Effective Health Care Program

Comparative Effectiveness Review
Number 27

Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update

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Comparative Effectiveness Review

Number 27

Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update

Update of Comparative Effectiveness Review No. 8, *Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes, Including New Drug Classes and Two-Drug Combinations*

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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 Children's Health Insurance Program (CHIP).

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.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update

Structured Abstract

Objectives. Given the number of medications available for type 2 diabetes mellitus, clinicians and patients need information about their effectiveness and safety to make informed choices. The objective of this review was to summarize the benefits and harms of medications (metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists), as monotherapy and in combination, for the treatment of adults with type 2 diabetes.

Data Sources. We searched the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases from inception through April 2010 for original English-language articles and sought unpublished data from the Food and Drug Administration and others.

Review Methods. Two reviewers independently screened titles to identify studies that assessed intermediate outcomes (e.g., hemoglobin A1c [HbA1c]), long-term clinical outcomes (e.g., mortality), and harms (e.g., hypoglycemia) in head-to-head monotherapy or combination therapy comparisons. Two reviewers serially extracted data for each article using standardized protocols, assessed applicability, and independently evaluated study quality.

Results. The review included 140 randomized controlled trials and 26 observational studies. We graded evidence as low or insufficient for long-term clinical outcomes of all-cause mortality, cardiovascular disease, nephropathy, and neuropathy. Most medications lowered HbA1c on average by 1 absolute percentage point, but metformin was more efficacious than the DPP-4 inhibitors. Two-drug combinations had similar HbA1c reduction. Compared with metformin, thiazolidinediones and sulfonylureas had a more unfavorable effect on weight (mean difference of +2.6 kg). Metformin decreased low density lipoprotein cholesterol relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylureas had a fourfold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a fivefold increased risk compared with metformin plus thiazolidinediones. Thiazolidinediones had an increased risk of congestive heart failure relative to sulfonylureas and bone fractures relative to metformin. Diarrhea occurred more often for metformin compared with thiazolidinedione users.

Conclusions. Comprehensive information comparing benefits and harms of diabetes medications can facilitate personalized treatment choices for patients. Although the long-term benefits and harms of diabetes medications remain unclear, the evidence supports use of metformin as a first-line agent. Comparisons of two-drug combinations showed little to no difference in HbA1c reduction, but some combinations increased risk for hypoglycemia and other adverse events.

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Background

Type 2 diabetes is a common chronic illness characterized by insulin resistance and eventually by decreased insulin secretion by pancreatic beta cells, leading to chronic hyperglycemia and associated long-term disease complications. In the United States, the prevalence of diabetes increased from 5.1 percent during 1988–1994 to 6.5 percent during 1999–2002.[1] Like many chronic illnesses, diabetes disproportionately affects older people. It is associated with obesity, and its 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 because of the 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 two to four times as high as in adults without diabetes.[2] 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, studies have had mixed results regarding the impact of intensive glycemic control (hemoglobin A1c [HbA1c] < 7 percent) on cardiovascular events and mortality. While older studies indicated that intensive glycemic control may reduce cardiovascular morbidity and mortality, recent studies have raised the possibility that intensive glycemic control has either no effect or a negative effect on cardiovascular morbidity and mortality. These mixed results suggest the need for further research, including investigation of the long-term safety of glucose-lowering therapies. In addition to questions about optimal glycemic control, recent studies have addressed concerns about excess cardiovascular risk associated with particular oral hypoglycemic agents, specifically the risk of rosiglitazone.

In 1995, the only drugs for treating type 2 diabetes were sulfonylureas and insulin. Since then, many new pharmacotherapy options have become available. At present, there are 11 classes of diabetes medications: biguanides (i.e., metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, an amylin analogue, bromocriptine, alpha-glucosidase inhibitors, colesevalam (a bile-acid sequestrant), and insulins. The newer agents are more costly than the older medications, and some are only approved as adjunctive therapies. In addition to having an increased number of medication choices, patients with type 2 diabetes often need to take more than one type of diabetes medication. In 2005–2006, 35 percent of all patients with diabetes were taking two classes of antidiabetes medications, and 14 percent were taking three or more classes, as compared to only 6 percent taking three or more classes in 1999–2000.[3]

In 2007, the Agency for Healthcare Research and Quality (AHRQ) published its first systematic review on the comparative effectiveness of oral medications for type 2 diabetes, *Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes* (Comparative Effectiveness Review No. 8). The review was unique because it included comparisons of all oral diabetes medications. It also had a broad scope, including intermediate outcomes such as glycemic control and clinical outcomes such as 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 HbA1c, 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 make it possible to assess the differential effects of the oral diabetes medications on all-cause mortality, cardiovascular mortality and morbidity, or 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 publication of that review, enough studies were published to merit an update to address research gaps and integrate newer evidence. Since the first review, two new medication classes have been approved by the U.S. Food and Drug Administration (FDA). Two injectable incretin mimetics, exenatide and liraglutide, were FDA approved in 2005 and 2010, respectively. The DPP-4 inhibitors sitagliptin and saxagliptin were FDA approved in 2006 and 2009. In addition, the review needed to be updated to include evidence about combinations of medications, including combinations of an oral medication with insulin therapy.

For this update, 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 HbA1c), weight, or lipids?

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

	Main intervention	Comparisons
Monotherapy as main intervention	Metformin	• Thiazolidinedione • Sulfonylurea • DPP-4 inhibitor • Meglitinides • GLP-1 agonist • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus meglitinides • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione	• Different thiazolidinedione • Sulfonylurea • DPP-4 inhibitor • Meglitinides • GLP-1 agonist
	Sulfonylurea	• DPP-4 inhibitor • Meglitinides • GLP-1 agonist
	DPP-4 inhibitor	• Meglitinides • GLP-1 agonist
Combination therapy as main intervention	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or one of the meglitinides or a DPP-4 inhibitor or a GLP-1 agonist or a basal insulin or a premixed insulin)	• Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin)
	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin)	• Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist)

Abbreviations: DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; GLP-1 agonist = glucagon-like peptide-1 receptor agonist

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 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 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 Question 4. Do the 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?

Conclusions

Summary Table B presents the main conclusions and strength of evidence from published studies 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 121 relevant articles with data from RCTs that addressed either HbA1c, body weight, or lipids. Fifty-one of the studies had also been included in the 2007 comparative effectiveness review.

HbA1c. We found that most diabetes medications (metformin, thiazolidinediones, sulfonylureas, and repaglinide) reduced HbA1c to a similar degree, by about 1 absolute percentage point when compared with baseline values, after 3 or more months of treatment. Metformin was more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy (by about 0.4 absolute percentage points). Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, and metformin plus DPP-4 inhibitors) were generally more effective in reducing HbA1c than was metformin monotherapy (by about 1 absolute percentage point). Most combinations of metformin, sulfonylureas, and thiazolidinediones had similar efficacies in lowering HbA1c. Although we included comparisons with the GLP-1 agonists, we graded the evidence for these comparisons as insufficient or low; therefore, we were limited in our ability to draw firm conclusions about their effectiveness.

Weight. Diabetes medications varied in terms of their effects on body weight. Notably, weight change was small to moderate, generally less than 2 kg between baseline and final values. Unlike thiazolidinediones or sulfonylureas, metformin was not associated with weight gain, with a mean difference of about −2.6 kg between metformin and the other drugs, in trials that lasted more than 3 months but generally less than 1 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. As compared with sulfonylureas, the GLP-1 agonists were associated with a relative weight change of about 2.5 kg.

Lipids. The effects on lipid levels varied across medication type, but most were small to moderate (changes of about 0.5 mg/dL to 16 mg/dL for LDL, 0.5 mg/dL to 4 mg/dL for high-density lipoprotein [HDL], and 0 mg/dL to 33 mg/dL for triglycerides [TG]), in studies that generally lasted between 3 and 12 months. Metformin had favorable effects on all the lipid classes: It decreased LDL more effectively than did sulfonylureas, rosiglitazone, or pioglitazone, and it decreased TG more efficiently than sulfonylureas or rosiglitazone. However, pioglitazone was more effective than metformin in decreasing TG. The addition of rosiglitazone to metformin increased LDL and HDL but also increased TG when compared to metformin monotherapy and to the combination of metformin and a sulfonylurea. The addition of pioglitazone to metformin also increased HDL but decreased TG when compared to the combination of metformin and a sulfonylurea. The addition of DPP-4 inhibitors to metformin did not have an effect on HDL in comparison with metformin monotherapy. We noted that one medication or class may have favorable effects on one lipid outcome and unfavorable effects on another lipid outcome. For instance, rosiglitazone was less effective than pioglitazone in decreasing LDL, and it increased HDL to a lesser extent than did pioglitazone, but both favorably decreased TG.

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

Although we identified 41 new studies in addition to the 25 studies included in the 2007 evidence report, the new studies were generally of short duration (less than 1 year) and had few long-term events (such as deaths and cardiovascular disease), making any estimates of risk difference very imprecise. Therefore, most comparisons for this key question had a low strength of evidence. Metformin was associated with slightly lower all-cause mortality and cardiovascular disease mortality than were sulfonylureas. However, the evidence was limited by inconsistency between the trials and observational studies and the 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 when compared with any other oral diabetes agent or placebo, although the results for all-cause mortality and cardiovascular morbidity were not significant.

We found few studies with the newer DPP-4 inhibitors and GLP-1 agonists, but overall the evidence on these newer agents was insufficient to allow us to make any meaningful conclusions. Few studies included insulin added to oral medications or compared other two-drug combination therapies.

Few studies addressed microvascular outcomes of nephropathy, retinopathy, or neuropathy. We found moderate strength of evidence that pioglitazone is better than metformin at reducing short-term nephropathy, based on two short-duration RCTs. Only three comparisons were included for the outcome of neuropathy, and these studies were limited by their small 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

This Key Question was addressed by 107 studies.

Hypoglycemia. Hypoglycemic episodes were three to seven times as frequent in people taking sulfonylureas as in those taking metformin, thiazolidinediones, or DPP-4 inhibitors. Combination therapies that included a sulfonylurea plus metformin also had an excess hypoglycemia risk when compared to metformin plus a thiazolidinedione.

Congestive heart failure. Based on a single RCT with moderate risk of bias, we found low strength of evidence that the risk of congestive heart failure (CHF) was higher with combination therapy containing rosiglitazone than with a combination of metformin and a sulfonylurea (relative risk [RR] 2.1). We also found a higher risk of CHF with thiazolidinedione monotherapy than with sulfonylurea monotherapy. We were unable to draw any useful conclusions about CHF risk from other drug comparisons of interest, either because of an absence of evidence, conflicting results, or the low quality of the studies.

Gastrointestinal side effects. Metformin was associated with higher risk of gastrointestinal side effects than were all other medications, regardless of whether the metformin was 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 the availability of only a few studies and events limited the assessment of consistency and precision of the results. We did find a high strength of evidence showing that thiazolidinediones, either in combination with another medication or as monotherapy, were associated with a 1.5-fold higher risk of bone fractures than was metformin alone or in combination with sulfonylurea.

We also found little evidence regarding liver injury and cancer, outcomes included in the 2007 evidence report. However, in agreement with other reviews, we found a moderate strength of evidence for a lack of increased risk of lactic acidosis with metformin treatment, as compared to a sulfonylurea or a combination of metformin and sulfonylurea.

Key Question 4: Differences in Subgroups

Twenty-eight studies applied to Key Question 4. We found that when compared to men, women taking rosiglitazone either as monotherapy or in combination were at higher risk for bone fractures than were those taking metformin alone or in combination with sulfonylureas. However, for the majority of comparisons, the available studies did not have sufficient power to allow for subgroup analyses, and few studies occurred exclusively in a subpopulation. We found no conclusive information to predict which subgroups of patients might differentially respond to alternative treatments.

Remaining Issues

In this review, we have synthesized the current literature about the comparative effectiveness and safety of diabetes medications when used alone or in two-drug combinations. We focused primarily on the relative differences between drugs in our analyses. However, in the figures in the main body of the report, we also included footnotes with information about the range of absolute differences from baseline to followup in the comparison arms for readers who wish to estimate the magnitude of effect in absolute terms. We identified some deficiencies in the

published literature that need to be addressed by future research in order to meet the decision making needs of patients, physicians, and policymakers. 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 they commonly used run-in periods to avoid enrolling patients with adverse effects or poor adherence; all these factors may limit the applicability of these studies. 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 and renal disease risk.
2. Results reported in subgroups of the population were rare, especially with regard to 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, indicating areas where future studies could address additional medication comparisons to support clinicians in decisionmaking.

1. The published literature is deficient in studies of the comparative effectiveness of two-drug combinations that are focused on either their effectiveness or safety, and thus the interaction between the two medications.
2. The comparative effectiveness literature is sparse with regard to monotherapy and combination therapy comparisons of meglinitides, DPP-4 inhibitors, and GLP-1 agonists with other first-line diabetes medications.
3. Few studies have included comparisons with a basal or premixed insulin added to metformin or thiazolidinediones.

Outcomes of Interest

Overall, few studies contained sufficient data on event rates to make it possible to analyze 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, or clinical outcomes, such as time to dialysis, as outcomes in their comparisons of these medications.
3. We identified few observational studies that examined macular edema, cancer, and fractures as related to thiazolidinediones, insulin, 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 of the addition of insulin to a regimen, relative to the addition of another oral agent.

2. Few studies on harms lasted longer than 2 years. This is a shorter duration of exposure than is typically seen in clinical practice, in which these drugs may be prescribed for decades. Some adverse effects, such as congestive heart failure, may take years to develop, and others, such as fractures, may result from cumulative exposure. The FDA approval process focuses on short-term harms, providing less incentive for pharmaceutical companies to engage in longer term studies.

Setting

Study settings are relevant to understanding the applicability of the findings to the general population of patients with diabetes in the United States.

- Few trials reported the study setting or source for participant recruitment, such as an outpatient clinical or subspecialty clinical setting. This information 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 that studies consistently report between-group comparisons of changes from baseline, as well as measures of dispersion such as standard errors, to improve the interpretation of the significance of their findings.
2. We recommend improvements in adverse event and long-term outcome reporting, with predefined outcomes and definitions and a description of methods for ascertainment.
3. We recommend that trials report the steps taken to ensure randomization and allocation concealment.
4. We recommend that observational studies of the comparative effectiveness and safety of 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.
6. We recommend that studies allowing use of "background" medications identify which medications were allowed and stratify their results by the combination therapy, which includes the background medication(s) plus the study drug(s).
7. We recommend conducting a network meta-analysis to assess indirect comparisons, which were not addressed in this report.

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 HbA1c), weight, or lipids?		
HbA1c	High	Metformin and second-generation sulfonylureas showed similar changes in HbA1c, with a pooled between-group difference of 0.07% (95% CI -0.12% to 0.26%) for studies lasting longer than 3 months but usually less than 1 year in duration.
	High	Combination therapies were better than monotherapy regimens at reducing HbA1c, with 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 HbA1c reduction.
	Moderate	When compared with DPP-4 inhibitors, metformin had a greater reduction in HbA1c, with a pooled between-group difference of -0.4% (95% CI -0.5% to -0.2%).
	Moderate	Comparisons of metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone showed similar reductions in HbA1c, with an absolute reduction in HbA1c of around 1% as compared with baseline values, with trials lasting 1 year or less.
	Moderate	Metformin plus DPP-4 inhibitor was favored over metformin alone for HbA1c reduction.
	Moderate	The combination of metformin plus thiazolidinedione had a similar efficacy in reducing HbA1c as the combination of metformin plus sulfonylurea.
	Low	The combination of pioglitazone plus sulfonylurea was minimally favored over metformin plus pioglitazone, by an absolute difference of 0.03%.
	Low	The combination of metformin plus a premixed insulin analogue was minimally favored over metformin plus a basal insulin, by an absolute difference of 0.30% to 0.43%.

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 (continued)

Outcome	Level of Evidence*	Conclusions
Body weight	High	Metformin maintained or decreased weight to a greater extent than did thiazolidinediones (pooled between-group difference of -2.6 kg, 95% CI -4.1 kg to -1.2 kg), the combination of metformin plus a thiazolidinedione (pooled between-group difference of -2.2 kg, 95% CI -2.6 kg to -1.9 kg), or the combination of metformin plus a sulfonylurea (pooled between-group difference of -2.3 kg, 95% CI -3.3 kg to -1.2 kg). Thiazolidinediones alone or in combination were associated with weight gain.
	High	Metformin maintained or decreased weight to a greater extent than did sulfonylureas, with a pooled between-group difference of -2.7 kg (95% CI -3.5 kg to -1.9 kg).
	High	Sulfonylureas and the meglitinides had similar effects on body weight.
	Moderate	GLP-1 agonists decreased weight to a greater extent than did sulfonylureas (pooled between-group difference of -2.5 kg, 95% CI -3.8 kg to -1.1 kg).
	Moderate	Metformin plus sulfonylurea had a more favorable effect on weight than did either the combinations of a thiazolidinedione plus sulfonylurea (pooled between-group difference of -3.2 kg, 95% CI -5.2 kg to -1.1 kg) or metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95% CI -1.3 kg to -0.4 kg).
	Moderate	Metformin decreased weight to a greater extent than did DPP-4 inhibitors (pooled between-group difference of -1.4 kg, 95% CI -1.8 kg to -1.0 kg).
	Moderate	Metformin had no significantly different effect on weight than did the combination of metformin plus DPP-4 inhibitors (pooled between-group difference of -0.2 kg, 95% CI -0.7 kg to 0.2 kg).
	Low	Metformin plus GLP-1 agonists decreased weight to a greater extent than did several combination therapies (metformin plus sulfonylurea, metformin plus thiazolidinedione, metformin plus basal insulin, or metformin plus DPP-4 inhibitor).
	Low	Metformin plus DPP-4 inhibitors decreased weight to a greater extent than did two standard combinations, metformin plus thiazolidinedione or metformin plus sulfonylurea.
LDL cholesterol	High	Metformin decreased LDL to a greater extent than did sulfonylureas, which generally had little effect on LDL, with a pooled between-group difference of -10.1 mg/dL (95% CI -13.3 mg/dL to -7.0 mg/dL).
	High	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did metformin monotherapy (pooled between-group difference of 14.5 mg/dL, 95% CI 13.3 mg/dL to 15.7 mg/dL),
	Moderate	Metformin decreased LDL cholesterol to a greater extent than did pioglitazone, which increased LDL cholesterol, with a pooled between-group difference in LDL of -14.2 mg/dL (95% CI -15.3 mg/dL to -13.1 mg/dL).
	Moderate	Metformin decreased LDL cholesterol to a greater extent than did rosiglitazone, with a pooled between-group difference in LDL of -12.8 mg/dL (95% CI -24.0 mg/dL to -1.6 mg/dL).
	Moderate	Metformin decreased LDL to a greater extent than did DPP-4 inhibitors, with a pooled between-group difference of -5.9 mg/dL (95% CI -9.7 mg/dL to -2.0 mg/dL).
	Moderate	The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did a combination of metformin and a second-generation sulfonylurea, with a pooled between-group difference in LDL of 13.5 mg/dL (95% CI 9.1 mg/dL to 17.9 mg/dL).

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 (continued)

Outcome	Level of Evidence*	Conclusions
HDL cholesterol	High	Metformin increased HDL to a lesser extent than did pioglitazone, with a pooled between group difference of -3.2 mg/dL (95% CI -4.3 mg/dL to -2.1 mg/dL).
	High	Sulfonylureas were similar to metformin in terms of changes in HDL.
	High	The combination of metformin and rosiglitazone increased HDL to a greater extent than did metformin monotherapy (pooled between-group difference 2.8 mg/dL, 95% CI 2.2 mg/dL to 3.5 mg/dL).
	Moderate	Rosiglitazone increased HDL to a lesser extent than did pioglitazone (pooled between-group difference of -2.3 mg/dL, 95% CI -3.5 mg/dL to -1.2 mg/dL).
	Moderate	Rosiglitazone alone was similar to metformin in terms of changes in HDL.
	Moderate	Pioglitazone increased HDL to a greater extent than did sulfonylureas (pooled between-group difference of 4.3 mg/dL, 95% CI 1.9 mg/dL to 6.6 mg/dL).
	Moderate	The combination of metformin and pioglitazone increased HDL by about 5 mg/dL relative to the combination of metformin and a sulfonylurea.
	Moderate	The combination of metformin and rosiglitazone increased HDL to a greater extent than did the combination of metformin and a sulfonylurea (pooled between-group difference 2.7 mg/dL, 95% CI 1.4 mg/dL to 4.1 mg/dL).
	Moderate	The combination of metformin and DPP-4 inhibitors had similar effect on HDL as did metformin monotherapy (pooled between-group difference was 0.5 mg/dL, 95% CI -1.5 mg/dL to 2.5 mg/dL).
	Low	The combination of pioglitazone with another medication was favored for the following comparisons: pioglitazone plus metformin versus metformin monotherapy, metformin plus pioglitazone versus metformin plus sulfonylurea, and pioglitazone plus sulfonylurea versus metformin plus sulfonylurea, with a range of between-group differences from 3.1 mg/dL to 10.5 mg/dL.
Triglycerides	High	Pioglitazone decreased TG to a greater extent than did metformin (pooled between-group difference -27.2 mg/dL, 95% CI -30.0 mg/dL to -24.4 mg/dL).
	High	Metformin monotherapy decreased TG to a greater extent than did the combination of metformin and rosiglitazone, with a pooled between-group difference in TG of -14.5 mg/dL (95% CI -15.7 mg/dL to -13.3 mg/dL).
	Moderate	Metformin decreased TG to a greater extent than did rosiglitazone, which increased TG, with a pooled between-group difference of -26.9 mg/dL (95% CI -49.3 mg/dL to -4.5 mg/dL).
	Moderate	Metformin decreased TG to a greater extent than did sulfonylureas (pooled between-group difference -8.6 mg/dL, 95% CI -15.6 mg/dL to -1.6 mg/dL).
	Moderate	The combination of metformin plus rosiglitazone and the combination of metformin plus sulfonylurea had similar effects on TG.
	Moderate	The combination of metformin and pioglitazone decreased TG to a greater extent than did the combination of metformin and a sulfonylurea, with between-group differences ranging from -10 mg/dL (p = 0.30) to -24.9 mg/dL (p = 0.045).
	Moderate	Sulfonylureas and meglitinides had similar effects on TG (pooled between-group difference 0.2 mg/dL, 95% CI -3.8 mg/dL to 4.2 mg/dL).

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 (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	Compared to sulfonylureas, metformin was associated with a slightly lower risk of all-cause mortality in observational studies, but the results were inconsistent between trials and observational studies, and all had a moderate risk of bias.
	Low	Many RCTs were of short duration (less than 1 year) and had few deaths, limiting the precision of the results.
	Insufficient	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, comparisons with an insulin preparation, and the majority of combination therapy comparisons.
Cardiovascular disease mortality	Low	Metformin was associated with a slightly lower risk of cardiovascular mortality than was a second-generation sulfonylurea, but the results were imprecise and had a moderate risk of bias.
	Low	The risk of cardiovascular mortality was similar between metformin and each of the thiazolidinediones as monotherapy, with high imprecision of results, inconsistencies, and a moderate risk of bias.
	Low	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of lower risk of fatal myocardial infarction, with consistent direction of the results but high imprecision.
	Insufficient	No studies addressed several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons.
Cardiovascular and cerebrovascular morbidity (nonfatal myocardial infarction and stroke)	Low	A comparison of the risk of cardiovascular morbidity between metformin and thiazolidinedione as monotherapy was inconclusive, with high imprecision and inconsistency in the direction of the findings.
	Low	Metformin alone was slightly favored over a combination of metformin and rosiglitazone in terms of a lower risk of non-fatal ischemic heart disease, with a consistent direction of the results but high imprecision and a failure to reach statistical significance. The pooled odds ratio (OR) for combined fatal and non-fatal ischemic heart disease events was 0.43, 95% CI 0.17 to 1.10. The range of rates for non-fatal ischemic heart disease for the comparison group, metformin, ranged from 0 to 2.9%.
	Insufficient	No studies addressed several comparisons, including most DPP-4 inhibitors and GLP-1 agonist comparisons, pioglitazone versus rosiglitazone, and the majority of combination therapy comparisons.
Microvascular outcomes (retinopathy, nephropathy, neuropathy)	Moderate	Pioglitazone was more effective than metformin in reducing the urinary albumin-to-creatinine ratio (15% and 19% decrease in 2 trials), likely indicating less nephropathy.
	Low	Three comparisons were included for the outcome of neuropathy, but studies were at high risk for bias, with low sample sizes and poorly defined outcomes.
	Insufficient	No studies addressed 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 outcomes, 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	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with metformin, with a pooled OR of 4.6 (95% CI 3.2 to 6.5). The range of rates for mild to moderate hypoglycemia in the metformin group was 0 to 17.7%, with a median rate of 0%.
	High	The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones, with a pooled OR of 3.9 (95% CI 3.0 to 4.9). The range of rates for mild to moderate hypoglycemia in the thiazolidinedione group was 0 to 92.1%, with a median rate of 4.4%.
	High	The risk of hypoglycemia with metformin plus sulfonylurea exceeds the risk of metformin plus thiazolidinediones, with a pooled OR of 5.8 (95% CI 4.3 to 7.7). The range of rates for mild to moderate hypoglycemia in the metformin plus thiazolidinediones group ranged from 0 to 9.3%, with a median rate of 1.3%.
	Moderate	The risk of hypoglycemia with sulfonylurea exceeds the risk with DPP-4 inhibitors (20 events versus none in a single study).
	Moderate	The risk of hypoglycemia was similar between metformin and thiazolidinediones.
	Moderate	The risk of hypoglycemia with metformin plus sulfonylurea exceeded the risk with metformin alone, with an OR range of 0.6 to 9.3.
	Moderate	The risk of hypoglycemia was modestly higher for meglitinides than for metformin, with an OR of 3.0 (95% CI 1.8 to 5.2). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 24%, with a median rate of 3.7%.
	Moderate	The risk of hypoglycemia was higher for metformin plus a thiazolidinedione than for metformin alone, with an OR of 1.6 (95% CI 1.0 to 2.4). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 9.1%, with a median rate of 1.4%.
	Moderate	The combination of metformin and DPP-4 inhibitor had similar risk of hypoglycemia as that of metformin alone.
	Moderate	The combination of metformin with a sulfonylurea had a higher risk of hypoglycemia than metformin with GLP-1 agonist.
	Moderate	Metformin combined with a basal insulin had a modestly lower risk of hypoglycemia when compared to metformin combined with a premixed insulin, with the RR ranging from 0.34 to 0.94 in 5 trials.
Gastrointestinal (GI) side effects	High	Metformin was associated with twice as many GI adverse events, most commonly diarrhea, nausea, and vomiting, as were thiazolidinediones.
	High	The rates of GI adverse effects were similar for thiazolidinediones and sulfonylureas.
	Moderate	Metformin was associated with more frequent GI adverse events than were DPP-4 inhibitors.
	Moderate	Metformin was associated with twice as many GI adverse event rates as were second-generation sulfonylureas.
	Moderate	Metformin monotherapy was associated with more frequent GI adverse events than were either the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione, if the metformin component was of a lower dose than in the metformin monotherapy arm.
	Moderate	The combination of metformin and sulfonylurea was associated with slightly more frequent GI adverse events than were seen with a combination of a thiazolidinedione and a sulfonylurea.
Congestive heart failure	Moderate	The risk of CHF was higher for thiazolidinediones than for sulfonylureas (OR 1.68, 95% CI 0.99 to 2.85).
	Insufficient	No long-term trials assessed the comparative effects of the DPP-4 inhibitors and GLP-1 agonists on the risk of heart failure

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 (continued)

Outcome	Level of Evidence*	Conclusions
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	The risk of lactic acidosis was similar for metformin and sulfonylurea alone and for the two in combination.
Macula edema	Insufficient	Only one trial reported on macular edema. The evidence was insufficient for all comparisons.
Cancer	Insufficient	Few studies addressed the outcome of cancer.
Liver injury	High	The risk of liver injury was similar for thiazolidinediones and sulfonylureas.
	Moderate	The rates of liver injury were similar between thiazolidinediones and metformin.
Fractures	High	The risk of fracture was higher for thiazolidinediones than for metformin. In one large RCT the RR was 1.57 (95% CI 1.13 to 2.17) and women in the thiazolidinedione arm had a higher fracture risk than men. The fracture rate was 4.1% in the reference (metformin) arm.
	High	The risk of fracture was higher for combination therapy with a thiazolidinedione than for metformin plus sulfonylurea, with higher risk in women than in men. In one large RCT, the RR was 1.57 (95% CI 1.26 to 1.97) for the rosiglitazone combination therapy arm, as compared to the combination of metformin plus sulfonylurea arms. The fracture rate in the reference (metformin + sulfonylurea) arm was 1.6%.

Abbreviations: GI = gastrointestinal; HDL = high density lipoprotein; HbA1c = hemoglobin A1c; kg = kilograms; LDL = low density lipoproteins; mg/dL = milligrams per deciliter; RCT = randomized controlled trial; RR = relative risk; TG = triglycerides
* 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.

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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 beta cells lose their ability to maintain the high insulin levels needed to counter liver and muscle insulin resistance and beta 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 percent during 1988–1994 to 6.5 percent during 1999–2002.[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[4] and is increasing, mostly attributable to costly complications of the disease.[5]

Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. In addition, there is a twofold to fourfold increased death rate from cardiovascular disease in adults with type 2 diabetes compared to adults without diabetes.[6] Management of hyperglycemia using diet and pharmacologic therapy is the cornerstone of treatment for type 2 diabetes, along with management of coexisting lipid abnormalities and hypertension. Results from randomized controlled trials have demonstrated that the risk of microvascular complications, particularly retinopathy, can be reduced with good glycemic control in patients with type 2 diabetes.[7-9] However, studies have had mixed results regarding the impact of intensive glycemic control (hemoglobin A1c [HbA1c] < 7 percent) on cardiovascular events and mortality. While older studies indicated that intensive glycemic control may reduce cardiovascular morbidity and mortality,[10,11] recent studies have raised the possibility that intensive glycemic control has either no effect or a negative effect on cardiovascular morbidity and mortality.[12,13] These mixed results suggest the need for further research, including investigation of the long-term safety of glucose-lowering therapies.[8,11,14]

Early data from the United Kingdom Prospective Diabetes Study 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.[8] However, in the last two years, several major trials have found no benefit from intensive glycemic control.[12-13] In fact, the Action to Control Cardiovascular Disease in Diabetes study identified an increased risk for death from cardiovascular causes and higher total mortality among those participants treated with an intensive glucose control strategy.[13] There have been concerns, too, about an increased risk of ischemic heart disease and congestive heart failure associated with specific oral hypoglycemic agents, specifically rosiglitazone, from the thiazolidinedione class.[15,16] National trends in the treatment of diabetes have reflected the public's concern about this drug, with a 63 percent decrease in rosiglitazone use between 2004 and 2007.[17-19]

In 1995, the only drugs for treating diabetes were sulfonylureas and insulin. Since 1995 many new pharmacotherapy options have become available. Currently there are 11 classes of diabetes medications, including sulfonylureas, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, biguanides, an amylin analogue, thiazolidinediones, bromocriptine, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, colesevalam (a bile-acid sequestrant), and

insulins (Table 1).[17] 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 U.S. dollars*
ORAL AGENTS			
Biguanides			
Metformin	Glucophage, Glucophage XR	Oral: 500 to 2550 mg divided doses (qd to tid) Max dose: 2550 mg; 2000 mg for XR	Tablets 500 mg (100): $35.57 850 mg (100): $38.63 1000 mg (100): $45.97 Tablet, 24-hour 750 mg (100): $114.98
Thiazolidinediones			
Pioglitazone	Actos	Oral: 15 to 30 mg qd max dose: 45 mg qd	15 mg (30): *$144.36* 30 mg (30): *$220.61* 45 mg (30): *$239.29*
Rosiglitazone	Avandia	Oral: 4 to 8 mg qd or 2 to 4 mg bid max dose: 8 mg qd or 4 mg qd with insulin or sulfonylurea	2 mg (60): *$158.94* 4 mg (30): *$117.95* 8 mg (30): *$214.31*
Sulfonylureas			
Glimepiride	Amaryl	Oral:1 to 8 mg qd max dose: 8 mg qd	1 mg (100): $13.41 2 mg (100): $21.74 4 mg (100): $41.00
Glipizide	Glucotrol, Glucotrol XL or GITS	Oral: 5 to 15 mg qd or 5 to 20 mg bid max dose: 20 mg bid, 20 mg qd for XL	Tablets 5 mg (100): *$64.07* 10 mg (100): *$117.58* Tablet, 24-hour 2.5 mg (30): *$19.00* 5 mg (100): *$63.34* 10 mg (100): *$125.52*
Glyburide	Micronase, Diabeta, Glynase Prestab	Oral: 2.5-20 mg qd or bid max dose: 20 mg qd	Tablets 1.25 mg (100): $12.44 2.5 mg (100): $18.93 5 mg (30): $28.31
Dipeptidyl peptidase-4 inhibitors			
Sitagliptin	Januvia	Oral: 25 to 100 mg qd recommended dose is 100 mg qd	100 mg (30): *$192.52*
Saxagliptin	Onglyza	Oral: 2.5-5 mg qd	Not listed
Meglitinides			
Repaglinide	Prandin	Oral: 0.5 to 4 mg before meals max dose:16 mg	0.5 mg (100): *$194.14* 1 mg (100): *$194.14* 2 mg (90): *$194.14*
Nateglinide	Starlix	Oral: 60 to 120 mg before meals	60 mg (100): *$177.31* 120 mg (100): *$184.22*
NON-INSULIN SUBCUTANEOUS AGENTS			
GLP-1 agonists			
Exenatide injection	Byetta	SC injection: 5-10 mcg SC bid	5 mcg/0.02 mL solution 1.2 mL: *$231.20* 10 mcg/0.04 mL solution 2.4 mL: *$271.32*
Liraglutide injection	Victoza	SC injection: 1.6-1.8 mg SC qd	Not listed
INSULIN			
Long- or intermediate-acting insulin			
NPH insulin	Humulin N Novolin N	NA	Humulin N: 100 unit/mL suspension 10 mL vial: *$33.20* Novolin N: not listed

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

Drug	Trade name	Dosing	Cost in U.S. dollars*
Insulin detemir	Levemir	NA	100 unit/mL solution 10 mL vial: *$103.18*
Insulin glargine	Lantus	1-80 units daily	100 unit/mL solution 10 mL vial: *$103.16*
Premixed insulin			
50% NPH: 50% Regular	Humulin 50/50	NA	Not listed
70% NPH: 30% Regular	Humulin 70/30 Novolin 70/30	NA	Humulin: 10 mL vial: *$143.34*
50% lispro protamine suspension: 50% lispro	Humalog Mix 50/50	NA	10 mL vial: *$111.24*
75% lispro protamine suspension: 25% lispro	Humalog Mix 75/25	NA	10 mL vial: *$111.24*
70% aspart protamine suspension: 30% aspart	NovoLog Mix 70/30	NA	10 mL vial: *$111.20*

Abbreviations: bid = twice daily; GITS = gastrointestinal therapeutic system; HCl = hydrogen chloride; max = maximum; mcg = micrograms; mg = milligram; mL = milliliter; NA = not applicable; NPH = neutral protamine Hagedorn; qd = once daily; SC = subcutaneous; tid = three-times daily; U.S. = 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 U.S. dollars (Red Book Pharmacy's Fundamental Reference, 2009 Edition); Prices for branded medications are italicized.

With the increasing number of available medication choices for diabetes, patients are being managed with a greater number of classes of medications in combination. During 2005–2006, 35.3 percent of all patients with diabetes were taking two classes of antidiabetes medications and 14.2 percent were taking three or more classes, compared to only 5.6 percent percent taking three or more classes during 1999–2000.[20] Some experts advocate earlier use of combination therapies to prevent the progressive beta 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.[17]

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.[21] 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 HbA1c, most drugs except for metformin and acarbose caused increases in body weight, and only metformin decreased low-density lipoprotein 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.

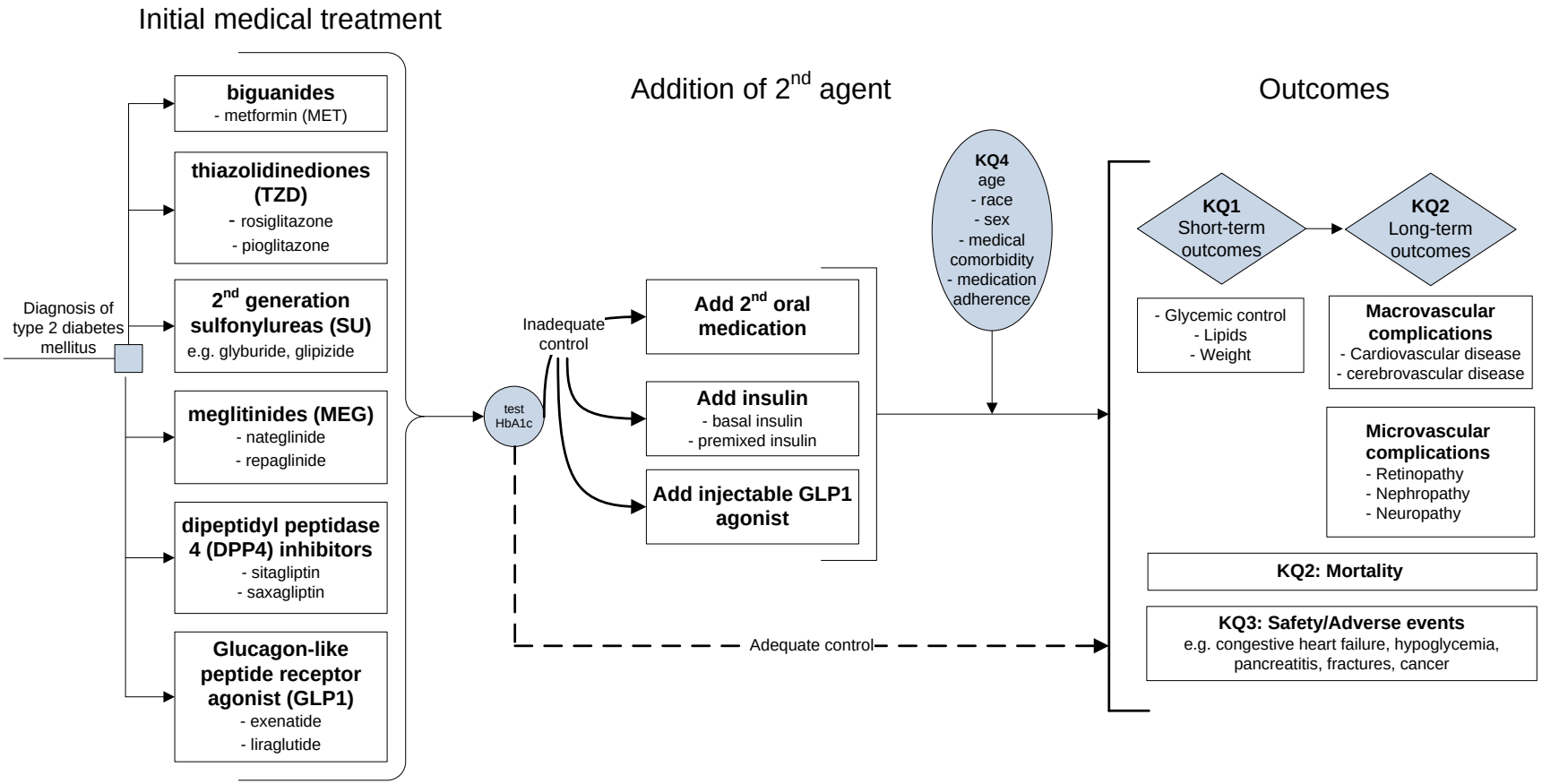
In the years following publication of that review, enough studies were published to merit an update to address research gaps and integrate newer evidence. Since the first review, the Food and Drug Administration (FDA) approved two new medication classes. The noninsulin injectable GLP-1 agonists, exenatide and liraglutide, were FDA-approved in 2005 and 2010, respectively. The DPP-4 inhibitors, sitagliptin and saxagliptin, were FDA-approved in 2006 and 2009. 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 (Figure 1). It highlights the comparisons and outcomes of interest that correspond to each of the key questions in our review.

When beginning medical treatment, patients usually begin with one of five drug classes, (Table 1) which have all been FDA-approved for monotherapy. These include biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, meglitinides, and the GLP-1 agonists. Clinical guidelines of the American Diabetes Association recommend monitoring the HbA1c to determine the need for changing the medication dose or adding another agent to improve glycemic control.[22,23] If the HbA1c is not adequately controlled, clinicians typically add an additional oral hypoglycemic medication, or may add insulin or a noninsulin injectable medication like a GLP-1 agonist. Both intermediate- and long-term outcomes are monitored as indicators of effectiveness. Intermediate outcomes include HbA1c, weight, and lipids. In addition, clinicians monitor short-term and long-term safety and adverse effects of the drug.

Figure 1. Conceptual model



Abbreviations: HbA1c = hemoglobin A1c; KQ=key question; NPH = neutral protamine Hagedorn

Scope and Key Questions

AHRQ commissioned this Comparative Effectiveness Review to update Comparative Effectiveness Review No. 8, The Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes.[21] 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 review, to assess the utility and impact of the review in subsequent guideline development, and to refine the key questions for this update. Based on this process, there are several notable distinctions from the 2007 Review, 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 medication classes: GLP-1 agonists (exenatide, liraglutide) and DPP-4 inhibitors (sitagliptin, and saxagliptin);
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; and
5. The exclusion of the alpha-glucosidase inhibitors (e.g., acarbose) because they are less frequently prescribed in the United States, have lower efficacy for glycemic control, and have high rates of gastrointestinal side effects limiting tolerability.[21]

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 (Table 2 and Appendix A) for the intermediate outcomes of glycemic control (in terms of HbA1c), 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 (Table 2) 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 (Table 2) 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 Question 4. Do safety and effectiveness of these treatment options (Table 2) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, and 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 • Sulfonylurea • DPP-4 inhibitor • Meglitinides • GLP-1 agonist • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus meglitinides
	Thiazolidinedione	• Different thiazolidinedione • Sulfonylurea • DPP-4 inhibitor • Meglitinides • GLP-1 agonist
	Sulfonylurea	• DPP-4 inhibitor • Meglitinides • GLP-1 agonist
	DPP-4 inhibitors	• DPP-4 inhibitor • Meglitinides • GLP-1 agonist
	Meglitinides	• GLP-1 agonist
Combination therapy as main intervention	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinide or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin)	• Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin)
	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin)	• Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist)

Abbreviations: DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; GLP-1 agonist = glucagon-like peptide-1 receptor agonist

Methods

The Agency for Healthcare Research and Quality (AHRQ) requested an update to Comparative Effectiveness Review No. 8, 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.

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 review. 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 nonpregnant 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.[24] For each included guideline, two reviewers abstracted the recommendations on medical management and whether the recommendations agreed with the key findings from the 2007 review.

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 April 2010), Embase® (1974 to April 2010), and the Cochrane Central Register of Controlled Trials (1966 to April 2010). We updated the MEDLINE search to December 2010 for long-term clinical outcomes (i.e., all-cause mortality, cardiovascular morbidity and mortality, nephropathy and neuropathy). 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 review,[21] 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 Web site,
- 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 Web site (available at: www.clinicalstudyresults.org) and ClinicalTrials.gov (available at: 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 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.

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. □ All studies included human subjects. □ 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. o Biguanides (metformin) o Thiazolidinediones (rosiglitazone, pioglitazone) o Second-generation sulfonylureas (glyburide, glibenclamide, glipizide, glimepiride) o Dipeptidyl peptidase-4 inhibitor (sitagliptin, saxagliptin) o Meglitinides (repaglinide, nateglinide) o Glucagon-like peptide-1 analogs (exenatide, liraglutide) o Combination of metformin plus a thiazolidinedione o Combination of metformin plus a sulfonylurea o Combination of metformin plus dipeptidyl peptidase-4 inhibitor o Combination of metformin plus a meglitinide o Combination of metformin plus glucagon-like peptide-1 analog o Combination of metformin plus a basal insulin (insulin glargine, insulin detemir, NPH insulin) o 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) o Combination of a thiazolidinedione and a sulfonylurea o Combination of a thiazolidinedione and a meglitinide □ 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. □ 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. □ For Key Question 1, we included the following outcomes: HgbA1c, weight, and serum lipid levels (HDL, LDL, TG). o We did not include data on total cholesterol or other measures of glycemic variability. □ For Key Question 2, we included the following outcomes: all-cause mortality, cardiovascular disease mortality, cardiovascular and cerebrovascular disease morbidity, retinopathy, neuropathy, and nephropathy. o We excluded biologic markers of outcomes, such as vascular endothelial function or carotid intima medial thickness. □ 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). □ For Key Question 1, we included only RCTs. □ For Key Questions 2 and 3, we included only RCTs, non-RCTs, cohort studies with a comparison group, and case-control studies. □ 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

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 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 review. First, this review includes interventions that were excluded from the initial review: dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) analogs, combination metformin plus DPP-4 inhibitor, combination metformin plus a meglitinide, combination metformin plus GLP-1 analogs, 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. We did not update the initial review on acarbose. Second, this review includes outcomes that were not included in the initial review: fractures, cholecystitis, and macular edema. We did not update the initial review 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 rereviewed 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.[25] 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, hemoglobin A1c [HbA1c] 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 randomized controlled trials (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 dropouts.[26] 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.[27]

We developed a quality assessment tool for observational studies based on the recommendations in the Guide for Conducting Comparative Effectiveness Reviews[27] and quality forms previously developed by our EPC.[28] 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.[27]

In the initial 2007 review, we did not assess the quality of observational studies or nonrandomized 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 three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose). We combined medications by class, except for the thiazolidinediones, which were considered as individual drugs (rosiglitazone and pioglitazone) due to their differences in effects.

For continuous outcomes, 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.[29] 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 three 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 review. The studies included in the 2007 review 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. The categories were based on the definitions of hypoglycemia provided in the studies. Usually, severe hypoglycemia was defined as requiring assistance. In previously included studies from the 2007 review, 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 followup; 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 percent confidence intervals surrounding the estimate (STATA Intercooled, version 9.2, StataCorp, College Station, TX).

For continuous outcomes, we used a random-effects model with the DerSimonian and Laird formula to derive pooled posttreatment weighted mean differences.[30] For the outcome of hypoglycemia, we calculated pooled odds ratios using the Peto method because trial arms had balanced sample sizes.[31] Because congestive heart failure and ischemic heart disease were rare events, we calculated pooled fixed-effects odds ratios using the treatment arm continuity correction (reciprocal of the sample size in the opposite treatment group in cells with 0 events).[32] 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.[33] A value greater than 50 percent 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[34] and Eggers tests[35] 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 resubmitted 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, at least three investigators 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.[27] 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).

Peer Review and Public Commentary

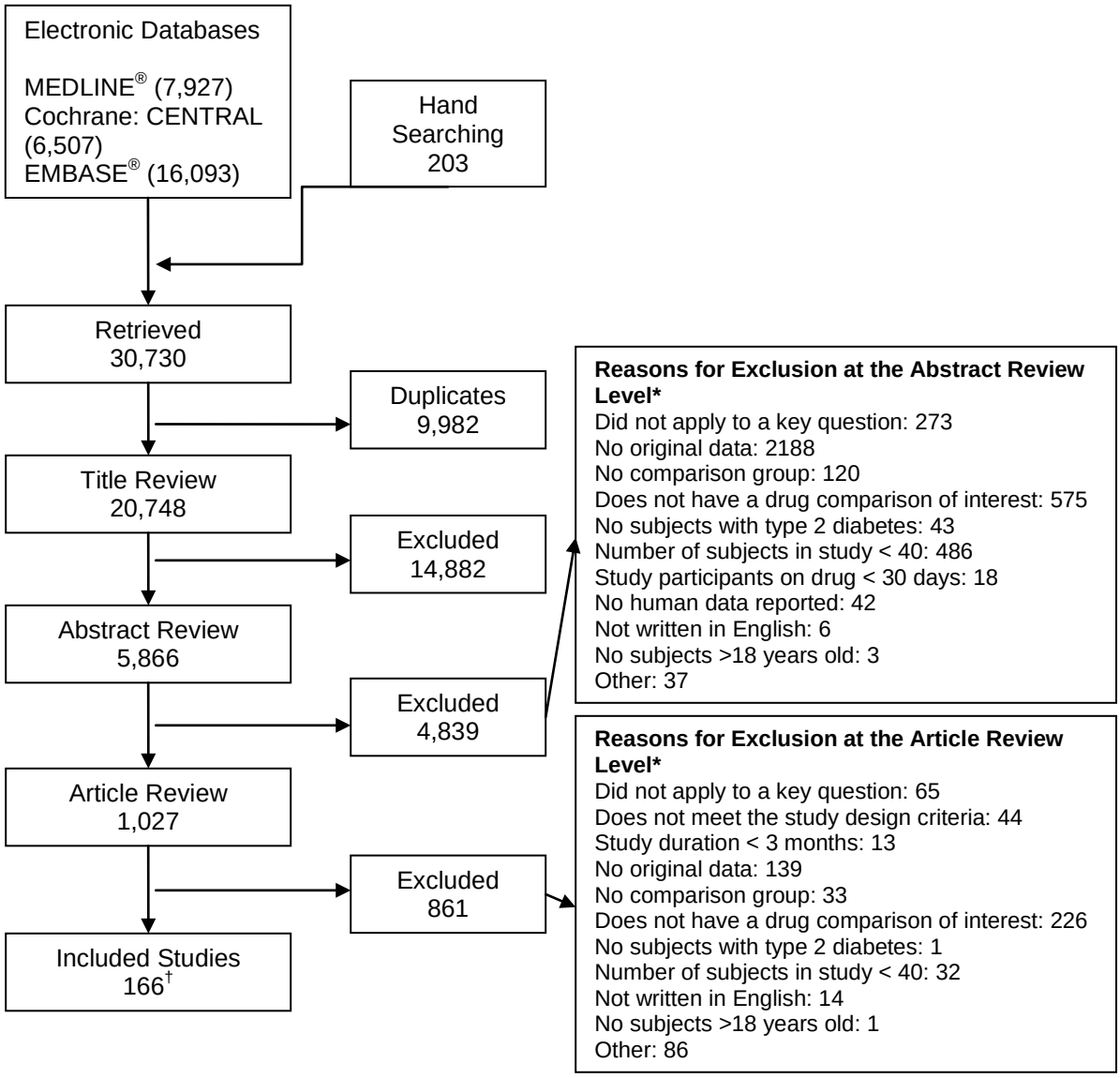
A draft of the evidence report was reviewed by the peer reviewers, AHRQ representatives, and the EPC Program’s Scientific Resource Center. The draft report also was posted to a Web site for public comment. In response to the comments of the peer reviewers and the public, we revised the evidence report and submitted a summary of the comments and their disposition to AHRQ.

Results

Search Results

A summary of the search results is presented in Figure 2. From the search, we retrieved 20,748 unique citations. After a review of the titles and abstracts, 1,027 were deemed eligible for further review, and the full articles were retrieved. A total of 166 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
Abbreviation: 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 HbA1c), weight, or lipids?

Key Points and Evidence Grades

HbA1c

Monotherapy Versus Monotherapy

- Most oral diabetes medications had similar efficacy in achieving reductions in HbA1c, with absolute reduction by around 1 percent compared with baseline values. The strength of evidence was graded high for metformin versus sulfonylurea with a pooled between-group difference of 0.1 percent (95 percent confidence interval [CI] -0.1 percent to 0.3 percent). The strength of evidence was graded as moderate for the following comparisons: metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone.
- Metformin had a greater reduction in hemoglobin A1c (HbA1c) compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, with a pooled between-group difference of -0.4 percent (95 percent CI -0.5 percent to -0.2 percent), with moderate strength of evidence.

Combination Therapy Versus Monotherapy

- All combination therapies were better at reducing HbA1c than monotherapy regimens, with between-group differences of about 1 percent. 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 DPP-4 inhibitors.

Combination Therapy Versus Combination Therapy

- The combination of metformin plus thiazolidinedione had similar efficacy in reducing HbA1c compared to the combination of metformin plus sulfonylurea, with moderate strength of evidence.
- Nine other combination therapy comparisons had low strength of evidence, making it difficult to draw firm conclusions. However, the majority showed similar efficacy in reducing HbA1c.
    - Five combinations showed similar efficacy in reducing HbA1c: metformin plus repaglinide versus metformin plus thiazolidinedione, metformin plus sitagliptin versus metformin plus thiazolidinedione, metformin plus sulfonylurea versus metformin plus DPP-4 inhibitor, metformin plus thiazolidinedione versus metformin plus glucagon-like peptide-1 (GLP-1) agonist, and metformin plus GLP-1 agonist versus metformin plus basal insulin.
    - The combination of metformin plus GLP-1 agonist reduced HbA1c more than metformin plus DPP-4 inhibitors, with a pooled between-group difference of -0.6 percent (95 percent CI -0.8 percent to -0.4 percent). Two other comparisons only

minimally favored one combination over another with differences in HbA1c ranging from 0.03 percent to 0.09 percent: metformin plus sulfonylurea favored versus thiazolidinediones plus sulfonylurea, and thiazolidinediones plus sulfonylureas favored versus metformin plus thiazolidinediones.

Weight

Monotherapy Versus Monotherapy

- When compared with thiazolidinediones, metformin maintained or decreased weight with a pooled between-group difference of -2.6 kg (95 percent CI -4.1 kg to -1.2 kg). The strength of evidence was graded as high, favoring metformin.
- When compared with sulfonylureas, metformin maintained or decreased weight with a pooled between-group difference of -2.7 kg (95 percent CI -3.5 kg to -1.9 kg). The strength of evidence was graded as high, favoring metformin.
- Sulfonylureas had similar effects on body weight as the meglitinides when used as monotherapy, with a high evidence grade.
- When compared with sulfonylureas, GLP-1 agonists decreased weight (pooled between-group difference of -2.5 kg, 95 percent CI -3.8 kg to -1.1 kg). The strength of evidence was graded moderate favoring GLP-1 agonists.
- When compared with DPP-4 inhibitors, metformin had greater weight reduction (pooled between-group difference of -1.4 kg (95 percent CI -1.8 kg to -1.0 kg). The strength of evidence was graded as moderate, favoring metformin.
- Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg, 95 percent CI -1.9 kg to -0.6 kg). While this was graded as low evidence for the monotherapy comparisons, it was strengthened by the combination comparisons (described below) which favor metformin plus sulfonylurea over metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95 percent CI -1.3 kg to -0.4 kg) with a moderate grade of evidence.

Combination Therapy Versus Monotherapy

- 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 percent CI -2.6 kg to -1.9 kg) or metformin plus a sulfonylurea (pooled between-group difference of -2.3 kg, 95 percent CI -3.3 kg to -1.2 kg). The strength of evidence was graded high for these comparisons.
- Metformin monotherapy had no significant differences in weight when compared with the combination of metformin plus DPP-4 inhibitors (pooled between-group difference of -0.2 kg, 95 percent CI -0.7 kg to 0.2 kg). The strength of evidence was graded moderate for this comparison.

Combination Therapy Versus Combination Therapy

- Metformin plus sulfonylurea had a more favorable effect on weight compared with both the combinations of a thiazolidinedione plus sulfonylurea (between-group difference of -3.2 kg, 95 percent CI -5.2 kg to -1.1 kg) and metformin plus a thiazolidinedione (between-group difference of -0.9 kg, 95 percent CI -1.3 kg to -0.4 kg). Both comparisons had moderate strength of evidence.

- Several combination therapies, metformin plus sulfonylurea, metformin plus thiazolidinedione, metformin plus basal insulin, and metformin plus DPP-4 inhibitor, were compared with metformin plus GLP-1 agonists, all favoring the combination of metformin plus GLP-1 agonists which decreased weight.
  - While all the individual comparisons were graded as low evidence, the data as a whole suggested a beneficial effect on weight for the combination of metformin plus GLP-1 agonists compared with several other standard combination therapies. The range in between group differences was 1.9 kg to 12.3 kg, and all but one study had less than a 5 kg between-group difference.
- The combination of metformin plus DPP-4 inhibitors decreased weight when compared with the combinations of metformin plus thiazolidinedione or metformin plus sulfonylurea. While these individual comparisons are graded as low strength of evidence due to few studies with the same comparators, the data suggest that metformin plus DPP-4 inhibitors may have a more favorable effect on weight than the other two standard combinations. The range of between-group differences was small (1.5 kg to 2.5 kg).

Low-Density Lipoproteins.

Monotherapy Versus Monotherapy

- Metformin decreased low-density lipoproteins (LDL) while sulfonylureas generally had little effect on LDL (pooled between-group difference favoring metformin of -10.1 mg/dL, 95 percent CI -13.3 mg/dL to -7.0 mg/dL), with high strength of evidence.
- Rosiglitazone and pioglitazone increased LDL while metformin decreased LDL with moderate strength of evidence. The pooled between-group differences comparing metformin to rosiglitazone and pioglitazone were -12.8 mg/dL (95 percent CI -24.0 mg/dL to -1.6 mg/dL) and -14.2 mg/dL (95 percent CI -15.3 mg/dL to -13.1 mg/dL), respectively.
- Metformin decreased LDL compared to DPP-4 inhibitors, with a pooled between-group difference of -5.9 mg/dL (95 percent CI -9.8 mg/dL to -2.0 mg/dL), with moderate strength of evidence.

Combination Therapy Versus Monotherapy

- The combination of metformin and rosiglitazone increased LDL compared to metformin monotherapy (pooled between-group difference of 14.5 mg/dL, 95 percent CI 13.3 mg/dL to 15.7 mg/dL), with high strength of evidence.

Combination Therapy Versus Combination Therapy

- The combination of metformin and a sulfonylurea decreased LDL more than the combination of metformin and rosiglitazone (pooled between-group difference -13.5 mg/dL, 95 percent CI -17.9 mg/dL to -9.1 mg/dL), with moderate strength of evidence.

High-Density Lipoproteins

Monotherapy Versus Monotherapy

- Pioglitazone increased high-density lipoproteins (HDL) compared to metformin (pooled between-group difference of 3.2 mg/dL, 95 percent CI 2.1 mg/dL to 5.7 mg/dL) with high strength of evidence.
- Neither rosiglitazone nor sulfonylureas had an effect on HDL relative to metformin, with high strength of evidence for sulfonylureas and moderate for rosiglitazone
- Rosiglitazone increased HDL less than pioglitazone (pooled between-group difference of -2.3 mg/dL, 95 percent CI -3.5 mg/dL to -1.2 mg/dL), with moderate strength of evidence. Pioglitazone increased HDL when compared with sulfonylureas (pooled between-group difference of 4.3 mg/dL, 95 percent CI 1.9 mg/dL to 6.6 mg/dL), with moderate strength of evidence.

Combination Therapy Versus Monotherapy

- The combination of rosiglitazone and metformin increased HDL relative to metformin monotherapy (pooled between-group difference of 2.8 mg/dL, 95 percent CI 2.2 mg/dL to 3.5 mg/dL), with high strength of evidence.
- The combination of metformin and DPP-4 inhibitors did not affect HDL relative to metformin monotherapy. The pooled between-group difference in HDL for metformin compared to the combination of metformin and saxagliptin was 0.5 mg/dL (95 percent CI -1.5 mg/dL to 2.5 mg/dL) with moderate strength of evidence

Combination Therapy Versus Combination Therapy

- The combination of rosiglitazone or pioglitazone with metformin increased HDL compared to the combination of metformin and a sulfonylurea. The strength of evidence was graded as moderate for these comparisons:
  - The pooled between-group difference for the combination of metformin and rosiglitazone compared to the combination of metformin and a sulfonylurea was 2.7 mg/dL (95 percent CI 1.4 mg/dL to 4.1 mg/dL).
  - The combination of metformin and pioglitazone increased HDL by about 5 mg/dL compared to the combination of metformin and a sulfonylurea.
- The combination comparisons with pioglitazone favored the pioglitazone containing arm (range of between-group differences were 3.1 mg/dL to 10.5 mg/dL) for the following comparisons:
  - The combination of pioglitazone plus metformin versus metformin monotherapy, the combination of metformin plus pioglitazone versus the combination of metformin plus sulfonylurea, and the combination of sulfonylurea plus pioglitazone versus the combination of metformin plus sulfonylurea. The strength of evidence was graded as low for each individual comparison.

Triglycerides

Monotherapy Versus Monotherapy

- Pioglitazone decreased triglycerides (TG) more than metformin (pooled between-group difference -27.2 mg/dL, 95 percent CI -30.0 mg/dL to -24.4 mg/dL), with high strength of evidence.
- Metformin decreased TG relative to rosiglitazone which increased TG (pooled between-group difference -26.9 mg/dL, 95 percent CI -49.3 mg/dL to -4.5 mg/dL), with moderate strength of evidence.
- Metformin decreased TG compared to sulfonylureas (pooled between-group difference -8.6 mg/dL, 95 percent CI -15.6 mg/dL to -1.6 mg/dL) with moderate strength of evidence.
- Sulfonylureas and meglitinides had similar effects on TG (pooled between-group difference 0.2 mg/dL, 95 percent CI -3.8 mg/dL to 4.2 mg/dL), with moderate strength of evidence.

Combination Therapy Versus Monotherapy

- Metformin monotherapy decreased TG compared to the combination of metformin and rosiglitazone (pooled between-group difference -14.5 mg/dL, 95 percent CI -15.7 mg/dL to -13.3 mg/dL), with high strength of evidence.

Combination Therapy Versus Combination Therapy

- The combination of metformin and rosiglitazone had similar effects on TG compared to a combination of metformin and a sulfonylurea, with moderate strength of evidence.
- The combination of metformin and pioglitazone decreased TG compared to the combination of metformin and a sulfonylurea by about 15 mg/dL, with moderate strength of evidence.

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 nineteen randomized controlled trials (RCTs) (reported in 122 articles) evaluated intermediate clinical outcomes for adults with type 2 diabetes, and met our inclusion criteria (Appendix G, Tables 2 and 3). One hundred four, 79, and 74 of these RCTs reported HbA1c, weight, and lipid outcomes, respectively. All trials were parallel-arm RCTs except one, which used a crossover design.[36] About half the trials answering Key Question 1 occurred partly or exclusively in the United States (n = 32), Italy (n = 13), and/or were multinational (n = 28); 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 (United Kingdom Prospective Diabetes Study [UKPDS], Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes [RECORD], and A Diabetes Outcome Progression Trial [ADOPT]).[16,37,38] Only seven studies reported receiving no pharmaceutical support,[39-45] while about one-quarter of RCTs (n = 33) 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 percent) excluded older subjects (generally older than 75 to 80 years old). Almost all the studies reported a diverse gender mix among the participants. About 20 percent of the RCTs did not report race. When race was reported, most subjects were Caucasian. The mean baseline HbA1c among study subjects varied from 6 to12 absolute percentage points, with most subjects having a mean baseline HbA1c between 7 and 9 absolute percentage points.

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

Comparison	HbA1c	Weight/BMI	LDL	HDL	TG
MONOTHERAPY COMPARISONS					
Metformin versus					
TZD	Neither Favored; Mod	Favors Met; High	Favors Met; Mod[‡] Favors Met; High[§]	Neither Favored; Mod[‡] Favors Pio; High[§]	Favors Met; Mod[‡] Favors Pio; High[§]
SU	Neither Favored; High	Favors Met; High	Favors Met; High	Neither Favored; High	Favors Met; Mod
DPP-4 inhibitor	Favors Met; Mod	Favors Met; Mod	Favors Met; Mod	Neither Favored; Low	Neither Favored; Low
Meglitinides	Neither Favored; Low* Favors Met; Low[†]	Unclear; Low	Unclear; Low	Unclear; Low	Unclear; Low
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + TZD	Favors Met+TZD; High	Favors Met; High	Favors Met; High[‡] Unclear; Low[§]	Favors Met+Rosi; High[‡] Favors Met+Pio; Low[§]	Favors Met; High[‡] Unclear; Low[§]
Metformin + SU	Favors Met+SU; High	Favors Met; High	Neither Favored; Low	Neither Favored; Low	Neither Favored; Low
Metformin + DPP-4 inhibitor	Favors Met+DPP-4; Mod	Neither Favored; Mod	Neither Favored; Low	Neither Favored; Mod	Favors Met+DPP-4; Low
Metformin + meglitinides	Favors Met+Meg; Low	Favors Met; Low	Unclear; Low	Neither Favored; Low	Favors Met+Meg; Low
TZD versus					
TZD	Neither Favored; Mod	Neither Favored; Low	Favors Pio; Low	Favors Pio; Mod	Neither Favored; Low
SU	Neither Favored; Mod	Favors SU; Low	Favors SU; Low[‡§]	Favors Rosi; Low[‡] Favors Pio; Mod[§]	Unclear; Low[‡] Favors Pio; Low[§]
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Unclear; Low* Neither Favored; Low[†]	Unclear; Low	Unclear; Low[‡§]	Unclear; Low[‡] Favors Pio; Low[§]	Unclear; Low[‡] Favors Pio; Low[§]
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
SU versus					
DPP-4 inhibitor	Neither Favored; Low	Unclear; Low	Neither Favored; Low	Neither Favored; Low	Neither Favored; Low
Meglitinides	Neither Favored; High* Neither Favored; Low[†]	Neither Favored; High	Neither Favored; Low	Neither Favored; High	Neither Favored; Mod
GLP-1 agonist	Unclear; Low	Favors GLP-1; Mod	Unclear; Low	Insufficient	Unclear; Low
DPP-4 inhibitor versus					
Meglitinides	Insufficient	Insufficient	Insufficient	Unclear; Low	Insufficient
GLP-1 agonist	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	HbA1c	Weight/BMI	LDL	HDL	TG
COMBINATION COMPARISONS					
Metformin + TZD versus					
Metformin + SU	Neither favored; Mod	Favors Met+SU; Mod	Favors Met+SU; Mod‡ Favors Met+SU; Low§	Favors Met+Rosi; Mod‡ Favors Met+Pio; Low§	Neither favored; Mod‡ Favors Met+Pio; Mod§
Metformin + meglitinides	Neither favored; Low* Insufficient†	Unclear; Low	Favors Met+Meg; Low‡ Insufficient§	Favors Met+Rosi; Low‡ Insufficient§	Neither favored; Low‡ Insufficient§
Metformin + DPP-4 inhibitor	Neither favored; Low	Favors Met+DPP4; Low	Insufficient‡§	Low; Unclear‡ Insufficient§	Low; Favors Met+Sita‡ Insufficient§
Metformin + GLP-1 agonist	Neither favored; Low	Favors Met+GLP1; Low	Unclear; Low‡§	Favors Met+Rosi; Low‡ Insufficient§	Favors Met+GLP1; Low‡ Insufficient§
TZD + SU	Favors TZD+SU; Low	Insufficient	Insufficient‡ Neither favored; Low§	Insufficient‡ Favors Met+Pio; Low§	Insufficient‡ Favors Met+Pio; Low§
Met + SU versus					
Metformin + meglitinides	Insufficient* Unclear; Low†	Unclear; Low	Unclear; Low	Neither favored; Low	Unclear; Low
Metformin + DPP-4 inhibitor	Neither favored; Low	Favors Met+DPP4; Low	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Unclear; Low	Favors Met+GLP1; Low	Insufficient	Insufficient	Insufficient
TZD + SU	Favors Met+SU; Low	Favors Met+SU; Mod	Unclear; Low‡ Favors Met+SU; Low§	Unclear; Low‡ Favors Pio+SU; Low§	Unclear; Low‡ Favors Pio+SU; Low§
Metformin + premixed insulin	Unclear; Low	Favors Met+Basal; Low	Insufficient	Insufficient	Insufficient
Met + Basal Insulin versus					
Metformin + premixed insulin	Neither favored; Low	Neither favored; Low	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Neither favored; Low	Favors Met+GLP1; Low	Insufficient	Insufficient	Insufficient
Met + DPP-4 inhibitor versus					
Met + GLP-1 agonist	Favors Met+GLP1; Low	Favors Met+GLP1; Low	Unclear; Low	Neither favored; Low	Unclear; Low

Abbreviations: BMI = body mass index; HDL = high density lipoprotein; HbA1c = 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

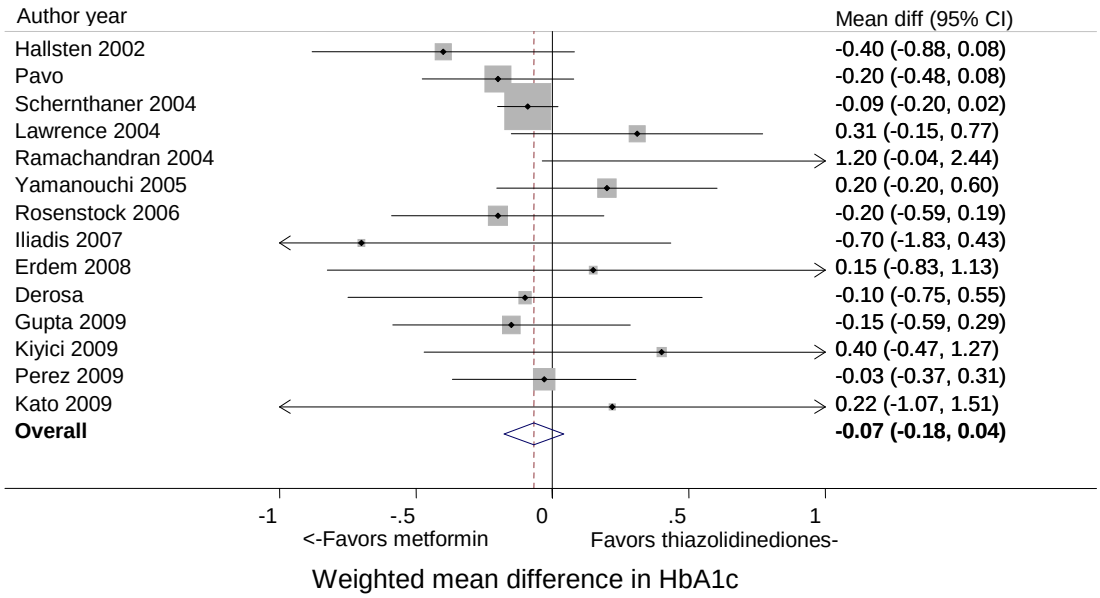
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change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

The Evidence About Hemoglobin A1c (Appendix G, Table 4)

Metformin versus thiazolidinediones. Fourteen RCTs lasting around a year or less directly compared metformin versus thiazolidinedione, showing no between-group differences in HbA1c, with a pooled between-group difference of -0.1 percent (95 percent CI -0.2 percent to 0.04 percent) (Figure 3).[39,45-57] We conducted a standard sensitivity analysis testing the relative effect of each individual study to the combined point estimate. Only removing the study by Lawrence et al. affected the combined point estimate resulting in a pooled mean difference of -0.1 percent (95 percent CI -0.2 percent to -0.003 percent) which minimally favored 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 HbA1c comparing metformin with thiazolidinediones



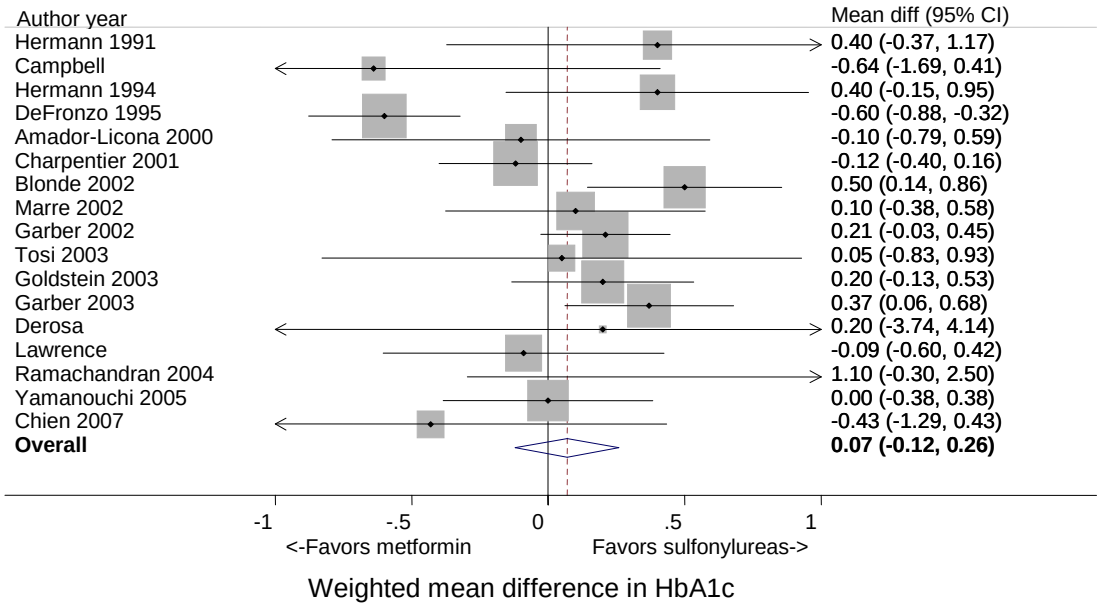
Abbreviations: CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 14.47 with 13 degrees of freedom (p = 0.34)
I-squared statistic = 10%
The range in change scores for HbA1c for the comparison group, thiazolidinediones, was -2.6% to -0.3%. The median change was -1.0%.

We excluded two studies from the meta-analysis, one with a median study duration of 4 years[38] and one which reported median HbA1c instead of means.[58] 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.[38] While they found a statistically significant difference between groups favoring rosiglitazone (mean difference between groups 0.1 percent, 95 percent CI 0.05 percent to 0.2 percent), the clinical relevance of this difference is less clear. Of note, the HbA1c 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 HbA1c.[58]

Metformin versus sulfonylureas. We combined 17 studies comparing metformin with a second-generation sulfonylurea and showed similar changes in HbA1c in both groups, with a pooled between-group difference of 0.1 percent (95 percent CI -0.1 percent to 0.3 percent) (Figure 4).[36,50,51,53,59-71] Removing the 1-year study by DeFronzo et al. changed the results of the meta-analysis, favoring second-generation sulfonylureas slightly with a pooled between-group difference of 0.2 percent (95 percent CI 0.02 percent to 0.3 percent);[70] which may reflect the slightly longer study duration.

Figure 4. Mean difference in HbA1c comparing metformin with sulfonylureas



CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
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 16 degrees of freedom (p = 0.003)
I-squared statistic = 63%
The range in change scores for HbA1c for the comparison group, sulfonylureas, was -2.5% to 0.5%. The median change was -1.2%.

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 between-group difference of 0.2 percent, 95 percent CI 0.01 percent to 0.3 percent), while those lasting 6 months to a year showed no between-group differences in medications (pooled between-group difference of -0.1 percent, 95 percent CI -0.5 percent to 0.3 percent). The small possible difference of 0.18

percent seen with studies lasting less than 6 months has questionable clinical relevance. Baseline HbA1c and dosing ratio did not explain the heterogeneity.

The two long-term studies excluded from the meta-analysis (ADOPT and UKPDS) lasting longer than 4 years have conflicting results related to glycemic control. ADOPT favored metformin over sulfonylurea after a median followup of 4 years.[38] 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 HbA1c after 10 years of followup for those subjects where other diabetes medications were added to their monotherapy regimen.[8] 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.[38] 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 -0.3 percent, 95 percent CI -0.2 percent to -0.4 percent). Of note, the glyburide group reduced HbA1c more than metformin initially, but then the HbA1c started to rise after about 6 months in all groups. The HbA1c 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.[37] They compared the proportion of subjects who achieved a target HbA1c less than 7 percent after 9 years of followup between metformin and sulfonylurea, and appeared to favor sulfonylurea slightly (13 percent versus 21 percent respectively with nonoverlapping confidence intervals). However, only 25 percent of subjects were able to achieve a target HbA1c after 9 years on monotherapy alone.

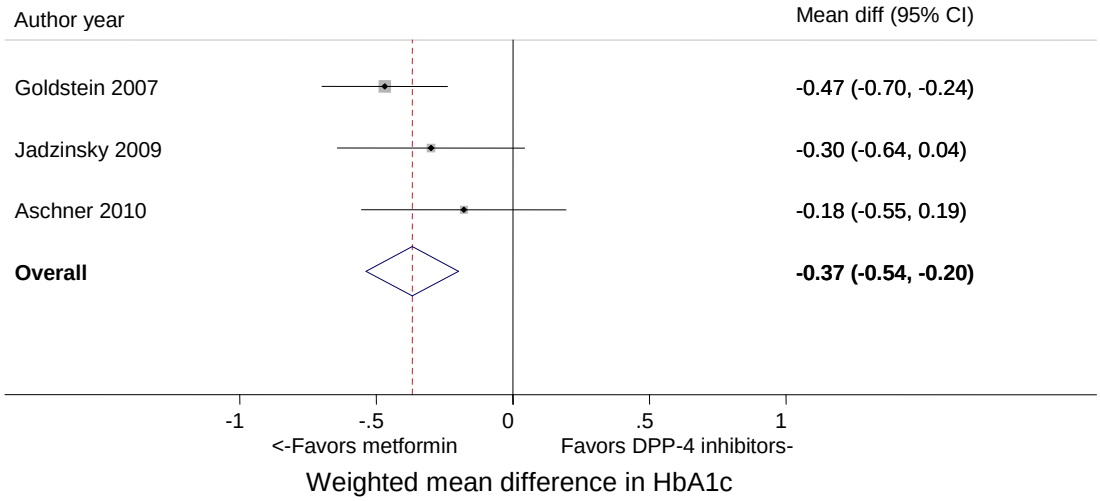
The rest of the UKPDS[72-74] studies were excluded from this section of the report since they were allowed to add other diabetes medications to their initial monotherapy groups, making it impossible to discern comparative drug effects. We describe it here briefly since it is a well known study with the longest followup (up to 10 years). The UKPDS was a multicenter trial conducted in the United Kingdom comparing different types of treatment for type 2 diabetes. Patients were recruited starting in 1977, and initially put on a diet with 50 percent 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 percent 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 HbA1c between groups.[8,72-74] After 10 years, the change in median HbA1c from baseline was similar in both the

metformin and glibenclamide arms for the main randomization group as reported in a figure (+1.3 percent versus +1.0 percent).[8] The median HbA1c results were not broken down by medication type in the primary diet failure group at 10 years. After 6 years, the reported 95 percent CI for the mean final HbA1c was 7.1 percent to 9.4 percent for metformin and 6.8 percent to 9.7 percent for glibenclamide/chlorpropamide in overweight patients in the primary diet failure group.[72] Of note, the main randomization group of UKPDS demonstrated that HbA1c 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.[8]

Metformin versus DPP-4 inhibitors. Three short-duration RCTs (reported in four articles) compared metformin with DPP-4 inhibitors, reporting greater reductions in HbA1c by metformin, with a pooled between-group difference of -0.4 percent (95 percent CI -0.5 percent to -0.2 percent) (Figure 5).[75-78] Two studies used metformin compared with sitagliptin,[76,77] and one study compared metformin with saxagliptin.[78] One RCT was reported in two articles.[75,76] The first article was a 24-week RCT,[75] while the second article was the 30-week continuation study with a higher loss to followup.[76] The between-group difference in HbA1c of -0.5 percent favored metformin over sitagliptin at both 24 and 54 weeks of followup. We included the 24-week study in the meta-analysis since the other two studies in the meta-analysis were both 24 weeks long. No substantial heterogeneity was found in the meta-analysis. A standard sensitivity analysis was conducted to determine if any one study strongly influenced the results. The removal of the study by Goldstein et al.[75] changed the pooled between-group difference to -0.2 percent (95 percent CI -0.5 percent to 0.008 percent), showing no significant differences between-groups. There would be no reason to exclude this trial compared to the other trials, however. In fact, one study used an underdosed metformin arm compared to the maximum dose DPP-4 inhibitor, thereby strengthening the result that favors metformin.[78]

Figure 5. Mean difference in HbA1c comparing metformin with DPP-4 inhibitors

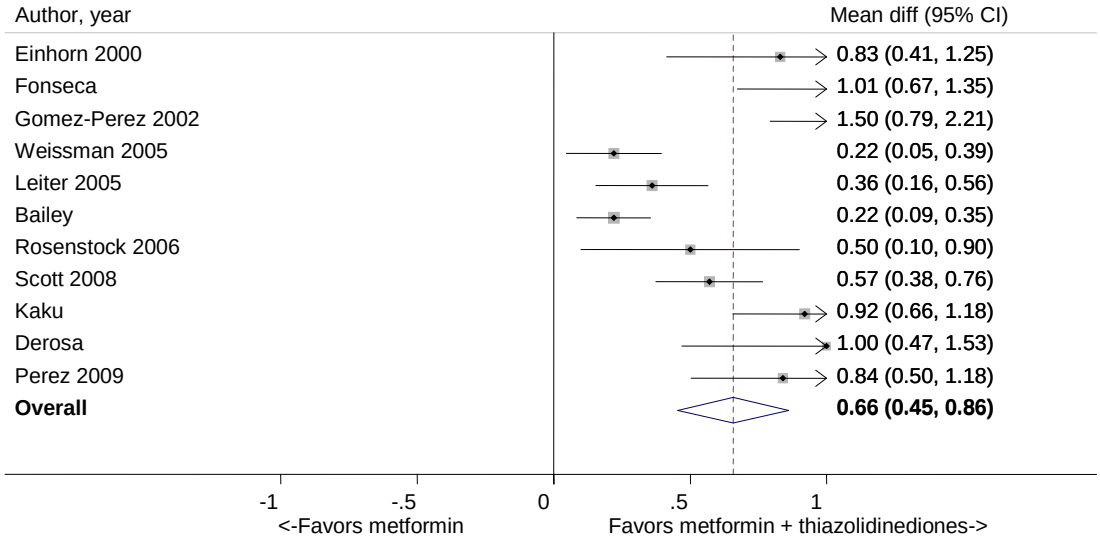


CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; HbA1c = hemoglobin A1c
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal 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 = 1.87 with 2 degrees of freedom (p = 0.39)
I-squared statistic = 0%
The range in change scores for HbA1c for the comparison group, DPP-4 inhibitors, was -1.7% to -0.4%. The median change was -0.7%.

Metformin versus meglitinides. Three RCTs (reported in four articles) lasting 3 months to 1 year compared metformin with meglitinides, showing similar effects on HbA1c.[79-82] One study favored the slightly underdosed metformin arm compared with the nateglinide arm (-0.3 percent between-group difference).[79] This same study reported in a second article showed no between-group differences in HbA1c; however, they evaluated only the subset of patients who were treatment naïve.[80] The other two studies evaluated metformin and repaglinide at comparable doses showing non-meaningful between-group differences of 0.1 percent and 0.05 percent.[81,82]

Metformin versus a combination of metformin and thiazolidinediones. Eleven studies compared metformin with the combination of metformin plus a thiazolidinedione (most rosiglitazone except for four studies with pioglitazone),[46,49,56,83-90] showing a greater improvement in HbA1c with the combination in all the studies. The pooled between-group difference was 0.7 percent (95 percent CI 0.5 percent to 0.9 percent) (Figure 6). No single study markedly affected the results. Despite the substantial heterogeneity reported, all studies favored the combination arm. Metaregression showed that baseline HbA1c was a significant source of heterogeneity (p = 0.01) while study duration and dosing ratio were not. Studies with higher baseline HbA1c (HbA1c > 8 percent) had greater between-group differences (pooled between-group difference of 0.9 percent (95 percent CI 0.7 percent to 1.1 percent) than studies with lower baseline HbA1c (HbA1c < 8 percent; pooled between-group difference of 0.4 percent, 95 percent CI 0.2 percent to 0.7 percent).

Figure 6. Mean difference in HbA1c comparing metformin with combination of metformin and thiazolidinediones

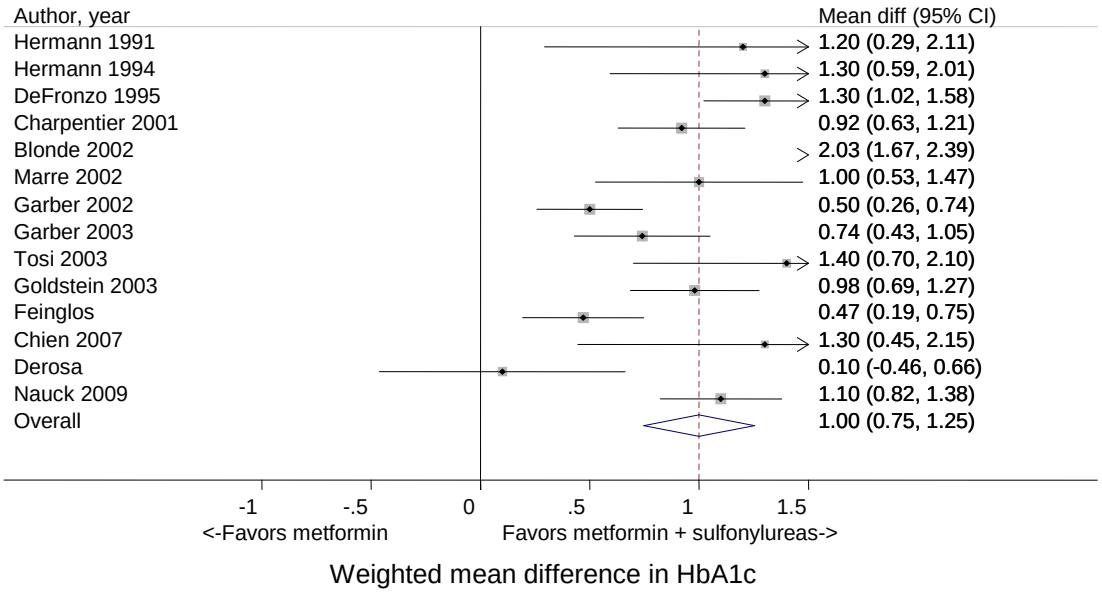


CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals 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 = 63.83 with 10 degrees of freedom (p = 0.0000)
I-squared statistic = 84%
The range in change scores for HbA1c for the comparison group, a combination of metformin and thiazolidinediones, was -2.3% to -0.33%. The median change was -0.83%.

Metformin versus a combination of metformin and sulfonylureas. Fourteen RCTs compared metformin with the combination of metformin plus a second-generation sulfonylurea with all of the studies favoring the combination arm over monotherapy (pooled between-group difference of 1.0 percent, 95 percent CI 0.8 percent to 1.3 percent) (Figure 7).[36,46,59,61-65,68-71,91,92]

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 HbA1c compared with other studies.[63] Three of the six dose-response studies showed a dose-response gradient favoring greater reductions in HbA1c with a higher dose combination than with a lower dose combination.[63,64,68] 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.[36]

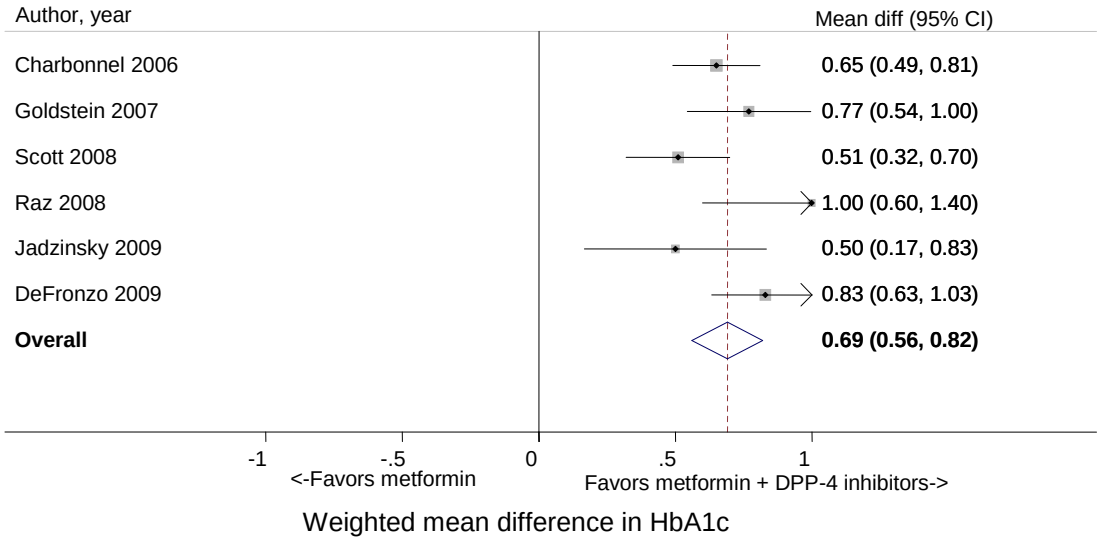
Figure 7. Mean difference in HbA1c comparing metformin with combination of metformin and sulfonylureas



CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
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%
The range in change scores for HbA1c for the comparison group, a combination metformin and sulfonylurea, was -2.3% to -0.7%. The median change was -1.6%.

Metformin versus a combination of metformin and DPP-4 inhibitors. Six RCTs directly compared metformin with the combination of metformin plus a DPP-4 inhibitor—all favoring the combination arm, with a pooled between-group difference of 0.7 percent (95 percent CI 0.6 percent to 0.8 percent) (Figure 8).[75,78,85,93-95] No single study markedly influenced the results, and no substantial heterogeneity was found. One RCT was published twice, first with the 24-week RCT results[75] and second as a 30-week continuation[76] 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.[75] The 54-week results also favored the combination arm over the monotherapy arm, with a between-group difference of 0.8 percent.[76] They also showed a small dose-response effect in the combination arms, with the 2,000 mg metformin and 100 mg sitagliptin arm reducing HbA1c more than the 1,000 mg metformin plus 100 mg sitagliptin arm (mean change from baseline -1.8 percent versus -1.4 percent respectively).

Figure 8. Mean difference in HbA1c comparing metformin with combination of metformin and DPP-4 inhibitors



CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; HbA1c = hemoglobin A1c
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 = 179.59 with 5 degrees of freedom (p = 0.00)
I-squared statistic = 97%
The range in change scores for HbA1c for the comparison group, a combination of metformin and DPP-4 inhibitor, was -2.5% to -0.7%. The median change was -0.9%.

