemia (defined as finger stick glucose < 50mg%) was reported in 3% of those treated with sulfonylurea but none in those treated with metformin.

**Metformin versus sitagliptin.** In a pre-approval trial, sitagliptin was tested against metformin in a 24-week trial. Adverse events were very similar except for gastrointestinal side effects which were much higher with metformin (54/364 versus 11/179). The rates of hypoglycemia, cancer, fractures, and cholecystitis were very low in both groups.[154] This is likely to be the same data as was published by Williams-Herman.[63]

**Metformin versus a combination of metformin and thiazolidinediones.** In a pre-approval trial, the addition of a thiazolidinedione to metformin resulted in no increased rate of hypoglycemia when compared to rates with metformin alone.[171] This differs from the published data which suggests that patients treated with the combination have slightly more hypoglycemia.

In another study, metformin was compared to metformin with rosiglitazone (4 mg and 8 mg) in a 26-week trial in the US. Hypoglycemia requiring assistance was reported in 1 patient on 4 mg rosiglitazone, 1 patient on 8 mg rosiglitazone and none in the metformin arm.[152]

**Metformin versus a combination of metformin and sulfonylureas.** The combination of metformin and sulfonylurea was evaluated against metformin in a 28-week trial. Hypoglycemia was reported in 3% of patients on metformin, 11% of patients on a fixed combination of 250 mg/1.25 mg and 38 % of patients on 500 mg/2.5 mg. While no patient on metformin had hypoglycemia below 50 mg/dL, 8 of 158 patients in the low dose combination group and 26 of 168 in the high dose combination group reported hypoglycemia less than 50 mg/dL. In the same study the frequency of GI adverse events was 43.4% with metformin monotherapy, 31.6% with the low dose combination ($p = 0.037$) and 38.3 % with the higher dose combination (difference with metformin not significant).[153] One study evaluated metformin 500 mg and a low dose combination and a high dose combination with approximately 160 participants in each group. One patient on metformin reported symptoms of hypoglycemia compared to 22 patients on combination therapy. There were no reports of serious hypoglycemia. GI adverse events occurred in 39% of metformin recipients versus 35% of metformin with sulfonylurea recipients.[155]

One study evalauted the safety profile of combination of metformin plus sulfonylurea versus metformin (500 mg).[156] The study reported a higher incidence of GI adverse effects in metformin group (20.3%) compared to in any of the three combination groups (15.9%, 12.2% and 11.6% respectively). Hypoglycemia (defined as finger stick glucose less than 50 mg/dL) was reported in 5%, 8% and 9% of those treated with the combination but none in those treated with metformin.

**Metformin versus a combination of metformin and sitagliptin.** One trial for FDA approval of the combination of metformin and sitagliptin reported on the adverse outcomes of this combination (two dose levels) compared to metformin alone (two dose levels). The rates of hypoglycemia were low in the subjects treated in the combination group (6/372) and similar to that in the metformin groups (3/364). There was a single report of congestive heart failure in the combination group. Cancers were rare and equivalent in the groups as were fractures. Similarly,

GI adverse events were reported in 49 participants in the combination groups and 54 in the metformin groups.[154] This is probably the same data as was published by Williams-Herman.[63]

**Thiazolidinediones versus sulfonylureas.** This was a 52-week active-controlled study at different centers in Europe which compared two dosing levels of rosiglitazone to glyburide. Hypoglycemia was reported in 25/207 patients on glyburide compared to 1/200 patients on 2 mg rosiglitazone and 3/191 on 4 mg rosiglitazone. Nearly half of the events in the glyburide arm occurred in the first 14 days of treatment.[152]

Another trial evaluated rosiglitazone 2mg twice daily versus glyburide 10 mg twice daily for 26 weeks. No hypoglycemia was reported in the thiazolidinedione group versus 6 of 106 patients in sulfonylurea group. Hypoglycemia requiring assistance was reported by one patient in the sulfonylurea group.[172] One additional study was double-blind placebo-controlled in which patients were randomized to rosiglitazone 1 mg or rosiglitazone 2mg or placebo and continued concurrent sulfonylurea therapy for 60 weeks in Europe**.** Hypoglycemia was reported in 2 % of patients on sulfonylurea alone compared to 3.4% and 5.3% on low dose thiazolidinedione with sulfonylurea and high-dose thiazolidinedione with sulfonylurea, respectively.[172]

A 52-week, double-blind RCT assessed the risk of hypoglycemia in those treated with a thiazolidinedione and those treated with a sulfonylurea.[173] A higher incidence of hypoglycemia was reported in patients treated with glyburide (12.1%) compared to those treated with rosiglitazone, 2 mg twice daily (0.5%) or rosiglitazone 4 mg twice daily (1.6%).

**Sulfonylureas versus sitagliptin.** One pre-approval trial of sitagliptin compared to glipizide showed markedly higher rates of hypoglycemia with glipizide when compared to sitagliptin (187/584 versus 29/588). The rates of congestive heart failure were low and similar (1 versus 1), as were GI sides effects (69 versus 74), cancer (7 versus 5) and cholecystitis (2 versus 0).[154] This is consistent with the published literature.

## Applicability

The applicability of this body of studies to the question of harm depends largely on the characteristics of the participants enrolled in the trials and how different the enrolled subjects are from the population of patients with diabetes who may experience harms when treated with these drugs. Additionally, the evidence can only be considered highly applicable if the doses of the drugs administered are comparable to that which is used in practice and the treated patients are monitored at a frequency comparable to that used in practice. We have no concerns about the applicability of these studies regarding the latter two criteria – the tested drug regimens are quite comparable by dose, frequency and monitoring to those used in a usual care setting.