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 percent to -1.08 percent). We separated out nateglinide from repaglinide combinations since indirect monotherapy comparisons suggest nateglinide has less effect on HbA1c than repaglinide.[21]

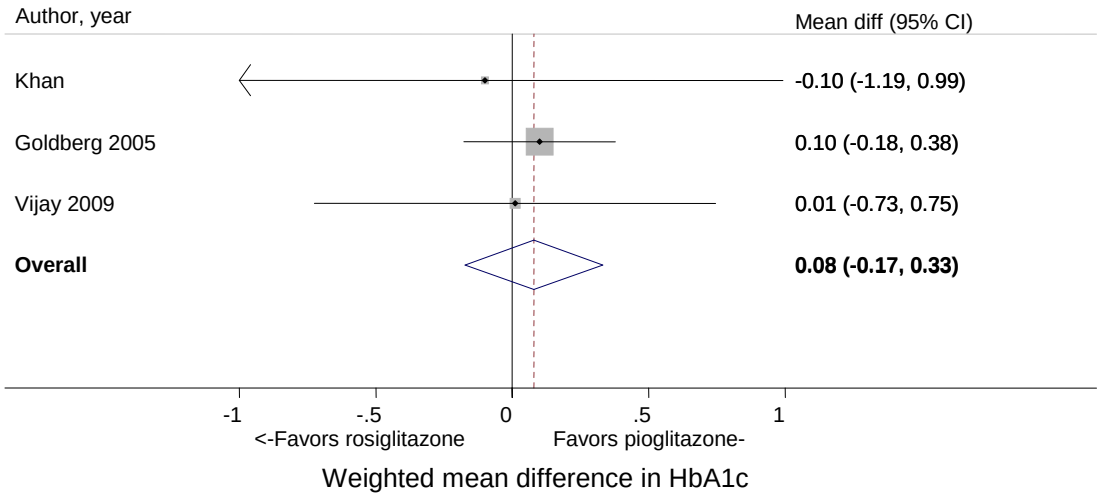
Two similarly dosed 24-week studies reported in three articles compared metformin versus metformin plus nateglinide, showing greater reductions in HbA1c in the combination arms compared with the monotherapy arms (range in between-group differences of -0.5 percent to -0.8 percent).[79,80,96] Only one of these RCTs reported that this between-group difference was also statistically significant,[96] while the other study did not report on the between-group statistical significance in either article.[79,80]

One additional short duration study compared metformin versus metformin plus repaglinide, which also favored the combination therapy over monotherapy (between-group difference of -1.1 percent , 95 percent CI -1.8 percent to -0.3 percent).[82]

Rosiglitazone versus pioglitazone. Three RCTs with similar dosing of the medications compared rosiglitazone with pioglitazone, and showed no significant between-group differences in HbA1c, with a pooled between-group difference of 0.1 percent (95 percent CI -0.2 percent to

0.3 percent) (Figure 9).[97-99] No one study significantly influenced the results, and no substantial heterogeneity was found.

Figure 9. Mean difference in HbA1c comparing rosiglitazone with pioglitazone



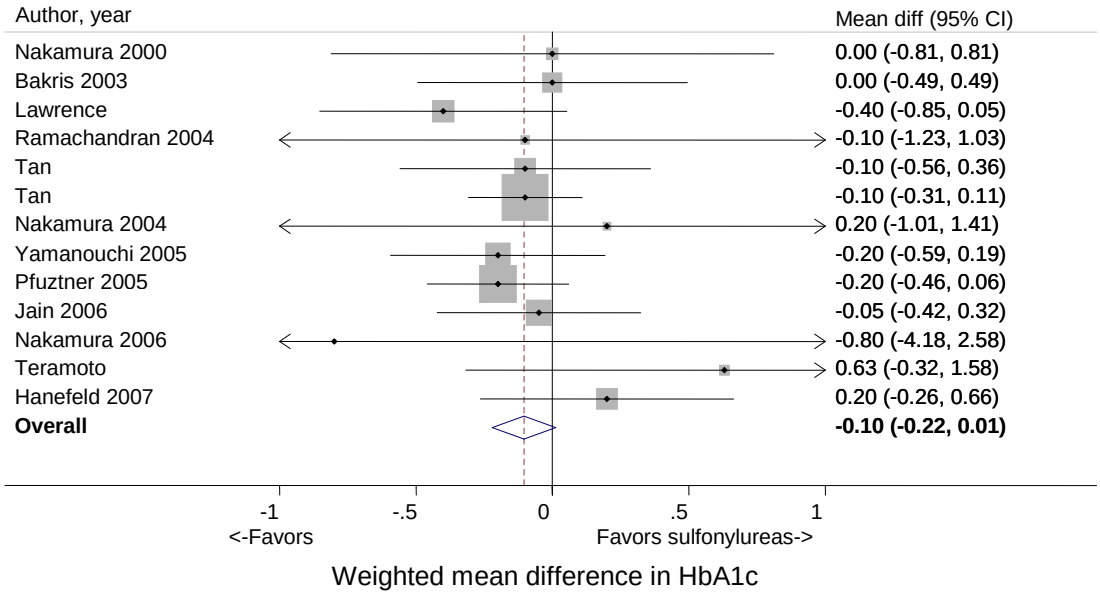
CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals 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 = 0.16 with 2 degrees of freedom (p = 0.92)
I-squared statistic = 0%
The range in change scores for HbA1c for the comparison group, pioglitazone, was -1.3% to -0.2%. The median change was -0.7%.

Thiazolidinediones versus sulfonylureas. Both thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) and second-generation sulfonylureas (glibenclamide, glimepiride, and glyburide) had similar effects on HbA1c, with a pooled mean difference between-groups of -0.1 percent (95 percent CI -0.2 percent to 0.01 percent) (Figure 10).[41,50,51,53,100-108] When we combined the 3 out of 13 studies with comparable dosing,[53,100,107] the results were similar with a weighted mean difference of -0.1 percent (95 percent CI -0.4 percent to 0.2 percent). In a standard sensitivity analysis which tests the relative influence of each individual study on the combined point estimate, we found that removal of one study influenced the pooled results. When the study by Hanefeld et al.[100] was removed from the main meta-analysis, the pooled mean difference favored TZDs slightly, with a pooled mean difference between-groups of -0.1 percent (95 percent CI -0.2 percent to -0.004 percent). However, the study by Hanefeld et al[100] is similar to the other studies, and should not be removed from the overall meta-analysis. 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).[38] 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 -0.4, 95 percent CI -0.5 percent to -0.3 percent). Of note, glyburide reduced HbA1c more than

rosiglitazone initially. The HbA1c then rose higher in the glyburide arm compared with the rosiglitazone arm after 1.5 years.

Figure 10. Mean difference in HbA1c comparing thiazolidinediones with sulfonylureas



CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
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 = 7.07 with 12 degrees of freedom (p = 0.85)
I-squared statistic = 0%
The range in change scores for HbA1c for the comparison group, sulfonylureas, was -2.5% to 1.5%. The median change was -0.9%.

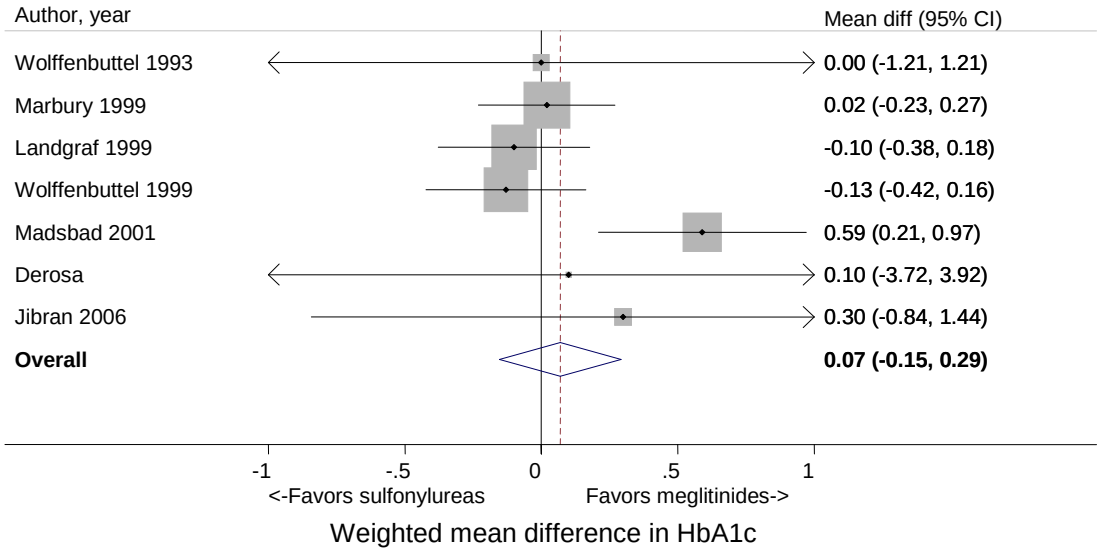
Thiazolidinediones versus meglitinides. Two 24-week similar quality head-to-head trials compared thiazolidinediones with repaglinide specifically, and showed no consistent effects favoring one of the medications.[109,110] These inconsistent results may be due to different thiazolidinediones, or different 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 percent).[110] The other study with more comparable dosing between rosiglitazone and repaglinide favored rosiglitazone with a between-group difference of 0.39 percent.[109]

A one-year RCT compared pioglitazone with nateglinide at comparable doses, and reported similar reductions in HbA1c in each arm (-1.6 percent and -1.4 percent respectively).[108]

Sulfonylureas versus DPP-4 inhibitors. One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[111] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg per day) similarly reduced HbA1c (-0.77 percent versus -1.00 percent 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 between-group difference of 0.1 percent (95 percent CI -0.2 percent to 0.3 percent) (Figure 11).[112-118] 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.[113,117,118]

Figure 11. Mean difference in HbA1c comparing sulfonylureas with meglitinides



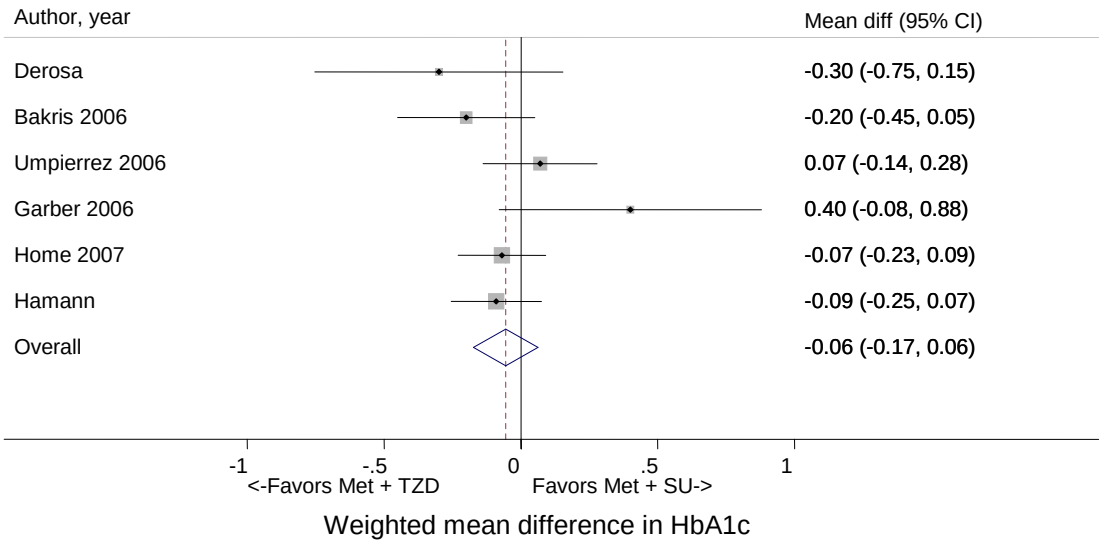
CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals 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%
The range in change scores for HbA1c for the comparison group, meglitinides, was -1.2% to 0.58%. The median change was -0.2%.

Two short-duration RCTs compared a slightly under-dosed glibenclamide arm with nateglinide at somewhat higher doses, showing no significant differences between groups (range in non-significant between-group differences of -0.5 percent to -0.2 percent).[108,119] We did not include these studies in a meta-analysis due to potential differences in glycemic control between nateglinide and repaglinide.

Sulfonylurea versus GLP-1 agonists. Three RCTs compared sulfonylureas directly with liraglutide with conflicting results. We did not combine these trials in a meta-analysis due to dosing differences within and between studies. One comparably dosed small RCT reported no statistically significant differences between the two arms.[120] The two other larger RCTs favored the liraglutide arm,[121,122] yet one of these studies underdosed the sulfonylurea arm compared with the liraglutide arm making it difficult to discern true drug differences versus dosing differences.[121]

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 HbA1c between groups of -0.1 percent (95 percent CI -0.2 percent to 0.1 percent) (Figure 12).[123-128] 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.[46,129] Both studies underdosed the metformin in the metformin plus sulfonylurea arms, and found between-group differences in HbA1c favoring the metformin plus thiazolidinedione arms (-0.3 percent 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.

Figure 12. Mean difference in HbA1c comparing combination of metformin and thiazolidinediones with combination of metformin and sulfonylureas



CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea; TZD = 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 random-effects pooled estimate.

Test for heterogeneity: Q = 7.45 with 5 degrees of freedom (p = 0.19)

I-squared statistic = 33%

The range in change scores for HbA1c for the comparison group, a combination of metformin and sulfonylurea, was -1.5% to 0.9%. The median change was -0.9%.

In the meta-analysis, we included the shorter duration RECORD study since the study duration was more comparable to the other included studies.[124] 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.[16,124] They randomly assigned subjects to addition of rosiglitazone or to a combination of metformin and sulfonylurea, and the 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.[16,124] The between-group difference in HbA1c of -0.07 percent was small and not significant in the 516 subjects with 18-month followup.[124] In the article reporting on the mean followup of 5.5 years in 2,222 subjects,

the between-group difference in HbA1c of -0.29 percent significantly favored metformin plus rosiglitazone over metformin plus sulfonylurea.[16] 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.[16]

Combination of metformin and thiazolidinediones versus combination of metformin and DPP-4 inhibitors. Two short-duration RCTs compared metformin plus rosiglitazone with the combination of metformin plus sitagliptin, showing similar reductions in HbA1c in each arm. One double-blind study with comparable dosing of the medications showed no between-group differences in HbA1c (mean difference of -0.1 percent, 95 percent CI -0.3 percent to 0.1 percent).[85] The other RCT compared a submaximally dosed metformin plus rosiglitazone arm to a maximally dosed metformin plus sitagliptin arm, and showed similar reductions in HbA1c after 16 weeks (-0.6 percent in rosiglitazone combination arm versus -0.4 percent in sitagliptin combination arm).[130]

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.[131]

Combination of metformin and thiazolidinediones versus combination of metformin and GLP-1 agonists. One 20-week RCT with comparable dosing of medications compared the combination of metformin and rosiglitazone with the combination of metformin and exenatide, showing no significant between-group differences in HbA1c (between-group difference of -0.1 percent, $p = 0.7$).[132]

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 percent ($p = 0.04$).[129]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. One double-blinded moderately sized RCT compared fixed dose metformin plus sulfonylurea (mean dose of sulfonylurea was 10 mg) with the combination of fixed dose metformin plus fixed dose sitagliptin (100 mg), showing no between group-differences in HbA1c after 1 year (mean between-group difference of -0.01 percent, 95 percent CI -0.1 percent to 0.1 percent).[133] This RCT was extended a second year and continued to show no statistically significant between-group differences in HbA1c.[134]

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 showing conflicting results.[135,136] These differences may reflect differences in dosing. The first RCT compared the combination of metformin (mean dose 2,500 mg) plus glibenclamide (mean dose

12.5 mg) with metformin (mean dose 2,500 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 percent.[135] The second RCT showed no significant difference between groups (between-group difference of -0.3 percent) despite the higher dosed metformin plus nateglinide arm.[136]

Combination of metformin and sulfonylureas versus combination of metformin and GLP-1 agonists. Two RCTs compared metformin plus sulfonylurea with metformin plus a GLP-1 agonist with conflicting results. One small comparably dosed RCT lasting a year compared the combination of metformin and glibenclamide with the combination of metformin and exenatide, reporting no significant between-group differences in HbA1c (between-group difference of -0.3 percent, $p > 0.05$).[44] A second comparably dosed medium-sized RCT directly compared the combination of metformin and glimepiride with two different dosing arms of the combination of metformin and liraglutide (titrated to a maximum dose of 1.2 mg of liraglutide in one combination arm and 1.8 mg in a second liraglutide combination arm).[92] Both dosing comparisons showed greater reductions in HbA1c in the metformin plus liraglutide arms (between-group differences of -1.1 percent, 95 percent CI -1.3 percent to -0.9 percent for both arms). No dose-response gradient was reported. It is unclear whether the differences were due to differences in study medications, study duration, or other study characteristics.

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.[137,138] These differences may have been due to differences in dosing of the medications. The RCT[137] that showed no significant between-group differences in HbA1c (-0.11 percent, $p = 0.238$) 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 percent, $p = 0.027$) did not clearly report mean total or maximum doses.[138] Another possible difference may have been the type of premixed insulin analogue.

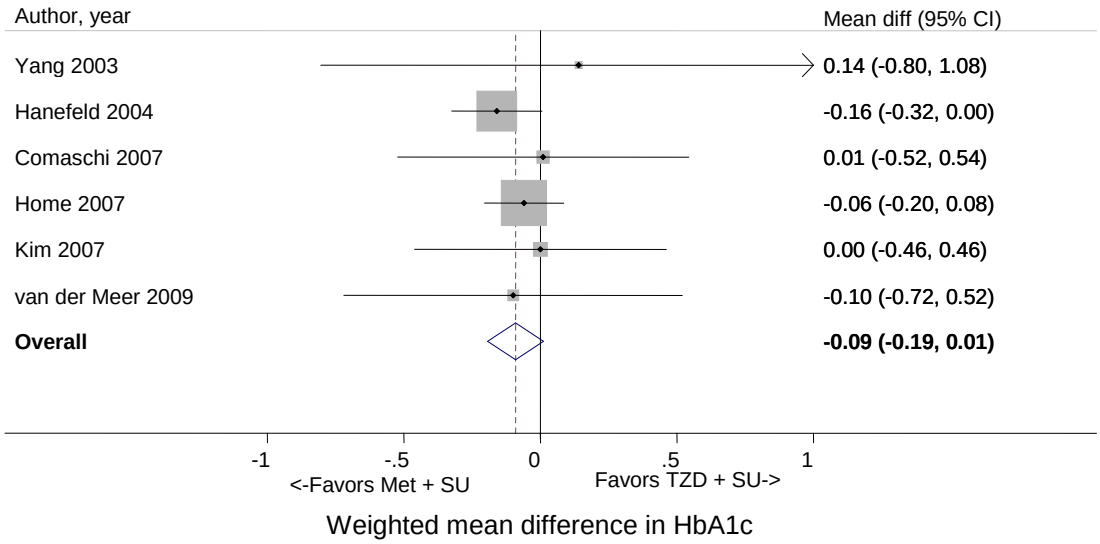
Combination of metformin and sulfonylureas versus combination of thiazolidinediones and sulfonylureas. Six similar RCTs directly compared the combination of metformin and sulfonylurea with the combination of thiazolidinediones and sulfonylurea, showing no between-group differences in HbA1c (pooled between-group difference of -0.1 percent, 95 percent CI -0.2 percent to 0.01 percent) (Figure 13).[42,124,129,139-141] 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[16,142] since both studies had other articles in the meta-analysis that presented the shorter term glycemic results[124,140] which were more comparable to the other RCTs. The RECORD study was a multicenter open label RCT evaluating 4,447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[16,124] 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.[16,124] The between-group

difference in HbA1c of -0.06 percent was small and not significant in the 573 subjects with 18-month followup.[124] In the article reporting on the mean followup of 5.5 years in 2,225 subjects, the between-group difference in HbA1c of 0.26 percent significantly favored rosiglitazone plus sulfonylurea over metformin plus sulfonylurea.[16] 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.[16]

The second RCT excluded was a 2-year followup[142] of the 1-year study[140] presented in the meta-analysis. Both articles presented similar between-group differences in HbA1c between the combination of thiazolidinedione plus sulfonylurea and metformin plus sulfonylurea (nonsignificant between-group differences of -0.16 percent and -0.13 percent).

Figure 13. Mean difference in HbA1c comparing combination of metformin and sulfonylureas with combination of thiazolidinediones and sulfonylureas



CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea; TZD = 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 random-effects pooled estimate.

Test for heterogeneity: Q = 1.37 with 5 degrees of freedom (p = 0.93)

I-squared statistic = 0%

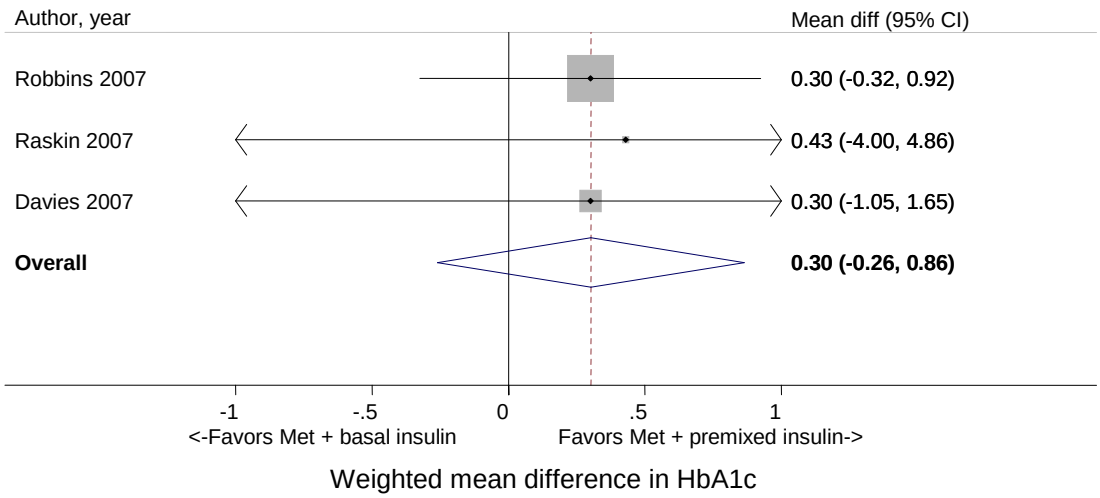
The range in change scores for HbA1c for the comparison group, a combination of thiazolidinediones and sulfonylureas, was -1.3% to 0.6%. The median change was -1.1%.

Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. One 26-week RCT with comparable dosing of medications directly compared the combination of metformin and sitagliptin with the combination of metformin and liraglutide in 2 dosing arms (maximum dose liraglutide 1.2 mg in one arm and 1.8 mg in the second combination arm), showing statistically significant greater reductions in HbA1c in the metformin and liraglutide combination arms.[143] The between-group differences in HbA1c ranged from -0.34 percent when compared with the lower dosed liraglutide combination arm to -0.60 percent when compared with the higher dosed liraglutide combination arm.[143]

Combination of metformin and GLP-1 agonists versus combination of metformin and basal insulin. One small 56-week RCT compared the combination of metformin and exenatide with the combination of metformin and glargine insulin, showing similar reductions in HbA1c (between-group difference of -0.1 percent).[144] The exenatide combination arm had about 25 percent of their subjects on higher than the maximum recommended dose of exenatide.

Combination of metformin and basal insulin versus combination of metformin and premixed insulin. Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in HbA1c (pooled between-group difference of 0.3 percent, 95 percent CI -0.3 percent to 0.9 percent) (Figure 14).[145-147] No single study strongly influenced the results, and no substantial heterogeneity was found.

Figure 14. Mean difference in HbA1c comparing combination of metformin and basal insulin with combination of metformin and premixed insulin



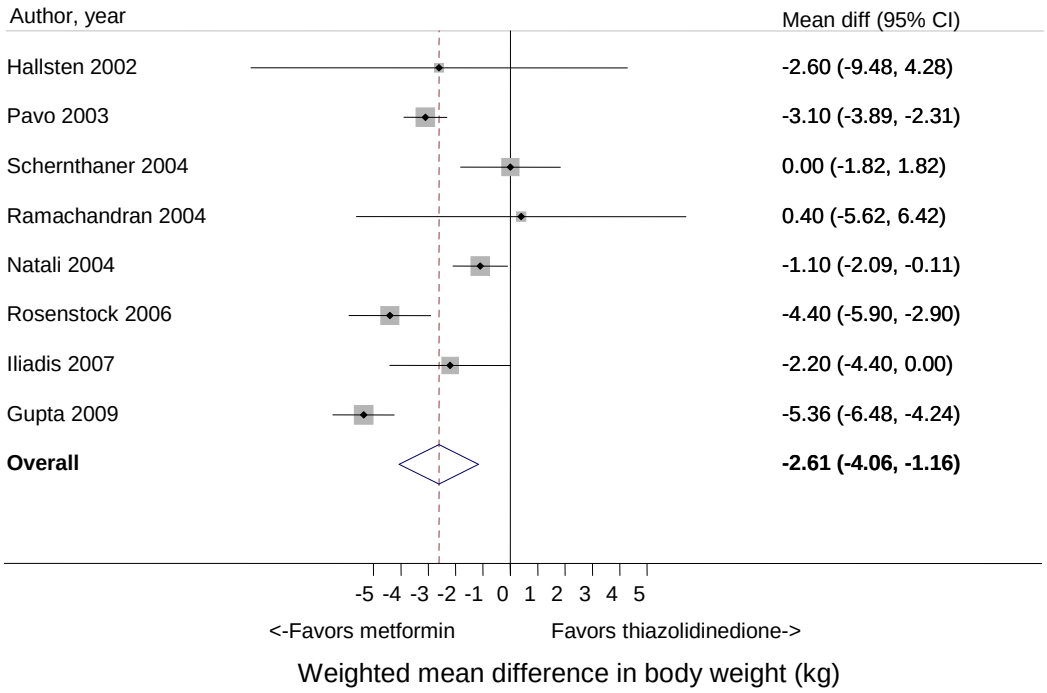
CI = confidence interval; diff = difference; HbA1c = hemoglobin A1c; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 0.003 with 2 degrees of freedom (p = 0.99)
I-squared statistic = 0%
The range in change scores for HbA1c for the comparison group, combination metformin and premixed insulin, was -2.9% to 0.7%. The median change was -1.1%.

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 percent CI -4.1 kg to -1.2 kg) (see Figure 15).[47-49,51,52,54,55,148] All the metformin arms had small decreases in weight while the thiazolidinedione arms had mild increases in weight except for two studies.[48,51] 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. Meta-regression suggested that differences in baseline weight between studies (p = 0.07) may have contributed to the heterogeneity. We

excluded two studies from the meta-analysis that had consistent results favoring metformin, since the median study duration was 4 years for one study[38] and no measure of variability was reported for the second study.[56] 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 diabetic adults, where weight was evaluated as a secondary outcome. The between-group difference in weight was -6.9 kg (95 percent CI -6.3 kg to -7.4 kg) favoring metformin. The second shorter duration RCT reported weight gain (1.6 kg) with pioglitazone and weight loss (-1.3 kg) with metformin, but no measures of variability.[56]

Figure 15. Mean difference in weight comparing metformin with thiazolidinediones

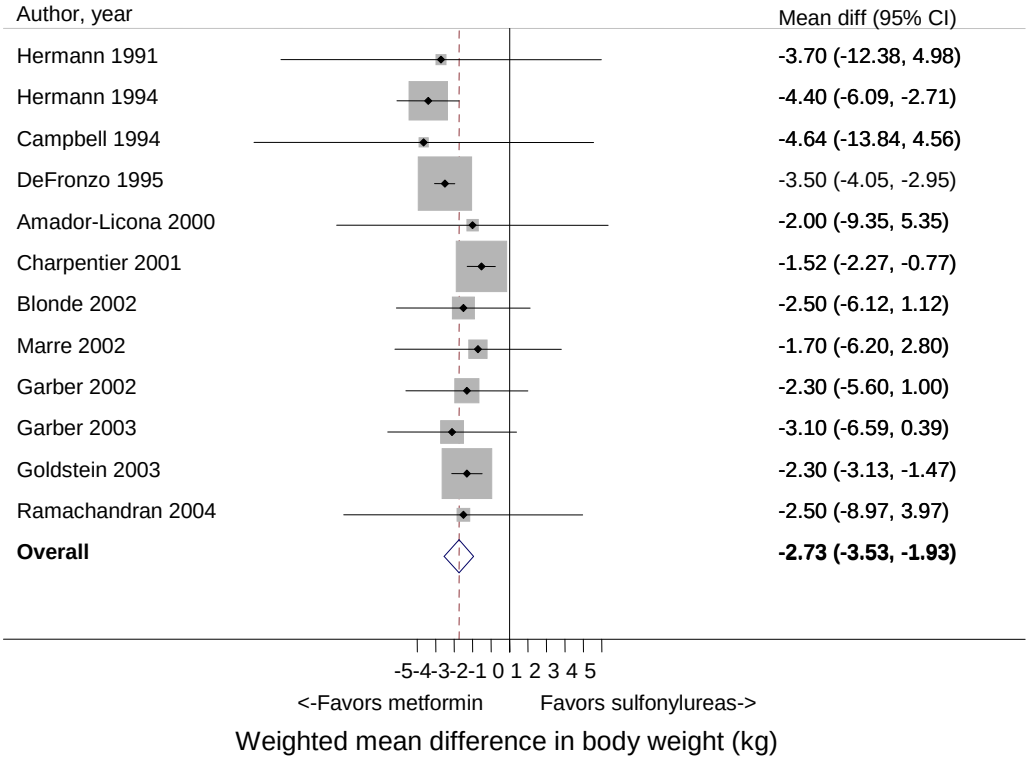


CI = confidence interval; diff = difference; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each 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%
The range in change scores for weight for the comparison group, thiazolidinediones, was -2 kg to 2.4 kg. The median change was -0.3 kg.

Metformin versus sulfonylureas. We combined 12 studies comparing metformin with a second-generation sulfonylurea, with a pooled mean difference of -2.7 kg (95 percent CI -3.5 kg to -1.9 kg) favoring metformin (Figure 16).[51,61-71] 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 percent CI -2.5 kg to -1.4 kg) (Figure 17).[51,61-66,71] Four studies lasting 24 weeks or longer were combined and favored metformin, with a

pooled between-group difference of -3.6 kg (95 percent CI -4.1 kg to -3.1 kg) (Figure 18).[67-70] Heterogeneity tests were not significant once we stratified the meta-analyses by study duration.

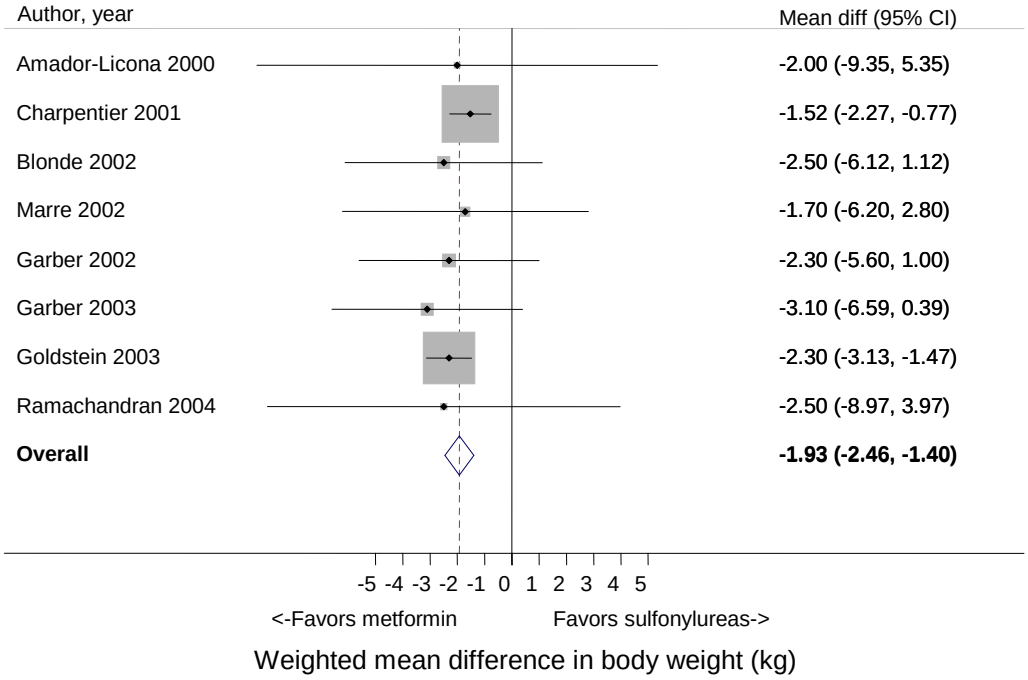
Figure 16. Mean difference in weight comparing metformin with sulfonylureas



CI = confidence interval; diff = difference; kg = kilogram
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 range in change scores for weight for the comparison group, sulfonylureas, was -0.3 kg to 2.67 kg. The median change was 1.6 kg.

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 percent CI -2.0 kg to -3.1 kg).[38] 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.

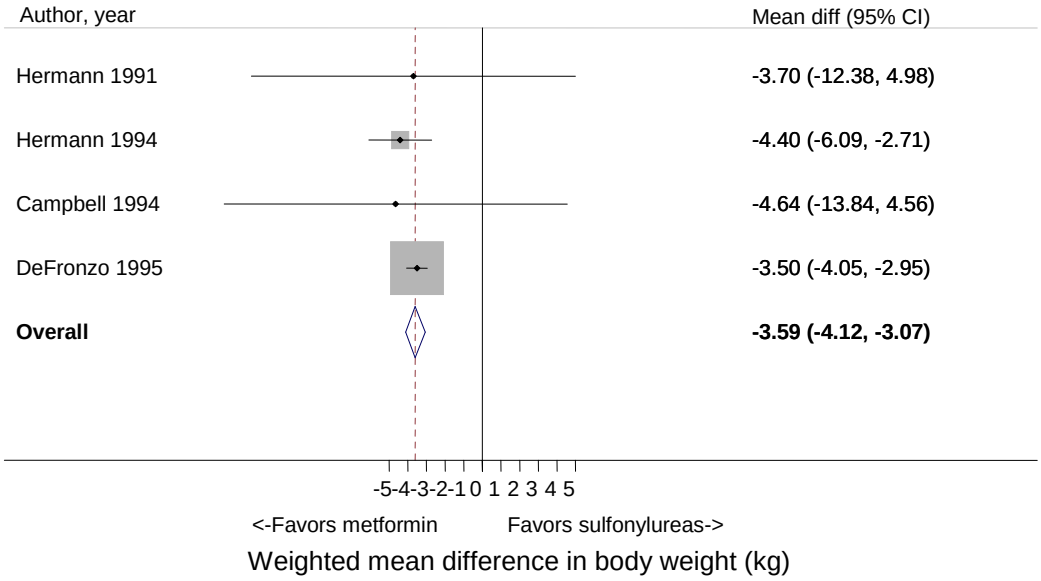
Figure 17. Mean difference in weight comparing metformin with sulfonylureas among studies less than 24 weeks in duration



CI = confidence interval; diff = difference; kg = kilogram
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%
The range in change scores for weight for the comparison group, sulfonylureas, was -0.3 kg to 1.7 kg. The median change was 0.9 kg.

The UKPDS,[8,72,74] while consistent with the above meta-analysis, was excluded from this section of the report since they were allowed to add other diabetes medications to their initial 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.[74] 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 nonobese subjects taking glibenclamide.[72] In the 10-year followup comparing obese subjects on metformin with obese and nonobese subjects on glibenclamide, the between-group difference still favored metformin at -2 kg.[8] 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 2 years, while metformin maintained weight in the first 2 years and then had some weight gain after that.[8]

Figure 18. Mean difference in weight comparing metformin with sulfonylureas among studies 24 weeks or longer in duration

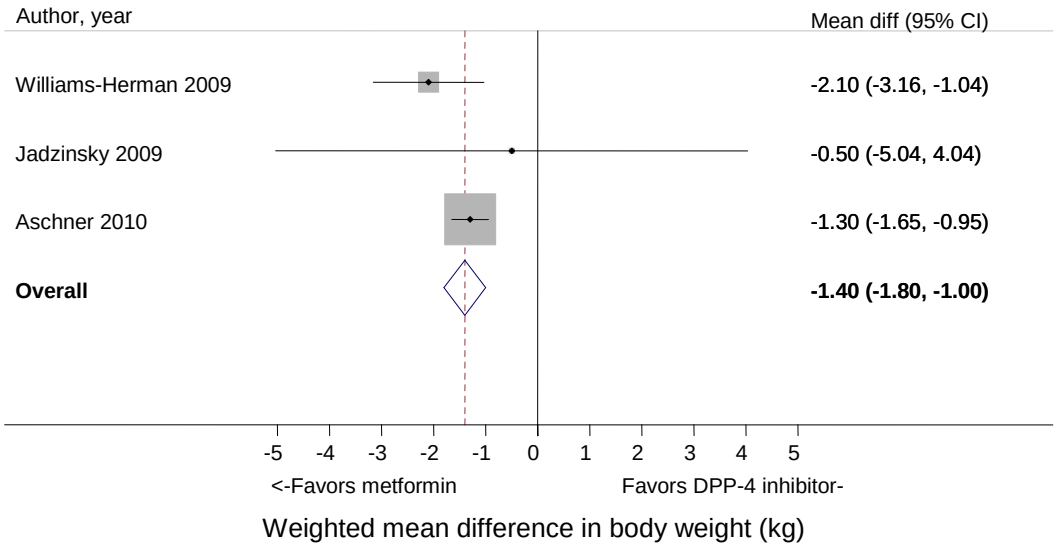


CI = confidence interval; diff = difference; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each 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%
The range in change scores for weight for the comparison group, sulfonylureas, was -0.3 kg to 3.3 kg. The median change was 2.7 kg.

Metformin versus DPP-4 inhibitors. Three short duration RCTs (reported in four articles) compared metformin with DPP-4 inhibitors, reporting greater reductions in weight with metformin (pooled between-group difference of -1.4 kg, 95 percent CI -1.8 kg to -1.0 kg) (Figure 19).[75-78] No substantial heterogeneity was found in the meta-analysis, and no single study markedly influenced the results. Two studies used metformin compared with sitagliptin,[76,77] and one study compared metformin with saxagliptin.[78] One RCT was reported in two articles.[75,76] The first article was a 24-week RCT,[75] while the second article was the 30-week continuation study with a higher loss to followup.[76] The higher dosed metformin arm had greater weight loss from baseline compared with the lower dose metformin arm. We included the 24-week study in the meta-analysis since the other two studies in the meta-analysis were both 24 weeks long.

Metformin versus meglitinides. Two small comparably-dosed RCTs lasting about a year compared metformin with repaglinide, suggesting metformin may reduce weight compared with repaglinide (range in between-group differences from -2.0 kg to -3.4 kg).[81,82] One study reported this difference as nonsignificant,[81] and one reported only that there were significant differences from baseline in both arms.[82] The small number of subjects may have precluded the ability to detect significant differences between groups.

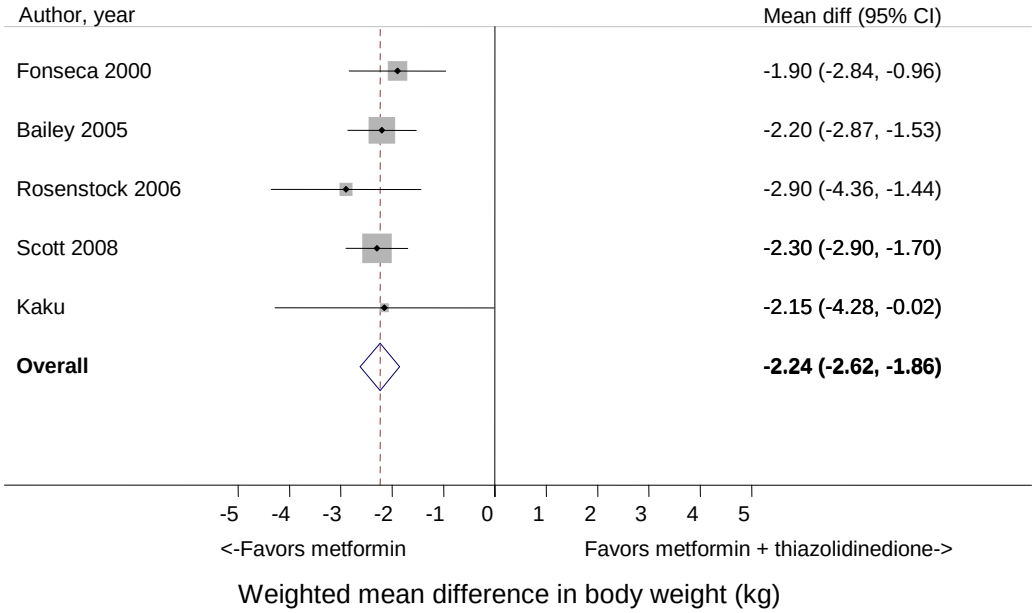
Figure 19. Mean difference in weight comparing metformin with DPP-4 inhibitors



CI = confidence interval; diff = difference; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; kg = kilogram
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 = 2.10 with 2 degrees of freedom (p = 0.35)
I-squared statistic = 5%
The range in change scores for weight for the comparison group, DPP-4 inhibitors, was -1.1 kg to 0.6 kg. The median change was -0.6 kg.

Metformin versus a combination of metformin and thiazolidinediones. We combined five studies that directly compared metformin monotherapy with the combination of metformin plus a thiazolidinedione (mostly rosiglitazone), showing a pooled between-group difference in weight of -2.2 kg (95 percent CI -2.6 kg to -1.9 kg) favoring metformin (Figure 20).[49,84,85,87,90] 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.[83] While consistent with the meta-analysis results, we did not have sufficient quantitative data to include it with the other studies. Another study was excluded from the meta-analysis since no measures of variability were reported; however, this study was consistent with the meta-analysis findings.[56] The 24-week RCT reported weight gain (0.7 kg) with combination metformin and pioglitazone and weight loss (-1.3 kg) with metformin monotherapy.[56]

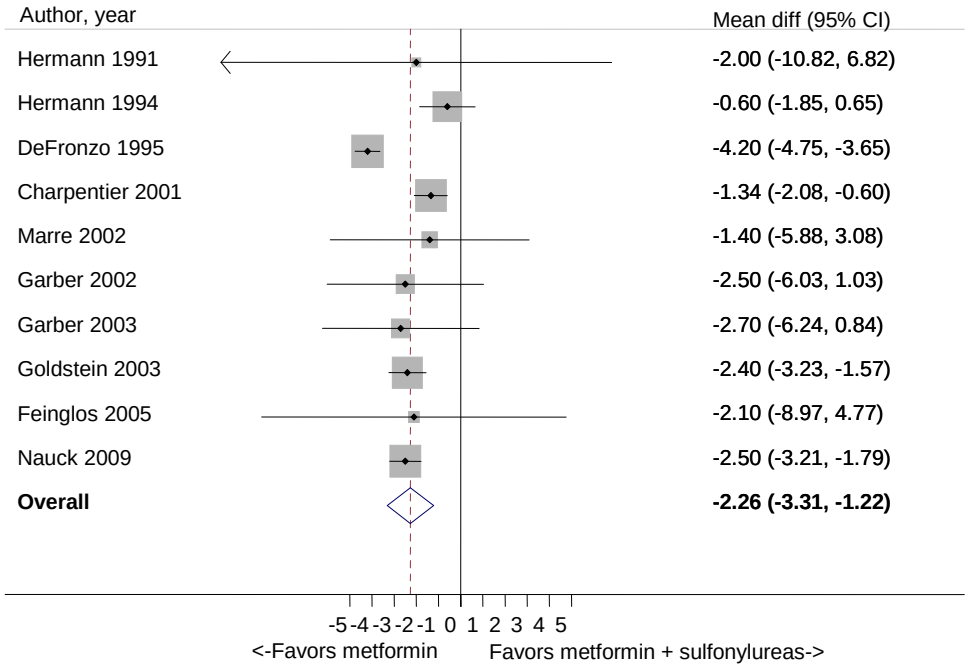
Figure 20. Mean difference in weight comparing metformin with combination metformin and thiazolidinediones



CI = confidence interval; diff = difference; kg = kilogram
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%
The range in change scores for weight for the comparison group, a combination of metformin and thiazolidinedione, was 0.7 kg to 1.7 kg. The median change was 1.5 kg.

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 between-group difference of -2.3 kg (95 percent CI -3.3 kg to -1.2 kg) (Figure 21).[61,62,64,65,68-71,91,92] No single study markedly influenced the results. While heterogeneity existed, all studies favored the metformin arm over the combination arm with 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.

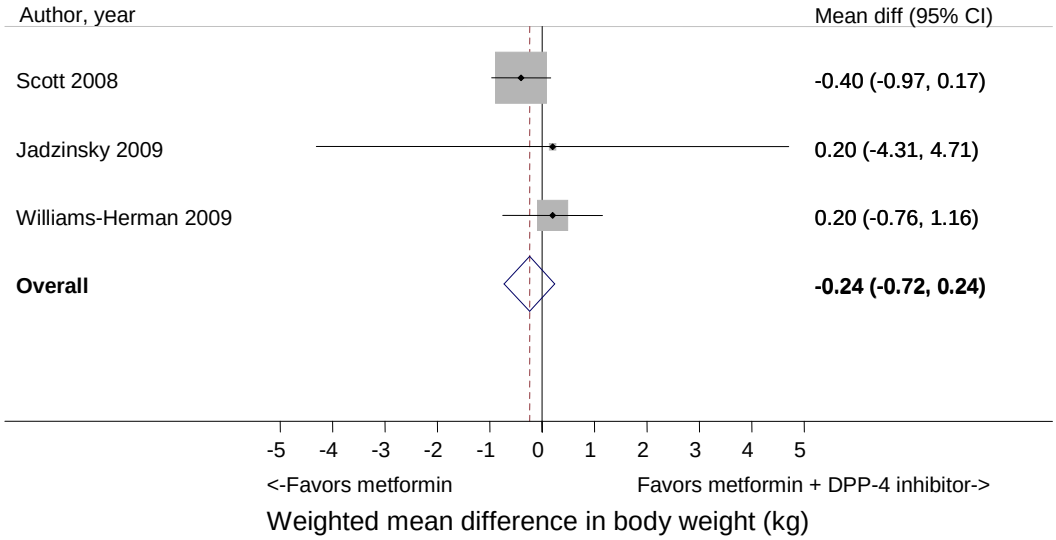
Figure 21. Mean difference in weight comparing metformin with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; kg = kilogram
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%
The range in change scores for weight for the comparison group, a combination of metformin and sulfonylureas, was -0.3 kg to 1.9 kg. The median change was 0.7 kg.

Metformin versus a combination of metformin and DPP-4 inhibitors. Three RCTs directly compared metformin with the combination of metformin plus a DPP-4 inhibitor, with a pooled between-group difference of -0.2 kg (95 percent CI -0.7 kg to 0.2 kg) (Figure 22).[75,78,8]5 No single study markedly influenced the results, and no substantial heterogeneity was found. Only three out of six studies had sufficient quantitative data to combine in a meta-analysis. The other three studies reported results that were consistent with the meta-analysis.[85,94,95] One RCT was published twice, first with the 24-week RCT results[75] and second as a 30-week continuation study.[76] The 24-week study was included in the meta-analysis since the study duration was more similar to the other included studies. The 54-week results were consistent with the 24-week results, reporting a significant weight loss from baseline in both groups with overlapping confidence intervals or a non-significant between-group difference of 0.2 kg.[76] 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).

Figure 22. Mean difference in weight comparing metformin with combination metformin and DPP-4 inhibitors

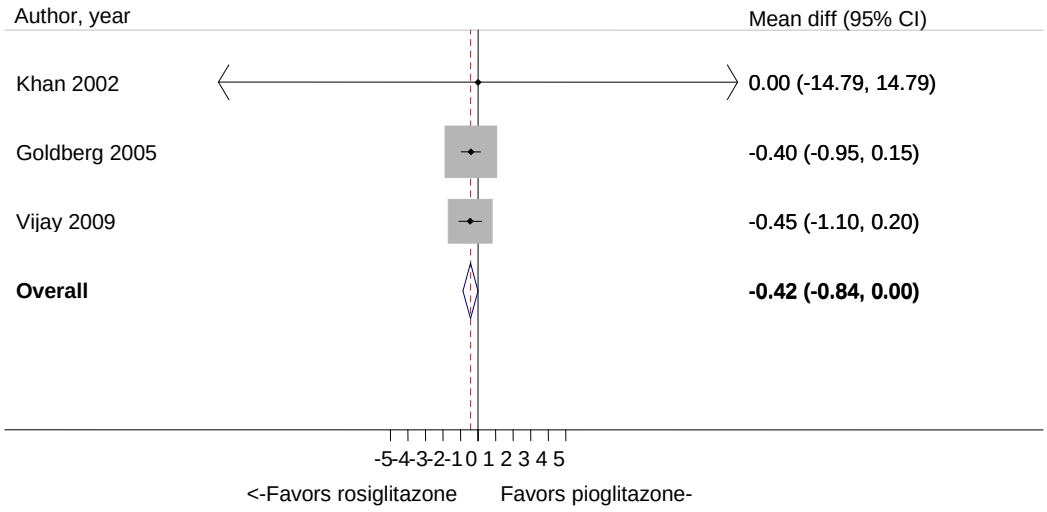


CI = confidence interval; diff = difference; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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 = 1.16 with 2 degrees of freedom (p = 0.56)
I-squared statistic = 0%
The range in change scores for weight for the comparison group, a combination of metformin and DPP-4 inhibitors, was -1.1 kg to 0.6 kg. The median change was -0.4 kg.

Metformin versus a combination of metformin and meglitinides. Two RCTs compared metformin with combination of metformin plus meglitinides; both slightly favoring the monotherapy metformin arms.[82-96] One small 3-month RCT compared metformin (mean dose 1800 mg) versus metformin (mean dose 1,800 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, $p < 0.05$).[82] 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).[96]

Rosiglitazone versus pioglitazone. Three RCTS with similar dosing of medications compared rosiglitazone with pioglitazone, and showed no significant between-group differences in weight, with a pooled between-group difference of -0.4 kg (95 percent CI -0.8 kg to 0.0 kg) (Figure 23).[97-99] No one study significantly influenced the results, and no substantial heterogeneity was found. All three short-duration studies showed an increase in weight from baseline, ranging from 0.7 kg to 2 kg for both thiazolidinediones.

Figure 23. Mean difference in weight comparing rosiglitazone with pioglitazone

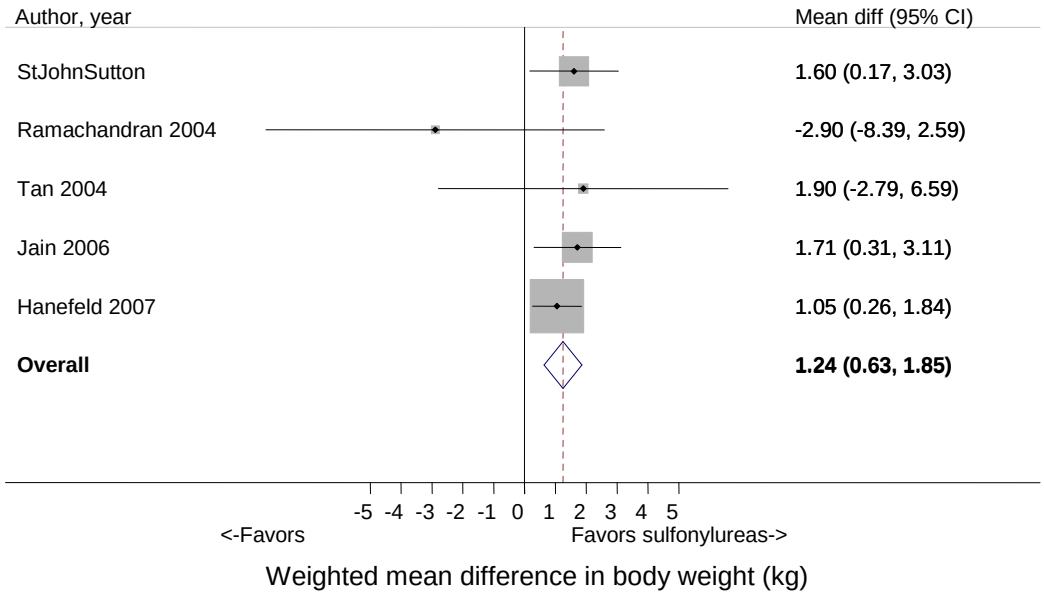


CI = confidence interval; diff = difference; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each 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 = 0.02 with 2 degrees of freedom (p = 0.99)
I-squared statistic = 0%
The range in change scores for weight for the comparison group, pioglitazone, was 1.2 kg to 2.0 kg. The median change was 2.0 kg.

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 between-group difference of 1.2 kg (95 percent CI 0.6 kg to 1.9 kg) (Figure 24).[51,100,101,106,149] One study showed a dose response relationship between rosiglitazone and weight; patients treated with rosiglitazone (4 mg per day) gained 1.8 kg and those treated with 8 mg per day gained 3.0 kg over 52 weeks compared with the glibenclamide arm which gained 1.9 kg.[100] No single study markedly influenced the results, and no substantial heterogeneity was found.

We excluded two RCTs from the meta-analysis due to the longer study duration of 3 to 4 years.[38,150] Both RCTs had results that were consistent with the meta-analysis. As mentioned previously, the ADOPT study was a double-blind RCT evaluating 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.[38] 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 percent 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. The second large 3-year multicenter study comparing pioglitazone and glibenclamide showed a 5.2 kg weight gain in the pioglitazone-treated group and a 0.9 kg weight gain in the glibenclamide-treated group.[150]

Figure 24. Mean difference in weight comparing thiazolidinediones with sulfonylureas



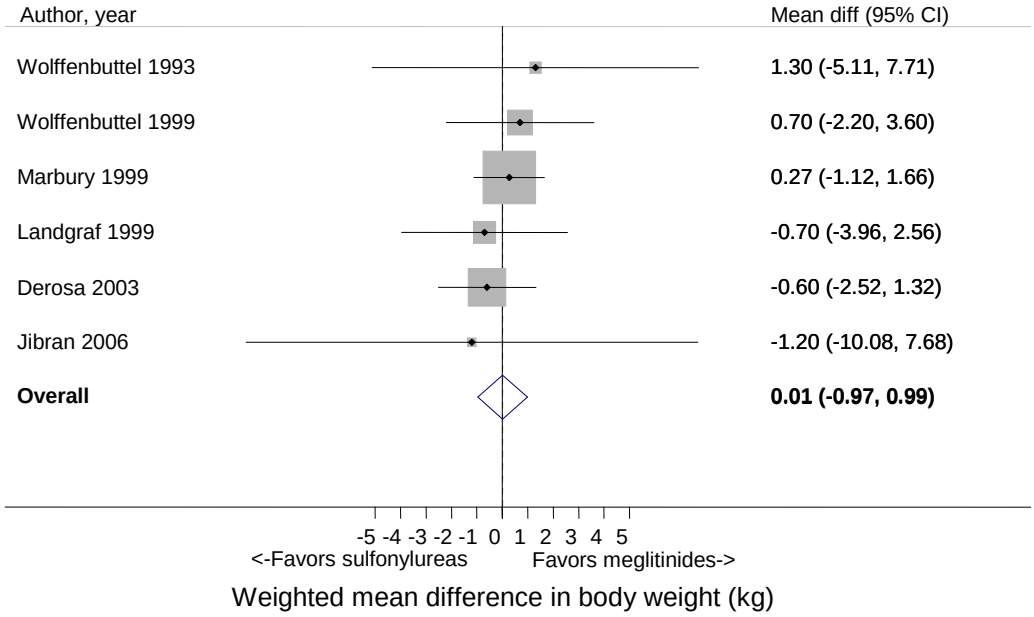
CI = confidence interval; diff = difference; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each 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%
The range in change scores for weight for the comparison group, sulfonylureas, was 1.1 kg to 3.4 kg. The median change was 1.9 kg.

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).[109,110]

Sulfonylureas versus DPP-4 inhibitors. One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide, showing a potential benefit in weight of sitagliptin over glipizide.[111] 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 percent 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 (95 percent CI 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 between-group difference of 0.01 kg (95 percent CI -1.0 kg to 1.0 kg) (Figure 25).[112,113,115-118] Heterogeneity tests were not significant, and no single study markedly influenced this result. Most studies showed no change in weight in both treatment arms.

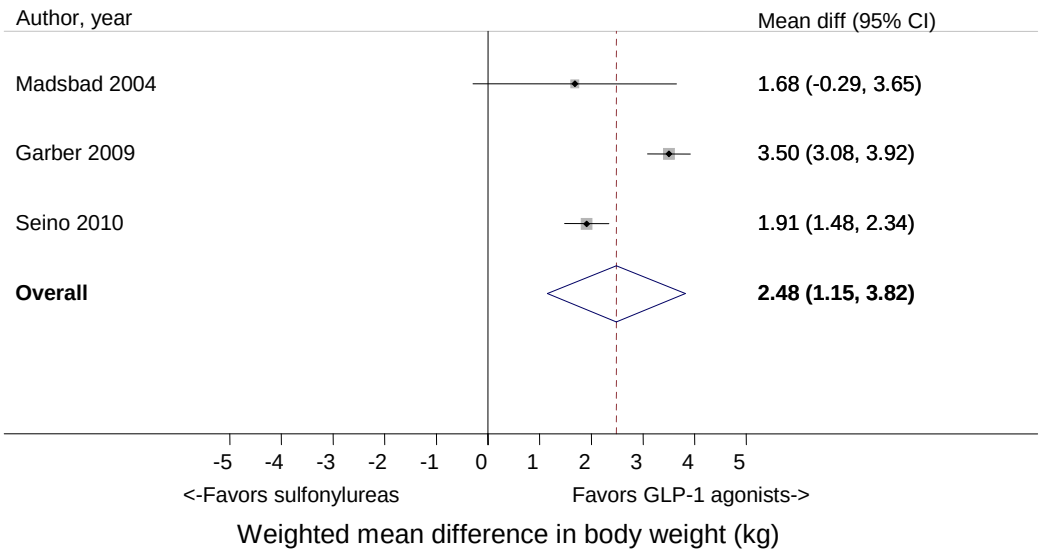
Figure 25. Mean difference in weight comparing sulfonylureas with meglitinides



CI = confidence interval; diff = difference; kg = kilogram
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%
The range in change scores for weight for the comparison group, meglitinides, was -1.7 kg to 0.2 kg. The median change was -0.1 kg.

Sulfonylureas versus GLP-1 agonists. Three RCTs comparing sulfonylureas directly with liraglutide showed greater weight gain with sulfonylurea (pooled between-group difference of 2.5 kg, 95 percent CI 1.2 kg to 3.8 kg) (Figure 26).[120-122] No single study strongly influenced the results. Substantial heterogeneity was found. Metaregression found statistically significant differences due to drug dosing (p = 0.017). Given the low power of metaregression when only 3 studies are evaluated, other characteristics such as study duration may have partly explained the heterogeneity (p = 0.15). The one study with the largest between-group difference in weight[122] lasted at least 24 weeks longer than the other two studies. Additionally, one of the two studies with a lower between-group difference under-dosed the sulfonylurea arm[121] while the study with more comparable and higher drug doses had a larger between-group difference. All three studies however showed weight gain with sulfonylureas and weight loss with liraglutide when compared with baseline weight.

Figure 26. Mean difference in weight comparing sulfonylureas with GLP-1 agonists



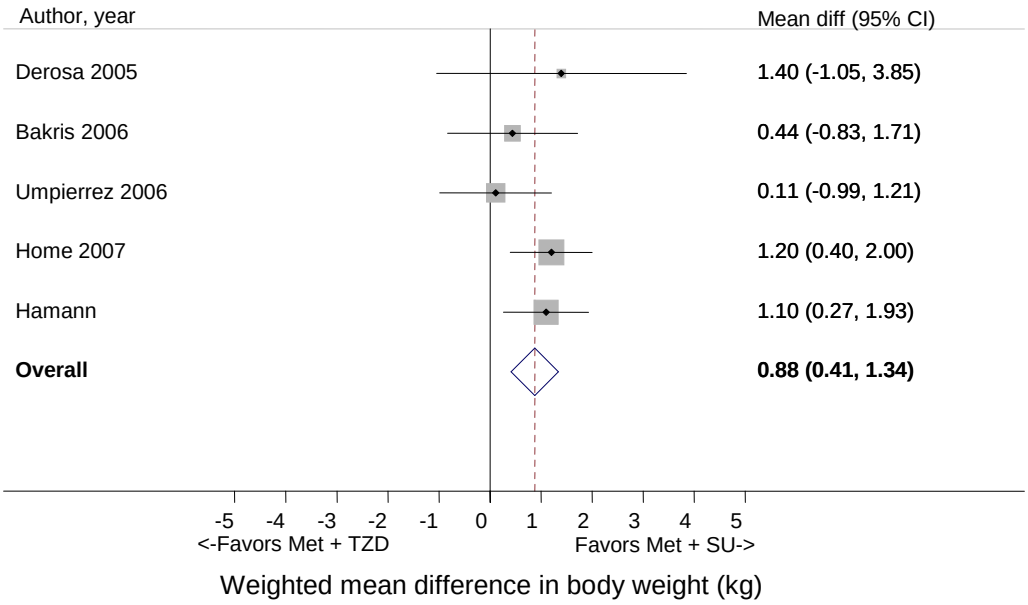
CI = confidence interval; diff = difference; GLP-1 agonists = glucagon-like peptide-1 agonists; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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 = 28.23 with 2 degrees of freedom (p = 0.00)
I-squared statistic = 93%
The range in change scores for weight for the comparison group, GLP-1 agonist, was -2.5 kg to 1.0 kg. The median change was -0.7 kg.

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 percent CI 0.4 kg to 1.3 kg) (Figure 27).[123-126,151] 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.[124] 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.[16,124] Body weight was increased significantly with rosiglitazone plus metformin compared to sulfonylurea plus metformin, with a mean difference between-groups of 1.2 kg (95 percent CI 0.4 kg to 2.0 kg) after 18 months[124] which increased to 3.8 kg after 5 years of followup.[16]

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.[128] 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.

Figure 27. Mean difference in weight comparing combination metformin and thiazolidinediones with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; kg = kilogram; Met = metformin; SU = sulfonylureas; TZD = 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 = 3.41 with 4 degrees of freedom (p = 0.49)
I-squared statistic = 0%
The range in change scores for weight for the comparison group, a combination of metformin and sulfonylureas, was -4.5 kg to 1.7 kg. The median change was 1.5 kg.

Combination of metformin and thiazolidinediones versus combination of metformin and DPP-4 inhibitors. Two short duration RCTs compared metformin plus rosiglitazone with the combination of metformin plus sitagliptin, showing weight loss in the metformin plus sitagliptin arms and weight gain in the metformin plus thiazolidinedione arms. Neither study reported on the between-group difference in weight, only on the difference from baseline for each arm. In one study, the metformin plus rosiglitazone arm had an increase in weight from baseline of 1.5 kg (95 percent 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 percent CI -0.8 kg to 0.0 kg).[85] The nonoverlapping confidence intervals suggest that this difference between groups is statistically significant. The other open label 16-week RCT showed a statistically significant weight loss from baseline with the metformin plus sitagliptin arm (-1.2 kg, p = 0.0008) and a nonsignificant small weight gain with the metformin plus rosiglitazone arm (0.3 kg, p = 0.59).[130]

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.[131]

Combination of metformin and thiazolidinediones versus combination of metformin and GLP-1 agonists. One 20-week RCT with comparable dosing of medications compared the combination of metformin and rosiglitazone with the combination of metformin and exenatide, favoring the combination of metformin and exenatide with a between-group difference of 2.7 kg ($p < 0.001$).[132] The metformin and rosiglitazone arm showed weight gain from baseline (+1.5 kg) while the metformin and exenatide arm showed weight loss from baseline (-1.2 kg).[132]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. One double-blinded moderately sized RCT compared fixed-dose metformin plus sulfonylurea (mean dose of sulfonylurea was 10 mg) with the combination of fixed dose metformin plus fixed dose sitagliptin (100 mg), 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 percent CI -3.1 kg to -2.0 kg).[133] This RCT was extended a second year and continued to show weight loss in the metformin plus sitagliptin arm (-1.6 kg) and weight gain in the metformin plus glipizide arm (+0.7 kg) with a between-group mean difference of -2.3 kg (95 percent CI -3.0 kg to -1.6 kg).[134]

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.[136,152] One study showed a small but significant between-group difference of -1.2 kg favoring the metformin plus nateglinide arm ($p = 0.01$).[136] The other comparable study did not report quantitative data, only stating no clinically relevant changes in weight were found in either group.[152]

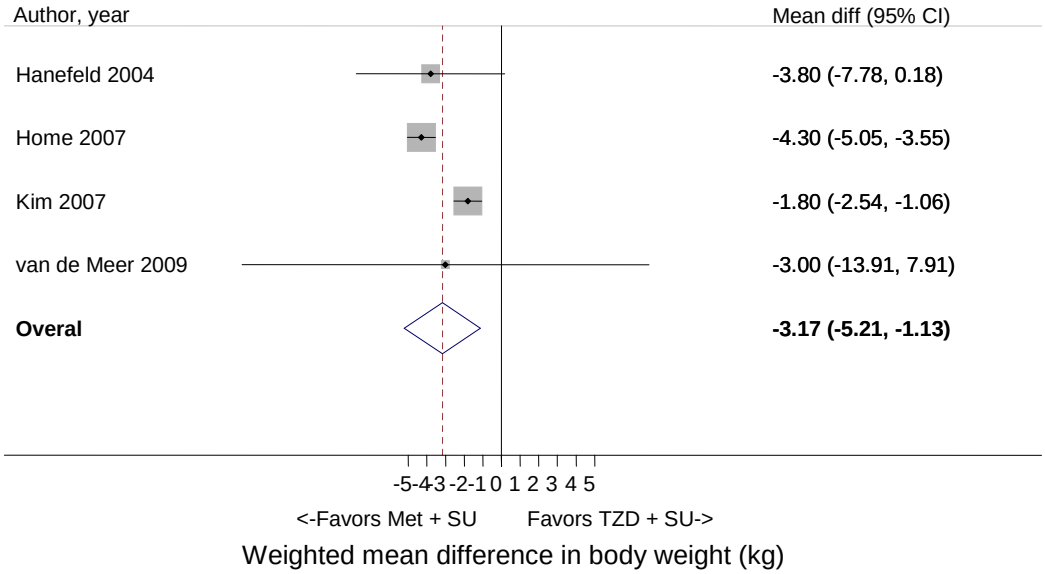
Combination of metformin and sulfonylurea versus combination of metformin and GLP-1 agonists. Two RCTs compared metformin plus sulfonylurea with metformin plus a GLP-1 agonist, favoring the combination of metformin and GLP-1 agonist (between-group differences of 3.8 kg and 12.3 kg).[44,92] Both RCTs showed weight loss with the combination of metformin and GLP-1 agonists and weight gain with the combination of metformin and sulfonylurea. One RCT with comparable dosing of medications lasting a year compared the combination of metformin and glibenclamide with the combination of metformin and exenatide, reporting weight loss with metformin and exenatide (-8 kg, $p < 0.001$) and weight gain with metformin and glibenclamide (4.3 kg, $p < 0.05$).[44] This article did not report on the between-group difference in weight.[44] Another short-duration RCT with comparable dosing of medications directly compared the combination of metformin and glimepiride with three different dosing arms of the combination of metformin and liraglutide (0.6 mg, 1.2 mg and 1.8 mg).[92] All three dosing comparisons showed a dose response effect on weight in the metformin plus liraglutide arms (range in weight loss of -1.8 kg to -2.8 kg with greater weight loss using higher doses) and a weight gain in metformin and glimepiride arm (1 kg). The between-group differences in weight were statistically significant for this study.[92]

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).[137,138] None of the study arms decreased weight from baseline.

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 plus a sulfonylurea, favoring the metformin plus sulfonylurea arms with a pooled between-group difference of -3.2 kg (95 percent CI -5.2 kg to -1.1 kg) (Figure 28).[124,126,140,142] 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.

Figure 28. Mean difference in weight comparing combination metformin and sulfonylureas with combination thiazolidinediones with sulfonylureas



CI = confidence interval; diff = difference; kg = kilogram; Met = metformin; SU = sulfonylureas; TZD = 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 = 21.67 with 3 degrees of freedom (p = 0.0001)
I-squared statistic = 86%
The range in change scores for weight for the comparison group, a combination of thiazolidinedione and sulfonylureas, was -1 kg to 3 kg. The median change was 2.2 kg.

We included only the shorter duration results for the RECORD study[124] 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.[16] The RECORD study was a multicenter open label RCT evaluating 4,447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[16,124] 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

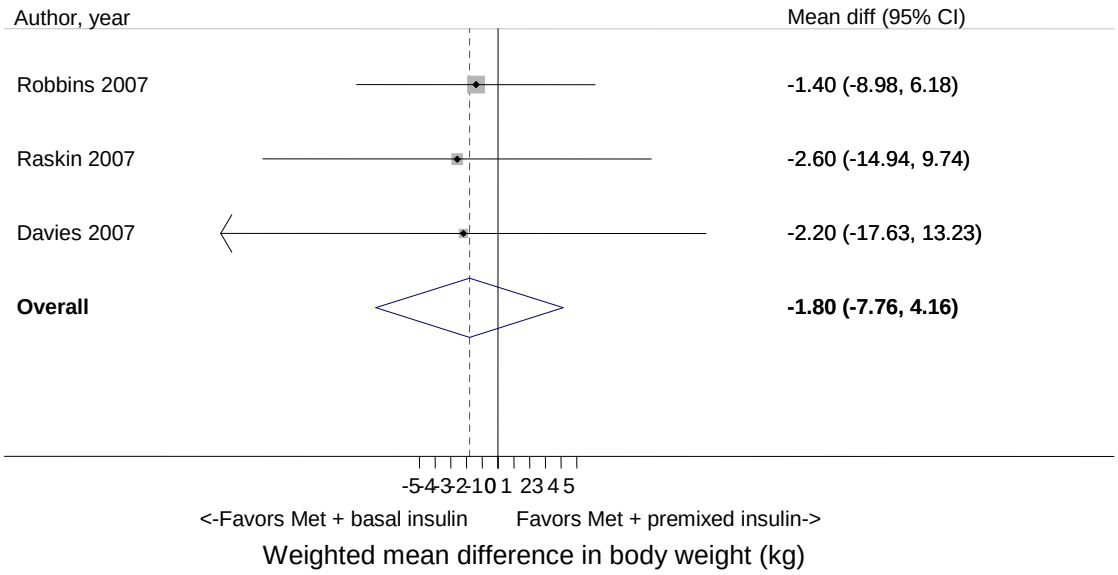
(significant between-group differences of 4.3 kg in the 18-month followup and 5.9 kg in the estimated 5-year followup).

Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. One 26-week RCT with comparable dosing of medications directly compared the combination of metformin and sitagliptin with the combination of metformin and liraglutide in 2 dosing arms (maximum dose liraglutide 1.2 mg in one arm and 1.8 mg in the second combination arm), showing a significantly greater weight loss in the metformin and liraglutide arms compared to the metformin and sitagliptin arm. The mean difference between groups in weight was –2.4 kg (95 percent CI –3.1 kg to –1.7 kg) for the liraglutide (1.8 mg) plus metformin arm versus the combination of metformin plus sitagliptin and -1.9 kg (95 percent CI –2.6 kg to -1.2 kg) for the liraglutide (1.2 mg) plus metformin arm versus the combination of metformin plus sitagliptin.[143]

Combination of metformin and GLP-1 agonists versus combination of metformin and basal insulin. One small 56-week RCT compared the combination of metformin and exenatide with the combination of metformin and glargine insulin, showing statistically significant weight loss with the metformin plus exenatide treated group compared to the metformin plus glargine insulin treated group (between group difference of -4.6 kg, $p < 0.0001$).[144] Of note, the exenatide combination arm had about 25 percent of their subjects on higher than the maximum recommended dose of exenatide. Weight returned to baseline 12 weeks after discontinuation of treatment in both arms.

Combination of metformin and basal insulin versus combination of metformin and premixed insulin. Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in weight (pooled mean difference of -1.8 kg, 95 percent CI -7.8 kg to 4.2 kg) (Figure 29).[145-147] No single study strongly influenced the results, and no substantial heterogeneity was found.

Figure 29. Mean difference in weight comparing combination metformin and basal insulin with combination metformin and premixed insulin

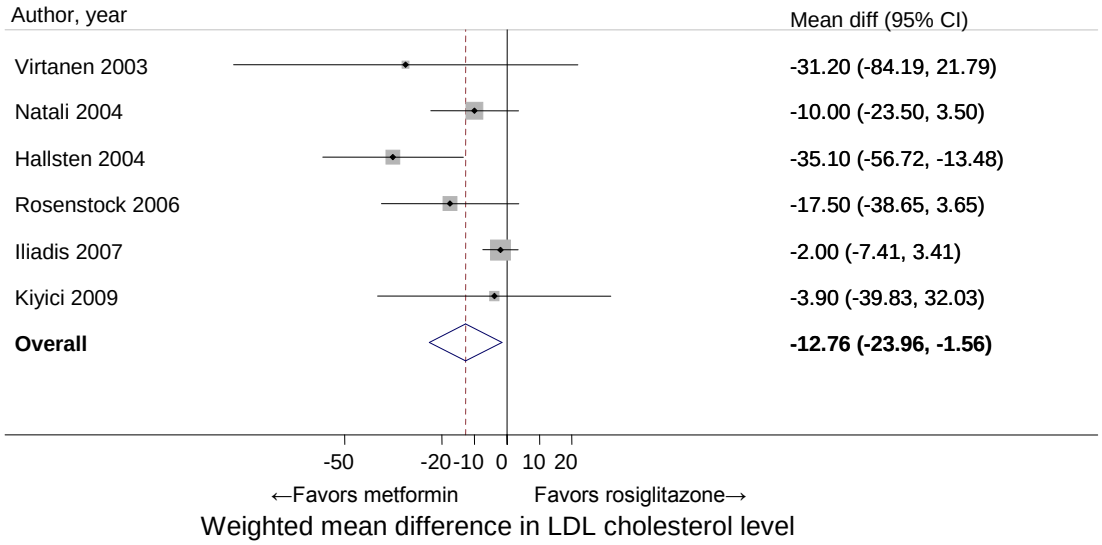


CI = confidence interval; diff = difference; kg = kilogram; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 range in change scores for weight for the comparison group, combination metformin and premixed insulin, was 0.9 kg to 5.6 kg. The median change was 2.2 kg.

The Evidence About Low-Density Lipoproteins (Appendix G, Table 4)

Metformin versus rosiglitazone. Six RCTs compared metformin to rosiglitazone and favored metformin (pooled between-group difference -12.8 mg/dL, 95 percent CI -24.0 mg/dL to -1.6 mg/dL) (Figure 30).[45,48,49,148,153,154] 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.[49,148,153] 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.[58]

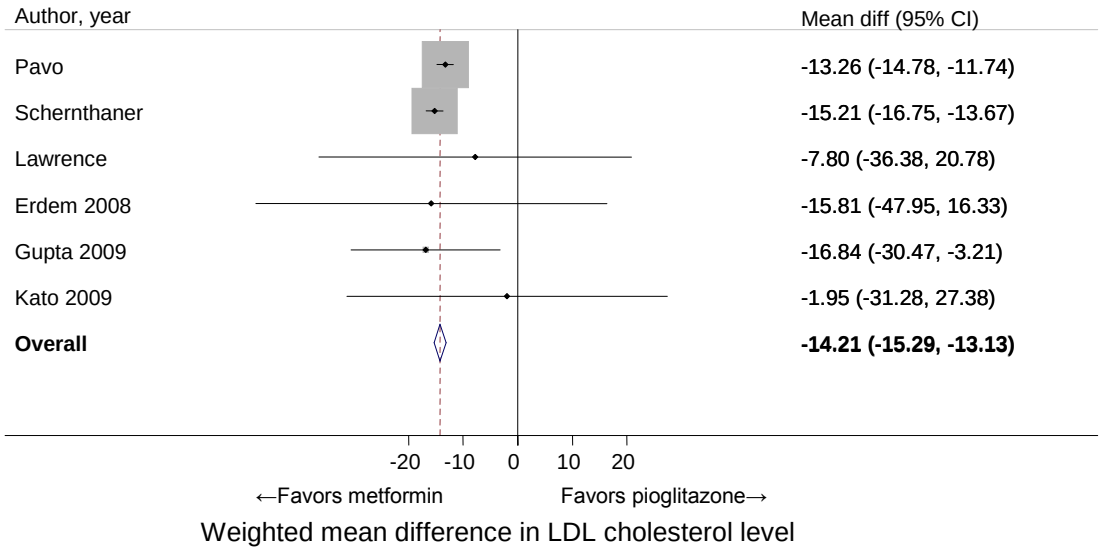
Figure 30. Mean difference in LDL comparing metformin with rosiglitazone



CI = confidence interval; diff = difference; 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 = 11.38 with 5 degrees of freedom (p = 0.04)
I-squared statistic = 56%
The range in change scores for LDL for the comparison group, rosiglitazone, was -3.9 mg/dL to 23.4 mg/dL. The median change was 5.1 mg/dL.

Metformin versus pioglitazone. Six studies compared metformin to pioglitazone favoring metformin (pooled between-group difference in LDL -14.2 mg/dL, 95 percent CI -15.3 mg/dL to -13.1 mg/dL) (Figure 31).[39,47,52-54,57] No one study significantly influenced results, and there was no evidence of heterogeneity.

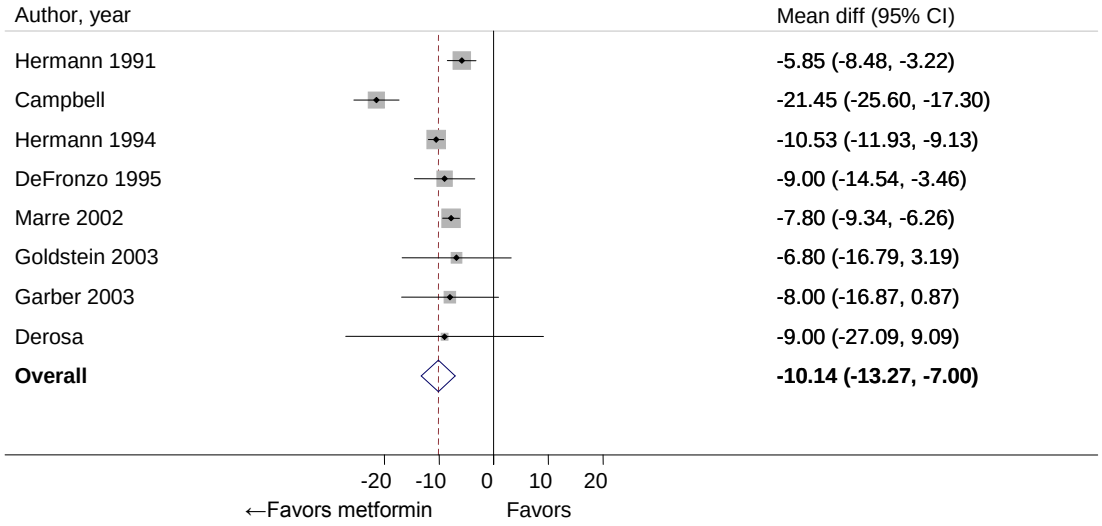
Figure 31. Mean difference in LDL comparing metformin with pioglitazone



CI = confidence interval; diff = difference; 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 = 4.13 with 5 degrees of freedom (p = 0.53)
I-squared statistic = 0%
The range in change scores for LDL for the comparison group, pioglitazone, was -4.0 mg/dL to 10.5 mg/dL. The median change was 7.2 mg/dL.

Metformin versus sulfonylureas. Eight RCTs compared metformin with sulfonylureas with a pooled between-group difference in LDL of -10.1 mg/dL (95 percent CI -13.3 mg/dL to -7.0 mg/dL) which favored metformin (Figure 32).[60-62,64,67,68,70,155] 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.[63]

Figure 32. Mean difference in LDL comparing metformin with sulfonylureas



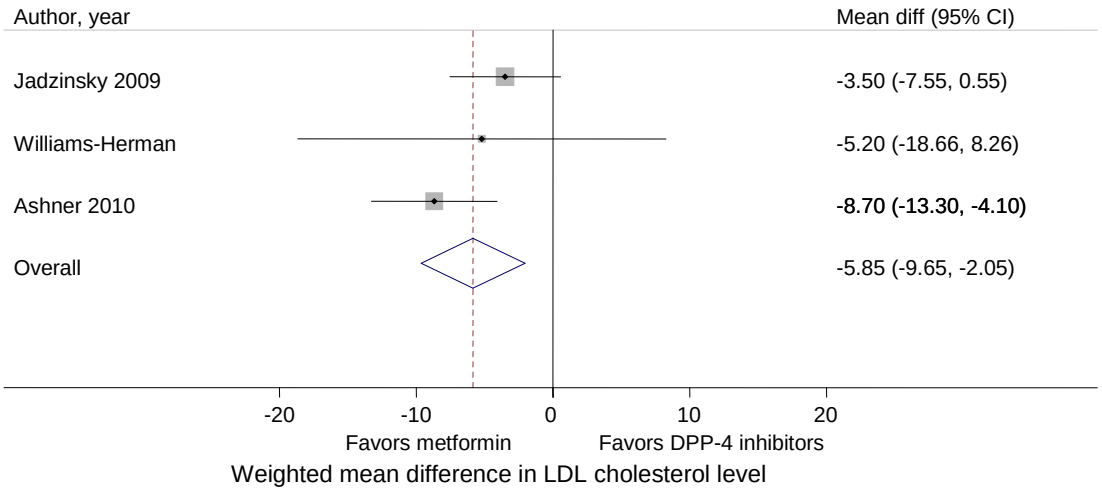
CI = confidence interval; diff = difference; LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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%
The range in change scores for LDL for the comparison group, sulfonylurea, was -3.9 mg/dL to 5.1 mg/dL. The median change was 1.4 mg/dL.

Metformin versus DPP-4 inhibitors. Three RCTs compared metformin with DPP-4 inhibitors with a pooled between-group difference in LDL of -5.9 mg/dL (95 percent CI -9.7 mg/dL to -2.0 mg/dL) favoring metformin (Figure 33).[76-78] No one study significantly influenced results, and there was no evidence of heterogeneity.

Metformin versus meglitinides. As seen in the previous report,[21] 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 ($p > 0.05$).[81]

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 percent CI -15.7 mg/dL to -13.3 mg/dL) (Figure 34).[49,85-88,90,156] No one study significantly affected results, and there was no evidence of statistical heterogeneity.

Figure 33. Mean difference in LDL comparing metformin with DPP-4 inhibitors



CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; LDL = low density lipoprotein; mg/dL = milligrams per deciliter

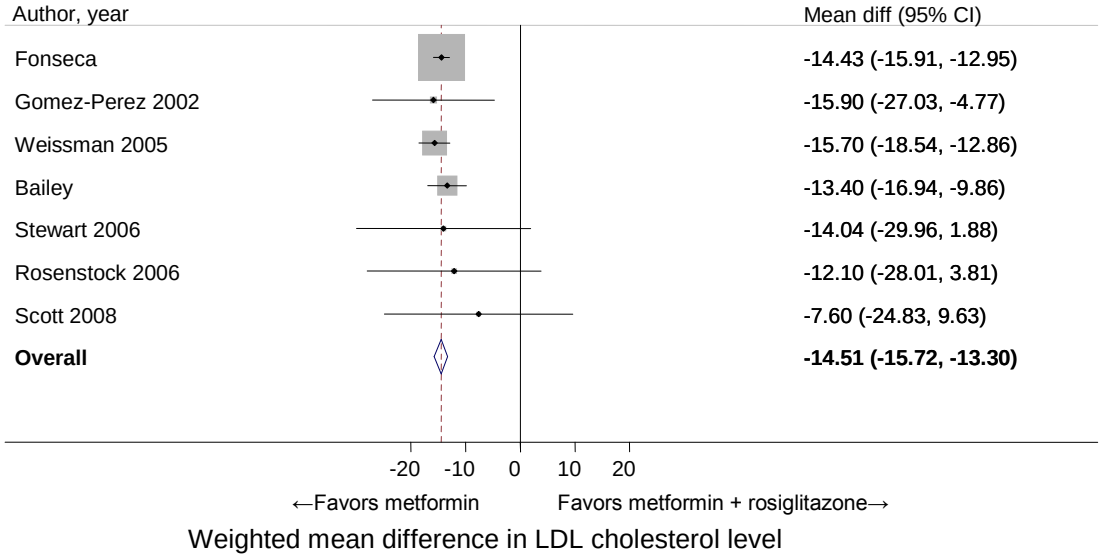
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates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

Test for heterogeneity: Q = 2.77 with 2 degrees of freedom (p = 0.25)

I-squared statistic = 28%

The range in change scores for LDL for the comparison group, DPP-4 inhibitors, was -1.6 mg/dL to 11.2 mg/dL. The median change was -0.5 mg/dL.

Figure 34. Mean difference in LDL comparing metformin with combination metformin and rosiglitazone

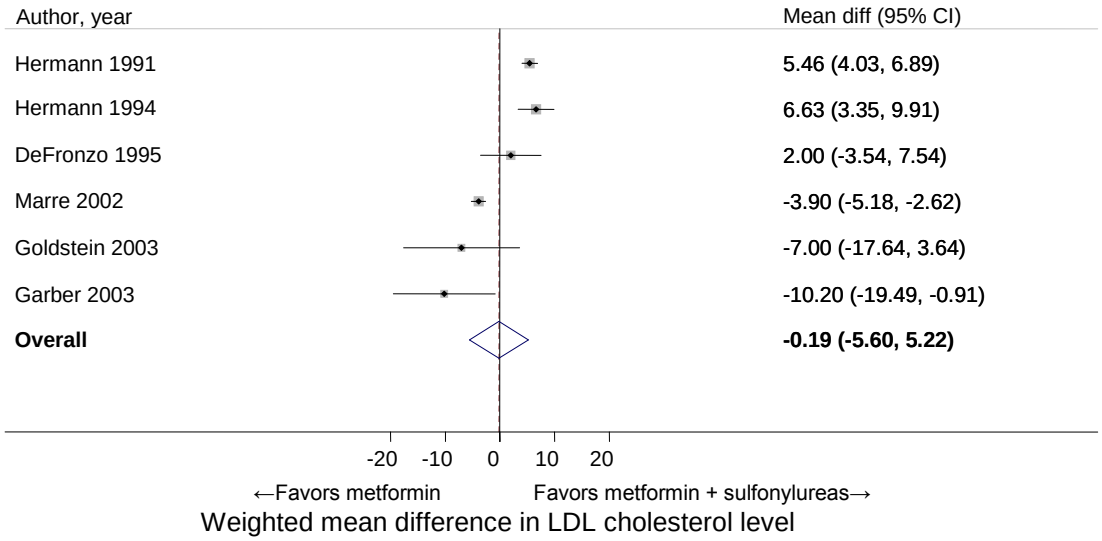


CI = confidence interval; diff = difference; LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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%
The range in change scores for LDL for the comparison group, a combination of metformin and rosiglitazone, was -0.3 mg/dL to 20.4 mg/dL. The median change was 16.4 mg/dL.

Metformin versus a combination of metformin and pioglitazone. Two RCTs compared the effect of metformin to the combination of metformin and pioglitazone on LDL. One RCT found a between-group difference of -2.6 mg/dL,[84] and the other reported a between-group difference in percentage change from baseline of 4.2 percentage points.[89] Statistical significance was 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 percent CI -5.6 mg/dL to 5.2 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 35).[61 62 64 68 70 155] 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,[68 70 155] and longer duration studies (24 to 26 weeks) tended to favor metformin.[61 62 64] Another study reported no changes in lipid values between groups but did not provide quantitative results.[63]

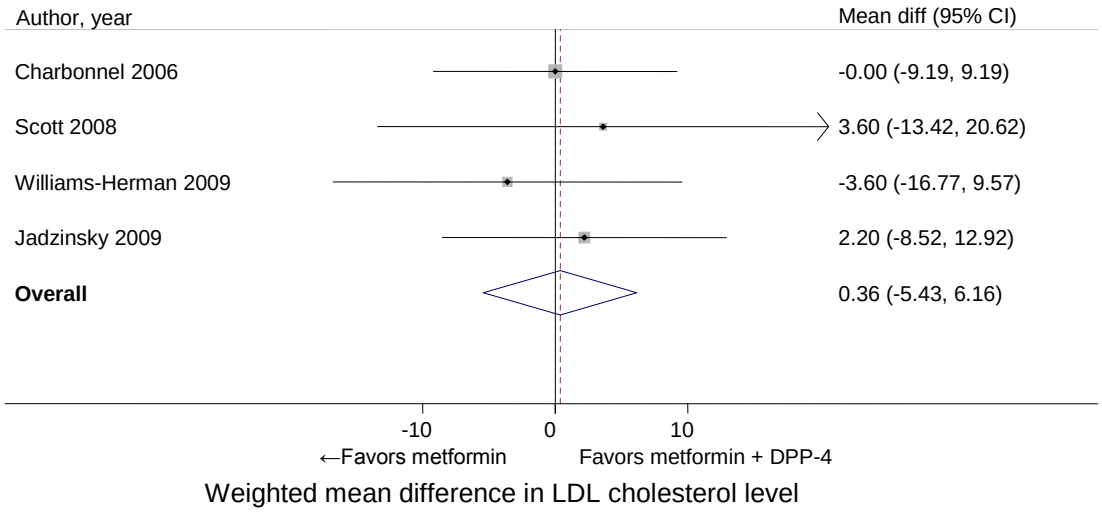
Figure 35. Mean difference in LDL comparing metformin with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; 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%
The range in change scores for LDL for the comparison group, a combination of metformin and sulfonylureas, was -7.8 mg/dL to 4.5 mg/dL. The median change was -4.5 mg/dL.

Metformin versus a combination of metformin and DPP-4 inhibitors. Four RCTs found no between-group difference in LDL for metformin compared to the combination of metformin and a DPP-4 inhibitor (pooled between-group difference -0.4 mg/dL, 95 percent CI -5.4 mg/dL to 6.2 mg/dL) (Figure 36).[76,78,85,94] 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).[76] 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.[76] The 54-week results were similar to those at 24-weeks; significance of the between-group difference was not reported, but the 95 percent CIs for percentage change in LDL from baseline were overlapping.[76] 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 percent at 24 weeks and -4.1 percent at 54 weeks) compared to the 1000 mg metformin plus 100 mg sitagliptin arm (mean change in LDL from baseline 1.4 percent at 24 weeks and -0.3 percent at 54 weeks). Another study studied two combination arms: metformin plus saxagliptin 5 mg once daily and metformin plus saxagliptin 10 mg once daily.[78] We included the arm with saxagliptin dosing of 5 mg per day in the meta-analysis since this is the FDA-approved dose.[78] However, percent changes in LDL were similar in both arms, -4.6 mg/dL and -3.8 mg/dL for the 5- and 10-mg saxagliptin arms, respectively.[78]

Figure 36. Mean difference in LDL comparing metformin with combination metformin and DPP-4 inhibitors

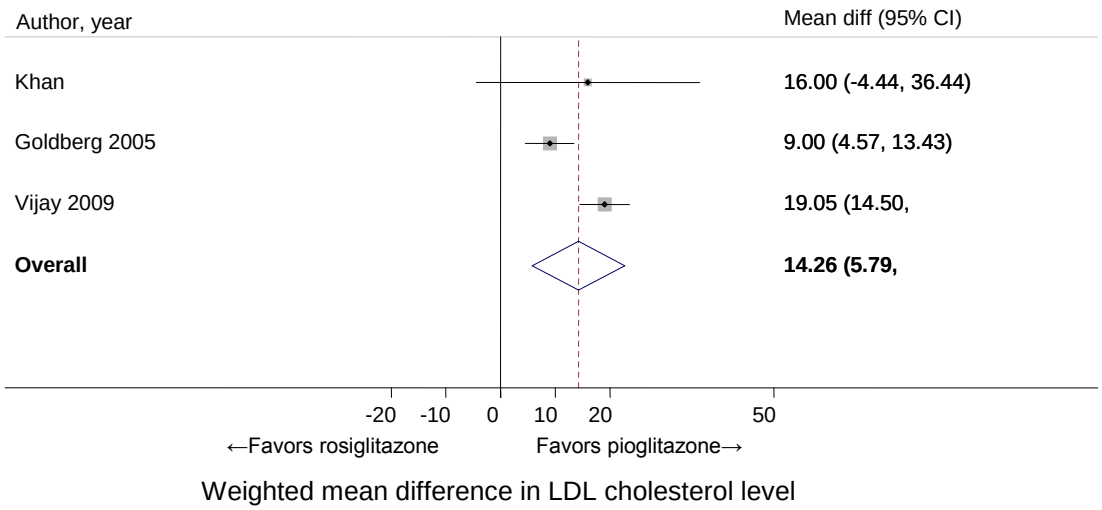


CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the 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 = 0.61 with 3 degrees of freedom (p = 0.90)
I-squared statistic = 0%
The range in change scores for LDL for the comparison group, a combination of metformin and DPP-4 inhibitors, was -4.6 mg/dL to 9.2 mg/dL. The median change was -0.9 mg/dL.

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.[96]

Rosiglitazone versus pioglitazone. Three RCTs comparing rosiglitazone directly with pioglitazone showed a greater increase in LDL with rosiglitazone, (pooled between-group difference of 14.3 mg/dL, 95 percent CI 5.8 mg/dL to 22.7 mg/dL) (Figure 37).[97-99] No one study significantly influenced results. While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone. Due to these differences, pioglitazone and rosiglitazone were not combined for comparisons including these thiazolidinediones for the LDL section.

Figure 37. Mean difference in LDL comparing rosiglitazone with pioglitazone



CI = confidence interval; diff = difference; 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 = 9.65 with 2 degrees of freedom (p = 0.008)
I-squared statistic = 79%
The range in change scores for LDL for the comparison group, pioglitazone, was -18 to 12.3 mg/dL. The median change was -13.7 mg/dL.

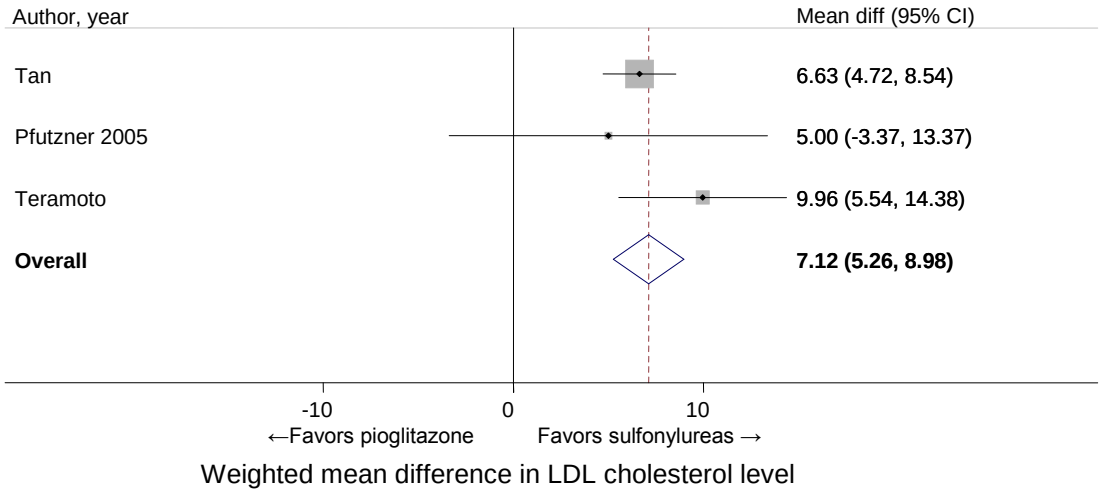
Rosiglitazone versus sulfonylureas. Two RCTs compared rosiglitazone to a sulfonylurea, and in both studies, rosiglitazone (8 mg daily) increased median LDL relative to a sulfonylurea (range in median between-group difference 15.2 mg/dL to 19.5 mg/dL).[100,149] Statistical significance of between-group 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.[100]

Pioglitazone versus sulfonylureas. Three RCTs compared pioglitazone to a sulfonylurea (pooled between-group difference in LDL 7.1 mg/dL, 95 percent CI 5.3 mg/dL to 9.0 mg/dL) (Figure 38).[41,105,106] No one study affected results, and there was no significant heterogeneity. Rosiglitazone versus meglitinides. As seen in the previous evidence report,[21] a single RCT compared rosiglitazone to repaglinide and found a between-group difference in LDL of 15 mg/dL.[109]

Pioglitazone versus meglitinides. As seen in the previous report,[21] a single RCT compared pioglitazone to repaglinide and found a between-group difference in LDL of -16 mg/dL.[110]

Sulfonylureas versus DPP-4 inhibitors. One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[111] After 12 weeks, both high dose sitagliptin (100 mg a day) and glipizide (maximum dose 20 mg a day) increased LDL (5.5 percent versus 2.2 percent respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[111]

Figure 38. Mean difference in LDL comparing pioglitazone with sulfonylureas



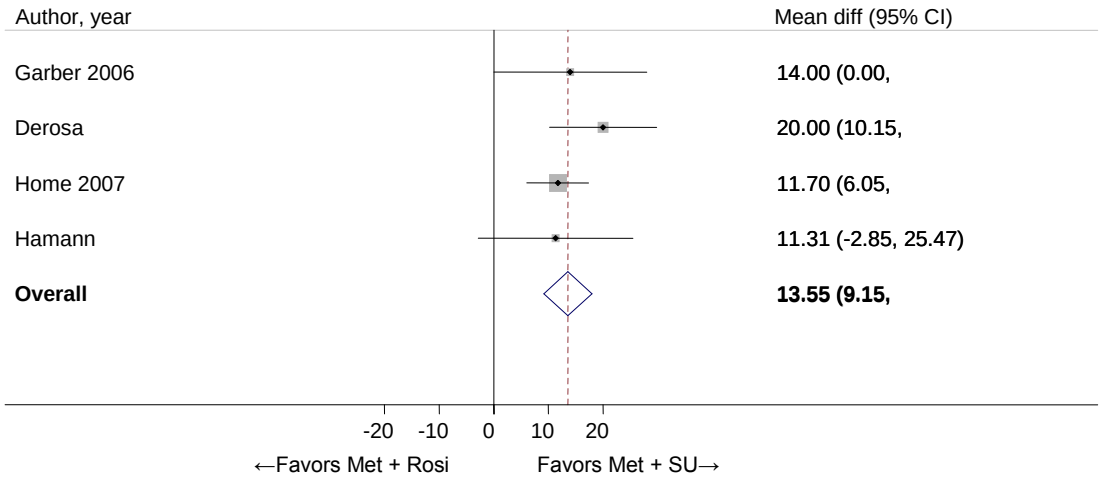
CI = confidence interval; diff = difference; LDL = low density lipoprotein; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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 = 2.08 with 2 degrees of freedom (p = 0.35)
I-squared statistic = 4%
The range in change scores for LDL for the comparison group, sulfonylureas, was -8 mg/dL to -1.2 mg/dL. The median change was -1.4 mg/dL.

Sulfonylureas versus meglitinides. As seen in the previous evidence report,[21] 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).[113,117] An additional RCT reported no difference between nateglinide and glibenclamide in LDL, but no quantitative results were provided.[119]

Sulfonylurea versus GLP-1 agonists. A single RCT compared a sulfonylurea to liraglutide and found a non-significant between-group difference in LDL: 2.7 mg/dL (95 percent CI -1.5 mg/dL to 6.6 mg/dL).[121] Of note, the dose used in the sulfonylurea arm was low relative to that used in the liraglutide arm.[121]

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 percent CI 9.1 mg/dL to 17.9 mg/dL) comparing metformin and rosiglitazone with metformin and a sulfonylurea (Figure 39).[123,124,128,157] 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.[124] 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).[16]

Figure 39. Mean difference in LDL comparing combination of metformin and rosiglitazone with combination of metformin and sulfonylureas



CI = confidence interval; diff = difference; LDL = low density lipoprotein; Met = metformin; mg/dL = milligrams per deciliter; Rosi = rosiglitazone; SU = sulfonylurea
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%
The range in change scores for LDL for the comparison group, a combination of metformin and sulfonylureas, was -16 mg/dL to -4 mg/dL. The median change was -8.2 mg/dL.

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.[126]

Combination of metformin and rosiglitazone versus combination of metformin and DPP-4 inhibitors. Two RCTs compared metformin plus rosiglitazone with the combination of metformin plus sitagliptin showing between-group differences in percentage change in LDL from baseline of 14.8 percentage points (95 percent CI 5.7 percent to 23.9 percent)[85] and 0.1 percent.[130]

Combination of metformin and rosiglitazone 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).[131]

Combination of metformin and rosiglitazone versus combination of metformin andGLP-1 agonists. A single RCT 20 weeks in duration compared the combination of metformin and rosiglitazone to the combination of metformin and exenatide yielding a between-group difference in LDL of 14.7 mg/dL.[132] Significance was not reported.[132]

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.[158]

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.[135-136] One study reported that LDL decreased by less than 5 percent in both groups.[136] 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).[135]

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).[42] At 18 months, the RECORD trial reported a between-group difference in LDL of -18.7 mg/dL (p < 0.001)[124] and -12.1 mg/dL (p < 0.0001) at 5.5 years[124] 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).[140,141]

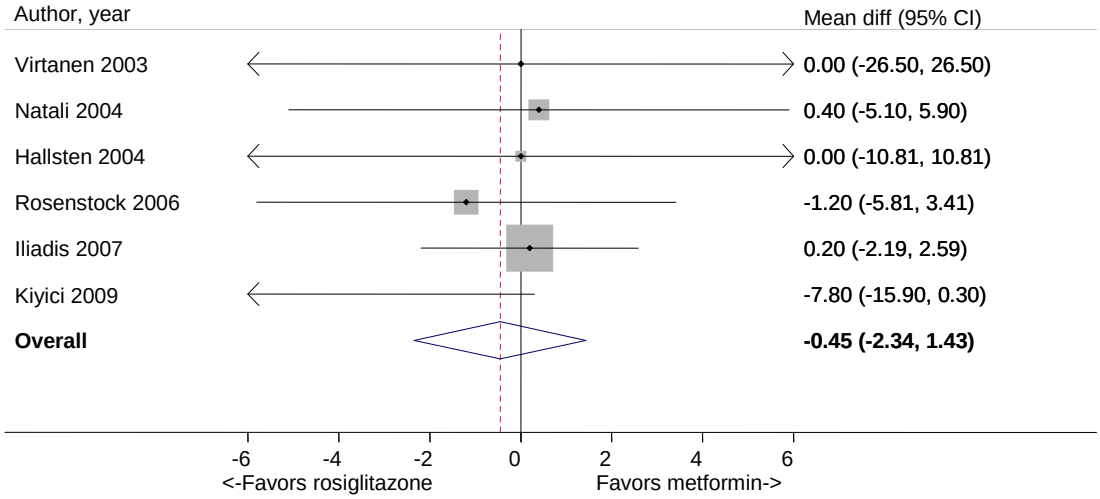
Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. A single RCT lasting 26 weeks compared the combination of metformin and sitagliptin with the combination of metformin and one of 2 doses of liraglutide.[143] LDL increased in all arms, and the dose of liraglutide did not affect this change: mean between-group difference in LDL 1.9 mg/dL (95 percent CI -6.6 mg/dL to 2.7 mg/dL, daily dose of liraglutide 1.2 mg) and 3.1 mg/dL (95 percent CI -7.7 mg/dL to 1.5 mg/dL, daily dose of liraglutide 1.8 mg) for the metformin plus sitagliptin arm compared with the metformin plus liraglutide arms.[143]

The Evidence About High-Density Lipoproteins (Appendix G, Table 4)

Metformin versus rosiglitazone. Six RCTs reported no between-group difference in HDL for metformin compared to rosiglitazone (pooled between-group difference -0.5 mg/dL, 95 percent CI -2.3 mg/dL to 1.4 mg/dL) (Figure 40).[45,48,49,148,153,154] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

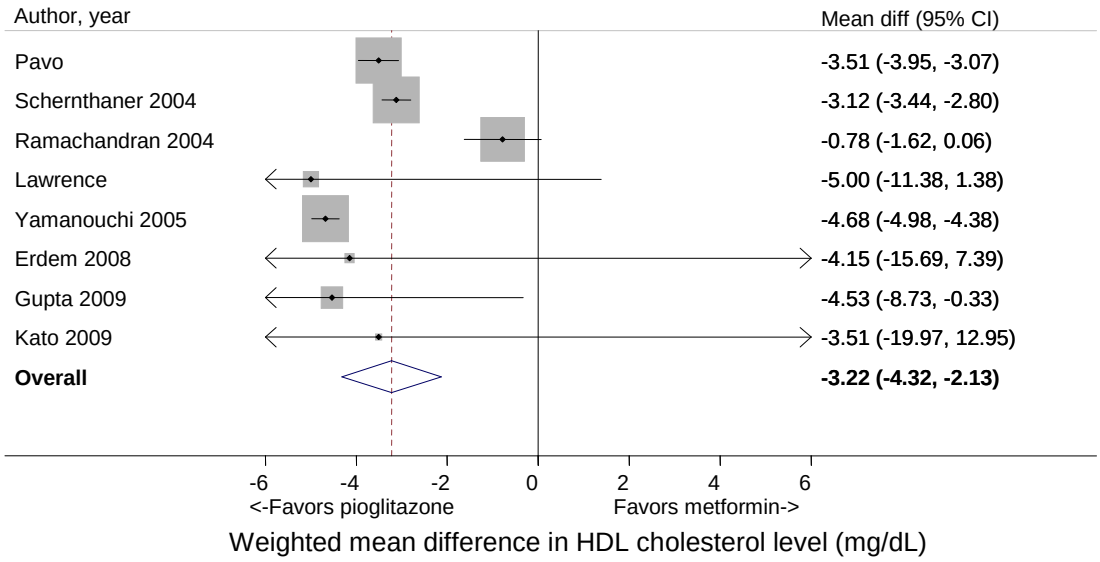
Metformin versus pioglitazone. Eight RCTs favored pioglitazone over metformin with a pooled between-group difference in HDL of -3.2 mg/dL (95 percent CI -4.3 mg/dL to -2.1 mg/dL) (Figure 41).[39,47,50-54,57] No one study significantly affected results. While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone.

Figure 40. Mean difference in HDL comparing metformin with rosiglitazone



CI = confidence interval; diff = difference; 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 = 3.65 with 5 degrees of freedom (p = 0.60)
I-squared statistic = 0%
The range in change scores for HDL for the comparison group, rosiglitazone, was 0.8 mg/dL to 7.8 mg/dL. The median change was 3.5 mg/dL.

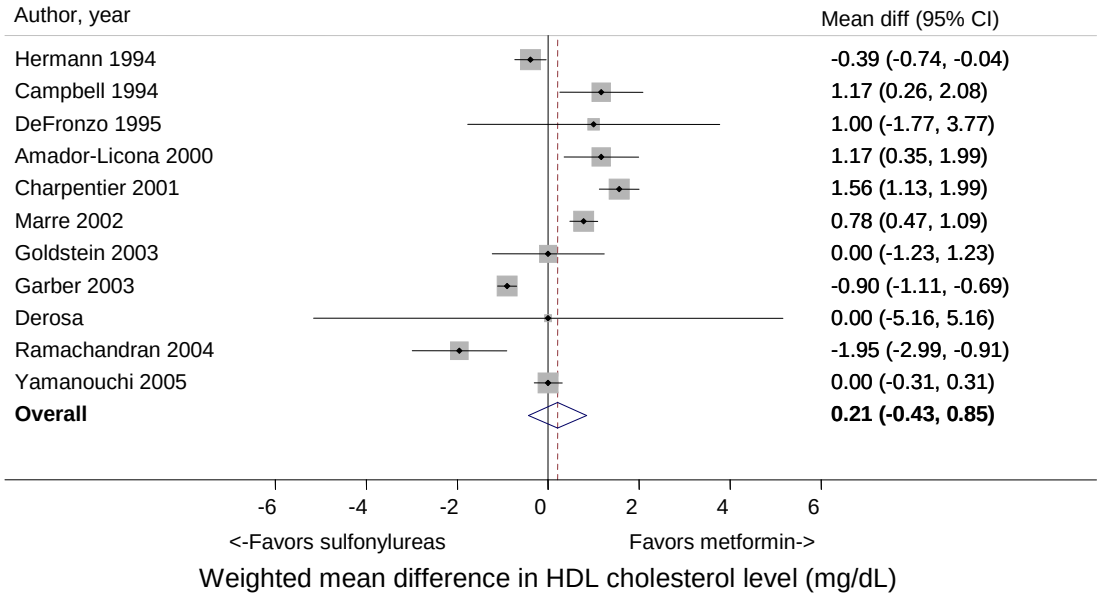
Figure 41. Mean difference in HDL comparing metformin with pioglitazone



CI = confidence interval; diff = difference; 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 = 100.55 with 7 degrees of freedom (p = 0.0000)
I-squared statistic = 93%
The range in change scores for HDL for the comparison group, pioglitazone, was -1.9 mg/dL to 9.4 mg/dL. The median change was 4.5 mg/dL.

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 percent CI -0.4 mg/dL to 0.8 mg/dL) (Figure 42).[50,51,60-52,64,66-68,70,71] No one study significantly affected results. There was no obvious source of the observed heterogeneity on metaregression. Another study reported no changes in lipid values between groups but did not provide quantitative results.[63]

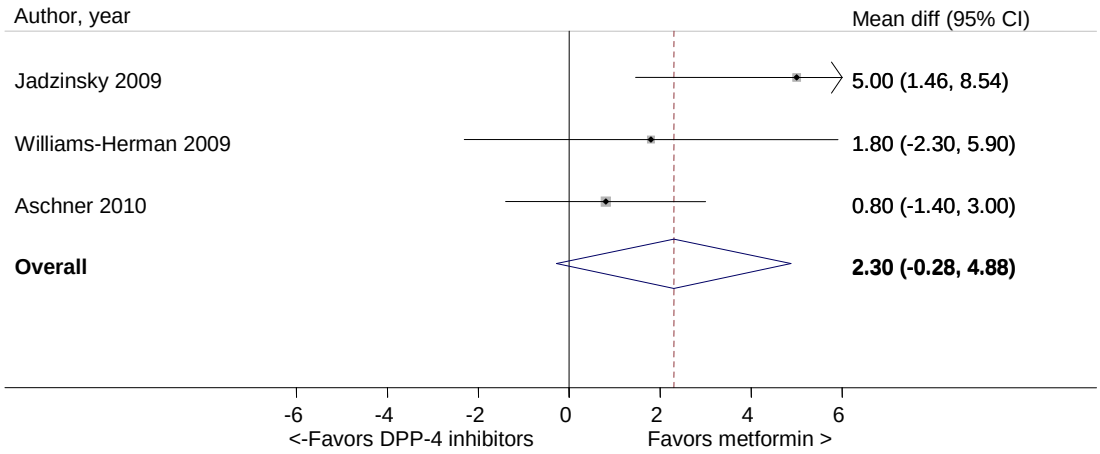
Figure 42. Mean difference in HDL comparing metformin with sulfonylureas



CI = confidence interval; diff = difference; 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 = 175.80 with 10 degrees of freedom (p = 0.0000)
I-squared statistic = 94%
The range in change scores for HDL for the comparison group, sulfonylureas, was -0.4 mg/dL to 5.9 mg/dL. The median change was 0.5 mg/dL.

Metformin versus DPP-4 inhibitors. Three RCTs compared metformin with DPP-4 inhibitors on HDL with a pooled between-group difference of 2.3 mg/dL (95 percent CI -0.28 mg/dL to 4.9 mg/dL) (Figure 43).[76-78] Removal of the largest study[77] led to a statistically significant pooled between-group difference in HDL favoring metformin. Only 3 studies were included in this meta-analysis making it difficult to understand the significance of this. There was no statistical evidence of heterogeneity.

Figure 43. Mean difference in HDL comparing metformin with DPP-4 inhibitors

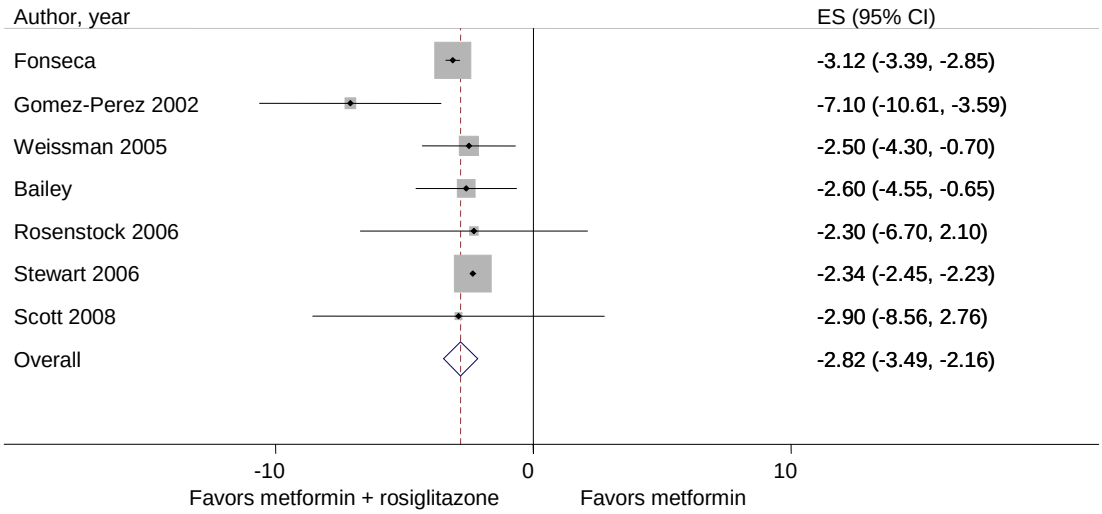


CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the 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 = 3.90 with 2 degrees of freedom (p = 0.14)
I-squared statistic = 49%
The range in change scores for HDL for the comparison group, DPP-4 inhibitors, was 0.5 mg/dL to 6.2 mg/dL. The median change was 3.9 mg/dL.

Metformin versus meglitinides. As seen in the previous evidence report,[21] 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.[81]

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 percent CI -3.5 mg/dL to -2.2 mg/dL) (Figure 44).[49,85-88,90,156] 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 44. Mean difference in HDL comparing metformin with combination metformin and rosiglitazone

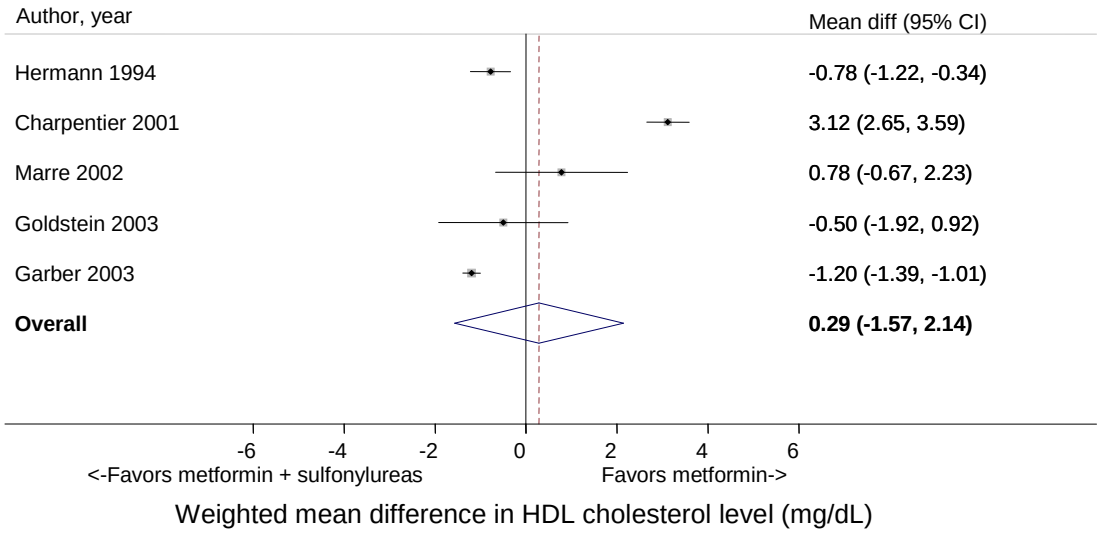


CI = confidence interval; diff = difference; HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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 = 34.57 with 6 degrees of freedom (p = 0.0000)
I-squared statistic = 83%
The range in change scores for HDL for the comparison group, a combination of metformin and rosiglitazone, was 1.8 mg/dL to 6.4 mg/dL. The median change was 3.5 mg/dL.

Metformin versus a combination of metformin and pioglitazone. Two RCTs favored the combination of metformin and pioglitazone over metformin on the change in HDL.[84,89] One reported a between-group difference of 6.4 mg/dL (significance not reported),[84] and the other found a statistically significant percentage difference in percentage change from baseline (8.7 percent).[89]

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 percent CI -1.6 mg/dL to 2.1 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 45).[61,62,64,68,71,91] 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).[71] Removal of this study from the meta-analysis led to a significant pooled between-group difference of -0.75 mg/dL (95 percent CI -1.3 mg/dL to -0.2 mg/dL).[71] Another study reported no changes in lipid values between groups but did not provide quantitative results.[63]

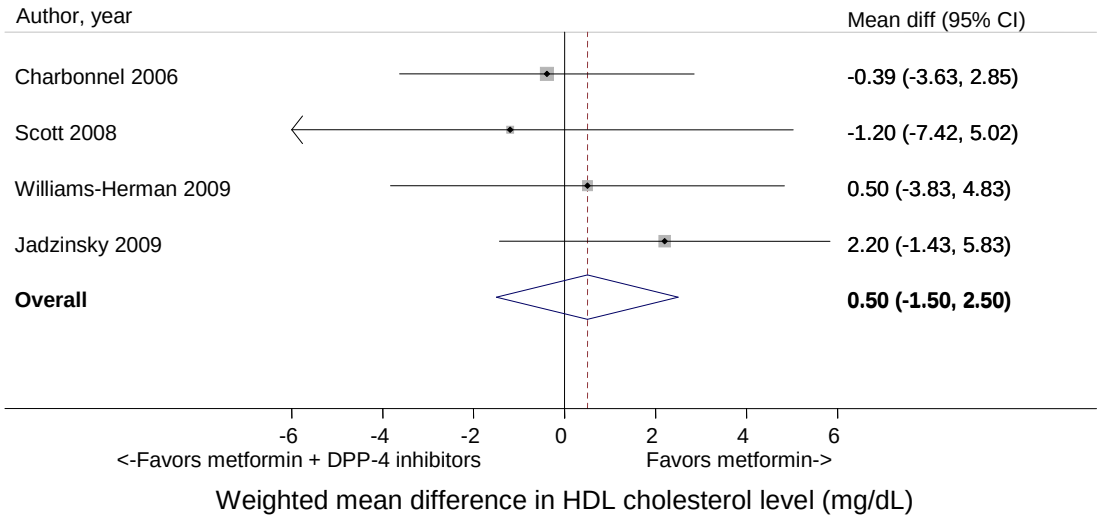
Figure 45. Mean difference in HDL comparing metformin with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; 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 = 282.15 with 4 degrees of freedom (p = 0.0000)
I-squared statistic = 99%
The range in change scores for HDL for the comparison group, a combination of metformin and sulfonylurea, was -1.2 mg/dL to 1.6 mg/dL. The median change was 0.8 mg/dL.

Metformin versus a combination of metformin and DPP-4 inhibitors. Four RCTs found no between-group difference in HDL for metformin compared to the combination of metformin and sitagliptin (pooled between-group difference 0.5 mg/dL, 95 percent CI -1.5 mg/dL to 2.5 mg/dL) (Figure 46).[76,78,85,94] 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).[76] 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.[76] The 54-week results were similar to those at 24 weeks; significance of the between-group difference was not reported, but the 95 percent CIs for percentage change in HDL from baseline were overlapping.[76] 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 percent at 24 weeks and 7.2 percent at 54 weeks) compared to the 1,000 mg metformin plus 100 mg sitagliptin arm (mean change in HDL from baseline 3.6 percent at 24 weeks and 5.1 percent at 54 weeks). Another study varied the dose of saxagliptin (5 mg and 10 mg daily) in two separate combination arms.[78] We included the lower-dose arm in the meta-analysis since this is the FDA-approved dose. HDL increased similarly in the lower and higher dose combination arms.[78]

Figure 46. Mean difference in HDL comparing metformin with combination metformin and DPP-4 inhibitors



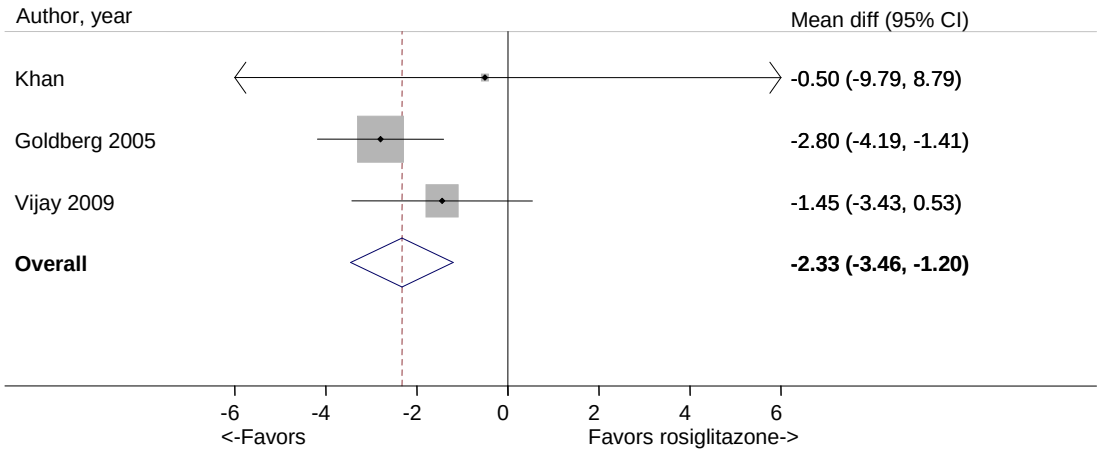
CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the 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 = 1.42 with 3 degrees of freedom (p = 0.70)
I-squared statistic = 0%
The range in change scores for HDL for the comparison group, a combination of metformin and DPP-4 inhibitors, was -4.8 mg/dL to 6.7 mg/dL. The median change was 1.2 mg/dL.

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.[96]

Rosiglitazone versus pioglitazone. Three RCTs directly comparing rosiglitazone with pioglitazone showed that pioglitazone increased HDL more than rosiglitazone (pooled between-group difference of -2.3 mg/dL, 95 percent CI -3.5 mg/dL to -1.2 mg/dL) (Figure 47).[97-99] No one study significantly influenced results. While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone. Due to these differences, pioglitazone and rosiglitazone were not combined for comparisons including these thiazolidinediones for the HDL section. Removal of the largest study led to loss of significance of the pooled estimate, but the pooled estimate still favored pioglitazone.

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).[100,149] 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.[100]

Figure 47. Mean difference in HDL comparing rosiglitazone with pioglitazone



CI = confidence interval; diff = difference; 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 = 1.35 with 2 degrees of freedom (p = 0.51)
I-squared statistic = 0%
The range in change scores for HDL for the comparison group, pioglitazone, was 2 mg/dL to 5.2 mg/dL. The median change was 4.7 mg/dL.

Pioglitazone versus sulfonylureas. Six RCTs favored pioglitazone over a sulfonylurea (pooled between-group difference in HDL 4.3 mg/dL, 95 percent CI 1.9 mg/dL to 6.6 mg/dL) (Figure 48).[41,50,51,105,106,108] Removal of either of the 2 largest studies[50,106] resulted in pooled between-group differences (3.8 mg/dL and 4.7 mg/dL) that were nonsignificant. Meta-regression suggested that study duration was a potential source of heterogeneity (p = 0.04). Increased study duration was associated with an increase in between-group differences in HDL.

Rosiglitazone versus meglitinides. As seen in the previous evidence report,[21] a single RCT compared rosiglitazone to repaglinide and found a between-group difference in HDL of 1.3 mg/dL.[109]

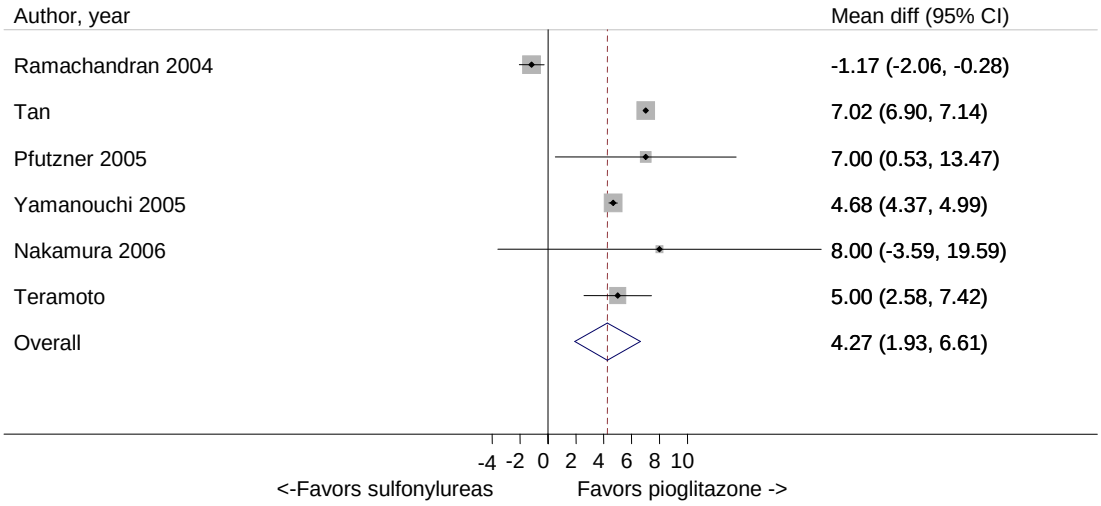
Pioglitazone versus meglitinides. Two RCTs compared pioglitazone with a meglitinide and found a between-group difference in HDL of 7 mg/dL in both studies.[108,110] Neither study commented on the statistical significance of this difference.

Sulfonylureas versus DPP-4 inhibitors. One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[111] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg per day) increased HDL (4.6 percent versus 2.8 percent respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[111]

Sulfonylureas versus meglitinides. Six RCTs compared a sulfonylurea to a meglitinide and found no significant difference in HDL (pooled between-group difference -0.7 mg/dL, 95 percent

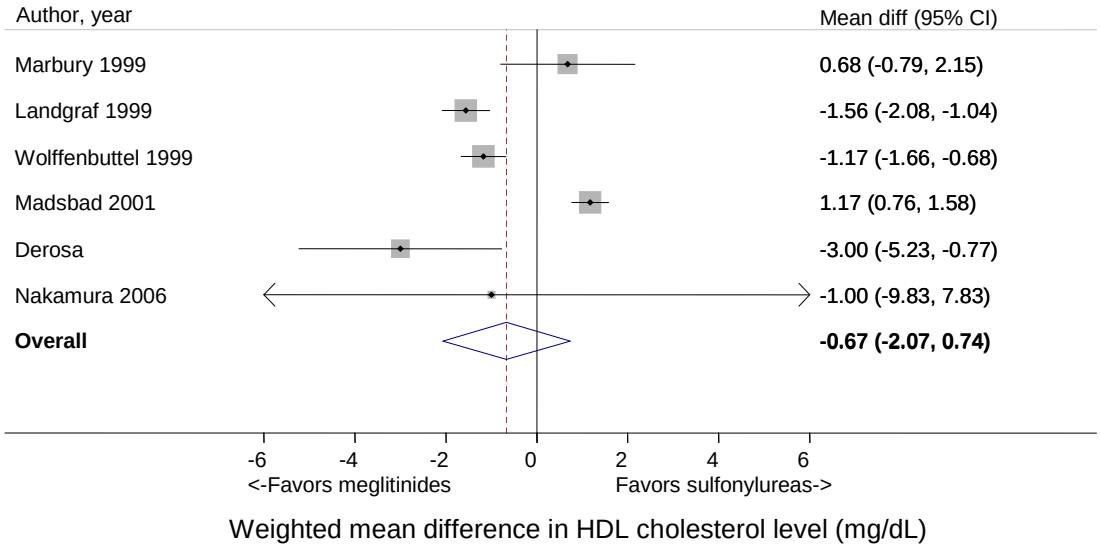
CI -2.1 mg/dL to 0.7 mg/dL) (Figure 49).[108,113-117] Removal of one of the larger studies resulted in a statistically significant pooled between-group difference (-1.2 mg/dL, 95 percent CI -1.9 mg/dL to -0.4 mg/dL).[114] This study did not appear to be different from the other studies and was therefore 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 consistent with the results of the meta-analysis, but no quantitative results were provided.[119]

Figure 48. Mean difference in HDL comparing pioglitazone with sulfonylureas



CI = confidence interval; diff = difference; 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 = 485.49 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 99%
The range in change scores for HDL for the comparison group, sulfonylureas was -4.5 mg/dL to 5.9 mg/dL. The median change was 0.5 mg/dL.

Figure 49. Mean difference in HDL comparing sulfonylureas with meglitinides

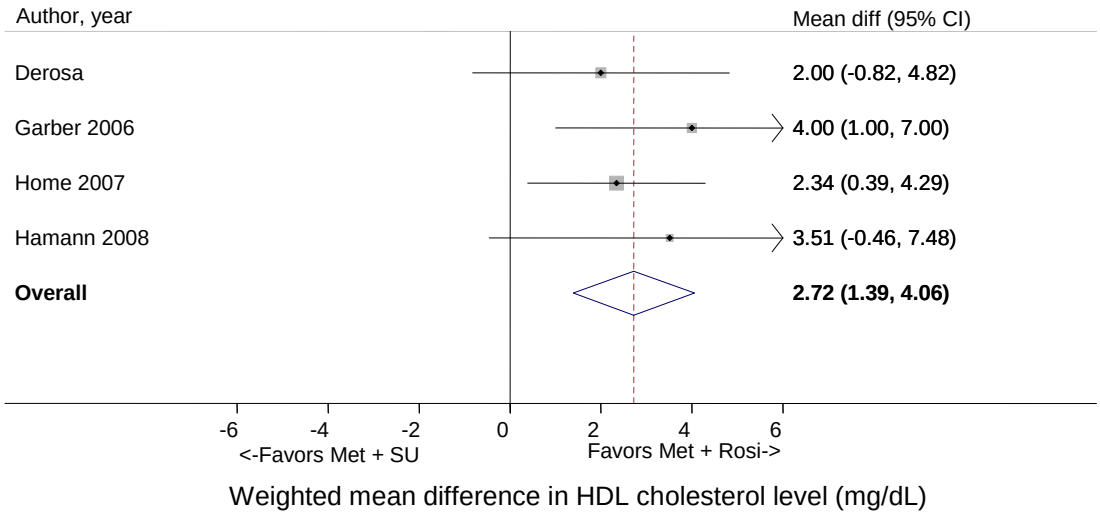


CI = confidence interval; diff = difference; HDL = high density lipoproteins; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 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 = 92.38 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 95%
The range in change scores for HDL for the comparison group, meglitinides was -0.8 mg/dL to 1.2 mg/dL. The median change was 1.1 mg/dL.

Sulfonylureas versus GLP-1 agonists. A single RCT compared a sulfonylurea with liraglutide and found a non-significant between-group difference in HDL: -0.4 mg/dL (95 percent CI -1.2 mg/dL to 1.9 mg/dL).[121] Of note, the dose used in the sulfonylurea arm was low relative to that used in the liraglutide arm.[121]

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 percent CI 1.4 mg/dL to 4.1 mg/dL) comparing combination metformin and rosiglitazone with combination metformin and a sulfonylurea (Figure 50).[123,124,128,157] 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.[124] 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, $p < 0.0001$).[16]

Figure 50. Mean difference in HDL comparing combination metformin and rosiglitazone with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; HDL = high density lipoproteins; Met = metformin; mg/dL = milligrams per deciliter; Rosi = rosiglitazone; SU = 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 = 1.25 with 3 degrees of freedom (p = 0.74)
I-squared statistic = 0%
The range in change scores for HDL for the comparison group, a combination of metformin and sulfonylureas, was -2 mg/dL to 1.2 mg/dL. The median change was 0.4 mg/dL.

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.[126,158] 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 ($p = 0.0001$).[126,158]

Combination of metformin and rosiglitazone versus combination of metformin and DPP-4 inhibitors. 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 percent, 95 percent CI 0.6 percent to 9.2 percent).[85] Another small RCT 16 weeks in duration found that the mean percent decrease in HDL from baseline was slightly greater in the metformin plus rosiglitazone arm compared with the metformin plus sitagliptin arm (mean difference in percentage change from baseline of -1 percent, significance not reported).[130]

Combination of metformin and rosiglitazone 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 ($p < 0.0001$).[131]

Combination of metformin and rosiglitazone versus combination of metformin and GLP-1 agonists. A single small RCT 20 weeks in duration compared metformin plus rosiglitazone with metformin plus exenatide and found a between-group mean difference in HDL of 0.8 mg/dL (significance not reported).[132]

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.[158]

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.[135,136] One study reported that HDL increased by approximately 5 percent in both groups.[136] The other study showed no between-group difference (0 mg/dL) in HDL as well.[135]

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.[138]

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).[42] At 18 months, the RECORD trial reported a between-group difference in HDL of -0.4 mg/dL (p > 0.05)[124] and -1.6 mg/dL (p < 0.0001) at 5.5 years[124] 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.[140,141,158] In one study, the between-group difference in median HDL was 3.1 mg/dL (p = 0.009),[141] 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).[140,158]

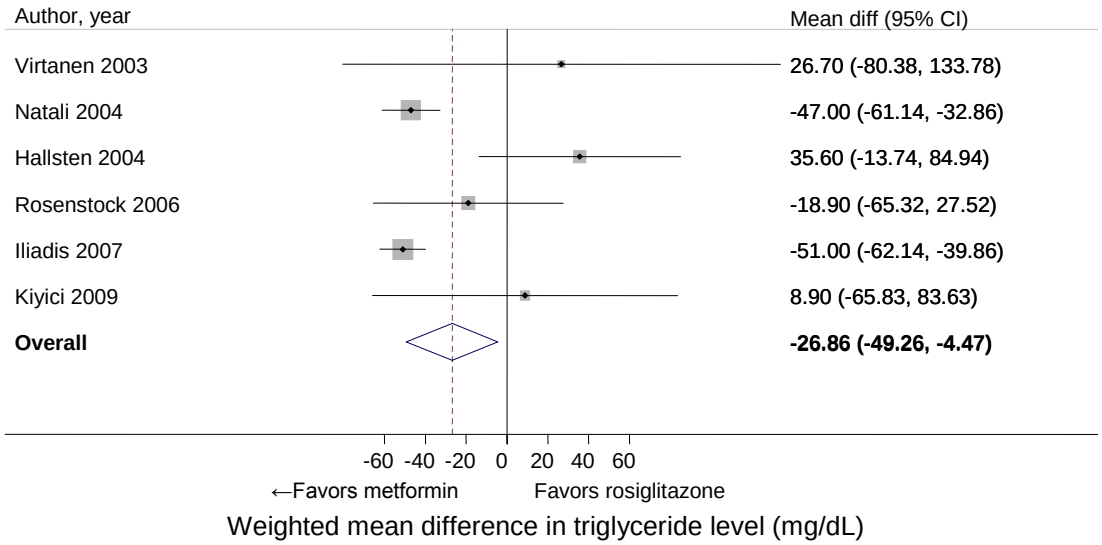
Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. A single RCT lasting 26 weeks compared the combination of metformin and sitagliptin with the combination of metformin and one of 2 doses of liraglutide.[143] HDL did not change in any arm, and thus there was no between-group difference in HDL change regardless of liraglutide dose.[143]

The Evidence About Triglycerides (Appendix G, Table 4)

Metformin versus rosiglitazone. Six RCTs favored metformin over rosiglitazone in terms of lowering TG levels (pooled between-group difference -26.9 mg/dL, 95 percent CI -49.3 mg/dL

to -4.5 mg/dL) (Figure 51).[45,48,49,148,153,154] When either of the largest studies was excluded from the meta-analysis, the point estimate still favored metformin but the confidence interval included 0.[48,148] We performed meta-regression because of substantial heterogeneity. Study duration and dose were possible sources of heterogeneity with longer study duration and higher relative dose of metformin associated with a greater pooled between-group difference in TG. 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, but the results were consistent with the meta-analysis.[58]

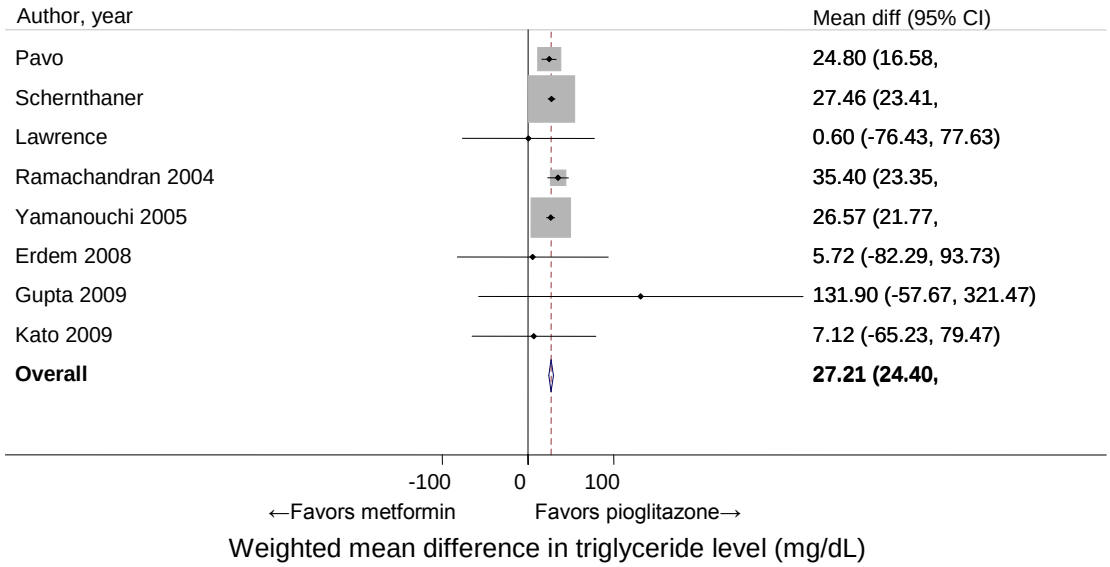
Figure 51. Mean difference in triglycerides comparing metformin with rosiglitazone



CI = confidence interval; diff = difference; 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 = 16.38 with 5 degrees of freedom (p = 0.006)
I-squared statistic = 70%
The range in change scores for triglycerides for the comparison group, rosiglitazone, was -44 mg/dL to 22 mg/dL. The median change was -4.2 mg/dL.

Metformin versus pioglitazone. Eight RCTs compared metformin to pioglitazone and found a pooled between-group difference in TG of 27.2 mg/dL (95 percent CI 24.4 mg/dL to 30.0 mg/dL) (Figure 52).[39,47,50-54,57] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

Figure 52. Mean difference in triglycerides comparing metformin with pioglitazone



CI = confidence interval; diff = difference; 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 = 4.34 with 7 degrees of freedom (p = 0.74)
I-squared statistic = 0%
The range in change scores for triglycerides for the comparison group, pioglitazone, was -155.6 mg/dL to -8.0 mg/dL. The median change was -26.6 mg/dL.

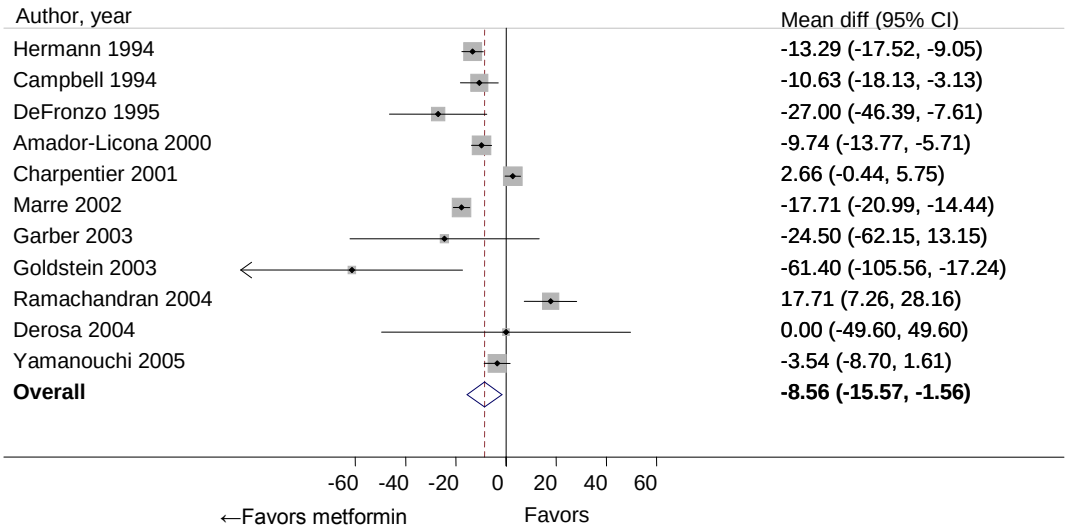
Metformin versus sulfonylureas. Eleven RCTs favored metformin over sulfonylurea (pooled between-group difference in TG -8.6 mg/dL, 95 percent CI -15.6 mg/dL to -1.6 mg/dL) (Figure 53).[50,51,60-62,64,66-68,70,71] Removal of one study resulted in loss of statistical significance (pooled between-group difference -6.9 mg/dL (95 percent CI -13.9 mg/dL to 0.1 mg/dL).[64] 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.[63]

Metformin versus DPP-4 inhibitors. Three RCTs found that sitagliptin decreased TG more than metformin, but the pooled between-group difference was not significant (3.4 mg/dL, 95 percent CI -0.4 mg/dL to 7.2 mg/dL) (Figure 54).[76-78] No one study significantly influenced results, and there was no evidence of heterogeneity.

Metformin versus meglitinides. As seen in the previous evidence report,[21] 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.[81]

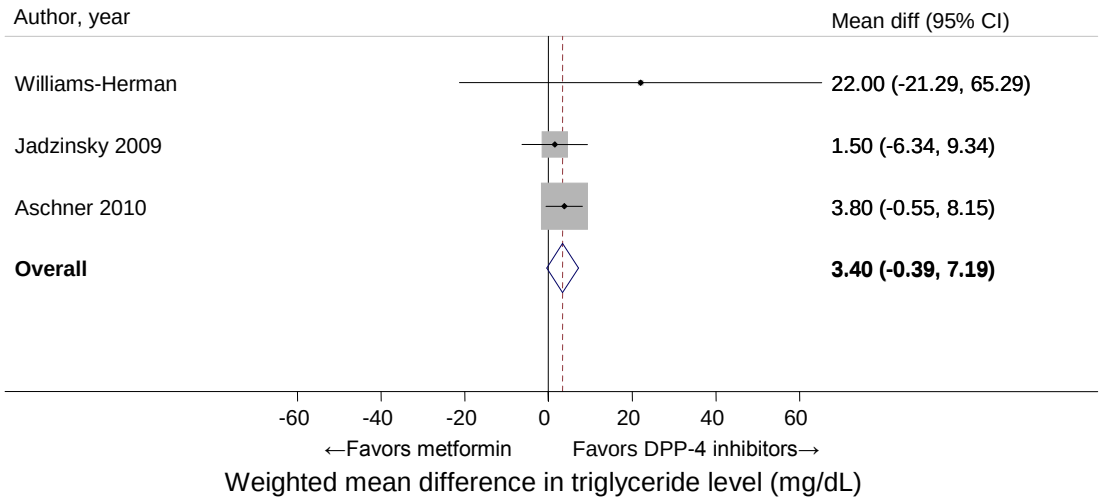
Metformin versus a combination of metformin and rosiglitazone. Seven RCTs compared metformin to the combination of metformin and rosiglitazone (pooled between-group difference in TG -14.5 mg/dL, 95 percent CI -15.7 mg/dL to -13.3 mg/dL) (Figure 55).[49,85-88,90,156] No one study significantly affected results, and there was no statistical evidence of heterogeneity.

Figure 53. Mean difference in triglycerides comparing metformin with sulfonylureas



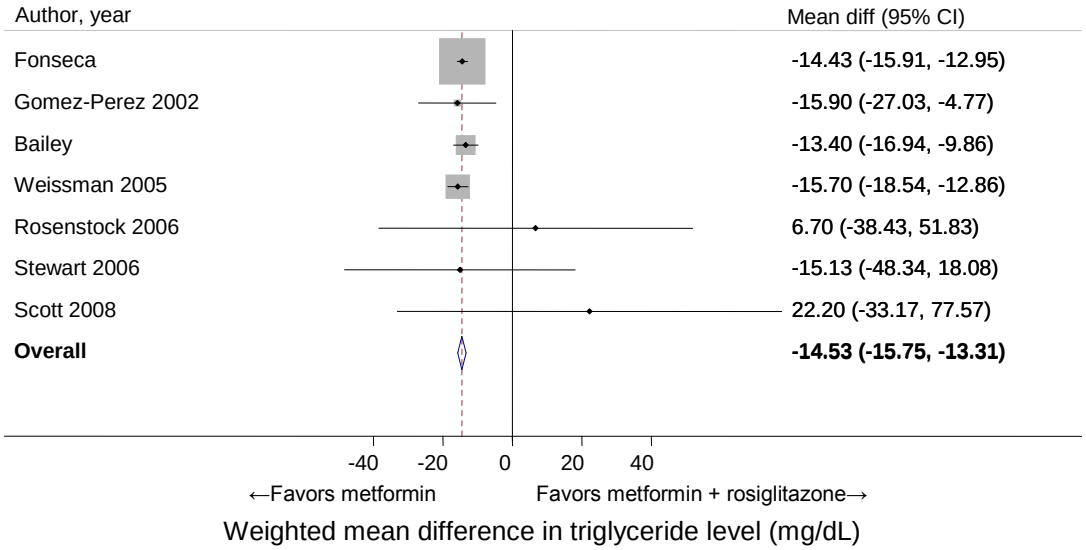
CI = confidence interval; diff = difference; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 122.78 with 10 degrees of freedom (p = 0.0000)
I-squared statistic = 92%
The range in change scores for triglycerides for the comparison group, sulfonylureas, was -44.5 mg/dL to 59.8 mg/dL. The median change was 0 mg/dL.

Figure 54. Mean difference in triglycerides comparing metformin with DPP-4 inhibitors



CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; 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 = 0.97 with 2 degrees of freedom (p = 0.62)
I-squared statistic = 0%
The range in change scores for triglycerides for the comparison group, DPP-4 inhibitors, was -3.7 mg/dL to 6 mg/dL. The median change was -3 mg/dL.

Figure 55. Mean difference in triglycerides comparing metformin with combination metformin and rosiglitazone

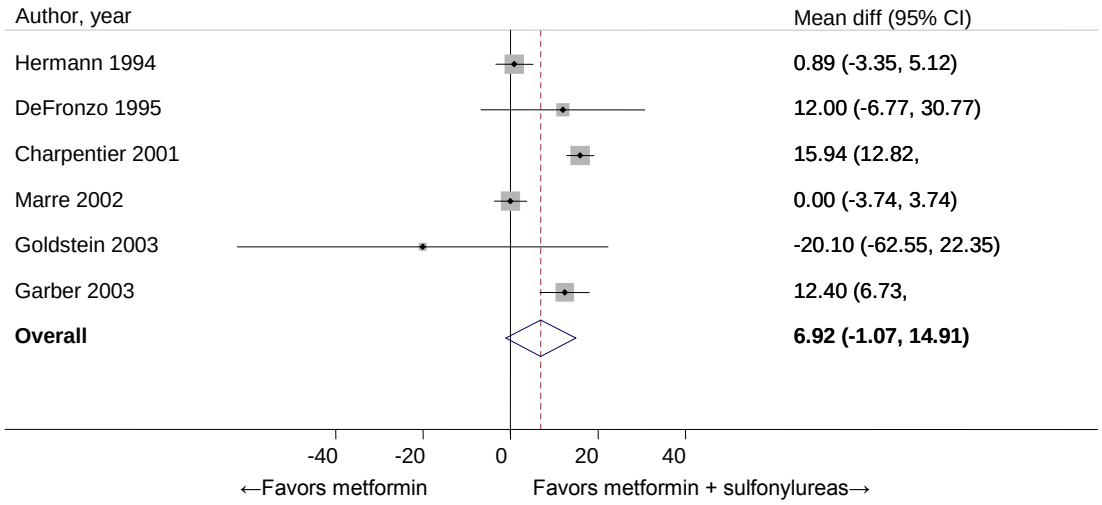


CI = confidence interval; diff = difference; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 3.66 with 6 degrees of freedom (p = 0.72)
I-squared statistic = 0%
The range in change scores for triglycerides for the comparison group, a combination of metformin and rosiglitazone, was -33.7 mg/dL to 11.8 mg/dL. The median change was 0 mg/dL.

Metformin versus a combination of metformin and pioglitazone. Two RCTs compared metformin to the combination of metformin and pioglitazone.[84,89] One RCT found a between-group difference of -6.1 mg/dL (significance not reported),[84] and the other reported statistically significant between-group percentage change in percentage change from baseline of 18.2 percent.[89]

Metformin versus a combination of metformin and sulfonylureas. As seen in the previous evidence report,[21] six RCTs found no between-group difference in TG (pooled between-group difference 6.9 mg/dL, 95 percent CI -1.1 mg/dL to 14.9 mg/dL) for metformin compared to the combination of metformin and a sulfonylurea (Figure 56).[61,62,64,68,70,71] 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 percent CI 0.2 mg/dL to 17.7 mg/dL).[64] Two studies reported no changes in lipid values between groups but did not provide quantitative results.[63,91]

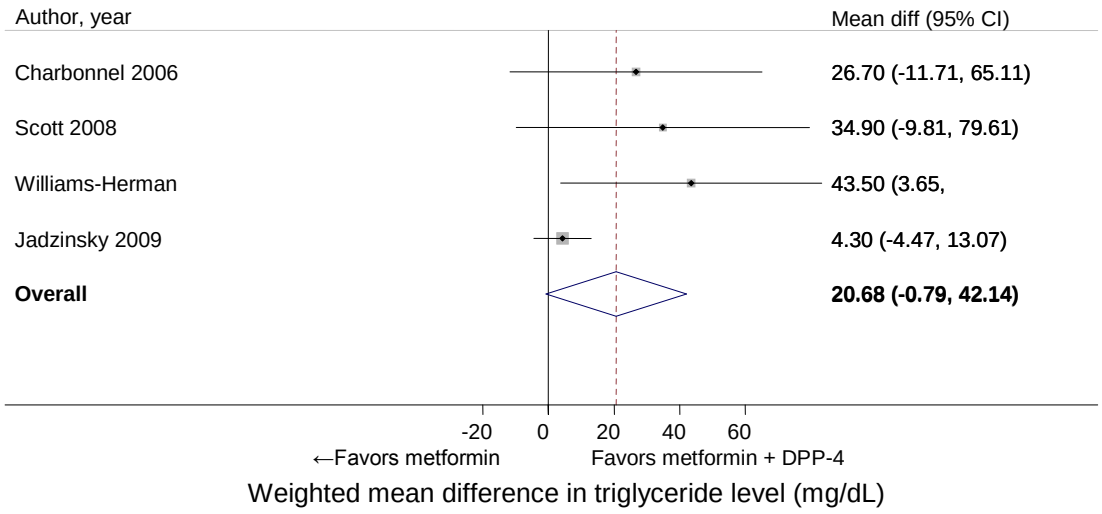
Figure 56. Mean difference in triglycerides comparing metformin with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; 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 = 57.40 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 91%
The range in change scores for triglycerides for the comparison group, a combination of metformin and sulfonylureas, was -17.8 mg/dL to 18.5 mg/dL. The median change was -10.2 mg/dL.

Metformin versus a combination of metformin and DPP-4 inhibitors. Four RCTs compared metformin to the combination of metformin and sitagliptin and found that metformin decreased TG less than the combination with a pooled between-group difference of 20.7 mg/dL (95 percent CI -0.8 mg/dL to 42.1 mg/dL) (Figure 57).[76,78,85,94] Removal of the largest study led to a significant pooled between-group difference (34.8 mg/dL, 95 percent CI 11.3 mg/dL to 58.3 mg/dL). There was no statistical evidence of heterogeneity. One study evaluated TG at 24 weeks and after a continuation (at 54 weeks).[76] 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.[76] The 54-week results were similar to those at 24 weeks.[76] Results suggested a dose-response relationship with the 2000 mg metformin and 100 mg sitagliptin arm decreasing TG (mean change from baseline -10.1 percent at 24 weeks ($p < 0.05$) and -7.1 percent 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 percent at 24 weeks ($p > 0.05$) and -4.6 percent at 54 weeks ($p > 0.05$)).[76] Another study evaluated two combination arms: metformin plus saxagliptin 5 mg once daily and metformin plus saxagliptin 10 mg once daily.[78] We included the arm with saxagliptin at 5 mg per day in the meta-analysis since this is the FDA-approved dose.[78] However, percent changes in TG were similar in both arms, -5.8 percent and -4.5 percent for the 5 and 10 mg saxagliptin arms, respectively.[78]

Figure 57. Mean difference in triglycerides comparing metformin with combination metformin and DPP-4 inhibitors

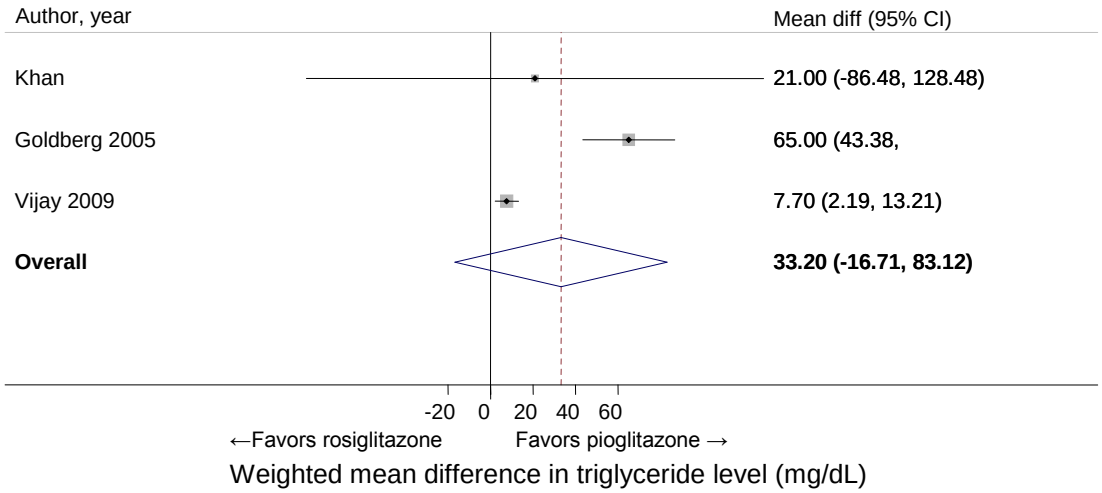


CI = confidence interval; diff = difference; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the 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 = 6.03 with 3 degrees of freedom (p = 0.11)
I-squared statistic = 50%
The range in change scores for triglycerides for the comparison group, a combination of metformin and DPP-4 inhibitors, was -16 mg/dL to 7.7 mg/dL. The median change was -10.2 mg/dL.

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.[96]

Rosiglitazone versus pioglitazone. Three RCTs compared rosiglitazone with pioglitazone and demonstrated a favorable effect of pioglitazone on TG relative to rosiglitazone (pooled between-group difference 33.2 mg/dL, 95 percent CI -16.7 mg/dL to 83.1 mg/dL comparing rosiglitazone to pioglitazone) (Figure 58).[97-99] Removal of either of the largest studies led to a statistically significant difference which still favored pioglitazone (pooled between-group difference 63.3 mg/dL, 95 percent CI 42.1 mg/dL to 84.5 mg/dL and pooled between-group difference 7.7 mg/dL, 95 percent CI 2.2 mg/dL to 13.2 mg/dL).[98,99] While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone. Due to these differences, pioglitazone and rosiglitazone were not combined for comparisons including these thiazolidinediones for the TG section.

Figure 58. Mean difference in triglycerides comparing rosiglitazone with pioglitazone



CI = confidence interval; diff = difference; 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 = 25.37 with 2 degrees of freedom (p = 0.0000)
I-squared statistic = 92%
The range in change scores for triglycerides for the comparison group, pioglitazone, was -51 mg/dL to -15 mg/dL. The median change was -33.0 mg/dL.

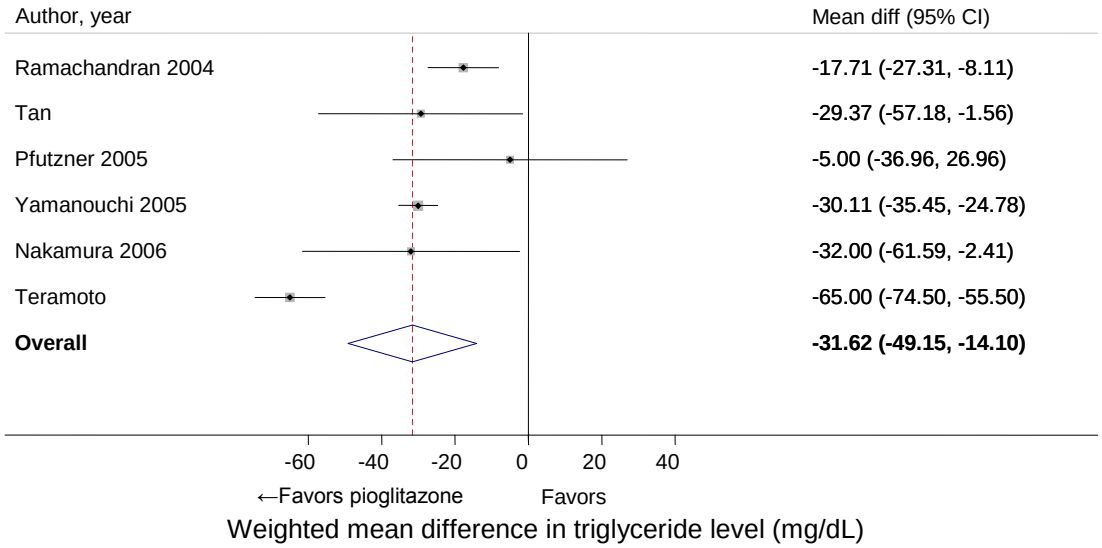
Rosiglitazone versus sulfonylureas. In one RCT, rosiglitazone (8 mg/day) and a sulfonylurea both decreased TG at 52 weeks (mean between-group difference 11 mg/dL for rosiglitazone relative to sulfonylurea) which was reported to be nonsignificant.[149] Another RCT found that at 4 mg/day, rosiglitazone 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.[100]

Pioglitazone versus sulfonylureas. Six RCTs favored pioglitazone over a sulfonylurea (pooled between-group difference -31.6 mg/dL, 95 percent CI -49.1 mg/dL to -14.1 mg/dL) (Figure 59).[41,50,51,105,106,108] While there was statistical evidence of heterogeneity, point estimates from all studies favored pioglitazone. No one study significantly influenced results.

Rosiglitazone versus meglitinides. As seen in the previous evidence report,[21] 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.[109]

Pioglitazone versus meglitinides. As seen in the previous evidence report,[21] one RCT found that compared with repaglinide, pioglitazone caused a greater absolute reduction in TG (between-group difference -96 mg/dL), but statistical significance was not reported.[110] A small RCT comparing pioglitazone to nateglinide found a between-group difference in TG of -32 mg/dL favoring pioglitazone, but statistical significance was not reported.[108]

Figure 59. Mean difference in triglycerides comparing pioglitazone with sulfonylureas

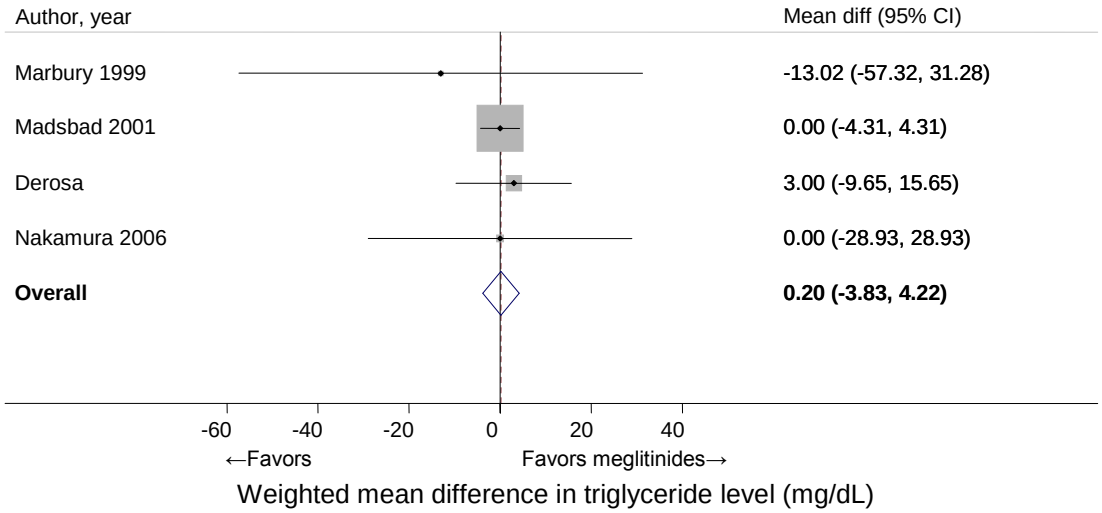


CI = confidence interval; diff = difference; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 57.26 with 5 degrees of freedom (p = 0.0000)
I-squared statistic = 91%
The range in change scores for triglycerides for the comparison group, sulfonylrueas, was -44 mg/dL to 7.3 mg/dL. The median change was -3.6 mg/dL.

Sulfonylureas versus DPP-4 inhibitors. One double-blind moderately sized RCT directly compared four doses of sitagliptin to glipizide upward titrated to 20 mg daily.[111] After 12 weeks, both high dose sitagliptin (100 mg per day) and glipizide (maximum dose of 20 mg a day) increased TG (3.6 percent versus 7.0 percent respectively) with overlapping confidence intervals for the placebo-subtracted change from baseline in each group.[111]

Sulfonylureas versus meglitinides. Four RCTs compared sulfonylureas with a meglitinide and found no difference in TG (pooled between-group difference of 0.2 mg/dL, 95 percent CI -3.8 mg/dL to 4.2 mg/dL) (Figure 60).108,[113,114,117] 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.[116,119]

Figure 60. Mean difference in triglycerides comparing sulfonylureas with meglitinides

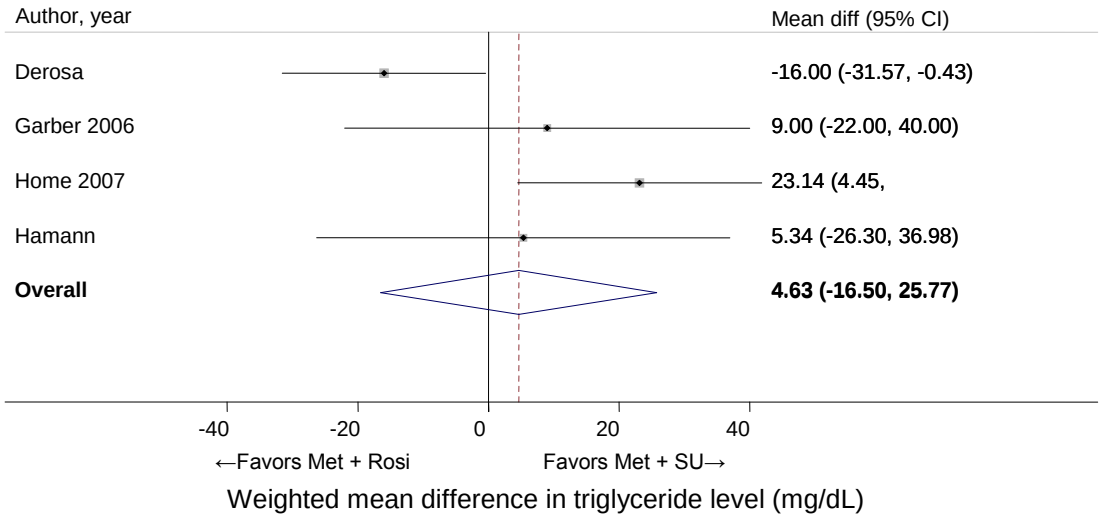


CI = confidence interval; diff = difference; mg/dL = milligrams per deciliter
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence 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 = 0.54 with 3 degrees of freedom (p = 0.91)
I-squared statistic = 0%
The range in change scores for triglycerides for the comparison group, meglitinides, was -18 mg/dL to 6.57 mg/dL. The median change was 1.0 mg/dL.

Sulfonylureas versus GLP-1 agonists. A single RCT compared a sulfonylurea with liraglutide and found a nonsignificant between-group difference in TG: 4.4 mg/dL (95 percent CI -9.7 mg/dL to 8.0 mg/dL).[121] Of note, the dose used in the sulfonylurea arm was low relative to that used in the liraglutide arm.[121]

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 percent CI -16.5 mg/dL to 25.8 mg/dL) (Figure 61).[123,124,128,159] Removal of one study[159] from the meta-analysis led to statistical significance of the between-group difference (16.5 mg/dL, 95 percent 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 metaregression. 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.[124] 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).[16]

Figure 61. Mean difference in triglycerides comparing combination metformin and rosiglitazone with combination metformin and sulfonylureas



CI = confidence interval; diff = difference; Met = metformin; mg/dL = milligrams per deciliter; Rosi = rosiglitazone; SU = sulonylureas
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%
The range in change scores for triglycerides for the comparison group, combination metformin and sulfonylureas, was -41 mg/dL to 13.4 mg/dL. The median change was -5.6 mg/dL.

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.[126,158] In both studies, TG decreased in the metformin and pioglitazone arm. TG decreased in the metformin and sulfonylurea arm in one study[126] and increased slightly in another.[158] 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.[126,158]

Combination of metformin and rosiglitazone versus combination of metformin and DPP-4 inhibitors. 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 percent, 95 percent CI 6.7 percent to 29.2 percent).[85] Another small RCT 16 weeks in duration found that the mean percent decrease in TG from baseline was greater in the metformin plus rosiglitazone arm compared with the metformin plus sitagliptin arm (mean difference in percentage change from baseline of 25.4 percent, significance not reported).[130]

Combination of metformin and rosiglitazone 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).[131]

Combination of metformin and rosiglitazone versus combination of metformin and GLP-1 agonists. A single small RCT 20 weeks in duration compared metformin plus rosiglitazone with metformin plus exenatide and found a between-group mean difference in TG of 36.3 mg/dL (significance not reported).[132]

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.[158]

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.[135,136] One study reported that TG decreased by approximately 10 percent in both groups.[136] The other study reported a decrease in TG in 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 70/30 insulin aspart 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.[138]

Combination of metformin and sulfonylurea versus combination of rosiglitazone and sulfonylureas. One RCT lasting only 12 weeks reported less of a decrease in TG in the metformin plus sulfonylurea compared with the rosiglitazone plus sulfonylurea arm (between-group difference 20.5 mg/dL, p = 0.63).[42] The RECORD trial reported a between-group difference in HDL of -0.4 mg/dL (p > 0.05) at 18 months[124] and -1.6 mg/dL (p < 0.0001) at 5.5 years[16] 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.[141] 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.[158] 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).[140] Another small RCT reported median TG at baseline and 24 weeks and found that median TG increased by 17.7 mg/dL in the metformin plus sulfonylurea arm compared with the pioglitazone and sulfonylurea arm (significance not reported).[160]

Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. A single RCT lasting 26 weeks compared the combination of metformin and sitagliptin with the combination of metformin and one of 2 doses of liraglutide.[143] TG decreased

in all arms. Compared with metformin plus sitagliptin, TG decreased less in the metformin plus 1.2 mg liraglutide arm (between group difference -18.6 mg/dL, 95 percent CI -40.7 mg/dL to 3.5 mg/dL) but decreased more in the metformin plus 1.8 mg liraglutide arm (between-group difference 2.7 mg/dL, 95 percent CI -18.6 mg/dL to 24.8 mg/dL).[143]

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 ($p = 0.02$, number of studies (N) = 6). 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 with larger between-group differences. Including a few larger studies with smaller between-group differences and smaller studies with larger between-group differences may have slightly changed the effect size, but would have been unlikely to change the overall conclusions showing that metformin reduces triglycerides compared with rosiglitazone. The second comparison with significant publication bias was metformin versus metformin plus thiazolidinedione for HbA1c outcome ($p = 0.002$, number of studies (N) = 11). 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 U.S. population with type 2 diabetes. The studies had generally applicable populations, interventions, outcomes, and settings to adults with type 2 diabetes in the United States 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 U.S. population of type 2 diabetes.[161] 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, Hispanics, and Pima Indians).[2,162,163]

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 four 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 United States, they did occur in similar settings. About half the trials occurred partly or exclusively in the United States (n = 32), Italy (n = 13), and/or were multinational (n = 28); the rest of the trials occurred in developed or newly industrialized countries. However, few of the trials (about 10 percent) 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 lower risk of all-cause mortality compared with a sulfonylurea, with low strength of evidence because of moderate risk of bias from primarily observational studies, and inconsistent results when compared to a 4-year RCT.
- We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons; rosiglitazone versus pioglitazone; comparisons involving insulin in combination with an oral agent; and the majority of other combination therapy comparisons, including those using insulin.

Cardiovascular Mortality

- Only one RCT, the RECORD trial, had cardiovascular disease mortality as its primary outcome, and the completeness of its outcome ascertainment has been a source of concern.
- The majority of studied 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, with the majority of studies being observational.
- Risk of cardiovascular mortality was similar between metformin and thiazolidinediones as monotherapy, with low strength of evidence because of high imprecision and moderate risk of bias.
- Metformin alone was slightly favored over a combination of metformin and rosiglitazone for lower risk of fatal myocardial infarction, with consistent direction of results, but high imprecision.
- We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons; rosiglitazone versus pioglitazone; and the majority of combination therapy comparisons, including those using insulin.

Cardiovascular and Cerebrovascular Morbidity

- Only six studies reported any cerebrovascular morbidity outcomes (stroke, transient ischemic attack).
- The majority of these comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few cardiovascular or cerebrovascular events, limiting the precision of results.
- Risk of cardiovascular and cerebrovascular morbidity between metformin and thiazolidinedione as monotherapy was inconclusive, with low strength of evidence because of high imprecision and inconsistency in direction of findings.
- Metformin alone was slightly favored over a combination of metformin and rosiglitazone for lower risk of combined fatal and non-fatal ischemic heart disease, with consistent direction of results but high imprecision, which did not reach the level of statistical significance. The pooled odds ratio (OR) for combined fatal and nonfatal ischemic heart disease events was 0.463, 95 percent CI 0.17 to 1.10.
- We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons; rosiglitazone versus pioglitazone; and the majority of combination therapy comparisons, including those using insulin.

Retinopathy

- We found insufficient evidence for the outcome of retinopathy.

Nephropathy

- For most comparisons addressed in this review, there was insufficient evidence about nephropathy. Where evidence was available, it was mostly of low strength because the

studies were at moderate to high risk for bias, provided imprecise results, or used surrogate outcomes that provided indirect evidence only.
- The only comparison with moderately strong evidence showed that pioglitazone has favorable effects on renal function compared to metformin over a treatment period of 1 year. It is unclear whether the statistically significant reductions in urinary albumin-to-creatinine ratio translate into lower rates of nephropathy.

Neuropathy

- For most comparisons addressed in this review, there was insufficient evidence about neuropathy.
- We found low strength of evidence for three comparisons for the outcome of neuropathy: metformin versus metformin plus a thiazolidinedione; metformin versus metformin plus DPP-4 inhibitors; and metformin plus a thiazolidinedione versus metformin plus a sulfonylurea. Where evidence was available, it was graded as low strength because studies were at high risk for bias, had low sample sizes, and had poorly defined outcomes. As a consequence, we could not draw any conclusions regarding the comparative effects of oral diabetes drugs on neuropathy.

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

Study Design and Population Characteristics

Sixty-six studies (totaling 67 publications) reported on the comparative effectiveness of oral diabetes medications on long-term outcomes (Appendix G, Tables 6 and 7). Twenty-three studies occurred in North America, approximately 16 in Europe, and several were multicontinent studies.

Forty-eight studies were RCTs, with the study duration ranging from 12 weeks to 6 years. Fifteen of the RCTs lasted 1 year or more in duration. Only one RCT had a long-term outcome as the primary outcome;[16] 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. Two studies used a crossover design.[164,165] Thirty-seven RCTs reported support from a pharmaceutical company.

There were 16 cohort studies and 1 case-control cohort study with duration of followup ranging from 6 months to 8 years, which analyzed data from twelve unique cohorts, with four studies coming from the Saskatchewan Health databases[166-169] and three studies coming from the U.K. General Practice Research Database (GPRD).[170-172] Two observational studies reported support from a pharmaceutical company.

The mean age of participants ranged from approximately 48 years to 75 years, with the majority of studies reporting a mean age in the mid-50s. Participants were about 50 percent female and the majority Caucasian. Two RCTs reported greater than 25 percent African American participants;[85,131] two studies reported 70 percent to 80 percent Hispanic participants;[88,130] and four studies were based in Asia.[59,108,121,173] Most trials excluded people with coexisting illness, such as renal, cardiovascular, or liver disease.

Table 5. Strength of evidence and key findings 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	Neither favored; Low	Neither favored; Low	Unclear; Low	Favors Pio*; Mod
SU	Favors Met; Low	Favors Met; Low	Unclear; Low	Unclear*; Low Insufficient†
DPP-4 inhibitor	Unclear; Low	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + TZD	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient* Unclear†; Low
Metformin + SU	Neither favored; Low	Unclear; Low	Favors Met; Low	Insufficient
Metformin + DPP-4 inhibitor	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient* Unclear†; Low
Metformin + meglitinide	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient
TZD versus				
TZD	Insufficient	Insufficient	Unclear; Low	Insufficient
SU	Neither favored; Low	Unclear; Low	Unclear; Low	Unclear*; Low
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Insufficient	Insufficient	Insufficient	Unclear*; Low
GLP-1 agonist	Unclear; Low	Insufficient	Unclear; Low	Insufficient
SU versus				
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor versus				
Meglitinide	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient

Table 5. Strength of evidence and key findings 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
COMBINATION COMPARISONS				
Metformin + another agent versus				
Metformin + TZD	Unclear; Low	Unclear; Low	Unclear; Low	Low. Conclusion unclear for nephropathy and neuropathy.
Metformin + SU	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient
Metformin + meglitinide	Unclear; Low	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Unclear; Low	Unclear; Low	Unclear; Low	Insufficient
Metformin + GLP-1 agonist	Insufficient	Unclear; Low	Insufficient	Insufficient
Metformin + basal insulin	Insufficient	Unclear; Low	Unclear; Low	Insufficient
Metformin + premixed insulin	Unclear; Low	Unclear; Low	Insufficient	Insufficient
TZD + another agent versus				
Metformin + TZD	Insufficient	Insufficient	Unclear; Low	Insufficient
Metformin + SU	Unclear; Low	Insufficient	Unclear; Low	Insufficient
Metformin + meglitinide	Unclear; Low	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Unclear; Low	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Unclear; Low	Insufficient	Unclear; Low	Insufficient

CVD = cardiovascular disease; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; GLP-1 agonist = glucagon-like peptide 1 agonist; Met = metformin; Pio = pioglitazone; 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.

* Key finding for nephropathy.

† Key finding for neuropathy.

The Evidence About All-Cause Mortality (Appendix G, Table 8)

Forty four studies reported the number of deaths by treatment group. Thirty-one studies were RCTs, and 13 studies were observational studies based on data from 7 unique cohorts. Most of the RCTs were of short duration and had no deaths in at least one of the treatment arms. Twenty-nine of the 31 RCTs had support from a pharmaceutical company.

Metformin Versus Thiazolidinediones

Randomized controlled trials. 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, Canada, and Europe, randomized participants to treatments with rosiglitazone, metformin, or glyburide for a median duration of 4 years.[38] There were 1,454 participants in the metformin arm and 1,456 in the rosiglitazone arm, and there was a similar number of deaths in each of these two arms with 31 (2.1 percent) and 34 (2.3 percent) deaths during followup respectively. Another trial comparing metformin and rosiglitazone of 32 weeks duration reported no deaths in either arm.[49] The other two trials compared metformin and pioglitazone.[52,53] 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.[52]

Observational studies. Two cohort studies compared the effects of thiazolidinediones and metformin. One cohort study using data from the U.K. GPRD found no significant difference in all-cause mortality between users of rosiglitazone as monotherapy (n = 8,442) and users of metformin as monotherapy (n = 68,181) with users of rosiglitazone having an adjusted hazard ratio (HR) of 1.07 (95 percent CI 0.77 to 1.49) compared to metformin users over a mean followup period of 7.1 years.[171] Another cohort study used data from the Cleveland Clinic electronic health record system (EHR) on people with newly and previously diagnosed diabetes from 1998 to 2006.[174] It also found no significant difference in all-cause mortality between users of rosiglitazone as monotherapy for their initial treatment of diabetes compared with users of metformin as initial monotherapy (adjusted HR 1.33, 95 percent CI 0.93 to 1.91) or between users of pioglitazone as monotherapy for their initial treatment of diabetes compared to users of metformin as initial monotherapy (adjusted HR 1.08, 95 percent CI 0.78 to 1.51). This study, however, did not describe the followup time of participants, nor did it describe what, how many, or when other medications might have been added on to these initial regimens during the study period.

Metformin versus sulfonylureas. Five RCTs and 11 observational studies, reporting findings from 5 unique cohorts, evaluated the effect of metformin versus a sulfonylurea (Table 6).

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.[38] Three smaller trials were of short duration (16 to 18 weeks) and reported no deaths in either treatment arm.[59,61,62] One 29-week study had a single death in the metformin arm and no deaths in the sulfonylurea arm.[70]

Observational studies. Three observational studies[166,168,169] 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 OR of all-cause mortality of 0.60 (95 percent CI 0.49 to 0.74) for those on metformin compared with sulfonylurea monotherapy, adjusted for age, sex, chronic disease score, and nitrate use.[168] Similar results were found in another study which found that higher doses of sulfonylurea were associated with even higher risk of death.[166]

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

Author, year	Number of deaths: metformin versus sulfonylurea	Measure of association	Estimate of the measure of association (95% CI) (sulfonylurea as reference group)
Randomized controlled trials			
Chien, 2007[59]	0/17 versus 0/17	NR	NR
Kahn, 2006[38]	31/1454 versus 31/1441	NR	NR
Garber, 2003[61]	0/164 versus 0/151	NR	NR
Goldstein, 2003[62]	0/76 versus 0/84	NR	NR
DeFronzo, 1995[70]	1/210 versus 0/209	NR	NR
Cohort studies			
Kahler, 2007[175]	82/2988 versus 1005/19053	Adjusted OR	0.87 (0.68 to 1.10)
Simpson, 2006[166]	39.6/1000 person-years versus 61.4/1000 person-years	Unadjusted OR*	0.55 (0.47 to 0.63)
Johnson, 2002[168]	159/1150 versus 750/3033	Adjusted OR	0.60 (0.49 to 0.74)
Eurich, 2005[169]	69/208 versus 404/773	Adjusted HR	0.70 (0.54 to 0.91)
Evans, 2006[176]	4.7% versus 17.9%	NR	NR
Gulliford, 2004[170]	144/2232 versus 1030/6620	Unadjusted OR*	0.35 (0.29 to 0.42)
Fisman, 2001[177]	25/79 versus 324/953	Unadjusted OR*	0.90 (0.56 to 1.47)
Fisman, 1999[178]	20/78 versus 234/1041	NR	NR
Tzoulaki, 2009[171]	NR	Adjusted HR*	0.81 (0.74 to 0.88)
Pantalone, 2008[174]	NR	Adjusted HR	0.54 (0.46 to 0.64)

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

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.[169] This study reported a higher number of deaths among those on a sulfonylurea alone. The sulfonylurea group had 404 deaths out of 773 people (52 percent) compared with 69 deaths out of 208 people in the metformin group (33 percent). Adjusted multivariate analyses confirmed these findings, with a lower HR of death among those on metformin of 0.70 (95 percent CI 0.54 to 0.91) compared with those on sulfonylurea monotherapy, after adjusting for age, sex, chronic disease score, medications, and number of physician visits before diagnosis of heart failure.

A cohort study that followed people receiving care through the U.K. 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 percent CI 1.15 to 1.77).[176]

Three observational studies[170-172] reported all-cause mortality from the cohort based on the UK GPRD, which maintains de-identified health records of about 5 million people, and compared metformin versus a sulfonylurea as monotherapy. One of these studies, with patient data from 1992 to 1998 and with a mean duration of followup of 1.7 to 3.5 years, described a higher rate of death among users of sulfonylurea alone compared with metformin. The crude mortality rate was 58.6 per 1000 person-years in the sulfonylurea group compared with a crude

mortality rate of 25.5 per 1000 person-years in the metformin group, with an unadjusted OR of 0.35 (95 percent CI 0.29 to 0.42) among those on metformin compared to sulfonylurea.[170] A study using the same database but extending the "enrollment period" from 1990 to 2005 with a longer mean followup period of 7.1 years per person also found a significantly lower risk of mortality in those using metformin as monotherapy compared to sulfonylureas with an adjusted HR of 0.81 (95 percent CI 0.74 to 0.88).[171] A nested case-control study using this data drew the same conclusions and found that, over a median followup period of 3.5 years, those on metformin monotherapy had an adjusted relative risk (RR) of death from any cause of 0.70 (95 percent CI 0.64 to 0.75) compared with users of sulfonylurea monotherapy. This lower risk of death persisted among metformin users regardless of the duration of metformin use, which was categorized as less than 4 months, 4 to 8 months, or at least 8 months.[172]

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.[177]

A large cohort, the Veterans' Health Administrations' Diabetes Epidemiology Cohort, includes all veterans with diabetes who have received care at the Department of Veterans Affairs (VA) centers since October 1996. In that cohort, analysis showed a higher number of deaths among subjects taking sulfonylureas (1,005 deaths of 19,053 people [5.3 percent]) compared with subjects taking metformin only (82 deaths out of 2,988 people (2.7 percent)).[175] The adjusted OR for death for metformin versus sulfonylurea was 0.87 (95 percent CI 0.68 to 1.10), after adjusting for propensity score plus age, diabetes duration, HbA1c, serum creatinine, number of physician visits related to diabetes, and use of medications for dyslipidemia and hypertension.[175]

Finally, the cohort study based on data from the Cleveland Clinic EHR found a lower risk of all-cause mortality among users of metformin as initial monotherapy compared with users of sulfonylureas, with an adjusted HR of 0.54 (95 percent CI 0.46 to 0.64); however, limitations of this study include its lack of description of followup time and lack of description or adjustment for addition of other diabetes medications during the study period.[174]

Metformin versus meglitinides. Only one 24-week trial assessed the mortality of participants on metformin compared to a meglitinide and reported one death in the metformin arm and no deaths in the nateglinide arm.[79]

Metformin versus DPP-4 inhibitors. Two short-term RCTs compared the effects of metformin as monotherapy compared to sitagliptin as monotherapy and reported deaths during the study period. One multinational trial over 24 weeks, with 328 participants on metformin monotherapy and 335 participants on sitagliptin monotherapy, reported 3 deaths in the metformin arm and no deaths in the sitagliptin arm.[78] The second trial, also multinational and lasting 24 weeks, with 439 participants on metformin monotherapy and 455 participants on sitagliptin monotherapy, reported 1 death in the sitagliptin arm due to metastatic lung cancer, thought not to be related to the study medication.[77]

Metformin versus a combination of metformin and thiazolidinediones. Four RCTs of relatively short duration, ranging from 24 to 32 weeks, and one 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.[49] For three other

RCTs, each reported one death in the combination therapy arm and no deaths in the metformin monotherapy arm.[86,87,90] 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.[179]

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.