The majority of the evidence about harms of these drugs comes from trials lasting two years or less. This duration of exposure of the subjects to the drug is shorter than would typically be seen in practice where these drugs may be prescribed for decades. Nonetheless, for the majority of the harms from the drugs, such as hypoglycemia or lactic acidosis, the incidence rate per year is *not* expected to increase with the duration of exposure to the drug. It is less clear with other harms like congestive heart failure whether this may be dependent on the duration of exposure. If the harms do increase with exposure-time, these relatively short trials are not entirely applicable to addressing this question.

The most pronounced threat to the applicability of these studies to addressing the question about harm is the enrolled population. The vast majority of studies had a mean age of participants in their 50s. Fewer than ten studies enrolled older participants and these had a mean

age in the low 60s. The prevalence of diabetes increases with age and these trials of harms from hypoglycemic agents are not necessarily applicable to older adults in their 70s and 80s or older. Further, the trials were very restrictive in their inclusion criteria, as is necessary for the safety of the participants. Thus, these studies are not necessarily applicable to the broader patient population with diabetes, many of whom have some renal insufficiency and coronary artery disease. The studies' populations were primarily Caucasian, although some of the trials in Asia enrolled only Asian patients. The proportion of participants of African descent was uniformly low (nearly always less than 10%), so the applicability of these results to that large patient population can not be assured.

# Key Question 4: Do safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular and cerebrovascular outcomes?

## Key Points

- Few studies had sufficient power to assess comparative effectiveness by subgroup. The evidence favoring one medication over another across subgroups is unclear.

Twenty-five studies reported comparative effectiveness and safety for sub-populations relevant to Key Question 4. Three studies[147 148 170] focused on a specific population for the study and the others conducted subgroup analyses of larger clinical trials or cohorts.

We included 19 RCTs and 6 cohort studies that addressed this key question. The majority of trials evaluated differences in the outcome of glycemic control by baseline HgbA1c.[64 71 79 81 112 113 119 174] Other trial outcomes included weight gain,[147 175 176] nephropathy,[151] fractures,[170] and congestive heart failure.[177] The cohort study outcomes focused on mortality[138 141 148 178] and congestive heart failure.[158 167] None of the studies conducted subgroup analyses on adverse events or mortality by age. We were unable to draw conclusions based on subgroup analyses and studies conducted in population subgroups because of the small number of studies available for each comparison of interest for each subgroup.

## The Evidence for Comparative Effectiveness and Safety in Sub-Populations

**Subpopulations by baseline glycemic control.** The majority of studies with subgroup analyses examined differences by baseline HgbA1c.[63 64 71 79 81 112 113 119 174] One RCT of metformin plus nateglinide versus metformin plus glyburide found that in both treatment arms, patients with higher baseline HgbA1c had a greater mean decrease in HgbA1c than patients with lower baseline HgbA1c.[112] Eight other trials similarly found that among all treatment arms, patients with higher HgbA1c had greater HgbA1c reduction (see Table 23). One study of metformin versus glibenclamide found that the percent of patients achieving target glucose control did not vary by baseline HgbA1c.[179] A study of patients treated with nateglinide plus metformin versus metformin alone found that the subgroup of patients with lower baseline

HgbA1c treated with high-dose nateglinide plus metformin had increased rates of hypoglycemic symptoms compared with patients with higher baseline HgbA1c.[81]

**Subpopulations by age, sex or race.** Five studies examined the impact of age on glycemic control, and while four found no difference in the effect on HgbA1c,[64 71 79 112] one found that patients over age 46 were more likely to require combination therapy to reach target glucose control than younger patients.[176] One study of the impact of diabetes treatment on congestive heart failure hospitalizations and cardiovascular mortality in patients with baseline New York class II or III heart failure found that among patients over age 64 years, higher rates of heart failure progression were noted in the pioglitazone users compared with glyburide users whereas no significant difference was seen in younger patients.[177]

Five studies examined the impact of sex on glycemic control, and found no differences in the effect on HgbA1c.[64 71 79 112 176] However, a retrospective analysis of the ADOPT trial by sex found that women treated with rosiglitazone were at increased risk of fracture relative to those treated with metformin or glyburide (HR 1.57 and 1.61, respectively)[170] over a median followup of four years. Consistent with the ADOPT trial, the RECORD study reported higher fracture risk in women compared with men (RR 1.82, 95% CI: 1.37 to 2.41 versus 1.23, 95% CI: 0.85 to 1.77) in the rosiglitazone plus metformin or sulfonylurea arm, as compared to the metformin plus sulfonylurea active control arm. The fractures occurred predominantly in the upper limb, distal lower limb, and were not hip fractures.[14]

One study examined impact of race on HgbA1c reduction, and found no impact on glycemic control.[112] A retrospective study of all-cause mortality among patients treated with hypoglycemic agents found that in women, metformin use was associated with lower mortality rate at one year than use of sulfonylureas, whereas in men mortality was increased in metformin users compared to sulfonylurea users.[178] Higher rates of heart failure progression in patients with baseline congestive heart failure were found among men treated with pioglitazone compared with glyburide, but rates were similar among women.[177] A retrospective study of heart failure development among patients with diabetes treated with metformin, insulin, or sulfonylurea found that women were less likely to develop heart failure than men across all treatment modalities.[158]

**Subpopulations by obesity or duration of diabetes.** Four studies found no effect of body mass index on HgbA1c reduction or glycemic control.[64 71 112 176] A study evaluating rosiglitazone plus metformin combination therapy versus metformin monotherapy found that among patients treated with metformin monotherapy fewer obese patients had at least one adverse event than non-obese patients, most commonly diarrhea and headache.[147] Another study of efficacy at achieving an HgbA1c less than 7% found that obese patients treated with metformin had greater chance of achieving the targeted HgbA1c level without additional agents than patients treated with sulfonylurea or insulin.[29] An important consideration in obese patients is medication impact on weight control, and a prospective study found that obese patients allocated to insulin had a greater mean increase in body weight than those allocated to sulfonylurea, and those allocated to metformin, on average, lost weight.[176]