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[59]	0/14 versus 0/42	NR	NR
Garber, 2003[61]	0/164 versus 2/171	NR	NR
Goldstein, 2003[62]	0/76 versus 0/87	NR	NR
DeFronzo, 1995[70]	1/210 versus 0/213	NR	NR
Cohort studies			
Kahler, 2007[175]	82/2988 versus 468/13820	Unadjusted OR*	0.81 (0.63 to 1.02)
Gulliford, 2004[170]	144/3099 versus 159/2735	Unadjusted OR*	0.79 (0.63 to 1.00)
Johnson, 2002[168]	159/1150 versus 635/4683	NR	NR
Eurich, 2005[169]	69/208 versus 263/852	NR	NR
Fisman, 2001[177]	25/79 versus 111/253	Unadjusted OR*	0.59 (0.35 to 1.01)
Fisman, 1999[178]	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

Randomized controlled trials. 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[59,62] and one study reported two deaths in the combination arm and no deaths in the metformin monotherapy arm.[61] Another study reported one death in the metformin as monotherapy arm and no deaths in the combination therapy arm.[70]

Observational studies. 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 percent of those in the combination treatment arm died compared to 2.7 percent in the metformin treatment arm, with an unadjusted OR of death of metformin compared to combination therapy of 0.81 (95 percent CI 0.63 to 1.02).[175] In the U.K. GPRD cohort, which followed people for about 6 years, 5.8 percent 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 percent in the metformin monotherapy group, with an unadjusted OR of mortality of 0.79 (95 percent CI 0.63 to 1.00) for those on metformin alone compared to those on combination therapy.[170]

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 percent versus 13.6 percent, respectively).[168] Even among the subgroup of people with heart failure, there was a similar rate of death between these two treatment groups, 33 percent for those on metformin alone and 31 percent for those on the metformin plus sulfonylurea combination therapy.[169]

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 percent for those on combination therapy compared to a mortality rate of 31.6 percent for those on metformin alone, with an unadjusted OR of 0.59 (95 percent CI 0.35 to 1.01) of mortality for those in metformin compared to combination therapy, over a mean period of 7.7 years.[177]

Metformin versus a combination of metformin and DPP-4 inhibitors. Three RCTs looked at the effect of metformin as monotherapy versus metformin combined with sitagliptin. One was a multinational study of 190 participants over approximately 30 weeks. In this study, there was one death due to a myocardial infarction in the metformin group and no deaths in the combination treatment group.[93] The second was a 24-week multinational RCT which reported three deaths in the metformin monotherapy arm (n = 328) and no deaths in the combination treatment groups (n = 643).[78] The third was a 54-week multinational trial of 1,091 patients, which reported one death in each arm.[76]

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.[79]

Rosiglitazone versus pioglitazone. One cohort study used the Cleveland Clinic EHR to compare the effects of rosiglitazone and pioglitazone on all-cause mortality. This cohort of people with newly and previously diagnosed diabetes from 1998 to 2006 found that those on initial pioglitazone monotherapy had no significant difference in risk of death compared with those on initial rosiglitazone monotherapy, with an adjusted HR of 0.81 (95 percent CI 0.52 to 1.27). This study, however, did not describe the followup time of participants, nor did it describe what, how many, or when other medications might have been added on to these initial regimens.[174]

Thiazolidinediones versus sulfonylureas. Three RCTs and one cohort study compared the effect of a thiazolidinedione and a sulfonylurea.

Randomized clinical trials. The largest and longest duration of these trials was the ADOPT trial, which reported a similar number of deaths in the rosiglitazone arm compared with the glyburide arm (2.3 percent versus 2.2 percent, respectively).[38] A smaller trial lasting 56 weeks reported two deaths in the glyburide arm and no deaths in the pioglitazone arm.[101] Another trial reported no deaths in either the thiazolidinedione or sulfonylurea arms.[100]

Observational study. The cohort from the Cleveland Clinic EHR compared risk of all-cause mortality between initial users of pioglitazone monotherapy versus initial users of sulfonylurea monotherapy as well as between users of rosiglitazone monotherapy versus initial users of sulfonylurea monotherapy. This study found that those in the pioglitazone group had a significantly lower risk of death compared with the sulfonylurea group, with an adjusted HR of 0.59 (95 percent CI 0.43 to 0.81). Those in the rosiglitazone did not have a statistically significant difference in risk of death compared with those in the sulfonylurea group, with an adjusted HR of 0.73 (95 percent CI 0.51 to 1.02). Again, followup time was not specified, and participants could have changed medication regimens during the study period.[174]

Sulfonylureas versus meglitinides. One RCT compared the effects of a sulfonylurea with a meglitinide. This 1-year U.S. study reported three deaths among the 362 participants randomized to the repaglinide group and one death among the 182 randomized to glyburide.[117]

Sulfonylureas versus GLP-1 agonists. One 24-week RCT from Japan compared the effects of use of glibenclamide and liraglutide as monotherapy and reported on deaths. This short-term study reported one death in the liraglutide arm due to gastroenteritis, which required hospitalization and subsequent cardio-respiratory arrest, and no deaths in the sulfonylurea arm.[121]

Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas. Two RCTs[123,125] 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.[123] 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.[125]

Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides. One U.S. 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.[131]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. One multinational RCT compared the effect of the combination of metformin plus a sulfonylurea (glipizide) with the combination of metformin plus sitagliptin. This study randomized 1,172 participants to the 2 treatment arms. At 52 weeks, they reported two deaths in the metformin plus sulfonylurea combination arm and one death in the metformin plus sitagliptin combination arm.[133] At 2 years of followup, they had 519 participants and reported 8 deaths in the metformin plus sulfonylurea arm due to various causes including sudden cardiac death, myocardial infarction, cancer, sepsis, and suicide, and still only one death in the metformin plus sitagliptin arm, which was due to trauma.[134]

Combination of metformin and sulfonylureas versus combination of metformin and meglitinides. Two U.S. RCTs[136,152] and one Italian cohort study[180] 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.[136] 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.[152]

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 6,344 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 2,013 person-months.[180]

Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones. One large multinational RCT, the 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 2,220 in the rosiglitazone group and 157 deaths out of 2,227 in the metformin plus sulfonylurea combination group with an HR of mortality of 0.86 (95 percent CI 0.68 to 1.08) for those on rosiglitazone compared to those not on rosiglitazone.[16]

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.[137,138]

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.[140]

The Evidence About Cardiovascular Mortality (Appendix G, Table 8)

Twelve trials and 4 cohort studies contained 14 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 percent).[38] A smaller 24-week RCT of metformin versus pioglitazone did not report any cardiovascular deaths in either arm.[53]

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 percent versus 0.1 percent), without report of a statistical test.[38]

In addition, four cohort studies compared metformin with a second-generation sulfonylurea.[167,168,176,177] Two of these studies were from the Saskatchewan Health databases, a longitudinal cohort of the residents of this Canadian province. They identified more than 4,000 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 percent CI 0.49 to 0.84), after adjusting for age, sex, chronic disease score, and nitrate use.[168] 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 percent CI 0.58 to 1.00).[167] 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 percent CI 1.18 to 2.45).[176]

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 1,000 person-years versus 24.5 per 1,000 person-years, respectively).[177]

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.[79]

Metformin versus a combination of metformin and thiazolidinediones. Two large RCTs[87,90] and one study that reported the combined results of two smaller RCTs[179] 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.[87] 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.[90] 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.[179] We pooled these three RCTs with four RCTs reporting nonfatal ischemic heart disease events (Figure 62).

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.[176,177]

Compared with those on metformin monotherapy, one cohort study reported a risk ratio of 1.94 (95 percent CI 1.25 to 3.01) in subjects who were started on metformin, with sulfonylurea subsequently added-on and 2.50 (95 percent CI 1.69 to 3.71) in those started on sulfonylurea with metformin subsequently added-on, but the numbers in these groups were small.[176] 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 1,000 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.[177]

Metformin versus a combination of metformin and DPP-4 inhibitors. We identified two RCTs. One was a 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.[93] The second RCT was a multinational trial with 1,091 participants, and reported one sudden cardiovascular death in the metformin arm in the first 24-weeks of the trial, which was prior to starting metformin treatment, and no cardiovascular deaths in the combination arm.[76]

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.[79] In all arms, there was a single death attributed to cardiovascular disease and it occurred in the metformin alone arm.

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.[38]

Sulfonylureas versus meglitinides. A 1-year RCT with 576 participants reported one cardiovascular death in the glyburide arm and one in the repaglinide arm.[117]

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.[131]

Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones. The RECORD study was an open-label noninferiority 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.[16] 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 percent CI 0.59 to 1.18).

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. One RCT reported in two articles, providing 52-week[133] and 2-year data,[134] compared metformin plus the sulfonylurea, glipizide, versus metformin plus sitagliptin. After 52 weeks, 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.[133] No additional cardiovascular mortality was reported during the second year of the trial.[134]

Combination of metformin and DPP-4 inhibitors versus combination of metformin plus GLP-1 agonists. One 26-week open-label RCT randomized 665 patients with poorly controlled diabetes on metformin alone to the addition of oral sitagliptin (100 mg), or one of two doses of daily subcutaneous injections of liraglutide (1.2 mg or 1.8 mg). It reported one fatal cardiac arrest in the metformin plus sitagliptin arm and none in the metformin plus liraglutide arms.[143]

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 percent soluble, rapid-acting insulin aspart and 70 percent intermediate-acting protamine-bound aspart in each injection.[138] There was one death from myocardial infarction in the metformin plus premixed insulin arm and none in the metformin plus glibenclamide arm.

Combination of metformin and basal insulin versus combination of metformin and premixed insulin. A 32-week open-label crossover study randomized 97 patients to metformin plus insulin glargine versus metformin plus insulin lispro 75/25 twice daily. It reported one fatal myocardial infarction in the metformin plus insulin lispro arm and no such events in the metformin plus glargine arm.[165]

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

Seventeen trials and seven cohort studies contained eighteen head-to-head comparisons of interest for the outcome of cardiovascular disease morbidity. We identified six studies that reported one of the cerebrovascular disease morbidity outcomes.

Metformin versus thiazolidinediones. Three RCTs[38,49,55] and five retrospective cohort studies[171,173,174,181,182] compared metformin versus rosiglitazone. One small 24-week RCT[53] and four cohort studies[171,173,174,182] compared metformin versus pioglitazone.

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). The study reported minimal differences between the metformin and rosiglitazone arms for nonfatal myocardial infarction and stroke (1.4 percent versus 1.7 percent for nonfatal myocardial infarction, 1.3 percent versus 1.1 percent for stroke, respectively), without a statistical test.[38] The other smaller RCTs did not show any difference in event rates.[49,55] Among the cohort studies, three reported no increased risk of ischemic heart disease for rosiglitazone compared with metformin.[171,174,181]

Two cohort studies comparing metformin with rosiglitazone showed increased risk of cardiovascular disease associated with rosiglitazone.[173,182] A 6-year retrospective cohort study of newly diagnosed patients with diabetes used Taiwan's National Health Insurance, and reported higher risk for myocardial infarction (HR 2.09, 95 percent CI 1.36 to 3.24), angina pectoris (adjusted HR 1.79, 95 percent CI 1.39 to 2.30), and transient ischemic attack (adjusted HR 2.57, 95 percent CI 1.33 to 4.96), but not stroke (adjusted HR 1.61, 95 percent CI 0.72 to 3.62) for rosiglitazone compared with metformin. A higher proportion of patients prescribed thiazolidinediones as monotherapy had previous cardiovascular disease compared with the metformin group.[173]

One 24-week RCT of 60 patients compared metformin with pioglitazone in two of three of its arms and reported no cardiovascular events in either group.[53] Four cohort studies comparing metformin and pioglitazone[171,173,174,182] showed no significant difference in cardiovascular disease risk between groups.

Metformin versus sulfonylureas. Two RCTs[38,68] and five cohort studies[167,171,173,174,181] reported outcomes for metformin versus a second-generation sulfonylurea

The ADOPT trial, described above, also contained a glyburide arm. Incidences of nonfatal myocardial infarction and stroke in the glyburide arm were 1.0 percent and 1.2 percent, respectively, showing minimal difference compared with the metformin arm (1.4 percent and 1.3 percent, respectively), without a statistical test.[38] Two large cohort studies did not show significant differences in cardiovascular events.[171,174] Tzoulaki et al. reported the results of a large cohort study of 91,521 people with diabetes in the United Kingdom general practice research database and described no increase in the risk of incident myocardial infarction in its fully adjusted model for users of second-generation sulfonylureas compared with metformin users (adjusted HR 1.09, 95 percent CI 0.94 to 1.27).[171]

Conversely, two cohort studies described higher risk of cardiovascular disease morbidity for a sulfonylurea versus metformin.[167,181] In the retrospective cohort study from Saskatchewan health databases, metformin was associated with a decreased risk of nonfatal cardiovascular hospitalization as compared with unspecified sulfonylurea (HR 0.78, 95 percent CI 0.63 to 0.97) in the fully adjusted model.[167] McAfee et al. reported a 23 percent risk reduction of the composite outcome of acute myocardial infarction or coronary revascularization for metformin as compared with sulfonylurea monotherapy (HR 0.77, 95 percent CI 0.62 to 0.96), in a propensity score matched cohort study.[181] Hsaio et al. only reported crude cardiovascular event rates for this comparison.[173]

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.[79]

Metformin versus a combination of metformin and thiazolidinediones. Six RCTs[49 85-88 156] and two cohort studies[173,181] compared metformin with a combination of metformin plus rosiglitazone and reported the incidence of ischemic cardiac events. One of the cohorts also reported metformin versus metformin plus pioglitazone.[173] 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.[85] The five RCTs that had at least one event in were pooled with the three RCTs reporting nonfatal ischemic heart disease events (totaling seven studies because one study contributed one fatal and one nonfatal event) in a meta-analysis.[49,86-88,90,156,179] In a fixed effects model using treatment arm continuity correction for arms with zero events, the pooled odds ratio of ischemic heart disease events was 0.43 (95 percent CI 0.17 to 1.10) for metformin compared with metformin plus thiazolidinedione, which was not statistically significant (Figure 62). Neither Begg's nor Egger's tests for publication bias were statistically significant, and the funnel plot for these seven studies was fairly symmetrical, indicating a low likelihood of publication bias.

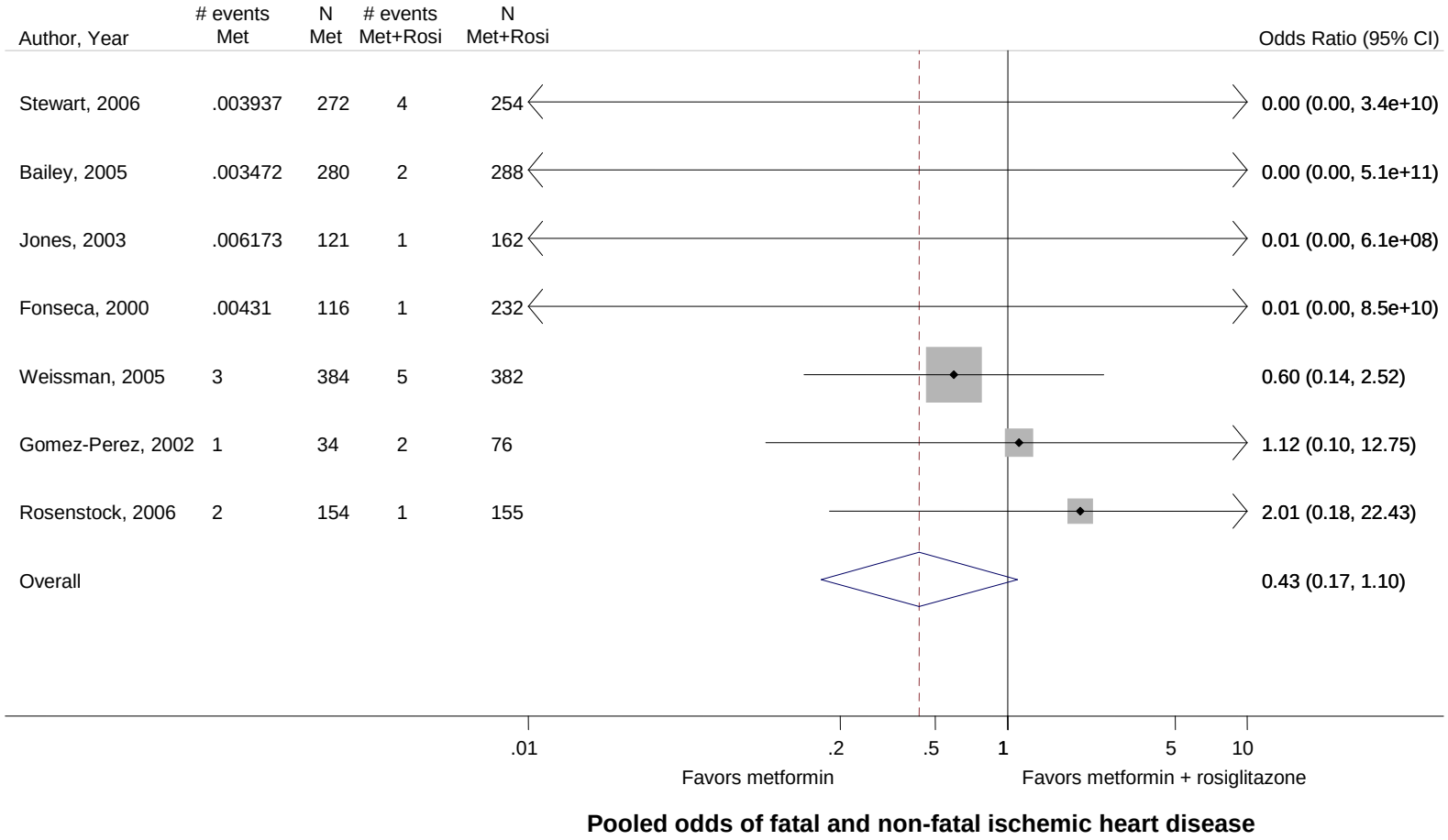
McAfee et al., a large retrospective cohort study, showed minimal difference in incidence rate ratios (IRR) for the composite outcome of hospitalization for myocardial infarction or coronary revascularization between subjects treated with metformin (IRR 13.90, 95 percent CI 11.80 to 16.27) compared with metformin plus rosiglitazone (IRR 14.26, 95 percent CI 9.37 to 20.86).[181] Hsaio et al. only reported crude cardiovascular event rates for this comparison.[173]

Metformin versus a combination of metformin and sulfonylureas. One RCT[68] and one cohort study[181] assessed this comparison for cardiovascular morbidity. In a 6-month RCT, Hermann et al. reported a 5 percent versus 14 percent rate of unspecified cardiovascular adverse events in the metformin versus combination metformin plus sulfonylurea arms, respectively.[68] 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 started on metformin compared with metformin plus sulfonylurea (adjusted incidence rate of 13.90 versus 19.44, respectively per 1,000 person-years).[181] Hsaio et al. did not report adjusted analyses for this comparison.[173]

Metformin versus a combination of metformin and DPP-4 inhibitors. One 30-week RCT in 190 participants reported three cases (3.1 percent) of angina pectoris in the metformin plus sitagliptin arm and none in the metformin alone arm.[93] A shorter 18-week study also reported two coronary artery disease events in the metformin plus sitagliptin arm and none in the metformin alone arm.[85]

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.[79]

Figure 62. Pooled odds ratio of fatal and nonfatal ischemic heart disease comparing metformin with combination of metformin and rosiglitazone



CI = confidence interval; Met = metformin; Rosi = 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.
Test for heterogeneity: Q = 2.80 with 6 degrees of freedom (p = 0.83)
I-squared statistic = 0%

Rosiglitazone versus pioglitazone. No RCTs directly compared rosiglitazone with pioglitazone for cardiovascular outcomes, but we identified three cohort studies that included this comparison.[171,173,174] Tzoulaki et al. (described under the rosiglitazone versus sulfonylurea comparison) and Pantalone et al. did not show any significant risk difference for ischemic heart disease in rosiglitazone versus pioglitazone users.[171,174] Hsaio et al. reported a higher incidence of composite cardiovascular events (which included angina pectoris and myocardial infarction) in rosiglitazone versus pioglitazone users, but no adjusted statistical analyses was presented and there was evidence of differences in previous cardiovascular disease rates between the two groups.[173]

Thiazolidinediones versus sulfonylureas. Two RCTs[38,149] and three retrospective cohort studies[173,181,182] compared rosiglitazone with a sulfonylurea. One RCT[101] and two cohort studies[173,174] compared pioglitazone with a sulfonylurea. The ADOPT trial (described in detail under metformin versus thiazolidinedione) reported minimal differences between the rosiglitazone arms and sulfonylurea arms for non-fatal myocardial infarction and stroke (1.7 percent versus 1.0 percent for non-fatal myocardial infarction, 1.3 percent versus 1.2 percent for stroke, respectively).[38] A 52-week RCT with 351 participants reported a higher incidence of "cardiac-related" adverse events in the rosiglitazone versus glyburide groups (15.4 percent versus 12.1 percent, respectively). These events included mitral insufficiency, tachycardia, myocardial infarction, and palpitations.[149]

Results from the three cohort studies comparing rosiglitazone with second-generation sulfonylureas were not consistent. One 36-month retrospective cohort study reported a lower adjusted incidence rate for the composite outcome of hospitalization for myocardial infarction or coronary revascularization for rosiglitazone compared with sulfonylureas (adjusted incidence rate of 15.71 versus 19.55 per 1,000 person-years).[181] Another cohort study showed no significant differences in risk for myocardial infarction or stroke, but elevated risk for transient ischemic attack (adjusted HR 1.90, 95 percent CI 1.02 to 3.57) and angina pectoris (adjusted HR 1.45, 95 percent CI 1.15 to 1.85) for rosiglitazone versus sulfonylurea.[173] Brownstein et al. reported an elevated adjusted risk for myocardial infarction for rosiglitazone compared with a sulfonylurea (RR 1.4, 95 percent CI 1.0 to 2.0).

A 56-week RCT with 502 participants randomly assigned participants to glyburide or pioglitazone. It reported fewer cardiovascular adverse events, defined as coronary artery disease, myocardial infarction, and chest pain, in the pioglitazone arm compared with the glyburide arm (1 percent versus 3 percent).[101] One cohort study reported no significant difference in coronary artery disease between pioglitazone and sulfonylurea users.[174]

Sulfonylureas versus meglitinides. Two 1-year RCTs compared glyburide with repaglinide.[116,117] One RCT with over 500 participants reported 5 percent cardiovascular adverse events in the repaglinide arm and 2 percent in the glyburide arm without a statistical test.[117] The other RCT had 242 participants and stated that cardiac events occurred with similar frequencies between treatment arms.[116]

Sulfonylureas versus GLP-1 agonists. One 24-week double-blind RCT of 411 patients randomized to oral glibenclamide versus once-daily subcutaneous liraglutide reported one acute myocardial infarction in the liraglutide arm and none in the glibenclamide arm.[121]

Combination of metformin and rosiglitazone versus combination of metformin and pioglitazone. One cohort study reported a higher risk of myocardial infarction for metformin plus pioglitazone compared with metformin plus rosiglitazone (HR 6.34, 95 percent CI 1.80 to 22.31), although the estimated precision was very low, with a wide confidence interval. There was no difference in risk of stroke, angina pectoris, and transient ischemic attack for this same comparison.[173]

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.[129]

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.[131]

Combination of metformin and thiazolidinediones versus combination of metformin and DPP-4 inhibitors. 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.[85]

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 nonfatal myocardial infarctions were combined and showed no difference between the two combined rosiglitazone arms and metformin plus sulfonylurea arm (HR 1.14, 95 percent CI 0.80 to 1.63). Fatal and nonfatal stroke were also combined and showed no difference between the two combined rosiglitazone arms and metformin plus sulfonylurea (HR 0.72, 95 percent CI 0.49 to 1.06).[16]

Combination of metformin and thiazolidinediones versus combination of metformin and DPP-4 inhibitors. One 16-week open-label trial randomized 169 patients with inadequate glycemic control on metformin alone to rosiglitazone versus sitagliptin and reported one transient ischemic attack each in the rosiglitazone and sitagliptin arms.[130]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. In a 52-week trial with 1,172 participants, there was one myocardial infarction in the metformin plus glipizide arm compared with none in the metformin plus sitagliptin arm.[133] There were no additional events reported at 2 years of followup.[134]

Combination of metformin and DPP-4 inhibitors versus combination of metformin plus GLP-1 agonists. One 26-week open-label RCT randomized 665 patients on metformin alone to the addition of oral sitagliptin (100 mg), or one of two doses of daily subcutaneous injections of

liraglutide (1.2 mg or 1.8 mg). It reported the occurrence of "cardiac disorders" in one patient on metformin plus 1.8 mg liraglutide and in one patient on metformin plus sitagliptin.[143]

Combination of metformin and 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 glargine versus metformin plus insulin lispro 75/25 twice daily.[164] In addition, there was an 8-week lead-in period when patients received neutral protamine Hagedorn 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.[164]

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 percent versus 0.11 percent for myocardial infarction and 0.01 percent versus 0.18 percent for stroke, respectively).[183]

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.[16]

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 percent versus 3.1 percent respectively) but no statistical test results were provided.[140]

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 nine trials reporting on nephropathy as an outcome.[52,66,102-104,108,125,140,184] 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 = 1,176[52] and n = 639[140]) 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 percent[140] and 19 percent,[52] 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).[66] 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. Five small trials compared a thiazolidinedione (pioglitazone or rosiglitazone) with a sulfonylurea.[102-104,108,184] One trial found significantly less albuminuria in patients receiving pioglitazone compared with glibenclamide.[102] Two other trials also reported reductions in albuminuria with pioglitazone but the differences compared with patients receiving a sulfonylurea were either not significant[184] or not reported.[103] Another small trial included patients with longstanding diabetes and microalbuminuria and reported reduced urinary albumin excretion with pioglitazone compared to glibenclamide, but no formal statistical comparisons between groups were shown.[108]

One trial compared 12-month treatment with rosiglitazone and glyburide[104] 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.

Thiazolidinediones versus meglitinides. One small trial of patients with longstanding diabetes and microalbuminuria compared pioglitazone and nateglinide and reported reduced urinary albumin excretion with pioglitazone as compared with nateglinide. No formal statistical comparisons between groups were shown.[108]

Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas. One trial[125] 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.[88,93,129] In all three studies, neuropathy was reported under adverse effects.

Metformin versus a combination of metformin and thiazolidinediones. One trial[88] 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 DPP-4 inhibitors. The other trial[93] reported on the incidence of (undefined) diabetic neuropathy with metformin alone (n = 2, 2.1 percent) and metformin plus sitagliptin (n = 4, 4.2 percent) but did not provide a statistical comparison.

Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas. In a 6-month trial[129] neuropathy was not a prespecified 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.

Summary of Results of Updated Search Through December 2010 for Long-Term Clinical Outcomes

We screened 805 records and identified 4 articles that addressed Key Question 2's long term clinical outcomes (Appendix H). Two were RCT's;[185,186] one[185] trial was a 50-week extension of a previously included 54-week study.[76] The other two articles were observational studies.[187,188] Results of these four studies were consistent with our review's findings and did not change the conclusions or strength of evidence grades.

Gray Literature

We found eight unpublished reports from clinicaltrials.gov and the Food and Drug Administration (FDA) Web site 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 2,902 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.[189] 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.[190] 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.[189] 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.[189]

Metformin versus DPP-4 inhibitors. 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.[191]

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.[192]

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.[193]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. 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.[191]

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 U.S. Among the RCTs, the two with the longest study duration were 6 years[38] and 7.5 years,[16] 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 most patients with diabetes are cared for by primary care physicians. In the 29 trials identified since the 2007 report, four reported recruitment from outpatient primary care settings.[16,78,131,184] Six studies reported excluding greater than 10 percent of participants following a run-in period, which may limit their generalizability to outpatient settings with varying degrees of medication adherence.[49,123,125,133,156,164]

Overall, participants were middle-aged, which is fairly representative of the U.S. population with type 2 diabetes, but most studies excluded people greater than age 74. Participants were about 50 percent female and the majority was identified as Caucasian. Notably, two RCTs reported greater than 25 percent African American participants,[85,131] although many studies did not report any racial-ethnic breakdown of the participants. Two RCTs took place in Mexico,[66,88] and one in both Mexico and Colombia,[130] with 70 percent to 80 percent Hispanic participants.[88] Most trials had similar exclusion criteria for coexisting illnesses, such as renal, cardiovascular, and hepatic disease, with the implication that participants were overall less complicated, and thus at lower risk for long-term complications of diabetes.

A majority of studies were conducted in the United States or multinational Europe, where the practice of medicine related to the treatment of diabetes is fairly similar. Most studies received pharmaceutical company 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 OR for mild to moderate hypoglycemic events of 4.6 (95 percent CI 3.2 to 6.5) 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 OR of 3.9, 95 percent CI 3.0 to 4.9 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 six times as high as 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 DPP-4 inhibitors.
- Moderate grade evidence showed a modest increase (OR 3.0, 95 percent CI 1.8 to 5.2) 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 (OR 1.6, 95 percent CI 1.0 to 2.4).
- Moderate grade evidence showed that metformin with aDPP-4 inhibitor has similar risk of hypoglycemia as metformin alone.
- Moderate grade evidence showed that metformin with a sulfonylurea has a higher risk of hypoglycemia than metformin with liraglutide.
- Moderate grade evidence showed a modestly lower risk of hypoglycemia when metformin is combined with a basal insulin rather than a premixed insulin.
- The evidence about hypoglycemia for the other comparisons had low strength or was insufficient.
- No monotherapy or combination therapy convincingly demonstrated more occurrences of severe hypoglycemia than another.

Liver Injury

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

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 DPP-4 inhibitors and GLP-1 agonists 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

- High grade evidence showed that metformin was associated with more frequent GI adverse events compared with thiazolidinediones.
- High strength of evidence demonstrated that the rates of GI adverse effects were similar between thiazolidinediones and sulfonylureas.
- Moderate strength of evidence showed that metformin was associated with more frequent GI adverse events compared with second-generation sulfonylureas.
- Moderate strength of evidence showed 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.
- Moderate strength of evidence suggested 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.
- Moderate strength of evidence showed that metformin was associated with more frequent GI adverse events compared with DPP-4 inhibitors.

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

Study Design and Population Characteristics

One hundred thirteen studies are included for Key Question 3 describing adverse effects during treatment (Appendix G, Tables 10 and 11). We included 38 articles from the Comparative Effectiveness Review (CER) published in 2007 that described adverse events for our comparisons of interest and identified an additional 74 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.

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

Comparison	Hypoglycemia	Liver Injury	GI adverse events	CHF	Macular edema	Pancreatitis and cholecystitis	Fractures
MONOTHERAPY COMPARISONS							
Metformin versus							
TZD	Neither favored; Mod	Neither favored; Mod	Favors TZD; High	Neither favored; Mod	Insufficient	Favors Met*; Low Insufficient†	Favors Met; High
SU	Favored Met; High	Unclear; Low	Favors SU; Mod	Favors Met; Mod	Insufficient	Insufficient	Unclear; Low
DPP-4 inhibitor	Neither favored; High	Insufficient	Favors DPP-4; Mod	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Favors Met; Mod	Insufficient	Favors Meg‡; Low	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + TZD	Favors Met; Mod	Insufficient	Favors Met+TZD‡; Mod	Insufficient	Insufficient	Favors Met+TZD*; Low Insufficient†	Favors Met; Low
Metformin + SU	Favors Met; Mod	Insufficient	Favors Met+SU§; Mod	Insufficient	Insufficient	Insufficient* Favors Met†; Low	Unclear; Low
Metformin + DPP-4 inhibitor	Neither favored; Mod	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Unclear; Low
Metformin + meglitinides	Favors Met; Low	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Insufficient
TZD versus							
TZD	Favors Rosi; Low	Unclear; Low	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient
SU	Favors TZD; High	Neither favored; High	Neither favored; High	Favors SU; Mod	Insufficient	Neither favored*; Low Insufficient†	Favors SU; High
DPP-4 inhibitors	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Favors TZD; Low	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
SU versus							
DPP-4 inhibitors	Favors DPP4; Mod	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Favors Meg; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Favors GLP1; High	Insufficient	Favors SU; Low	Insufficient	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor versus							
Meglitinides	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient* Neither favored†; Low	Insufficient

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

Comparison	Hypoglycemia	Liver Injury	GI adverse events	CHF	Macular edema	Pancreatitis and cholecystitis	Fractures
COMBINATION COMPARISONS							
Metformin + another agent versus							
Metformin + TZD	Favors Met+TZD; High	Neither favored; Low	Neither favored; Low	Insufficient	Favors Met+ other; Low	Insufficient	Favors Met+ other; High
Metformin + SU	Unclear; Low	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + meglitinides	Insufficient	Insufficient	Favors Met+SU¶; Low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + DPP-4	Insufficient	Insufficient	Neither favored; Low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1	Insufficient	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Favors Met+Basal Insulin; Mod	Insufficient	Unclear; Low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
TZD + another agent versus							
Metformin + TZD	Favors Met+TZD; Low	Insufficient	Insufficient	Favors Met+ TZD; Low	Insufficient	Insufficient	Insufficient
Metformin + SU	Favors TZD+SU; Low	Neither favored; Low	Favors TZD combination; Mod	Favors Met+SU; Low	Insufficient	Insufficient	Favors Met+SU; High
Metformin + meglitinides	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + DPP-4	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Insufficient	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.

‡ For diarrhea only.

§ When lower dose of metformin.

¶ For dyspepsia.

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. Mod = 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.

The Evidence About Hypoglycemia (Appendix G, Table 12)

From the 2007 CER[21] we included 29 RCTs,[36,50,60,61,63-65,68,70,71,79,81,86,87,89-91,106,109,110,114-119,128,140,149] and 3 cohort studies that reported hypoglycemia.[194-196] Of the newly identified studies, 51 wereRCTs,[38,44,49,59,75-78,80,82,84,85,92-96,100,101,111,112,120-123,125,126,129-134,136-138,142,144-147,150,152,156,164,165,179,184,197,198] one was a nonrandomized trial[199] and four were cohort studies.[183,200-202] The high-quality study from by Home, et al. (RECORD), was not used to look at hypoglycemic events because the authors did not report the number of affected people stratified by the therapy accompanying the thiazolidinedione (e.g., rosiglitazone plus sulfonylurea or rosiglitazone plus metformin).[16]

Metformin versus thiazolidinediones. This comparison was addressed by a single, large trial.[38] 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 percent CI 0.80 to 1.0) with just a single serious event in each group.[38]

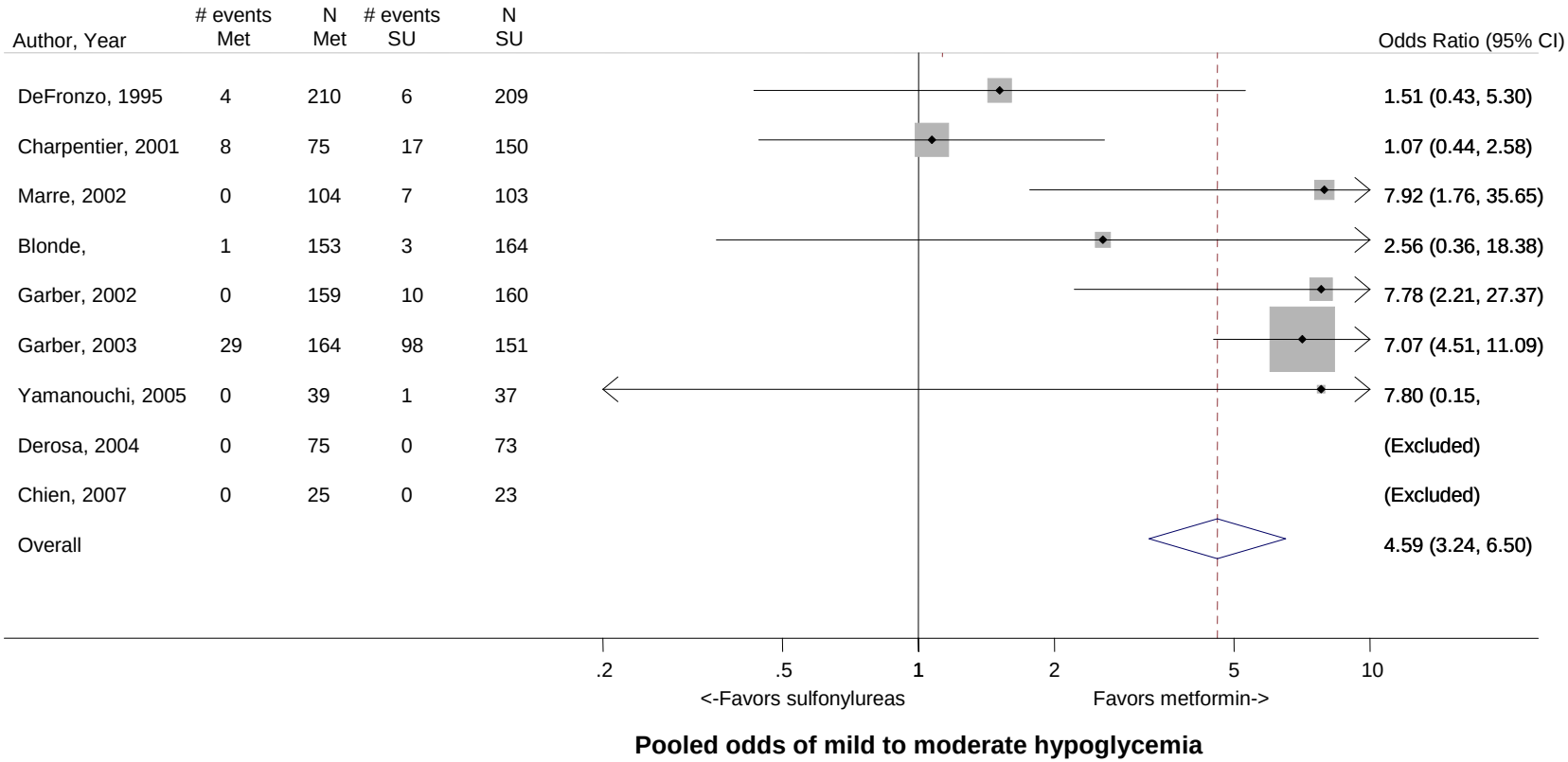
Metformin versus sulfonylureas. Nine RCTs were eligible for pooling,[50,59-61,63-65,70,71] although two studies had no events in either arm.[59] There was moderate statistical heterogeneity between these studies with an I-squared of 68 percent. The pooled odds ratio having at least one mild or moderate hypoglycemic event was 4.6 (95 percent CI 3.2 to 6.5) with use of sulfonylurea relative to metformin (Figure 63). Only one study reported on severe hypoglycemia and found no significant difference between arms ($p = 0.18$).[68]

Two additional RCTs could not be pooled and had results in the same direction as those in the pooled analysis (Table 9).[38,198]

Metformin versus DPP-4 inhibitors. Three studies looked at this comparison for hypoglycemic outcomes.[76-78] The first study of sitagliptin was a continuation of that by Goldstein et al.[75] Two of 182 patients randomized to metformin and two of 179 randomized to sitagliptin had mild or moderate hypoglycemic symptoms.[76] A more recent study reported that 3.3 percent of the 522 patients treated with metformin had mild or moderate hypoglycemic symptoms while 1.7 percent of the 528 treated with 100 mg daily of sitagliptin did ($p = 0.12$). There were no patients with severe hypoglycemia in the metformin group and two patients in the sitagliptin group.[77] The other study reported 13 patients of 328 treated with metformin and five patients of 335 treated with 10 mg of saxagliptin with mild hypoglycemia and no patient in either group with severe symptoms.[78]

Metformin versus meglitinides. Five RCTs reported mild or moderate hypoglycemia for this comparison.[79-82,197] One had no events in either arm.[81] There was minimal statistical heterogeneity between these studies (I-squared = 0.0 percent). The odds ratio for hypoglycemia was 3.0 (95 percent CI 1.8 to 5.2) for meglitinides compared to metformin (Figure 64). No additional trials or observational studies reported this outcome.

Figure 63. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing metformin with sulfonylureas



CI = confidence interval; Met = metformin; SU = sulfonylurea

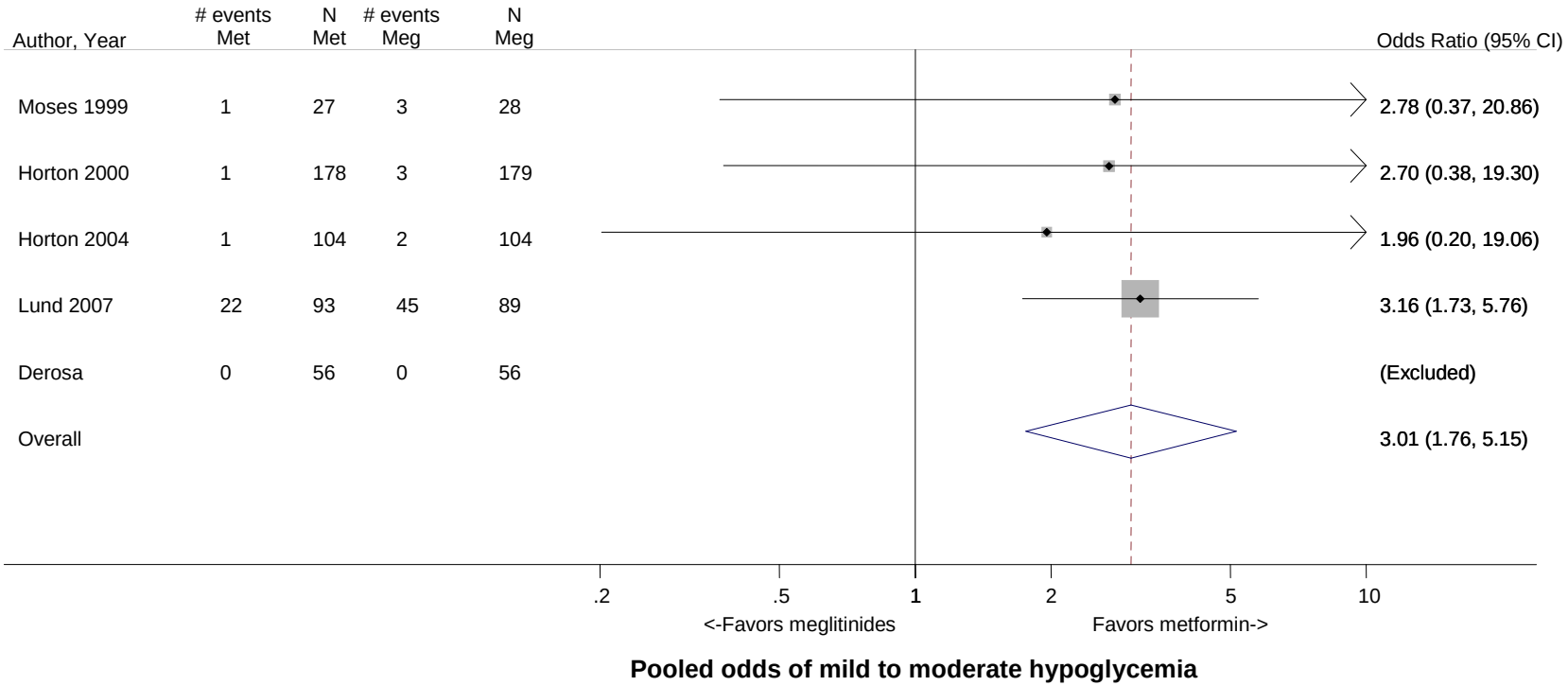
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates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

Test for heterogeneity: Q = 18.68 with 6 degrees of freedom (p = 0.005)

I-squared statistic = 67.9%

The range of rates for mild to moderate hypoglycemia for the comparison group, sulfonylureas, was 0% to 64.9%. The median rate was 2.8%.

Figure 64. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing metformin with meglitinides



CI = confidence interval; Meg = meglitinides; Met = metformin
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 = 0.18 with 3 degrees of freedom (p = 0.98)
I-squared statistic = 0%
The range of rates for mild to moderate hypoglycemia for comparison group, meglinitides, was 0 to 50%. The median rate was 1.9%.

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

Author, year	Outcome	Results	Comments
Kahn, 2006[38]	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, HbA1c = 7.3% at baseline
Wright, 2006[198]	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, HbA1c 6.9% at baseline, mostly non-obese participants

HbA1c = hemoglobin A1c; UKPDS = United Kingdom Prospective Diabetes Study

Metformin versus a combination of metformin and thiazolidinediones. Eight RCTs were acceptable for pooling for the outcome of mild or moderate hypoglycemia (Figure 65).[49,84-87,89,90,156] There was minimal statistical heterogeneity. The odds ratio from the fixed effects model was 1.6 (95 percent CI 1.0 to 2.4) favoring metformin alone for the outcome of hypoglycemia. No additional trials or observational studies reported this outcome.

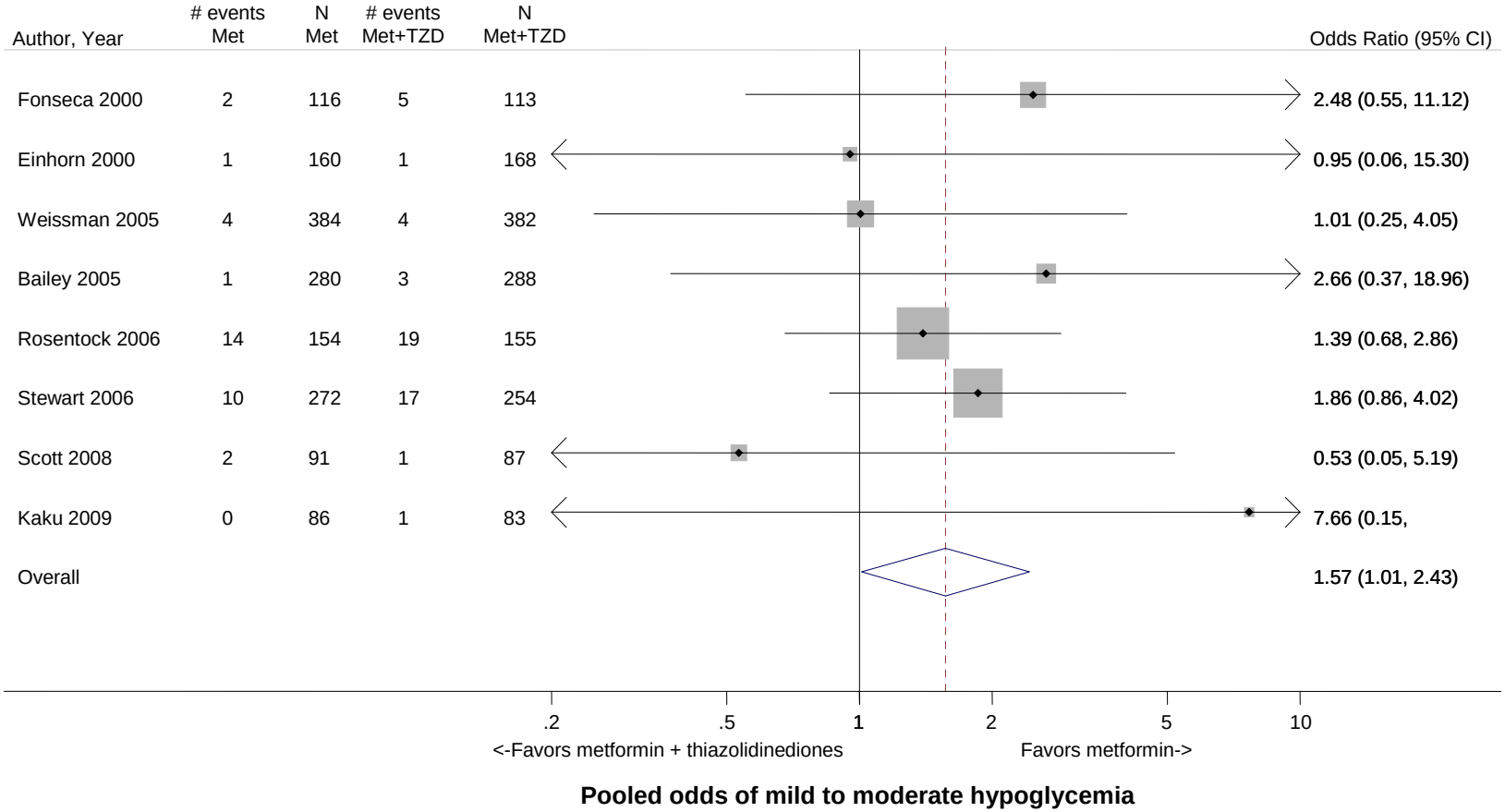
Metformin versus a combination of metformin and sulfonylureas. There were nine RCTs of this comparison (Table 10).[59,61,63,64,68,70,71,91,92] Seven reported mild or moderate hypoglycemia and were pooled, but there was substantial statistical heterogeneity (I-squared of 73 percent) so this pooled outcome is not reported.

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 (metformin as the reference group)
Defronzo, 1995[70]	Individuals with mild or moderate hypoglycemia	4/210 versus 38/213	RR = 9.3 (95% CI 3.4 to 26)
Charpentier, 2001[71]	Individuals with mild or moderate hypoglycemia	8/75 versus 30/147	RR = 2 (95% CI 0.9 to 4)
Blonde, 2002[63]	Individuals with mild or moderate hypoglycemia	1/153 versus 22/162	RR = 20.8 (95% CI 3 to 152) Definition of hypoglycemia required symptoms with a measured glucose < 60 mg/dl
Marre, 2002[64]	Individuals with mild or moderate hypoglycemia	0/104 versus 12/103	RR = 25 (95% CI 1.5 to 421)
Garber, 2003[61]	Individuals with mild or moderate hypoglycemia	29/164 versus 59/171	RR = 2 (95% CI 1.3 to 2.9)
Feinglos, 2005[91]	Individuals with mild or moderate hypoglycemia	2/56 versus 9/56	RR = 4.5 (95% CI 1.0 to 20)
Chien, 2007[59]	Individuals with mild or moderate hypoglycemia	0/25 versus 0/26	Most subjects had been on both medications before the trial began.
Hermann, 1994[68]	Individuals with severe hypoglycemia	8/38 versus 24/72	RR = 1.6 (95% CI 0.8 to 3.2)
Nauk, 2009[92]	Individuals with severe hypoglycemia	0/122 versus 0/244	Not a significant difference

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

Figure 65. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus thiazolidinedione



CI = confidence interval; Met = metformin; TZD = 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 = 2.93 with 7 degrees of freedom (p = 0.89)
I-squared statistic = 0%The range of rates for mild to moderate hypoglycemia for comparison group, a combination of metformin and thiazolidinedione, was 0.6% to 12.2%. The median rate was 1.1%.

Metformin versus a combination of metformin and DPP-4 inhibitors. Five articles, describing four trials, examined hypoglycemia with metformin compared to metformin with sitagliptin.[75,76,85,93,94] Williams-Herman et al,[76] is an extension of the Goldstein et al. trial.[75] There was minimal heterogeneity between these studies. The addition of sitagliptin to metformin does not raise the risk of mild or moderate hypoglycemia (odds ratio [OR] = 0.9, 95 percent CI 0.4 to 2.3) (Figure 66). No additional trials or observational studies reported this outcome.

Two trials examined metformin compared to metformin plus saxagliptin at doses ranging from 2.5 mg to 10 mg.[78,95] In one, 13 of 328 patients treated with metformin had mild hypoglycemia while 11 of 320 patients in the 5 mg saxagliptin plus metformin group had hypoglycemia and 16 of 323 in the 10 mg saxagliptin plus metformin group did. Two patients in the higher dose arm had severe hypoglycemia defined as serum glucose < 50 mg/dl with symptoms.[78] In the other trial, 9 of 170 metformin-treated patients had mild hypoglycemia; when saxagliptin was added the counts were 15 of 192, 10 of 191, and 7 of 181 in the groups receiving 2.5 mg, 5 mg, and 10 mg, respectively. One patient in each arm had severe symptoms, including the metformin only arm.[95]

Metformin versus a combination of metformin and meglitinides. Three studies reported mild or moderate hypoglycemia for this comparison.[80,92,96] There was minimal statistical heterogeneity between the studies. One high-quality study had very few affected individuals and used a low dose of nateglinide.[96] Results are unclear but suggest possibly an increased risk of hypoglycemia with the combination (Figure 67). No additional trials or observational studies reported this outcome.

Rosiglitazone versus pioglitazone. This was addressed by a single, retrospective cohort study.[202] The subjects had poor glycemic control at cohort entry with a mean HbA1c of 9.5 percent in the rosiglitazone group and 9.6 percent 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).

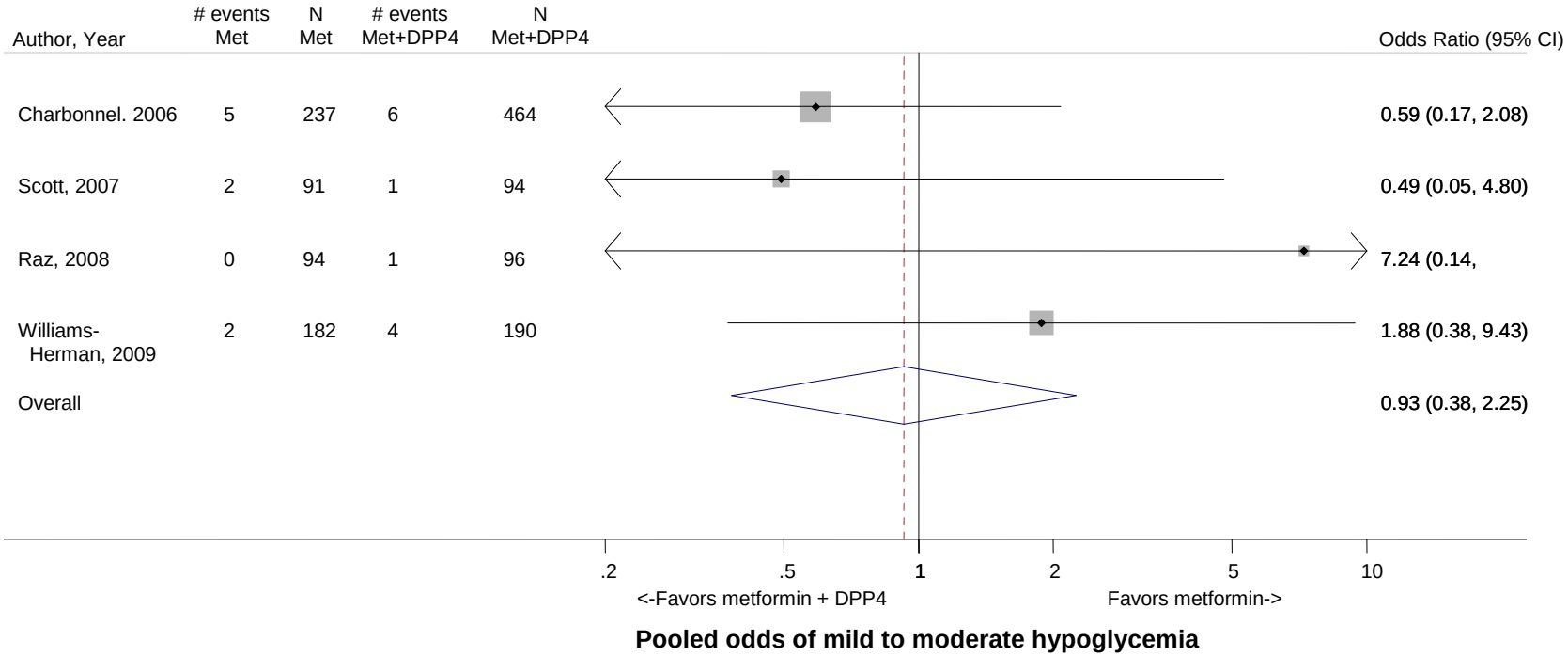
Thiazolidinediones versus sulfonylureas. Nine studies examined hypoglycemic outcomes for this comparison.[38,50,100,101,106,149,150,184,200] Two looked at counts of events rather than individuals,[38,184] and one described only the severe events in both arms.[149] The pooled results for mild or moderate hypoglycemia for the five studies reporting affected individuals showed a higher risk of hypoglycemia among those on a sulfonylurea than on any thiazolidinedione (OR = 3.9, 95 percent CI 3.1 to 4.9) (Figure 68).

However, the large multicontinent RCT (ADOPT) reported no significant difference in the number of events in each group (1,341 out of 1,456 in the group on rosiglitazone and 1338 out of 1,441 in the sulfonylurea group, p = 0.44).[38] 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).[184] A cohort study evaluating a population over age 65 years reported that 2.6 percent of recipients of sulfonylurea reported hypoglycemia and 2.2 percent of thiazolidinedione recipients, which are not significantly different percentages.[200]

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

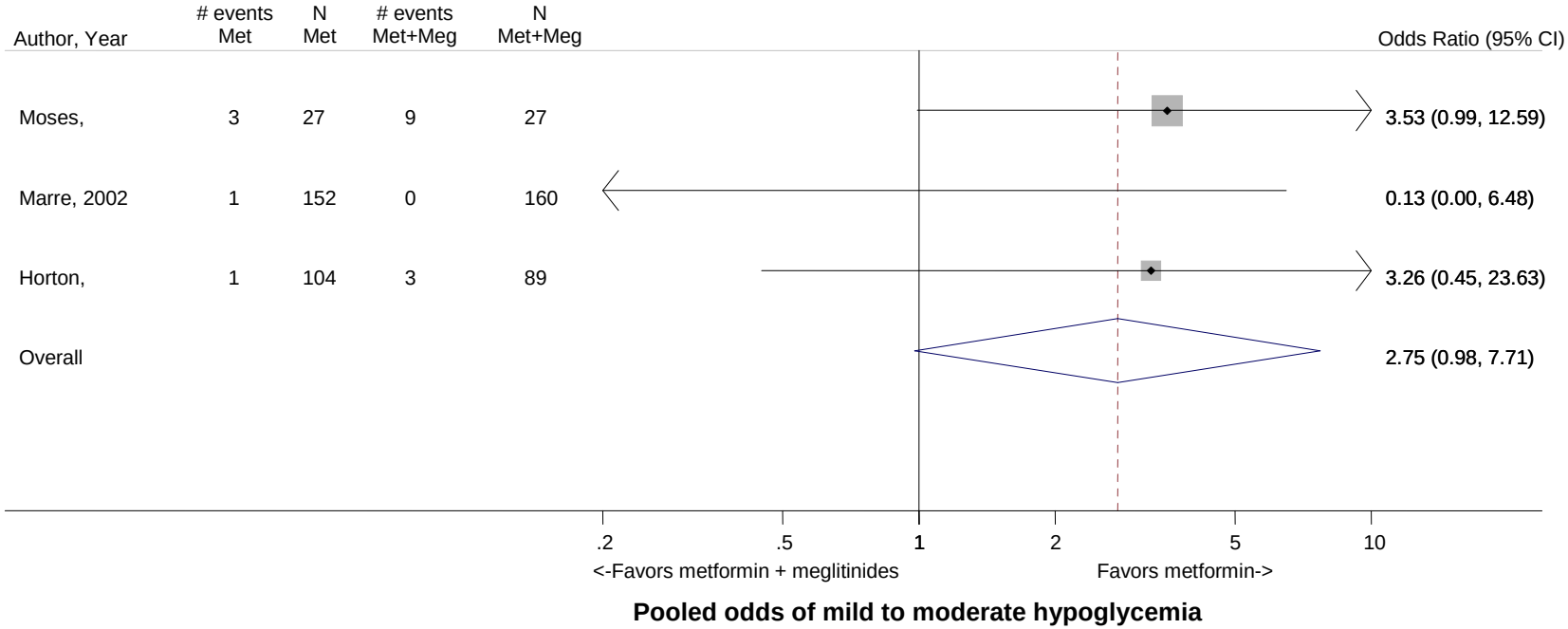
in the ADOPT trial[38]); 0 to 3 percent of the sulfonylurea-treated patients had severe events.[38,50,100,149]

Figure 66. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus DPP-4 inhibitors



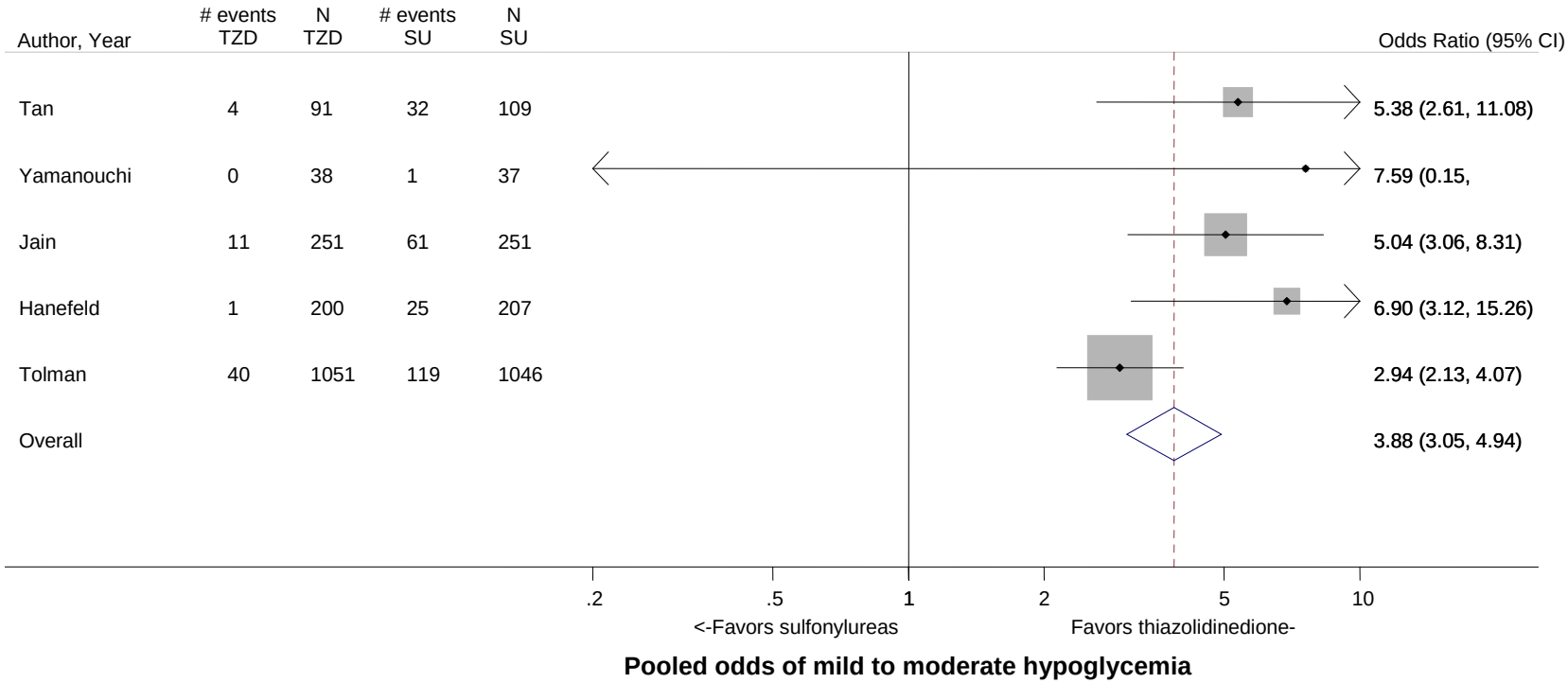
CI = confidence interval; DPP4 inhibitors = dipeptidyl peptidase-4 inhibitors; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 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 = 2.59 with 3 degrees of freedom (p = 0.46)
I-squared statistic = 0%
The range of rates for mild to moderate hypoglycemia for comparison group, a combination of metformin and DPP-4 inhibitors, was 0 to 2.1%. The median rate was 1.5%.

Figure 67. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing metformin with metformin plus meglitinides



CI = confidence interval; Meg = meglitinides; Met = metformin
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 = 2.52 with 2 degrees of freedom (p = 0.28)
I-squared statistic = 20.7%
The range of rates for mild to moderate hypoglycemia for comparison group, a combination of metformin and meglitinides, was 0 to 33%. The median rate was 3.4%.

Figure 68. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing thiazolidinediones with sulfonylureas



CI = confidence interval; SU = sulfonylureas; TZD = 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 = 6.78 with 4 degrees of freedom (p = 0.15)
I-squared statistic = 41%
The range of rates for mild to moderate hypoglycemia for comparison group, sulfonylureas, was 2.7% to 29.4%. The median rate was 12.1%.

Thiazolidinediones versus meglitinides. Two RCTs reported hypoglycemic outcomes for this comparison (Table 11).[109,110]

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

Author, year	Outcome	Results (thiazolidinediones versus meglitinides)	RR and comments (thiazolidinediones as reference group)
Jovanovic, 2004[110]	Individuals with mild or moderate hypoglycemia	4/62 versus 8/61	RR = 1.2 (95% CI 0.8 to 1.8)
Raskin, 2004[109]	Individuals with mild or moderate hypoglycemia	1/62 versus 4/63	RR = 1.6 (95% CI 1.0 to 2.6)
	Severe hypoglycemia	None	NA

CI = confidence interval; NA = not applicable; RR = relative risk

Sulfonylureas versus DPP-4 inhibitors. A single high-quality RCT examined hypoglycemia with this comparison.[111] Subjects had a mean HbA1c of 7.9 percent 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.[112,114-119,203] One looked only at severe events,[114] and one trial focused on the comparison while patients were fasting in observance of Ramadan.[203] 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 (OR = 0.8, 95 percent CI 0.6 to 1.1) (Figure 69).

In the trial by Madsbad et al., there were no severe hypoglycemic events in either treatment group.[114] The high quality trial by Mafauzy et al. randomized patients to repaglinide or glibenclamide during the period of Ramadan.[203] The number of hypoglycemic events with midday blood glucose less than 81 mg/dL was significantly lower in the meglitinide group (2.8 percent) than in the sulfonylurea group (7.9 percent) ($p < 0.001$).

Sulfonylureas versus GLP-1 agonists. Three trials compared a sulfonylurea (glibenclamide or glimepiride) to liraglutide.[120-122] One was a small 12-week dose-finding study that reported a single episode of mild hypoglycemia among the 30 individuals receiving 0.6 mg of liraglutide daily and no episodes in the higher dose group (0.75 mg). Four of 26 patients in the glimepiride group had mild hypoglycemic episodes.[120] The larger trial which also used glimepiride found 12 of 251 (1.2 mg of liraglutide) and 8 of 247 (1.8 mg of liraglutide) episodes of mild hypoglycemia, compared to 26 of 248 in the sulfonylurea group, which is significantly higher in the sulfonylurea group. The number of episodes was comparable in the 1.2 mg of liraglutide group and the 1.8 mg of liraglutide group.[204] The other trial used glibenclamide and compared it to 0.9 mg of liraglutide.[121] There were 45 of 132 individuals with symptomatic hyperglycemia in the glibenclamide group (and 228 events) compared to 36 individuals of 268 in the liraglutide group (and 61 events), significantly favoring the liraglutide arm. There were also more episodes of measured low blood sugar among the glibenclamide treated individuals ($p < 0.0001$). There was no severe hypoglycemia in this trial.

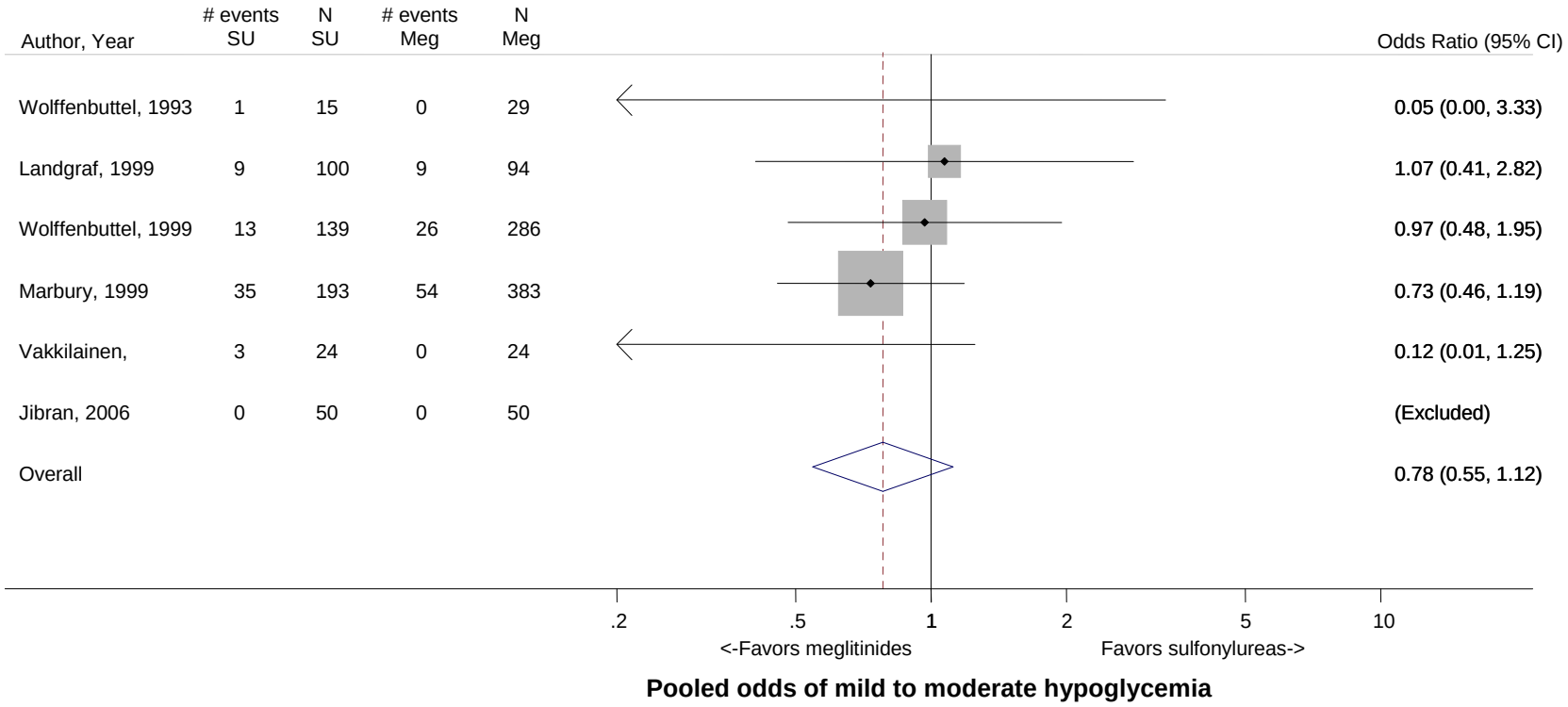
Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas. Five trials examined hypoglycemic outcomes,[123,125,126,128,129] as did one

nonrandomized interventional study.[201] Among those reporting mild or moderate hypoglycemia, there was minimal heterogeneity between studies (Figure 70). 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.[123] 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.

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.[128] This study included patients with high HbA1c upon enrollment and had a higher proportion of Asian patients than most studies (12 percent Asian).

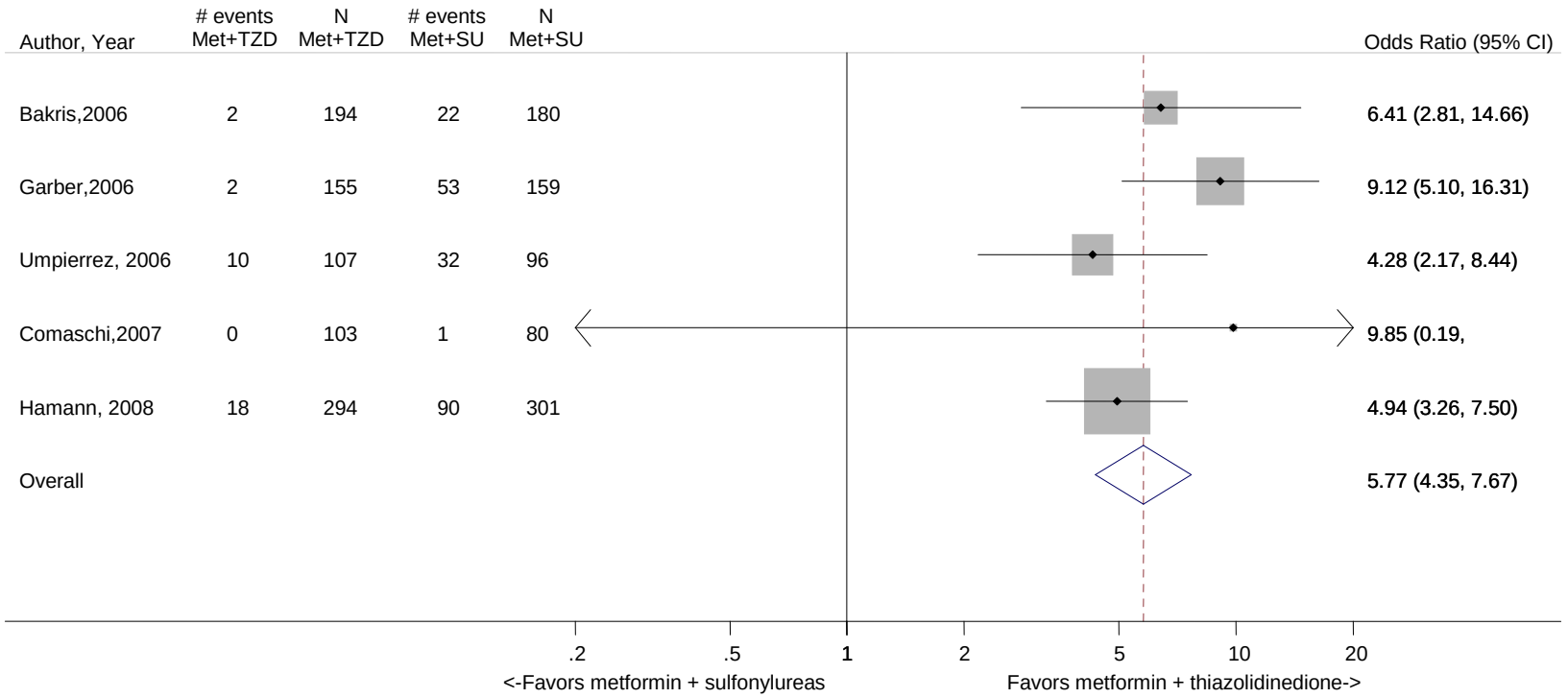
One nonrandomized trial compared addition of pioglitazone with addition of glibenclamide in patients taking metformin, with a mean followup of 42 months.[201] More patients receiving glibenclamide had hypoglycemic events than those who received pioglitazone (34 out of 250 compared to five out of 250, respectively).

Figure 69. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing sulfonylureas with meglitinides



CI = confidence interval; Meg = meglitinides; SU = 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 = 4.89 with 4 degrees of freedom (p = 0.30)
I-squared statistic = 18.2%
The range of rates for mild to moderate hypoglycemia for comparison group, meglitinides was 0% to 14.1%. The median rate was 4.6%.

Figure 70. Pooled odds ratio of having at least one mild or moderate hypoglycemic event comparing combination metformin and thiazolidinediones with combination metformin and sulfonylureas



CI = confidence interval; Met = metformin; SU = sulfonylureas; TZD = 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 = 3.79 with 4 degrees of freedom (p = 0.44)
I-squared statistic = 0%
The range of rates for the comparison group, a combination of metformin and sulfonylureas, was 1.3% to 33.3%. The median rate was 29.9%.

Combination of metformin and thiazolidinediones versus combination of metformin and meglitinides. A single RCT reported hypoglycemia for this comparison.[131] 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, 8 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 percent 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 thiazolidinediones versus combination of metformin and another agent. One study randomized 56 patients to metformin and rosiglitazone and 56 to metformin and sitagliptin. One patient in the rosiglitazone group withdrew for hypoglycemia but it is not clearly reported how many in each group experienced hypoglycemia.[205] The other study randomized 45 patients to metformin and rosiglitazone and 45 to metformin and exenatide. No patients receiving rosiglitazone described hypoglycemia while two receiving exenatide did, although this difference was not statistically significant.[132] There were no severe hypoglycemic events in the latter study.

Combination of metformin and sulfonylureas versus combination of metformin and another agent. Nine trials examined hypoglycemia for metformin plus sulfonylurea compared to metformin plus another drug (Table 12).[44,92,133,134,136-138,152,199]

Combination of metformin and exenatide versus metformin and a basal insulin. A single small study evaluated this comparison.[144] More patients receiving insulin had hypoglycemic events than patients receiving exenatide. Of the 33 patients receiving insulin, 24 percent had hypoglycemia while 8 percent of the 36 receiving exenatide with their metformin had hypoglycemia. There was no severe hypoglycemia in either arm.

Combination of metformin and a basal insulin versus combination of metformin and another insulin. Five trials examined the comparison of metformin plus insulin glargine to metformin plus another insulin preparation (Table 13).[145-147,164,165]

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 (combination metformin and another agent as reference)
Gerich, 2005[136]	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[152]	Metformin + sulfonylurea versus metformin + meglitinides	Severe	1/40 versus 0/35	No significant difference
Nauck, 2007[133]	Metformin + sulfonylurea versus metformin + sitagliptin	Severe	7/584 versus 1/588	RR = 7.0 (95% CI 0.9 to 57)
Malone, 2003[137]	Metformin + sulfonylurea versus metformin + insulin	Nocturnal	(N = 597 in trial) Greater number of participants with nocturnal hypoglycemia ($p < 0.01$) with metformin plus sulfonylurea than metformin plus insulin.	NA
		Severe	Comparable number with severe hypoglycemia	p = 1.0
Kvapil, 2006[138]	Metformin + sulfonylurea versus metformin + insulin	Mild or moderate	9/114 versus 13/108	RR = 1.5 (95% CI 0.7 to 3.4)
Nauck, 2009[92]	Metformin + sulfonylurea versus metformin + liraglutide	Mild and separately reports severe	17% versus 3% of patients	Same in low dose and high dose groups receiving liraglutide; no severe episodes in any arm
Seck, 2010[134†]	Metformin + sulfonylurea versus metformin + sitagliptin	Severe	18/584 versus 2/588	RR = 9.1 (95% CI 2.1 to 39)
Derosa, 2010[44]	Metformin + sulfonylurea versus metformin + exenatide	Withdrawal from study for hypoglycemia	3/65 versus 0/63	Not calculable
Dimic, 2009[199*]	Metformin + sulfonylurea versus metformin + repaglinide	Moderate	7/30 versus 5/30, patients each with one episode	RR = 1.4 (95% CI 0.5 to 3.9)

CI = confidence interval; NA = not available; RR = relative risk

* patients assigned a treatment, not clearly randomized

† Continuation of Nauck, 2007[133]

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 (combination metformin and another insulin as reference group)
Malone, 2004[164]	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	None	NA
Malone, 2005[165]	Metformin + glargine versus metformin + lispro 75/25	Mild or moderate	0.44 versus 0.61 events/patient/30 days	P = 0.47; more daytime hypoglycemia with lispro 75/25 but less nocturnal hypoglycemia
		Severe	None	NA
Raskin, 2007[146]	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[145]	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)
Davies, 2007[147]	Metformin + NPH versus metformin + NPH/regular 70/30	Mild or moderate	7/29 versus 8/27	RR = 0.81 (95% CI 0.34 to 1.9); a poorly conducted trial

CI = confidence interval; NA = not available; NPH = neutral protamine Hagedorn; RR = relative risk

Combination of metformin and thiazolidinediones versus combination of thiazolidinediones and sulfonylureas. A single large cohort study examined this comparison.[183] 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.[142] This was the longer term followup on the patients enrolled in the study first reported by Hanefeld et al.[140] There was a 10 percent withdrawal rate from adverse events and an 8 percent 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 percent CI 0.9 to 2).

Severe hypoglycemia. As noted above, relatively few studies separately described severe hypoglycemia.[38,44,68,78,92,95,114,133,134,136,137,145,152,164,165] The definitions differed across studies, but it was most commonly defined as hypoglycemia requiring assistance for resolution. The studies that compared metformin with a sulfonylurea to metformin with another agent were the studies that most commonly reported this outcome. In the seven studies reporting, only one found a higher rate of severe hypoglycemia in the arm with a sulfonylurea than in the arm with sitagliptin. Otherwise, none of the comparisons reporting this outcome found more severe

hypoglycemia in one arm relative to the other. Many of the studies were underpowered to demonstrate differences for this infrequent outcome.

The Evidence About Liver Injury (Appendix G, Table 12)

Metformin versus thiazolidinediones. One 52-week trial compared metformin and pioglitazone and reported on changes in liver enzymes.[52] There were 3 instances of hepatotoxicity leading to drug discontinuation—1 patient of 597 treated with metformin and 2 of 597 treated with pioglitazone. Liver enzyme abnormalities were more frequent. In the metformin group, 2.2 percent of participants had an increase in alanine transaminase to 3 times the upper limit of normal as did 0.9 percent of pioglitazone-treated patients ($p = 0.06$). In both groups, the mean alanine transaminase, gamma-glutamyltransferase concentrations, and alkaline phosphatase concentrations decreased during the trial. Additionally, a single cohort study assessed liver injury with metformin as compared with pioglitazone, using propensity scores to match subjects based on disease severity.[206] The incidence of liver failure or hepatitis was defined using claims data. For the 1,847 subjects in each group for the metformin versus pioglitazone comparison, the rate of liver failure or hepatitis was 0.8 percent and 0.4 percent, respectively, which was not statistically different in Cox proportional hazard models.

Metformin versus sulfonylureas. The ADOPT study, a large 6-year parallel-arm RCT, compared metformin with glyburide, with over 1,400 subjects in each arm.[38] The average age in the metformin group was 57.9 (standard deviation [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 percent among the 1,341 individuals in the metformin group and 0.8 percent 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 percent CI 26.3 IU/liter to 28.1 IU/liter) compared to the metformin group (24.9 IU/liter; 95 percent 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.[206] 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 percent among the 1,847 people treated with rosiglitazone and 0.5 percent among the 1,847 treated with pioglitazone.

Thiazolidinediones versus sulfonylureas. This comparison was addressed with the ADOPT study, described above, which compared rosiglitazone with glyburide.[38] 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 1,456 people randomized to rosiglitazone or the 1,441 people randomized to glyburide. The cohort study discussed above also compared pioglitazone versus any sulfonylurea and assessed rates of liver failure and hepatitis.[206] The incidence of hepatitis, defined with claims data, was 0.6 percent among the 1,474 individuals treated with pioglitazone and 1 percent in the 1,474 individuals treated with any sulfonylurea, which was not significant. One additional large trial reported this outcome.[150] None of the 1,051 patients receiving

pioglitazone had liver enzyme abnormalities while four of the 1,046 individuals receiving glyburide did (p = 0.06).

Combination of metformin and thiazolidinediones versus combination of metformin and sulfonylureas. One RCT examined liver injury as an adverse event for this comparison.[127] Liver injury was defined as an ALT or aspartate aminotransferase 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.[139] 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. One additional trial describing liver enzyme changes reported this as an outcome (rather than as an adverse event) and saw improvement in gamma-glutamyl transpeptidase, alanine aminotransferase, and alkaline phosphatase in both groups over the 52-week trial.[140]

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

Seven trials[38,83,141,149,150,164,184] and 11 observational studies[171,173,174,183,195,200,202,207-210] reported on the outcome of heart failure for our comparisons of interest.

Metformin versus thiazolidinediones. Three trials[38,83,141] and four observational studies[171,173,174,200] examined heart failure for this comparison (Table 14). Low grade evidence showed that thiazolidinediones increase the risk of heart failure when compared to metformin. The ADOPT study, a large long-term RCT of median duration of treatment of 4 years, which compared metformin with rosiglitazone, with over 1,400 subjects in each arm. There was no difference between the incidences of investigator reported heart failure in these two arms.[38]

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

Author, year	Study design	Comparison	Heart failure incidence (metformin as reference group)
Kahn, 2006[38]	RCT	Rosiglitazone versus metformin	22/1456 versus 19/1454 versus
Leiter, 2005[83]	RCT	Rosiglitazone versus metformin	3/405 versus 0/78
Van der Meer, 2009[141]	RCT	Pioglitazone versus metformin	No events reported in either arm
Asche, 2008[200]	Observational study	Thiazolidinedione versus metformin	19/889 versus 0/2326
Pantalone, 2009[174]	Observational study	Rosiglitazone versus metformin	HR 1.16 (95% CI 0.78 to 1.73)
		Pioglitazone versus metformin	HR 1.38 (95% CI 1.00 to 1.90)
Hsiao, 2009[173]	Observational study	Rosiglitazone versus metformin	HR 1.30 (95% CI 0.89 to 1.89)
		Pioglitazone versus metformin	HR 1.54 (95% CI 0.65 to 3.64)
Tzoulaki, 2009[171]	Observational study	Rosiglitazone versus metformin	HR 0.61 (95% CI 0.33 to 1.15)
		Pioglitazone versus metformin	HR 1.17 (95% CI 0.77 to 1.77)

CI = confidence interval; HR = hazard ratio for TZDs with metformin as references group; RCT = randomized controlled trial

Metformin versus sulfonylureas. Five observational studies reported on the risk of heart failure events with the sulfonylureas compared to metformin.[174,195,207,208,211]

A retrospective cohort study from Canada reported a higher rate of heart failure with a sulfonylurea (96 percent of SU users used glyburide) compared to metformin (adjusted HR 1.2, 95 percent CI 1.0 to 1.5). The risk of heart failure associated with sulfonylureas was dose-responsive with increasing risk with higher doses.[208] Another retrospective cohort study of nearly 30,000 patients using the General Practitioner Research Database in the U.K. reported a higher incidence of heart failure with sulfonylurea monotherapy (27/1000 person-years) compared to metformin monotherapy (19/1000 person-years).[195] A short observational study of around 10 months reported a lower risk of incident heart failure hospitalization among metformin users (HR 0.7, 95 percent CI 0.5 to 1.0, p = 0.05) compared to sulfonylurea users.[207] Another observational study reported a lower risk of congestive heart failure with metformin compared with sulfonylureas (HR 0.76, 95 percent CI 0.64 to 0.91, p = 0.003).[174] Yet another observational study reported a higher risk of congestive heart failure with second-generation sulfonylureas compared with metformin (HR 1.18, 95 percent CI 1.04 to 1.34, p = 0.011).[171]

Rosiglitazone versus pioglitazone. Four observational studies reported on this comparison.[173,174,202,210] A prospective observational study from Ontario reported a statistically significant lower risk of congestive heart failure among patients on pioglitazone compared to rosiglitazone (HR 0.77, 95 percent CI 0.69 to 0.87).[210] Another observational study reported 66 cases of congestive heart failure among 2,093 participants exposed to rosiglitazone monotherapy compared with 13 cases of heart failure among 495 participants exposed to pioglitazone monotherapy (3.33 percent versus 2.66 percent).[173] Another observational study reported no difference in the risk of congestive heart failure with pioglitazone compared with rosiglitazone (HR 1.19, 95 percent CI 0.74 to 1.91, p = 0.48).[174] One prospective observational study in Australia reported nearly similar rates of pulmonary edema when pioglitazone (2/107) was compared to rosiglitazone (3/96).[202]

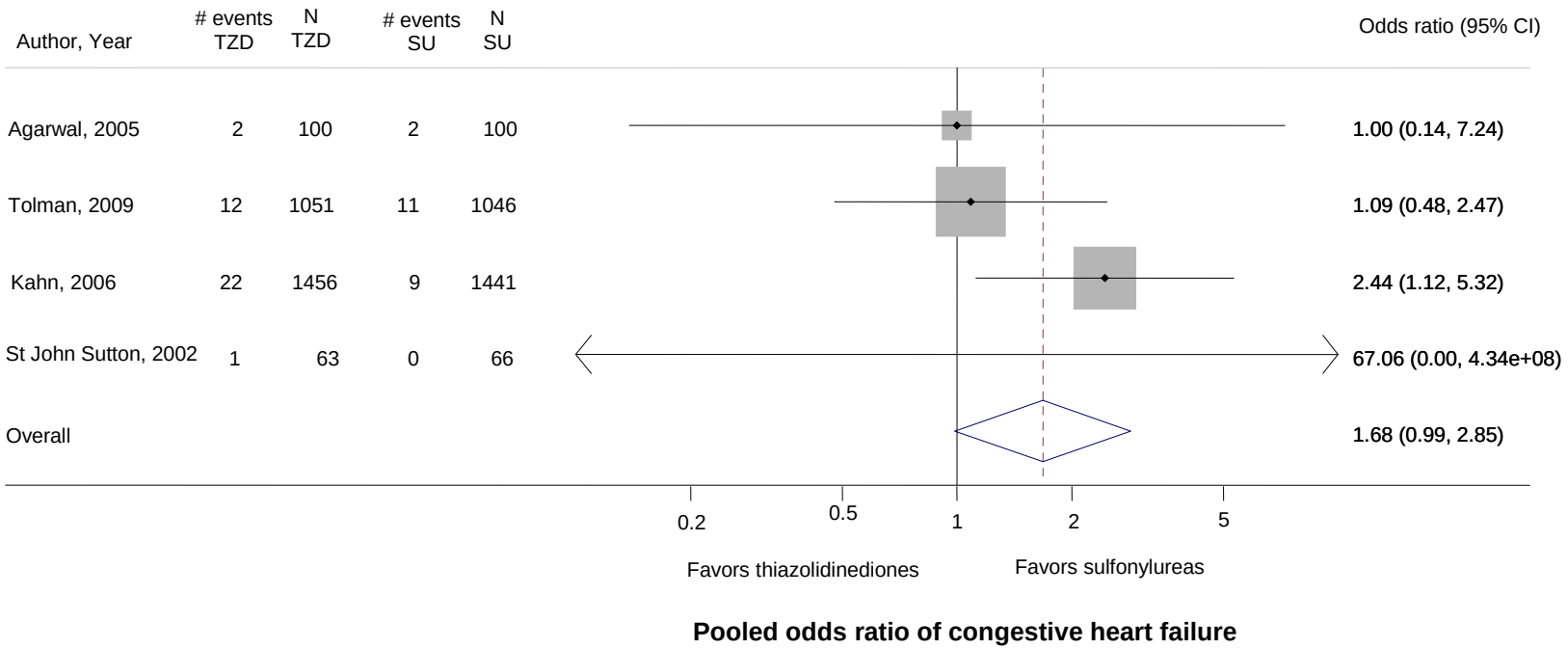
Thiazolidinediones versus sulfonylureas. Four trials[38,149,150,184] and four observational studies[173,174,200,207,208] examined outcomes for this comparison (Table 15). A meta-analysis of the 4 RCTs[38,149,150,184] showed an increased risk of congestive heart failure with thiazolidinediones compared with second-generation sulfonylureas which did not reach statistical significance but could not rule out a clinically significant excess associated with the thiazolidinediones (RR 1.68, 95 percent CI 0.99 to 2.85) (Figure 71). There was no evidence of statistical heterogeneity among the included studies (I^2 = 0 percent). Moderate grade evidence showed that thiazolidinediones increase the risk of heart failure when compared with sulfonylureas.

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

Author, year	Study design	Comparison	Heart failure incidence (sulfonylurea as reference)
Asche, 2008[200]	Observational study	Thiazolidinedione versus sulfonylurea	19/889 and 0/2223
Karter, 2005[207]	Observational study	Pioglitazone versus sulfonylurea	HR = 1.3 (95% CI 0.85 to 1.92) for incident hospitalization for heart failure
Pantalone, 2009[174]	Observational study	Rosiglitazone versus sulfonylurea	HR = 0.88 (95% CI 0.60 to 1.31), p = 0.55
		Pioglitazone versus sulfonylurea	HR = 1.05 (95% CI 0.77 to 1.43), p = 0.76
Hsiao, 2009[173]	Observational study	Rosiglitazone versus sulfonylurea	HR = 1.22 (95% CI 0.86 to 1.74), p = 0.26
		Pioglitazone versus sulfonylurea	HR = 1.37 (95% CI 0.58 to 3.20), p = 0.46

CI = confidence interval; HR = hazard ratio

Figure 71. Pooled odds ratio of congestive heart failure comparing thiazolidinediones with second-generation sulfonylureas



CI = confidence interval; RR = relative risk
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 = 2.37 with 3 degrees of freedom (p = 0.50)
I-squared statistic = 0%

Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones. The RECORD trial was a long-term open-label noninferiority trial designed to assess cardiovascular outcomes with rosiglitazone. Low grade evidence from the RECORD showed that the combination of thiazolidinediones and another agent (second or third generation 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 percent CI 1.35 to 3.27).[16]

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.[164]

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).[183]

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.[62,63] Both the trials were conducted in the United States 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 four RCTs[93,101,143,197] and one observational study[212] which reported on cancer outcomes.

Metformin versus sulfonylureas. A retrospective cohort study of 62,089 patients reported on cancer outcomes in the U.K. in The Health Information Network in U.K. General Practices.[212] Compared with those using metformin alone, users of sulfonylureas reported a higher risk of cancer (HR 1.36, 95 percent CI 1.19 to 1.54, $p < 0.001$).

Metformin versus meglitinides. Additionally, we identified a single crossover RCT reporting cancer outcomes that compared metformin to meglitinides.[197] 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.

Metformin versus a combination of metformin and sulfonylureas. In the same study, compared with metformin alone, users of both metformin and sulfonylureas reported no difference in the risk of cancer (HR 1.08, 95 percent CI 0.96 to 1.21, $p = 0.21$).[212]

Metformin versus a combination of metformin and DPP-4 inhibitors. 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.[93] Three cases of cancer were reported in the metformin only group while none were reported in the combination metformin and sitagliptin group.

Thiazolidinediones versus sulfonylureas. In a 56-week, multicenter trial in the United States and Puerto Rico conducted among 502 individuals randomly assigned to pioglitazone (n = 251) or second-generation sulfonylurea, glyburide (n = 251),[101] two events of stage 4 colon cancer (0.8 percent) were reported in the sulfonylurea group while none were reported in the thiazolidinedione group.

Combination of metformin and DPP-4 inhibitors versus combination of metformin and GLP-1 agonists. One case of cancer was reported in each group in another 26-week open label RCT that compared 221 participants randomized to the liraglutide and metformin group, compared with 219 participants in the sitagliptin and metformin combination group.[143]

The Evidence About Severe Allergic Reactions

None of the studies included in the report 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 rosiglitazone versus metformin was 1.57 (95 percent CI 1.13 to 2.17). They also included a subgroup analysis to examine fracture risk by sex (see Key Question 4). Among the 1,840 women, there were 111 fractures, 60 (9.3 percent) in the rosiglitazone arm, 30 (5.1 percent) in the metformin arm, and 21 (3.5 percent) in the glyburide arm. This represented an increased HR for risk of fracture for rosiglitazone versus metformin (HR 1.81, 95 percent CI 1.17 to 2.80, p = 0.008) among women. There was no excess risk among men.[213] A 24-week RCT reported on one wrist fracture in the metformin monotherapy group (wrist fracture in males (n = 210) without any fractures reported in the pioglitazone group (n = 189).[56] A retrospective study in the U.K. GPRD reported no statistically significant difference in the risk of fractures when rosiglitazone was compared with metformin (HR 1.09, 95 percent CI 0.72 to 1.68, p = 0.69) or when pioglitazone was compared with metformin (HR 1.28, 95 percent CI 0.93 to 1.77, p = 0.127).[171]

Metformin versus sulfonylureas. Two RCTs reported on fractures for the comparison of metformin and second-generation sulfonylureas.[59,213] In the ADOPT subanalysis described above,[213] there were slightly more fractures in the metformin arm (59 out of 1,454, 4.1 percent) compared with the glyburide arm (49 out of 1441, 3.4 percent) 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.[59]

The risk of fractures associated with second-generation sulfonylureas was not statistically different when compared with metformin alone (HR 1.09, 95 percent CI 0.97 to 1.23, p = 0.129) in a retrospective study in the U.K. general practice research database.[171]

Metformin versus a combination of metformin and thiazolidinediones. A 24-week RCT reported one wrist fracture in a male patient in the metformin monotherapy group (n = 210) compared with one wrist fracture in a female in the combination of metformin and pioglitazone group (n = 201).[56] A retrospective study in the U.K. GPRD reported a higher risk of non-hip fractures with rosiglitazone combination therapy compared with metformin alone after adjusting for potential confounders (HR 1.53, 95 percent CI 1.25 to 1.88, p < 0.01).[171] A cross-sectional study of males having diabetes reported a higher risk of fractures among those treated with rosiglitazone plus metformin compared with metformin alone (66.7 percent versus 27.3 percent, p = 0.01), with a significantly higher odds of fractures in the combination arm (OR 6.5, 95 percent CI 1.3 to 38.1, p = 0.03) after adjusting for age and body mass index.[214]

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 with no fractures in the two combination metformin plus glyburide groups (n = 42).[59]

Metformin versus a combination of metformin and DPP-4 inhibitors. One 30-week multicontinent, parallel-arm RCT randomized 190 subjects to metformin or metformin plus sitagliptin.[93] 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[101,213] and one observational study.[215] In the ADOPT subanalysis on fracture risk, there was an increased HR (2.13, 95 percent CI 1.30 to 3.51) for rosiglitazone as compared with glyburide.[213] A second trial randomized subjects to pioglitazone or glyburide.[101] There were no reported cases of ankle fracture among the 251 individuals in the pioglitazone arm. Two ankle fractures (incidence of 0.2 percent) were reported among the 251 participants in the glyburide group, without a statistical test.

Another prospective study reported on the comparison between thiazolidinediones and first- and second-generation sulfonylureas acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, and tolbutamide for fractures among men and women.[215] Thiazolidinediones were associated with an increased risk of all fractures compared with sulfonylureas (HR 1.28, 95 percent CI 1.12 to 1.45, p < 0.001) after adjusting for various confounders. Compared with the sulfonylureas, the hazard ratios for any fractures with the thiazolidinediones did not reach statistical significance for men (HR 1.15, 95 percent CI 0.95 to 1.40, p = 0.14) but was statistically significantly higher for women (HR 1.40, 95 percent CI 1.18 to 1.67, p < 0.001). Among women, both pioglitazone (HR 1.70, 95 percent CI 1.30 to 2.23, p < 0.001) and rosiglitazone (HR 1.29, 95 percent CI 1.04 to 1.59, p = 0.02) were significantly associated with an increased risk of fractures compared with the sulfonylureas.

Combination of metformin and sulfonylureas versus combination of metformin or sulfonylureas and thiazolidinediones. The RECORD study was an open-label noninferiority multicenter RCT with 4,447 participants with type 2 diabetes taking either metformin or a

second- or third-generation sulfonylurea, glyburide/glibenclamide (normal or micronized), gliclazide or glimepiride randomly assigned to one of three arms, metformin plus rosiglitazone, sulfonylurea plus rosiglitazone, or metformin plus sulfonylurea.[16] 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 2,220 participants (2.3 percent) versus 36 out of 2227 participants (1.6 percent) in the metformin plus sulfonylurea arms. The risk ratio was 1.57 (95 percent 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 percent CI 1.37 to 2.41 versus 1.23, 95 percent CI 0.85 to 1.77). The fractures occurred predominantly in the upper limb, distal lower limb, and not hip or femur fractures.[16]

The Evidence About Acute Pancreatitis (Appendix G, Table 12)

We identified five trials that reported on the rates of acute pancreatitis with the specific drug comparisons.[92,121,122,143,144]

Metformin versus a combination of metformin and sulfonylureas. The Liraglutide Effect and Action in Diabetes (LEAD) 2 trial reported one patient with acute pancreatitis in the metformin plus glimepiride arm among 242 exposed patients compared with none in the metformin arm among 121 exposed patients.[92]

Sulfonylureas versus GLP-1 agonists. The Liraglutide Versus Glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono) trial also reported two participants with pancreatitis in the liraglutide arm (n = 498) compared with none having pancreatitis in the glimepiride arm, (n = 248)[122] for 52 weeks. Another 24-week trial that compared liraglutide (n = 272) to glibenclamide (n = 139) also reported no episodes of pancreatitis.[216]

DPP-4 inhibitors versus GLP-1 agonists. Another 26-week trial that compared liraglutide (n = 446) with sitagliptin (n = 219) reported no episodes of pancreatitis.[143]

Combination of metformin and GLP-1 agonist versus combination of metformin and basal insulin. One patient on metformin plus exenatide developed pancreatitis (n = 36) compared with none in the metformin plus insulin glargine arm (n = 33) in another RCT.[144]

The Evidence About Cholecystitis (Appendix G, Table 12)

Three RCTs reported on the outcome of cholecystitis.[54,87,150]

Metformin versus thiazolidinediones. 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.[54]

Metformin versus combination of metformin and thiazolidinediones. In an RCT, one patient had cholecystitis (n = 280) in the metformin arm compared with none (n = 288) in the metformin plus rosiglitazone arm.[87]

Thiazolidinediones versus sulfonylureas. A 3-year RCT reported that four participants developed cholecystitis NOS (not otherwise specified) and zero participants developed acute cholecystitis NOS among 1,051 patients randomized to pioglitazone, compared with 3 patients developing cholecystitis NOS and 1 participant developing acute cholecystitis NOS among 1,046 patients randomized to glyburide.[150]

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.[131]

The Evidence About Gastrointestinal Effects (Appendix G, Table 12)

Fifty-one studies examined GI adverse events, which included nausea, abdominal pain, diarrhea, or a composite outcome. We included 21 studies[36,52,54,60-63,65,66,68,70,71,79,81,86-88,110,128,140,159] from the 2007 CER[21] and identified 30 additional studies[38,44,49,56,59,76-78,80,84,85,92-95,100,101,121-123,126,132,133,142,145,150,152,156,197,200] for the update that reported GI adverse events for comparisons of interest.

Metformin versus thiazolidinediones. Five RCTs compared GI adverse events between metformin and either rosiglitazone or pioglitazone (Table 16).[38,49,52,54,56] GI adverse event 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.[38,59-53,65,66,68,70,71] GI adverse events rates were consistently higher in the metformin arm compared with a sulfonylurea (Table 17).

One retrospective cohort study compared the risk of adverse events associated with the use of metformin, sulfonylureas, and thiazolidinediones among geriatric patients in an outpatient settings.[200] 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.

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

Author, year	Outcome	Event rates (metformin versus thiazolidinediones)
Kahn, 2006[38]	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[49]	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[52]	Diarrhea	11.1% (66/597) versus 3.2% (19/597)
	Nausea	4.2% (25/597) versus 2.3% (14/597)
Pavo, 2003[54]	Diarrhea	16% (16/100) versus 3% (4/105)
Perez, 2009[56]	Diarrhea	15.3% (32/210) versus 2.6% (5/189)

GI = gastrointestinal

Metformin versus DDP-4 inhibitors. Two RCTs compared metformin and sitagliptin. The first assessed the incidence of total GI adverse events, including abdominal pain, diarrhea, nausea, and vomiting.[76] Compared with the arm with highest dose of metformin, the sitagliptin arm had fewer GI adverse events overall (31 percent versus 20 percent), and less diarrhea (12 percent versus 4 percent), nausea (10 percent versus 1 percent), and vomiting (3 percent versus 1 percent). There was no reported difference between groups for abdominal pain. The second RCT also compared metformin with sitagliptin for the combined outcomes of diarrhea, nausea, abdominal pain, and vomiting and found a higher incidence in the metformin group (20.7 percent versus 11.6 percent). When each outcome was looked at individually, it became evident that diarrhea accounted for most of this difference (incidence 10.9 percent versus 3.6 percent) followed by nausea (3.1 percent versus 1.1 percent) and vomiting (1.3 percent versus 0.4 percent).[77]

One RCT compared metformin with saxagliptin and found a higher incidence of diarrhea in the metformin arm (24 percent versus 10 percent).[78]

Metformin versus meglitinides. Four RCTs compared GI adverse events between metformin and a meglitinide (Table 18).[79-81,197] Composite GI adverse events rates were generally higher in the metformin arm compared with a meglitinide, but one trial[80] reported higher diarrhea rates, but similar rates for abdominal pain and dyspepsia.

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

Author, year	Outcome	Event rates (metformin versus sulfonylureas)
Chien, 2007[59]	Combined GI events	32% (8/25) versus 13% (3/23)
Kahn, 2006[38]	Combined GI events	38% (557/1454) versus 22% (316/1441)
	Nausea	11.7% (170/1454) versus 6.9% (99/1441)
	Vomiting	5.8% (84/1454) versus 3.1% (45/1441)
	Diarrhea	23.7% (345/1454) versus 9.9% (142/1441)
	Abdominal discomfort	15.4% (224/1454) versus 11.3% (163/1441)
Garber, 2003[61]	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[63]	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[68]	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, 200362	Diarrhea	17.3% (13/75) versus 13.1% (11/84)
Derosa, 2004[60]	Nausea and diarrhea	2.4% (2/75) versus 0% (0/73)
Charpentier, 2001[71]	Diarrhea	7% (5/75) versus 1% (1/150)
DeFronzo, 1995[70]	Nausea and diarrhea	1.4% (3/210) versus 1.0% (2/209)
Amador-Licona, 2000[66]	Diarrhea and abdominal pain	14.3% (4/28) for metformin; event rates are not reported for sulfonylurea
Garber, 2002[65]		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

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

Author, year	Outcome	Event rates (metformin versus meglitinides)
Lund, 2007[197]	Combined GI events	70% (65/83) versus 47% (47/82)
Horton, 2004[80]	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[81]	Withdrawal for GI symptoms	3.6% (2/56) versus 0% (0/56)
Horton, 2000[79]	Withdrawal for GI symptoms	3.4% (6/178) versus 0.6% (1/179)

GI = gastrointestinal

Metformin versus a combination of metformin and thiazolidinediones. Eight RCTs compared the rates of GI adverse events between metformin and a combination of metformin and a thiazolidinedione, generally showing similar rates between the two groups (Table 19).[49,56,84-88,156]

In studies that showed lower rates of diarrhea in the combination arm, the dose of metformin was lower 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[84]	Constipation & Abdominal Pain	2.3% (2/86) versus 2.4% (2/83)
Scott, 2008[85]	Combined GI events	9% (8/91) versus 7% (6/87)
Rosenstock, 2006[49]	Diarrhea	51% (79/154) versus 47% (73/155) (Minimal difference in rates of nausea, vomiting and dyspepsia)
Stewart, 2006[156]	Diarrhea	18% (49/272) versus 8% (20/254)
Bailey, 2005[87]	Withdrawal due to GI events	5.4% (15/280) versus 3% (9/288)
Weissman, 2005[86]	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[88]	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
Perez, 2009[56]	Diarrhea	15.3% (32/210) versus 9% (18/201)

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

Metformin versus a combination of metformin and sulfonylureas. Ten RCTs examined GI adverse events comparing metformin and metformin plus a second-generation sulfonylurea.[36,59,61-63,65,68,70,71,92] One RCT compared subjects with GI adverse events between metformin and a combination of metformin plus glyburide and favored the combination arm.[59] It reported an incidence of 32 percent for metformin alone versus 7.69 percent in the metformin/lowest dose glyburide combination ($p = 0.021$).[59] 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[21] compared GI events between metformin versus metformin plus glyburide or glibenclamide.[36,61,63,65,68,70] Three studies did not significantly favor either arm;[62,70,92] the others found fewer events in the combination arm for at least one GI adverse event, most commonly diarrhea.[36,61,63,65,68,71] 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 DPP-4 inhibitors. 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).[76,85,93,94] Two RCTs compared the incidence of diarrhea between metformin and metformin plus saxagliptin (Table 20).[78,95] One RCT reported a higher incidence of diarrhea in the group receiving metformin and high dose saxagliptin than in the group receiving metformin alone or the group receiving metformin and low dose saxagliptin.[78] A second RCT found a higher incidence of diarrhea in the metformin only group than in the two groups receiving saxagliptin and metformin.[95]

Metformin versus a combination of metformin and meglitinides. One RCT compared diarrhea, abdominal pain, dyspepsia, and nausea between metformin and metformin plus nateglinide.[80] The incidence of diarrhea and dyspepsia were similar between the treatment groups, but the incidence of abdominal pain was 6.7 percent in the metformin arm compared with 12.4 percent 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).[38,100,101,150]

Table 20. Randomized controlled trials comparing metformin with a combination of metformin and DPP-4 inhibitors for gastrointestinal effects

Author, year	Outcome	Event rates (metformin versus combination of metformin and DPP-4 inhibitor)
Williams-Herman, 2009[76]	Combined GI events	31% (57/182) versus 29% (53/182) (no difference)
	Diarrhea	7% versus 13% (high dose combination) and 9% (low dose combination)
	Abdominal Pain	4% versus 3% (high dose combination) and 4% (low dose combination)
	Vomiting	0% versus 2% (high dose combination) and 4% (low dose combination)
Scott, 2008[85]	Combined GI events	9% (8/91) versus 1% (1/94)
Raz, 2008[93]	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[94]	Combined GI events	10.5% (25/237) versus 11.9% (55/464) (no difference)
Jadzinsky,2009[78]	Diarrhea	7.3% (24/328) versus 9.6% (31/323) versus 6.9% (22/320); metformin versus higher dose saxagliptin combination versus lower dose saxagliptin combination
DeFronzo,2009[95]	Diarrhea	11.2% (20/179) versus 5.5% (10/181) versus 5.8% (11/191) versus 9.9% (19/192); metformin versus higher dose versus intermediate dose versus lower dose saxagliptin combination

GI = gastrointestinal

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

Author, year	Outcome	Event rates (thiazolidinediones versus sulfonylureas)
Jain, 2006[101]	Diarrhea	6.0% (15/251) versus 6.4% (16/251) (no difference)
Hanefeld, 2007[100]	Combined GI events	5.5% versus 3.4% (no difference) (4mg dose of rosiglitazone)
Kahn, 2006[38]	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)
Tolman, 2009[150]	Diarrhea	8.8% (93/1051) versus 7.6% (80/1046)

GI = gastrointestinal; mg = milligram

Thiazolidinediones versus meglitinides. A single RCT compared diarrhea incidence between pioglitazone and repaglinide and reported slightly fewer events in the pioglitazone arm (3 percent versus 5 percent).[110]

Sulfonylureas versus GLP-1 agonists. One RCT compared constipation between glibenclamide and liraglutide and found a similar incidence: 5/132 versus 15/268 (3.8 percent versus 5.6 percent). The same study also compared diarrhea and found an incidence of 5/132 versus 17/268 (3.8 percent versus 6.3 percent).[121]

One RCT compared GI adverse events between glimepiride and liraglutide and found significantly more events in the liraglutide group.[122] Overall, the incidence of participants with GI adverse events was 49 percent and 51 percent in the liraglutide groups (at 1.2 mg and 1.8 mg respectively) and 26 percent in the glimepiride arm. Nausea was reported by 27.5 percent and 29.3 percent of participants in the liraglutide groups (at 1.2 mg and 1.8 mg respectively) compared with 8.5 percent in the glimepiride group ($p < 0.0001$ for both comparisons). Vomiting was seen in 9.3 percent and 12.4 percent of patients in the liraglutide groups versus 3.6 percent of patients on glimepiride. Diarrhea was seen in 15.5 percent (liraglutide 1.2 mg, $p = 0.0283$), 18.7 percent (liraglutide 1.8 mg, $p = 0.0017$) and 8.9 percent (glimepiride group).

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).[123,126,128,159]

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[126]	Diarrhea	4.7% (5/104) versus 6% (6/96) (no difference)
Hamann, 2008[123]	Combined GI events	13% (38/294) versus 18% (54/301)
Derosa, 2005[159]	Flatulence	4.2% (2/48) versus 2.1% (1/47)
Garber, 2006[128]	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 GLP-1 agonists. One RCT compared metformin and rosiglitazone to metformin and exenatide for the individual outcomes of diarrhea and vomiting and found a higher incidence for both outcomes in the exenatide group (diarrhea: 4 percent versus 7 percent; vomiting: 0 percent versus 22 percent, respectively).[132]

Combination of metformin and thiazolidinediones versus combination of metformin and DPP-4 inhibitors. 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.[85]

Combination of metformin and sulfonylureas versus combination of metformin and DPP-4 inhibitors. One RCT compared diarrhea, abdominal pain, nausea, and vomiting between metformin with glipizide and metformin with sitagliptin and did not favor either arm.[133]

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 percent versus 3 percent).[152]

Combination of metformin and sulfonylureas versus combination of metformin and GLP-1 agonists. One RCT compared metformin and glibenclamide versus metformin and exenatide for vomiting and diarrhea with a similar incidence of adverse events in both groups (vomiting: 1/65 versus 1/63; diarrhea: 1/65 versus 2/63).[44]

Another RCT compared metformin and glimepiride versus metformin and liraglutide for the combined outcomes of nausea, vomiting, and diarrhea and found a higher incidence in the liraglutide group (17 percent versus 40 percent and 44 percent respectively as the total dose of liraglutide increased from 1.2 mg to 1.8 mg.[92]

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.[145]

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.[140,142] One RCT compared diarrhea incidence and reported a higher incidence of diarrhea in the metformin combination arm (14.4 percent versus 3.4 percent). 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 percent in the metformin combination arm versus 3 percent in the thiazolidinedione combination arm; withdrawals: 23 percent in the metformin combination arm versus 12 percent in the thiazolidinedione combination arm, respectively).[140]

Publication Bias

For each meta-analysis, we examined graphical displays of publication bias and found little. We appreciate the insensitivity of these methods when the number of studies is low. We think it is more relevant to KQ3 to recognize the selective reporting of outcomes. The body of literature about adverse events is smaller than that for efficacy outcomes suggesting selective reporting of adverse event outcomes. Additionally, it is hard to know in the literature where the absence of a statement about an adverse event is evidence that it did not occur, or that it just was not reported in the publication. We conservatively opted to assume that it was just not reported and drew no conclusions from the absence of statements about adverse events.

Gray Literature

Metformin versus sulfonylureas. One study evaluated the safety profile of metformin versus sulfonylurea.[193] The study reported a higher incidence of GI adverse drug effects in the metformin group (20.3 percent) compared to the sulfonylurea groups (12.9 percent). Hypoglycemia (defined as finger stick glucose < 50 mg/dl) was reported in 3 percent of those treated with sulfonylurea but none in those treated with metformin.

Metformin versus DPP-4 inhibitors. 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.[191] This is likely to be the same data as was published by Williams-Herman.[76]

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.[217] 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 United States. Hypoglycemia requiring assistance was reported in one patient on 4 mg rosiglitazone, one patient on 8 mg rosiglitazone and no patients in the metformin arm.[189]

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 percent of patients on metformin, 11 percent of patients on a fixed combination of 250 mg/1.25 mg and 38 percent 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 percent with metformin monotherapy, 31.6 percent with the low dose combination ($p = 0.037$) and 38.3 percent with the higher dose combination (difference with metformin not significant).[190] 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 percent of metformin recipients versus 35 percent of metformin with sulfonylurea recipients.[192]

One study evaluated the safety profile of combination of metformin plus sulfonylurea versus metformin (500 mg).[193] The study reported a higher incidence of GI adverse effects in metformin group (20.3 percent) compared to in any of the three combination groups (15.9 percent, 12.2 percent and 11.6 percent respectively). Hypoglycemia (defined as finger stick glucose less than 50 mg/dL) was reported in 5 percent, 8 percent and 9 percent of those treated with the combination but none in those treated with metformin.

Metformin versus a combination of metformin and DPP-4 inhibitors. 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.[191] This is probably the same data as was published by Williams-Herman.[76]

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.[189]

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.[218] 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 percent of patients on sulfonylurea alone compared to 3.4 percent and 5.3 percent on low dose thiazolidinedione with sulfonylurea and high-dose thiazolidinedione with sulfonylurea, respectively.[218]

A 52-week, double-blind RCT assessed the risk of hypoglycemia in those treated with a thiazolidinedione and those treated with a sulfonylurea.[219] A higher incidence of hypoglycemia was reported in patients treated with glyburide (12.1 percent) compared to those treated with rosiglitazone, 2 mg twice daily (0.5 percent) or rosiglitazone 4 mg twice daily (1.6 percent).

Sulfonylureas versus DPP-4 inhibitors. One preapproval 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).[191] 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 2 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 10 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 percent), so the applicability of these results to that large patient population cannot 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 or safety by subgroup. The evidence favoring one medication over another across subgroups is unclear.

Twenty-eight studies reported comparative effectiveness and safety for subpopulations relevant to Key Question 4. Three studies[179,180,213] focused on a specific population for the study and the others conducted subgroup analyses of larger clinical trials or cohorts.

We included 21 RCTs and 7 cohort studies that addressed this key question. The majority of trials evaluated differences in the outcome of glycemic control by baseline HbA1c.[75,78,85,93,96,133,136,138,220] Other trial outcomes included weight gain,[179,221,222] nephropathy,[184] fractures,[213] and congestive heart failure.[223] The cohort study outcomes focused on mortality[166,169,180,224] and congestive heart failure.[195,207] 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 Subpopulations

Subpopulations by baseline glycemic control. The majority of studies with subgroup analyses examined differences by baseline HbA1c.[75-78,85,93,96,133,136,138,220] One RCT of metformin plus nateglinide versus metformin plus glyburide found that in both treatment arms, patients with higher baseline HbA1c had a greater mean decrease in HbA1c than patients with lower baseline HbA1c.[136] Ten other trials similarly found that among all treatment arms, patients with higher HbA1c had greater HbA1c 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 HbA1c.[225] A study of patients treated with nateglinide plus metformin versus metformin alone found that the subgroup of patients with lower baseline HbA1c treated with high-dose nateglinide plus metformin had increased rates of hypoglycemic symptoms compared with patients with higher baseline HbA1c.[96] One study investigated the efficacy of sitagliptin versus metformin in terms of HbA1c lowering by baseline HbA1c.[77]

Subpopulations by age, sex or race. Five studies examined the impact of age on glycemic control, but we were unable to draw conclusions regarding comparative medication effectiveness in older adults with diabetes. Five found no difference in the effect on HbA1c,[75,77,85,93,136] one found that patients over age 46 were more likely to require combination therapy to reach target glucose control than younger patients.[222] 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.[223]

Six studies examined the impact of sex on glycemic control, and found no differences in the effect on HbA1c.[75,77,85,93,136,222] 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)[213] over a median followup of 4 years. Consistent with the ADOPT trial, the RECORD study reported higher fracture risk in women compared with men (RR 1.82, 95 percent CI 1.37 to 2.41 versus 1.23, 95 percent 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.[16]

Two studies examined the impact of race on HbA1c reduction, and found no impact on glycemic control.[77,136] 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 1 year than use of sulfonylureas, whereas in men mortality was increased in metformin

users compared to sulfonylurea users.[224] 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.[223] 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.[195]

None of the studies we included assessed the impact of socioeconomic status or education level on glycemic control or outcomes.

Subpopulations by obesity, duration of diabetes, or geographical region. Five studies found no effect of body mass index on HbA1c reduction or glycemic control.[75,77,85,136,222] 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.[179] Another study of efficacy at achieving an HbA1c less than 7 percent found that obese patients treated with metformin had greater chance of achieving the targeted HbA1c level without additional agents than patients treated with sulfonylurea or insulin.[37] 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.[222]

Four studies found no impact of the duration of diabetes on glycemic control.[75,77,85,93] One study found that among patients treated with glibenclamide, the percent of patients achieving targeted glycemic control varied inversely with duration of diabetes.[225]

One RCT compared sitagliptin and metformin and found that glycemic control did not differ by "geographical region" (regions not specified).[77]

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 high-dose sulfonylurea users (chlorpropamide, tolbutamide, glipizide, and glyburide) had higher risk of heart failure[208] and increased mortality[166] 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.[166,208] These findings were from observational studies so there was likely to be residual confounding, related to the patients' need for higher doses.

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 comorbidity.[180] 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 percent CI 0.44 to 0.97 and 0.54, 95 percent CI 0.42 to 0.70, respectively). This mortality benefit persisted after mean followup of 2.5 years.[169] No studies in our review specifically reported the comparative effectiveness of medications in patients with other underlying cardiovascular disease risk factors, such as hypertension.

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 but not glyburide. There was no significant difference in reduction of baseline microalbuminuria between the two groups.104 No studies included in our review compared the safety and efficacy of diabetes medications by patients' renal function.

Observational studies. Seven cohort studies reported on subpopulations.[166,169,180,195,207,215,224] Three studies only reported analyses adjusted for several key patient characteristics but did not specifically report differences by group.[166,169,207]

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 percent CI 0.30 to 0.79), whereas among men the risk appeared to be increased (adjusted 1-year HR 1.82, 95 percent CI 1.25 to 2.64).[224] Another study favored metformin over sulfonylurea or repaglinide for all-cause age-adjusted mortality in people with prior ischemic heart disease.[180]

One study supported the finding from a RCT[223] 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.[195]

One cohort study of 84,339 patients from British Columbia, Canada, compared fracture rates in users of pioglitazone, rosiglitazone and sulfonylureas in men and women. In women, the overall fracture rate among users of any thiazolidinedione was greater than sulfonylureas (adjusted HR 1.34, 95 percent CI 1.10 to 1.64), but this was not the case for men. For both women and men, pioglitazone use was associated with higher risk of peripheral fracture (defined by the International Classification of Diseases, 9th Edition [ICD-9] codes) compared with sulfonylurea (adjusted HR for women 1.77, 95 percent CI 1.32 to 2.38 and adjusted HR for men 1.61; 95 percent CI 1.18 to 2.20). Rosiglitazone use was not associated with increased fracture risk in men or women.[215]

Table 23. Results from randomized controlled trials reporting outcomes in a subpopulation

Subgroup	Outcome				
	HbA1c	**Weight**	**CHF**	**Fractures**	**Nephropathy**
Elevated baseline HbA1c	**Met vs. met + sita:**[75,93] Favors met + sita **Met vs. sita:**[77] Conclusion unclear **Met vs. met + saxa**:[78] Favors met + saxa **Met vs. met + meg:**[96] Favors met + meg **Met + rosi vs. met + sita:**[85] Favors met + rosi **Met + SU vs. met + meg:**[136] Conclusion unclear **Met + glipizide vs. met + sita:**[133] Favors met + glipizide **Met + SU vs. met + premixed:**[138] Favors met + premixed	No evidence	No evidence	No evidence	No evidence
Age	**Met vs. sita:**[77] Conclusion unclear **Met vs. met + sita:**[75,93] Favors met + sita across age groups **Met + rosi vs. met + sita:**[85] Conclusion unclear **Met + SU vs. met + meg:**[136] Conclusion unclear	No evidence	**TZD vs. SU:**[223] Favors SU over pio in patients over age 64 with baseline CHF	No evidence	No evidence

Table 23. Results from randomized controlled trials reporting outcomes in a subpopulation (continued)

Subgroup	Outcome				
	HbA1c	Weight	CHF	Fractures	Nephropathy
Sex	**Met vs. met + sita:**[75,93] Favors met + sita regardless of sex **Met + TZD vs. met + sita:**[85] Conclusion unclear **Met + SU vs. met + meg:**[136] Conclusion unclear **Met vs. sita:**[77] Conclusion unclear	**Met vs. met + pio:**[221] Favors met + pio for weight control regardless of gender	**TZD vs. SU:**[223] Favors SU over pio in men with baseline CHF; Women less likely to develop heart failure than men across all treatment modalities	**Met vs. TZD vs. SU:**[213,215] Glyburide and met favored over rosi in pre- and post-menopausal women; difference in men unclear	No evidence
Duration of diabetes	**Met vs. met + sita:**[75,93] Favors met + sita regardless of duration **Met + TZD vs. met + sita:**[85] Conclusion unclear **Met vs. sita:**[77] Conclusion unclear	**No evidence**	**No evidence**	**No evidence**	No evidence
Prior treatment	**Met vs. met + SU:**[92] Favors met + SU regardless of prior treatment. **Met + insulin glargine vs. met + premixed:**[145] Favors met + premixed regardless of prior number of injections **Met + TZD vs. met + meg:**[131] Conclusion unclear **Met vs. sita:**[77] Conclusion unclear	**No evidence**	**TZD vs. SU:**[223] Favors SU over pio in patients with baseline CHF and insulin use.	**No evidence**	No evidence

Table 23. Results from randomized controlled trials reporting outcomes in a subpopulation (continued)

Subgroup	Outcome				
	HbA1c	Weight	CHF	Fractures	Nephropathy
Obesity	**Met vs. SU:**[37] Favors SU among obese patients in long-term treatment (over 9 years) **Met vs. met + rosi:**[179] Favors met + rosi among overweight and obese patients **Met vs. met + sita:**[75,93] Favors met + sita across BMI groups **Met + rosi vs. met + sita:**[85] Conclusion unclear **Met + SU vs. met + nateglinide:**[136] Conclusion unclear **Met vs. sita:**[77] Conclusion unclear	**Met vs. SU:**[222] Obese patients lost more weight with met **Met vs. met + rosi:**[179] Favors met for weight loss among obese patients	No evidence	No evidence	No evidence
Geo-graphic region	**Met vs. sita:**[77] Conclusion unclear				
Elevated DBP	No evidence	No evidence	No evidence	No evidence	**Pio vs. SU:**[184] Conclusion unclear
Race	**Met + SU vs. met + nateglinide:**[136] Conclusion unclear	No evidence	No evidence	No evidence	
Baseline proteinuria	No evidence	No evidence	No evidence	No evidence	**Pio vs. SU:**[184] Conclusion unclear **Rosi vs. SU:**[104] Conclusion unclear

BMI = body mass index; CHF = congestive heart failure; DBP=diastolic blood pressure; HbA1c = hemoglobin A1c; Meg = meglitinides; Met = metformin; Pio = pioglitazone; Premixed = premixed insulin; Rosi = rosiglitazone; Saxa = saxagliptin; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione

Quality Assessment

Quality assessment of trials. Out of the 143 trials included in this report, only six were described as non-randomized trials and two were a crossover study (Appendix G, Table 13). Among the 136 RCTs, 35 percent described their randomization scheme and another 58 percent 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 (74 percent) described the withdrawals and dropouts. Although we evaluated the quality of the studies included in our 2007 CER, we used a different approach for the additional articles identified for this update. Among the 55 trials included from the 2007 review, only about one third of them received the highest two quality scores (4 or 5) on the five-point scale used in our update. Among the 88 trials identified for the update, 37 percent were rated as "good" quality, 46 percent as "fair" quality and 17 percent as "poor" quality.

Quality assessment of observational studies. We assessed the quality of the 26 observational studies newly identified for the update (Appendix G, Table 14). In the 2007 review, we did not assess the quality of observational studies. Of the newly identified studies, 42 percent reported the study setting or study population from which the study sample was drawn, 88 percent described inclusion/exclusion criteria, and 73 percent provided at least some description of key characteristics of the study population. Thirty-one percent of the studies provided details about treatment, which included treatment type, dose, timing and duration of medication. Seventy-seven percent of studies described and objectively measured the outcomes of interest. 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 five of the prospective cohort studies described the number of participants who were lost to followup after the start of the period of observation. Twenty-five of 26 observational studies were rated as having fair or good overall quality.

Articles Reporting More Than One Study

Nine studies reported on more than one study (see Table 24).[226-234] 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[226]	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[227]	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[228]	Individual studies were included in the report
Perez, 2004[229]	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[230]	Individual studies were included in the report
Belcher, 2005[231]	Individual studies were included in the report
Charbonnel, 2005[232]	Individual studies were included in the report
Ceriello, 2005[233]	Individual studies were included in the report
Rendell, 2003[234]	Individual studies were included in the report

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

Discussion

This systematic review addresses the comparative effectiveness and safety of diabetes medications used most frequently in the United States as monotherapy and in combination therapy with each other and with insulin preparations. This review updates and adds to a previous comparative effectiveness review (CER)[21] published in 2007 comparing the effectiveness and safety of oral diabetes medications, mainly as monotherapy.

Prior to beginning this update, we conducted an extensive preliminary literature review and assessed evidence gaps identified in the 2007 review. We built upon the prior systematic review by focusing on the head-to-head comparisons of medications that should be of greatest relevance to clinicians and their patients (Table 2). We broadened the scope by including two newer medication classes, namely the Glucagon-like peptide-1 (GLP-1) receptor agonists and the Dipeptidyl peptidase-4 (DPP-4) inhibitors and two-drug combinations of medications. We identified 166 articles, which included 75 trials and 19 observational studies that have been published since we completed our 2007 review. We included 19 articles with newer medication class comparisons, 77 articles that contained either metformin or a thiazolidinedione in combination with another medication, and 8 articles with comparisons that included insulin preparations in combination with oral medications (Table 2). Our comprehensive review of the newer medications classes in comparison to other medications and comparisons of combination therapies is an important contribution to the literature because it is the first to address this many comparisons for a wide range of outcomes in patients with type 2 diabetes mellitus.

We defined our key questions similarly to the 2007 review, focusing on intermediate outcomes (Key Question 1), long-term clinical outcomes (Key Question 2), adverse events (Key Question 3) and subpopulations (Key Question 4). As expected, intermediate clinical outcomes such as hemoglobin A1c (HbA1c) levels were studied more frequently in randomized controlled trials (RCTs) than long-term clinical outcomes of diabetes, with 121 RCTs included in Key Question 1 about glycemic control and other intermediate outcomes, 66 articles that applied to Key Question 2 on long-term clinical outcomes, 107 articles for Key Question 3 on adverse events, and 28 articles that contained information for Key Question 4, addressing medication effectiveness and safety in subpopulations.

Key Findings and Implications

Overall, we were unable to definitively support one drug or combination of drugs over another for mortality, macrovascular and microvascular complications of diabetes. Compared with other medications, metformin alone and in combination, had the highest benefit to risk ratio for intermediate outcomes, with similar efficacy for HbA1c reduction as other drugs, but less weight gain and less risk of hypoglycemia.

Intermediate Outcomes

Hemoglobin A1c (HbA1c). Most diabetes medications (metformin, thiazolidinediones, sulfonylureas, and repaglinide) reduced HbA1c to a similar degree by about 1 absolute percentage point when compared with baseline values. Metformin reduced HbA1c more than the DPP-4 inhibitors as monotherapy by about 0.4 absolute percentage points. Combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, and metformin plus DPP-4 inhibitors) generally were more effective at reducing

HbA1c compared with metformin monotherapy by about 1 absolute percentage point. These results were consistent with the 2007 systematic review,[21] except that we did not have any data on the DPP-4 inhibitors at that time because they were not yet Food and Drug Administration (FDA)-approved. Although we included comparisons with the GLP-1 agonists, evidence for these comparisons was graded as insufficient or low, limiting our ability to draw firm conclusions. Although we could not draw firm conclusions on the comparative effectiveness of 2-drug combinations due to few head to head studies, we did find that most combination therapies showed similar reductions in HbA1c.

Two other recent systematic reviews compared HbA1c with add-on treatments to metformin.[235,236] One review identified 16 placebo-controlled trials and 11 comparisons with active comparators of metformin combination therapy and concluded that sulfonylureas were superior to thiazolidinediones in reducing HbA1c in combination with metformin.[235] In our pooled analysis of direct comparisons, we did not detect a significant difference in these combinations, which was confirmed in a recent network meta analysis.[236] Our review adds to these recently published reviews by including add-on therapies to thiazolidinediones, including more articles and additional meta-analyses.

Weight. Diabetes medications varied in their effects on body weight. Notably, weight gain was small to moderate, even in the longer duration RCTs such as U.K. Prospective Diabetes Study (UKPDS)[8] and A Diabetes Outcome Progression Trial (ADOPT)[38] (less than 5 kg). However, even small amounts of weight gain (5 percent to 10 percent of body weight) may be associated with increased insulin resistance.[237]

Metformin consistently had a more favorable effect on weight when compared with other diabetes medications such as thiazolidinediones, sulfonylureas, and DPP-4 inhibitors. As monotherapy, metformin was associated with between-group differences of -2.6 kg when compared with thiazolidinediones, -2.7 kg when compared with sulfonylureas and -1.4 kg when compared with DPP-4 inhibitors. Our results on weight related to comparisons among thiazolidinediones, metformin, and sulfonylureas were consistent with the 2007 review, which showed weight gain for thiazolidinediones and sulfonylureas when compared with placebo, and weight neutrality when metformin was compared with placebo.[21] The findings on the GLP-1 agonists and their associated weight loss were similar with another systematic review.[238]

We also found high strength of evidence for some combination therapies. For example, metformin plus sulfonylurea had a slightly more favorable effect on weight than either metformin plus a thiazolidinedione or a thiazolidinedione plus a sulfonylurea. Drug effects on weight may impact the choice of drug added for second line combination therapy in a patient not well controlled on a single agent. One explanation for metformin's favorable effect on weight is that it was due to the removal of pretrial medications that increased weight in the run-in period. This suggests that a beneficial effect on weight is seen in direct comparisons between medications only when the other medication has a clearly adverse effect on weight. The mechanism of weight loss for the GLP-1 agonists is not yet well understood, but animal studies suggest a centrally mediated anorectic effect of GLP-1.[239,240]

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 low-density lipoproteins (LDL), 10 to 30 mg/dL in triglycerides (TG), and 3 to 5 mg/dL in high-density lipoproteins (HDL).

In general, we found that metformin had favorable effects on all the lipid classes; it decreased LDL and TG, and modestly increased HDL. Metformin decreased LDL relative to sulfonylureas, rosiglitazone and pioglitazone, and decreased TG relative to sulfonylureas and rosiglitazone. However, pioglitazone decreased TG more than metformin. Compared with metformin alone, the combination of rosiglitazone and metformin increased LDL and HDL, but also increased TG. The addition of pioglitazone to metformin also increased HDL but decreased TG over the combination of metformin and a sulfonylurea. The addition of DPP-4 inhibitors to metformin did not have an effect on HDL relative to metformin monotherapy. Our updated review contributes to the literature by including DPP-4 inhibitors and GLP-1 agonists for lipid outcomes. However, we found insufficient or low strength of evidence for most of these comparisons because of the limited number of studies. Similar to our 2007 review,[21] we noted that one medication or class may have favorable effects on one lipid outcome and unfavorable effects on another lipid outcome. For instance, rosiglitazone increased LDL more than pioglitazone, and increased HDL less than pioglitazone, but both favorably decreased TG. Varying effects on lipid fractions such as these may account for differences in cardiovascular risk between medications. Decisions regarding medications that may adversely affect lipids are important because of the importance of cardiovascular disease risk reduction in patients with diabetes.[241]

Long-Term Clinical Outcomes

Despite the inclusion of two additional large RCTs[16,38] and 39 other studies since the 2007 systematic review, we found, overall, low or insufficient 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. Compared with the 2007 review, we have additional trials for each drug-drug comparison specifically for metformin versus a thiazolidinedione, metformin versus a sulfonylurea, and comparisons with meglitinides.

Using the trials identified in the 2007 review, Selvin et al. conducted meta-analyses of each drug versus any other drug comparators.[242] Treatment with metformin was associated with a decreased risk of ischemic heart disease (pooled OR 0.74; 95 percent 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 and had a wide confidence interval.[242]

In September 2010, the FDA placed restrictions on the use of rosiglitazone, through a Risk Evaluation and Mitigation Strategy, which in part, will require clinicians to attest to and document that the drug's benefits outweigh the cardiovascular risks. This decision was made after a federal medical advisory panel concluded that rosiglitazone was associated with myocardial ischemia, but voted to keep it on the market.[243] Their conclusion was based on recent observational data[18,210] and meta-analyses by Nissen and Wolski,[15,19] as well as increased understanding of the pharmacology of rosiglitazone.[244] Although the FDA acknowledged the limitations of the study designs, there was little evidence to clearly disprove the concerns.[245] Other analyses including the original 2007 review[21,242,246,247] have not shown an elevated risk of myocardial ischemia, but had very imprecise point estimates.

A notable addition to this update was the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, which reported that the combined arms of

rosiglitazone plus metformin and rosiglitazone plus sulfonylurea were noninferior to metformin plus sulfonylurea for the primary endpoint of hospitalization or death from cardiovascular disease.[16] However, these findings were inconclusive for myocardial infarction, for which there was a nonsignificant slightly increased risk in the two arms that included rosiglitazone (combined with metformin or sulfonylurea).[16] As the FDA acknowledged, the RECORD trial was open label with a noninferiority design which may have limited its ability to ascertain the cardiovascular effects of rosiglitazone.[245]

Our updated review informs the debate around rosiglitazone by providing a comprehensive comparative risk and benefit assessment in relation to all other hypoglycemic agents on a wide range of outcomes, not only cardiovascular ischemic risk. We followed a prespecified protocol and engaged a research team that was not invested in either side of the rosiglitazone debate. Other than the risk of heart failure associated with the thiazolidinediones, we found no conclusive evidence of excess ischemic cardiovascular risk associated with rosiglitazone, consistent with the original review. However, the methods for this review differed from those by Nissen and Wolski.[15,19] We included studies that occurred only in people with type 2 diabetes and had active comparators, while Nissen et al. included studies in people with other chronic diseases and placebo-controlled trials. In light of the potential ischemic risk of rosiglitazone and the multiple other available medications to treat diabetes, clinicians will need to determine when the benefits of rosiglitazone outweigh the potential risk for individual patients, in keeping with the FDA's recommendations.

In addition to comparisons with the controversial drug, rosiglitazone, we included other drugs and comparisons of high clinical interest for long-term clinical outcomes. 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.[242] However, the large A Diabetes Outcome Progression Trial (ADOPT),[38] 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[38] 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 2007 review, six studies reported this outcome, which were all excluded from this updated review because participants were either taking additional background medications or because there was no comparison of interest (e.g., gliclazide versus glibenclamide). In the 2007 review, three studies reported on the outcome of retinopathy. The most notable study was the U.K. PDS, which reported no difference in progression to retinopathy between a sulfonylurea and metformin at 12 years of followup.[8] Unfortunately, we found no additional studies examining this clinically important 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 on 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 its profound implications for patient quality of life, this will be an important area for future research.

The paucity of robust evidence on cardiovascular outcomes and other important clinical outcomes for diabetes medications may reflect the emphasis of most studies on glycemic control, a surrogate marker, for drug approval. Future research and longer studies will be needed to address this evidence gap.

Adverse Events

We focused our review on the comparative safety of diabetes medications as monotherapy and in combination therapy, and refer readers to our 2007 review for additional details about specific adverse effects reported in placebo-controlled trials. In this update, we confirmed the elevated risk of hypoglycemia associated with sulfonylureas, either alone or in combination, compared with the other hypoglycemic agents. For example, we showed a more than four-fold higher risk of hypoglycemia associated with sulfonylureas compared with metformin alone, and an almost 6-fold higher risk of hypoglycemia for metformin plus a sulfonylurea compared with metformin plus a thiazolidinedione. We also demonstrated that the newer drug class, DPP-4 inhibitors had a lower risk of hypoglycemia than sulfonylureas, and a risk comparable to that of metformin.

We confirmed a doubling of the risk of heart failure with the thiazolidinedione class of medications, particularly compared with sulfonylureas, which was also reported in two recent meta-analyses.[248,249] In fact, both the thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4) according to the FDA boxed warnings on the thiazolidinediones.[250,251] The excess deaths and hospitalizations associated with heart failure with the thiazolidinediones in RECORD[16] 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 2007 review: macular edema, cholecystitis, pancreatitis, and fractures, because of safety concerns that emerged after the review. The 2007 review reported an increased risk of cholecystitis with pioglitazone in an unpublished pooled analysis from the FDA.[21] However, in this updated review we 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.[252-253] 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 percent 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.[254]

Patients with diabetes may have an increased baseline risk of acute pancreatitis.[255] The current drug labels for exenatide and sitagliptin have been strengthened with information from spontaneous post-marketing reports of severe pancreatitis including hemorrhagic pancreatitis occurring after exenatide therapy.[256] The clinical trials with the GLP-1 agonists may have been underpowered to detect these rare occurrences of pancreatitis. However, a recent claims database study failed to show any significant relationship between the GLP-1 agonists, DPP-4 inhibitors and pancreatitis.[257]

Our results for lactic acidosis support the results from the 2007 review, as well as the Cochrane systematic review on this topic[258] 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.[258]

As with the 2007 systematic review, we evaluated cancer as an outcome. We included four 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.[259] 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 percent 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. Although we did not identify additional evidence about diabetes medications and cancer risk, several recent studies have highlighted that this is an area of active research.[260,261] In particular, a large German cohort study published in 2009 showed a positive association between cancer incidence and insulin for all insulin types. Another study suggested a relationship between cancer risk and treatment with insulin glargine compared with human insulin,[260] while another study did not observe the association.[262] A recent study extracted cancer diagnosis information from ADOPT and RECORD, with nearly 39,000 person-years of drug exposure, and showed no advantage of metformin over rosiglitazone and sulfonylureas in terms of cancer rates.[263]

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.[264] 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.[265]

We confirmed the results of our 2007 review showing more frequent gastrointestinal adverse events for metformin compared with thiazolidinediones and sulfonylureas.[21] We also reported higher gastrointestinal side effects with metformin compared with the newer DPP-4 inhibitors, but graded the strength of evidence as low because of inconsistency of effects.

Two-Drug Combinations, Including Addition of Insulin Preparations

In this update, we included comparisons of two-drug combinations of medications that contained either metformin or a thiazolidinedione in combination with another medication, two-drug combinations compared to metformin alone, and combinations of a medication with either basal or premixed insulin preparations compared with non-insulin two-drug combinations (Table 2). Overall, we found that most combinations of two drugs when compared to monotherapy had additive effects, both in terms of improved glycemic control, but also risk for adverse events and weight gain, confirming the 2007 review and other reviews.[21]

Comparative benefit of a two-drug combination over another was less clear, and several combinations had evidence of similar effects on glycemic control. Our conclusion is similar to a recent network meta-analysis of the effect of non-insulin medications added to metformin.[236] One combination comparison favored metformin plus GLP-1 analogs over metformin plus DPP-4 inhibitors, showing a 0.6 absolute percentage point greater reduction in HbA1c. The clinical meaning of this small between-group difference is unclear. Despite little to no difference in HbA1c among the combination therapies, we found that some combinations clearly had increased risk for adverse events and weight gain. Thiazolidinediones in combination with either metformin or sulfonylureas increased weight gain compared with metformin plus sulfonylurea. In contrast, metformin plus a GLP-1 agonist decreased weight compared with several other two-drug combinations, but we found low strength of evidence because of the paucity of studies using the same comparators (see below).

Although this review does not provide a comprehensive review of the addition of insulin preparations to oral medications, we did include several clinically relevant comparisons. We were unable to draw any firm conclusions about the use of premixed insulin preparations compared with basal insulin, in combination with oral agents, with regard to glycemic control or long term clinical outcomes. There was a modestly lower risk of hypoglycemia when metformin was combined with a basal insulin rather than a premixed insulin preparation, confirming a recent CER on premixed insulin analogues, also commissioned by AHRQ.[266] In addition, two recent systematic reviews compared NPH insulin with longer-acting synthetic insulins, glargine or detemir. Most studies had combined insulin with oral medications. They reported no difference in glycemic control between the two insulin products, and also found slightly lower hypoglycemia with the longer-acting insulins.[267,268]

Newer Diabetes Classes of Medications: DPP-4 Inhibitors and GLP-1 Agonists

Eight articles contained comparisons with the new GLP-1 receptor agonists, exenatide or liraglutide, and 12 articles contained comparisons with the DPP-4 inhibitors, sitagliptin or saxagliptin, either as monotherapy or combination therapy. 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,[22] a comparison of interest we included for this updated review, but did not have explicit recommendations for the DPP-4 inhibitor class. The American Association of Clinical Endocrinologists/American College of Endocrinology's consensus algorithm recommends consideration of a DPP-4 inhibitor either as initial monotherapy or second line therapy, and a GLP-1 agonist as initial combination therapy with metformin when the HbA1c is greater than or equal to 7.6 percent.[23]

We found that the DPP-4 inhibitors improved HbA1c to a lesser extent than metformin as monotherapy, but that when added to metformin there was improved HbA1c without additional hypoglycemia risk. These findings are consistent with a Cochrane systematic review[269] and another recent systematic review.[270]

The majority of comparisons with the GLP-1 agonists for the intermediate outcomes (KQ1) were graded with low strength of evidence because of few studies within each comparison, and evidence was insufficient for the long-term outcomes and most safety outcomes. Despite this limitation, the GLP-1 agonists combined with metformin showed similar HbA1c reduction, when compared to metformin plus basal insulin or metformin plus a thiazolidinedione. In addition, the GLP-1 agonists showed decreases in weight compared with sulfonylureas alone, as well as in

combination with metformin compared with other standard combination therapies. The largest recent systematic review of the GLP-1agonists identified 21 RCTs (six unpublished) and showed a reduction in HbA1c by one absolute percentage point in comparison with placebo, with weight loss, as well as a low risk of hypoglycemia.[238] Since exenatide's release, the FDA published alerts about postmarketing case reports of pancreatitis[271] and acute renal failure and insufficiency.[272] In the studies we included, the event rates for these complications were too low to draw any conclusions.

Limitations

Several important limitations to our updated systematic review deserve mention. Because this was an update of a comprehensive review published in 2007, 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 review. 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 review that had included placebo controlled trials, for most drug comparisons this was probably true.[273] However, this assumption may be less valid for the newer medications of saxagliptin, sitagliptin, nateglinide, exenatide and liraglutide, 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,[8,9,12,72-74,274-277] some of which compared HbA1c 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 2007 systematic review but excluded from this updated review.[274] Another unintended consequence of requiring these prespecified comparisons of interest was that some of the recent studies of exenatide[278-281] as add-on therapy to oral medications did not 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[282-286] compared a drug of interest with any other unspecified drug for an adverse event outcome, and this was not a comparison of interest.

We selected key questions focused on intermediate and long-term clinical outcomes through an extensive topic refinement process at the beginning of this process, which involved input from stakeholders on the Technical Expert Panel. Diabetes care is a rapidly growing and very extensive field, and we note the omission of key outcomes. For example, we did not collect information about several patient-reported outcomes, such as medication adherence and barriers to adherence, or health-related quality of life. These outcomes are important because they may mediate the efficacy of treatment outcome, and also have significant value to patients and clinicians. Future reviews with methodologies designed to capture many different study designs, including qualitative studies, and use of a wide range of measures, are most needed to address these outcomes. Although we assessed the mean difference in HbA1c between intervention groups in Key Question 1, we did not include the durability of HbA1c changes over time as an outcome, which may best be addressed using long-term well-designed observational studies.

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 between-group differences and the measures of dispersion, thereby hindering efforts to estimate effect size across trials. Some trials underdosed comparison medications, limiting our ability to draw conclusions about efficacy. In addition, because of our interest in the comparative effectiveness of drugs, we focused primarily on the relative differences between drugs in our forest plots. In the forest plots, however, we also included footnotes with information about the range of absolute differences from baseline to followup in the comparison arms for readers who wish to estimate the magnitude of effect in absolute terms. 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 updated systematic review, we synthesized current literature about the comparative effectiveness and safety of diabetes medications when used as monotherapy 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, providers, 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 and renal disease 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 meglitinides, DPP-4 inhibitors, and GLP-1 agonists, 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, 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, insulin, 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. The FDA approval process focuses on short-term harms, providing less incentive for pharmaceutical companies to engage in longer term trials.

Setting

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

- 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 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.
6. We recommend that studies allowing use of "background" medications report which medications were allowed and stratify results by the combination therapy, which includes the background medication(s) plus the study drug(s).
7. We recommend conducting a network meta-analysis to assess indirect comparisons, which were not addressed in this report.

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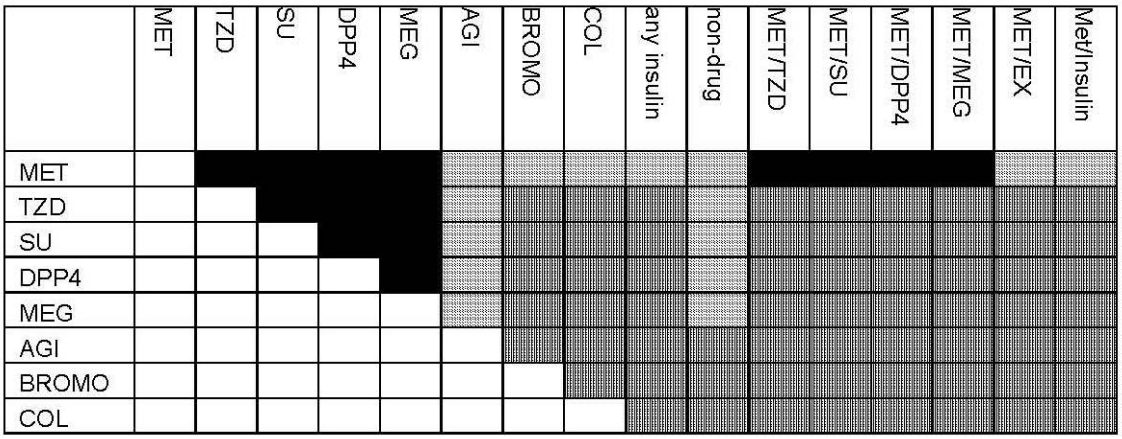
Abbreviations

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
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
HbA1c	Hemoglobin A1c
HR	Hazard ratio
HR	Hazard ratio
IRR	Incidence rate ratios
IU	International units
kg	Kilograms
LDL	Low density lipoproteins
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
U.K.	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
U.S.	United States
VA	Department of Veterans Affairs

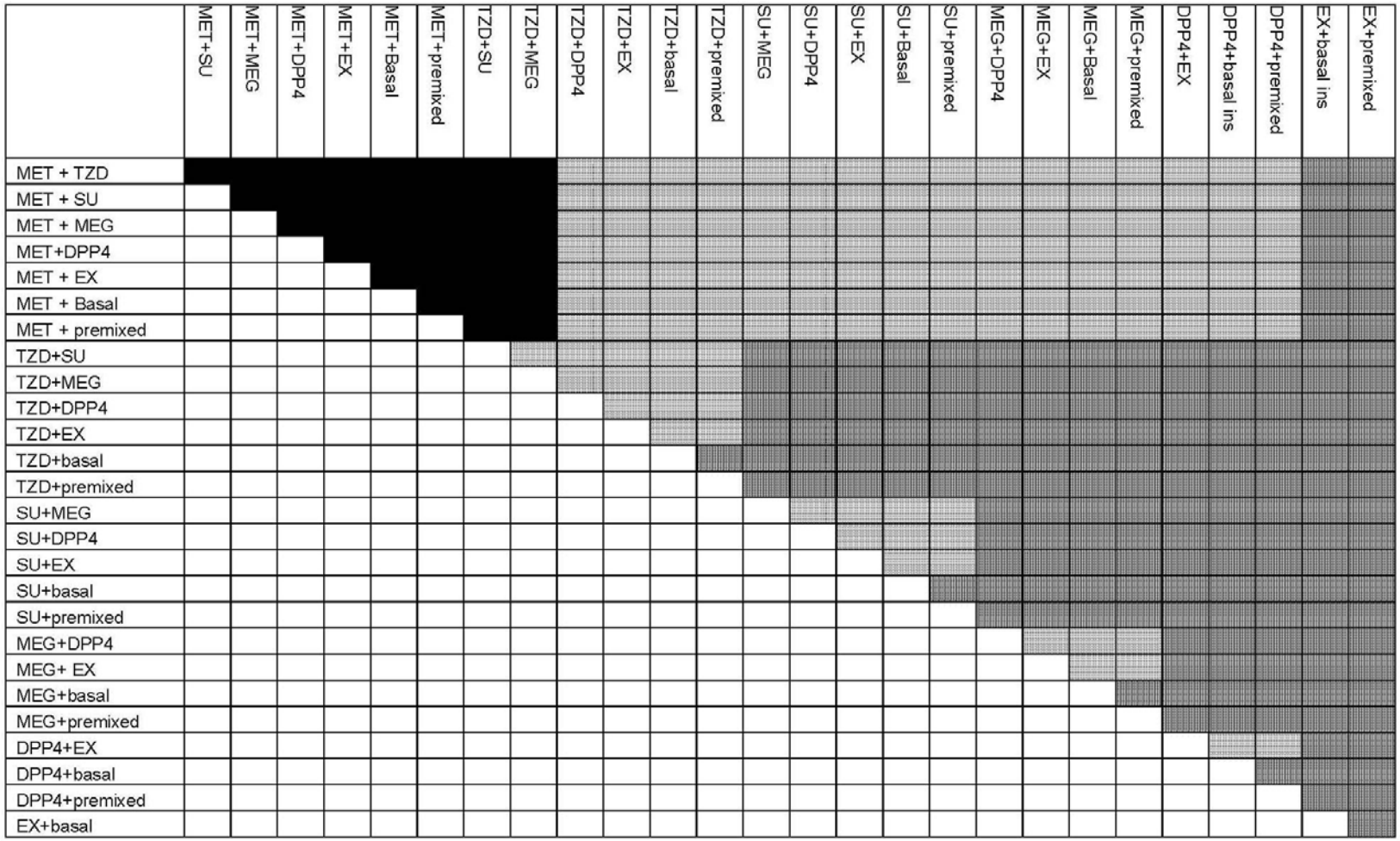
Appendix A. Medication Comparisons

Table 1. Monotherapy comparisons considered for review



Black boxes indicate comparisons that were included in the review; light gray boxes indicate comparisons that were not included, but tallied; and dark gray boxes indicate comparisons that were excluded from the review.
AGI = alpha-glucosidase inhibitors; BROMO – bromocriptine; COL = colesevalam; DPP4 = dipeptidyl peptidase-4 inhibitors; MEG = meglitinides; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione

Table 2. Combination comparisons considered for review



Black boxes indicate comparisons that were included in the review; light gray boxes indicate comparisons that were not included, but tallied; and dark gray boxes indicate comparisons that were excluded from the review.

AGI = alpha-glucosidase inhibitors; basal = basal insulin; BROMO = bromocriptine; COL = colesevalam; DPP4 = dipeptidyl peptidase-4 inhibitors; EX = exenatide; MEG = meglitinides; MET = metformin; premixed = premixed insulin; SU = sulfonylurea; TZD = thiazolidinedione

Appendix B. Detailed Electronic Database Search Strategies

MEDLINE Strategy

Terms	Returns
(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (“thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] or “metformin”[mh] or “acarbose”[mh] or thiazolidinedione*[tiab] or pioglitazone[tiab] or rosiglitazone[tiab] or sulfonylurea*[tiab] or sulphonylurea*[tiab] or glipizide[tiab] or glyburide[tiab] or glimepiride[tiab] or glibenclamide[tiab] or biguanide*[tiab] or metformin[tiab] or “insulin secretagogues”[tiab] or meglitinide*[tiab] or repaglinide[tiab] or nateglinide[tiab] or “alpha-glucosidase inhibitors”[tiab] or “alpha-glucosidase inhibitor”[tiab] or acarbose[tiab] or “Dipeptidyl-Peptidase IV Inhibitors”[mh] or sitagliptin*[tiab] or saxagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or bromocriptine[mh] or bromocriptine[tiab] or colesevelam[tiab] or “Glucagon-Like Peptide 1”[mh] or liraglutide[tiab] or exenatide[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])	7927

Embase Strategy

('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND ('thiazolidinedione'/exp or 'rosiglitazone'/exp or 'pioglitazone'/exp or 'glipizide'/exp or 'glyburide'/exp or ‘glimepiride’/exp or 'metformin'/exp or 'alpha glucosidase inhibitor'/exp or 'acarbose'/exp or ‘sitagliptin’/exp or ‘colesevelam”/exp or thiazolidinedione*:ti,ab or pioglitazone:ti,ab or rosiglitazone:ti,ab or sulfonylurea*:ti,ab or sulphonylurea*:ti,ab or glipizide:ti,ab or glyburide:ti,ab or glimepiride:ti,ab or glibenclamide:ti,ab or biguanide*:ti,ab or metformin:ti,ab or ‘insulin secretagogues’:ti,ab or meglitinide*:ti,ab or repaglinide:ti,ab or nateglinide:ti,ab or ‘alpha-glucosidase inhibitors’:ti,ab or ‘alpha-glucosidase inhibitor’:ti,ab or acarbose:ti,ab or ‘Dipeptidyl-Peptidase IV Inhibitor’/exp or saxagliptin/exp or saxagliptin*:ti,ab or sitagliptin/exp or sitagliptin*:ti,ab or dpp-4:ti,ab or dpp-iv:ti,ab or 'bromocriptine mesilate'/exp or bromocriptine:ti,ab or colesevelam:ti,ab or exenatide/exp or exenatide:ti,ab or liraglutide/exp or liraglutide:ti,ab) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)	16093

The Cochrane Central Register of Controlled Trials (CENTRAL)

(diabetes near type-2) or (diabet*:ti,ab,kw and (“non-insulin dependent”:ti,ab,kw or type-2:ti,ab,kw or “type II”:ti,ab,kw or “type 2”:ti,ab,kw)) AND (thiazolidinedione*:ti,ab,kw or pioglitazone:ti,ab,kw or rosiglitazone:ti,ab,kw or sulfonylurea*:ti,ab,kw or sulphonylurea*:ti,ab,kw or glipizide:ti,ab,kw or glyburide:ti,ab,kw or glimepiride:ti,ab,kw or glibenclamide:ti,ab,kw or biguanide*:ti,ab,kw or metformin:ti,ab,kw or “insulin secretagogues”:ti,ab,kw or meglitinide*:ti,ab,kw or repaglinide:ti,ab,kw or nateglinide:ti,ab,kw or “alpha-glucosidase inhibitors”:ti,ab,kw or “alpha-glucosidase inhibitor”:ti,ab,kw or acarbose:ti,ab,kw or “Dipeptidyl-Peptidase IV Inhibitors”:ti,ab,kw or saxagliptin*:ti,ab,kw or sitagliptin*:ti,ab,kw or liraglutide:ti,ab,kw or exenatide:ti:ab,kw or bromocriptine:ti,ab,kw or colesevelam:ti,ab,kw)	6507

Appendix C. Hand-Searched Journals

All Journals Hand Searched

February 2009–September 2009

American Journal of Medicine
Clinical Therapeutics
Diabetic Medicine
Diabetes and Metabolism
Diabetes
Diabetes Care
Diabetes, Obesity & Metabolism
Diabetes Research and Clinical Practice
Diabetologia
Hormone and Metabolic Research
Journal of Clinical Endocrinology and Metabolism
Lancet
Metabolism: Clinical and Experimental
Practical Diabetes International

Appendix D. Forms

Project Diabetes Medications (Switch) User lisa.wilson (My Settings)
Messages 1 new

DistillerSR

Review | Datarama | Reports | References | Edit Forms | Manage Levels | Manage Users | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to Does this article POTENTIALLY apply to any of our key questions? Click here to see drug matrix. Yes No

Submit Form and go to

DistillerSR

Project Diabetes Medications (Switch) User lisa.wilson (My Settings)
Messages 1 new

Review | Datarama | Reports | References | Edit Forms | Manage Levels | Manage Users | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries.

Submit Form and go to

Diabetes Medications
Abstract Review Form

1. Exclude article because **(check all that apply)** :

- ☐ Exclude, but pull for handsearching (e.g. systematic review article that applies to key question)
- ☐ Does not apply to any of the key questions
- ☐ No original data (e.g. Review article, commentary or editorial)
- ☐ No concurrent control or comparison group (e.g. case series or case report or pre-post design; note that case-control studies should be included)
- ☐ Does not have a drug comparison of interest (see list below)
- ☐ No subjects with type 2 diabetes mellitus, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes
- ☐ Only applies to KQ1 and is not a RCT - DO NOT USE
- ☐ Number of subjects in study < 40
- ☐ Study participants on drug < 30 days or 1 month
- ☐ No human data reported (e.g. evaluates outcomes in animals only)
- ☐ Not written in English
- ☐ No subjects > or = 18 years old
- ☐ Other reason for exclusion:

2. Unclear

- ☐ Unclear — pull for full article review

To see the drug matrix, click here.
To see the list of drug names, click here. To see the key questions, click here.

3. Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority)**:

Monotherapy - Green	Main intervention **(select one)** ○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) Clear Response	Comparison **(select all that apply)** ☐ TZD alone ☐ Sulfonylurea alone ☐ Sitagliptin alone (DPP-4 inhibitor) ☐ Meglitinides alone ☐ Metformin + TZD (only vs. metformin alone) ☐ Metformin + SU (only vs. metformin alone) ☐ Metformin + sitagliptin (only vs. metformin alone) ☐ Metformin + meglitinides (only vs. metformin alone)
Combination - Green	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin Clear Response	Comparison **(select all that apply)** ☐ Metformin + TZD ☐ Metformin + SU ☐ Metformin + meglitinides ☐ Metformin + sitagliptin ☐ Metformin + exenatide ☐ Metformin + any HG ☐ Metformin + basal insulin ☐ Metformin + premixed insulin ☐ TZD + SU ☐ TZD + meglitinides

4. TALLY - Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority)**:

Monotherapy - Yellow	Main intervention **(select one)** ○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD	Comparison **(select all that apply)** ☐ TZD + meglitinides

open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

- Metformin + SU
- Metformin + meglitinides
- Metformin + sitagliptin
- Metformin + exenatide
- Metformin + any HG
- Metformin + basal insulin
- Metformin + premixed insulin
- TZD + SU
- TZD + meglitinides
- TZD + sitagliptin
- TZD + exenatide
- SU + meglitinides
- SU + sitagliptin
- SU + exenatide
- Meglitinides + sitagliptin
- Meglitinides + exenatide
- Sitagliptin + exenatide

Clear Response

- TZD + sitagliptin
- TZD + exenatide
- TZD + basal insulin
- TZD + premixed insulin
- SU + meglitinides
- SU + sitagliptin
- SU + exenatide
- SU + basal insulin
- SU + premixed insulin
- Meglitinides + sitagliptin
- Meglitinides + exenatide
- Meglitinides + basal insulin
- Meglitinides + premixed insulin
- Sitagliptin + exenatide
- Sitagliptin + basal insulin
- Sitagliptin + premixed insulin

11. Comments (limit: 250 characters)

Submit Form and go to

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Messages 1 new

Review | Dataranna | Reports | References | Edit Forms | Manage Levels | Manage Users | Logout

Refkit 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to

Diabetes Medication

Article Review Form

Key Question	Study Design Criteria	Study Duration Criteria
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative effectiveness of the treatment options in terms of HgBA1c, weight or lipids?	Exclude if not a randomized controlled trial	Exclude if study duration < 3-months or 90-days
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative effectiveness of the treatment options in terms of the following clinical outcomes? • All cause mortality (study must report # deaths or how many were alive at end of study) • Cardiovascular morbidity (e.g. myocardial infarction and peripheral arterial disease) • Cerebrovascular disease (e.g. stroke) • Retinopathy • Nephropathy • Neuropathy	Exclude if this is not a randomized controlled trial, non-randomized controlled trial, cohort with a comparison group or a case-control study	Exclude if study duration < 3-months or 90-days
In adults ≥ age 18 with type 2 diabetes mellitus what is the comparative safety of the treatment options in terms of the following adverse events and side effects? • Hypoglycemia • Liver failure • Congestive heart failure • Severe lactic acidosis • Cancer • Severe allergic reactions • Hip and non-hip fractures • Pancreatitis • Cholecystitis • Macular edema and decreased vision • GI side effects • All Other Serious Adverse events	Exclude if this is not a randomized controlled trial, non-randomized controlled trial, cohort with a comparison group or a case-control study	Exclude if study duration <3-months or 90-days Tally if study duration 1-3 mont

1. Exclude article because **(check all that apply)**.

- ☐ Does not apply to any of the key questions
- ☐ Does not meet the study design criteria for any of the corresponding questions (see above)
- ☐ Study duration < 3-months or 90-days
- ☐ No original data (e.g. Review article, commentary or editorial)
- ☐ No comparison group (e.g. case series or case report or pre/post design; note: case-control studies should be included)
- ☐ Does not have a drug comparison of interest (see list of comparisons). (Exclude if additional medications are not specified, such as "any oral hypoglycemic" or "any of the following..", or if study lists possible medications without stratification by arm
- ☐ No subjects with type 2 diabetes mellitus, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. Exclude if it only evaluates people with impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, gestational diabete
- ☐ Only includes pregnant women with diabetes
- ☐ Number of type 2 diabetes patients in study < 40
- ☐ No human data reported (e.g. evaluates outcomes in animals only)
- ☐ Not written in English
- ☐ No subjects > or = 18 years old
- ☐ Exclude, but pull for handsearching (e.g. systematic review article that applies to key question)
- ☐ Other reason for exclusion:

2. Exclude, but tally, studies that evaluate adverse outcomes and are 1-3-months long

- ☐ Evaluates adverse outcomes and is 1-3 months long

If not excluded in Q1, then please answer Q3.

3. Comparisons of Interest

A. Green Comparisons

Monotherapy - Green ☐ Check here if green monotherapy comparison and skip to end	Main intervention • Metformin alone • TZD alone • Sulfonylurea alone • Sitagliptin alone (DPP-4 inhibitor)	Comparison • TZD alone • Sulfonylurea alone • Sitagliptin alone (DPP-4 inhibitor) • Meglitinides alone • Metformin + TZD (only vs. metformin alone) • Metformin + SU (only vs. metformin alone) • Metformin + sitagliptin (only vs. metformin alone) • Metformin + meglitinides (only vs. metformin alone)
Combination - Green ☐ Check here if green combination comparison and skip to end	Main intervention • Metformin + TZD • Metformin + SU • Metformin + meglitinides • Metformin + sitagliptin • Metformin + exenatide • Metformin + basal insulin • Metformin + premixed insulin	Comparison • Metformin + TZD • Metformin + SU • Metformin + meglitinides • Metformin + sitagliptin • Metformin + exenatide • Metformin + basal insulin • Metformin + premixed insulin • TZD + SU • TZD + meglitinides

B. Yellow Comparisons

If article does NOT include one of the green comparisons, please check off which of the following other comparisons it addresses **(check all that apply)**
If article includes both a green and a yellow comparison, mark the green comparison in Q3A and skip to the end. The yellow comparison will be captured during data abstraction. Do NOT mark the yellow comparison here.

Monotherapy - Yellow	Main intervention **(select one)** ○ Metformin alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevelam (alone) (only vs. metformin alone) Any insulin (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide


SU + exenatide
Meglitinides + sitagliptin
Meglitinides + exenatide
Sitagliptin + exenatide
Clear Response
Meglitinides + premixed insulin
Sitagliptin + exenatide
Sitagliptin + basal insulin
Sitagliptin + premixed insulin
9. Comments (limit 250 characters)
Submit Form
and go to

DistillerSR

Project Diabetes Medications (Switch) User lisa.wilson (My Settings)
Messages 1 new

Review | Datarama | Reports | References | Edit Forms | Manage Levels | Manage Users | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to

Diabetes Medications
Study Design Form

Fill out this form for all included studies.

1. In what country does the study occur? **(check all that apply)**

- [ ] United States
- [ ] Canada
- [ ] United Kingdom
- [ ] Japan
- [ ] Multinational Europe
- [ ] Multi-continent
- [ ] Other (specify):
- [ ] Not reported

2. What study design is used? **(check only one response)**

- ○ Randomized controlled trial
- ○ Non-randomized trial
- ○ Prospective or retrospective cohort
- ○ Cross-sectional study
- ○ Case-control
- ○ Other (specify):

3. Select trial type **(check all that apply)**

- [ ] Parallel arms
- [ ] Factorial design
- [ ] Crossover design
- [ ] Other (specify):
- [ ] None of the above apply to the trial/Not applicable (not a trial)

4. Was there a run-in period in which >10% of participants were excluded? **(check only one response)**

- ○ Yes
- ○ Fewer than 10% of participants were excluded during run-in
- ○ Run-in period but number of participants excluded was not reported
- ○ No run-in period
- ○ Not applicable

5. Was there a washout period? **(check only one response)**

- ○ Yes (specify how long in days):
- ○ No
- ○ Not reported
- ○ Not applicable/Not a crossover trial

6. Was there pharmaceutical support (funding or drug given for free) of the study? **(check only one response)**

- ○ Yes
- ○ No
- ○ Not reported

7. Study enrollment period (years of medical record collection for cohort inception) **Enter 4-digit year for start, end or both years**

- [ ] Start year:
- [ ] End year:
- [ ] Neither year reported

8. What was the total intended followup duration or maximum possible followup?	9. Specify units: **(check only one response)**
○ Duration: ○ Not reported	○ Weeks ○ Months ○ Years ○ Not applicable

10. What was the planned interval for any contact with the study participants after study drug was titrated (e.g. monitoring)? **(check only one response)**

- ○ < 6 months
- ○ >= 6 months
- ○ Not reported
- ○ Not applicable

11. Which subgroup analyses were conducted? **(check all that apply)**

- [ ] Age
- [ ] Baseline HbA1c
- [ ] Comorbid conditions
- [ ] Gender
- [ ] Obesity
- [ ] Prior treatment
- [ ] Other (specify):
- [ ] No subgroup analyses were conducted

Study Population Questions

12. What was the source(s) of the population from which subjects were enrolled in the study? **(check all that apply)**

- [ ] Inpatient/hospital
- [ ] Outpatient: primary care
- [ ] Outpatient: subspecialty care setting
- [ ] Community
- [ ] Other (specify):
- [ ] Not reported

13. What was the total number of patients screened?

- ○ N:
- ○ Not reported
- ○ Not applicable (for cohort studies, claims data, etc)

14. What was the total number at enrollment or cohort inception?

- ○ N:
- ○ Not reported

15. Please select and specify the exclusion criteria. Any inclusion criteria should be entered as exclusion criteria e.g. if the inclusion criteria is type 2 diabetes, the exclusion criteria would be no type 2 diabetes.

- [ ] Age (specify):
- [ ] Male
- [ ] Female
- [ ] Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT))
- [ ] Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance)
- [ ] History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina)
- [ ] Poorly controlled on prior treatments (e.g. "failed initial treatment")
- [ ] Contraindication or history of intolerance to metformin
- [ ] Neuropathy
- [ ] Retinopathy

- ☐ HbA1c > (specify):
- ☐ HbA1c < (specify):
- ☐ BMI or weight (specify):
- ☐ Pregnant
- ☐ Nursing
- ☐ Not using adequate contraception
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Not reported

TALLY - Article includes the following comparisons of medications **(check all that apply; drugs/combinations are listed in order of priority)**:

Monotherapy - Yellow	Main intervention **(select one)** ○ Metformine alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Monotherapy - Yellow	Main intervention **(select one)** ○ Metformine alone ○ TZD alone ○ Sulfonylurea alone ○ Sitagliptin alone (DPP-4 inhibitor) ○ Meglitinides alone Clear Response	Comparison **(select all that apply)** ☐ Acarbose alone ☐ Bromocriptine (cycloset) alone (only vs. metformin alone) ☐ Colesevalam (alone) (only vs. metformin alone) ☐ Any insulin (only vs. metformin alone) ☐ Non-drug or placebo ☐ Metformin + exenatide (only vs. metformin alone) ☐ Metformin + insulin (only vs. metformin alone)
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + any HG ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide

	○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin
Combination - Yellow	Main intervention **(select one)** ○ Metformin + TZD ○ Metformin + SU ○ Metformin + meglitinides ○ Metformin + sitagliptin ○ Metformin + exenatide ○ Metformin + anyHG ○ Metformin + basal insulin ○ Metformin + premixed insulin ○ TZD + SU ○ TZD + meglitinides ○ TZD + sitagliptin ○ TZD + exenatide ○ SU + meglitinides ○ SU + sitagliptin ○ SU + exenatide ○ Meglitinides + sitagliptin ○ Meglitinides + exenatide ○ Sitagliptin + exenatide Clear Response	Comparison **(select all that apply)** ☐ TZD + meglitinides ☐ TZD + sitagliptin ☐ TZD + exenatide ☐ TZD + basal insulin ☐ TZD + premixed insulin ☐ SU + meglitinides ☐ SU + sitagliptin ☐ SU + exenatide ☐ SU + basal insulin ☐ SU + premixed insulin ☐ Meglitinides + sitagliptin ☐ Meglitinides + exenatide ☐ Meglitinides + basal insulin ☐ Meglitinides + premixed insulin ☐ Sitagliptin + exenatide ☐ Sitagliptin + basal insulin ☐ Sitagliptin + premixed insulin

24. Comments **(limit 250 characters)**

25. Comments **(limit 250 characters)**

26. Comments **(limit 250 characters)**

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Oral Diabetes Medications Update
Intervention Form

Instructions:
1) Complete this form for all RCT's, cohort studies, and cross-over studies.
2) For cross-over studies, please record each portion of the crossover as a separate comparison
3) Do not use this form for case-control studies. Please use "Case Control Intervention and Outcomes Form."

1. Indicate the following: **(Mandatory question; please check one)**

○ Main intervention ○ Comparison A ○ Comparison B ○ Comparison C ○ Comparison D ○ Comparison E ○ Total ○ Other (specify):

For monotherapy comparisons where the main intervention is using a single drug, complete the first row only.
For combination comparisons, complete the first row for metformin or a TZD, and complete the second row for the additional drug. For metformin and TZD combinations, use the first row for metformin and the second row for TZD.

Intervention **(Please select one; interventions listed in order of priority)**	Dosing	Total daily dose after run-in **(include units; OK to calculate if not explicitly stated)**	Duration of dose titration
○ Metformin **Thiazolidinediones** ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ Any in the SU class **DPP-IV Inhibitors** ○ Sitagliptin **Meglitinides** ○ Nateglinide ○ Repaglinide Clear Response	○ Fixed ○ Varied (specify target below) ○ Not specified Clear Response If varied, please indicate the target: ☐ Glucose ☐ HgbA1c ☐ Prespecified target dose ☐ Not specified	**Titration of drug** ☐ Total starting dose: ☐ Maximum total dose ☐ Unclear ☐ Not specified ☐ Fixed dose **(i.e. No titration)** **Other** ☐ **Mean total dose** ☐ Median total dose	☐ Duration of dose titration (specify #:) ☐ Unclear ☐ Not specified ☐ Not applicable Units ○ Days ○ Weeks ○ Months ○ Years ○ Other (specify): Clear Response
Complete this row ONLY if another drug is added on to metformin or a TZD. Additional drug (specify): ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ Any in the SU class **DPP-IV Inhibitors** ○ Sitagliptin **Meglitinides** ○ Nateglinide ○ Repaglinide **GLP-1** ○ Exenatide **Basal insulin** ○ Insulin glargine ○ NPH ○ Insulin determir **Premixed insulin** ○ NPH/regular 70/30 ○ Insulin aspart 70/30 ○ Insulin lispro 75/25 ○ No additional drug/monotherapy ○ Insulin lispro 50/50 Clear Response	○ Fixed ○ Varied (specify target below) ○ Not specified Clear Response If varied, please indicate the target: ☐ Glucose ☐ HgbA1c ☐ Prespecified target dose ☐ Not specified	**Titration of drug** ☐ Total starting dose: ☐ Maximum total dose ☐ Unclear ☐ Not specified Starting frequency of administration **(insulin only)** ○ QD ○ BID ○ TID ○ Other ○ Not specified Clear Response Frequency of administration for final dose **(insulin only)** ○ QD ○ BID ○ TID ○ Other ○ Not specified Clear Response ☐ Fixed dose **(i.e. No titration)** **Other** ☐ **Mean total dose** ☐ Median total dose	☐ Duration of dose titration (specify #:) ☐ Unclear ☐ Not specified ☐ Not applicable Units ○ Days ○ Weeks ○ Months ○ Years ○ Other (specify): Clear Response

Please complete the baseline characteristics for this study group:

Total N at enrollment for this intervention group

Age

☐ Mean ☐ Range

Report age categories in addition to mean or range if provided

Age category ☐ specify ☐ n ☐ %

Age category ☐ specify ☐ n ☐ %
Age category ☐ specify ☐ n ☐ %
Age category ☐ specify ☐ n ☐ %
Age category ☐ specify ☐ n ☐ %
Age category ☐ specify ☐ n ☐ %

☐ Age not reported

Male

☐ n ☐ % ☐ Gender not reported

Race/Ethnicity

African American ☐ n ☐ %
Asian or Asian American ☐ n ☐ %
Caucasian ☐ n ☐ %
Hispanic or Latino ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %
Other race/ethnicity ☐ specify ☐ n ☐ %

☐ Race/ethnicity not reported

BMI/Weight

☐ Mean weight (include units) ☐ Mean BMI

Only report other measures if mean weight or BMI is not reported

Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:

☐ BMI/weight not reported

HgbA1c

☐ Mean HgbA1c

Only report other measures if mean HgbA1c is not reported

Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:

☐ HgbA1c not reported

Duration of diabetes

☐ Mean (years)

Only report other measures if mean duration of diabetes is not reported

Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:
Other measures ☐ specify measure: ☐ value:

☐ Duration of diabetes not reported

Number of withdrawals

Comments **(limit 250 characters)**

61. Comments **(limit 250 characters)**

62. Comments **(limit 250 characters)**

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Diabetes Medications Outcomes Form

Fill out this form for all included studies

Outcome of interest being reported on this form **(check only one outcome under KQ1, KQ2, or KQ3 on this form)**:

Key Question 1

Outcome	Units
☐ HgbA1c	☐ % ☐ Cut-point (only if mean or median not reported; specify):
☐ LDL	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ HDL	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ Triglycerides	☐ mmol/L ☐ umol/L ☐ mg/dL
☐ Weight	☐ kg ☐ lbs
☐ BMI (only if weight is not reported)	☐ kg/m2

Key Question 2

☐ All cause mortality

Cardiovascular Mortality

☐ Fatal myocardial infarction
☐ Other (e.g., sudden cardiac death) (specify):
☐ Composite outcome (list if specified):
☐ Unspecified

Cardiovascular Morbidity

☐ Non-fatal myocardial infarction (specify how defined):
☐ Other (e.g., acute coronary syndrome, arrhythmia, cardiac procedures, like percutaneous coronary intervention (PCI)) (congestive heart failure will be captured under Key Question 3) (specify):
☐ Composite outcome (list if specified):
☐ Unspecified

Cerebrovascular Mortality/Disease

☐ Fatal stroke
☐ Non-fatal stroke (specify how defined):
☐ Other (e.g., transient ischemic attack) (specify):

Incident diabetic retinopathy (macular edema will be captured under Key Question 3)

☐ Incident diabetic retinopathy (specify):
☐ Not specified

Incident diabetic nephropathy (e.g., changes in proteinuria or microalbuminuria, ESRD, dialysis outcomes, etc.)

☐ Incident diabetic nephropathy (specify):
☐ Not specified

Incident diabetic neuropathy

☐ Incident diabetic neuropathy (specify):
☐ Not specified

Key Question 3

Adverse event or side effect

☐ Hypoglycemia - mild/minor (specify):
☐ Hypoglycemia - moderate (specify):
☐ Hypoglycemia - severe/major (specify):
☐ Liver failure (specify):
☐ Congestive heart failure (specify):
☐ Severe lactic acidosis (specify):
☐ Cancer (specify):
☐ Severe allergic reaction (specify):
☐ Hip fracture (specify):
☐ Non-hip fracture (specify):
☐ Pancreatitis (specify):
☐ Cholecystitis (specify):
☐ Macular edema (specify):
☐ Decreased vision (specify):
☐ Gastrointestinal side effects (specify):
☐ Other severe adverse event (specify):

If applies to Key Question 3 (adverse events and/or safety outcomes), please answer questions 21-23.

21. Was the mode of Adverse Event collection Active or Passive?

☐ Active (Active ascertainment of harms indicates (a) that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests, usually performed at pre-specified time intervals and/or (b) that the potential occurrence of harmful events are collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery. These events are potentially expected harms as a result of the intervention.)

☐ Passive (Passive ascertainment of harms occurs when study participants spontaneously report (on their own initiative) or are allowed to report harmful events not probed with active ascertainment. In some studies, laboratory or diagnostic tests are only ordered if a particular event is suspected. For example, a study participant is suspected of having a stroke based on clinical presentation; the authors would indicate that brain imaging tests would then be ordered to confirm the presence or absence of the stroke.)

☐ Not reported

22. Did the study specify frequency and timing of adverse event collection?

☐ Yes
☐ No
☐ Not applicable

23. Was the analysis for this outcome "intention-to-treat" (i.e., not per-protocol or "on treatment analysis")?

☐ Yes
☐ No
☐ Not reported

Please report results for outcome specified above

Dichotomous Outcomes (Most of outcomes for Key Questions 2 and 3)

Table I. Incidence of the outcome by intervention group

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis (use number enrolled in each group)	Outcome measure	Denominator (specify): ☐ Days ☐ Weeks ☐ Months ☐ Years ☐ Persons ☐ Person-years ☐ Other (specify): ☐ Not applicable	p-value (Record exact p-value)	Indicate reference group
Main intervention		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison D		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ specify other numerator type ☐ specify other numerator value			☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Table II. Measure of association for comparison of outcome between intervention groups

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate ☐ Relative risk (RR) ☐ Relative hazrad (HR) ☐ Odds ratio (OR) ☐ Risk difference ☐ Other (specify):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	95% Confidence Interval	p-value (Record exact p-value)	Indicate reference group
Main						

intervention				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison D				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

What were the results adjusted for in the final model?

- ☐ Age
- ☐ Sex
- ☐ Race
- ☐ BMI or weight
- ☐ Glycemic control
- ☐ Comorbidities
- ☐ Duration of diabetes
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Results are not adjusted
- ☐ RCT that did not adjust for any baseline difference

Continuous outcomes (Most of outcomes for Key Question 1)

Table III. Mean difference from other intervention group measures of outcome

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ☐ Mean ☐ Median ☐ Other (specify):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record exact p-value)	Indicate reference group
Main intervention				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D

						☐ Comparison E ☐ Other (specify):
Comparison B				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison D				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Table IV. Mean difference from baseline to final measures of outcome
(If values decrease, be sure to indicate with a negative sign (-)).

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ☐ Mean ☐ Median ☐ Other (specify):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record exact p-value)
Main intervention				☐ Lower limit ☐ Upper limit	
Comparison A				☐ Lower limit ☐ Upper limit	
Comparison B				☐ Lower limit ☐ Upper limit	
Comparison C				☐ Lower limit ☐ Upper limit	
Comparison D				☐ Lower limit ☐ Upper limit	
Comparison E				☐ Lower limit ☐ Upper limit	

Complete tables V and VI only if the point estimate AND measure of variability in tables III and IV are not reported.