Three studies found no impact of the duration of diabetes on glycemic control.[64 71 79] One study found that among patients treated with glibenclamide, the percent of patients achieving targeted glycemic control varied inversely with duration of diabetes.[179]

**Subpopulations by required medication dosage.** Two retrospective studies examined outcomes among patients who required higher than median doses of sulfonylurea and metformin and found that these high-dose sulfonylurea users (chlorpropamide, tolbutamide, glipizide, and glyburide) had higher risk of heart failure[168] and increased mortality[138] than those treated with

lower doses of these medications. Notably, high-dose users of metformin were not at elevated risk of heart failure or increased mortality.[138 168]

**Subpopulations by prior comorbid conditions.** A retrospective cohort study concluded that patients with a prior diagnosis of ischemic heart disease treated with either sulfonylurea or repaglinide had higher all-cause mortality than those treated with metformin alone after adjusting for age, sex, and co-morbidity.[148] A retrospective cohort study of patients with heart failure treated with metformin monotherapy, sulfonylurea monotherapy, or combination therapy found that use of metformin, alone or in combination, was associated with reduced all-cause 1-year mortality compared with sulfonylurea monotherapy (adjusted HR 0.66, 95% CI 0.44 to 0.97 and 0.54, 95% CI 0.42 to 0.70, respectively). This mortality benefit persisted after mean followup of 2.5 years.[141]

A trial of rosiglitazone versus glyburide for reduction of urinary albumin excretion found that among patients with baseline microalbuminuria (baseline urine albumin to creatinine ratio ≥ 30 ug/mg) there was a correlation between reduction in mean blood pressure and reduction in albumin excretion (r = 0.875) for patients treated with rosiglitazone. There was no significant correlation in patients treated with glyburide.[88]

**Observational studies.** Six cohort studies reported on subpopulations.[138 141 148 158 167 178] Three studies only reported analyses adjusted for several key patient characteristics but did not specifically report differences by group.[138 141 167]

Two observational studies reported on mortality in subpopulations. One retrospective cohort study included 8,494 participants in a nationwide population-based followup study of Danish patients with a myocardial infarction. Among women, the use of metformin was associated with a lower mortality rate than the use of sulfonylureas (adjusted 1-year HR = 0.49, 95% CI: 0.30 to 0.79), whereas among men the risk appeared to be increased (adjusted 1-year HR = 1.82, 95% CI: 1.25 to 2.64).[178] Another study favored MET over SU or repaglinide for all-cause age-adjusted mortality in people with prior ischemic heart disease.[148]

One study supported the finding from a RCT[177] that men were more likely to develop congestive heart failure than women regardless of pharmacologic treatments, which included various monotherapy and combination therapies for the cohort study.[158]

**Table 23. Results from randomized controlled trials reporting outcomes in a sub-population**

| Subgroup | Outcome | | | | |
|---|---|---|---|---|---|
| | HgbA1c | Weight | CHF | Fractures | Nephropathy |
| **Elevated baseline HgbA1c** | **Metformin vs. metformin + sitagliptin:**[64 79] Favors metformin + sitagliptin<br><br>**Metformin vs. metformin + meglitinides:**[81] Favors metformin + meglitinides<br><br>**Metformin + rosiglitazone vs. metformin + sitagliptin:**[71] Favors metformin + rosiglitazone<br><br>**Metformin + sulfonylurea vs. metformin + meglitinides:**[112] Conclusion unclear<br><br>**Metformin + glipizide vs. metformin + sitagliptin:**[113] Favors metformin + glipizide<br><br>**Metformin + sulfonylurea vs. metformin + premixed insulin:**[119] Favors metformin + premixed insulin | No evidence | No evidence | No evidence | No evidence |

**Table 23. Results from randomized controlled trials reporting outcomes in a sub-population (continued)**

| Subgroup | Outcome | | | | |
|---|---|---|---|---|---|
| | HgbA1c | Weight | CHF | Fractures | Nephropathy |
| **Age** | **Metformin vs. metformin + sitagliptin:**[64 79] Favors metformin + sitagliptin across age groups<br><br>**Metformin + rosiglitazone vs. metformin + sitagliptin:**[71] Conclusion unclear<br><br>**Metformin + sulfonylurea vs. metformin + meglitinides:**[112] Conclusion unclear | No evidence | **Thiazolidinediones vs. sulfonylureas:**[177] Favors sulfonylurea over pioglitazone in patients over age 64 with baseline CHF. | No evidence | No evidence |
| **Sex** | **Metformin vs. metformin + sitagliptin:**[64 79] Favors metformin + sitagliptin regardless of sex<br><br>**Metformin + thiazolidinedione vs. metformin + sitagliptin:**[71] Conclusion unclear<br><br>**Metformin + sulfonylurea vs. metformin + meglitinides:**[112] Conclusion unclear | **Metformin vs. metformin + pioglitazone:**[175] Unclear | **Thiazolidinedione vs. sulfonylurea:**[177] Favors sulfonylurea over pioglitazone in men with baseline CHF; Women less likely to develop heart failure than men across all treatment modalities | **Metformin vs. thiazolidinedione vs. sulfonylurea:**[170] Glyburide and metformin significantly favored over rosiglitazone in pre- and post-menopausal women; no difference in men. | No evidence |

**Table 23. Results from randomized controlled trials reporting outcomes in a sub-population (continued)**

| Subgroup | Outcome | | | | |
|---|---|---|---|---|---|
| | HgbA1c | Weight | CHF | Fractures | Nephropathy |
| **Duration of diabetes** | **Metformin vs. metformin + sitagliptin:**[64 79] Favors metformin + sitagliptin regardless of duration<br><br>**Metformin + thiazolidinedione vs. metformin + sitagliptin:**[71] Conclusion unclear | No evidence | No evidence | No evidence | No evidence |
| **Prior treatment** | **Metformin vs. metformin + sulfonylurea:**[78] Favors metformin + sulfonylurea regardless of prior treatment.<br><br>**Metformin + insulin glargine vs. metformin + premixed insulin:**[120] Favors metformin + premixed insulin regardless of prior treatment<br><br>**Metformin + thiazolidinedione vs. metformin + meglitinides:**[110] Favors metformin + thiazolidinedione for prior mono or combination therapy | No evidence | **Thiazolidinedione vs. sulfonylurea:**[177] Favors sulfonylurea over pioglitazone in patients with baseline CHF and prior insulin use. | No evidence | No evidence |

**Table 23. Results from randomized controlled trials reporting outcomes in a sub-population (continued)**

| Subgroup | Outcome | | | | |
|---|---|---|---|---|---|
| | HgbA1c | Weight | CHF | Fractures | Nephropathy |
| **Obesity** | **Metformin vs. sulfonylurea:**[29] Favors sulfonylurea among obese patients in long-term treatment (over 9 years)<br><br>**Metformin vs. metformin + rosiglitazone:**[147] Favors metformin + rosiglitazone among obese patients<br><br>**Metformin vs. metformin + sitagliptin:**[64 79] Favors metformin + sitagliptin across BMI groups<br><br>**Metformin + rosiglitazone vs. metformin + sitagliptin:**[71] Conclusion unclear<br><br>**Metformin + sulfonylurea vs. metformin + nateglinide:**[112] Conclusion unclear | **Metformin vs. sulfonylurea:**[176] Obese patients lost more weight with metformin<br><br>**Metformin vs. metformin + rosiglitazone:**[147] Favors metformin for weight loss among obese patients | No evidence | No evidence | No evidence |
| **Elevated DBP** | No evidence | No evidence | No evidence | No evidence | **Pioglitazone vs. sulfonylurea:**[151] Conclusion unclear |

**Table 23. Results from randomized controlled trials reporting outcomes in a sub-population (continued)**

| Subgroup | Outcome | | | | |
|---|---|---|---|---|---|
| | HgbA1c | Weight | CHF | Fractures | Nephropathy |
| **Race** | **Metformin + sulfonylurea vs. metformin + nateglinide:**[112] Conclusion unclear | No evidence | No evidence | No evidence | |
| **Baseline proteinuria** | No evidence | No evidence | No evidence | No evidence | **Pioglitazone vs. sulfonylurea:**[151] Conclusion unclear<br><br>**Rosiglitazone vs. sulfonylurea:**[88] Favors rosiglitazone |

BMI = body mass index; CHF = congestive heart failure; DBP=diastolic blood pressure; HgbA1c = hemoglobin A1c

## Quality Assessment

Out of the 120 trials included in this report, only five were described as non-randomized trials and one was a cross-over study (Appendix G, Table 13). Among the 114 RCTs, 32% described their randomization scheme and another 59% were described as being double-blinded. About one-third of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials described the withdrawals and dropouts (81%). The studies included in the 2007 CER had quality evaluated at the time of that review and we used a different overall rating process for the additional articles identified for the updated CER. Among the 55 trials included from the 2007 CER, only about one third of them received the highest two quality scores (4 or 5), on a five point scale. Among the 65 trials identified for the update, 44% were rated as 'good' quality, 42% as 'fair' quality and 14% as 'poor' quality.

We performed a quality assessment of observational studies for the 14 observational studies newly identified for the update (Appendix G, Table 14). Quality was not assessed for observational studies for 2007 CER. Four completely reported the study setting or study population from which the study sample was drawn, twelve adequately described inclusion/exclusion criteria, and half provided some description of key characteristics of the study population. Only six of the studies provided details about treatment, which included treatment type, dose, timing and duration of medication, but 11 adequately described the outcomes of interest and how they were measured. The majority of studies conducted appropriate statistical analyses and presented results adjusted, or stratified for differences in groups or stated that the groups were comparable at baseline. Only one study described the number of participants who were lost to followup after the start of the period of observation. In summary, all 14 of the observational studies were rated as having fair overall quality.

## Articles Reporting More Than One Study

Nine studies reported on more than one study (see Table 24).[180-188] Since many of these studies pooled data from studies already included in our review, we did not abstract that data. For articles that pooled data from studies not included in our review, we abstracted and reported the results. The results from these studies are consistent with the findings from our review.

**Table 24. Summary of studies reporting on more than one study**

| Author, year | Results of pooled studies if not duplicated or already in our report |
|---|---|
| Belcher, 2004[180] | Mean blood pressure was slightly reduced by all treatments, with pioglitazone treatment resulting in the largest falls (approximately 1.5 mmHg). Hospitalizations for cardiac or cerebrovascular events were similar with the different treatments. Overall mortality was 7 of 1857 for pioglitazone and 10 of 1856 for non-pioglitazone treatments, of which 3 and 6 were cardiac deaths, respectively. The incidence of congestive cardiac failure was similar with pioglitazone (12/1857) and non-pioglitazone (10/1856) treatments. |
| Khan, 2004[181] | Pioglitazone, alone or combined with metformin or sulfonylurea, resulted in mean decreases in triglycerides (9 to 11%), and mean increases in HDL cholesterol (17 to 20%). |
| Davidson, 2004[182] | Individual studies were included in the report |
| Perez, 2004[183] | This study mostly discusses subfractionations of lipids. They do state that pioglitazone in combination with metformin or sulfonylurea was significantly associated with an increase in HDL after 24 weeks. For pioglitazone plus metformin only, LDL increased from baseline significantly. |
| Belcher, 2005[184] | Individual studies were included in the report |
| Belcher, 2005[185] | Individual studies were included in the report |
| Charbonnel, 2005[186] | Individual studies were included in the report |
| Ceriello, 2005[187] | Individual studies were included in the report |
| Rendell, 2003[188] | Individual studies were included in the report |