Table V. Baseline measure of outcome

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ☐ Mean ☐ Median ☐ Other (specify):	Measure of variability ☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence interval ☐ IQR	p-value (Record exact p-value)
Main intervention				☐ Lower limit ☐ Upper limit	
Comparison A				☐ Lower limit ☐ Upper limit	
Comparison B				☐ Lower limit ☐ Upper limit	
Comparison C				☐ Lower limit ☐ Upper limit	
Comparison D				☐ Lower limit ☐ Upper limit	
Comparison E				☐ Lower limit ☐ Upper limit	

Table VI. Final measures of outcome

Intervention	N for analysis	Point estimate (please specify	Measure of variability		p-value (Record exact p-	Indicate reference group

group (Please be consistent with the labeling in the intervention form)		negative/positive sign) ☐ Mean ☐ Median ☐ Other (specify):	☐ SE ☐ SD ☐ Other (specify):	☐ 95% Confidence Interval ☐ IQR	value)	
Main intervention				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison A				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison B				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison C				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison D				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):
Comparison E				☐ Lower limit ☐ Upper limit		☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Baseline ☐ Other (specify):

Table VII. Other measures

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Other measure	Other measure	p-value (Record exact p-value)	Indicate reference group
Main intervention					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison A					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison B					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison C					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E

					☐ Other (specify):
Comparison D					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):
Comparison E					☐ Main intervention ☐ Comparison A ☐ Comparison B ☐ Comparison C ☐ Comparison D ☐ Comparison E ☐ Other (specify):

Comments **(limit 250 characters)**

Comments **(limit 250 characters)**

Comments **(limit 250 characters)**

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Diabetes Medications

Quality Form for Trials

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?

- ○ Yes
- ○ No
- ○ Not reported

2. If yes to Q1, was the randomization scheme described AND appropriate?

- ○ Yes: Appropriate randomization is if each study participant is allowed to have the same chance of receiving study drug
- ○ No: Randomization described and inappropriate (e.g. allocation using date of birth)
- ○ No:not described

3. Was the study described as double blind?

- ○ Yes
- ○ No
- ○ Not reported/Can't tell

4. If yes to Q3, was the method of double blinding described AND appropriate?

- ○ Yes: appropriate double blinding is if neither the person doing the assessments nor the study participant could identify the intervention being assessed OR if the use of active placebos, identical palcebos or dummies is mentioned
- ○ No: the study was described as double blind AND inappropriate (e.g. comparison of tablet vs. lifestyle)
- ○ No: no description of double blinding available and unable to tell if appropriate or not

5. Was there a description of withdrawals and dropouts?

- ○ Yes: the number and the reasons for withdrawals in each group was stated or it was stated that there were no withdrawals (if subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis)
- ○ No

6. Please rate the overall quality of the study

- ○ Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
- ○ Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
- ○ Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Clear Response

7. Comments **(limit 250 characters)**

8. Comments **(limit 250 characters)**

9. Comments **(limit 250 characters)**

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Diabetes Medications
Quality Form for Observational Trials

1. Did the study describe the setting or population from which the study sample was drawn?

- ○ Yes, complete description including an appropriate sampling scheme (consecutive, random)
- ○ Yes, but without description of sampling scheme or used a scheme that could bias results (convenience)
- ○ No or insufficient to replicate

2. Were the inclusion and exclusion criteria for subjects described?

- ○ Yes
- ○ No

3. Is there description of key characteristics of the enrolled subjects that could affect outcomes?

- ○ Yes with detailed description of covariates expected to affect outcomes (e.g. age, duration of diabetes, other therapies)
- ○ Some description of covariates (e.g., age, sex)
- ○ No

4. Is there sufficient detail about the treatment?

- ○ Yes, describes the treatment type, dose, timing and duration of medications AND the results for all subjects who took medication
- ○ No, Either omits relevant information on treatment and intensity (dose or duration) OR does not report the results for all subjects exposed to the medication
- ○ No, does neither

5. Is there sufficient detail about one or more outcomes and are they objectively measured?

- ○ Yes
- ○ Some description of outcomes but poorly detailed
- ○ No

6. Is the statistical analysis described and appropriate for the primary comparison?

- ○ Yes
- ○ No

7. Are the results presented adjusted or stratified for differences in groups or stated that the groups were comparable at baseline?

- ○ Yes
- ○ No
- ○ Not applicable

8. Does the study describe the number of participants who were lost to follow-up after the start of the period of observation?

- ○ Yes
- ○ No
- ○ Not applicable (e.g. cross-sectional study)
- ○ Unclear

9. What percentage of patients was lost to follow-up?

- ○ <10% in any group
- ○ 10-20% in any group
- ○ >20%
- ○ Not reported

10. Please rate the overall quality of the study.

○ Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.

○ Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

○ Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

11. Comments **(limit 250 characters)**

12. Comments **(limit 250 characters)**

13. Comments **(limit 250 characters)**

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Appendix E. Tallies for Comparisons Not Included in Review

Main intervention	Comparator	Number of studies
Metformin	Acarbose	3
Metformin	Any insulin	3
Metformin	Placebo or any non-drug intervention	21
Metformin	Metformin + GLP-1 agonist	5
Metformin	Metformin + insulin	3
Thiazolidinedione	Acarbose	1
Thiazolidinedione	Placebo or any non-drug intervention	38
Sulfonylurea	Acarbose	6
Sulfonylurea	Placebo or any non-drug intervention	18
DPP-4 inhibitor	Placebo or any non-drug intervention	9
Meglitinides	Placebo or any non-drug intervention	10
GLP-1 agonist	Placebo or any non-drug intervention	1
Metformin + thiazolidinedione	Thiazolidinedione + DPP-4 inhibitor	3
Metformin + thiazolidinedione	Thiazolidinedione + GLP-1 agonist	1
Metformin + thiazolidinedione	Sulfonylurea + meglitinides	1
Metformin + sulfonylurea	Thiazolidinedione + basal insulin	1
Metformin + sulfonylurea	Sulfonylurea + basal insulin	2
Metformin + GLP-1 agonist	Thiazolidinedione + GLP-1 agonist	1
Metformin + GLP-1 agonist	Sulfonylurea + GLP-1 agonist	1
Metformin + basal insulin	Sulfonylurea + basal insulin	2
Metformin + premixed insulin	Sulfonylurea + premixed insulin	1
Metformin + premixed insulin	Meglitinides + premixed insulin	1

Additionally, our team attempted to tally, but found no studies evaluating the following comparisons:

- metformin versus bromocriptine
- metformin versus colesevalam
- sitagliptin versus acarbose
- meglitinides versus acarbose
- combination of metformin and either thiazolidinediones, meglitinides, sitagliptin, or premixed insulin versus combinations of thiazolidinedione and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and thiazolidinedione versus a combination that contains either a sulfonylurea, meglitinides, or sitagliptin and either a meglitinides, sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and sulfonylurea versus combinations of thiazolidinedione and either sitagliptin, exenatide, or premixed insulin
- combination of metformin and sulfonylurea versus a combination of sulfonylurea and either meglitinides, sitagliptin, exenatide, or premixed insulin
- combination of metformin and sulfonylurea versus a combination that contains either a meglitinides or sitagliptin and either a sitagliptin, exenatide, or premixed insulin
- combination of metformin and a basal insulin versus a combination of thiazolidinedione and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of metformin and basal insulin versus a combination that contains either a meglitinides or sitagliptin and either a sitagliptin, exenatide, or premixed insulin

- combination of thiazolidinedione and either sulfonylurea, meglitinides, sitagliptin, or exenatide versus a combination of thiazolidinediones and either meglitinides, sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of sulfonylurea and either meglitinides, sitagliptin, or exenatide versus a combination of sulfonylureas and either sitagliptin, exenatide, basal insulin, or premixed insulin
- combination of meglitinides and either sitagliptin or exenatide versus a combination of meglitinides and either exenatide, basal insulin, or premixed insulin
- combination of sitagliptin and exenatide versus a combination of sitagliptin and either basal insulin or premixed insulin

Appendix F. Excluded Articles

Aaboe K, Knop FK, Vilsboll T et al. Twelve weeks treatment with the DPP-4 inhibitor sitagliptin improves glycaemic control, but does not improve GLP-1 secretion, in patients with type 2 diabetes - A randomised trial. Diabetologia: Diabetologia 2009; 52(S1):S294. Other reason

Abbasi AA, Kasmikha R, Sotingeanu DG. Metformin-induced lacticacidemia in patients with type 2 diabetes mellitus. Endocr Pract 2000; 6(6):442-6. Does not have a drug comparison of interest

Abbatecola AM, Paolisso G. Rosiglitazone and cognitive stability in older persons with type 2 diabetes and mild cognitive impairment. Diabetologia: Diabetologia 2009; 52(S1):S67. Does not meet the study design criteria

Abbatecola AM, Rizzo MR, Barbieri M et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology 2006; 67(2):235-40. Does not apply

Abe M, Okada K, Kikuchi F, Matsumoto K. Clinical investigation of the effects of pioglitazone on the improvement of insulin resistance and blood pressure in type 2-diabetic patients undergoing hemodialysis. Clin Nephrol 2008; 70(3):220-8. Does not apply

Abraira C, Duckworth WC, Moritz T. Glycaemic separation and risk factor control in the Veterans Affairs Diabetes Trial: an interim report. Diabetes Obes Metab 2009; 11(2):150-6. No original data

Agarwal R. Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Renal Physiol 2006; 290(3):F600-5. Does not apply

Agrawal A, Sautter MC, Jones NP. Effects of rosiglitazone maleate when added to a sulfonylurea regimen in patients with type 2 diabetes mellitus and mild to moderate renal impairment: a post hoc analysis. Clin Ther 2003; 25(11):2754-64. Does not have a drug comparison of interest

Aguilar C, Reza A, Garcia JE, Rull JA. Biguanide related lactic acidosis: incidence and risk factors. Arch Med Res 1992; 23(1):19-24. Does not have a drug comparison of interest

Ahren B, Lundquist I, Schersten B. Effects of glipizide on various consecutive insulin secretory stimulations in patients with type 2 diabetes. Diabetes Res 1986; 3(6):293-300. Less than 40 subjects with type 2 diabetes

Ahren B, Simonsson E, Larsson H et al. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. Diabetes Care 2002; 25(5):869-75. Study duration less than 3 months

Akanuma Y, Kosaka K, Kanazawa Y, Kasuga M, Fukuda M, Aoki S. Long-term comparison of oral hypoglycemic agents in diabetic retinopathy. Gliclazide vs. other sulfonylureas. Diabetes Res Clin Pract 1988; 5(2):81-90. Does not have a drug comparison of interest

Alba M, Ahren B, Inzucchi SE et al. Initial combination therapy with sitagliptin and pioglitazone: Complementary effects on postprandial glucose and islet cell function. Can J Diabetes 2009; 33(3):319-20. Does not meet the study design criteria

Albertini JP, McMorn SO, Chen H, Mather RA, Valensi P. Effect of rosiglitazone on factors related to endothelial dysfunction in patients with type 2 diabetes mellitus. Atherosclerosis 2007; 195(1):e159-66. Does not have a drug comparison of interest

Alfonso A, Koops MK, Mong DP, Vigersky RA. Glycemic control with regular versus lispro insulin sliding scales in hospitalized Type 2 diabetics. J. Diabetes Complications 2006; 20(3):153-7. Does not have a drug comparison of interest

Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004; 116(4):230-5. Does not have a drug comparison of interest

Allen KV, McAulay V, Sommerfield AJ, Frier BM. Hypoglycaemia is uncommon with a combination of antidiabetic drugs and bedtime NPH insulin for type 2 diabetes. Pract. Diabetes Int. 2004; 21(5):179-82. Does not meet the study design criteria

Alvarez Guisasola F, Mavros P, Nocea G, Alemao E, Alexander CM, Yin D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008; 10 Suppl 1:8-15. Does not apply

Ambrosius WT, Danis RP, Goff DC Jr et al. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. Arch Ophthalmol 2010; 128(3):312-8. Does not have a drug comparison of interest

Anon. "PROactive" study shows Takeda's ACTOS® (pioglitazone HCl) reduces heart attacks, strokes and deaths in patients with type 2 diabetes. Publ. Takeda Res. Lab. 2005. Other reason

Anon. A randomised, multi-centre, phase IV, double-blind, parallel group study comparing the effects of 52 weeksĆ administration of AVANDAMET and metformin plus sulphonylurea on change in HbA1c from baseline in overweight type 2 diabetics poorly controlled on metformin. Other reason

Anon. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (Diabetes Care (1999) 22 (960-964)). Diabetes Care 1999; 22(11):1922. No original data

Anon. Clinical news updates from the 2005 AHA Scientific Sessions. Formulary 2006; 41(1):18-26. No original data

Anon. Comparison of the Blood Sugar Lowering Effect Between Repaglinide Plus Metformin and Repaglinide Alone in Type 2 Diabetics Not Previously Treated With Oral Sugar-lowering Drugs. ClinicalTrials.gov identifier: NCT00819741. Other reason

Anon. Diabetes drugs may cause heart-failure hazard. Health News 2004; 10(1):15. Does not meet the study design criteria

Anon. DPP-IV inhibitor better tolerated than metformin. Pharm. J. 2005; 275(7370):436. No original data

Anon. Drugs for type 2 diabetes. Treat Guidel Med Lett 2008; 6(71):47-54. No original data

Anon. Dual PPAR agonist improves glycemic control, lipids in type 2 diabetes. Geriatrics 2005; 60(8):12. No original data

Anon. Effect of AC2993 (synthetic exendin-4) compared with insulin glargine in patients with type 2 diabetes also using combination therapy with sulfonylurea and metformin. Eli Lilly Clinical Trial Registry Summary 2007. Does not have a drug comparison of interest

Anon. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):854-65. Does not have a drug comparison of interest

Anon. Effect of Repaglinide and Metformin Combination Tablet or Rosiglitazone and Metformin in Fixed Dose Combination on Blood Glucose Control in Patients With Type 2 Diabetes. ClincalTrials.gov identifier: NCT00399711. Other reason

Anon. Effects of metformin or repaglinide therapy for diabetes on serum markers for CVD. Nat Clin. Pract Endocrinol Metab 2008; 4(8):427. No original data

Anon. Efficacy and safety of pioglitazone. Aust J. Pharm 2008; 89(1064):62-3. No original data

Anon. Efficacy and Safety of Repaglinide and Metformin Combination Therapy in Type 2 Diabetes Failing on OAD. ClinicalTrials.gov identifier: NCT00491725. Other reason

Anon. Efficacy and Safety of Repaglinide and Metformin Combined in Type 2 Diabetes. ClinicalTrials.gov identifier: NCT00491725. Other reason

Anon. Efficacy of exenatide [AC2993, synthetic exendin-4, LY2148568] compared with twice-daily biphasic insulin aspart in patients with type 2 diabetes using sulfonylurea and metformin. Eli Lilly Clinical Trial Registry Summary 2007. 2007. Other reason

Anon. Erratum: Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: A randomised controlled trial (International Journal of Clinical Practice (2009) 63 (1395-1406)). Int J Clin Pract 2010; 64(2):277. Other reason

Anon. Exenatide (Byetta) for type 2 diabetes. Med Lett Drugs Ther 2005; 47(1210):45-6. No original data

Anon. First reports of serious adverse drug reactions in recent weeks. Drugs Ther Perspect 2006; 22(3):20-1. No original data

Anon. Improved risk profile with pioglitazone. Br J Diabetes Vasc Dis 2003; 3(6):446. No original data

Anon. Inhaled insulin superior to rosiglitazone in patients with uncontrolled type 2 diabetes. Formulary 2003; 38(7):408. No original data

Anon. Insulin sensitizer affects lipids. Health News 2005; 11(1):2. No original data

Anon. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):837-53. Does not have a drug comparison of interest

Anon. Janumet. JAAPA 2007; 20(6):14. No original data

Anon. Landmark PROactive trial investigates effect of ACTOS (pioglitazone HCl) on cardiovascular disease progression: More than 5,000 patients with type 2 diabetes studied. Publ. Takeda Res. Lab. 2004; 2004(-). Other reason

Anon. New data shows Takeda's ACTOS(registered trademark) (pioglitazone HCl) reduced heart attacks by 28 percent in people with type 2 diabetes. Publ. Takeda Res. Lab. 2005; 2005(-). Other reason

Anon. Oral agents for type 2 diabetes reduce HbA1c, are weight neutral. Geriatrics: Geriatrics 2006; 61(9):2 p following 13. No original data

Anon. PERISCOPE: pioglitazone offers the right cluster of effects to confer benefit in type 2 diabetes. Cardiovasc J Afr 2008; 19(3):159-62. No original data

Anon. Pre-meal inhaled insulin lowers HbA1c levels more effectively than rosiglitazone. Formulary 2005; 40(11):396. No original data

Anon. Primary prevention of cerebrovascular and cardiovascular events with an oral antidiabetic agent in patients with type 2 diabetes at high risk for cerebral infarction. UMIN CTR [Https://Center.Umin.Ac.Jp] 2009. Not written in English

Anon. PROactive study shows reduced heart attacks and strokes in type 2 diabetics on pioglitazone HCI (Actos) therapy. Cardiovasc J S Afr 2005; 16(5):286-7; discussion 287. No original data

Anon. Rosiglitazone decreases coronary restenosis. Cardiol Rev 2003; 20(8):11. No original data

Anon. Rosiglitazone increased heart failure but did not differ from metformin plus sulphonylurea for other CV outcomes at interim analysis. Evid.-Based Med. 2007; 12(6):170. No original data

Anon. Rosiglitazone plus metformin combination improves glycaemic control in diabetes. Pharm J 2004; 273(7317):375. No comparison group

Anon. Sitagliptin combined with sulphonylureas: new indication. Other treatments are preferable. Prescrire Int 2009; 18(99):14-5. No original data

Anon. Summaries for patients. A comparison of three insulin regimens (morning glargine, bedtime glargine, or bedtime neutral protamine Hagedorn) in addition to a pill for treating type 2 diabetes. Ann Intern Med 2003; 138(12):I33. No original data

Anon. Summaries for patients. Comparison of two types of insulin added to diabetes pills in poorly controlled type 2 diabetes. Ann Intern Med 2008; 149(8):I-46. No original data

Anon. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: A randomized trial (Annals of Internal Medicine (2007) 146 (477-485)). Ann Intern Med. 2007; 146(12):896. No original data

Anon. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. Diabetes Care 2005; 28(2):421-2. No comparison group

Anon. Thiazolidinediones could exacerbate BMD loss in elderly women. Nat. Clin. Pract. Endocrinol. Metab. 2006; 2(12):654-5. No original data

Anonymous. RAS - Rosiglitazone and Atherosclerosis Study: a 1 year randomised, double-blind. parallel group, placebo controlled study to evaluate the efficacy of rosiglitazone on the progression of intima-media thickness in the carotid artery in subjects with insulin resistance syndrome and/or type 2 diabetes mellitus. Http://Ctr.Gsk.Co.Uk/Summary/Rosiglitazone/IV_049653_334.Pdf 2004. No original data

Anwar A, Azmi KN, Hamidon BB, Khalid BA. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. Med J Malaysia 2006; 61(1):28-35. Other reason

Arauz-Pacheco C, Ramirez LC, Rios JM, Raskin P. Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. Am J Med 1990; 89(6):811-3. Does not meet the study design criteria

Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000; 23(11):1605-11. Does not have a drug comparison of interest

Asche CV, McAdam-Marx C, Shane-McWhorter L, Sheng X, Plauschinat CA. Association between oral antidiabetic use, adverse events and outcomes in patients with type 2 diabetes. Diabetes Obes Metab 2008; 10(8):638-45. Does not have a drug comparison of interest

Ascic-Buturovic B. The effects of combined insulin and metformin therapy in obese patients with diabetes mellitus type 2 in the early stage of the disease. Bosn J Basic Med Sci 2006; 6(2):54-8. Does not meet the study design criteria

Avery MA, Chittiboyina A, Patny A. Novel Tricyclic (alpha)-Alkoxyphenyl Propanoic Acid Derivatives: Dual PPAR(alpha)/(gamma) Agonists with Hypolipidemic and Antidiabetic Activity. Chemtracts 2003; 16(11):653-9. No original data

Baba S, Nakagawa S, Takebe K et al. Comparison of gliclazide and glibenclamide treatment in non-insulin-dependent diabetes. Tohoku J Exp Med 1983; 141 Suppl:693-706. Does not have a drug comparison of interest

Babich MM, Pike I, Shiffman ML. Metformin-induced acute hepatitis. Am J Med 1998; 104(5):490-2. No comparison group

Bachmann W, Sieger C, Haslbeck M, Lotz N. Combination of insulin and glibenclamide (gl) in the treatment of adult-onset diabetes (type 2). Diabetologia 1981; 21(3):21. Less than 40 subjects with type 2 diabetes

Bahadori B, Trinker M, Wallner SJ, Yazdani-Biuki B, Wascher TC. Diabetes mellitus and weight control: Differences of respiratory quotient in type 2 diabetic obese subjects receiving sulfonylureas and non-diabetic obese controls. Nutrition 2003; 19(2):159-60. Does not have a drug comparison of interest

Bain SC, Stella P, Cao A. Significantly reduced body mass index with liraglutide 1.2 mg treatment versus glimepiride may have an impact on cardiovascular risk in patients with type 2 diabetes. Diabetic Medicine: Diabet. Med. 2010; 27(Suppl 1):79. No original data

Baksi A, James RE, Zhou B, Nolan JJ. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. Acta Diabetol 2004; 41(2):63-9. Does not have a drug comparison of interest

Balkrishnan R, Rajagopalan R, Shenolikar RA, Camacho FT, Anderson RT. Outcomes associated with introduction of thiazolidinedione therapy in Medicaid enrolled patients with type 2 diabetes: an updated and expanded retrospective analysis. Curr Med Res Opin 2006; 22(3):551-9. Does not have a drug comparison of interest

Ballani P, Tran MT, Navar MD, Davidson MB. Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. Diabetes Care 2006; 29(11):2504-5. Less than 40 subjects with type 2 diabetes

Ballary C, Desai A. Efficacy and safety of a combination of metformin and rosiglitaone in patients with type 2 diabetes mellitus--a postmarketing study. J Indian Med Assoc 2003; 101(2):113-4, 123. No comparison group

Barnes DJ et al. Microalbuminuria in type 2 diabetic patients: a cross sectional study. Ann Clin Biochem 1994; 31 (Pt 6):588-9. No original data

Barnett AH et al. Multicentre study to assess quality of life and glycaemic control of Type 2 diabetic patients treated with insulin compared with oval hypoglycaemic agents. Practical Diabetes International. 1996; 13(6):179-83. Does not have a drug comparison of interest

Barnett AH, Burger J, Johns D et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther 2007; 29(11):2333-48. Does not have a drug comparison of interest

Barnett AH, Burger J, Johns D et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther 2007; 29(11):2333-48. Does not have a drug comparison of interest

Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. Diabetes Care 2006; 29(8):1818-25. Does not have a drug comparison of interest

Barnett AH, Grant PJ, Hitman GA et al. Rosiglitazone in Type 2 diabetes mellitus: an evaluation in British Indo-Asian patients. Diabet Med 2003; 20(5):387-93. Does not have a drug comparison of interest

Barranco C. Pioglitazone improves cardiovascular risk markers for patients with diabetes. Nat. Clin. Pract. Cardiovasc. Med. 2005; 2(9):438. No original data

Barzilay JI et al. Coronary artery disease and coronary artery bypass grafting in diabetic patients aged > or = 65 years (report from the Coronary Artery Surgery Study [CASS] Registry). Am J Cardiol 1994; 74(4):334-9. Does not apply

Baynes C, Feher MD, Elkeles RS. The effect of treatment of non-insulin-dependent diabetes mellitus (NIDDM) on serum lipids and lipoproteins. Q. J. MED. 1989; 72(267):579-87. No original data

Bech P, Moses R, Gomis R. The effect of prandial glucose regulation with repaglinide on treatment satisfaction, wellbeing and health status in patients with pharmacotherapy naive Type 2 diabetes: a placebo-controlled, multicentre study. Qual Life Res 2003; 12(4):413-25. Does not have a drug comparison of interest

Beck-Nielsen H, Lindskov HO, Richelsen B. Mechanism of action of glibenclamide in type 2 (non-insulin dependent) diabetes during long-term treatment. Diabetologia 1982; 23(2):No. 16. Does not apply

Belcher G, Matthews DR. Safety and tolerability of pioglitazone. Exp Clin Endocrinol Diabetes 2000; 108(Suppl 2):267-73. Does not meet the study design criteria

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Belden H. New diabetes treatment combines two drugs into one. Drug Topics 2006; 150(17). No original data

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Bell DS, Mayo MS. Outcome of metformin-facilitated reinitiation of oral diabetic therapy in insulin-treated patients with non-insulin-dependent diabetes mellitus. Endocr Pract 1997; 3(2):73-6. Does not apply

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Bell DS, Yumuk V. Frequency of severe hypoglycemia in patients with non-insulin-dependent diabetes mellitus treated with sulfonylureas or insulin. Endocr Pract 1997; 3(5):281-3. Does not apply

Bell DSH, Wyne KL. Use of fixed-dose oral combinations. Postgrad. Med. 2006; 119(2). No original data

Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med 1999; 159(3):281-4. Does not apply

Bengel FM, Abletshauser C, Neverve J et al. Effects of nateglinide on myocardial microvascular reactivity in Type 2 diabetes mellitus--a randomized study using positron emission tomography. Diabet Med 2005; 22(2):158-63. Does not have a drug comparison of interest

Bergenstal R, Wysham C, Yan P, MacConell L, Malloy J, Porter L. Duration-2: Exenatide once weekly demonstrated significant glycaemic control and weight reduction compared to sitagliptin or pioglitazone after 26 weeks of treatment. Diabetic Medicine: Diabet. Med. 2010; 27(2):5. No original data

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Bergman AJ, Cote J, Yi B et al. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. Diabetes Care 2007; 30(7):1862-4. No subjects with type 2 diabetes

Bermudez-Pirela VJ, Cano C, Medina MT et al. Metformin plus low-dose glimeperide significantly improves Homeostasis Model Assessment for insulin resistance (HOMA(IR)) and beta-cell function (HOMA(beta-cell)) without hyperinsulinemia in patients with type 2 diabetes mellitus. Am J Ther 2007; 14(2):194-202. Does not have a drug comparison of interest

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Best JD, Drury P, Davis T, Taskinen M-R, Kesaniemi A, Keech A. Metformin, sulphonylurea and insulin therapies maintain glycaemic control over five years in 4900 people with type 2 diabetes. Diabetologia: Diabetologia 2009; 52(S1):S93. No original data

Best JH, Yan P, Malloy J. DURATION 2: Weight-related quality of life, psychological well-being, and satisfaction with exenatide once weekly compared to sitagliptin or piaglitazone after 26 weeks of treatment. Diabetologia: Diabetologia 2009; 52(S1):S292-S293. Other reason

Bhansali A, Masoodi SR. Efficacy of once- or twice-daily extended release metformin compared with thrice-daily immediate release metformin in type 2 diabetes mellitus. J Assoc Physicians India 2005; 53:441-5. Does not have a drug comparison of interest

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Appendix G. Evidence Tables

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence (KQ1). Outcome: Hemoglobin A1c

# of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. TZD							
16	5592	Medium	Consistent for short-duration studies. One long-term study Inconsistent.	Direct	Precise	No effect; Neither drug favored	Moderate
Met vs. SU							
19	6936	Low	Consistent	Direct	Precise	No effect; Neither drug favored	High
Met vs. DPP-4 Inhibitors							
3	1908	Medium	Consistent	Direct	Precise	Small; Favored Met	Moderate
Met vs. Nateg							
1	267	Medium	NA	Direct	Imprecise	Small; Favored Met	Low
Met vs. Repag							
2	167	Medium	Consistent	Direct	Imprecise	No effect; Neither drug favored	Low
Met vs. Met + TZD							
11	3495	Low	Consistent	Direct	Precise	Small; Favored Met + TZD	High
Met vs. Met + SU							
14	3619	Low	Consistent	Direct	Precise	Small; Favored Met + SU	High
Met vs. Met + DPP-4 Inhibitors							
6	4263	Medium	Consistent	Direct	Precise	Small; Favored Met + DPP-4 Inhibitor	Moderate
Met vs. Met + Nateg							
2	969	Low	Consistent	Direct	Imprecise	Small; Favored Met + Nateg	Low
Met vs. Met + Repag							
1	54	Low	NA	Direct	Precise	Small; Favored Met + Repag	Low
Rosi vs. Pio							
3	886	Medium	Consistent	Direct	Precise	No effect; Neither drug favored	Moderate
TZD vs. SU							
14	5578	Medium	Consistent	Direct	Precise	No effect; Neither drug favored	Moderate
TZD vs. Repag							
2	225	High	Inconsistent	Direct	Precise	Small; Unable to determine which drug favored	Low
TZD vs. Nateg							
1	34	Medium	NA	Direct	Imprecise	No effect; Neither drug favored	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence (KQ1).Outcome: Hemoglobin A1c (continued)

# of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
SU vs. DPP-4 Inhibitors							
1	618	Low	NA	Direct	Imprecise	No effect; Neither drug favored	Low
SU vs. Repag							
7	1543	Low	Consistent	Direct	Precise	No effect; Neither drug favored	High
SU vs. Nateg							
2	82	Medium	Consistent	Direct	Imprecise	No effect; Neither drug favored	Low
SU vs. GLP-1 Agonists							
3	1310	Medium	Inconsistent	Direct	Precise	Unable to determine	Low
Met + TZD vs. Met + SU							
8	2729	Low	Consistent for short-term trials. One long-term study Inconsistent.	Direct	Precise	No effect; Neither drug combination favored in the short term	Moderate
Met + TZD vs. Met + DPP-4 Inhibitors							
2	293	Medium	Consistent	Direct	Precise	No effect; Neither drug combination favored	Low
Met + TZD vs. Met + Repag							
1	561	Medium	NA	Direct	Precise	No effect; Neither drug combination favored	Low
Met + TZD vs. Met + GLP-1 Agonists							
1	90	Medium	NA	Direct	Imprecise	No effect; Neither drug combination favored	Low
Met + TZD vs. TZD + SU							
1	170	Medium	NA	Direct	Imprecise	Small; Favored combination of TZD + SU	Low
Met + SU vs. Met + DPP-4 Inhibitors							
1	1172	Low	NA	Direct	Precise	No effect; Neither drug combination favored	Low
Met + SU vs. Met + Nateg							
2	661	Low	Inconsistent	Direct	Imprecise	Unable to determine	Low
Met + SU vs. Met + GLP-1 Agonists							
2	1215	Medium	Inconsistent	Direct	Imprecise	Unable to determine	Low
Met + SU vs. Met + Premixed Insulin							
2	827	Medium	Inconsistent	Direct	Imprecise	Unable to determine	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence (KQ1).Outcome: Hemoglobin A1c (continued)

# of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + SU vs. TZD + SU							
6	1844	Medium	Consistent for short term trials. One longer study Inconsistent.	Direct	Precise	No effect; Neither drug combination favored	Moderate
Met + DPP-4 Inhibitors vs. Met + GLP-1 Agonists							
1	661	Medium	NA	Direct	Precise	Small; Favored combination of Met + GLP-1 Agonist	Low
Met + GLP-1 Agonists vs. Met + Basal Insulin							
1	69	High	NA	Direct	Imprecise	No effect; Neither drug favored	Low
Met + Basal Insulin vs. Met + Premixed Insulin							
3	530	Medium	Consistent	Direct	Precise	No effect; Neither drug combination favored	Low

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

* Directness was graded based on how well the evidence for a particular comparison related to the outcome of hemoglobin A1c.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Weight

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. TZD							
10	5239	Low	Consistent	Direct	Precise	Small; Favored Met	High
Met vs. SU							
13	5067	Medium	Consistent	Direct	Precise	Small; Favored Met	High
Met vs. DPP-4 Inhibitors							
3	1908	Medium	Consistent	Direct	Precise	Small; Favored Met	Moderate
Met vs. Meg (both Repag)							
2	166	High	Possibly Inconsistent	Direct	Imprecise	Unable to determine	Low
Met vs. Met + TZD							
7	2647	Low	Consistent	Direct	Precise	Small; Favored Met monotherapy	High
Met vs. Met + SU							
10	2510	Low	Consistent	Direct	Precise	Small; Favored Met monotherapy	High
Met vs. Met + DPP-4 Inhibitors							
6	4263	Medium	Consistent	Direct	Precise	No effect; Neither drug favored	Moderate
Met vs. Met + Meg							
2	521	Low	Consistent	Direct	Imprecise	Small; Favored Met monotherapy	Low
TZD vs. TZD							
3	886	Medium	Consistent	Direct	Precise	No effect; Neither drug favored	Low
TZD vs. SU							
7	6226	High	Consistent	Direct	Precise	Small; Favored SU	Low
TZD vs. Meg							
2	198	High	Consistent	Direct	Imprecise	Unable to determine	Low
SU vs. DPP-4 Inhibitors							
1	618	Low	NA	Direct	Imprecise	Unable to determine	Low
SU vs. Meg (all Repag)							
6	1326	Low	Consistent	Direct	Precise	No effect; Neither drug favored	High
SU vs.GLP-1 Agonists							
3	1310	Medium	Consistent	Direct	Imprecise	Small; Favored GLP-1 Agonist	Moderate
Met + TZD vs. Met + SU							
6	2407	Low	Consistent	Direct	Precise	Small; Favored Met + SU	Moderate
Met + TZD vs. Met + DPP-4 Inhibitors							
2	293	Medium	Consistent	Direct	Imprecise	Small; Favored Met + DPP-4 Inhibitor	Low
Met + TZD vs. Met + Meg							
1	561	Medium	NA	Direct	Imprecise	Unable to determine	Low
Met + TZD vs. Met + GLP-1 Agonists							
1	90	Low	NA	Direct	Precise	Small; Favored Met + GLP-I Agonist	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Weight (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + SU vs. Met + DPP-4 Inhibitors							
1	1172	Low	NA	Direct	Precise	Small; Favored Met + DPP-4 Inhibitor	Low
Met + SU vs. Met + Meg							
2	494	Low	Inconsistent	Direct	Imprecise	Unable to determine	Low
Met + SU vs. Met + GLP-1 Agonists							
2	1215	Medium	Consistent	Direct	Imprecise	Small; Favored Met + GLP-I Agonist	Low
Met + SU vs. Met + Premixed Insulin							
2	819	Low	Consistent	Direct	Precise	No effect; Neither drug combination favored	Low
Met + SU vs. TZD + SU							
4	2341	Low	Consistent	Direct	Imprecise	Small; Favored Met + SU	Moderate
Met + DPP-4 Inhibitors vs. Met + GLP-1 Agonists							
1	661	Medium	NA	Direct	Precise	Small; Favored Met + GLP-1 Agonist	Low
Met + GLP-1 Agonists vs. Met + Basal Insulin							
1	69	High	NA	Direct	Imprecise	Small; Favored Met + GLP-1 Agonist	Low
Met + Basal Insulin vs. Met + Premixed Insulin							
3	530	Medium	Consistent	Direct	Imprecise	No effect; Neither drug combination favored	Low

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

* Directness was graded based on how well the evidence for a particular comparison related to the outcome of weight.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Low density lipoprotein

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. Rosi							
7	511	Low	Consistent	Direct	Imprecise	Large; Favored Met	Moderate
Met vs. Pio							
6	1526	Low	Consistent	Direct	Precise	Large; Favored Met	High
Met vs. SU							
9	1774	Medium	Consistent	Direct	Precise	Large; Favored Met	High
Met vs. DPP-4 Inhibitors							
3	663	Medium	Consistent	Direct	Imprecise	Small; Favored Met	Moderate
Met vs. Meg							
1	112	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + Rosi							
7	2445	Low	Consistent	Direct	Precise	Large; Favored Met	High
Met vs. Met + Pio							
2	423	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + SU							
7	1845	Medium	Inconsistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Met + DPP-4 Inhibitors							
4	1943	Medium	Inconsistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Met + Meg							
1	467	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
TZD vs. TZD							
2	846	High	Consistent	Direct	Imprecise	Small; Favored Pio	Low
Rosi vs. SU							
2	716	Medium	Consistent	Direct	Imprecise	Large; Favored SU	Low
Pio vs. SU							
3	465	High	Consistent	Direct	Precise	Small; Favored SU	Low
TZD vs. DPP-4 Inhibitors							
0		NA	NA	NA	NA	NA	Insufficient
Rosi vs. Meg							
1	54	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Pio vs. Meg							
1	56	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Low density lipoprotein (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
SU vs. DPP-4 Inhibitors							
1	618	Low	NA	Direct	Imprecise	No effect; Neither favored	Low
SU vs. Meg							
2	668	Medium	Consistent	Direct	Imprecise	No effect; Neither favored	Low
SU vs. GLP-1 Agonists							
1	400	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
DPP-4 Inhibitors vs. Meg							
0		NA	NA	NA	NA	NA	Insufficient
Met + Rosi vs. Met + SU							
4	1708	Low	Consistent	Direct	Imprecise	Large; Favored Met + SU	Moderate
Met + Pio vs. Met + SU							
1	205	Low	NA	Direct	Imprecise	Small; Favored Met + SU	Low
Met + Rosi vs. Met + DPP-4 Inhibitors							
2	293	Medium	Consistent	Direct	Imprecise	Unable to determine, Favored Met + DPP-4 Inhibitor	Low
Met + Rosi vs. Met + Meg							
1	561		NA	Direct	Precise	Large; Favored Met + Meg	Low
Met + Rosi vs. Met + GLP-1 Agonists							
1	90	Medium	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + Pio vs. Pio + SU							
1	170	Medium	NA	Direct	Imprecise	No effect; Neither favored	Low
Met + SU vs. Met + Meg							
3	661	Low	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + SU vs. Rosi + SU							
2	696	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + SU vs. Pio + SU							
2	717	Medium	Consistent	Direct	Imprecise	Small; Favored Met + SU	Low
Met + DPP-4 Inhibitors vs. Met + GLP-1 Agonists							
1	661	Low	NA	Direct	Imprecise	Unable to determine, unable to determine	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Low density lipoprotein (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + DPP-4 Inhibitors vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Premixed Insulin vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Premixed Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

* Directness was graded based on how well the evidence for a particular comparison related to the outcome of low density lipoprotein

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: High density lipoprotein

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. Rosi							
6	393	Medium	Consistent	Direct	Precise	No effect; Neither favored	Moderate
Met vs. Pio							
8	506	Medium	Consistent	Direct	Precise	Small; Favored Pio	High
Met vs. SU							
12	1953	Medium	Consistent	Direct	Precise	No effect; Neither favored	High
Met vs. DPP-4 Inhibitors							
3	2100	Medium	Inconsistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Meg							
1	112	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + Rosi							
7	2689	Low	Consistent	Direct	Precise	Small; Favored Rosi	High
Met vs. Met + Pio							
2	470	Medium	Consistent	Direct	Imprecise	Large; Favored Met + Pio	Low
Met vs. Met + SU							
7	1841	Medium	Inconsistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Met + DPP-4 Inhibitors							
4	2271	Medium	Inconsistent	Direct	Precise	No effect; Neither favored	Moderate
Met vs. Met + Meg							
1	467	Low	NA	Direct	Imprecise	No effect; Neither favored	Low
TZD vs. TZD							
3	886	High	Consistent	Direct	Precise	Small; Favored Pio	Moderate
Rosi vs. SU							
2	790	Medium	Consistent	Direct	Imprecise	Large; Favored Rosi	Low
Pio vs. SU							
5	616	Medium	Consistent	Direct	Imprecise	Small; Favored Pio	Moderate
TZD vs. DPP-4 Inhibitors							
0		NA	NA	NA	NA	NA	Insufficient
Rosi vs. Meg							
1	74	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Pio vs. Meg							
2	94	High	Consistent	Direct	Imprecise	Small; Favored Pio	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: High density lipoprotein (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
SU vs. DPP-4 Inhibitors							
1	618	Low	NA	Direct	Imprecise	No effect; Neither favored	Low
SU vs. Meg							
6	1108	Low	Consistent	Direct	Precise	No effect; Neither favored	High
DPP-4 Inhibitors vs. Meg							
0		NA	NA	NA	NA	NA	Insufficient
DPP-4 Inhibitors vs. GLP-1 Agonists							
1	400	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + Rosi vs. Met + SU							
4	1738	Low	Consistent	Direct	Imprecise	Small; Favored Met + Rosi	Moderate
Met + Pio vs. Met + SU							
2	388	Medium	Consistent	Direct	Precise	Large; Favored Met + Pio	Low
Met + Rosi vs. Met + DPP-4 Inhibitors							
2	181	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + Rosi vs. Met + Meg							
1	561	?	NA	Direct	Precise	Small; Favored Met + Rosi	Low
Met + Rosi vs. Met + GLP-1 Agonists							
1	90	Medium	NA	Direct	Imprecise	Small; Favored Met + Rosi	Low
Met + Pio vs. Pio + SU							
1	170	Medium	NA	Direct	Imprecise	Small; Favored Met + Pio	Low
Met + TZD vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + SU vs. Met + Meg							
2	661	Low	Consistent	Direct	imprecise	No effect; Neither favored	Low
Met + SU vs. Met + Premixed Insulin							
1	230	Low	NA	Direct	imprecise	No effect; Neither favored	Low
Met + SU vs. Rosi + SU							
2	980	Medium	Inconsistent	Direct	imprecise	Unable to determine, unable to determine	Low
Met + SU vs. Pio + SU							
3	864	Medium	Consistent	Direct	imprecise	Small; Favored Pio + SU	Low
Met + SU vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: High density lipoprotein (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + DPP-4 Inhibitors vs. Met + liraglutide							
1	661	Medium	NA	Direct	Precise	No effect; Neither favored	Low
Met + DPP-4 Inhibitors vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + DPP-4 Inhibitors vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Premixed Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

* Directness was graded based on how well the evidence for a particular comparison related to the outcome of high density lipoprotein.

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Triglycerides

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. Rosi							
7	459	Medium	Inconsistent	Direct	imprecise	Large; Favored Met	Moderate
Met vs. Pio							
8	506	Medium	Consistent	Direct	Precise	Large; Favored Pio	High
Met vs. SU							
12	1531	Medium	Consistent	Direct	Imprecise	Small; Favored Met	Moderate
Met vs. DPP-4 Inhibitors							
3	2100	Medium	Consistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Meg							
1	112	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + Rosi							
7	2470	Low	Consistent	Direct	Precise	Large; Favored Met	High
Met vs. Met + Pio							
2	479	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Met vs. Met + SU							
8	1584	Medium	Inconsistent	Direct	Imprecise	No effect; Neither favored	Low
Met vs. Met + DPP-4 Inhibitors							
4	2594	Medium	Consistent	Direct	Imprecise	Large; Favored Met + DPP-4 Inhibitor	Low
Met vs. Met + Meg							
1	467	Low	NA	Direct	Imprecise	Small; Favored Met + Meg	Low
TZD vs. TZD							
3	886	High	Consistent	Direct	Imprecise	No effect; Neither favored	Low
Rosi vs. SU							
2	716	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Low
Pio vs. SU							
6	616	High	Consistent	Direct	Imprecise	Large; Favored Pio	Low
TZD vs. DPP-4 Inhibitors							
0		NA	NA	NA	NA	NA	Insufficient
Rosi vs. Meg							
1	74	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Pio vs. Meg							
2	94	High	Consistent	Direct	Imprecise	Large; Favored Pio	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Triglycerides (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
SU vs. DPP-4 Inhibitors							
1	618	Low	NA	Direct	Imprecise	No effect; Neither favored	Low
SU vs. Meg							
6	1113	Medium	Consistent	Direct	Precise	No effect; Neither favored	Moderate
SU vs. GLP-1 Agonists							
1	400	High	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
DPP-4 Inhibitors vs. Meg							
0		NA	NA	NA	NA	NA	Insufficient
Met + Rosi vs. Met + SU							
4	1735	Low	Consistent	Direct	Imprecise	No effect; Neither favored	Moderate
Met + Pio vs. Met + SU							
2	388	Medium	Consistent	Direct	Precise	Large; Favored Met + Pio	Moderate
Met + Rosi vs. Met + DPP-4 Inhibitors							
2	673	Medium	Consistent	Direct	Imprecise	Unable to determine, Favored Met + DPP-4 Inhibitor	Low
Met + Rosi vs. Met + Meg							
1	181		NA	Direct	Imprecise	No effect; Neither favored	Low
Met + Rosi vs. Met + GLP-1 Agonists							
1	90	Medium	NA	Direct	Imprecise	Large; Favored Met + GLP-1 Agonist	Low
Met + Pio vs. Pio + SU							
1	170	Medium	NA	Direct	Imprecise	Small; Favored Pio + SU	Low
Met + TZD vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + SU vs. Met + Meg							
2	661	Low	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Insufficient
Met + SU vs. Met + Premixed Insulin							
1	230	Low	NA	Direct	Unable to determine	No effect; Neither favored	Low
Met + SU vs. Rosi + SU							
2	3390	Medium	Inconsistent	Direct	Imprecise	Unable to determine, unable to determine	Insufficient
Met + SU vs. Pio + SU							
4	942	Medium	Inconsistent	Direct	Imprecise	Unable to determine, Favored Pio + SU	Low

Table 1. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Triglycerides (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + SU vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + DPP-4 Inhibitors vs. Met + GLP-1 Agonists							
1	661	Low	NA	Direct	Imprecise	Unable to determine, unable to determine	Low
Met + DPP-4 Inhibitors vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + DPP-4 Inhibitors vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Meg vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + GLP-1 Agonists vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. Met + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Basal Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient
Met + Premixed Insulin vs. TZD + Another agent							
0		NA	NA	NA	NA	NA	Insufficient

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

* Directness was graded based on how well the evidence for a particular comparison related to the outcome of triglycerides.

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2010[121] Japan	Neither year reported 24 weeks	Yes	< 6 months	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 weeks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 weeks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Derosa, 2010[44] Italy	Neither year reported 12 months	No run-in period	< 6 months	No	128/128 patients identified from case notes and clinical registers	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
DeFronzo, 2010[287] U.S.	Start Year 2006 End Year 2008 20 weeks	No run-in period	< 6 months	Yes	NR/137 NR	Age <18 or >75 years, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 weeks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other ODM (other than metformin)
Aschner, 2010[77] Multicontinent	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	2068/1050 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, CK > 2x upper limit normal
Seck, 2010[134] NR	Neither year reported 2 years	Run-in period but number of participants excluded was NR	< 6 months	Yes	2141/1172 NR	Age <17 or >78 years
Pratley, 2010[143] Multicontinent Europe, U.S., and Canada	Start year 2008 End year 2009 26 months	No run-in period	>= 6months	Yes	1302/665 “Office-based”- possibly out patient	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemic or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Home, 2009[16] Multinational Europe	Start year 2001 End year 2003 7.5 Years	Run-in period but number of participants excluded was NR	>= 6 months	Yes	7428/4458 Outpatient primary care	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception
Raskin, 2009[131] NR	Neither year reported 26 Weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient primary care	Age <18 years, pregnant, nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260 mg/dL, any disease or abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, allergy to study drugs or related compounds, history of hypoglycemia unawareness or recurrent severe hyperglycemia
Derosa, 2009[46] Italy	Neither year reported 15 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	NR	271/252 Outpatient primary care, computerized clinic registry	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5%, BMI <25 kg/m^2 or >30 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Van der Meer, 2009[141] Netherlands	Neither year reported 24 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	173/80 NR	Age <45 or >65 years, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mmHg, DBP <85 mmHg, prior TZD or insulin use
Kaku, 2009[84] Japan	Start year 2005 40 Weeks	Yes	< 6 months	Yes	NR/236 NR	Age ≤ 20 and ≥65 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, gastrointestinal, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre-coma within the preceding 26 weeks, if on any medications that might affect glycemic control, drug or alcohol dependency

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gupta, 2009[47] NR	Neither year reported 16 Weeks	No run-in period	< 6 months	Yes	247/51 NR	Age <35 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pregnant, not using adequate contraception, FPG >200 mg/dL, individuals using orlistat, sibutramine, ephedrine, steroids, significant lung diseases, significant neurologic diseases, baseline BP>140/90 mmHg, prior use of TZD, beta blockers, smokers, alcohol abuse and using drugs, patients using metal objects precluding required scans
Williams-Herman, 2009[76] NR	Neither year reported 54 Weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 years, HbA1c <7.5% or >11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (>=75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM
Derosa, 2009[135] Italy	Neither year reported 12 Months	Fewer than 10% of participants were excluded during run-in	>= 6 months	NR	NR/248 Inpatient/hospital	Age >18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 7%, BMI <25 kg/m^2 OR >28 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia, no hypertension
Nauck, 2009[92] Multicontinent	Neither year reported 26 Weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	1662/1087 NR	Age <18 or >80 years, HbA1c <7% or >11% if on monotherapy; 10% if on combination therapy (both greater than 3 months), BMI >40 kg/m^2, used insulin in last 3 months

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Vijay, 2009[99] India	Neither year reported 4 months	No run-in period	< 6 months	NR	NR/40 Outpatient subspecialty care setting	Age <30 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <8%, BMI >36 kg/m^2, unstable weight for at least 3 months before study, pre-existing chronic diseases, any amount of smoking during previous 6 months, previous use of insulin or any TZDs, on medications such as glucocorticoids or other drugs that affect glucose metabolism, lipid lowering drugs or psychoactive substances and alcohol
Kiyici, 2009[45] Turkey	Neither year reported 52 weeks	No run-in period	< 6 months	No	NR/50 Outpatient subspecialty care setting	Age <30 or >65 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >8%, BMI >40 kg/m^2, gastrointestinal disease, rheumatological, or neoplastic, infectious diseases, history of using anti-diabetic medications, any endocrine disease except diabetes or hyperlipidemia, smoking, microvascular complications of diabetes, history of substance abuse
Jonker, 2009[160] Netherlands	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	173/78 Outpatient Primary care setting	Age <45 or >65 years, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, no Type 2 DM, prior use of TZD/insulin, BP >150/85 mm Hg

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Perez, 2009[56] U.S., multinational Europe	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	1436/600 NR	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglycerides >500 mg/dL, discontinued metformin and TZD therapy due to lack of efficacy

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009[130] U.S., multicontinent	Start year 2007 End year 2008 16 months	No run-in period	< 6 months	Yes	356/169 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% (6.5% if on metformin combination therapy) or >10% (9.5% if on metformin combination therapy), BMI > 40 kg/m^2, LDL <50 mg/dL or triglycerides ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 weeks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Tolman, 2009[150] U.S.	Start year 2000 End Year 2005 3 years	No run-in period	< 6 months	Yes	NR/2120 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7%, BMI <20kg/m^2 or >48 kg/m^2, not taking metformin and/or SU, history of ketoacidosis, history of TZD use other than troglitazone before 4/00

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jadzinsky, 2009[78] Multicontinent	Start year 2006 End year 2008 24 weeks	Fewer than 10% participants excluded during run-in period	< 6 months	Yes	2936/1394 Outpatient Primary care setting	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c <8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CV events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
DeFronzo, 2009[95] NR	Neither year reported 24 weeks	Yes	< 6 months	Yes	1462/743 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BMI >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40%
Bunck, 2009[144] Sweden, Finland, and Netherlands	Start year 2004 End year 2007 56 weeks	No run-in period	< 6 months	Yes	150/69 NR	Age <30 or >75 years, HbA1c <6.5% or >9.5%, BMI <25 kg/m^2 or >40 kg/m^2, metformin treatment not at a stable dose for at least 2 months, no other blood glucose lowering medications allowed in 3 months prior to study, no changes in other medications known to affect beta cell function (ACEI, beta blockers)

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2009[122] U.S., Mexico	Start year 2006 End year 2007 52 weeks	Fewer than 10 % participants excluded during run-in period	< 6 months	Yes	NR/746 NR	Age <18 or >80 years, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Kato, 2009[57] Multinational Europe	Neither year reported 12 weeks	No run-in period	NR	NR	NR/50 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, no Type 2 DM, no metabolic syndrome, not on continuous diet/exercise therapy, no anemia, no history of heart failure
Erdem, 2008[39] Turkey	Neither year reported 12 weeks	No run-in period	< 6 months	No	53/44 outpatient department of internal medicine clinic	Age <30 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >35 kg/m^2, other chronic disease as detected by history and physical

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Scott, 2008[85] Multi-continent	Neither year reported 18 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 weeks on stable dose of metformin, insulin use, Type 1 DM, glucose >270 mg/dL
Seufert, 2008[142] Multicontinent	Neither year reported 104 weeks	No run-in period	NR	Yes	NR/1269 NR	Age <35 or >75 years, history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <7.5% or >11%, pregnant, nursing, fasting C-peptide >1.5 ng/mL, ketoacidosis, symptomatic heart failure, acute malabsorption, chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years
Hamann, 2008[123] Multinational Europe, Mexico	Neither year reported 52 weeks	Yes	< 6 months	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any oral antidiabetic drug other than metformin in the prior 12 weeks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin <11.0 g/dl for men and <10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Schwarz, 2008[152] U.S.	Neither year reported 104 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0% or >11.0%, BMI <22 kg/m^2 or >45 kg/m^2, FBG >270 mg/dL, history of lactic acidosis, congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM
Comaschi, 2008[158] Italy	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, fasting C-peptide <0.33 nmol/L, had not received treatment with a stable dose of either metformin or an SU as a monotherapy for at least 3 months before study entry, on other oral hypoglycemic agents, insulin, benzoic acid, long treatments with beta-blockers, or corticosteroids
Iliadis, 2007[48] Greece	Neither year reported 18 weeks	Run-in period but number of participants excluded was NR	NR	NR	NR/48 Outpatient subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), diagnosis of Type 2 DM >3 years, use of any diabetes medication, no Type 2 DM, any heart failure

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Robbins, 2007[145] U.S., Multinational Europe, multi-continent, India, Australia	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	433/317 NR	Age <35 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)
Chien, 2007[59] Taiwan	Neither year reported 16 weeks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c > 12% and FPG>250 mg/dL at screening visit, HbA1c < 7% and FPG<140 mg/dL at screening visit, BMI <18.5 kg/m^2 or >35 kg/m2, current significant GI disorder, hyperglycemic hyperosmolar non-ketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 weeks, history of cancer in 5 yr, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or gliclazide<10 mg/day, glimepiride<4mg/d, gliclazide<160mg/d)

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2007[288] Italy	Neither year reported 12 months	Fewer than 10% of participants were excluded during run-in	< 6 months	No	NR/248 NR	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <7.0%, BMI <25 kg/m^2 or >28 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, non-Caucasians, SBP <130 mm Hg, DBP <85 mm Hg
Turkmen Kemal, 2007[58] Turkey	Start year 2005 6 months	No run-in period	< 6 months	NR	46/46 Outpatient subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient on diuretics, uncontrolled hypertension
Comaschi, 2007[129] Italy	Neither year reported 6 months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age <35 years, HbA1c < 7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3months, fasting C-peptide <0.33 nmol/L
Home, 2007[124] Multinational Europe, Australia and New Zealand	Start year 2000 End year 2002 18 months	Run-in period but number of participants excluded was NR	>= 6 months	NR	7428/4458 NR	Age <40 or >75 years, HbA1c <7% or >9%, BMI <25 kg/m^2

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Teramoto, 2007[41] Japan	Neither year reported 24 weeks	Yes	NR	No	126/92 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), any medication affecting glucose metabolism, history of diabetic ketoacidosis, history of diabetic coma or pre-coma, Cushing's syndrome, history of allergy to thiazolizinediones, tumor therapy, receiving insulin for severe infection
Goldstein, 2007[75] Multicontinent	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with less than 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose >280 mg/dl after run-in period, no Type 2 DM, Type 1 DM
Davies, 2007[147] United Kingdom	Neither year reported 4 months	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/82 NR	Age <30 or >80 years, history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c >7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2 weeks, duration of Type 2 DM <12 months, c-peptide levels <0.33, severe concurrent disease, serum Cr >150umol/l

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Lund, 2007[197] Denmark	Start year 2001 End year 2002 8 months	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	127/96 Outpatient subspecialty care setting	Age <40 years for onset of diabetes diagnosis, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >9.5% with ongoing ODMs prior to study start; 10.5 on 2 visits with >1m interval, HbA1c <6.5% after run-in period, BMI >27 kg/m^2, pregnant, insulin treated Type 2 DM, secondary DM, Factor II, VII, X <0.7, ongoing co-existing illness with life shortening prognosis, mental retardation or reduced intellectual behavior, history of drug abuse, weight loss of >5kg in past 6 months prior to study start, fasting C-peptide <300 of non fasting glucagon stimulated C-peptide <600, ketonuria, ketoacidosis
Nauck, 2007[133] U.S., multinational Europe, multi-continent	Neither year reported 52 weeks	Yes	< 6 months	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 weeks of screening, history of Type 1 DM, other treatments for hypoglycemia
Kim, 2007[42] South Korea	Neither year reported 12 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	No	NR/120 Outpatient primary care, Outpatient subspecialty care setting	Age <30 or >70 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), duration of diabetes >5 years, not on a stable medication with a SU and/or alpha glucosidase inhibitor for at least 3 months, episodes of ketonuria or ketoacidosis, current malignancy, tuberculosis, rheumatic disease, thyroid disease, corticosteroid treatment, previous TZD or metformin treatment

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Raskin, 2007[146] US	Neither year reported 28 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	N/NR NR	Age <18 or >75 years, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275lbs), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use
Hanefeld, 2007[100] Multinational Europe	Neither year reported 52 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG < 7mmol/l or >15 mmol/l, C peptide <0.27 nmol/l
Scott, 2007[111] U.S.	Neither year reported 12 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	2186/743 NR	Age <21 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Kahn, 2006[38] Multicontinent	Start year 2000 End year 2006 6 years	No run-in period	NR	Yes	6676/4360 NR	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or >180 mg/dL, history of lactic acidosis

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Charbonnel, 2006[94] Multicontinent	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	1464/701 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 weeks of screening, FPG >14.4mmol/l
Rosenstock, 2006[49] Multicontinent	Start year 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[101] U.S., Puerto Rico	Neither year reported 56 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <7.5% or >11.5%, pregnant, nursing, duration of diabetes > than 2 years, intolerance to rosiglitazone, pioglitazone, or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg /day, oral anti-diabetic drugs, concurrent participation in another investigational study, serum creatinine level >1.5 mg/dl for men, 1.4 mg/dl for women, 1+ proteinuria, anemia (<10 g/dl women, <12 g/dl men), BMI ≤20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Stewart, 2006[156] Multinational Europe	Start year 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1397/526 NR	Age < 18 or > 70 years, history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG <6.0 mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bakris, 2006[125] U.S., multi-continent, South America, Europe	Neither year reported 32 weeks	Yes	< 6 months	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI <22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Umpierrez, 2006[126] U.S.	Neither year reported 28 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	538/210 Outpatient primary care, Outpatient subspecialty care setting	Age <18 or >79 years, HbA1c <7.5% and >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis
Nakamura, 2006[108] Japan	Neither year reported 12 weeks	No run-in period	< 6 months	NR	NR/68 NR	HbA1c >6.5%, history of ketoacidosis, treatment other than by diet alone, fasting C-peptide level of less than 0.33 mmol/l, hematuria, non-diabetic renal disease, microalbuminura defined as a median urinary albumin excretion of 20 to 200 ug/min
Kvapil, 2006[138] Multinational Europe	Neither year reported 16 weeks	No run-in period	< 6 months	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria is not adequately controlled on metformin

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jibran, 2006[112] Pakistan	Start year 2000 End year 2001 12 months	NA	< 6 months	NR	NR/100 Outpatient subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g., failed initial treatment), no Type 2 DM, on insulin
Derosa, 2006[157] Italy	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/99 Outpatient primary care, Outpatient subspecialty care setting	History of ketoacidosis, background retinopathy, nephropathy, neuropathy, impaired liver or kidney function, anemia, CVD or cerebrovascular conditions, pregnant, lactating, of child bearing potential while not taking adequate contraceptive
Garber, 2006[128] U.S.	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >78 years, any liver disease, any kidney disease, history of CVD, HbA1c ≤7% or ≥12% no Type 2 DM, other
Derosa, 2005[151] Italy	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/99 case-report forms or computerized clinic registers	Age ≤18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c <7.5%, BMI ≤25.3 kg/m^2, pregnant, nursing, not using adequate contraception, if no Type 2 DM for minimum 6 months based on ADA criteria, if no metabolic syndrome based on NCEP ATP III, if no hypertension, triglycerides ≤150mg/dl, C-peptide ≤1.0ng/ml, history of ketoacidosis, anemia, receiving lipid-lowering meds, anticoagulation, glimepiride, or a TZD

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gerich, 2005[136] U.S.	Neither year reported 2 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), neuropathy, retinopathy, HbA1c <7% or >11%, BMI < 22 kg/m^2 and >45 kg/m^2, not using adequate contraception, FPG ≥15 mmol/l, if Type 1 DM, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, history of lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sig risk to the subject, had to be drug naive
Derosa, 2005[127] Italy	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Leiter, 2005[83] Canada	Neither year reported 32 weeks	No run-in period	< 6 months	Yes	720/613 Outpatient primary care	Age <20 or >80 years, HbA1c <9.5%, no Type 2 DM, FBG <7 and >14 mmol/l

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Weissman, 2005[86] U.S.	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <6.5% or >8.5% for patients having received prior combination treatment, HbA1c <7% or >10% prior monotherapy or drug naive patients, no Type 2 DM, other
Bailey, 2005[87] U.K., 14 European countries	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other
Betteridge, 2005[289] U.K.	Not extracted 104 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 years, HbA1c <7.5% or >11%, no Type 2 DM
Yamanouchi, 2005[50] Japan	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other
Goldberg, 2005[98] U.S., Puerto Rico, Mexico, and Columbia	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <35 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7% or >11.5%, if naive to ODM therapy, HbA1c <7% or >9.5% if previously treated with ODM, no Type 2 DM, other
Pfutzner, 2005[105] Germany	Not extracted 26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, other
Derosa, 2005[159] Italy	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <18 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Langenfeld, 2005[290] Germany	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, no Type 2 DM, other
Feinglos, 2005[91] U.S.	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >81 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other
Smith, 2004[291] U.S., Multinational Europe	Neither year reported 52 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/598 NR	Age <36 or >81 years, BMI <22 or >38 kg/m^2, FPG <126 or >270 mg/dL, fasting C-peptide >0.79 ng/ml
Hallsten, 2004[153] Finland	Neither year reported 26 weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	NR/44 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, diabetes meds, oral corticosteroid treatment, BP >160/100 mm Hg
Nakamura, 2004[102] Japan	Neither year reported 12 months	No run-in period	>= 6 months	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >6.5%, BP <140/90 mm Hg, controlled on diet alone, C-peptide <0.33 mmol/l, creatinine <1.5 mg/dL, no antihypertensive medications, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Horton, 2004[80] NR	Neither year reported 24 Weeks	Yes	< 6 months	Yes	701/401 NR	Age <30 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), neuropathy, retinopathy, HbA1c <6.8% or >11%, Type 1 or secondary DM, diabetes >3 month duration, FPG <15 mmol/l, diabetic complication, on corticosteroids, non treatment naive
Ramachandran, 2004[51] India	Not extracted 14 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <30 or >60 years, treatment experienced, HbA1c >11%, no Type 2 DM, other
Schernthaner, 2004[52] Europe	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Derosa, 2004[60] Italy	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <46 or >67 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Tan, 2004[106] Denmark, Finland, Norway, and Sweden	Not extracted 52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5 or >9.5 for patients receiving ODM, no Type 2 DM, other
Tan, 2004[107] Mexico	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >11% in patients who were not receiving ODMs, and <7.5 or >9.5 in patients who were receiving ODM monotherapy, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Natali, 2004[148] London and Italy	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c >10% after washout, other
Raskin, 2004[109] U.S.	Not extracted 12 titration and 12 maintenance weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 years, HbA1c <7% or >12% during previous monotherapy with SU or metformin at 50% or more of maximal recommended dose for at least 3 months, no Type 2 DM, other
Jovanovic, 2004[110] U.S.	Not extracted 12 titration and 12 maintenance weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 years, HbA1c <7% or >12%, no Type 2 DM, other
Hanefeld, 2004[140] Canada, U.K., Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Lawrence, 2004[53] U.K.	Not extracted 12 titration and 12 maintenance weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <45 or >80 years, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes <7% or >10% and for low-dose ODM >7.5%, no Type 2 DM, other
Madsbad, 2004[120] Multinational Europe	Start year 2000 End year 2001 12 weeks	No run-in period	< 6 months	Yes	311/193 Outpatient Primary Care setting	Age <30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs
Malone, 2003[137] 14 countries not specified	Neither year reported 16 Weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test	Age <30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days
Yang, 2003[139] China	Neither year reported 12 Weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/211 NR	Age <35 or >70 years, poorly controlled on prior treatments (e.g., failed initial treatment), no Type 2 DM as defined by WHO, not treated with diet and SU for 6-months
Garber, 2003[61] U.S.	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >79 years, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tosi, 2003[36]* Italy	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Goldstein, 2003[62] U.S.	Not extracted 18 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% and >12.0%, other
Derosa, 2003[81] Italy	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any kidney disease, history of CVD, treatment experienced, HbA1c <7%, no Type 2 DM, other
Derosa, 2003[113] Italy	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any kidney disease, history of CVD, HbA1c <7.0%, no Type 2 DM, other
Pavo, 2003[54] Russia and Hungary	Not extracted 32 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other
Bakris, 2003[104] U.S. and U.K.	Not extracted 52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	NR
Virtanen, 2003[154] Finland	Not extracted 26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <45 or >75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Marre, 2002[96] Multicontinent	Neither year reported 24 weeks	Yes	< 6 months	Yes	680/467 NR	Age <30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.8% or >11%, BMI <20 or >35 kg/m^2, DM at least 6 months, FPG >15 mmol/l, gastroparesis, change in body weight during run-in, treated with diabetes meds other than metformin 3 months before study
Vakkilainen, 2002[119] Finland	Neither year reported 12 weeks (planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/48 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >10%, BMI >33 kg/m^2, FPG >15 mmol/l, total cholesterol >6.5 mmol/l, triglycerides >4.5 mmol/l, thyroid disease, smoking, nicotine therapy, use of lipid lowering agents, insulin, hormone replacement therapy
Hallsten, 2002[55] Finland	Not extracted 26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Blonde, 2002[63] U.S.	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
St John Sutton, 2002[149] U.S	Not extracted 52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Marre, 2002[64] Netherlands, Denmark, Portugal, France, Belgium	Not extracted 4 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 years, any liver disease, any kidney disease, history of CVD, other
Garber, 2002[65] U.S.	Not extracted 20 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Gomez-Perez, 2002[88] Mexico	Not extracted 26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Khan, 2002[97] U.S.	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, other
Charpentier, 2001[71] France	Not extracted 20 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 years, any kidney disease, history of CVD, no Type 2 DM, other
Madsbad, 2001[114] Denmark and Scandinavia	Not extracted 12 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤39 or ≥76 years, any liver disease, any kidney disease, HbA1c <6.5% or >10%, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Amador-Licona, 2000[66] Mexico	Not extracted 12 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age >65 years, any liver disease, history of CVD, other
Einhorn, 2000[89] U.S.	Not extracted 16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Fonseca, 2000[90] U.S.	Not extracted 26 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other
Nakamura, 2000[103] Japan	Not extracted 3 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Horton, 2000[79] U.S.	Not extracted 24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 years, any kidney disease, HbA1c <6.8% or >11%, no Type 2 DM, other
Turner, 1999[37] U.K.	Start year 1977 End year 1991 9 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/4075 23 UKPDS centers	Age <25 or >65 years, FPG<6 mmol/l x 2, individuals on diet only therapy who maintained their blood sugars <6 mmol/l on followup visits

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Moses, 1999[82] Australia	Neither year reported 4 to 5 months	No run-in period	NR	NR	108/83 NR	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c < 7.1%, BMI <21 kg/m^2, no Type 2 DM, not on metformin for more than 6 months, alcohol abuse, drug use, intention to become pregnant, history of lactic acidosis, vitamin B12 <150 pmol/l with anemia
Landgraf, 1999[115] Germany, Austria, and Netherlands	Not extracted 14 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Marbury, 1999[117] US and Canada	Not extracted 12 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <37 or >75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, retinopathy, HbA1c <6.5% or >14.6%, no Type 2 DM, other
Wolffenbuttel, 1999[116] Germany, Austria, and Netherlands	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.5% if treated with diet only, >12% if treated with diet plus ODM, other
DeFronzo, 1995[70] U.S.	Not extracted 29 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other

Table 2. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year Country	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hermann, 1994[68] Sweden	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	No Type 2 DM, other
Campbell, 1994[67] U.K.	Not extracted 52 weeks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >69 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Wolffenbuttel, 1993[118] Netherlands	Not extracted 12 (4 week titration, 8 week treatment) (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, HbA1c <7.0% or >12.0%, no Type 2 DM, other
Hermann, 1991[69] Sweden	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Hermann, 1991[155] Sweden	Not extracted 6 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	No Type 2 DM, other

*Crossover study, no washout period

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI disorder = gastrointestinal disorders; HbA1c = hemoglobin A1c; kg = kilogram; kg/m^2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; mm Hg = millimeters of mercury; mmol/l = millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = not reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl

oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study;US = United States; WHO = World Health Organization; yrs = years

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[121]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Derosa, 2010[44]	Metformin + glibenclamide, 65	NR	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 45	NR	67	NR	28.7 NR	8.8	NR	4
DeFronzo, 2010[132]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Aschner, 2010[77]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[134]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, Other: 4	30.9 NR	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, Other: 3.1	31.3 NR	7.3	5.7	328
Pratley, 2010[143]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, Other: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, Other: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, Other: 4	33.1 94.6 kg	8.4	6.4	52

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Home, 2009[16]	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5kg	7.8	6.1	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3kg	8	7.9	NR
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0kg	8	7.9	NR
Raskin, 2009[131]	Metformin + repaglinide, 187	54.8 (20 to 87)	58	AA: 16, Asian: 4, C: 75, American Indian: 1, Other: 4	32.9 NR	8.45	7.4	62
	Metformin + repaglinide, 187	54.5	59	AA: 13, Asian: 5, C: 80, American Indian: 1, Other: 2	32.5 NR	8.29	7.3	58
	Metformin + rosiglitazone, 187	55.5 (28 to 83)	51	AA: 13, Asian: 2, C: 79, American Indians: 1, Others: 4	32.2 NR	8.46	7.1	58
Derosa, 2009[46]	Metformin, 67	55 (50 to 60)	51	C: 100	27.2 77.7 kg	9.1	NR	7
	Metformin + glimepiride, 66	57.7 (51.7-64.7)	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57 (50 to 64)	49	C: 100	27.4 76.4 kg	9.3	NR	9
	Pioglitazone, 69	54 (48 to 60)	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[141]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Kaku, 2009[84]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9
Gupta, 2009[47]	Metformin, 17	56.9	37.5	C: 62.5	36.4 97.8 kg	6.0	NR	1
	Pioglitazone, 16	59.2	25	C: 78.5	35.7 98.5 kg	6.2	NR	2
	Pioglitazone, 18	55.7	33	C: 50	34.3 95.3 kg	6.4	NR	0
Williams-Herman, 2009[76]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Derosa, 2009[135]	Metformin + glibenclamide, 114	56 (52 to 60)	51	NR	26.5 NR	8.2	4	5
	Metformin + nateglinide, 119	55 (50 to 60)	49	NR	26.4 NR	8.1	4	5
Nauck, 2009[92]	Metformin, 122	56	60	AA: 3, Asian: 7, C: 88, Other: 3	31.6 NR	8.4	8	48
	Metformin + glimepiride, 244	57	57	AA: 2, Asian: 9, C: 89, Other: 1	31.2 NR	8.4	8	34
	Metformin + liraglutide, 242	57	59	AA: 2, Asian: 7, C: 88, Other: 2	30.9 NR	8.4	8	51
	Metformin + liraglutide, 241	57	54	AA: 4, Asian: 8, C: 88, Other:1	31.1 NR	8.3	7	44
Vijay, 2009[99]	Rosiglitazone, 20	47.75	NR	NR	32.01 82.46 kg	9.10	15.40	NR

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 20	48.1	NR	NR	32.26 81.90 kg	9.27	16.55	NR
Kiyici, 2009[45]	Metformin, 16	52.4	NR	NR	31.6 NR	6.7	NR	NR
	Rosiglitazone, 19	50.7	NR	NR	31.2 NR	7.1	NR	NR
Jonker, 2009[160]	Metformin + glimepiride, 39	56.4	100	NR	29.1 NR	7	NR	NR
	Pioglitazone + glimepiride, 39	56.8	100	NR	28 NR	7.1	NR	NR
Perez, 2009[56]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[130]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2	NR 79.6 kg	8.17	8.35	11
Tolman, 2009[150]	Pioglitazone, 1063	54 (20-82)	57.2	AA: 14.5, Asian: 3.4, C: 59.8, H: 19.1	32.5 NR	9.5	5.86	649
	Glibenclamide, 1057	55 (19-81)	55.5	AA: 13.2, Asian: 2.5, C: 62.1, H: 18.7	32.5 NR	9.5	5.61	641
Jadzinsky, 2009[78]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, Other: 5	29.9 NR	9.4	2	58
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, Other: 5.9	30.3 NR	9.5	1.4	62
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, Other: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, Other: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[95]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, Other: 12	31.7 NR	8.1	6.7	44

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, Other: 9.4	31.2 NR	8.1	6.4	48
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, Other: 9.9	31.1 NR	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, Other: 10.1	31.6 NR	8.1	6.7	40
Bunck, 2009[144]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	6
	Metformin + glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	3
Garber, 2009[122]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, Other: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, Other: 7	32.8 92.8 kg	8.3	5.3	74
	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, Other: 5	32.3 92.5 kg	8.3	5.2	89
Kato, 2009[57]	Metformin, 25	58.6	56	NR	27.5 NR	7.1	NR	NR
	Pioglitazone, 25	51.4	48	NR	28.4 NR	7.4	NR	NR
Erdem, 2008[39]	Metformin, 27	55.09	33	NR	31.41 NR	6.74	NR	4
	Pioglitazone, 26	54.9	31	NR	30.41 NR	6.34	NR	5
Iliadis, 2007[48]	Metformin, 16	57.8	NR	NR	30.8 80.8 kg	7.8	20.9 months	1
	Rosiglitazone, 16	56.3	NR	NR	31 83.2 kg	7.2	30.7 months	2
Scott, 2008[85]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Others: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seufert, 2008[142]	Metformin + sulfonylurea, 320	60	54.7	NR	30 NR	8.8	7.1	58
	Pioglitazone + sulfonylurea, 319	60	53.6	NR	30.2 NR	8.81	7	38
Robbins, 2007[145]	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[123]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[59]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
Derosa, 2007[288]	Metformin + glibenclamide, 114	56	51	NR	26.5 NR	8.2	4	10
	Metformin + nateglinide, 119	55	49	NR	26.4 NR	8.1	5	5
Schwarz, 2008[152]	Metformin + glyburide, 40	70.4	50	AA: 11.1, C: 77.8, Other: 11	33.5 NR	7.7	2.5	18
	Metformin + nateglinide, 35	70.1	51.5	AA: 9.1, C: 78.8, Other: 12.1	30.4 NR	7.8	1.7	14
Comaschi, 2008[158]	Metformin + glibenclamide, 80	59.9	55	NR	29.85 81.9 kg	8.57	NR	13
	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8kg	8.7	NR	15

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Turkmen Kemal, 2007[58]	Metformin, 16	56.8 (40 to 70)	25	NR	34.5 NR	6.3	1.5	0
	Rosiglitazone, 13	55.92 (42 to 68)	30	NR	30.8 75 kg	6.2	2.75	1
Comaschi, 2007[129]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
Home, 2007[124]	Metformin + rosiglitazone, 259	57	54	NR	32.7 93kg	7.9	6.1	52
	Metformin + sulfonylurea, 265	57	52	NR	NR 91kg	7.8	7	22
	Metformin + sulfonylurea, 284	60	52	NR	NR 83kg	8	8.1	54
	Rosiglitazone + sulfonylurea, 311	61	49	NR	NR 84kg	8	7.9	74
Teramoto, 2007[41]	Glibenclamide, 46	56.4	76	NR	25.2 NR	8.36	NR	5
	Pioglitazone, 46	57	72	NR	24.7 NR	8.01	NR	7
Goldstein, 2007[75]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4	182
	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
Lund, 2007[197]	Metformin, 48	59.45	77	C: 100	24.71 74.81 kg	7.34	(Median: 3 years)	12*
	Repaglinide, 48	63.31	75	C: 100	24.82 75.57 kg	7.57	(Median: 5 years)	8†
Nauck, 2007[133]	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, Other: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, Other: 3.7	31.2 89.5 kg	7.7	6.5	202
Kim, 2007[42]	Metformin + glimepiride, 60	57.6	50	NR	25.8 66.7 kg	7.7	3.4	4
	Rosiglitazone + glimepiride, 60	56.5	52.63	NR	25.7 68.1 kg	8.1	3.5	3
Raskin, 2007[146]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, Other: 1	31.2 88.7kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, Other: 1	30.8 86.2kg	9.9	NR	6
Hanefeld, 2007[100]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, Other: 1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, Other: 3	28.8 NR	8.2	6	9
	Rosiglitazone, 195	60.4	68	AA: 0, C: 8, Other: 2	28.7 NR	8.1	5.9	12
Scott, 2007[111]	Glipizide, 123	54.7 (21 to 76)	56.9	AA: 3.3, Asian: 4.9, C: 61, Other: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, Other: 21.1	30.5 NR	7.9	4.9	7

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Sitagliptin, 123	55.6 (34 to 76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, Other: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, Other: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	49.6	AA: 6.4, Asian: 7 5.6, C: 68.8, multiracial: 6.4, Other: 12.8	30.8 NR	7.9	4.3	18
Davies, 2007[147]	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4 kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Kahn, 2006[38]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, Other: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, Other: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 76 5.2, Other: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539
Charbonnel, 2006[94]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, Other: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Rosenstock, 2006[49]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, Other: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, Other: 3	32.8 NR	8.8	2.7	22

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Jain, 2006[101]	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, Other: 0.4	32.8 94.3 kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, 0ther: 0.4, Native American: 1 0.4	32.5 93.9 kg	9.2	0.8	117
Stewart, 2006[156]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /Other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[125]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Umpierrez, 2006[126]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, Other: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, Other: 0	33.81 NR	8.31	5.9	17
Kvapil, 2006[138]	Metformin + aspart 70/30, 116	56.4	46	NR	30.4 85.1 kg	9.	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30.5 84.0 kg	9.4	8.1	5
Derosa, 2005[151]	Metformin + glimepiride, 49	52	47	NR	26.8 75.6 kg	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 74.2 kg	8.0	5	2

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gerich, 2005[136]	Metformin + glyburide, 209	53.5	48	AA: 16.7, Asian: 0.5, C: 65.2, Other: 17.7	33.5 NR	8.3	2.0	87
	Metformin + nateglinide, 219	52.6	51	AA: 13, Asian: 2.4, C: 64.4, Other: 20.2	33.3 NR	8.4	1.5	78
Derosa, 2005[127]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2
Smith, 2004[291]	Glyburide, 203	60	70	NR	28.7 NR	8.2	6.4	0
	Rosiglitazone, 384	61	33	NR	28.7 NR	8.1	6	NR
Hallsten, 2004[153]	Metformin, 9	54	56	NR	29.9 NR	6.8	NR	2
	Rosiglitazone, 14	59.4	79		29 NR	6.6	NR	NR
Nakamura, 2004[102]	Glibenclamide, 15	55	53	NR	NR NR	7.8	19.2	0
	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR
Horton, 2004[80]	Metformin, 104	55.4	67.3	NR	29.9 NR	8.3	3.7	NR
	Metformin + nateglinide, 89	57.7	65.2	NR	30.6 NR	8.2	3.4	NR
	Nateglinide, 104	57.9	56.7	NR	29.9 NR	8.1	4.7	NR
Malone, 2003[137]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, Other: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, Other: 3	29.8 83.0 kg	9.17	8.0	25
Yang, 2003[139]	Metformin + sulfonylurea	NR	NR	NR	NR NR	8.59	NR	NR
	Rosiglitazone + sulfonylurea	NR	NR	NR	NR NR	8.61	NR	NR

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Marre, 2002[96]	Metformin, 152	56.4	55.3	AA: 3.3, Asian: 2.6, C: 90.8	29.6 NR	8.25	6.5	16
	Metformin + nateglinide, 155	57.9	61.3	AA: 4.5, Asian: 3.2, C: 90.3	29.4 NR	7.99	7.2	18
	Metformin + nateglinide, 160	57.3	61.3	AA: 3.8, Asian: 3.1, C: 91.3	29.3 NR	8.18	6.8	15
Turner, 1999[37]	Any in the Sulfonylurea class, 1305	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 340	NR	NR	NR	NR NR	NR	NR	NR
	Total, 4075	53	NR	AA: 9, Asian: 10, C: 81	29 NR	(median: 9.1)	NR	4 loss to followup
Moses, 1999[82]	Metformin, 27	57.8	63	Asian: 7, C: 85, Not specified: 7	31.8 NR	8.6	8	0
	Metformin + repaglinide, 27	57.2	67	C: 96, Not specified: 4	33.2 NR	8.3	5.9	0
	Repaglinide, 28	60.3	54	Asian: 7, C: 93	31.3 NR	8.6	7	0
Jibran, 2006[112]	Glibenclamide, 50	45.8	20	NR	30.4 72.7 kg	10.2	0	0
	Repaglinide, 50	46.6	32	NR	27.1 65.8 kg	9.9	0	0
Leiter, 2005[83]	Metformin, 78	60	56	C: 78, Other: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Other: 24	33 NR	7.5	5.3	18
Derosa, 2006[157]	Metformin + rosiglitazone, 48	54	52	NR	26.6 NR	8	5	4 from both groups
	Metformin + glimepiride, 47	52	49	NR	26.8 NR	7.9	4	4 from both groups
Garber, 2006[128]	Metformin + rosiglitazone, 158	56 (24 - 78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	Not extracted
	Metformin + glibenclamide, 160	56 (31 - 78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nakamura, 2006[108]	Pioglitazone, 17	56	53	NR	NR NR	8	16	NR
	Glibenclamide, 18	53.5	56	NR	NR NR	7.8	16.5	NR
	Nateglinide, 16	53.5	56	NR	NR NR	7.7	16.6	NR
Weissman, 2005[86]	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2 kg	8.05	NR	Not extracted
	Metformin, 351	55.7	NR	NR	33.8 96.7 kg	7.97	NR	Not extracted
Bailey, 2005[87]	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9 kg	7.4	6	Not extracted
	Metformin, 280	57.6	57	AA: <1, C: 98, Asian: 1, H: 0, O: 1	32.1 89.5 kg	7.5	6.1	Not extracted
Betteridge, 2005[289]	Metformin + pioglitazone, 317	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + unspecified sulfonylurea, 320	NR	NR	NR	NR NR	NR	NR	Not extracted
	Pioglitazone + unspecified sulfonylurea, 319	NR	NR	NR	NR NR	NR	NR	Not extracted
Yamanouchi, 2005[50]	Pioglitazone, 38	55.2	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	Not extracted
	Glimepiride, 37	55.6	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	Not extracted
	Metformin, 39	54.7	20	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	Not extracted
Goldberg, 2005[98]	Pioglitazone, 369	55.9	53.9	AA: 2.4, C: 64.8, Asian: 2.7, H: 28.5, O: 1.6	33.7 93.7 kg	7.6	3.9	Not extracted
	Rosiglitazone, 366	56.3	54.9	AA: 2.7, C: 59.8, Asian: 3.3, H: 32.2, O: 1.9	32.6 92.5 kg	7.5	4	Not extracted
Pfutzner, 2005[105]	Glimepiride, 84	63	61.9	AA: 0, C: 96.4, Asian: 0, H: 0, O: 3.7	31.8 NR	7.44	6.9	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 89	62.2	61.8	AA: 0, C: 98.8, Asian: 0, H: 0, O: 1.1	31.7 NR	7.52	7.4	Not extracted
Langenfeld, 2005[290]	Pioglitazone, 89	62	61.8	AA: 0; C: 98.9; Asian: 0; H: 0; O: 1.1	31.7 NR	7.52	7.4	Not extracted
	Glimepiride, 84	63	61.9	AA: 0; C: 96.4; Asian: 0; H: 0; O: 3.6	31.8 NR	7.44	6.9	Not extracted
Derosa, 2005[159]	Metformin + glimepiride, 47	52	49	NR	26.8 NR	7.9	4	Not extracted
	Metformin + rosiglitazone, 48	54	52	NR	26.6 NR	8	5	Not extracted
Feinglos, 2005[91]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	Not extracted
	Metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	Not extracted
Ramachandran, 2004[51]	Glimepiride, 18	45.3	50	AA: 0, C: 0, Asian: 0, H: 0, O: 100	24.6 65.7 kg	10.2	0	Not extracted
	Metformin, 21	44.4	71	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.7 67.7 kg	9.6	0	Not extracted
	Pioglitazone, 23	45.1	74	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.5 68.9 kg	9.3	0	Not extracted
Schernthaner, 2004[52]	Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	Not extracted
	Pioglitazone, 597	57	52.6	NR	31.2 88.2 kg	8.7	3.4	Not extracted
Derosa, 2004[60]	Glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	Not extracted
	Metformin, 83	58	51	NR	28.1 NR	8.4	NR	Not extracted
Tan, 2004[106]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	62.6 months	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 91	60	62	AA: 0, C: 99, Asian: 0, H: 0, O: 1	30.2 88.4 kg	8.4	57.1 months	Not extracted
Tan, 2004[107]	Glimepiride, 123	55.7	53	AA: 0, C: 1, Asian: 0, H: 99, O: 0	28.8 74.5 kg	8.45	81.2 months	Not extracted
	Pioglitazone, 121	55.1	45	AA: 0, C: 0, Asian: 0, H: 100, O: 0	29.3 74.2 kg	8.54	77.8 months	Not extracted
Natali, 2004[148]	Metformin, 28	58	79	NR	28 NR	7.8	6.3	Not extracted
	Rosiglitazone, 24	59	92	NR	27.6 NR	7.7	6.5	Not extracted
Raskin, 2004[109]	Repaglinide + rosiglitazone, 127	57.5	51	AA: 17, C: 65, Asian: 0, H: 3, O: 15	NR NR	NR	7.3	Not extracted
	Repaglinide, 63	58.5	62	AA: 16, C: 63, Asian: 0, H: 2, O: 19	NR NR	NR	7.2	Not extracted
	Rosiglitazone, 62	56.6	53	AA: 13, C: 68, Asian: 0, H: 0, O: 19	NR NR	NR	7.4	Not extracted
Jovanovic, 2004[110]	Pioglitazone, 62	56.2	50	AA: 11, C: 82, Asian: 0, H: 3, O: 3	32.1 NR	9.1	6.1	Not extracted
	Repaglinide, 61	57.8	59	AA: 11, C: 75, Asian: 0, H: 5, O: 8	31.2 NR	9	6.9	Not extracted
Hanefeld, 2004[140]	Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	Not extracted
	Unspecified sulfonylurea + pioglitazone, 31	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	Not extracted
Lawrence, 2004[53]	Metformin, 20	59.5	60	NR	(Median 29.2) NR	8.04	NR	Not extracted
	Pioglitazone, 20	60.4	70	NR	(Median 30.6) NR	7.43	NR	Not extracted
Madsbad, 2004[120]	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0
	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2
Garber, 2003[61]	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	Not extracted
	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	Not extracted
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	Not extracted
Tosi, 2003[36]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
	Glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 39	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
Goldstein, 2003[62]	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	Not extracted
	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	Not extracted
Derosa, 2003[81]	Metformin, 56	52	58	NR	24.7 72.3 kg	7.4	5	Not extracted
	Repaglinide, 56	55	52	NR	25.2 70.2 kg	7.6	4	Not extracted
Derosa, 2003[113]	Glimepiride, 62	54	48	NR	26.4 77.1 kg	7.8	NR	Not extracted
	Repaglinide, 62	56	50	NR	26.1 76.4 kg	8	NR	Not extracted
Pavo, 2003[54]	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	0.53	Not extracted
	Pioglitazone, 105	54.2	43.8	NR	31.3 86.6 kg	8.6	0.47	Not extracted
Bakris, 2003[104]	Rosiglitazone, 57	5.1	75	NR	NR NR	9.1	NR	Not extracted
	Glyburide, 64	56.1	71	NR	NR NR	9.5	NR	Not extracted
Virtanen, 2003[154]	Metformin, 13	58	62	NR	29.9 88.8 kg	6.9	NR	Not extracted
	Rosiglitazone, 14	58	71	NR	29.1 83.7 kg	6.8	NR	Not extracted
Vakkilainen, 2002[119]	Glibenclamide, 20	63	NR	NR	28.8 NR	7.6	NR	Not extracted
	Nateglinide, 23	63	NR	NR	27.8 NR	7.6	NR	Not extracted
Hallsten, 2002[55]	Metformin, 13	57.8	62	NR	29.9 NR	6.9	NR	Not extracted
	Rosiglitazone, 14	58.6	71	NR	29.3 NR	6.8	NR	Not extracted
Blonde, 2002[63]	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	Not extracted
	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	Not extracted
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	Not extracted
St John Sutton, 2002[149]	Glyburide, 99	56.1 (40 - 76)	71	AA: 3, C: 76, Asian: 0, H: 0, O: 21	(BMI ≥27: 65.7) NR	9.5	6.2	Not extracted
	Rosiglitazone, 104	55.1 (40 - 77)	75	AA: 5, C: 73, Asian: 0, H: 0, O: 22	(BMI ≥27: 67.3) NR	9.1	5.3	Not extracted
Marre, 2002[64]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	Not extracted
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	Not extracted
	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	Not extracted
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	Not extracted
Garber, 2002[65]	Glyburide, 161	56.5	50.9	AA: 9.3, C: 78.3, Asian: 0, H: 8.7, O: 3.7	30.3 87.2 kg	8.21	2.81	Not extracted
	Metformin + glyburide, 158	56.9	57.6	AA: 12.7, C: 74.1, Asian: 0, H: 11.4, O: 1.9	30.1 88.8 kg	8.25	3.52	Not extracted
	Metformin + glyburide, 165	58.1	58.2	AA: 6.1, C: 79.4, Asian: 0, H: 9.7, O: 4.9	29.6 86.7 kg	8.18	3.3	Not extracted
	Metformin, 161	56	57.8	AA: 4.3, C: 80.7, Asian: 0, H: 12.4, O: 2.5	30.4 88.6 kg	8.26	2.98	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gomez-Perez, 2002[88]	Metformin + rosiglitazone, 35	51.7 (40 - 73)	29	AA: 0, C: 0, Asian: 0, H: 80, O: 20	28 NR	NR	11.1	Not extracted
	Metformin + rosiglitazone, 36	54.2 (42 - 76)	19	AA: 0, C: 11, Asian: 0, H: 72, O: 17	27.6 NR	NR	10.7	Not extracted
	Metformin, 34	53.4 (40 - 68)	29	AA: 0, C: 3, Asian: 0, H: 76, O: 21	28.5 NR	NR	9.1	Not extracted
Khan, 2002[97]	Pioglitazone, 67	57.8	52	NR	35.2 NR	8	NR	Not extracted
	Rosiglitazone, 60	57.1	45	NR	35.6 NR	7.9	NR	Not extracted
Charpentier, 2001[71]	Metformin + glimepiride, 147	56.8 (36 - 70)	59	NR	29.5 81.2 kg	6.4	5.6	Not extracted
	Glimepiride, 150	55.4 (35 - 70)	58	NR	29.3 81 kg	6.5	5.3	Not extracted
	Metformin, 75	56.7 (36 - 69)	60	NR	29.2 82.2 kg	6.8	7	Not extracted
Madsbad, 2001[114]	Glipizide, 81	62	64	NR	28 83.6 kg	7.2	7	Not extracted
	Repaglinide, 175	60.2	61	NR	28 82.9 kg	7.3	8.1	Not extracted
Amador-Licona, 2000[66]	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	Not extracted
	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	Not extracted
Einhorn, 2000[89]	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	Not extracted
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	Not extracted
Fonseca, 2000[90]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, O: 12.7	29.8 NR	8.9	8.3	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, O: 12.9	30.2 NR	8.9	7.5	Not extracted
	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	Not extracted
Nakamura, 2000[103]	Glibenclamide, 15	61	53	NR	NR NR	7.8	14	Not extracted
	Pioglitazone, 15	60	47	NR	NR NR	7.7	16	Not extracted
Horton, 2000[79]	Metformin + nateglinide, 172	58.4	59	AA: 11.6, C: 82.6, Asian: 0.6, H: 0, O: 5.2	30 NR	8.4	4.5	Not extracted
	Metformin, 178	56.8	68	AA: 9.6, C: 79.2, Asian: 2.2, H: 0, O: 9	29.6 NR	8.4	7.5	Not extracted
	Nateglinide, 179	58.6	61	AA: 9.5, C: 82.1, Asian: 2.8, H: 0, O: 5.6	29.6 NR	8.3	4.7	Not extracted
Landgraf, 1999[115]	Glibenclamide, 100	63	57	AA: 6, C: 93, Asian: 0, H: 0, O: 1	27.5 79 kg	8	10	Not extracted
	Repaglinide, 94	61	60	AA: 0, C: 96, Asian: 0, H: 0, O: 4	27.6 80 kg	7.8	10	Not extracted
Marbury, 1999[117]	Glyburide, 182	58.7	66	AA: 9, C: 79, Asian: 0, H: 0, O: 12	29.1 NR	8.9	8.3	Not extracted
	Repaglinide, 362	58.3	67	AA: 9, C: 77, Asian: 0, H: 0, O: 14	29.4 NR	8.7	7.2	Not extracted
Wolffenbuttel, 1999[116]	Placebo + glyburide, 139	61	68	NR	28 81.3 kg	7	(Median 6)	Not extracted
	Repaglinide, 286	61	62	NR	28.4 81.5 kg	7.1	(Median 6)	Not extracted
DeFronzo, 1995[70]	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	Not extracted
	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	Not extracted
	Metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	Not extracted
Hermann, 1994[68]	Glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	Not extracted
	Metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	Not extracted
	Metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	Not extracted
	Metformin, 25	60 (34 - 74)	NR	NR	NR 78.6 kg	6.9	4	Not extracted
Campbell, 1994[67]	Glipizide, 24	57	33	NR	31.2 82.2 kg	11.8	2.8	Not extracted
	Metformin, 24	57	33	NR	29.6 78.2 kg	11.5	2.3	Not extracted
Wolffenbuttel, 1993[118]	Glibenclamide, 15	62 (45 - 75)	25	NR	26.1 70.9 kg	(Range 7.0 - 12.0)	9	Not extracted
	Repaglinide, 29	62 (45 - 75)	25	NR	26.1 74 kg	(Range 7.0 - 12.0)	9	Not extracted
Hermann, 1991[69]	Metformin, 16	60 overall (38 - 73 overall)	64 overall	NR	27 76.5 kg	6.7	NR	Not extracted
	Glibenclamide, 17	60 overall (38 - 73 overall)	64 overall	NR	29.2 84.1 kg	6.6	NR	Not extracted
	Metformin + glibenclamide, 11	60 overall (38 - 73 overall)	64 overall	NR	26.1 74.4 kg	7.8	NR	Not extracted

Table 3. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on intermediate outcomes (KQ1) (continued)

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + glibenclamide, 12	60 overall (38 - 73 overall)	64 overall	NR	30 87.3 kg	7.7	NR	Not extracted
Hermann, 1991[155]	Glibenclamide, 34	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 72	60 (34 - 74)	79	NR	28.4 82.3 kg	NR	NR	Not extracted
	Metformin, 38	NR	NR	NR	NR NR	NR	NR	Not extracted

AA = African American; BHI = biphasic human insulin; C = Caucasian; H = Hispanic; kg = kilogram; NPH = neutral protamine Hagedorn; NR = not reported; sd = standard deviation

* 5 while on metformin prior to second crossover; 2 during washout period; and 5 while on repaglinide after crossover

† 2 excluded on repaglinide prior to first crossover; 1 during washout, and 5 after first crossover while on metformin

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin versus thiazolidinedione						
Kiyici, 2009[45]	Grp1: Metformin Fixed Mean: 850 mg Grp2: Rosiglitazone Fixed Mean: 4 mg	Grp1 B: 6.7 (0.9) F: 6.4 (0.6) p:> 0.05 F-B: -0.3 Grp2 B: 7.1 (0.9) F: 6.4 (0.6) p:0.008 F-B: -0.7 Grp1-Grp2: 0.4	Grp1 B: 136.5 (27.3) F: 128.7 (31.2) p:> 0.05 F-B: -7.8 Grp2 B: 120.9 (27.3) F: 117 (39) p:> 0.05 F-B: -3.9 Grp1-Grp2: -3.9	Grp1 B: 46.8 (3.9) F: 46.8 (7.8) p:> 0.05 F-B: 0 Grp2 B: 42.9 (3.9) F: 50.7 (11.7) p:0.018 F-B: 7.8 Grp1-Grp2: -7.8 p: 0.015	Grp1 B: 124.6 (71.2) F: 115.7 (62.3) p: > 0.05 F-B: -8.9 Grp2 B: 142.4 (53.4) F: 124.6 (71.2) p: > 0.05 F-B: -17.8 Grp1-Grp2: 8.9	
Perez, 2009[56]	Grp1: Metformin Fixed Start: 850 mg Grp2: Pioglitazone Fixed	Grp1 F-B: -0.99 Grp2 F-B: -0.96 Grp1-Grp2: -0.03 (0.17)				Grp1 F-B: -1.28 Grp2 F-B: 1.64 Grp1-Grp2: -2.92
Kato, 2009[57]	Grp1: Metformin Fixed Max: 500 mg Grp2: Pioglitazone Fixed Max: 15 mg	Grp1 B: 7.14 (1.4) F: 6.31 (0.9) p:<0.01 F-B: -0.83 Grp2 B: 7.37 (1.8) F: 6.32 (1.2) p:<0.01 F-B: -1.05 Grp1-Grp2: 0.22	Grp1 B: 134.94 (32.37) F: 133.38 (33.93) F-B: -1.56 Grp2 B: 127.14 (28.6) F: 127.53 (26.52) F-B: 0.39 Grp1-Grp2: -1.95	Grp1 B: 54.6 (12.09) F: 60.45 (14.43) F-B: 5.85 Grp2 B: 57.72 (19.5) F: 67.08 (21.06) F-B: 9.36 Grp1-Grp2: -3.51	Grp1 B: 145.07 (61.41) F: 134.39 (74.76) F-B: -10.68 Grp2 B: 143.29 (96.12) F: 125.49 (66.75) p: <0.05 F-B: -17.8 Grp1-Grp2: 7.12	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2009[46]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Pioglitazone Varied Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.2 (1.3) F: 8.2 (0.7) p: <0.01 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.1 (SE: 0.33)				
Gupta, 2009[47]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: every 1 wk increment by 500 mg Grp2: Pioglitazone + ADA diet Varied, glucose: FPG > 100 mg, HbA1c: 7.0% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.09 (0.13) Grp1-Grp2: -0.15 (SE: 0.22)	Grp1 F-B: -2.54 (5.36) Grp2 F-B: 14.3 (4.43) Grp1-Grp2: -16.84 (SE: 6.95)	Grp1 F-B: 1.67 (0.91) Grp2 F-B: 6.2 (1.94) Grp1-Grp2: -4.53 (SE: 2.14)	Grp1 F-B: -23.7 (14.7) Grp2 F-B: -72.8 (38.8) Grp1-Grp2: 49.1	Grp1 F-B: -3.21 (0.7) Grp2 F-B: 2.15 (1.09) Grp1-Grp2: -5.36
Gupta, 2009[47]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: every 1 wk increment by 500 mg Grp2: Pioglitazone + PC diet Varied, glucose: FPG > 100 mg, HbA1c: 7% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.42 (0.17) Grp1-Grp2: 0.18 (SE: 0.23)	Grp1 F-B: -2.54 (5.36) Grp2 F-B: 8.85 (6.45) Grp1-Grp2: -11.39 (SE: 1.42)	Grp1 F-B: 1.67 (0.91) Grp2 F-B: 8.11 (1.7) Grp1-Grp2: -6.44 (SE: 0.67)	Grp1 F-B: -23.7 (14.7) Grp2 F-B: -155.6 (95.6) Grp1-Grp2: 131.9	Grp1 F-B: -3.21 (0.7) Grp2 F-B: -2.59 (1.25) Grp1-Grp2: -0.62

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Erdem, 2008[39]	Grp1: Metformin Varied, glucose: 110 mg/dL Start: 1000 mg, Max: 2000 mg D: every 2 wks until goal Grp2: Pioglitazone Varied, glucose: 110 mg/dL Start: 15 mg, Max: 45 mg D: every 2 wks until goal	Grp1 B: 6.74 (1.3) F: 6.15 (0.53) p: 0.02 F-B: -0.59 Grp2 B: 6.34 (1.2) p: 0.31 F: 5.6 (0.7) p: 0.01 F-B: -0.74 Grp1-Grp2: 0.15 (SE: 0.50)	Grp1 B: 132.42 (30.9) F: 112.57 (27.8) F-B: -19.85 p: <0.001 Grp2 B: 132.66 (35.6) p: 0.98 F: 128.62 (30.51) F-B: -4.04 p: 0.76 Grp1-Grp2: -15.81 (SE: 16.4)	Grp1 B: 48.31 (13.1) F: 49.37 (11.8) F-B: 1.06 p: 0.39 Grp2 B: 48.04 (9.4) p: 0.94 F: 53.25 (10.7) F-B: 5.21 p: 0.01 Grp1-Grp2: -4.15 (SE: 5.89)	Grp1 B: 166.05 (81.8) F: 150.05 (67.3) p:0.32 Grp2 B: 183.95 (105.04) p: 0.54 F: 162.23 (84.6) p: 0.29 Grp1-Grp2: 5.72 (SE: 44.9)	
Iliadis, 2007[48]	Grp1: Metformin Varied, glucose: euglycemia Max: 1700 mg Grp2: Rosiglitazone Varied, glucose: euglycemia Max: 8 mg	Grp1 F-B: -1.7 (1.1) p: <0.001 Grp2 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.7 (SE: 0.59)	Grp1 F-B: 1 (17) p: NSG Grp2 F-B: 3 (24) p: NSG Grp1-Grp2: -2 (SE: 2.76)	Grp1 F-B: 1 (3) p: NSG Grp2 F-B: 0.8 (5) p: NSG Grp1-Grp2: 0.2 (SE: 1.22)	Grp1 F-B: -29 (101) p: NSG Grp2 F-B: 22 (73) p: NSG Grp1-Grp2: -51 (SE: 5.7)	Grp1 F-B: -2.5 (3.5) p: <0.05 Grp2 F-B: -0.3 (3.3) p: NSG Grp1-Grp2: -2.2
Turkmen Kemal, 2007[58]	Grp1: Metformin Fixed Start: 1700 mg D: 6 mos Grp2: Rosiglitazone Fixed Start: 8 mg	Grp1 B: 5.95 Range: 5.6 F: 5.85 Range: 1.9 Grp2 B: 6 Range: 2.4 F: 5.95 Range: 1.9	Grp1 B: Median: 3.4 range: 2.69 mmol/l F: Median: 2.62 range: 1.78 mmol/l Grp2 B: Median: 2.88 range: 2.48 mmol/l F: Median: 2.48 range: 1.81 mmol/l		Grp1 B: Median: 4.27 range: 5.93 F: Median: 3.36 range: 5.36 Grp2 B: Median: 3.17 range: 3.96 F: Median: 3.28 range: 3.31	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kahn, 2006[38]	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.07 (CI: 0.06, 0.09) Grp2-Grp1: -0.13 (CI: -0.22, -0.05) p: 0.002				Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: 0.7 (CI: 0.6, 0.8) Grp1-Grp2: 6.9 (CI: 6.3, 7.4) p: <0.001
Rosenstock, 2006[49]	Grp1: Metformin Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	Grp1 B: 8.8 (1.0) F: 7.0 (1.0) F-B: -1.8 Grp2 B: 8.8 (1.0) F: 7.2 (1.0) F-B: -1.6 Grp1-Grp2: -0.2 (SE 0.20)	Grp1 B: 116 (CV: 33.9) F: 103.6 (CV: 35.5) F-B: -12.4 Grp2 B: 114.6 (CV: 40.5) F: 119.7 (CV: 58) F-B: 5.1 Grp1-Grp2: -17.5 (SE: 10.79)	Grp1 B: 42.9 (CV: 23.8) F: 43 (CV: 23) F-B: 0.1 Grp2 B: 42.8 (CV: 24.5) F: 44.1 (CV: 27) F-B: 1.3 Grp1-Grp2: -1.2 (SE: 2.35)	Grp1 B: 175.7 (CV: 62.3) F: 148.7 (CV: 58.3) Grp2 B: 166.6 (CV: 67.6) F: 158.5 (CV: 74.8) Grp1-Grp2: -18.9 (SE: 23.7)	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 1.7 (IQR: -1.2, - 4.5)
Hallsten, 2004[153]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1 g bid D: 2 wks Grp2: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid D: 2 wks			Grp1 F-B: 3.9 (SE: 3.9) p: >0.05 Grp2 F-B: 3.9 (SE: 3.9) p: >0.05 Grp1-Grp2: 0 (SE: 5.52)	Grp1 F-B: 0.2 (0.2) p: >0.05 Grp2 F-B: -0.2 (0.2) p: >0.05 Grp1-Grp2: 35.6 (SE: 25.1)	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Yamanouchi, 2005[50]	Grp1: Metformin Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men	Grp1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp1-Grp2: 0.2		Grp1 B: 53.82 (4.68) F: 58.11 (3.51) F-B: 4.29 p: NSG Grp2 B: 51.87 (3.51) F: 51.48 (4.68) F-B: -0.39 p: NSG Grp1-Grp2: 4.68	Grp1 B: 219.83 (112.14) F: 185.12 (96.12) F-B: -39.16 p: NSG Grp2 B: 205.59 (101.46) F: 197.58 (94.34) F-B: -8.01 p: NSG Grp1-Grp2: -31.15	
Ramachandran, 2004[51]	Grp1: Metformin Varied Start: 250 mg, Max: 850 mg Grp2: Pioglitazone Varied Start: 15 mg, Max: 30 mg	Grp1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: 0.05 Grp2 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: 0.01 Grp1-Grp2: 1.2		Grp1 B: 38.22 (5.85) F: 42.9 (7.8) F-B: 4.68 p: <0.01 Grp2 B: 39 (7.8) F: 42.9 (11.7) F-B: 3.9 Grp1-Grp2: 0.78	Grp1 B: 258.1 (213.6) F: 195.8 (124.6) F-B: -62.3 p: <0.05 Grp2 B: 249.2 (222.5) F: 222.5 (160.2) F-B: -26.7 Grp1-Grp2: -35.6	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp1-Grp2: -0.4
Schernthaner, 2004[52]	Grp1: Metformin Varied Start: 850 mg up to 3 times/day, Max: 2550 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.68 (0.98) F: 7.18 F-B: -1.5 Grp2 B: 8.69 (1.02) F: 7.28 F-B: -1.41 Grp1-Grp2: -0.09	Grp1 B: 138.84 F: 134.16 F-B: -4.68 Grp2 B: 138.84 F: 149.37 F-B: 10.53 Grp1-Grp2: -15.21	Grp1 B: 44.07 F: 50.31 F-B: 6.24 Grp2 B: 44.07 F: 47.19 F-B: 3.12 Grp1-Grp2: 3.12 p: 0.001	Grp1 B: 234.96 F: 180.67 F-B: -54.29 Grp2 B: 232.29 F: 205.59 F-B: -26.7 Grp1-Grp2: -27.59 p: 0.001	Grp1 F-B: 1.9 Grp2 F-B: -2.5 Grp1-Grp2: 4.4

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Lawrence, 2004[53]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.04 (0.9) F: 6.9 (0.5) F-B: -1.12 (0.84) p: <0.01 Grp2 B: 7.43 (0.9) F: 6.62 (0.5) F-B: -0.81 (0.63) p: <0.01 Grp1-Grp2: -0.31 p: NSG	Grp1 B: 200.5 (42.6) F: 200.9 (50.5) F-B: 0.4 Grp2 B: 194.2 (43.2) F: 202.4 (46.9) F-B: 8.2 Grp1-Grp2: -7.8	Grp1 B: 49.6 (11.8) F: 52.7 (11.1) F-B: 3.1 p: <0.05 Grp2 B: 48.7 (9.4) F: 46.8 (8.5) F-B: -1.9 p: NSG Grp1-Grp2: 5	Grp1 B: 203 (149) F: 176 (115) F-B: -27 p: NSG Grp2 B: 202 (110) F: 175.6 (114.4) F-B: -26.4 Grp1-Grp2: -0.6	
Pavo, 2003[54]	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.6 F: 7.1 F-B: -1.5 p: <0.0001 Grp2 B: 8.6 F: 7.3 F-B: -1.3 p: <0.0001 Grp1-Grp2: -0.2 p: 0.28	Grp1 F-B: -7.02 p: 0.04 Grp2 F-B: 6.24 p: 0.055 Grp1-Grp2: -13.26 p: 0.003	Grp1 F-B: 8.58 Grp2 F-B: 5.07 Grp1-Grp2: 3.51 p: 0.02	Grp1 F-B: -80.99 p: 0.001 Grp2 F-B: -56.07 p: 0.03 Grp1-Grp2: -24.92	Grp1 B: 86.1 (15.6) F: 86.8 F-B: -0.7 (0.4) Grp2 B: 88.9 (15.9) F: 90.2 F-B: 2.4 Grp1-Grp2: -3.1 p: <0.0001
Hallsten, 2002[55]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid	Grp1 B: 6.9 (0.2) F: 6.2 (0.2) F-B: -0.7 p: <0.0001 Grp2 B: 6.8 (0.2) F: 6.5 (0.2) F-B: -0.3 p: <0.05 Grp1-Grp2: -0.4 p: NSG				Grp1 B: 83.7 (7.9) F: 84.3 (3.5) F-B: 0.6 p: NSG Grp2 B: 88.8 (10.8) F: 86.8 F-B: -2 p: <0.05 Grp1-Grp2: -2.6

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Natali, 2004[148]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Rosiglitazone Fixed Start: 4 mg bid		Grp1 B: 118 (SE: 25) F: 120 F-B: 2 Grp2 B: 120 (SE: 29) F: 131 F-B: 11 Grp1-Grp2: -10 (CI: -23, 4)	Grp1 B: 46 (SEM: 9) F: 50 F-B: 4 Grp2 B: 46 (SEM: 15) F: 49 F-B: 3 Grp1-Grp2: 0.4 (CI: -5, 6) p: NSG	Grp1 B: 142 (SEM 7.3) F: 178 F-B: 36 (32) Grp2 B: 196 (SEM 251) F: 152 F-B: -44 (41) Grp1-Grp2: 47 p: NSG	Grp1 B: 80.4 (SEM 10.1) F: 80.9 F-B: 0.5 (0.5) p: NSG Grp2 B: 77.3 (SEM 12.5) F: 76.7 F-B: -0.6 (0.4) p: NSG Grp1-Grp2: 1.1 p: NSG
Virtanen, 2003[154]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid		Grp1 B: 109.2 (SE: 7.8) F: 101.4 (SE: 7.8) F-B: -7.8 Grp2 B: 113.1 (SE: 7.8) F: 136.5 (SE: 7.8) F-B: 23.4 Grp1-Grp2: -31.2	Grp1 B: 42.9 (SE: 3.9) F: 46.8 (SE: 3.9) F-B: 3.9 p: NSG Grp2 B: 42.9 (SE: 3.9) F: 46.8 (SE: 3.9) F-B: 3.9 p: NSG Grp1-Grp2: 0	Grp1 B: 151.3 (SE: 17.8) F: 133.5 (SE: 17.8) F-B: -17.8 Grp2 B: 106.8 (SE: 8.9) F: 115.7 (SE: 17.8) F-B: 8.9 Grp1-Grp2: -26.7 p: NSG	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin versus sulfonylurea						
Chien, 2007[59]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean dose: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Final mean dose: 19 mg D: 4 wks	Grp1 B: 8.88 (1.08) F: 8.98 F-B: 0.09 (SE: 0.37) p: NS Grp2 B: 8.69 (0.94) F: 9.21 F-B: 0.52 (SE: 0.24) p: 0.018 Grp1-Grp2: -0.43 (SE: 0.44)				
Kahn, 2006[38]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.24 (CI: 0.23, 0.26)				Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: -0.2 (CI: -0.3, 0.0)
Turner, 1999[37]	Grp1: Metformin Varied, glucose: FPG <6 mmol/L Max: 2550 mg/day D: 9 yrs Grp2: Any in the Sulfonylurea class Varied, glucose: 6 mmol/L Max: Chlorpropramide-500 mg; Glyburide 20 mg D: 9 yrs	Grp1 Proportion achieving HbA1c<7% at 3 yrs: 44 (CI: 42, 46) 6 yrs: 34 (CI: 32, 37) 9 yrs: (CI: 11, 15) Grp2 Proportion achieving HbA1c<7% at 3 yrs: 45 (CI: 43, 48) 6 yrs: 28 (CI: 26, 30) 9 yrs: (CI: 19, 23)				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Yamanouchi, 2005[50]	Grp1: Metformin Fixed Start: 750 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: 0		Grp1 B: 51.87 (3.51) F: 51.48 (4.68) F-B: -0.39 p: NSG Grp2 B: 52.65 (4.29) F: 52.26 (4.29) F-B: -0.39 p: NSG Grp1-Grp2: 0	Grp1 B: 205.59 (101.46) F: 197.58 (94.34) F-B: -8.01 p: NSG Grp2 B: 234.07 (121.93) F: 229.62 (112.14) F-B: -4.45 p: NSG Grp1-Grp2: -3.56	
Ramachandran, 2004[51]	Grp1: Metformin Varied Start: 250 mg, Max: 850 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: <0.05 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: 1.1		Grp1 B: 39 (7.8) F: 42.9 (11.7) F-B: 3.9 p: NSG Grp2 B: 37.05 (11.7) F: 42.9 (7.8) F-B: 5.85 p: NSG Grp1-Grp2: -1.95	Grp1 B: 249.2 (222.5) F: 222.5 (160.2) F-B: -26.7 Grp2 B: 195.8 (124.6) F: 151.3 (80.1) F-B: -44.5 p: <0.05 Grp1-Grp2: 17.8	Grp1 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.5
Derosa, 2004[60]	Grp1: Metformin Varied Start: 1000 mg, Max: 1000 mg tid Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg bid	Grp1 B: 8.4 (1.0) F: 7 (0.9) F-B: -1.4 (CI: -5.7, -0.51) p: 0.01 Grp2 B: 8.5 (1.2) F: 6.9 (0.7) F-B: -1.6 (CI: -6.4, -0.47) p: 0.01 Grp1-Grp2: 0.2	Grp1 B: 144 (20) F: 130 (25) F-B: -14 (CI: -42, -8) Grp2 B: 135 (20) F: 130 (15) F-B: -5 (CI: 2.8, 9.6) Grp1-Grp2: -9 p: <0.05	Grp1 B: 43 (5) F: 45 (4) F-B: 2 p: NSG Grp2 B: 42 (4) F: 44 (6) F-B: 2 p: NSG Grp1-Grp2: 0	Grp1 B: 180 (25) F: 165 (25) F-B: -15 p: NSG Grp2 B: 160 (20) F: 145 (25) F-B: -15 p: NSG Grp1-Grp2: 0	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2003[61]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.67 (1.4) F: 6.75 F-B: -1.9 Grp1-Grp2: 0.37	Grp1 B: 122.7 (3.2) F: 117 F-B: -5.7 p:<0.05 Grp2 B: 122.2 (3.2) F: 124.5 F-B: 2.3 p: NSG Grp1-Grp2: -8	Grp1 B: 42.3 (0.9) F: 41.9 F-B: -0.4 p: NSG Grp2 B: 41.6 (1) F: 42.1 F-B: 0.5 p: NSG Grp1-Grp2: -0.9	Grp1 B: 256.8 (26.7) F: 217.2 F-B: -39.6 p: NSG Grp2 B: 236.3 (19.1) F: 221.2 F-B: -15.1 p: NSG Grp1-Grp2: -24.5	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91 (16.0) F: 93 F-B: 2 p: NSG Grp1-Grp2: -3.1
Tosi, 2003[36]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 15 mg	Grp1 B: 7.7 (1.4) F: 7.3 F-B: -0.4 Grp2 B: 7.85 (1.4) F: 7.4 F-B: -0.45 Grp1-Grp2: 0.05				
Goldstein, 2003[62]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed Start: 15 mg bid	Grp1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2 B: 8.9 (1.1) F: 8.5 (0.1) F-B: -0.4 Grp1-Grp2: 0.2	Grp1 B: 109.7 (35.2) F: 102.5 F-B: -7.2 (CI: -15, 0.6) Grp2 B: 111.2 (34.6) F: 110.8 F-B: -0.4 (CI: -6.7, 5.8) Grp1-Grp2: -6.8	Grp1 B: 42.3 (9.7) F: 42.7 F-B: 0.4 p: NSG Grp2 B: 43.5 (9.8) F: 43.9 F-B: 0.4 p: NSG Grp1-Grp2: 0	Grp1 B: 218.7 (120.2) F: 217.1 F-B: -1.6 (-25.3 to 22) Grp2 B: 213.8 (127.2) F: 273.6 F-B: 59.8 (22.5 to 97.1) p: <0.05 Grp1-Grp2: -60.4	Grp1 B: 94.2 (16.7 F: 91.5 F-B: -2.7 (SE: 0.3) Grp2 B: 90 (17.4) F: 89.6 F-B: -0.4 (SE: 0.3) Grp1-Grp2: -2.3

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Blonde, 2002[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg bid	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.64 (1.44) F: 9.5 F-B: -0.11 Grp1-Grp2: 0.5		Grp1-Grp2: p: NSG	Grp1 F-B: p: NSG Grp2 F-B: p: NSG	Grp1 B: 89.5 (16.9) F: 87.5 F-B: -2 Grp2 B: 88 (15.9) F: 88.5 F-B: 0.5 Grp1-Grp2: -2.5
Marre, 2002[64]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.88 (1.65) F: 7.58 F-B: -0.3 Grp1-Grp2: 0.1 p: NSG	Grp1 B: 148.2 (SE: 39) F: 136.5 F-B: -11.7 (SE: 31.2) Grp2 B: 152.1 (SE: 42.9) F: 148.2 F-B: -3.9 (SE: 39) Grp1-Grp2: -7.8 p: NSG	Grp1 B: 46.8 (11.7) F: 47.97 F-B: 1.17 p: NSG Grp2 B: 46.8 (11.7) F: 47.19 F-B: 0.39 p: NSG Grp1-Grp2: 0.78	Grp1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) Grp2 B: 204.7 (151.3) F: 204.7 (133.5) F-B: 0 Grp1-Grp2: -17.8 p: NSG	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 82.5 (15.4) F: 83.4 F-B: 0.9 Grp1-Grp2: -1.7
Garber, 2002[65]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.21 (1.09) F: 6.97 F-B: -1.24 Grp1-Grp2: 0.21				Grp1 F-B: -0.6 p: <0.05 Grp2 F-B: 1.7 Grp1-Grp2: -2.3

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Amador-Licona, 2000[66]	Grp1: Metformin Varied Start: 850 mg, Max: NR Grp2: Glibenclamide Varied Start: 5 mg, Max: NR	Grp1 B: 8.5 (1.5) F: 7.6 (0.8) F-B: -0.9 p: 0.003 Grp2 B: 8.4 (1.4) F: 7.6 (0.8) F-B: -0.8 p: 0.009 Grp1-Grp2: -0.1		Grp1 B: 31.98 (8.97) F: 35.49 (8.97) F-B: 3.51 p: 0.0001 Grp2 B: 36.66 (7.02) F: 39 (10.92) F-B: 2.34 p: 0.01 Grp1-Grp2: 1.17	Grp1 B: 195.8 (81.88) F: 178 (65.86) F-B: -17.8 p: 0.04 Grp2 B: 174.44 (81.88) F: 166.43 (97.9) F-B: -8.01 p: 0.67 Grp1-Grp2: -10.68	Grp1 B: 70.7 (14.8) F: 69.6 (14.3) F-B: -0.9 p: 0.07 Grp2 B: 73.2 (11.8) F: 74.1 (12.6) F-B: 0.9 p: 0.1 Grp1-Grp2: -1.7
Campbell, 1994[67]	Grp1: Metformin Varied Start: 500 mg bid, Max: 3000 mg Grp2: Glipizide Varied Start: 5 mg, Max: 30 mg	Grp1 B: 11.46 (1.92) F: 8.64 (1.21) F-B: -2.57 Grp2 B: 11.75 (2.11) F: 9.72 (1.91) F-B: -1.93 Grp1-Grp2: -0.64 p: <0.05	Grp1 B: 4.65 (1.07) F: 4.58 (1.19) F-B: -0.07 Grp2 B: 4.51 (1.26) F: 4.99 (1.16) F-B: 0.48 Grp1-Grp2: -0.55 p: NSG	Grp1 B: 35.88 (11.31) F: 37.05 (11.31) F-B: 1.17 Grp2 B: 36.27 (8.58) F: 36.27 (8.58) F-B: 0 Grp1-Grp2: 1.17 p: NSG	Grp1 B: 191.35 (130.83) F: 202.92 (163.76) F-B: 11.57 p: NSG Grp2 B: 183.34 (61.41) F: 205.59 (108.58) F-B: 22.25 Grp1-Grp2: -10.68	Grp1 B: 78.2 (15.7) F: 76.23 F-B: -1.97 Grp2 B: 82.2 (16.8) F: 84.8 F-B: 2.67 Grp1-Grp2: -4.57 p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[68]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.7 (SE: 0.3) F: 5.3 (SE: 0.1) F-B: -1.3 (SE: 0.2) p: 0.001 Grp1-Grp2: 0.4	Grp1 B: 142.74 (SE: 9.75) F: 131.82 (SE: 8.97) F-B: -5.85 (SE: 2.73) p: 0.052 Grp2 B: 153.27 (SE: 5.46) F: 157.56 (SE: 5.07) F-B: 4.68 (SE: 3.51) p: >0.1 Grp1-Grp2: -10.53	Grp1 B: 31.59 (SE: 2.34) F: 30.03 (SE: 1.56) F-B: -0.78 (SE: 0.78) p: >0.1 Grp2 B: 34.71 (SE: 1.95) F: 35.88 (SE: 1.95) F-B: 1.17 (SE: 0.78) p: >0.1 Grp1-Grp2: -0.39	Grp1 B: 179.78 (SE: 18.69) F: 173.55 (SE: 14.24) F-B: -6.23 (SE: 12.46) Grp2 B: 178.89 (SE: 32.93) F: 186.9 (SE: 31.15) F-B: 8.01 (SE: 11.57) Grp1-Grp2: -14.24 p: >0.1	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.8 (SE: 0.5) p: >0.1 Grp2 B: 82.6 (SE: 2.7) F: 86.2 (SE: 3.3) F-B: 2.8 (SE: 0.7) p: 0.001 Grp1-Grp2: -3.6
Hermann, 1991[69]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glibenclamide Varied Start: 3.5 mg, Max: 10.5 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 6.6 (1.3) F: 5.3 (0.5) F-B: -1.3 p: <0.001 Grp1-Grp2: 0.4	Grp1 F-B: 0.78 (SE: 3.9) Grp2 F-B: 5.07 (SE: 7.41) Grp1-Grp2: -5.85			Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG Grp2 B: 84.1 (13.2) F: 87.4 (14.8) F-B: 3.3 p: <0.01 Grp1-Grp2: 3.7

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
DeFronzo, 1995[70]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1 B: 8.9 F: 8.5 F-B: -0.4 (SE: 0.1) Grp2 B: 8.5 F: 8.7 F-B: 0.2 (SE: 0.1) Grp1-Grp2: -0.6 p: <0.001	Grp1 B: 134 (SE: 3) F: 129 (SE: 3) F-B: -6 (SE: 2) Grp2 B: 136 (SE: 3) F: 141 (SE: 3) F-B: 5 (SE: 2) Grp1-Grp2: -11 p: 0.009	Grp1 B: 37 (SE: 1) F: 38 (SE: 1) F-B: 1 Grp2 B: 39 (SE: 1) F: 40 (SE: 1) F-B: 0 Grp1-Grp2: 1 (SE: 1.41)	Grp1 B: 231 (SE: 12) F: 221 (SE: 13) F-B: -16 (SE: 7) Grp2 B: 210 (SE: 8) F: 227 (SE: 11) F-B: 21 (SE: 9) Grp1-Grp2: -37 p: 0.001	Grp1 B: 92.6 (14.5) F: 87.8 F-B: -3.8 (SE: 0.2) p: <0.001 Grp2 F-B: -0.3 (SE: 0.2) p: NSG Grp1-Grp2: -3.5
Charpentier, 2001[71]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Varied Start: 1 mg, Max: 6 mg	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2 B: 6.52 (1.13) F: 6.79 (1.43) F-B: 0.27 (SE: 0.09) Grp1-Grp2: -0.12 p: 0.369		Grp1 B: 46.41 (13.65) F: 48.36 F-B: 1.95 Grp2 B: 45.24 (12.87) F: 45.63 F-B: 0.39 Grp1-Grp2: 1.56 p: 0.14 across all treatment groups	Grp1 B: 171.77 (119.26) F: 185.12 F-B: 13.35 (104.13) Grp2 B: 189.57 (143.29) F: 200.25 F-B: 10.68 (108.58) Grp1-Grp2: 2.67 p: 0.029 across all treatment groups	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2 B: 81 F: 81.78 F-B: 0.78 (2.98) Grp1-Grp2: -1.52

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin versus DPP-IV inhibitors						
Jadzinsky, 2009[78]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Weeks Grp2: Saxagliptin Fixed	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -1.7 Grp1-Grp2: -0.3	Grp1 B: 126.7 F: 118.5 F-B: -4 (SE: 1.44) (CI: -6.8, -1.1) Grp2 B: 125.8 F: 121.7 F-B: -0.5 (SE: 1.48) (CI: -3.4, -2.4) Grp1-Grp2: -3.5	Grp1 B: 43.6 (SE: 0.66) F: 46.6 (SE: 0.71) F-B: 8.9 (SE: 1.36) (CI: 6.2, 11.5) Grp2 B: 43.4 (SE: 0.63) F: 44.4 (SE: 0.67) F-B: 3.9 (SE: 1.19) (CI: 1.6, 6.3) Grp1-Grp2: -3.5	Grp1 B: 228.1 (SE: 13.92) F: 207.2 (SE: 14.71) F-B: -1.5 (SE: 2.72) (CI: -6.8, 3.9) Grp2 B: 213.2 (SE: 9.91) F: 180 (SE: 7.06) F-B: -3 (SE: 2.93) (CI: -8.8, 2.8) Grp1-Grp2: 1.5	Grp1 F-B: -1.6 Grp2 F-B: -1.1 Grp1-Grp2: -0.5
Aschner, 2010[77]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 Weeks Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1 F-B: -0.55 (CI: -0.61, -0.5) Grp2 F-B: -0.38 (CI: -0.43, -0.32) Grp1-Grp2: -0.18 (CI: -0.25, -0.1)	Grp1 F-B: 2.5 (CI: -0.8, 5.8) Grp2 F-B: 11.2 (CI: 8, 14.5) Grp1-Grp2: -8.7 (CI: 4.1, 13.3)	Grp1 F-B: 7 (CI: 5.4, 8.6) Grp2 F-B: 6.2 (CI: 4.7, 7.8) Grp1-Grp2: 0.8 (CI: -1.4, 3)	Grp1 F-B: -1.2 (CI: -5.2, 2.7) Grp2 F-B: -3.7 (CI: -7.2, -0.2) Grp1-Grp2: 3.8 (CI: -0.5, 8.2)	Grp1 F-B: -1.9 (CI: -2.2, -1.7) Grp2 F-B: -0.6 (CI: -0.9, -0.4) Grp1-Grp2: -1.3 p: <0.001
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.5	Grp1 B: 105.3 (32.3) F: 102.3 (33.6) F-B: -3 Grp2 B: 115.1 (35.1) F: 113.5 (34.5) F-B: -1.6 Grp1-Grp2: -1.4 (SE: 8.25)	Grp1 B: 43.2 (9.4) F: 44.6 (10.4) F-B: 1.4 Grp2 B: 42.7 (9.5) F: 43.2 (10.1) F-B: 0.5 Grp1-Grp2: 0.9 (SE: 1.94)	Grp1 B: Median: 172 (113.5) F: Median: 179 (107) Grp2 B: Median: 149 (97.7) F: Median: 155 (113.5)	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: 0.6 (CI: -0.2, 1.4)

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.2	Grp1 B: 106.8 (34.2) F: 103.6 (31.5) F-B: -3.2 Grp2 B: 111.4 (35.1) F: 113 (35.3) F-B: 1.6 Grp1-Grp2: -4.8 (SE: 6.73)	Grp1 B: 42.7 (10.5) F: 45 (12.4) F-B: 2.3 Grp2 B: 42.7 (9.5) F: 43.2 (10.1) F-B: 0.5 Grp1-Grp2: 1.8 (SE: 2.09)	Grp1 B: Median: 167 (104.2) F: Median: 173 (120) Grp2 B: Median 147.5 (87.4 F: Median: 162.5 (94)	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: 0.6 (CI: -0.2, 1.4)
Goldstein, 2007[75]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.47				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0
Goldstein, 2007[75]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.16				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin versus meglitinides						
Lund, 2007[197]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1629 mg D: 12 dys Grp2: Repaglinide Varied, prespecified target dose Start: 1 mg, Max: 6 mg, Mean: 4.72 mg D: 12 dys					Grp1 B: 74.81 (10.1) F: 73.94 (9.88) F-B: -0.88 (CI: -1.45, -0.3) Grp2 B: 75.57 (9.85) F: 75.47 (10.08) F-B: 0.7 (CI: 0.12, 1.28) Grp1-Grp2: -1.58 (CI: -2.17, -0.99) p: <0.001
Horton, 2004[80]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Nateglinide Fixed Start: 120 mg qac	Grp1 F-B: -0.8 (SE: 0.1) p: <0.001 Grp2 F-B: -0.8 (SE: 0.1) p: <0.001 Grp1-Grp2: -0.8 (SE: 0.1) p: <0.005				
Moses, 1999[82]	Grp1: Metformin NR Grp2: Repaglinide Fixed Start: 0.5 mg, Max: 4.0 mg D: 12 to 28 days	Grp1 F-B: -0.33 (SE: 0.24; CI: -0.8, -0.5) Grp2 F-B: -0.38 (SE: 0.23; CI: -0.84, -0.08) Grp1-Grp2: 0.05 (SE: 0.33)				Grp1 F-B: -0.86 (SE: 0.5) Grp2 F-B: 2.98 (SE: 0.49) p: <0.05 Grp1-Grp2: -3.84

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2003[81]	Grp1: Metformin Varied Start: 500 mg bid, Max: 2500 mg Grp2: Repaglinide Varied Start: 0.5 mg bid, Max: 4 mg	Grp1 B: 7.4 (0.9) F: 6.5 F-B: -0.9 p: <0.01 Grp2 B: 7.6 (0.9) F: 6.8 F-B: -0.8 p: <0.01 Grp1-Grp2: -0.1 p: NSG	Grp1 B: 132.21 (26.13) F: 117 F-B: -15.21 (CI: -34.32 to -8.19) p: <0.05 Grp2 B:127.14 (25.35) F: 115.05 F-B: -12.09 (CI: -29.05 to 20.28) p: <0.065 Grp1-Grp2: -3.12	Grp1 B: 46.41 (8.19) F: 45.224 F-B: -1.17 Grp2 B: 42.51 (7.02) F: 45.63 F-B: 3.12 Grp1-Grp2: -4.29 p: NSG	Grp1 B: 176.22 (4.806) F: 152.19 F-B: -24.03 (-55.18 to -15.13) p: <0.05 Grp2 B: 156.64 (52.51) F: 140.62 F-B: -16.02 (-38.27 to 17.8) p: 0.065 Grp1-Grp2: -8.01	Grp1 B: 72.3 (7.1) F: 70.3 F-B: -2 (CI: -6, 4) p: 0.14 Grp2 B: 70.0 (6.5) F: 69.6 F-B: -0.4 (CI: -0.8, 0.28) p: >0.2 Grp1-Grp2: -1.6 p: NSG
Horton, 2000[79]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Nateglinide Fixed Start: 120 mg tid	Grp1 B: 8.4 (1.2) F: 7.6 F-B: -0.8 (SE: 0.1) p: 0.0001 Grp2 B: 8.3 (1.0) F: 7.8 F-B: -0.5 (SE: 0.1) p: 0.0001 Grp1-Grp2: -0.3 p: NSG				
Metformin versus metformin + thiazolidinedione						
Perez, 2009[56]	Grp1: Metformin Fixed Start: 850 mg Grp2: Metformin + pioglitazone Fixed	Grp1 F-B: -0.99 Grp2 F-B: -1.83 p: <0.0001 Grp1-Grp2: 0.84 (SE: 0.17)				Grp1 F-B: -1.28 Grp2 F-B: 0.69 Grp1-Grp2: -1.97

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2009[46]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp1-Grp2: 1.0 (SE: 0.27)				BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.4 (1.6) F: 26.9 (1.3) F-B: -1.8% Grp1-Grp2: 0
Rosenstock, 2006[49]	Grp1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks	Grp1 B: 8.8 (1.0) F: (1.0) F-B: -1.8 Grp2 B: 8.9 (1.1) F: 6.6 (1.0) F-B: -2.3 Grp1-Grp2: 0.5 (SE: 0.20) p: 0.008	Grp1 B: 116 (CV: 33.9) F: 103.6 (CV: 35.5) F-B: -12.4 Grp2 B: 113.8 (CV: 32.5) F: 113.5 (CV: 30.4) F-B: -0.3 Grp1-Grp2: -12.1 (SE: 8.1)	Grp1 B: 42.9 (CV: 23.8) F: 43 (CV: 23) F-B: 0.1 Grp2 B: 42.6 (CV: 21.8) F: 45 (CV: 25.5) F-B: 2.4 Grp1-Grp2: -2.3 (SE: 2.25)	Grp1 B: 175.7 (CV: 62.3) F: 148.7 (CV: 58.3) F-B: -27 Grp2 B: 180.3 (CV: 67.7) F: 146.6 (CV: 68.6) F-B: -33.7 Grp1-Grp2: 6.7	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 0.05 (IQR: -3.45, 3)
Leiter, 2005[83]	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Metformin + rosiglitazone Fixed; Varied, glucose: < 7 mmol/L Start: 1500 mg, Max: 1500 mg; Start: 4 mg, Max: 8 mg D: 8 wks	Grp1 F-B: -0.14 p: 0.93 Grp2 F-B: p: <0.001 Grp1-Grp2: -0.36 CI: 0.15 - 0.56				Grp1 F-B: no significant weight change Grp2 F-B: 1.6 (CI: 0.9, 2.3)

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kaku, 2009[84]	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg D: Unclear Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: Unclear; 16 wks	Grp1 F-B: 0.25 (0.92) (CI: 0.06, 0.45) p: 0.012 Grp2 F-B: -0.67 (0.8) (CI: -0.84, -0.49) p: <0.0001 Grp1-Grp2: 0.92 (SE: 0.13)	Grp1 F-B: 0.9 (20; CI: -3.34, 5.23) p: 0.6632 Grp2 F-B: 3.5 (23.2; CI: -1.59, 8.62) p: 0.1746 Grp1-Grp2: -2.6 (SE: 3.4)	Grp1 F-B: -1.1 (8.5; CI: -2.96, 0.68) p: 0.2175 Grp2 F-B: 5.3 (8.1; CI: 3.52, 7.09) p: <0.0001 Grp1-Grp2: -6.4 (SE: 1.30)	Grp1 F-B: -15.4 (93.8) (CI: -35.5, 4.7) p: 0.1316 Grp2 F-B: -9.3 (76.3) (CI: -26.1, 7.4) p: 0.2714 Grp1-Grp2: -6.1	Grp1 F-B: -0.47 Grp2 F-B: 1.68 Grp1-Grp2: -2.15
Scott, 2008[85]	Grp1: Metformin Fixed Start: >1500 mg Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.73 (0.88) F: 6.94 (0.75) F-B: -0.79 (CI: -0.92, -0.65) Grp1-Grp2: 0.57 (CI: 0.37, 0.76)	Grp1 B: 95.6 (30.8) F: 108.4 (33.6) F-B: mean % change: 16.7 (CI: 10.2, 23.3) Grp2 B: 99.2 (29.4) F: 119.6 (37.6) F-B: mean % change: 26.2 (CI: 19.7, 32.7) Grp1-Grp2: -7.6 (SE: 8.8)	Grp1 B: 43.5 (10.5) F: 44.1 (12.1) F-B: mean % change: 1.8 (CI: -1.3, 4.9) Grp2 B: 42.2 (10) F: 45.7 (10.5) F-B: mean % change: 9.2 (CI: 6.1, 12.2) Grp1-Grp2: -2.9 (SE: 2.89)	Grp1 B: 171.1 (73.3) F: 191.5 (111.1) F-B: mean % change from baseline: 11.9 (CI: 3.9, 19.9) Grp2 B: 201.6 (126.2) F: 199.8 (108.4) F-B: mean % change from baseline: 13.1 (CI: 5.2 - 21.1) Grp1-Grp2: 1.2 (CI: -10.1, 12.6)	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: 1.5 (CI: 1.0, 1.9) Grp2-Grp1: 2.3 (CI: 1.7, -2.9)
Stewart, 2006[156]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 3000 mg, Mean: 2627.9 mg D: 20 wks Grp2: Metformin + rosiglitazone Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1812.2 mg; Start: 4 mg , Max: 8 mg, Mean: 6.8 mg D: 18 wks		Grp1 B: 122.46 (CV: 34.53) F: 113.88 (CV: 35.66) F-B: -8.58 Grp2 B: 122.85 (CV: 37.08) F: 128.31 (CV: 34.06) F-B: 5.46 Grp1-Grp2: -14.0 (SE: 8.1)	Grp1 B: 45.63 (CV: 24.3) F: 46.41 (CV: 25.01) F-B: 0.78 Grp2 B: 45.63 (CV: 23.03) F: 48.75 (CV: 27.97) F-B: 3.12 Grp1-Grp2: -2.34 (SE: 0.05)	Grp1 B: 177.1 (CV: 55.39) F: 161.98 (CV: 55.08) F-B: -15.1 Grp2 B: 170.88 (CV: 53.65) F: 170.88 (CV: 57.35) F-B: Grp1-Grp2: -15.1 (SE: 16.9)	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Weissman, 2005[86]	Grp1: Metformin Varied Start: 1000 mg, Max: 2000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.97 (1.2) F: 7.26 F-B: -0.71 Grp2 B: 8.05 (1.2) F: 7.12 F-B: -0.93 Grp1-Grp2: 0.2	Grp1 B: 105.1 (CI: 103.4, 106.8) F: 101.6 (CI: 99.7, 103.6) F-B: -3.5 Grp2 B: 106.3 (CI: 104.5, 108.2) F: 118.5 (CI: 116.3, 120.7) F-B: 12.2 Grp1-Grp2: -15.7	Grp1 B: 43.7 F: 45.3 F-B: 1.6 Grp2 B: 45 F: 49.1 F-B: 4.1 Grp1-Grp2: -2.5	Grp1 B: 179.2 F: 176.8 (170.9 to 182.9) F-B: -2.4 p: NSG Grp2 B: 184.8 F: 196.6 (189.2 to 204.2) p: NSG F-B: 11.8 Grp1-Grp2: -14.2	
Bailey, 2005[87]	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.5 (1.0) F: 7.4 (1.1) F-B: -0.13 Grp2 B: 7.4 (1.0) F: 7.1 (1.1) F-B: -0.33 Grp1-Grp2: 0.22 p: 0.001	Grp1 B: 111.9 (CI: 109.7, 114.1) F: 114.9 (CI: 112.6, 117.2) F-B: 3 Grp2 B: 109.5 (CI: 107.1, 111.8) F: 125.9 (CI: 122.9, 128.9) F-B: 16.4 Grp1-Grp2: -13.4	Grp1 B: 47.2 F: 46.4 F-B: -0.8 p: <0.05 Grp2 B: 45.3 F: 47.1 F-B: 1.8 p: <0.05 Grp1-Grp2: -2.6	Grp1 B: 180.8 (175.5 to 186.3) F: 167.5 (161.8 to 173.4) p: <0.05 F-B: -13.3 Grp2 B: 189.3 (183.5 to 195.2) F: 189.4 (183.1 to 195.9) p: NSG F-B: 0.1 Grp1-Grp2: -13.4	Grp1 B: 89.5 (14.4) F: 88.6 F-B: -0.9 (SE: 0.2) Grp2 B: 90.9 (15.6) F: 92.2 F-B: 1.3 (SE: 0.22) Grp1-Grp2: -2.2
Gomez-Perez, 2002[88]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid	Grp1 B: 9.8 (SE: 0.3) F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 10.2 (SE: 0.2) F: 9.5 (SE: 0.3) F-B: -0.7 p: 0.052 Grp1-Grp2: 1 p: 0.0132	Grp1 B: 116 (27.7) F: 115 F-B: -1 (20.9) Grp2 B: 106.9 (25.7) F: 123.5 F-B: 16.6 (24.7) Grp1-Grp2: -15.9 (CI: -4.73, -27)	Grp1 B: 49.4 (11.9) F: 48.9 F-B: -0.5 (7.2) Grp2 B: 51.5 (10) F: 56.7 F-B: 5.2 (7) Grp1-Grp2: -5.7 p: <0.05	Grp1 B: 227.2 (126.8) F: 233.4 F-B: 6.2 Grp2 B: 204.4 (113.3) F: 199.9 F-B: -4.5 Grp1-Grp2: 10.7	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Gomez-Perez, 2002[88]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid	Grp1 B: 9.8 (SE: 0.3) F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 9.75 (SE: 0.2) F: 8.6 (SE: 0.4) F-B: -1.2 p: 0.008 Grp1-Grp2: 1.5 p: 0.0002	Grp1 B: 116 (27.7) F: 115 F-B: -1 (20.9) Grp2 B: 108.2 (30) F: 114.3 F-B: 6.1 (22.5) Grp1-Grp2: -7.1 p: NSG	Grp1 B: 49.4 (11.9) F: 48.9 F-B:-0.5 (7.2) Grp2 B: 51.5 (10.9) F: 57.9 F-B: 6.4 (7) Grp1-Grp2: -6.9 p: <0.05	Grp1 B: 227.2 (126.8) F: 233.4 F-B: 6.2 Grp2 B: 199.6 (133.2) F: 193.8 F-B: -5.8 Grp1-Grp2: 12	
Einhorn, 2000[89]	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; Start: 30 mg	Grp1 B: 9.75 (SE: 1.3) F-B: p: <0.05 Grp2 B: 9.86 (SE: 1.4) F-B: p: <0.05 Grp1-Grp2: -0.83 p: <0.05	Grp1 B: 119.3 (3.07) F: 128.5 F-B: 7.7% p: <0.05 Grp2 B: 118 (6.9) F: 132 F-B: 11.9% Grp1-Grp2: 4.20%	Grp1 B: 42.9 (0.95) F: 53.1 F-B: 10.2 Grp2 B: 42.1 (1) F: 43.6 F-B: 1.5 Grp1-Grp2: 8.7 p: ≤0.05	Grp1 B: 298.9 (24.9) F: 289.2 F-B: -9.7 Grp2 B: 300.4 (25.86) F: 308.9 F-B: 8.5 Grp1-Grp2: -18.2 p: 0.05	Grp1 F-B: -1.36 Grp2 F-B: 0.95 Grp1-Grp2: -2.31
Fonseca, 2000[90]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.5) F: 8.12 F-B: -0.78 Grp1-Grp2: 1.2 p: <0.001	Grp1 B: 118.17 (34.32) F: 122.07 (37.83) F-B: 3.9 Grp2 B: 116.61 (30.42) F: 134.94 (33.54) F-B: 18.33 Grp1-Grp2: -14.04	Grp1 B: 44.46 (10.92) F: 46.8 (11.31) F-B: 2.34 Grp2 B: 46.8 (14.43) F: 53.04 (16.38) F-B: 6.24 Grp1-Grp2: -3.9 p: 0.0002	Grp1 B: 246.53 (194.91) F: 247.42 (159.31) F-B: 0.89 Grp2 B: 228.73 (184.23) F: 228.73 (166.43) F-B: 0 Grp1-Grp2: 0.89 p: 0.56	Grp1 F-B: -1.2 Grp2 F-B: 0.7 Grp1-Grp2: -1.9 p: 0.0001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Fonseca, 2000[90]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.3) F: 8.34 F-B: -0.56 Grp1-Grp2: -1 p: <0.001	Grp1 B: 118.17 (34.32) F: 122.07 (37.83) F-B: 3.9 Grp2 B: 113.49 (32.76) F: 134.55 (40.56) F-B: 21.06 Grp1-Grp2: -17.16 p: <0.0001	Grp1 B: 44.4 (10.92) F: 46.8 (11.31) F-B: 2.4 Grp2 B: 46.02 (11.31) F: 51.48 (13.26) F-B: 5.46 Grp1-Grp2: -3.06 p: 0.0002	Grp1 B: 246.53 (194.91) F: 247.42 (159.31) F-B: 0.89 Grp2 B: 226.06 (138.84) F: 233.18 (139.73) F-B: 7.12 Grp1-Grp2: -6.23 p: 0.73	Grp1 F-B: -1.2 Grp2 F-B: 1.9 Grp1-Grp2: -3.1 p: 0.0001
Metformin versus metformin + sulfonylurea						
Derosa, 2009[46]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + glimepiride Fixed Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NR; 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: 0.1 (SE: 0.29)				BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.1 (1.4) F: 28.4 (2.2) F-B: 4.8% p: <0.05 Grp1-Grp2: -1.8
Nauck, 2009[92]	Grp1: Metformin Varied Start: 2000 mg, Max: 2000 mg Grp2: Metformin + glimepiride Varied; Fixed Start: 2000 mg, Max: 2000 mg; Start: 1 mg, Max: 4 mg D: NR; 3 wks	Grp1 F-B: 0.1 (SE: 0.1) Grp2 F-B: -1 (SE: 0.1) Grp1-Grp2: 1.1 (SE: 0.14)				Grp1 F-B: -1.5 (SE: 0.3) Grp2 F-B: 1 (SE: 0.2) Grp1-Grp2: -2.5

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Chien, 2007[59]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1723 mg; Start: 10 mg, Max: 20 mg, Final mean: 17.2 mg D: 4 wks	Grp1-Grp2: -1.3 p: 0.005				
Chien, 2007[59]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks	Grp1-Grp2: -1.34 p: 0.002				
Feinglos, 2005[91]	Grp1: Metformin Fixed Start: at least 1000 mg Grp2: Metformin + glipizide Fixed Start: at least 1000 mg; Start: 2.5 mg	Grp1 B: 7.64 F: 7.46 (SE: 0.1) F-B: -0.19 Grp2 B: 7.45 F: 6.8 (SE: 0.1) F-B: -0.66 Grp1-Grp2: 0.47 p: <0.0002		Grp1 F-B: p: NSG Grp2 F-B: p: NSG	Grp1 F-B: p: NSG Grp2 F-B: p: NSG	Grp1 B: 90.8 (18.4) F: 89.1 F-B: -1.7 Grp2 B: 90 (18.7) F: 90.4 F-B: 0.4 Grp1-Grp2: -2.1 p: < 0.0001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2003[61]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.78 (1.5) F: 6.43 F-B: -2.27 Grp1-Grp2: -0.74 p: 0.0003	Grp1 B: 122.7 (3.2) F: 115 F-B: -5.7 p:<0.05 Grp2 B: 118.3 (3.5) F: 122.8 F-B: 4.5 p:<0.05 Grp1-Grp2: -10.2	Grp1 B: 42.3 (0.9) F: 41.9 F-B: -0.4 p: NSG Grp2 B: 41.3 (0.9) F: 42.1 F-B: 0.8 p: NSG Grp1-Grp2: -1.2	Grp1 B: 256.8 (26.7) F: 217.2 F-B: -39.6 p: NSG Grp2 B: 248.4 (26.2) F: 196.4 F-B: -52 p: <0.05 Grp1-Grp2: 12.4	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91.9 (17.4) F: 93.5 F-B: 1.6 p: NSG Grp1-Grp2: -2.7
Tosi, 2003[36]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 400 mg, Max: 2400 mg; Start: 2.5 mg, Max: 15 mg	Grp1 B: 7.8 (1.4) F: 7.3 F-B: -0.5 Grp2 B: 7.8 (1.0) F: 5.9 F-B: -1.9 Grp1-Grp2: 1.4				
Goldstein, 2003[62]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2 B: 8.7 (1.2) F: 7.4 (0.1) F-B: -1.3 Grp1-Grp2: 1.06 p: <0.001	Grp1 B: 109.7 (35.2) F: 102.5 F-B: -7.2 (CI: -15, 0.6) Grp2 B: 119.7 (29.5) F: 119.5 F-B: -0.2 (CI: -6.7, 6.3) Grp1-Grp2: -7	Grp1 B: 42.3 (9.7) F: 42.7 F-B: 0.4 p: NSG Grp2 B: 43.2 (10.0) F: 44.1 F-B: 0.9 p: NSG Grp1-Grp2: -0.5	Grp1 B: 218.7 (120.2) F: 217.1 F-B: -1.6 (-25.3 to 22) p: NSG Grp2 B: 237.5 (192.2) F: 256 F-B: 18.5 (-16.8 to 53.7) p: NSG Grp1-Grp2: -20.1	Grp1 B: 94.2 (16.7) F: 91.5 F-B: -2.7 (SE: 0.3) Grp2 B: 95.1 (17.8) F: 94.8 F-B: -0.3 (SE: 0.3) Grp1-Grp2: -2.4 p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Blonde, 2002[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.42 (1.24) F: 7.9 F-B: -1.38 Grp1-Grp2: 1.77 p: <0.001	Grp1-Grp2: p: NSG	Grp1-Grp2: p: NSG	Grp1-Grp2: p: NSG	
Blonde, 2002[63]	Grp1: Metformin Varied Start: 500 mg , Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.41 (1.47) F: 7.9 F-B: -1.64 Grp1-Grp2: 2.03 p: <0.001	Grp1-Grp2: p: NSG	Grp1-Grp2: p: NSG	Grp1-Grp2: p: NSG	
Marre, 2002[64]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.89 (1.62) F: 6.69 F-B: -1.2 Grp1-Grp2: 1 p: <0.05	Grp1 B: 148.2 (39) F: 136.5 F-B: -11.7 (31.2) p: NSG Grp2 B: 152.1 (42.9) F: 144.3 F-B: -7.8 (27.3) p: NSG Grp1-Grp2: -3.9	Grp1 B: 46.8 (11.7) F: 47.97 F-B: 1.17 p: NSG Grp2 B: 46.8 (15.6) F: 47.19 F-B: 0.39 p: NSG Grp1-Grp2: 0.78	Grp1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) Grp2 B: 213.6 (160.2) F: 195.8 F-B: -17.8 (151.3) Grp1-Grp2: 0 p: NSG	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 84.7 (15.1) F: 85.3 F-B: 0.6 Grp1-Grp2: -1.4

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Marre, 2002[64]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.62 (1.61) F: 6.72 F-B: -0.9 Grp1-Grp2: 0.7 p: <0.05	Grp1 B: 148.2 (39) F: 136.5 F-B: -11.7 (31.2) p:NSG Grp2 B: 152.1 (35.1) F: 144.3 F-B: -7.8 (27.3) p:NSG Grp1-Grp2: -3.9	Grp1 B: 46.8 (11.7) F: 58.5 F-B: 1.17 p: NSG Grp2 B: 50.7 (11.7) F: 50.7 F-B: 0 p: NSG Grp1-Grp2: 1.17	Grp1 B: 204.7 (169.1) F: 186.9 F-B: -17.8 (89) Grp2 B: 222.5 (284.8) F: 178 F-B: -44.5 (186.9) Grp1-Grp2: 26.7 p: NSG	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 83.1 (13.3) F: 84.1 F-B: 1 Grp1-Grp2: -1.8
Garber, 2002[65]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.18 (1.14) F: 6.65 F-B: -1.53 Grp1-Grp2: 0.5 p: <0.001				Grp1 F-B: -0.6 Grp2 F-B: 1.4 p: <0.05 Grp1-Grp2: -2
Garber, 2002[65]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.25 (1.11) F: 6.77 F-B: -1.48 Grp1-Grp2: 0.45 p: <0.001				Grp1 F-B: -0.6 Grp2 F-B: 1.9 p: <0.05 Grp1-Grp2: -2.5

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[68]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 7.8 (SE: 0.3) F: 5.7 (SE: 0.3) F-B: -2.0 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.1 p: >0.1 across all treatment groups	Grp1 B: 142.74 (SE: 9.75) F: 131.82 (SE: 8.97) F-B: -5.85 (SE: 2.73) Grp2 B: 143.13 (SE: 5.46) F: 139.62 (SE: 4.68) F-B: -2.73 (SE: 2.34) Grp1-Grp2: -3.12	Grp1 B: 31.59 (SE: 2.34) F: 30.03 (SE: 1.56) F-B: -0.78 (SE: 0.78) p: >0.1 Grp2 B: 35.49 (SE: 1.56) F: 37.05 (SE: 1.95) F-B: 1.56 (SE: 1.17) p: >0.1 Grp1-Grp2: -0.78	Grp1 B: 179.78 (SE: 18.69) F: 173.55 (SE: 14.24) F-B: 8.01 (SE: 12.46) p: >0.1 Grp2 B: 175.33 (SE: 20.47) F: 168.21 (SE: 17.8) F-B: 5.34 (SE: 11.57) p: >0.1 Grp1-Grp2: 2.67	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.2 (SE: 0.5) p: >0.1 Grp2 B: 80.2 (SE: 2.4) F: 81 (SE: 2.5) F-B: 0.7 (SE: 0.4) p: >0.1 Grp1-Grp2: -0.9
Hermann, 1994[68]	Grp1: Metformin Varied Start: 1000 mg , Max: 3000 mg Grp2: Metformin + glyburide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 7.8 (SE: 0.3) F: 5.4 (SE: 0.3) F-B: -2.3 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.4 p: >0.1 across all treatment groups				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1994[68]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 2000 mg, Max: 3000 mg; Start: 7.0 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 8.4 (SE: 0.4) F: 6.2 (SE: 0.3) F-B: -2.2 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.3 p: >0.1 across all treatment groups				
Hermann, 1994[68]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75 mg, Max: 5.25 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.8 (SE: 0.1) F: 5.6 (SE: 0.1) F-B: -1.2 (SE: 0.1) p: 0.001 Grp1-Grp2: 0.3 p: >0.1 across all treatment groups				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Hermann, 1991[155]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.7 (1.1) F: 5.4 (0.9) F-B: -2.3 p: <0.001 Grp1-Grp2: 1.4	Grp1 F-B: 0.78 (SE: 3.9) Grp2 F-B: -6.24 (SE: 2.34) Grp1-Grp2: 7.02 p:<0.05			Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG Grp2 B: 87.3 (15.6) F: 87.3 (15.9) F-B: 0 p: NSG Grp1-Grp2: -0.4
Hermann, 1991[155]	Grp1: Metformin + diet Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.8 (1.4) F: 5.7 (0.8) F-B: -2.2 p: <0.001 Grp1-Grp2: 1.3				Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NSG Grp2 B: 74.4 (11.4) F: 76 (11.8) F-B: 1.6 p: <0.001 Grp1-Grp2: -2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Charpentier, 2001[71]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed; Varied Start: 850 mg tid; Start: 1 mg, Max: 6 mg	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2 B: 6.42 (1.08) F: 5.68 (0.99) F-B: -0.74 (SE: 0.8) Grp1-Grp2: 0.92 p: <0.001		Grp1 B: 46.41 (13.65) F: 48.36 F-B: 1.95 (9.36) Grp2 B: 46.41 (12.09) F: 45.24 F-B: -1.17 (9.87) Grp1-Grp2: 3.12 p: 0.14 across all treatment groups	Grp1 B: 171.77 (119.26) F: 185.12 F-B: 13.35 (104.13) Grp2 B: 169.99 (110.36) F: 167.32 F-B: -2.67 (93.45) Grp1-Grp2: 16.02 p: 0.029 across all treatment groups	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2 B: 81.2 F: 81.8 F-B: 0.6 (2.86) Grp1-Grp2: -1.34
DeFronzo, 1995[70]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	Grp1 B: 8.9 F: 8.5 F-B: -0.4 (SE: 0.1) Grp2 B: 8.8 F: 7.1 F-B: -1.7 (SE: 0.1) Grp1-Grp2: 1.3 p: <0.001	Grp1 B: 134 (SE: 3) F: 129 (SE: 3) F-B: -6 (SE: 2) Grp2 B: 137 (SE: 3) F: 128 (SE: 3) F-B: -8 (SE: 2) Grp1-Grp2: 2 p: NSG		Grp1 B: 231 (SE: 12) F: 221 (SE: 13) F-B: -16 (SE: 7) Grp2 B: 216 (SE: 10) F: 194 (SE: 9) F-B: -20 (SE: 7) Grp1-Grp2: 4	Grp1 F-B: -3.8 (SE: 0.2) p: <0.001 Grp2 F-B: 0.4 (SE: 0.2) p: NSG Grp1-Grp2: -4.2
Metformin versus metformin + DPP-IV inhibitor						
Jadzinsky, 2009[78]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Weeks Grp2: Metformin + saxagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 5mg D: 1 Weeks	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.5 p: <0.0001	Grp1 B: 126.7 F: 118.5 F-B: -4 (SE: 1.44) (CI: -6.8, -1.1) Grp2 B: 124.4 F: 114.8 F-B: -3.8 (SE: 1.85) (CI: -7.4, -0.1) Grp1-Grp2: 1.4	Grp1 B: 43.6 F: 46.6 F-B: 8.9 (SE: 1.36) (CI: 6.2, 11.5) Grp2 B: 43.9 F: 46 F-B: 6.2 (SE: 1.15) (CI: 3.9, 8.5) Grp1-Grp2: 0.9	Grp1 B: 228.1 (SE: 13.92) F: 207.2 (SE: 14.71) F-B: -1.5 (SE: 2.72) (CI: -6.8, 3.9) Grp2 B: 225.5 (SE: 13.92) F: 184.4 (SE: 9.17) F-B: -4.5 (SE: 2.82) (CI: -10.1, 1) Grp1-Grp2: 0.2	Grp1 F-B: -1.6 Grp2 F-B: -1.8 Grp1-Grp2: 0.2

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Jadzinsky, 2009[78]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Weeks Grp2: Metformin + saxagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 Weeks	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.8 p: <0.0001	Grp1 B: 126.7 F: 118.5 F-B: -4 (SE: 1.44) (CI: -6.8, -1.1) Grp2 B: 124.6 F: 114.2 F-B: -4.6 (SE: 1.73) (CI: -8.1, -1.2) Grp1-Grp2: 2.2	Grp1 B: 43.6 F: 46.6 F-B: 8.9 (SE: 1.36) (CI: 6.2, 11.5) Grp2 B: 43.7 F: 45.6 F-B: 6.7 (SE: 1.26) (CI: 4.2, 9.2) Grp1-Grp2: 1.1	Grp1 B: 228.1 (SE: 13.92) F: 207.2 (SE: 14.71) F-B: -1.5 (SE: 2.72) (CI: -6.8, 3.9) Grp2 B: 217.9 (SE: 10.23) F: 181.7 (SE: 8.86) F-B: -5.8 (SE: 3.55) (CI: -12.8, 1.2) Grp1-Grp2: 15.3	Grp1 F-B: -1.6 Grp2 F-B: -1.4 Grp1-Grp2: -0.2
DeFronzo, 2009[95]	Grp1: Metformin Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 2.5 mg	Grp1 F-B: Grp2 0 F-B: -0.59 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.73 (SE: 0.1) (CI: 0.53, 0.92) p: <0.0001				
DeFronzo, 2009[95]	Grp1: Metformin Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 5 mg	Grp1 F-B: 0 Grp2 F-B: -0.69 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.83 (SE: 0.1) (CI: 0.63, 1.02) p: <0.0001				
DeFronzo, 2009[95]	Grp1: Metformin Fixed Grp2: Metformin+ Saxagliptin Fixed NR; Mean: 10 mg	Grp1 F-B: 0 Grp2 F-B: -0.58 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.72 (SE: 0.1) (CI: 0.52, 0.91) p: <0.0001				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.5	Grp1 B: 105.3 (32.3) F: 102.3 (33.6) F-B: -3 Grp2 B: 115.1 (39.1) F: 110.1 (37.1) F-B: -5 Grp1-Grp2: 2 (SE: 7.8)	Grp1 B: 42.8 (9) F: 45.2 (11) F-B: 2.4 Grp2 B: 43.9 (11.1) F: 46.6 (13.5) F-B: 2.7 Grp1-Grp2: -0.3 (SE: 2.40)	Grp1 B: 150 (92.1) F: 174.5 (124.7) F-B: Median % change: 8.4 (CI: 0.5, 16.4) Grp2 B: 158 (97.7) F: 143 (94) F-B: Median % change: -7.1 (CI: -13.9, -0.2) Grp1-Grp2: 39.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -1.7 (CI: -2.4, -1.1)
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.1	Grp1 B: 107.3 (33.4) F: 102.5 (36.7) F-B: -4.8 Grp2 B: 115.1 (39.1) F: 110.1 (37.1) F-B: -5 Grp1-Grp2: 0.2 (SE: 7.8)	Grp1 B: 43.3 (10.8) F: 46.4 (12) F-B: 3.1 Grp2 B: 43.7 (9.3) F: 45.4 (11.3) F-B: 1.7 Grp1-Grp2: 1.4 (SE: 2.31)	Grp1 B: 150 (92.1) F: 174.5 (124.7) F-B: Median % change: 8.4 (CI: 0.5, 16.4) Grp2 B: 155 (104.2) F: 147 (95.8) F-B: Median % change: -4.6 (CI: -11.9, 2.7) Grp1-Grp2: 32.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.8
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.8	Grp1 B: 106.8 (34.2) F: 103.6 (31.5) F-B: -3.2 Grp2 B: 114.7 (37.1) F: 111 (32.4) F-B: -3.7 Grp1-Grp2: 0.5 (SE: 6.5)	Grp1 B: 43.2 (9.4) F: 44.6 (10.4) F-B: 1.4 Grp2 B: 43.1 (9.2) F: 44.3 (10.4) F-B: 1.2 Grp1-Grp2: 0.2 (SE: 1.88)	Grp1 B: 167 (104.2) F: 173 (120) F-B: Median % change: 4.9 (CI: -3.3, 13) Grp2 B: 158 (97.7) F: 143 (94) F-B: Median % change: -7.1 (CI: -13.9, -0.2) Grp1-Grp2: 21	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -1.7 (CI: -2.4, -1.1) Grp1-Grp2: 0.7

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Williams-Herman, 2009[76]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.4	Grp1 B: 108.2 (34.4) F: 104.6 (33.8) F-B: -3.6 Grp2 B: 114.7 (37.1) F: 111 (32.4) F-B: -3.7 Grp1-Grp2: 0.1 (SE: 6.6)	Grp1 B: 43.2 (9.4) F: 44.6 (10.4) F-B: 1.4 Grp2 B: 44.2 (10.9) F: 46 (12.2) F-B: 1.8 Grp1-Grp2: -0.4 (SE: 2.06)	Grp1 B: 167 (104.2) F: 173 (120) F-B: Median % change: 4.9 (CI: -3.3, 13) Grp2 B: 155 (104.2) F: 147 (95.8) F-B: Median % change: -4.6 (CI: -11.9, 2.7) Grp1-Grp2: 14	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.3
Raz, 2008[93]	Grp1: Metformin Fixed NR Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1 F-B: 0 (CI: -0.2, 0.3) Grp2 F-B: -1 (CI: -1.3, -0.7) p: <0.001 Grp1-Grp2: -1 (CI: -1.4, -0.6) p: <0.001				Grp1 F-B: -0.5 Grp2 F-B: -0.5 Grp1-Grp2: 0
Goldstein, 2007[75]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.58				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Goldstein, 2007[75]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.9 (CI: -2.06, -1.74) Grp1-Grp2: 1.08				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline
Goldstein, 2007[75]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.27				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline
Goldstein, 2007[75]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.9 (CI: -2.06, -1.74) Grp1-Grp2: 0.77 (SE: 0.12)				Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Charbonnel, 2006[94]	Grp1: Metformin Varied, glucose: , HbA1c: 7% - 10% Start: >=1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: >=1500 mg; Mean: 100 mg D: 19 wks	Grp1 B: 8.03 (0.82) F: 7.95 (1.1) F-B: -0.02 (CI: -0.15, 0.1) Grp2 B: 7.96 (0.81) F: 7.26 (0.97) F-B: -0.67 (CI: -0.77, -0.57) Grp1-Grp2: 0.65 (SE 0.08)	Grp1 B: 102.18 (31.6) F: 104.13 (32.8) F-B: 1.95 Grp2 B: 98.67 (30.8) F: 100.62 (32.0) F-B: 1.95 Grp1-Grp2: 0 (SE: 4.7)	Grp1 B: 44.85 (10.92) F: 45.63 (11.7) F-B: 0.78 Grp2 B: 45.63 (10.92) F: 46.8 (11.31) F-B: 1.17 Grp1-Grp2: -0.39 (SE: 1.65)	Grp1 F-B: 24.6 (CI: 16.8, 32.3) Grp2 F-B: 7.7 (CI: 1.5, 14) Grp1-Grp2: 16.9	Grp1 F-B: 0.6-0.7 p: <0.05 Grp2 F-B: 0.6-0.7 p: <0.05 Grp1-Grp2: p=0.835
Scott, 2008[85]	Grp1: Metformin Fixed Total starting dose: > 1500 mg Grp2: Metformin + sitagliptin Fixed Total starting dose: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.75 (0.99) F: 7.01 (0.86) F-B: -0.73 (CI: -0.87, -0.6) Grp1-Grp2: -0.51 (CI: -0.7, -0.32) p: <0.001	Grp1 B: 95.6 (30.8) F: 108.4 (33.6) F-B: Mean % change: 16.7 (CI: 10.2, 23.3) Grp2 B: 95.4 (30.8) F: 104.6 (35.1) F-B: Mean % change: 11.4 (CI: 5, 17.8) Grp1-Grp2: 3.6 (SE: 8.7)	Grp1 B: 43.5 (10.5) F: 44.1 (12.1) F-B: Mean % change: 1.8 (CI: -1.3, 4.9) Grp2 B: 43.9 (11.6) F: 45.7 (13.4) F-B: Mean % change: 4.3 (CI: 1.2, 7.3) Grp1-Grp2: -1.2 (SE: 3.18)	Grp1 B: 171.1 (73.3) F: 191.5 (111.1) F-B: Mean % change from baseline: 11.9 (CI: 3.9, 19.9) Grp2 B: 177.8 (80.7) F: 163.3 (74) F-B: Mean % change from baseline: -4.8 (CI: -12.7, 3.1)	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: -0.4
Metformin versus metformin + meglitinides						
Horton, 2004[80]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Metformin + nateglinide Fixed Start: 500 mg qac; Start: 120 mg qac	Grp1 F-B: -0.8 (SE: 0.1) p: <0.001 Grp2 F-B: -1.6 (SE: 0.1) p: <0.001 Grp1-Grp2: 0.8 (SE: 0.14)				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Marre, 2002[96]	Grp1: Metformin Fixed Start: 1000 mg bid Grp2: Metformin + nateglinide Fixed Start: 1000 mg bid; Start: 60 mg qac	Grp2-Grp1: -0.36 (CI: -0.59, -0.13) p: 0.003	Grp1-Grp2: 0.0 (CI: -3.9, 7.8) p: NSG	Grp1-Grp2: 0.0 (CI: -0.0, 3.9) p: NSG	Grp1-Grp2: -3.9 (CI: -11.7, 7.8) p: NSG	Grp1 F-B: 0.1 Grp2 F-B: 0.4 Grp1-Grp2: -0.3 (CI: -0.8, 0.2) p: >0.05
Marre, 2002[96]	Grp1: Metformin Fixed Start: 1000 mg bid Grp2: Metformin + nateglinide Fixed Start: 1000 mg bid; Start: 120 mg qac	Grp2-Grp1: -0.51 (CI: -0.82, -0.36) p: <0.001	Grp1-Grp2: 3.9 (CI: -0.0, 11.7) p: NSG	Grp1-Grp2: 0.0 (CI: -0.0, 3.9) p: NSG	Grp1-Grp2: -7.8 (CI: -15.6, -0.0) p: <0.05	Grp1 F-B: 0.1 Grp2 F-B: 1 Grp1-Grp2: -0.9 (CI: -1.4, 0) p: <0.001
Moses, 1999[82]	Grp1: Metformin NR Grp2: Metformin + repaglinide NR NR; Start: 0.5 mg tid, Max: 4.0 mg tid D: NR; 12 to 28 days	Grp1 F-B: -0.33 (SE: 0.24, CI: -0.8, -0.5) Grp2 F-B: -1.41 (SE: 0.23, CI: -1.87, -0.95) Grp1-Grp2: -1.08 (SE: 0.33, CI: -1.84, -0.33) p: 0.05				Grp1 F-B: -0.86 (SE: 0.51) Grp2 F-B: 2.41 (SE: 0.5) p: <0.05 Grp1-Grp2: -3.27
Horton, 2000[79]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Metformin + nateglinide Fixed Start: 500 mg qac; Start: 120 mg qac	Grp1 B: 8.4 (1.2) F: 7.6 F-B: -0.8 p: ≤0.0001 Grp2 B: 8.4 (1.1) F: 7.1 F-B: -1.3 p: ≤0.0001 Grp1-Grp2: 0.5				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Thiazolidinedione versus thiazolidinedione						
Vijay, 2009[99]	Grp1: Rosiglitazone Varied Start: 4 mg daily, Max: 4 mg bid D: NR Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg D: NR	Grp1 F-B: -1.26 (SD: 0.72) p: 0 Grp2 F-B: -1.27 (SD: 0.17) p: 0 Grp1-Grp2: 0.01	Grp1 F-B: 5.39 p: 0.39 Grp2 F-B: -13.66 (6.7) p: 0 Grp1-Grp2: 19.05	Grp1 F-B: 3.25 p: 0.01 Grp2 F-B: 4.7 (1.4) p: 0 Grp1-Grp2: -1.45	Grp1 F-B: -25.3 p: 0.013 Grp2 F-B: -33 (8.7) p: 0 Grp1-Grp2: 7.7	Grp1 F-B: 0.7 (0.3) p: 0.8 Grp2 F-B: 1.15 (0.4) p: 0 Grp1-Grp2: -0.45
Goldberg, 2005[98]	Grp1: Rosiglitazone Varied Start: 4 mg, Max: 8 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 7.5 (SE: 0.1) F: 6.9 F-B: -0.6 (SE: 0.1) p:<.05 Grp2 B: 7.6 (SE: 0.1) F: 6.9 F-B: -0.7 (SE: 0.1) p: <.05 Grp1-Grp2: 0.1	Grp1 B: 109.1 (SE: 1.4) F: 130.4 F-B: 21.3 (SE: 1.6) p: <0.05 Grp2 B: 107.1 (SE: 1.3) F: 119.4 F-B: 12.3 (SE: 1.6) p: <0.05 Grp1-Grp2: 9	Grp1 B: 39.8 (SE: 0.6) F: 42.2 F-B: 2.4 (SE: 0.5) Grp2 B: 38.8 (SE: 0.5) F: 44 F-B: 5.2 (SE: 0.5) Grp1-Grp2: -2.8 p: <0.001	Grp1 B: 235.3 (SE: 6.6) F: 248.4 F-B: 13.1 (SE: 7.8) p: NSG Grp2 B: 257.8 (SE: 8.2) F: 205.9 F-B: -51.9 (SE: 7.8) p: <0.05 Grp1-Grp2: 65	
Khan, 2002[97]	Grp1: Rosiglitazone Fixed Start: 2-8 mg Grp2: Pioglitazone Fixed Start: 15-45 mg	Grp1 B: 7.9 (1.9) F: 7.6 F-B: -0.3 Grp2 B: 8.0 (1.7) F: 7.8 F-B: -0.2 (SE: 0.1) Grp1-Grp2: -0.1 p: NSG	Grp1 B: 105.9 (29.7) F: 103.9 F-B: -2 p: NSG Grp2 B: 116.2 (38) F: 98.2 F-B: -18 p: <0.01 Grp1-Grp2: 16	Grp1 B: 45.3 (15.2) F: 48.6 F-B: 1.5 p: NSG Grp2 B: 44.7 (15.6) F: 46.7 F-B: 2.0 p: NSG Grp1-Grp2: -0.5	Grp1 B: 236 (222) F: 242 F-B: 6 p: NSG Grp2 B: 181 (110.1) F: 166 F-B: -15 p: NSG Grp1-Grp2: 21	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Thiazolidinedione versus sulfonylurea						
Nakamura, 2006[108]	Grp1: Pioglitazone Fixed Mean: 30 mg D: 12 Months Grp2: Glibenclamide Fixed Mean: 5 mg D: 12 Months	Grp1 B: 8 (1.4) F: 6.4 (1.2) p:<0.01 F-B: -1.6 Grp2 B: 7.8 (1.3) F: 7 (6.2) p:<0.01 F-B: -0.8 Grp1-Grp2: -0.8		Grp1 B: 32 (10) F: 40 (12) p:<0.05 F-B: 8 Grp2 B: 34 (8) F: 34 (10) p:NSG F-B: 0 Grp1-Grp2: 8	Grp1 B: 148 (42) F: 118 (28) p:<0.01 F-B: -30 Grp2 B: 144 (38) F: 146 (38) p: NSG F-B: 2 Grp1-Grp2: -32	
Teramoto, 2007[41]	Grp1: Pioglitazone Varied, glucose: <= 126 mg/dL Start: 15 mg, Max: 30 mg D: 15 wks Grp2: Glibenclamide Varied, glucose: <= 126 mg/dL Start: 1.25 mg, Max: 2.5 mg D: 15 wks	Grp1 F-B: -0.8 (1.14) p: <0.05 Grp2 F-B: -1.43 (1.09) p: <0.05 Grp1-Grp2: 0.63 (SE: 0.48)	Grp1 F-B: 8.65 (23.47) Grp2 F-B: -1.31 (24.94) Grp1-Grp2: 9.96 (SE: 2.25)	Grp1 F-B: 3.8 (8.2) p: <0.05 Grp2 F-B: -1.2 (6.3) Grp1-Grp2: 5 (SE: 1.23)	Grp1 F-B: -57.7 (111.5) p: <0.05 Grp2 F-B: 7.3 (112.7) Grp1-Grp2: -65 (SE: 4.8)	
Hanefeld, 2007[100]	Grp1: Rosiglitazone Fixed Mean: 4 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.3 p: 0.0003 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.4	Grp1 F-B: 7.8 (27.3) Grp2 F-B: -3.9 (27.3) Grp1-Grp2: 11.7 (SE: 1.66)	Grp1 F-B: Median: 0.12 CI: 0.09 - 0.15 p: <0.0001 Grp2 F-B: Median: 0.08 CI: 0.05 - 0.12 p: <0.0001	Grp1 F-B: -10 (351) p: NSG Grp2 F-B: -3 (86) p: NSG Grp1-Grp2: -7	Grp1 F-B: 1.75 Grp2 F-B: 1.9 Grp1-Grp2: -0.15
Hanefeld, 2007[100]	Grp1: Rosiglitazone Fixed Mean: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.5 p: <0.0001 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.2 (SE: 0.24)	Grp1 F-B: 15.6 (35.1) Grp2 F-B: -3.9 (27.3) Grp1-Grp2: 19.5 (SE: 1.78)	Grp1 F-B: Median: 0.17 CI: 0.12 - 0.22 p: <0.0001 Grp2 F-B: Median: 0.08 CI: 0.05 - 0.12 p: <0.0001	Grp1 F-B: 12 (92) p: NSG Grp2 F-B: -3 (86) p: NSG Grp1-Grp2: 15	Grp1 F-B: 2.95 Grp2 F-B: 1.9 Grp1-Grp2: 1.05 p: 0.01

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kahn, 2006[38]	Grp1: Rosiglitazone Varied, glucose: <140 mg/dL Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1-Grp2: -0.42 (CI: -0.5, -0.33) p: <0.001				Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <0.001
Jain, 2006[101]	Grp1: Pioglitazone Varied, glucose: FPG: 69-141 mg/dL Start: 15 mg, Max: 45 mg, Median: 45 mg D: 16 wks Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dL Start: 5 mg, Max: 15 mg, Median: 10 mg D: 16 wks	Grp1 B: 9.2 (1.26) F: 7.13 (1.26) F-B: -2.07 Grp2 B: 9.2 (1.20) F: 7.18 (1.20) F-B: -2.02 Grp1-Grp2: -0.05 p: 0.669				Grp1 F-B: 3.66 (6.14) p: <0.001 Grp2 F-B: 1.95 (5.35) Grp1-Grp2: 1.71
Smith, 2004[291]	Grp1: Rosiglitazone Varied Start: 8 mg Grp2: Glyburide Varied Median: 7.5 mg D: 12 wks	Grp1 F-B: -0.4 Grp2 F-B: 0.72 Grp1-Grp2: -1.1 p: >0.05				
Nakamura, 2004[102]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	Grp1 F-B: 1.7 (1) p: <0.05 Grp2 F-B: 1.5 (1.1) p: <0.05 Grp1-Grp2: 0.2 (SE: 0.62)				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Yamanouchi, 2005[50]	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 mg	Grp1 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: -0.2		Grp1 B: 53.82 (4.68) F: 58.11 (3.51) F-B: 4.29 p: NSG Grp2 B: 52.65 (4.29) F: 52.26 (4.29) F-B: -0.39 p: NSG Grp1-Grp2: 4.68	Grp1 B: 219.83 (112.14) F: 185.12 (96.12) F-B: -34.71 p: NSG Grp2 B: 234.07 (121.93) F: 229.62 (112.14) F-B: -4.45 p: NSG Grp1-Grp2: -30.26	
Pfutzner, 2005[105] Langenfeld, 2005[290]	Grp1: Pioglitazone Fixed Start: 45 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 6 mg	Grp1 B: 7.52 (0.85) F: 6.71 (0.89) F-B: -0.81 p: <0.05 Grp2 B: 7.44 (0.89) F: 6.83 (0.85) F-B: -0.61 p: <0.05 Grp1-Grp2: -0.2	Grp1 B: 136 (29) F: 133 (31) F-B: -3 Grp2 B: 137 (25) F: 129 (27) F-B: -8 Grp1-Grp2: 5 p: NSG	Grp1 B: 46 (11) F: 54 (13) F-B: 8 Grp2 B: 46 (14) F: 47 (12) F-B: 1 Grp1-Grp2: 7 p: 0.001	Grp1 B: 190 (109) F: 168 (102) F-B: -22 p: <0.005 Grp2 B: 202 (111) F: 185 (106) F-B: -17 p: <0.001 Grp1-Grp2: -5	
Ramachandran, 2004[51]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 30 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: <0.01 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: -0.1		Grp1 B: 38.22 (5.85) F: 42.9 (7.8) F-B: 4.68 p: <0.01 Grp2 B: 37.05 (11.7) F: 42.9 (7.8) F-B: 5.85 p: NSG e Grp1-Grp2: -1.17	Grp1 B: 258.1 (213.6) F: 195.8 (124.6) F-B: -62.3 p: <0.05 Grp2 B: 195.8 (124.6) F: 151.3 (80.1) F-B: -44.5 p: <0.05 Grp1-Grp2: -17.8	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.9