HDL = high density lipoprotein; LDL = low density lipoprotein; mmHg = millimeters of mercury

# Discussion

This report addresses the comparative effectiveness and safety of oral diabetes medications used most frequently in the United States as monotherapy and in combination therapy. This report updates and adds to a previous Comparative Effectiveness Report (CER)[17] published in 2007 comparing the effectiveness and safety of oral diabetes medications, mainly as monotherapy. We identified 153 articles, which included 65 trials and 14 observational studies that have been published since we completed our 2007 report.

Prior to beginning this review, we conducted an extensive preliminary review and assessed evidence gaps identified in the first report. We included two newer medication classes not included in the first review, namely the injectable glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, and the DPP-4 inhibitor, sitagliptin. We also expanded the scope of the review by including insulin therapy as a second line treatment in combination with oral medications, broadening the comparisons of interest to address two-drug combinations, and including additional safety outcomes.

We defined our key questions similarly to the first report, focusing on intermediate outcomes, long-term clinical outcomes, adverse events and sub-populations. As expected, intermediate clinical outcomes such as HgbA1c levels were studied more frequently in RCTs than long-term clinical outcomes of diabetes, with 113 articles included in Key Question 1 about glycemic control and other intermediate outcomes, 53 articles that applied to Key Question 2 on long-term clinical outcomes, 87 articles for Key Question 3 on adverse events, and 25 articles that contained information for Key Question 4, addressing medication effectiveness and safety in sub-populations.

In this update we build upon the previous evidence report by focusing on the head-to-head comparisons of medications that should be of greatest relevance to clinicians and their patients, which includes both monotherapy and combination therapy comparisons (Table 2). We focused our review on combinations that contained either metformin or a thiazolidinedione in combination with another medication, and identified 81 articles that met our inclusion criteria. Our comprehensive review of combination therapies is an important contribution to the literature because it is the first to include this many combinations for a range of outcomes. Overall, we found that a second oral agent is additive both in terms of improved glycemic control and increased risk for adverse events, which confirmed findings from the first report and subsequent review.[17 189]

Seven articles compared the new DPP-4 inhibitor, sitagliptin, with other agents either in monotherapy or combination comparisons. Overall, sitagliptin improved HgbA1c when added to metformin without additional hypoglycemia risk. However, we were unable to make clear conclusions about the safety and long-term effects of sitagliptin because of few available studies. Our findings on sitagliptin were consistent with a Cochrane systematic review[190] and another recent systematic review.[191]

Unfortunately, no studies using exenatide met the inclusion criteria for this report (see Limitations). The American Diabetes Association Consensus/European Association for the Study of Diabetes consensus statement has suggested the use of a GLP-1 receptor agonist as an add-on treatment to metformin,[18] a comparison of interest we included for this report. The largest recent systematic review of exenatide identified 21 RCTs (six unpublished) and showed a reduction in HgbA1c by one absolute percentage point in comparison with placebo, with a low risk of

hypoglycemia.[192] Since exenatide's release, the FDA published alerts about postmarketing case reports of pancreatitis[193] and acute renal failure and insufficiency.[194]

This review was also unique because we included five studies that compared the addition of either a premixed insulin or a basal insulin to an oral medication. We found that premixed insulin products in combination with metformin reduced HgbA1c to a greater extent than a basal insulin with metformin, but the hypoglycemia risk difference was unclear. In a recent comparative effectiveness report on premixed analogues, also commissioned by AHRQ, long-acting insulin analogues were associated with lower hypoglycemia risk but were inferior in decreasing HgbA1c levels compared with premixed insulin analogues.[195] In addition, two recent systematic reviews compared NPH insulin with longer-acting insulins, glargine or detemir. Most studies combined insulin with oral medications. They reported no difference in glycemic control between the two insulin products, and slightly lower hypoglycemia with the longer-acting insulins.[196 197]

# Key Findings and Implications

## Intermediate Outcomes

**Hemoglobin A1c.** We found that most oral diabetes medications (metformin, thiazolidinediones, sulfonylureas, and repaglinide) reduced HgbA1c to a similar degree by about 1 absolute percentage points when compared with baseline values. Combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, and metformin plus sitagliptin) were generally more effective at reducing HgbA1c compared with metformin monotherapy by about 1 absolute percentage points. These results were consistent with the 2007 report,[17] except that we did not have any data on sitagliptin at that time because it was not yet FDA-approved.

Another recent review compared HgbA1c with add-on treatments to metformin.[189] This review identified 16 placebo-controlled trials and 11 comparisons with active comparators of metformin combination therapy. They reported that sulfonylureas were superior to thiazolidinediones in reducing HgbA1c in combination with metformin.[189] In our pooled analysis of direct comparisons, we did not detect a significant difference in these combinations. Our review adds to this recently published review by including add-on therapies to thiazolidinediones, including more articles and additional meta-analyses.

**Weight.** Oral diabetes medications varied in their effects on body weight, with metformin being the only medication consistently associated with weight reduction or weight neutrality when compared with other oral diabetes medications that increased weight such as thiazolidinediones and sulfonylureas. As monotherapy, metformin was associated with between-group differences of -2.6 kg when compared with thiazolidinediones, and -2.7 kg when compared with sulfonylureas. Our results on weight were consistent with the 2007 Report, which showed weight gain for thiazolidinediones and sulfonylureas when compared with placebo, and weight neutrality when metformin was compared with placebo.[17]

We also found high strength of evidence for some combination therapies. Metformin plus sulfonylurea had a slightly more favorable effect on weight than metformin plus a thiazolidinedione or a thiazolidinedione plus a sulfonylurea. This finding may impact the choice of drug added for second line combination therapy in a patient not well controlled on a single agent. However, one explanation for the weight loss with metformin is that it was due to the removal of pre-trial medications that increased weight in the run-in period, as evidence suggests

that metformin is associated with weight neutrality, not loss. This suggests that any weight loss becomes significant in direct comparisons between medications only when the other medication has contrasting effects on weight.

Generally, weight gain was small to moderate even in the longer duration RCTs such as UKPDS[7] and ADOPT[30] (less than 5 kg). However, even small amounts of weight gain (5% to 10% of body weight) may be associated with increased insulin resistance.[198]

**Lipids.** Effects on lipid levels varied across medication type, but most effects were small to moderate. For instance, pooled analyses showed between-group differences of around 5 to 10 mg/dL in LDL, 10 to 30 mg/dL in TG, and 3 to 5 mg/dL in HDL. Since the 2007 CER no other systematic reviews addressed the outcome of lipids for these drug comparisons. Prior to the 2007 CER, a systematic review completed in 2004 assessed this outcome.[199] Our review updates our 2007 CER because we added comparisons and meta-analyses. In general, we found that metformin decreased LDL and TG, and modestly increased HDL. Metformin decreased TG and LDL relative to sulfonylureas and rosiglitazone, and pioglitazone, while also increasing LDL, and decreasing TG relative to metformin. The addition of rosiglitazone to metformin increased LDL and HDL but increased TG over metformin monotherapy and over the combination of metformin and a sulfonylurea. The addition of pioglitazone to metformin also increased HDL and decreased TG over the combination of metformin and a sulfonylurea. Our report also contributes to the literature by including sitagliptin for lipid outcomes. We found that the addition of sitagliptin to metformin decreased TG relative to metformin monotherapy, but the strength of evidence was low.

Similar to our 2007 CER,[17] we noted that one medication may have favorable effects on one lipid outcome and unfavorable effects on another lipid outcome. For instance, thiazolidinediones increased LDL but favorably decreased TGs and increased HDL. Decisions regarding medications that may adversely affect lipids are important because of the importance of cardiovascular disease risk reduction in patients with diabetes.[200]

## Long-Term Clinical Outcomes

Despite the inclusion of two additional large RCTs[14 30] and 26 other studies since the 2007 CER, we found, overall, low strength of evidence to support conclusions about the comparative effectiveness of diabetes medications, either in monotherapy and combination therapy, on all-cause mortality, or macrovascular and microvascular long-term diabetes complications. Using the trials identified in the 2007 CER, Selvin et al. CER conducted meta-analyses of each drug versus any other drug comparators.[201] Treatment with metformin was associated with a decreased risk of cardiovascular mortality (pooled OR 0.74; 95% CI 0.62 to 0.89) compared with any other oral diabetes agent or placebo, although the results for all-cause mortality and cardiovascular morbidity were not significant. Rosiglitazone was the only diabetes agent associated with an increased risk of cardiovascular morbidity or mortality when compared to any other comparator or placebo, but this result was not statistically significant.[201]

Compared with the 2007 CER, we have additional trials for each drug-drug comparison specifically for metformin versus a thiazolidinedione, metformin versus a sulfonylurea, and comparisons with meglitinides. A notable addition was the RECORD study, which reported that the combined arms of rosiglitazone plus metformin and rosiglitazone plus sulfonylurea were non-inferior to metformin plus sulfonylurea for the primary endpoint of hospitalization or death from cardiovascular disease (HR 1.08, 95% CI 0.89 to 1.31). However, these findings were

inconclusive for myocardial infarction, for which there was a non-statistically significant slightly increased risk in the two combined rosiglitazone (metformin or sulfonylurea plus rosiglitazone) arms.[14] The RECORD trial has recently been criticized for the cardiovascular disease rates, which were much lower than expected, and lower than rates in comparable large cohort studies. The low event rate may have precluded the statistical confirmation of excess risk of rosiglitazone, if present.[202]

Several large, well-done cohort studies concluded that the risk of all-cause mortality and cardiovascular disease morbidity and mortality was decreased for metformin compared with sulfonylureas, either alone or in combination with other medications, consistent with the analysis by Selvin et al.[201] However, the large ADOPT[30] RCT, which followed participants for a median of 4 years, did not identify any difference in risk between the sulfonylurea and metformin arms. The cohort studies are subject to confounding by indication, as sicker patients may be more likely to take sulfonylureas, and use them in combination. However, trials like ADOPT often exclude patients with comorbidities who are at highest risk for long-term complications.

Unfortunately, no studies reporting the outcome of retinopathy met our inclusion criteria. In the first report, six studies reported this outcome, which were all excluded from this CER because participants were either taking additional background medications or because there was no comparison of interest (e.g., gliclazide versus glibenclamide). In our previous CER, three studies reported on the outcome of retinopathy. The most notable study was the UKPDS, which reported no difference in progression to retinopathy between a sulfonylurea and metformin at 12 years of followup.[7] Unfortunately, we found no additional studies examining this outcome.

Also, few studies reported on the outcomes of nephropathy or neuropathy. We found pioglitazone had greater reductions in the albumin-to-creatinine ratio as compared with metformin, with unclear implications for long-term effects of diabetic nephropathy or chronic kidney disease progression. We were unable to make conclusions about neuropathy because of small sample sizes and inconsistent definitions of the outcome. Because few studies have considered neuropathy and it has profound implications for patient quality of life, this will be an important area for future research.

## Adverse Events

We confirmed a doubling of the risk of heart failure with the thiazolidinedione class of medications, particularly compared with sulfonylureas, which was reported in two recent meta-analyses.[203 204] In fact, both the thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage III or Stage IV) according to the FDA boxed warnings on the thiazolidinediones.[205 206] The excess deaths and hospitalizations associated with heart failure with the thiazolidinediones in RECORD[14] indicates that heart failure induced by thiazolidinediones is clinically important.

We included four new safety outcomes in addition to the others we addressed in the first report: macular edema, cholecystitis, pancreatitis, and fractures, because of safety concerns that emerged after the review. The 2007 CER reported an increased risk of cholecystitis with pioglitazone in an unpublished pooled analysis.[17] However, the current report found no additional evidence on this outcome for the comparisons of interest. Several case reports and case series have reported spontaneous macular edema associated with the thiazolidinedione class.[207 208] However, clinical trials are underpowered to detect rare adverse events and hence we did not detect any significant difference in the rates of macular edema, as we only identified one

trial reporting on this outcome. A recently published prospective cohort study in the Kaiser Permanente database of over 17,000 users of the thiazolidinediones reported an increased odds of macular edema with the thiazolidinediones (OR 2.6; 95% CI 2.4 to 3.0) compared to nonusers, significant even after adjustment for age and glycemic control. Notably, this cohort study also reported an increased risk of macular edema with insulin and meglitinides.[209]

Patients with diabetes have an increased risk of acute pancreatitis.[210] The current drug label for exenatide has been strengthened with information from spontaneous post-marketing reports of severe pancreatitis including hemorrhagic pancreatitis occurring after exenatide therapy.[211] However, a recent claims database study failed to show any significant relationship between exenatide or sitagliptin and pancreatitis.[212]

Our results for lactic acidosis support the results from our first report, as well as the Cochrane systematic review on this topic[213] showing no increased risk of lactic acidosis among metformin users. The Cochrane review reported similar rates between metformin users (5.1 cases per 100,000 patient-years) and those on other oral hypoglycemic agents or placebo (5.8 cases per 100,000 patient-years). Further, there was no statistically significant difference in the net change of lactate levels from baseline in metformin users compared to those on other oral hypoglycemic agents or placebo suggesting no increased risk of lactic acidosis with metformin compared to other oral hypoglycemic agents or placebo.[213]

As with the 2007 CER, we evaluated cancer as an outcome. We included three trials with inconclusive results. One retrospective cohort study not included for this outcome, because of uneven use of insulin, evaluated cancer mortality among the sulfonylurea cohort compared to the metformin cohort using the administrative data from Saskatchewan Health, Canada.[214] The mortality from cancer was higher in the sulfonylurea cohort (9.7 per 1000 person-years) than the metformin cohort (6.3 per 1000 person-years), with a hazard ratio for cancer mortality of 1.3 (95% CI 1.1 to 1.6), adjusted for age, sex, insulin use, and comorbidities. This study was limited by the use of administrative data and high risk for residual confounding.

We found high strength of evidence for comparative safety in terms of fracture risk. The RECORD study reported significantly increased risk of upper and lower limb fractures in women randomized to rosiglitazone combination therapy arms compared with metformin plus sulfonylureas. A prior systematic review that included ten studies evaluating the long-term effect of thiazolidinediones on fracture risk showed a significant increase in fracture risk, most apparent in women.[215] Fractures reported with the thiazolidinediones have been mainly those of the upper and lower limb and not hip fractures. Several recent observational studies have also reported an increased risk of fractures with the thiazolidinediones among men as well, but the risk appears to be higher among women and those of advanced age.[216-220]

# Limitations

Several important limitations to our report deserve mention. Because this was an update of a comprehensive review performed two years earlier, we focused our update *a priori* on studies with active control comparators, which are most relevant for clinical practice. Placebo-controlled trials had been included in the original 2007 CER. However, the majority of placebo-controlled trials are short-term and lacking long-term outcomes. However, the exclusion of placebo-controlled trials has implications for the review, including missed rare adverse events, such as macular edema and acute pancreatitis. To conclude from an active-control study that one medication is more effective than another requires prior knowledge that the active-control drug

has been studied previously and is known to be more effective than placebo. Because this was an update of the 2007 CER that had included placebo controlled trials, for most drug comparisons this was probably true.[221] However, this assumption may be less valid for the newer medications of sitagliptin, nateglinide, and exenatide, where evidence from other systematic reviews, such as Cochrane Reviews, will be also be helpful in making conclusions, and further studies will be needed.

In addition, our inclusion criteria required that all studies fit into one or more of the prespecified comparisons of interest (Table 2), which identified specific drug-drug or two-drug comparisons. For example, studies that included any number of "background medications" were excluded. Our rationale was to avoid contamination by use of background medications with unclear interactions with the intervention medications. This was especially important because of our goal of evaluating two-drug combinations. Applying the inclusion criteria, which required prespecified comparisons of interest, had several implications. This criteria required the exclusion of several large trials,[7 8 11 60-62 222-225] some of which compared HgbA1c lowering strategies, not individual medications, as well as some smaller trials and observational studies. Of note, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study was included in the first report but excluded from the current report.[222] Another unintended consequence of requiring these prespecified comparisons of interest was that none of the recent studies of exenatide[226-229] as add-on therapy to oral medications fit our inclusion criteria.

Another implication of the requirement of specific medication comparisons was the exclusion of several case control studies that did not report outcomes of interest by drug comparison. Although we applied very broad search terms and did not exclude studies by study design, we only identified seven case control studies and six of these were subsequently excluded from the review because they did not report their results to fit with the prespecified drug comparisons of interest for this review. For example, five studies[230-234] compared a drug of interest with any other unspecified drug for an adverse event outcome, and this was not a comparison of interest.

Limitations within the included studies have presented challenges to how we reported their outcomes and our ability to combine them in meta-analyses. For example, several studies failed to report the significance of reported between-group differences and the measures of dispersion, thereby hindering efforts to estimate effect size across trials.

Finally, many included trials were industry-sponsored, raising the possibility of publication bias and other forms of bias, such as selective reporting of outcomes. While publication bias generally was not found, these analyses have limited power due to small numbers of studies for many comparisons.

# Future Research

In this review, we synthesized current literature about the comparative effectiveness and safety of oral diabetes medications when used alone and in two-drug combinations. We identified some deficiencies in the published literature that need to be addressed by future research to meet the decision making needs of patients, physicians, and policy makers. We organized these deficiencies and recommendations using the PICOTS format for specifying research questions: patient populations, interventions, comparators, outcome measures of interest, timing, and settings.

## Populations

Studies often employed narrow inclusion criteria, enrolling patients at lowest risk for complications, and commonly used run-in periods to avoid enrolling patients with adverse effects or poor adherence, which may limit applicability. We identified the following research gaps related to target patient populations:

1. The literature is deficient in studies enrolling people with varying levels of underlying cardiovascular risk.
2. Results reported in subgroups of the population were rare, especially the elderly and people with multiple comorbid conditions, such as underlying chronic kidney disease.

## Interventions and Comparators

We identified the following gaps in the literature, where future studies could address additional medication comparisons to support clinicians in decision making.

1. The published literature is deficient in studies of the comparative effectiveness of two-drug combinations, focused either on their effectiveness or the safety and thus, interaction between two medications.
2. The comparative effectiveness literature is sparse on monotherapy and combination therapy comparisons of nateglinide, exenatide, or sitagliptin with other first line diabetes medications.
3. Few studies used comparisons with a basal or premixed insulin added to metformin or thiazolidinediones.

## Outcomes of Interest

Overall, few studies contained sufficient data on event rates for major clinically important adverse events and long-term complications of diabetes.

1. We identified few published studies on long-term clinical outcomes such as cardiovascular disease, stroke, nephropathy, and neuropathy.
2. Few studies used standard measures for diabetic nephropathy and kidney function, such as estimated glomerular filtration rate (GFR), or clinical outcomes like time to dialysis, as outcomes in the comparison of these medications.
3. We identified few observational studies that examined macular edema, cancer and fractures for thiazolidinediones and other medications.

## Timing

We identified several key deficiencies in study timing and duration of followup.

1. The literature is relatively deficient in studies of the short-term benefits, if any, of the addition of insulin to oral agents, and the long-term effects on mortality and

cardiovascular disease, from the addition of insulin to a regimen relative to the addition of another oral agent.

2. Few studies on harms lasted greater than 2 years, a shorter duration of exposure than typically seen in clinical practice, where these drugs may be prescribed for decades. Some adverse effects, like congestive heart failure, may take years to develop, and others like fractures, may be due to cumulative exposure.

## Setting

Study settings are relevant to understanding the applicability of the findings to the general U.S. population of patients with diabetes.

1. Few trials reported the study setting or source for participant recruitment, such as an outpatient clinical or subspecialty clinical setting, which is relevant because the majority of patients with diabetes are cared for by primary care physicians.

We also identified methodological problems and made recommendations to consider for future research:

1. We recommend studies consistently report between-group comparisons of changes from baseline, as well as measures of dispersion such as standard errors, to improve interpretation of the significance of their findings.
2. We recommend improved adverse event and long-term outcome reporting, with pre-defined outcomes and definitions, and a description of methods for ascertainment.
3. We recommend trials report the steps taken to ensure randomization and allocation concealment.
4. We recommend that observational studies of the comparative effectiveness and safety of oral diabetes medications report details of the treatment type, dose, timing and duration of use of the medication, when available.
5. We recommend that studies consistently report the number of deaths in each study arm, even if there were none.

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# Abbreviations

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| ACCORD | Action to Control Cardiovascular Disease in Diabetes |
| ADOPT | A Diabetes Outcome Progression Trial |
| AHRQ | Agency for Healthcare Research and Quality |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CER | Comparative effectiveness review |
| CI | Confidence interval |
| DPP-4 | Dipeptidyl peptidase-4 |
| EPC | Evidence-based Practice Center |
| FDA | Food and Drug Administration |
| GI | Gastrointestinal |
| GLP-1 | Glucagon-like peptide-1 |
| GPRD | General Practice Research Database |
| HDL | High density lipoproteins |
| HgbA1c | Hemoglobin A1c |
| HR | Hazard ratio |
| HR | Hazard ratio |
| IRR | Incidence rate ratios |
| IU | International units |
| kg | Kilograms |
| LDL | Low density lipoprotein |
| mg/dL | Milligrams per deciliter |
| MI | Myocardial infarction |
| NPH | Neutral protamine Hagedorn |
| OR | Odds ratio |
| PROactive | PROspective pioglitAzone Clinical Trial in macroVascular Events |
| RCT | Randomized controlled trial |
| RECORD | Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes |
| RR | Relative risk |
| TG | Triglycerides |
| UK | United Kingdom |
| UKPDS | United Kingdom Prospective Diabetes Study |
| US | United States |
| VA | Department of Veterans Affairs |