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Tan, 2004[106]	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5 mg	Grp1 B: 8.4 (0.7) F: 7.9 F-B: -0.5 p: <0.005 Grp2 B: 8.5 (0.8) F: 8.1 F-B: -0.4 p: <0.005 Grp1-Grp2: -0.1	Grp1 B: 141.18 F: 146.64 F-B: 5.46 p: NSG Grp2 B: 135.72 F: 134.55 F-B: -1.17 p: NSG Grp1-Grp2: 6.63		Grp1 B: 182.45 F: 150.45 F-B: -32.04 p: <0.05 Grp2 B: 202.03 F: 199.36 F-B: -2.67 p: NSG Grp1-Grp2: -29.37	Grp1 B: 88.7 (17.4) F: 91.7 F-B: 3 p: <0.001 Grp2 B: 89.1 (16) F: 90.2 F-B: 1.1 p: 0.008 Grp1-Grp2: 1.9 p: 0.002
Tan, 2004[106]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 45 mg Grp2: Glimepiride Varied Start: 2 mg, Max: 8 mg	Grp1 B: 8.54 (0.903) F: 7.76 F-B: -0.78 (0.162) p: <0.001 Grp2 B: 8.45 (1.02) F: 7.77 F-B: -0.68 (0.169) p: <0.001 Grp1-Grp2: -0.1 p: 0.638		Grp1 B: 46.02 F: 54.21 F-B: 8.19 p: <0.001 Grp2 B: 43.68 F: 44.85 F-B: 1.17 p: NSG Grp1-Grp2: 7.02		
Bakris, 2003[104]	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Start: NR, Max: 20 mg	Grp1 B: 9.1 (1.68) F: 8.2 F-B: -0.9 (1.38) Grp2 B: 9.5 (1.59) F: 8.6 F-B: -0.9 (1.39) Grp1-Grp2: 0 p: NSG				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Nakamura, 2000[103]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	Grp1 B: 7.7 (1.2) F: 6.8 (1.0) F-B: -0.9 p: <0.05 Grp2 B: 7.8 (1.1) F: 6.9 (1.2) F-B: -0.9 p: <0.05 Grp1-Grp2: 0				
St John Sutton, 2002[149]	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Start: NR, Max: 20 mg		Grp1 B: 140.2 F: 146.5 F-B: 6.3 to 7.7 Grp2 B: 135.4 F: 126.5 F-B: -8.9 Grp1-Grp2: 15.2	Grp1 F-B: Median: 7.7 p: <0.05 Grp2 NR	Grp1 B: 226.6 F: 223.8 F-B: -2.8 p: NSG Grp2 B: 189.6 F: 175.8 F-B: -13.8 p: NSG Grp1-Grp2: 11	Grp1 B: 86.2 (15.6) F: 91.2 F-B: 5 (CI: 3.7, 6.2) p: <0.05 Grp2 B: 85.1 (13.6) F: 88.5 F-B: 3.4 (CI: 2.7, 4.1) p: <0.05 Grp1-Grp2: 1.6
Thiazolidinedione versus meglitinides						
Nakamura, 2006[108]	Grp1: Pioglitazone Fixed Mean: 30 mg D: 12 Months Grp2: Nateglinide Fixed Mean: 270 mg D: 12 Months	Grp1 B: 8 (1.4) F: 6.4 (1.2) p:<0.01 F-B: -1.6 Grp2 B: 7.7 (1.2) F: 6.3 (1.3) p:<0.01 F-B: -1.4 Grp1-Grp2: -0.2		Grp1 B: 32 (10) F: 40 (12) p:<0.05 F-B: 8 Grp2 B: 35 (6) F: 36 (6) p:NSG F-B: 1 Grp1-Grp2: 7	Grp1 B: 148 (42) F: 118 (28) p:<0.01 F-B: -30 Grp2 B: 146 (40) F: 148 (36) p: NSG F-B: 2 Grp1-Grp2: -32	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Raskin, 2004[109]	Grp1: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid Grp2: Repaglinide Varied Start: 0.5 mg tid if HbA1c <8% and 1 mg tid if HbA1c >8%, Max: 4 mg tid	Grp1 B: 9 F: 8.5 F-B: -0.56 (SE: 0.14) Grp2 B: 9.3 F: 9.1 F-B: -0.17 (SE: 0.14) Grp1-Grp2: -0.39	Grp1 B: 125 (23.5) F: 139 (34.3) F-B: 14 Grp2 B: 124 (33.8) F: 123 (32.3) F-B: -1 Grp1-Grp2: 15	Grp1 B: 39.9 (10.6) F: 42.5 (11.3) F-B: 2.6 Grp2 B: 39.2 (10.5) F: 40.5 (11.5) F-B: 1.3 Grp1-Grp2: 1.3	Grp1 B: 245 (211) F: 246 (174) F-B: 1 Grp2 B: 306 (246) F: 284 (211) F-B: -22 Grp1-Grp2: 23	Grp1 F-B: 2.3 Grp2 F-B: 1.6 Grp1-Grp2: 0.7
Jovanovic, 2004[110]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Repaglinide Varied Start: 0.5 mg tid if HbA1c <8% and 1 mg tid if HbA1c >8%, Max: 4 mg tid	Grp1 B: 9.1 F: 9.5 F-B: 0.32 (SE: 0.16) Grp2 B: 9 F: 8.9 F-B: -0.18 (SE: 0.17) Grp1-Grp2: 0.5 p: NSG	Grp1 B: 106 (37) F: 116 (42) F-B: 10 Grp2 B: 124 (36) F: 118 (38) F-B: -6 Grp1-Grp2: 16	Grp1 B: 41 (8.8) F: 47.2 (9.4) F-B: 6.2 Grp2 B: 45.4 (12.5) F: 44.6 (11.8) F-B: -0.8 Grp1-Grp2: 7	Grp1 B: 291 (232) F: 200 (99) F-B: -91 Grp2 B: 174 (80) F: 179 (78) F-B: 5 Grp1-Grp2: -96	Grp1 F-B: 2 p: <0.05 Grp2 F-B: 0.3 Grp1-Grp2: 1.7
Sulfonylurea versus DPP-IV inhibitor						
Scott, 2007[111]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 100 mg, Max: 100 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.83 (0.95) F: 7.34 (1.01) F-B: -0.54 (CI: -0.68, -0.4) Grp1-Grp2: -0.22	Grp1 B: 115.05 (39.39) F: 114.27 (35.1) F-B: -0.78 Grp2 B: 115.44 (30.42) F: 115.44 (31.2) F-B: 0 Grp1-Grp2: -0.78	Grp1 B: 44.46 (9.75) F: 45.24 (10.92) F-B: 0.78 Grp2 B: 45.24 (10.53) F: 45.63 (11.31) F-B: 0.38 Grp1-Grp2: 0.4	Grp1 B: 171.77 (85.44) F: 174.44 (83.66) F-B: 2.67 Grp2 B: 179.78 (98.79) F: 192.24 (129.94) F-B: 12.46 Grp1-Grp2: -9.79	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Scott, 2007[111]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 50 mg, Max: 50 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.5 (1.14) F-B: -0.43 (CI: -0.56, -0.29) Grp1-Grp2: -0.33	Grp1 B: 115.05 (39.39) F: 114.27 (35.1) F-B: -0.78 Grp2 B: 118.95 (31.98) F: 119.73 (32.76) F-B: 0.78 Grp1-Grp2: -1.56	Grp1 B: 44.46 (9.75) F: 45.24 (10.92) F-B: 0.78 Grp2 B: 45.24 (10.53) F: 46.02 (10.14) F-B: 0.78 Grp1-Grp2: 0	Grp1 B: 171.77 (85.44) F: 174.44 (83.66) F-B: 2.67 Grp2 B: 177.11 (105.91) F: 164.65 (88.11) F-B: -12.46 Grp1-Grp2: 15.13	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change
Scott, 2007[111]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 25 mg, Max: 25 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.85 (0.88) F: 7.48 (0.98) F-B: -0.41 (CI: -0.55, -0.27) Grp1-Grp2: -0.35	Grp1 B: 115.05 (39.39) F: 114.27 (35.1) F-B: -0.78 Grp2 B: 115.44 (31.2) F: 115.44 (33.15) F-B: 0 Grp1-Grp2: -0.78	Grp1 B: 44.46 (9.75) F: 45.24 (10.92) F-B: 0.78 Grp2 B: 43.68 (9.75) F: 45.24 (10.14) F-B: 1.56 Grp1-Grp2: -0.78	Grp1 B: 171.77 (85.44) F: 174.44 (83.66) F-B: 2.67 Grp2 B: 177.11 (85.44) F: 174.44 (83.66) F-B: -2.67 Grp1-Grp2: 5.34	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change
Scott, 2007[111]	Grp1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks Grp2: Sitagliptin Fixed Start: 10, Max: 10	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.77 (1.22) F-B: -0.15 (CI: -0.29, -0.01) Grp1-Grp2: -0.61	Grp1 B: 115.05 (39.39) F: 114.27 (35.1) F-B: -0.78 Grp2 B: 117 (38.22) F: 119.73 (37.83) F-B: 2.73 Grp1-Grp2: -3.51	Grp1 B: 44.46 (9.75) F: 45.24 (10.92) F-B: 0.78 Grp2 B: 45.24 (8.97) F: 46.8 (9.36) F-B: 1.56 Grp1-Grp2: -0.78	Grp1 B: 171.77 (85.44) F: 174.44 (83.66) F-B: 2.67 Grp2 B: 161.09 (88.11) F: 161.09 (88.11) F-B: 0 Grp1-Grp2: 2.67	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Sulfonylurea versus meglitinides						
Nakamura, 2006[108]	Grp1: Glibenclamide Fixed Mean: 5 mg D: 12 Months Grp2: Nateglinide Fixed Mean: 270 mg D: 12 Months	Grp1 B: 7.8 (1.3) F: 7 (6.2) p:<0.01 F-B: -0.8 Grp2 B: 7.7 (1.2) F: 6.3 (1.3) p:<0.01 F-B: -1.4 Grp1-Grp2: 0.6		Grp1 B: 34 (8) F: 34 (10) p:NSG F-B: 0 Grp2 B: 35 (6) F: 36 (6) p:NSG F-B: 1 Grp1-Grp2: -1	Grp1 B: 144 (38) F: 146 (38) p: NSG F-B: 2 Grp2 B: 146 (40) F: 148 (36) p: NSG F-B: 2 Grp1-Grp2: 0	
Jibran, 2006[112]	Grp1: Glibenclamide Varied, glucose: fasting < 130 mg/dl, PP < 175 mg/dl Start: 5 mg, Max: 15 mg, Mean: 8.8 mg Grp2: Repaglinide Varied, glucose: fasting < 130 mg/dl, PP < 175 mg/dl Start: 0.5 mg tid, Max: 1.5 mg tid, Mean: 4.27 mg/day	Grp1 B: 10.2 (1.6) F: 9.4 (1.5) F-B: -0.7 (0.5) Grp2 B: 9.9 (1.6) F: 8.8 (1.7) F-B: -1.1 (0.3) Grp1-Grp2: 0.3 p: 0.001				Grp1 B: 72.7 (17.4) F: 71.7 (15.2) F-B: -1 Grp2 B: 65.8 (9.4) F: 66 (8.8) F-B: 0.2 Grp1-Grp2: -1.2
Derosa, 2003[113]	Grp1: Glimepiride Varied Start: 1 mg, Mean: 3 mg Grp2: Repaglinide Varied Start: 1 mg, Mean: 2.5 mg	Grp1 B: 7.8 (1.2) F: 6.7 (0.9) F-B: -1.1 (CI: -5.6, -0.54) p: <0.01 Grp2 B: 8 (1.1) F: 6.8 (0.8) F-B: -1.2 (CI: -6.2, -0.48) p: <0.01 Grp1-Grp2: 0.1 p: NSG	Grp1 B: 142 (24) F: 136 (25) F-B: -6 Grp2 B: 139 (22) F: 132 (18) F-B: -7 Grp1-Grp2: 1 p: NSG	Grp1 B: 44 (5) F: 43 (6) F-B: -1 Grp2 B: 43 (7) F: 45 (7) F-B: 2 Grp1-Grp2: -3 p: NSG	Grp1 B: 170 (36) F: 155 (39) F-B: -15 Grp2 B: 153 (32) F: 135 (36) F-B: -18 Grp1-Grp2: 3 p: NSG	Grp1 B: 77.1 (5.9) F: 76.6 (5.3) F-B: -0.5 Grp2 B: 76.4 (5.2) F: 76.5 (5.3) F-B: 0.1 Grp1-Grp2: -0.6 p: NSG

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Madsbad, 2001[114]	Grp1: Glipizide Varied Start: 5 mg, Max: 15 mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 4 mg	Grp1 B: 7.2 (1.4) F: 7.7 (SE: 0.2) F-B: 0.78 (CI: 0.46, 1.1) Grp2 B: 7.3 (1.2) F: 7.4 (SE: 0.15) F-B: 0.19 (-0.02, 0.4) Grp1-Grp2: 0.59 p: <0.05		Grp1 F-B: 0.78 p: NSG Grp2 F-B: 0 p: NSG Grp1-Grp2: 1.17 (1.56 to 3.5)	Grp1 F-B: 3.56 (-23.14 to 29.37) Grp2 F-B: 3.56 (-14.24 to 20.47) Grp1-Grp2: 0 (-31.15 to 31.15) p: NSG	
Landgraf, 1999[115]	Grp1: Glibenclamide Varied Start: 1.75 mg, 3.5 mg, 7.0 mg, 10.5 mg, Max: 10.5 mg Grp2: Repaglinide Varied Start: 0.5 mg, 1.0 mg, 2.0 mg, 4.0 mg tid, Max: 4 mg tid	Grp1 B: 8 F: 7.6 (SE: 0.1) F-B: -0.4 Grp2 B: 7.8 F: 7.5 (SE: 0.1) F-B: -0.3 Grp1-Grp2: -0.1		Grp1 F-B: 1.11 (SE: 0.03) Grp2 F-B: 1.15 (SE: 0.03) Grp1-Grp2: -0.04 p: 0.005		Grp1 B: 78.9 (12.8) F: 77.5 F-B: -1.4 p: NSG Grp2 B: 79.6 (10.3) F: 78.9 F-B: -0.7 p: NSG Grp1-Grp2: -0.7 p: NSG

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Wolffenbuttel, 1999[116]	Grp1: Glyburide Varied Start: 1.75 mg, Max: 10.5 mg Grp2: Repaglinide Varied Start: 1.5 mg, Max: 12 mg	Grp1 B: 7 (1.2) F: 7.45 F-B: 0.45 (CI: 0.22, 0.69) Grp2 B: 7.1 (1.4) F: 7.68 F-B: 0.58 (CI: 0.41, 0.7) Grp1-Grp2: -0.13 p: NSG		Grp1 B: 45.63 (12.48) F: 45.63 (12.48) F-B: 0 p: NSG Grp2 B: 44.85 (14.82) F: 46.02 (14.43) F-B: 1.17 p: NSG Grp1-Grp2: -1.17	Grp1 B: 163.76 F: 174.44 F-B: 10.68 p: NSG Grp2 B: 170.88 F: 178 F-B: 7.12 p: NSG Grp1-Grp2: 3.56	Grp1 B: 81.3 (12.2) F: 82 (11.9) F-B: 0.7 p: NSG Grp2 B: 81.5 (13.4) F: 81.5 (13.5) F-B: 0 p: NSG Grp1-Grp2: 0.7
Wolffenbuttel, 1993[118]	Grp1: Glyburide Varied Start: 5 mg, Max: 15 mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 4 mg	Grp1 B: 8.7 (1.8) F: 8.5 (2.0) F-B: -0.2 Grp2 B: 9 (1.9) F: 8.8 (2.0) F-B: -0.2 Grp1-Grp2: 0				Grp1 B: 70.9 (10.8) F: 70.5 (10.2) F-B: -0.4 p: NSG Grp2 B: 74 (9.6) F: 72.3 (9.4) F-B: -1.7 p: <0.05 Grp1-Grp2: 1.3
Marbury, 1999[117]	Grp1: Glyburide Varied Start: 2.5 mg, Max: 15 mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 12 mg	Grp1 B: 8.9 (1.6) F: 9.0 F-B: 0.1 (0.11) Grp2 B: 8.7 (1.7) F: 8.78 F-B: 0.08 (0.07) Grp1-Grp2: -0.02	Grp1 F-B: -6.51 Grp2 F-B: -5.03 Grp1-Grp2: -1.48 (CI: -6.499, 3.532) p: NSG	Grp1 F-B: -0.13 p: NSG Grp2 F-B: -0.81 p: NSG e Grp1-Grp2: 0.68 (CI: -0.8, 2.15)	Grp1 F-B: -6.45 Grp2 F-B: 6.57 Grp1-Grp2: -13.02 (CI: -31.24, 57.28) p: NSG	Grp1 F-B: 0.05 (SE: 0.5) Grp2 F-B: -0.22 (SE: 0.5) Grp1-Grp2: 0.27 p: NSG

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Vakkilainen, 2002[119]	Grp1: Glibenclamide Varied Start: 5 mg, Max: 10 mg Grp2: Nateglinide Fixed Start: 120 mg tid	Grp1 B: 7.6 (7.2 to 8.1) F: 6.9 (6.5 to 7.3) F-B: -0.7 p: <0.001 Grp2 B: 7.6 (7.2 to 8.0) F: 7.4 (7.0 to 7.9) F-B: -0.2 Grp1-Grp2: -0.5 p: NSG	Grp1 F-B: p: NSG Grp2 F-B: p: NSG	Grp1 F-B: p: NSG Grp2 F-B: p: NSG	Grp1 F-B: p: NSG Grp2 F-B: p: NSG	
Sulfonylurea versus GLP-1 agonist						
Seino, 2010[121]	Grp1: Glibenclamide Varied, prespecified target dose Start: 1.25 mg, Max: 2.5 mg D: 4 Weeks Grp2: Liraglutide Varied, prespecified target dose Start: 0.3 mg, Max: 0.9 mg D: 2 Weeks	Grp1 F-B: -1.88 (SE: 0.07) p: <0.0001 Grp2 F-B: -1.38 (SE: 0.09) p:<0.0001 Grp1-Grp2: 0.5 (CI: 0.3, 0.7) p<0.0001	Grp1-Grp2: 0.07 (CI: -0.04, 0.17) p: 0.2107	Grp1-Grp2: 0.01 (CI: -0.03, 0.05) p: 0.529	Grp1-Grp2: 0.05 (CI: -0.11, 0.21) p: 0.5434	Grp1 F-B: -0.92 (2.15) p: p<0.0001 Grp2 F-B: 0.99 (1.84) p: p<0.0001 Grp1-Grp2: 1.91 (CI: 1.48, 2.34) p: <0.0001
Garber, 2009[122]	Grp1: Glimepiride Varied, prespecified target dose Start: 2 mg, Max: 8 mg D: 2 Weeks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.2 mg D: 2 Weeks	Grp1 F-B: 0.51 (SD: 1.2) Grp2 F-B: 0.84 (SD: 1.23) Grp1-Grp2: 0.62 (CI: 0.42, 0.83) p<0.0001				Grp1 F-B: 1 (0.5) Grp2 F-B: -2 (0.5) Grp1-Grp2: 3
Garber, 2009[122]	Grp1: Glimepiride Varied, prespecified target dose Start: 2 mg, Max: 8 mg D: 2 Weeks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.8 mg D: 2 Weeks	Grp1 F-B: 0.51 (SD: 1.2) Grp2 F-B: 1.14 (SD: 1.24) Grp1-Grp2: 0.33 (CI: 0.13, 0.53) p: 0.0014				Grp1 F-B: 1 (0.5) Grp2 F-B: -2.5 (0.5) Grp1-Grp2: 3.5

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Madsbad, 2004[120]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.75 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.75 p: <0.0001 Grp1-Grp2: 0.01				Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.74 p: 0.1544 Grp1-Grp2: 1.68
Madsbad, 2004[120]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.045 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: 0.25 p: 0.1905 Grp1-Grp2: -0.49				Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.03 p: 0.9602 Grp1-Grp2: 0.97
Madsbad, 2004[120]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.225 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.34 p: 0.0877 Grp1-Grp2: -0.4				Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -1.2 p: 0.0184 Grp1-Grp2: 2.14
Madsbad, 2004[120]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.45 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.3 p: 0.1131 Grp1-Grp2: -0.44				Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: 0.27 p: 0.5838 Grp1-Grp2: 0.67
Madsbad, 2004[120]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.60 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.7 p: 0.0002 Grp1-Grp2: -0.04				Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.39 p: 0.4391 Grp1-Grp2: 1.33

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin + thiazolidinedione versus metformin + sulfonylurea						
Home, 2009[16]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: 0.01 (SE: 0.04) Grp1-Grp2: -0.29 (SE: 0.05) p: <0.0001	Grp1 F-B: -12.87 (SE: 1.56) Grp2 F-B: -20.67 (SE: 1.17) Grp1-Grp2: 7.8 (SE: 1.95)	Grp1 F-B: 4.68 (SE: 0.39) Grp2 F-B: 2.73 (SE: 0.39) Grp1-Grp2: 1.95 (SE: 0.55)	Grp1 F-B: -0.14 (SE: 0.04) Grp2 F-B: -0.14 (SE: 0.04) Grp1-Grp2: 0	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 0 (SE: 0.2) and -1.5 (SE: 0.2) Grp1-Grp2: 3.8
Derosa, 2009[46]	Grp1: Metformin + Pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos Grp2: Metformin + glimepiride Fixed; Varied, prespecified target dose Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NA; 3 mos	Grp1 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) p: <0.01 F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: -0.9 (SE: 0.25)				
Hamann, 2008[123]	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks	Grp1 F-B: -0.78 (SE: 0.06) Grp2 F-B: -0.86 (SE: 0.06) Grp1-Grp2: 0.09 (CI: -0.08, 0.25)	Grp1 B: 111.15 (CV: 33.29) F: 116.22 (CV: 35.93) F-B: 5.07 Grp2 B: 114.27 (CV: 37.68) F: 108.03(CV: 37.3) F-B: -6.24 Grp1-Grp2: 11.31 (SE: 7.22)	Grp1 B: 46.8 (CV: 23.99) F: 51.48 (CV: 30.1) F-B: 4.68 Grp2 B: 46.41 (CV: 21.6) F: 47.58 (CV: 21.76) F-B: 1.17 Grp1-Grp2: 3.51 (SE: 2.02)	Grp1 B: 189.57 (CV: 56.4) F: 171.77 (CV: 65.97) F-B: -17.8 Grp2 B: 180.67 (CV: 47.72) F: 157.53 (CV: 42.82) F-B: -23.14 Grp1-Grp2: 5.34	Grp1 F-B: 2.7 (SE: 0.3) Grp2 F-B: 1.6 (SE: 0.3) Grp1-Grp2: 1.1 p: 0.0016

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Comaschi, 2007[129]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg D: 22 wks	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: 0.192 Grp1-Grp2: 0.31 p: 0.054				
Comaschi, 2008[158]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50%; Fixed Start: 400 mg; Start: 2.5 mg D: 22 wks			Grp1 B: 42.51 (SE: 12.09) F: 44.85 (SE: 10.92) F-B: 2.34 p: 0.009 Grp2 B: 45.63 (SE: 13.26) F: 42.12 (SE: 12.87) p: <0.001 F-B: -3.51 p: <0.001 Grp1-Grp2: 5.85 p: <0.001	Grp1 B: 189.57 (SE: 97.9) F: 171.77 (SE: 101.46) F-B: -17.8 p: 0.067 Grp2 B: 178.89 (SE: 114.81) F: 181.56 (SE: 120.15) F-B: 2.67 p: 0.733 Grp1-Grp2: 2.67	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Home, 2007[124]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks; NR	Grp1 F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.66, -0.44) Grp1-Grp2: 0.07 (CI: -0.09, 0.23)	Grp1 F-B: 1.56 (CI: -2.73, 5.85) Grp2 F-B: -10.14 (CI: -14.04, -6.24) Grp1-Grp2: 11.7 (SE: 2.89) p: 0.01	Grp1 F-B: 3.12 (CI: 1.95, 4.29) Grp2 F-B: 0.78 (CI: -0.39, 1.94) Grp1-Grp2: 2.34 (SE: 0.99) p: 0.016	Grp1 F-B: 35.6 Grp2 F-B: 13.35 Grp1-Grp2: 23.14	Grp1 F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 1.1 (CI: 0.6, 1.6) (cohort1), -0.9 (CI: -1.4, -0.4) (cohort2) Grp1-Grp2 (cohort 1): 1.2 (CI: 0.4, 2) p: 0.003; Grp1-Grp2 (cohort 2): 4.3 (CI: 3.6, 5.1) p: <0.001
Bakris, 2006[125]	Grp1: Metformin + rosiglitazone Varied; Varied, glucose: <=6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied; Glucose: <=6.6 mmol/L Unclear; Start: 5 mg D: 3 wks; NR	Grp1 F-B: 0.72 (SE: 0.1) Grp2 F-B: 0.92 (SE: 0.08) Grp1-Grp2: -0.2 (SE: 0.12)				Grp1 F-B: 1.94 (4.63) Grp2 F-B: 1.5 (3.53) Grp1-Grp2: 0.44
Umpierrez, 2006[126]	Grp1: Metformin + pioglitazone NR; Varied, glucose: <120 mg/dL, HbA1c: <8.0% Start: 1.54 g, Max: 1.57g; Start: 30 mg, Max: 45 mg D: NR; Unclear Grp2: Metformin + glimepiride NR; Glucose: <120 mg/dL Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR; 6 wks	Grp1 F-B: -1.23 (SE: 0.073) p: 0.4825 Grp2 F-B: -1.3 (SE: 0.077) Grp1-Grp2: 0.07 (SE: 0.11)	Grp1 F-B: 8.5 (SE: 2.81) Grp2 F-B: -0.1 (SE: 2.87) Grp1-Grp2: 8.5 (SE: 4.01) p: 0.0001	Grp1 F-B: 4.8 (SE: 0.66) Grp2 F-B: -0.6 (SE: 0.7) p: 0.0001 Grp1-Grp2: 10 (SE: 9.53) p: 0.2953	Grp1 F-B: -14.2 (SE: 6.57) Grp2 F-B: -4.2 (SE: 7.06) p: 0.2953 Grp1-Grp2: -10 (SE: 9.6)	Grp1 F-B: 1.85 (SE: 0.38) Grp2 F-B: 1.74 (SE: 0.41) Grp1-Grp2: 0.11

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Derosa, 2005[127]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 4 mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 2 mg, Max: 2 mg	Grp1 B: 8 (0.7) F: 6.8 (0.6) p: <0.01 F-B: -1.2 Grp2 B: 7.9 (0.6) F: 7 (0.7) p: <0.05 F-B: -0.9 Grp1-Grp2: -0.3 (SE: 0.23)				
Derosa, 2005[151]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid; Start: 2 mg Grp2: Metformin + glimepiride Fixed Start: 500mg tid; Start: 4mg qday					Grp1 B: 74.2 (3.6) F: 68.3 (3) p: <0.01 F-B: -5.9 Grp2 B: 75.6 (4.2) F: 71.1 (3.2) p: <0.05 F-B: -4.5 Grp1-Grp2: -1.4
Derosa, 2006[157]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 4 mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 2 mg qday, Max: 2 mg qday		Grp1 B: 116 (15) F: 120 (17) F-B: 4 Grp2 B: 118 (13) F: 102 (11) F-B: -16 p: <0.05 Grp1-Grp2: 20 p: <0.05	Grp1 B: 42 (4) F: 44 (3) F-B: 2 Grp2 B: 43 (5) F: 43 (4) F-B: 0 Grp1-Grp2: 2 p: NSG		

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Garber, 2006[128]	Grp1: Metformin + rosiglitazone Varied Start: 1500-2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg		Grp1 B: 116 F: 125 F-B: 9 (35) Grp2 B: 119 F: 115 F-B: -4 (26) Grp1-Grp2: -14 (CI: -6, 22) p: NSG	Grp1 B: 45 F: 48 F-B: 3 (10) Grp2 B: 47 F: 45 F-B: -2 (10) Grp1-Grp2: 4 (CI: 1, 7) p: <0.05	Grp1 B: 218 F: 238 F-B: 21 (113) Grp2 B: 226 F: 238 F-B: 12 (133) Grp1-Grp2: 9 (CI: -22, 40) p: NSG	Grp1 B: 94 F: 95.4 F-B: 1.4 Grp2 B: 92 F: 95 F-B: 3 Grp1-Grp2: -1.5 p: <0.001
Derosa, 2005[159]	Grp1: Metformin + rosiglitazone Fixed Start: 1500 mg; Start: 4 mg Grp2: Metformin + glimepiride Fixed Start: 1500 mg, Start: 2 mg				Grp1 B: 186 (28) F: 129 (18) F-B: -57 Grp2 B: 178 (23) F: 137 (20) F-B: -41 Grp1-Grp2: -16 p: NSG	
Metformin + thiazolidinedione versus metformin + meglitinides						
Raskin, 2009[131]	Grp1: Metformin + rosiglitazone Varied, prespecified target dose; Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 8 mg D: 4 wks Grp2: Metformin + repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 10 mg D: 4 wks	Grp1-Grp2: -0.21 (CI: -0.452, 0.031)	Grp1 B: 111.9 (SE: 2.88) F: 121.2 (SE: 3.51) F-B: 9.576 p:0.0008 Grp2 B: 108.2 (SE: 2.87) F: 104.6 (SE: 2.89) F-B: -2.604 p: 0.4637 Grp1-Grp2: 12.9	Grp1 B: 44.8 (SE: 0.85) F: 49.4 (SE: 1.05) F-B: 4.479 p: <0.0001 Grp2 B: 44.3 (SE: 0.91) F: 44.2 (SE: 1.05) F-B: -0.151 p: NSG Grp1-Grp2: 4.63 p: <0.001	Grp1 B: 208.8 (SE: 21.88) F: 208.2 (SE: 16.20) F-B: -0.6 p: 0.9493 Grp2 B: 190.3 (SE: 10.77) F: 194.9 (SE: 10.66) F-B: 4.6 p: 0.8607 Grp1-Grp2: -5.2 p: 0.6007	Grp1-Grp2: not clinically relevant

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin + thiazolidinedione versus metformin + DPP-IV inhibitor						
Scott, 2008[85]	Grp1: Metformin + rosiglitazone NR; Fixed Start: >=1500 mg; Mean: 8 mg D: 10 wks; NA Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1-Grp2: -0.06 (CI: -0.25, 0.14)	Grp1 B: 99.2 (29.4) F: 119.6 (37.6) F-B: Mean % change: 26.2 (CI: 19.7, 32.7) Grp2 B: 95.4 (30.8) F: 104.6 (35.1) F-B: Mean % change: 11.4 (CI: 5, 17.8) Grp1-Grp2: 11.2 (SE: 8.8)	Grp1 B: 42.2 (10) F: 45.7 (10.5) F-B: Mean % change: 9.2 (CI: 6.1, 12.2) Grp2 B: 43.9 (11.6) F: 45.7 (13.4) F-B: Mean % change: 4.3 (CI: 1.2, 7.3) Grp1-Grp2: 1.7 (SE: 3.03)	Grp1 B: 201.6 (126.2) F: 199.8 (108.4) F-B: Mean % change: 13.1 (CI: 5.2, 21.1) Grp2 B: 177.8 (80.7) F: 163.3 (74) F-B: Mean % change: -4.8 (CI: -12.7, 3.1) Grp1-Grp2: 12.7	Grp1 F-B: 1.5 (CI: 1, 1.9) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: 1.9 (CI: 1.3, 2.5)
Rigby, 2009[130]	Grp1: Metformin + rosiglitazone Fixed Mean: 4 mg Grp2: Metformin + sitagliptin Fixed Mean: 100 mg	Grp1 B: 8.09 F: 7.53 F-B: -0.6 (CI: -0.83, -0.32) p: <0.0001 Grp2 B: 8.19 F: 7.79 F-B: -0.4 (CI: -0.64, -0.13) p: 0.0087 Grp1-Grp2: -0.2				Grp1 F-B: 0.26 p: 0.5935 Grp2 F-B: -1.15 p: 0.0008 Grp1-Grp2: 1.41
Metformin + thiazolidinedione versus metformin + GLP-1 agonist						
Defronzo, 2010[132]	Grp1: Metformin + rosiglitazone Varied NR; Start: 4 mg, Max: 8 mg D: NR Grp2: Metformin + exenatide Varied Start: 0.010 mg, Max: 0.02 mg D: NR	Grp1 F-B: -1 (SD: 0.1) p: <0.05 Grp2 F-B: -0.9 (SD: 0.1) p: <0.05 Grp1-Grp2: -0.1 p: 0.72	Grp1 F-B: 12.87 (3.9) p: <0.05 Grp2 F-B: -1.95 (3.9) p: >0.05 Grp1-Grp2: 14.82 p: 0.008	Grp1 F-B: 2.34 (1.17) p:>0.05 Grp2 F-B: 0.78 (1.17) p:>0.05 Grp1-Grp2: 1.56 p: 0.445	Grp1 F-B: 2.73 (6.63) p: >0.05 Grp2 F-B: -13.26 (6.63) p: <0.05 Grp1-Grp2: 15.99 p: 0.079	Grp1 F-B: 1.5 (0.5) p: <0.05 Grp2 F-B: -2.8 (0.5) p: <0.05 Grp1-Grp2: 4.3 p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin + thiazolidinedione versus thiazolidinedione + sulfonylurea						
Home, 2009[16]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: -0.44 (SE: 0.03) Grp1-Grp2: 0.16 (SE: 0.04) p: <0.0001	Grp1 F-B: -12.87 (SE: 1.56) Grp2 F-B: -8.58 (SE: 1.56) Grp1-Grp2: -4.29 (SE: 2.21)	Grp1 F-B: 4.68 (SE: 0.39) Grp2 F-B: 4.29 (SE: 0.39) Grp1-Grp2: 0.39 (0.55)	Grp1 F-B: -0.14 (SE: 0.04) Grp2 F-B: -0.13 (SE: 0.04) Grp1-Grp2: -0.01 p: 0.82	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 4.1 (SE: 0.2) Grp1-Grp2: -0.3
Comaschi, 2008[158]	Grp1: Metformin + pioglitazone Varied, HbA1c: NR Max: 3 g; Start: 15 mg, Max: 30 mg Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: <=7.5% Start: 15 mg, Max: 30 mg; NR D: 22wks		Grp1-Grp2: p: 0.28	Grp1 B: 42.51 (SE: 12.09) F: 44.85 (SE: 10.92) F-B: 2.34 p: 0.009 Grp2 B: 41.73 (SE: 12.87) F: 42.51 (SE: 13.26) F-B: 0.39 p: 0.617 Grp1-Grp2: 1.95	Grp1 B: 189.57 (SE: 97.9) F: 171.77 (SE: 101.46) F-B: -17.8 p: 0.067 Grp2 B: 186.01 (SE: 120.15) F: 157.53 (SE: 83.66) F-B: -28.48 p: 0.017 Grp1-Grp2: 10.68 p: <0.05	
Comaschi, 2007[129]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied, NR Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.3 p: 0.043				

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Home, 2007[124]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear D: 8 wks	Grp1 F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: 1.56 (CI: -2.73, 5.85) Grp2 F-B: 7.41 (CI: 3.12, 11.7) Grp1-Grp2: -18.72 (CI: -24.96, -12.48)	Grp1 F-B: 3.12 (CI: 1.95, 4.29) Grp2 F-B: 3.9 (CI: 2.73, 5.07) Grp1-Grp2: -0.78	Grp1 F-B: 35.6 (CI: 22.25, 48.95) Grp2 F-B: 21.36 (CI: 5.34, 37.38) Grp1-Grp2: 5.34 (CI: -17.8, 28.48)	Grp1 F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: -1.1
Metformin + sulfonylurea versus metformin + meglitinides						
Dimic, 2009[199]	Grp1: Metformin + glimepiride Fixed Grp2: Metformin + repaglinide Fixed Mean: 2000 mg; Mean: 6 mg daily	Grp1 F-B: -1.04 p: <0.001 Grp2 F-B: -1.54 p: <0.001 Grp1-Grp2: 0.5	Grp1 F-B: -0.55 p: <0.05 Grp2 F-B: -0.66 p: <0.05 Grp1-Grp2: 0.11	Grp1 F-B: 0.01 p:>0.05 Grp2 F-B: -0.66 p:<0.05 Grp1-Grp2: 0.67	Grp1 F-B: -0.4 p:>0.05 Grp2 F-B: -0.66 p:<0.05 Grp1-Grp2: 0.26	
Derosa, 2009[135]	Grp1: Metformin + glibenclamide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 7.5 mg, Max: 15 mg, Mean: 12.5 mg D: 6 mos Grp2: Metformin + nateglinide Fixed Start: 1500 mg, Max: 3000 mg, Mean: 2500 mg; Start: 180 mg, Max: 360 mg, Mean: 300 mg D: 6 mos	Grp1 B: 8.2 (1.1) F: 7.3 (0.6) F-B: -0.9 p: <0.05 Grp2 B: 8.1 (1.0) F: 6.4 (0.4) F-B: -1.7 p: <0.01 Grp1-Grp2: 0.8 (SE: 0.18) p: 0.05	Grp1 B: Median: 119 (12) F: Median: 104 (10) Grp2 B: Median: 121 (13) F: Median: 113 (11)	Grp1 B: Median: 42 (5) F: Median: 41 (4) Grp2 B: Median: 42 (5) F: Median: 43 (6)	Grp1 B: 161 (42) F: 140 (31) p: NSG F-B: -21 Grp2 B: 156 (40) F: 141 (33) p: NSG F-B: -15 Grp1-Grp2: -6	BMI Grp1 B: 26.5 (1.5) F: 26.9 (1.7) F-B: 0.4 Grp2 B: 26.4 (1.4) F: 26.8 (1.6) F-B: 0.4 Grp1-Grp2: 0
Schwarz, 2008[152]	Grp1: Metformin + glyburide Varied, glucose: <120 mg/dL Start: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 10 mg D: 12 wks Grp2: Metformin + nateglinide Varied, glucose: <120 mg/dL Start: 500 mg, Max: 2000 mg; Start: 360 mg, Max: 360 mg D: 12 wks	Grp1 F-B: -1.2 (SE: 0.1) p: <0.001 Grp2 F-B: -1.2 (SE: 0.2) p: <0.001 Grp1-Grp2: 0 (SE: 0.22)				Grp1-Grp2: no clinically relevant difference in weight

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Gerich, 2005[136]	Grp1: Metformin + glyburide Varied, glucose: FPG >=6.7 mmol/L; Fixed Start: 500 mg, Max: 2000 mg, Mean: 1459 mg; Start: 120 mg, Mean: 357 mg D: 12 wks; NA Grp2: Metformin + nateglinide Varied, glucose: FPG >=6.7 mmol/L Start: 500 mg, Max: 2000 mg, Mean: 1105 mg; Start: 1.25 mg, Max: 10 mg, Mean: 5.1 mg D: 12 wks	Grp1 B: 8.4 (1.2) F: 6.4 p: <0.0001 F-B: -1.5 (SE: 0.1) p: <0.0001 Grp2 B: 8.3 (1.1) F: 6.7 p: <0.0001 F-B: -1.2 (SE: 0.1) p: <0.0001 Grp1-Grp2: -0.3 (SE: 0.14) p: 0.173	Grp1 F-B: 5% decrease Grp2 F-B: 5% decrease	Grp1 F-B: 5% increase Grp2 F-B: 5% increase	Grp1 F-B: 10% decrease Grp2 F-B: 10% decrease	Grp1 F-B: -0.4 (0.4) p: 0.8143 Grp2 F-B: 0.8 (0.5) p: 0.0011 Grp1-Grp2: -1.2 p: 0.0115
Metformin + sulfonylurea versus metformin + DPP-IV inhibitor						
Seck, 2010[134]	Grp1: Metformin + glipizide Fixed NR; Start: 5, Max: 20, Mean: 9.2 mg D: 2 Years Grp2: Metformin + sitagliptin Fixed NR D: 2 Years	Grp1 F-B: -0.35 (CI: -0.44, -0.26) Grp2 F-B: -0.33 (CI: -42, -0.25) Grp1-Grp2: -0.01 (CI: -0.1, 0.08)				Grp1 F-B: 0.7 (CI: 0, 1.3) p: NSG Grp2 F-B: -1.6 (CI: -2.3, -1) p: NS Grp1-Grp2: 2.3 (1.6, 3) p: NSG
Nauck, 2007[133]	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: Unclear; 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Grp1-Grp2: -0.01 (CI: -0.09, 0.08)				Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin + sulfonylurea versus metformin + GLP-1 agonist						
Derosa, 2010[44]	Grp1: Metformin + glibenclamide NR Mean: 1500 mg; Start: 7.5 mg, Max: 15 mg D: NR Grp2: Metformin + exenatide NR NR; Start: 10 mcg, Max: 20 mcg D: NR	Grp1 B: 8.9 (0.8) F: 7.1 (0.2) p:NSG F-B: -1.8 p: <0.001 Grp2 B: 8.8 (0.7) F: 7.3 (0.3) F-B: -1.5 p: <0.001 Grp1-Grp2: -0.3 p: NSG				Grp1 B: 82.4 (9.1) F: 86.7 (11.2) p: <0.05 F-B: 4.3 p: <0.05 Grp2 B: 82 (8.3) F: 74 (4.1) F-B: -8 p: <0.001 Grp1-Grp2: 12.3
Nauck, 2009[92]	Grp1: Metformin + glimepiride Varied Start: 2000 mg, Max: 2000 mg; Start: 1 mg, Max: 4 mg Grp2: Metformin + liraglutide Fixed NR; Start: 0.6, Max: 1.2	Grp1-Grp2: 1.1 (CI: 0.9, 1.3)				Grp1 F-B: 1 (SE: 0.2) Grp2 F-B: -2.6 (SE: 0.2) Grp1-Grp2: 3.6 p: <0.01
Nauck, 2009[92]	Grp1: Metformin + glimepiride Varied Start: 2000 mg, Max: 2000 mg; Start: 1 mg, Max: 4 mg Grp2: Metformin + liraglutide Fixed NR; Start: 0.6 mg, Max: 1.8 mg	Grp1-Grp2: 1.1 (CI: 0.9, 1.3)				Grp1 F-B: 1 (SE: 0.2) Grp2 F-B: -2.8 (SE: 0.2) Grp1-Grp2: 3.8 p: <0.01

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Pratley, 2010[143]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10% NR; Start: 0.6 mg, Max: 1.2 mg D: NR	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.24 (CI: -1.37, -1.11) Grp1-Grp2: 0.34 (CI: 0.16, 0.51) p<0.0001	Grp1 F-B: 0.13 (CI: 0.04, 0.22) Grp2 F-B: 0.05 (CI: -0.04, 0.17) Grp1-Grp2: 0.08 (CI: -0.04, 0.2) p: 0.2055	Grp1 F-B: 0 (CI: -0.02, 0.02) Grp2 F-B: 0 (CI: -0.02, 0.03) Grp1-Grp2: 0 (CI: -0.03, 0.03) p:0.9225	Grp1 F-B: -0.4 (CI: -0.58, -0.22) Grp2 F-B: -0.43 (CI: -0.61, -0.25) Grp1-Grp2: 0.03 (CI: -0.21, 0.28) p: 0.8021	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -3.38 (CI: -3.91, -2.84) Grp1-Grp2: 2.42 (CI: 1.7, 3.14)
Pratley, 2010[143]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10% Unclear; Start: 0.6 mg, Max: 1.8 mg D: NR	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.5 (CI: -1.63, -1.37) Grp1-Grp2: 0.6 (CI: 0.43, 0.77) p<0.0001	Grp1 F-B: 0.13 (CI: 0.04, 0.22) Grp2 F-B: 0.08 (CI: -0.01, 0.17) Grp1-Grp2: 0.05 (CI: -0.07, 0.17) p: 0.4414	Grp1 F-B: 0 (CI: -0.02, 0.02) Grp2 F-B: 0 (CI: -0.02, 0.02) Grp1-Grp2: 0 (CI: -0.03, 0.03) p:0.9507	Grp1 F-B: -0.4 (CI: -0.58, -0.22) Grp2 F-B: -0.19 (CI: -0.38, 0) Grp1-Grp2: -0.21 (CI: -0.46, 0.04) p: 0.0962	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -2.86 (CI: -3.39, -2.32) Grp1-Grp2: 1.9 (CI: 1.18, 2.61)
Metformin + sulfonylurea versus thiazolidinedione + sulfonylurea						
Jonker, 2009[160]	Grp1: Metformin + glimepiride Fixed Start: 500 mg BD, Max: 1000 mg BD; NR D: 2 Weeks Grp2: Pioglitazone + glimepiride Fixed Start: 15 mg OD, Max: 30 mg OD; NR D: 2 Weeks	Grp1 B: 7 (0.1) F: 6.3 (SE: 0.1) p:0.146 F-B: -0.7 Grp2 B: 7.1 (0.2) F: 6.5 (SE: 0.1) F-B: -0.6 Grp1-Grp2: -0.1			Grp1 B: Median: 1.5 (IQR: 0.9, 2.1) F: Median: 1.7 (IQR: 0.9, 2.3) p: 0.596 Grp2 B: Median: 1.4 (IQR: 1, 2.2) F: Median: 1.4 (IQR: 0.9, 2.3)	

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Seufert, 2008[142]	Grp1: Metformin + sulfonylurea Fixed Max: 2550 mg, Mean: 2081 mg; NR D: 12 wks Grp2: Pioglitazone + sulfonylurea Fixed Max: 45 mg, Mean: 37 mg; NR D: 12 wks	Grp1 B: 8.8 F: 7.64 F-B: -1.16 Grp2 B: 8.82 F: 7.79 F-B: -1.03 Grp1-Grp2: 0.13 (CI: -0.06 - 0.31) p: 0.173				Grp1 F-B: -1.7 (4.5) Grp2 F-B: 3.2 (4.7) Grp1-Grp2: -4.9
Home, 2009[16]	Grp1: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1 F-B: -0.18 (SE: 0.04) Grp2 F-B: -0.44 (SE: 0.03) Grp1-Grp2: 0.26 (SE: 0.05) p: <0.0001	Grp1 F-B: -20.67 (SE: 1.17) Grp2 F-B: -8.58 (SE: 1.56) Grp1-Grp2: -12.09 (SE: 1.95)	Grp1 F-B: 2.73 (SE: 0.39) Grp2 F-B: 4.29 (SE: 0.39) Grp1-Grp2: 1.56 (SE: 0.55)	Grp1 F-B: -12.46 (SE: 3.56) Grp2 F-B: -11.57 (SE: 3.56) Grp1-Grp2: -0.89 (SE: 5.0) p: 0.82	Grp1 F-B: -1.5 (SE: 0.2) Grp2 F-B: 4.1 (SE: 0.2) Grp1-Grp2: -5.6 p: <0.001
van der Meer, 2009[141]	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed; Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR	Grp1 B: 7 (SE: 0.1) F: 6.3 (SE: 0.1) p: <0.001 F-B: -0.7 Grp2 B: 7.1 (SE: 0.2) F: 6.5 (SE: 0.1) p: <0.001 F-B: -0.6 Grp1-Grp2: -0.1 (SE: 0.32) p: 0.146	Grp1 B: 113.1 (SE: 3.9) F: 101.4 (SE: 7.8) p: 0.001 F-B: -11.7 Grp2 B: 97.5 (SE: 3.9) F: 97.5 (SE: 3.9) p: 0.38 F-B: 0 Grp1-Grp2: -11.7 (SE: 12.33)	Grp1 B: Median: 44.07 (IQR: 35.1, 55.38) F: Median: 39.78 (IQR: 33.54, 49.14) Grp2 B: Median: 41.73 (IQR: 36.66, 49.92) F: Median: 47.97 (IQR: 38.61, 56.94)	Grp1 B: Median: 133.5 (IQR: 80.1, 186.9) F: Median: 151.3 (IQR: 80.1, 204.7) p: 0.519 Grp2 B: Median: 124.6 (IQR: 89, 195.8) F: Median: 124.6 (IQR: 80.1, 204.7) p: 0.926 Grp1-Grp2: p:0.596	Grp1 B: 92 (2) F: 92 (3) F-B: 0 Grp2 B: 91 (2) F: 94 (4) F-B: 3 Grp1-Grp2: -3 p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Comaschi 2007[129]	Grp1: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3g; Start: 2.5 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR	Grp1 F-B: -1.29 p: 0.192 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.01 (SE: 0.27) p: 0.975				
Comaschi, 2008[158]	Grp1: Metformin + glibenclamide Varied, HbA1c: 7.50% Start: 400 mg; Start: 2.5 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50% Start: 15 mg, Max: 30 mg; Unclear D: 22 wks			Grp1 B: 45.63 (SE: 13.26) F: 42.12 (SE: 12.87) p: <0.001 F-B: -3.51 p: <0.001 Grp2 B: 41.73 (SE: 12.87) F: 42.51 (SE: 13.26) F-B: 0.39 p: 0.617 Grp1-Grp2: -3.9	Grp1 B: 178.89 (SE: 114.81) F: 181.56 (SE: 120.15) F-B: 2.67 p: 0.733 Grp2 B: 186.01 (SE: 120.15) F: 157.53 (SE: 83.66) F-B: -28.48 p: 0.017 Grp1-Grp2: 31.15 p: <0.05	
Home, 2007[124]	Grp1:Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear	Grp1 F-B: -0.61 (CI: -0.7, -0.51) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: -11.31 (CI: -15.6 , -7.41) Grp2 F-B: 7.41 (CI: 3.12, 11.7) Grp1-Grp2: -18.72 (SE: 3.18)	Grp1 F-B: 3.12 (CI: 1.95, 4.29) Grp2 F-B: 3.9 (CI: 0.73, 5.07) Grp1-Grp2: -0.39 (CI: -1.95, 0.78)	Grp1 F-B: 15.13 (CI: -1.78, 32.04) Grp2 F-B: 21.36 (CI: 5.34, 37.68) Grp1-Grp2: 5.34 (CI: -17.8, 28.48)	Grp1 F-B: -0.9 (CI: -1.4, -0.4) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: 4.3 (CI: 3.6, 5.1) p: <0.001

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Kim, 2007[42]	Grp1: Metformin + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 1000 mg; Start: 2 mg, Max: 7 mg Grp2: Rosiglitazone + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 4 mg; Start: 2 mg, Max: 7 mg	Grp1 F-B: -1.1 (CI: -1.4, -0.8) p: <0.001 Grp2 F-B: -1.1 (CI: -1.5, -0.8) p: <0.001 Grp1-Grp2: 0 (SE: 0.24) p: 0.615	Grp1 F-B: -6.24 (CI: -12.87,-0.78) p: 0.082 Grp2 F-B: -8.97 (CI: -1.56, 19.11) p: 0.158 Grp1-Grp2: 2.73 (SE: 6.11)	Grp1 F-B: -1.56 (CI: -0.39, 1.17) p: 0.246 Grp2 F-B: -4.29 (CI: -10.53, 1.56) p: 0.158 Grp1-Grp2: 2.73 p: 0.868	Grp1 F-B: -8.9 (CI: -29.37, 11.57) p: 0.389 Grp2 F-B: -23.97 (CI: -47.17, -11.57) p: 0.002 Grp1-Grp2: 20.47	Grp1 F-B: -0.5 (CI: -1.2, -0.2) p: 0.187 Grp2 F-B: 1.3 (CI: 0.8, 1.9) p: <0.00 Grp1-Grp2: -1.8 p: <0.001
Yang, 2003[139]	Grp1: Metformin + sulfonylurea Fixed; NR Start: 1000 mg; NR Grp2: Rosiglitazone + sulfonylurea Fixed Start: 4 mg; NR	Grp1 B: 8.59 (1.78) F: 7.61 (1.47) p: <0.01 F-B: -0.95 (1.5) p: <0.01 Grp2 B: 8.61 (1.77) F: 7.46 (1.44) p: <0.01 F-B: -1.09 (1.65) p: <0.01 Grp1-Grp2: 0.14 (SE: 0.48)				
Hanefeld, 2004[140]	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	Grp1 B: 8.8 (0.97) F: 7.45 (0.06) F-B: -1.36 Grp2 B: 8.82 (0.98) F: 7.61 (0.06) F-B: -1.2 Grp1-Grp2: -0.16 p: 0.065	Grp1 B: 139.23 (33.54) F: 142.74 (1.56) F-B: 3.12 Grp2 B: 139.62 (35.58) F: 132.99 (1.56) F-B: -6.24 Grp1-Grp2: 9.36 p: 0.0002	Grp1 B: 42.51 (9.36) F: 48.75 (0.39) F-B: 6.24 Grp2 B: 43.29 (10.53) F: 46.41 (0.39) F-B: 3.12 Grp1-Grp2: 3.12 p: <0.0001	Grp1 B: 219.83 (150.41) F: 178.89 (5.34) F-B: -40.94 Grp2 B: 211.82 (153.08) F: 191.35 (5.34) F-B: -20.47 Grp1-Grp2: -20.47 p: 0.008	Grp1 B: 85.3 (15.1) F: 88.1 F-B: 2.8 Grp2 B: 84.9 (14.5) F: 83.9 F-B: -1 Grp1-Grp2: 3.8

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Metformin + GLP-1 agonist versus metformin + basal insulin						
Bunck, 2009[144]	Grp1: Metformin + exenatide Fixed Mean: 2058 mg; Start: 5 ug b.i.d., Max: 20 micro g t.i.d. Grp2: Metformin + glargine Fixed Mean: 1798 mg; Start: 10 Units, Mean: 33.6	Grp1 B: 7.6 (0.1) F: 6.8 F-B: -0.8 (SD: 0.1) Grp2 B: 7.4 (0.1) F: 6.8 F-B: -0.7 (SD: 0.2) p: 0.55 Grp1-Grp2: -0.1				Grp1-Grp2: -4.6 (1.1) p: 0.0001
Metformin + long-acting insulin versus metformin + premixed insulin						
Robbins, 2007[145]	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg tid, Max: 1000 mg tid, Mean: 1636 mg; Mean: 0.6 U/kg Start: QD, Final: QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7 mmol/L Start: 500 mg tid, Max: 1000 mg tid, Mean: 1641 mg; Mean: 0.7 U/kg Start freq: NR, Final freq: tid	Grp1 F-B: -0.4 (0.9) Grp2 F-B: -0.7 (0.9) p: <0.001 Grp1-Grp2: 0.3 (SE: 0.32) p: <0.001				Grp1 B: 88.1 (19) F: 87.6 (19.3) p: 0.04 F-B: -0.5 Grp2 B: 89.1 (20.4) F: 90 (20.5) p: <0.001 F-B: 0.9 Grp1-Grp2: -1.4 p: <0.001
Raskin, 2007[146]	Grp1: Metformin + glargine Fixed; Varied, glucose: 4.4 - 6.1 mmol/L before breakfast and dinner NR; Start: 12 U/day, Mean: 0.57 IU/kg Start freq: QD, Final freq: QD Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 4.4 - 6.1 mmol/L NR; Start: 12 IU/day, Mean: 0.91 IU/kg Start freq: BID, Final freq: BID	Grp1 F-B: -2.46 (SE: 1.6) Grp2 F-B: -2.89 (SE: 1.6) Grp1-Grp2: 0.43 (SE: 2.26) p: 0.035				Grp1 F-B: 3 (4.3) Grp2 F-B: 5.6 (4.6) Grp1-Grp2: -2.6 p: 0.0004

Table 4. Comparative effectiveness of diabetes medications on intermediate outcomes (KQ1): baseline, final, and mean difference from baseline values for hemoglobin A1c, weight and lipids (continued)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	LDL, mean (SD)	HDL, mean (SD)	Triglycerides, mean (SD)	Weight, mean (SD)
Davies, 2007[147]	Grp1: Metformin + NPH Varied NR; Start: 10, Mean: 0.58 IU/kg D: NR Grp2: Metformin + BHI 70/30 Varied NR; Start: 10 IU, Mean: 0.63 IU/kg D: NR	Grp1 B: 10 (2.2) F: 9.2 (1.4) F-B: -0.8 Grp2 B: 9 (1.1) F: 7.9 (1.1) F-B: -1.1 Grp1-Grp2: 0.3				Grp1-Grp2: 0.7
Metformin + premixed insulin versus metformin + sulfonylurea						
Kvapil, 2006[138]	Grp1: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg, Mean: 0.30 U/kg Start freq: BID, Final freq: BID D: NA; Unclear Grp2: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg D: NA; Unclear	Grp1 F-B: -1.7 Grp2 F-B: -1.7 Grp1-Grp2: 0.2 (SE: 0.15) p: >0.05		Grp1-Grp2: -1.95 (SE: 1.17)	Grp1 F: 204.7 (SE: 133.5) Grp2 F: 178 (SE: 97.9) F-B: 17.8 Grp1-Grp2: -13.35 (SE: 12.46)	Grp1 F-B: 0.8 Grp2 F-B: 0.1 Grp1-Grp2: -0.66 (0.41) p: 0.1
Malone, 2003[137]	Grp1: Metformin + lispro 75/25 Varied; Varied, glucose: fasting and premeal glucose<7 mmol/L and 2-h post-prandial glucose <10 mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks; titrated throughout study period Grp2: Metformin + glibenclamide Varied; Varied, glucose: fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10 mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; titrated throughout study period	Grp2 B: 9.17 (1.5) F: 7.29 (1) F-B: -1.87 (1.35) p: <0.001 Grp1 B: 9.27 (1.55) p: 0.181 F: 7.33 (1.14) p: 0.661 F-B: -1.98 (1.28) p: <0.001 Grp1-Grp2: 011 (SE: 0.33) p: 0.288				Grp1 B: 83 (15.2) F: 84 (15.1) F-B: 1 Grp2 B: 81.7 (15.7) F: 82.2 (15.4) p: 0.33 F-B: 0.5 Grp1-Grp2: 0.5

ac or qac=before each meal ; ADA= American Diabetes Association; B=baseline; bid= twice a day; BMI=body mass index; CI=confidence interval; cv=coefficient of variation; D=duration of dose titration; dl=deciliter; F=final; F-B=mean difference from baseline to final; FPG=fasting plasma glucose; GLP-1 agonist = glucagon-like peptide-1 agonist; Grp1-Grp2=mean difference between the two groups; HDL=high density lipoprotein; IQR=inter quartile range; LDL=low density lipoprotein; Max=maximum; mg=milligram; mmol/l=millimoles per liter; mos=months; NA=not applicable; NR=not reported; NSG=not significant; PC= portion control; po=per oral; qday or qd=daily; SD=standard deviation; SE or SEM =standard error of the mean; tid= thrice a day; wks= weeks

All values for LDL, HDL, and triglycerides are reported in mg/dL. To convert to mmol/L, divide by 39 for LDL and HDL and divide by 89 for triglycerides.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence (KQ2). Outcome: All-cause mortality

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
4 RCTs	4457	Low	Consistent	Direct	Imprecise	Unclear	Low
Met vs. SU							
5 RCTs, 8 obs	50498	Medium	Inconsistent	Direct	Precise	Small, favors metformin	Low
Met vs. DPP-4 Inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met vs. Meg							
1 RCT	357	Low	NA	Direct	Imprecise	Unclear	Low
Met vs. Met + TZD							
5 RCTs	2554	Low	Consistent	Direct	Imprecise	Unclear	Low
Met vs. Met + SU							
4 RCTs, 6 obs	30211	Medium	Consistent	Direct	Precise	Small, neither favored	Low
Met vs. Met + DPP-4 Inhibitor							
1 RCT	190	Medium	NA	Direct	Imprecise	Unclear	Low
Met vs. Met + Meg							
1 RCT	350	Low	NA	Direct	Imprecise	Unclear	Low
TZD vs. TZD							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. SU							
3 RCTs	3986	Low	Consistent	Direct	Imprecise	Unclear	Low
TZD vs. DPP-4 Inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. DPP-4 Inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. Meg							
1 RCT	576	Medium	NA	Direct	Imprecise	Unclear	Low
Sitagliptin vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and TZD vs. Met and SU							
2 RCTs	970	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and Meg							
2 RCTs, 1 obs	4432	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and SU vs Met and DPP-4 Inhibitor							
1 RCT	1172	Low	NA	Direct	Imprecise	Unclear	Low
Met and Meg vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and DPP-4 Inhibitor vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Exenatide vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Basal Insulin vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence (KQ2). Outcome: All-cause mortality (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of Effect	
Met and Premixed Insulin vs. Met and SU							
2 RCTs	819	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and TZD vs. TZD and SU							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and SU vs. TZD and SU							
1 RCT	639	Medium	NA	Direct	Imprecise	Unclear	Low
Met and Meg vs. TZD and Met							
1 RCT	374	Medium	NA	Direct	Imprecise	Unclear	Low
Met and Sitagliptin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Exenatide vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Basal Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Premixed Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione

All other comparisons were graded as insufficient since there were no studies of those comparisons.

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.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cardiovascular disease mortality

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
2 RCTs	2950	Medium	Consistent	Direct	Imprecise	Small. Neither favored.	Low
Met vs. SU							
1 RCT 4 obs	16788	Medium	Consistent	Direct	Imprecise	Small. Met favored.	Low
Met vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met vs. Meg							
1 RCT	357	Low	NA	Direct	Imprecise	Unclear	Low
Met vs. GLP-1 agonist							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met vs. Met + TZD							
3 RCTs	1479	Low	Consistent	Direct	Imprecise	Small. Unclear.	Low
Met vs. Met + SU							
2 obs	4968	Medium	Consistent	Direct	Imprecise	Unclear	Low
Met vs. Met + DPP-4 inhibitor							
1	190	Low	NA	Direct	Imprecise	Unclear.	Low
Met vs. Met + Meg							
1	350	Low	NA	Direct	Imprecise	Unclear	Low
TZD vs. TZD							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. SU							
1	2897	Low	NA	Direct	Imprecise	Unclear	Low
TZD vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. GLP-1 agonist							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. Meg							
1	576	Low	NA	Direct	Imprecise	Unclear	Low
SU vs. GLP-1 agonist							
0	NA	NA	NA	NA	NA	NA	Insufficient
DPP-4 inhibitor vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and TZD vs. Met and Another Agent							
1 RCT	561	Low	NA	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and Another Agent							
2 RCTs	4447	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and Meg vs. Met and Another Agent							
None							Insufficient
Met and DPP-4 inhibitor vs. Met and Another Agent							
1 RCT	1172	Low	NA	Direct	Imprecise	Unclear	Low
Met and GLP-1 agonist vs. Met and Another Agent							
1 RCT	1172	Low	NA	Direct	Imprecise	Unclear	Low

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cardiovascular disease mortality (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of Effect	
Met and Basal Insulin vs. Met and Another Agent							
1 RCT	91	Low	NA	Direct	Imprecise	Unclear	Low
Met and Premixed Insulin vs. Met and Another Agent							
2	438	Low	Consistent	Direct	Imprecise	Unclear	Low
Met and TZD vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and SU vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Meg vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Sitagliptin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Exenatide vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Basal Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Premixed Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione

All other comparisons were graded as insufficient since there were no studies of those comparisons.

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.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cardiovascular and cerebrovascular disease morbidity

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of effect	
Met vs. TZD							
4 RCTs 9 obs	640, 910	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met vs. SU							
2 RCTs, 5 obs	609, 436	Low	Inconsistent	Direct	Imprecise	Unclear.	Low
Met vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met vs. Meg							
1 RCT	701	Low	NA	Indirect	Imprecise	Unclear	Low
Met vs. Met + TZD							
6 RCTs 1 obs	486,276	Low	Consistent	Direct	Imprecise	Small. Met favored.	Low
Met vs. Met + SU							
1 RCT, 1 obs	10449	Medium	Inconsistent	Direct	Imprecise	Small. Met favored.	Low
Met vs. Met + DPP-4 inhibitor							
2 RCTs	376	Low	Consistent	Direct	Imprecise	Unclear.	Low
Met vs. Met + Meg							
1	350	Low	NA	Indirect	Imprecise	Unclear	Low
TZD vs. TZD							
3 obs	585,454	High	Inconsistent	Direct	Imprecise	Unclear	Low
TZD vs. SU							
3 RCTs 5 obs	518914	Low	Inconsistent	Direct	Imprecise	Unclear.	Low
TZD vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
TZD vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. DPP-4 inhibitor							
0	NA	NA	NA	NA	NA	NA	Insufficient
SU vs. Meg							
2 RCTs	969	Low	Inconsistent	Direct	Imprecise	Unclear	Low
SU vs. GLP-1 agonist							
1 RCT	411	Low	NA	Direct	Imprecise	Unclear	Low
DPP-4 Inhibitor vs. Meg							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and TZD vs. Met and Another Agent							
4 RCTs 1 obs	474,644	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and SU vs. Met and Another Agent							
3 RCTs	6791	Low	Inconsistent	Direct	Precise	Unclear	Low
Met and Meg vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and DPP-4 inhibitor vs. Met and Another Agent							
1 RCT	665	Low	NA	Indirect	Imprecise	Unclear	Low
Met and GLP-1 agonist vs. Met and Another Agent							
1 RCT	665	Low	NA	Indirect	Imprecise	Unclear	Low

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cardiovascular and cerebrovascular disease morbidity (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Magnitude and Direction of effect	
Met and Basal Insulin vs. Met and Another Agent							
1 cross-over	105	Medium	NA	Direct	Imprecise	Unclear	Low
Met and Premixed Insulin vs. Met and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and TZD vs. TZD and Another Agent							
2 RCTs, 2 obs	488,535	Low	Inconsistent	Direct	Imprecise	Unclear	Low
Met and SU vs. TZD and Another Agent							
1 RCT	639	Low	NA	Indirect	Imprecise	Unclear	Low
Met and Meg vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and DPP-4 inhibitor vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and GLP-1 agonist vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Basal Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient
Met and Premixed Insulin vs. TZD and Another Agent							
0	NA	NA	NA	NA	NA	NA	Insufficient

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione

All other comparisons were graded as insufficient since there were no studies of those comparisons.

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.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Nephropathy

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias:	Consistency	Directness	Precision	Magnitude and Direction of effect	
Met vs. TZD							
2 RCT's	1715	Low	Consistent	Indirect	Precise	Small. Favors pioglitazone	Moderate
Met vs. SU							
1 RCT's	51	High	NA	Indirect	Imprecise	Unclear	Low
TZD vs. SU							
5 RCT's	375	High	Inconsistent	Indirect	Imprecise	Unclear	Low
TZD vs. Meg							
1 RCT	68	Low	NA	Indirect	Imprecise	Unclear	Low
Met and TZD vs. Met and Another Agent							
1 RCT's	389	Low	NA	Indirect	Imprecise	Unclear	Low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione

All other comparisons were graded as insufficient since there were no studies of those comparisons.

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.

Table 5. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Neuropathy

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias:	Consistency	Directness	Precision	Magnitude and Direction of effect	
Met vs. Met and TZD							
1 RCT's	105	Moderate	NA	Indirect	Imprecise	Unclear	Low
Met vs. Met and sitagliptin							
1 RCT's	190	High	NA	Indirect	Imprecise	Unclear	Low
Met and TZD vs. Met and Another Agent							
1 RCT's	183	High	NA	Indirect	Imprecise	Unclear	Low

Meg = meglitinides; Met = metformin; Nateg = nateglinide; Pio = pioglitazone; RCT, randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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.

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2010[121] Japan	RCT	Neither year reported 24 weeks	Yes	<6 months	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c < 7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 weeks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 weeks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Aschner, 2010[77] Multi-continent	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded not reported	NR	Yes	2068/1050 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, CK > 2x upper limit normal

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seck, 2010[134] NR	RCT	Neither year reported 2 years	Run-in period but number of participants excluded not reported	< 6 months	Yes	2141/1172 NR	Age <17 or >78 years
Pratley, 2010[143] Multi-continent, Europe, USA and Canada	RCT	Neither year reported 2 years	No run-in period	>= 6 months	Yes	1302/665 "office based"- possibly outpatient	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin ODM in past 3 months
Brownstein, 2010[182] United States	Cohort	Start year: 2000 End year: 2006 7 years	NA	NA	No	NA/34252 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age ≤18 years, HbA1c ≤ 6.0%, no diagnosis of DM with ICD-9 code of 250.XX

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Pantalone, 2009[174] United States	Cohort	Start year: 1998 End year: 2006 8 years	NA	NA	Yes	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Hsiao, 2009[173] Taiwan	Cohort	Start year: 2000 End year: 2005 6 years	NA	NA	NR	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period
Tzoulaki, 2009[171] United Kingdom	Cohort	Start year: 1990 End year: 2005 7.1 years (mean)	NA	NA	No	NA/91521 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <35 or >90 years, no diabetes, multiple or missing dates of death, missing information, no treatment with medications

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009[130] United States, Multi-continent	RCT	Start year: 2007 End year: 2008 16 weeks	No run-in period	< 6 months	Yes	356/169 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c < 7% (6.5% if on metformin combination therapy), BMI > 40 kg/m2, LDL<50mg/dl or TG > = 500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 weeks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for >=3 months (1500-2550 mg/day, Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Juurlink, 2009[210] Canada	Cohort	Start year: 2002 End year: 2008 3 years	NA	NA	No	NA/39736 Outpatient: Primary care	Age <66 years, patients on rosiglitazone or pioglitazone before the index date, patients on insulin before the index date
Jadzinsky, 2009[78] Multi-continent	RCT	Start year: 2006 End year: 2007 24 weeks	Fewer than 10% participants excluded	<6 months	Yes	2936/1394 Outpatient: primary care, Outpatint: subspecialty care	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c < 8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
Home, 2009[16] Multinational Europe	RCT	Start year: 2001 End year: 2003 7.5 years	Run-in period but number of participants excluded was NR	>= 6 months	Yes	7428/4458 Outpatient: primary care	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception, recent CAD event, heart failure

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Raskin, 2009[131] NR	RCT	Neither year reported 26 weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient: primary care	Age <18 years, pregnant, nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260 mg/dL, any disease of abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, allergy to study drugs or related compounds, history of hypoglycemia unawareness or recurrent severe hyperglycemia
Scott, 2008[85] Multi-continent	RCT	Neither year reported 18 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c < 7% or >11%, not on 10 weeks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Raz, 2008[93] Multi-continent	RCT	Neither year reported 30 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	544/190 NR	Age <18 or >78 years, HbA1c <8% after run-in or HbA1c >11% after run-in, BMI <20 kg/m^2 or >43 kg/m^2, pregnant, nursing, insulin within 8 weeks prior to screening, PPAR-G or incretin mimetics within 12 weeks prior to screening, Type 1 DM, FPG <7.2 mmol/l or >15.6 mmol/L consistently during run-in, no Type 2 DM

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[123] Multinational Europe, Mexico	RCT	Neither year reported 52 weeks	Yes	< 6 months	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 weeks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/dl for men and < 10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170 mmHg, DBP >100 mmHg
Schwarz, 2008[152] US	RCT	Neither year reported 104 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0% or >11.0%, BMI <22 or >45 kg/m^2, FBG >270 mg/dL, history of lactic acidosis, congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Monami, 2008[180] Italy	Cohort	Start year: 1993 End year: 2001 28 months	NA	NR	NR	NA (for cohort studies, claims data, etc)/1108 Outpatient: primary care, Geriatric clinic	Insulin treatment was an exclusion, not Type 2 DM by WHO 1985 criteria
Hanefeld, 2007[100] Multinational Europe	RCT	Neither year reported 52 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG: <7 mmol/l or >15 mmol/l, C-peptide <0.27 nmol/l
Comaschi, 2007[129] Italy	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33 nmol/L
Nauck, 2007[133] US, Multinational Europe, Multi-continent	RCT	Neither year reported 52 weeks	Yes	< 6 months	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 weeks of screening, history of Type 1 DM, other treatments for hypoglycemia

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kahler, 2007[175] US	Cohort	Start year: 1998 End year: 2001 3 years	NA	NA	No	> 1500000/39721 VHA Medical facilities	Age <18 years, non-respondents to 1999 LHSVE survey, medical facilities that do not have assays certified by the National Glycohemoglobin Standardization Program, less than 15 month window period after 1 year exposure to drug, alive as of 31 December 2000, fixed one year window of drug exposure
McAfee, 2007[181] US	Cohort	Start year: 2000 to 2004 End year: 2005 NR	NA	NA	Yes	NA (for cohort studies, claims data, etc)/31075 Ingenix research claims database	Age >18 years, less than 6 months in insurance plan, insulin or study drug given within 6 months prior to study, insulin or other drug given within 30 days after monotherapy initiation, no medical or pharmacy benefits
Nakamura, 2006[108] Japan	RCT	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/68 NR	HbA1c >6.5%, history of ketoacidosis, treatment other than by diet alone, fasting C-peptide level < 0.33 mmol/L, hematuria, non-diabetic renal disease, microalbuminura defined as a median urinary albumin excretion of 20 to 200 ug/min
Kahn, 2006[38] Multi-continent	RCT	Start year: 2000 End year: 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or > 180 mg/dL, history of lactic acidosis

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2006[49] Multi-continent	RCT	Start year: 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half live of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[101] US, Puerto Rico	RCT	Neither year reported 56 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c< 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to Rosi, Pio or Troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg/day, oral antidiabetic drugs, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria , anemia (< 10g/dl women, < 12g/dl men), BMI ≤20kg/m^2 or >45kg/m^2, hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Bakris, 2006[125] US, Multi-continent, South America, Europe	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kvapil, 2006[138] Multinational Europe	RCT	Neither year reported 16 weeks	No run-in period	< 6 months	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria includes not adequately controlled on metformin
Stewart, 2006[156] Multinational Europe	RCT	Start year: 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG < 6.0 mmol/l or > 8 mmol/l, prior history of exposure to thiazolidinediones within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Simpson, 2006[166] Canada	Cohort	Start year: 1991 End year: 1999 8 years	NA	NA	No	12272/5795 Saskatchewan health databases	Age <30 years, patients on insulin, patients on two or more ODM
Rosak, 2006[183] Germany	Cohort	Neither year reported 6 months	NA	< 6 months	Yes	NR/22808 Outpatient: primary care, Outpatient: subspecialty care setting	Not all treated with rosiglitazone

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Malone, 2005[165] Multinational Europe	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	119/97 NR	Age <30 or >75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control
Weissman, 2005[86] US	RCT	Neither year reported 24 weeks (planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% for subjects having received prior combination treatment (metformin + SU), HbA1c >8.5% for subjects having received prior combination treatment (Metformin + SU), BMI <27 kg/m^2, HbA1c < 7% for drug naive or prior monotherapy subjects, HbA1c > 10% for drug naive or prior monotherapy subjects, FPG < 126 mg/dL or >270 mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non -compliant patient with metformin up-titration
Bailey, 2005[87] UK, 14 European countries	RCT	24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gerich, 2005[136] US	RCT	Neither year reported 2 Years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), neuropathy, retinopathy, HbA1c < 7% or >11%, BMI <22kg/m^2 and >45 kg/m^2, not using adequate contraception, FPG ≥15mmol/L, if Type 1 DM, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, history of lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sig risk to the subject, had to be drug naive
Johnson, 2005[167] Canada	Cohort	Median followup periods for each group ranged from 4.6 to 5.6 yeas	Not extracted	Not extracted	No	Not extracted	Age < 30 years, no Type 2 DM, other
Eurich, 2005[169] Canada	Cohort	2.1 years (mean followup)	Not extracted	Not extracted	No	Not extracted	History of CVD, treatment experienced, other
Evans, 2005[176] Scotland	Cohort	Neither year reported 8 Years	Not extracted	NA	NR	6089/5730 NR	Diagnosed under the age of 35 years, requirement for insulin within 90 days of diagnosis or their first ODM prescription, ODM users before January 1994

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Agarwal, 2005[184] US	RCT	Start year: 2001 End year: 2003 16 Weeks	No run-in period	< 6 months	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2, class III or IV heart failure, NSAID use
Schernthaner, 2004[52] Europe	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Lawrence, 2004[53] U.K.	RCT	12 titration, 12 week maintenance (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <45 or >80 years, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% for low-dose ODM: >7.5%, no Type 2 DM, other
Nakamura, 2004[102] Japan	RCT	Neither year reported 12 Months	No run-in period	>= 6 months	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c > 6.5%, BP <140/90 mm Hg, controlled on diet alone, no history ketoacidosis, c peptide <0.33mmol/L, creatinine <1.5, no BP meds, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2004[140] Canada, U.K., Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and Netherlands	RCT	NR	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other
Malone, 2004[164] U.S.	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	145/111 NR	Age <30 or >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Gulliford, 2004[170] U.K., Wales, Scotland, and Ireland	Cohort	Median followup for each group ranged from 1.67 to 3.49 years	Not extracted	Not extracted	No	Not extracted	Treatment experienced, no Type 2 DM, other,
Garber, 2003[61] U.S.	RCT	16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age < 20 or >79 years, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2003[62] U.S.	RCT	18 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >12.0%, other
Bakris, 2003[104] likely U.S. and U.K.	RCT	52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	NR
Malone, 2003[137] 14 countries not specified	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test meals	Age <30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days
Jones, 2003[179] U.S.	RCT	Neither year reported 6 months	Run-in period but number of participants excluded was NR	< 6 months	NR	NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days
Hallsten, 2002[55] Finland	RCT	26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gomez-Perez, 2002[88] Mexico	RCT	26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
St John Sutton, 2002[149] US	RCT	52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or age >80 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Johnson, 2002[168] Canada	Cohort	5.1 years (mean followup)	Not extracted	Not extracted	No	Not extracted	Age <30 years, other
Fisman, 2001[177] Israel	Cohort	7.7 years (mean followup)	Not extracted	Not extracted	No	Not extracted	Age < 45 or >74 years, any liver disease, any kidney disease, other
Amador-Licona, 2000[66] Mexico	RCT	12 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other
Horton, 2000[79] US	RCT	24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 years, any kidney disease, HbA1c <6.8% or >11%, no Type 2 DM, other
Fonseca, 2000[90] US	RCT	26 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nakamura, 2000[103] Japan	RCT	3 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Wolffenbuttel, 1999[116] Germany, Austria, and Netherlands	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.5% if treated with diet only, HbA1c >12% if treated with diet plus oral, other
Marbury, 1999[117] US and Canada	RCT	12 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age >37 or <75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, retinopathy, HbA1c <6.5% or >14.6%, no Type 2 DM, other
Fisman, 1999[178] NR	Cohort	Neither year reported 6 years	NA	NA	NR	NR/14440 Community	Age < 45 and > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pacemaker, hepatitis, renal disease, malignancy, insulin, estrogen replacement
DeFronzo, 1995[70] U.S.	RCT	29 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other

Table 6. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on long term outcomes (KQ2) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of followup	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hermann, 1994[68] Sweden	RCT	6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	No Type 2 DM, other

ALT = alanine aminotransferase; AST = asparate aminotransferase; BID = twice a day; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine kinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/dl = grams per deciliter; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; ICD-9 = International Statistical Classification of Diseases and Related Health Problems-9; kg = kilogram; kg/m2 = kilogram per meter squared; LDL = low density lipoprotein; LHSVE = Large Health Survey of Veteran Enrollees; LVEF = left ventricular ejection fraction; mg/d = milligrams per day; mg/dl = milligrams/deciliter; mmHg = millimeters of mercury; mmol/L = millimoles per liter; NA = not applicable; nmol/L = nanomoles per liter; NPH = neutral protamine Hagedorn; NR = not reported; NSAID = non-steroidal anti-inflammatory drugs; ODM = oral diabetes medication; PPAR-G = peroxisome proliferator-activated receptor gamma; QD = once a day; RCT = randomized controlled trial; SBP = systolic blood pressure; SGOT = glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TG = triglycerides; TZD = thiazolidinedione; VHA = Veterans Health Administration; WHO = World Health Organization

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Brownstein, 2010[182]	Pioglitazone, 806	63.7	52	NR	NR NR	8.1	NR	NR
	Rosiglitazone, 1879	64	51.7	NR	NR NR	8	NR	NR
	Metformin, 12490	61.7	49.9	NR	NR NR	7.8	NR	NR
	Any in the Sulfonylurea class, 11200	65.8	57.5	NR	NR NR	7.7	NR	NR
Seino, 2010[121]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Aschner, 2010[77]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[134]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, Other: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, Other: 3.1	31.3 90.3 kg	7.3	5.7	328
Pratley, 2010[143]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, Other: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, Other: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, Other: 4	33.1 94.6 kg	8.4	6.4	52

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Pantalone, 2009[174]	Rosiglitazone, 1079	61.4	45.5	C: 86.8	32.7 NR	7.3	NR	NR
	Any in the Sulfonylurea Class, 7427	66.1	49.5	C: 78	31.1 NR	7.6	NR	NR
	Pioglitazone, 1508	61.6	48.3	C: 83.5	33 NR	7.4	NR	NR
	Metformin, 10436	56.8	41.18	C: 76.9	33.8 NR	7.7	NR	NR
Hsiao, 2009[173]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the Sulfonylurea class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Tzoulaki, 2009[171]	Metformin, 68181	66.3	50.6	NR	31.47 NR	8.13	5.59	NR
	Rosiglitazone, 8442	65.7	50.5	NR	31.7 NR	8.4	6.7	NR
	Any in the Sulfonylurea class, 58095	70.4	52.6	NR	28.5 NR	8.2	6.6	NR
Rigby, 2009[130]	Metformin + rosiglitazone, 56	54.7	41.1	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, Other: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, Unspecified: 1.8	NR 79.6 kg	8.17	8.35	11

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Juurlink, 2009[210]	Rosiglitazone, 22785	66-75 (69%) 76-85 (28%) >=86 (3%)	53.1	NR	NR NR	NR	NR	NR
	Pioglitazone, 16951	66-75 (69%) 76-85 (28%) >=86 (3%)	52.1	NR	NR NR	NR	NR	NR
Jadzinsky, 2009[78]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, Other: 5	29.9 NR	9.4	2	NR
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, Other: 5.9	30.3 NR	9.5	1.4	NR
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, Other: 6.4	30.2 NR	9.4	1.7	NR
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, Other: 5.4	30.2 NR	9.6	1.7	NR
Home, 2009[16]	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0 kg	8	7.9	NR
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3 kg	8	7.9	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5 kg	7.8	6.1	NR
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
Raskin, 2009[131]	Metformin + repaglinide, 187	54.5	58.8	AA: 13.4, Asian: 4.8, C: 78.8, American Indian and Alaskan Native: .5, Other: 1.6	32.5 NR	8.29	7.3	58
	Metformin + rosiglitazone, 187	55.5	50.8	AA: 13.4, Asian: 2, C: 79.1, American Indian and Alaskan Native: 1.1, Others: 4.3	32.2 NR	8.46	7.1	58

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + repaglinide, 187	54.8	57.8	AA: 16, Asian: 4.3, C: 74.9, American Indian and Alaskan Native: 0.5, Others: 4.3	32.9 NR	8.45	7.4	62
Scott, 2008[85]	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Others: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9
	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
Raz, 2008[93]	Metformin + sitagliptin, 96	53.6	51	AA: 3, C: 42, H: 32, Multiracial: 22, Not Specified: 1	30.1 81.5 kg	9.3	8.4	18
	Metformin, 94	56.1	41.5	AA: 1, C: 47, H: 25, Multiracial: 25, Not Specified: 2	30.4 81.2 kg	9.1	7.3	16
Hamann, 2008[123]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4 kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9 kg	8	6.4	71
Chien, 2007[59]	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
Schwarz, 2008[152]	Metformin + glyburide, 40	70.4	50	AA: 11.1, C: 77.8, Other: 11	33.5 NR	7.7	2.5	18
	Metformin + nateglinide, 35	70.1	51.5	AA: 9.1, C: 78.8, Other: 12.1	30.4 NR	7.8	1.7	14
Comaschi, 2007[129]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
McAfee, 2007[181]	Any in the Sulfonylurea class, 8977	52	56	NR	NR NR	NR	NR	NR
	Rosiglitazone + sulfonylurea, 1362	52	59	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 1362	52	59	NR	NR NR	NR	NR	NR
	Rosiglitazone, 8977	52	55	NR	NR NR	NR	NR	NR
	Metformin, 8977	52	55	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 1362	51	61	NR	NR NR	NR	NR	NR
Monami, 2008[180]	Metformin + repaglinide	NR	NR	NR	NR NR	NR	NR	0
	Metformin + sulfonylurea	NR	NR	NR	NR NR	NR	NR	0
Kahler, 2007[175]	Any in the Sulfonylurea class, 19053	68.2	NR	AA: 12.6, C: 78.6, Other: 8.8	29.6 NR	7.2	(<1: 12.8, 1-3: 32.2, 4-10: 33.4, >11: 20)	NR
	Metformin, 2988	64.9	96.9	AA: 12.7, C: 78.7, Other: 8.7	30.4 NR	7	(<1: 20.5, 1-3: 41.5, 4-10: 25.1, >11: 11.6)	NR
	Metformin + sulfonylurea, 13820	65.6	98.1	AA: 13.2, C: 77.5, Other: 9.3	30.3 NR	8	(<1: 4.5, 1-3: 21.2, 4-10: 43.3, >11: 29.1)	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	TZD, 675	67.1	97.5	AA: 8.7, C: 80.9, Other: 10.4	30.7 NR	7.9	(<1: 3.3, 1-3: 18.2, 4-10: 39.9, >11: 37.5)	NR
Nauck, 2007[133]	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, Other: 3.7	NR NR	7.7	6.5	202
	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, Other: 3.4	31.3 89.7 kg	7.6	6.2	172
Hanefeld, 2007[100]	Rosiglitazone, 189	60.6	57.7	AA: 0, C: 97, Other: 3	28.8 NR	8.2	6	9
	Glibenclamide, 203	60.1	70.4	AA: 0, C: 99, Other: 0.5	28.7 NR	8.2	6.4	13
	Rosiglitazone, 195	60.4	68.2	AA: 0, C: 98.5, Other: 1.5	28.7 NR	8.1	5.9	12
Nakamura, 2006[108]	Pioglitazone, 17	56	52.9	NR	NR NR	8.0	16	NR
	Glibenclamide, 18	53.5	55.6	NR	NR NR	7.8	16.5	NR
	Nateglinide, 16	53.5	56.3	NR	NR NR	7.7	16.6	NR
Kahn, 2006[38]	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, Other: 0.7	32.2 91.5 kg	7.36	(<1: 651, 1-2: 758, >2: 47)	539
	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, Other: 0.3	32.2 92 kg	7.35	(<1 year: 637, 1-2: 751, >2: 53)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, Other: 1	32.1 91.6 kg	7.36	(< 1 year: 673, 1-2: 724, >2: 57)	551
Rosenstock, 2006[49]	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, Other: 3	32.8 NR	8.8	2.7	22
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, Other: <1	32.5 NR	8.8	2.9	31
Jain, 2006[101]	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, Other: 0.4, Native American: 0.4	32.5 93.9 kg	9.2	0.8	117
	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, Other: 0.4	32.8 94.3 kg	9.2	0.78	123
Stewart, 2006[156]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian/Other Pacific Islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[125]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Rosak, 2006[183]	Metformin + rosiglitazone, 7705	60	50.2	NR	29.3 87.2 kg	8.1	3.9	545
	Rosiglitazone + sulfonylurea, 5511	65	48.2	NR	NR 81.3 kg	8.3	5.3	478
	Rosiglitazone, 1559	62.0	47.7	NR	28.7 83.8 kg	8.1 (median)	4.5	542
Simpson, 2006[166]	Metformin, 768	64.6	53	NR	NR NR	NR	NR	NR
	Glyburide, 2067	67.8	60	NR	NR NR	NR	NR	NR
Kvapil, 2006[138]	Metformin + glibenclamide, 114	58.1	45.6	NR	30.5 84.0 kg	9.4	8.1	5
	Metformin + aspart 70/30, 116	56.4	45.7	NR	30.4 85.1 kg	9.3	6.7	11

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Malone, 2005[165]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Gerich, 2005[136]	Metformin + glyburide, 209	53.5	48	AA: 16.7, Asian: 0.5, C: 65.2, Other: 17.7	33.5 NR	8.3	2.0	87
	Metformin + nateglinide, 219	52.6	51	AA: 13, Asian: 2.4, C: 64.4, Other: 20.2	33.3 NR	8.4	1.5	78
Agarwal, 2005[184]	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1
	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
Malone, 2004[164]	Pooled arms		63	NR	30.9 91.5 kg	8.7	9	NR
	Metformin + lispro 75/25	NR	NR	NR	NR NR	NR	NR	3 during this arm
	Metformin + glargine	NR	NR	NR	NR NR	NR	NR	7
Nakamura, 2004[102]	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR
	Glibenclamide, 15	55	53.3	NR	NR NR	7.8	19.2	0
Malone, 2003[137]	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, Other: 3	29.8 83.0 kg	9.17	8.0	25
	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, Other: 4	29.6 81.7 kg	9.27	7.4	29
Jones, 2003[179]	Metformin, 82	60	74	NR	28 NR	8.8	6	NR
	Metformin, 22	64	9	NR	23 NR	8.6	6.5	NR
	Metformin + rosiglitazone, 35	62	71	NR	23 NR	9.3	8	NR
	Metformin + rosiglitazone, 141	58	69	NR	28 NR	8.8	6	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + rosiglitazone, 142	57	57	NR	34 NR	8.8	5	NR
	Metformin, 121	58	70	NR	34 NR	8.7	5	0
Fisman, 1999[178]	Any in the Sulfonylurea class, 1041	60.5	76	NR	27 76 kg	NR	NR	NR
	Metformin + sulfonylurea, 266	60.9	66	NR	27 75 kg	NR	NR	0
	Metformin, 78	59.5	65	NR	29 80 kg	NR	NR	NR
Evans, 2005[176]	Metformin, 2286	60.2	51.20	NR	32.9 NR	7.7	2.7	NR
	Sulfonylurea, 3331	65.9	56.30	NR	28.6 NR	7.8	4.6	NR
	Metformin + sulfonylurea, 985	61.2	47.00	NR	33.2 NR	8.1	4.4	NR
	Metformin + sulfonylurea, 1252	63.6	55.10	NR	30.2 NR	8.2	4.8	NR
	Metformin + sulfonylurea,113	64	49.60	NR	30 NR	8	8.8	NR
Weissman, 2005[86]	Metformin, 384	55.7	NR	NR	33.8 96.7 kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2 kg	8.05	NR	76
Bailey, 2005[87]	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, Other: 1	32.1 89.5 kg	7.5	6.1	44
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, Other: 1	32.2 90.9 kg	7.4	6	30
Eurich, 2005[169]	Unspecified Sulfonylurea, 773	74.8	58	NR	NR NR	NR	NR	NR
	Metformin, 208	72.5	59	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 852	70	55	NR	NR NR	NR	NR	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Johnson, 2005[167]	Unspecified Sulfonylurea, 2138	67.8	59	NR	NR NR	NR	NR	NR
	Metformin, 923	64.3	52	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 1081	62	54	NR	NR NR	NR	NR	NR
Schernthaner, 2004[52]	Placebo + diet + Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	96
	Placebo + diet + pioglitazone, 597	57	52.6	NR	31.2 88.2 kg	8.7	3.4	98
Gulliford, 2004[170]	Unspecified Sulfonylurea, 6620	67	55	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 1868	61	51	NR	NR NR	NR	NR	NR
	Metformin, 2232	61	50	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 867	58	45	NR	NR NR	NR	NR	NR
Hanefeld, 2004[140]	Placebo + unspecified Sulfonylurea + pioglitazone, 319	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, Other: 0	30.2 85.3 kg	8.82	7	259
	Placebo + Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0 Other: 0.6	30 84.9 kg	8.8	7.1	279
Lawrence, 2004[53]	Metformin, 20	59.5	60	NR	29.2 NR	NR	NR	NR
	Pioglitazone, 20	60.4	70	NR	30.6 NR	NR	NR	NR
Garber, 2003[61]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, Other: 3.5	31.4 91.9 kg	8.8	3	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, Other: 3.3	31.1 91 kg	8.7	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, Other: 3.7	31.4 92.8 kg	8.5	2.6	NR
Goldstein, 2003[62]	Metformin + glipizide, 87	54.6	58.60	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, Other: 0	31.7 94 kg	8.7	5.9	NR
	Glipizide, 84	57.4	64.30	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, Other: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.80	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, Other: 0	31.6 93.8 kg	8.7	7.3	NR
Bakris, 2003[104]	Rosiglitazone, 104	55.1	72.1	NR	NR NR	9.1	NR	NR
	Glyburide, 99	56.1	71.7	NR	NR NR	9.5	NR	NR
Johnson, 2002[168]	Unspecified Sulfonylurea, 3033	67.2	59	NR	NR NR	NR	NR	NR
	Metformin, 1150	63.8	54	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 4683	62.1	54.3	NR	NR NR	NR	NR	NR
Hallsten, 2002[55]	Diet + rosiglitazone, 14	58.6	71.4	NR	29.3 NR	6.8	NR	NR
	Placebo + diet, 14	57.7	71.4	NR	30.3 NR	6.3	NR	NR
	Diet + Metformin, 13	57.8	61.5	NR	29.9 NR	6.9	NR	NR
St John Sutton, 2002[149]	Rosiglitazone, 104	55.1	75	AA: 5, C: 73, Asian: 0, H: 0, Other: 22	67.3% >=27kg/m^2 86.2 kg	9.1	5.3	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Glyburide, 99	56.1	71	AA: 3, C: 76, Asian: 0, H: 0, Other: 21	65.7% >=27 kg/m^2 85.1 kg	9.5	6.2	NR
Gomez-Perez, 2002[88]	Placebo + Metformin, 34	53.4	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7	28.6	C: 0, H: 80, Mestizo: 20	28 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2	19.4	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR
Fisman, 2001[177]	Glyburide, 953	59.8	76	NR	27 77 kg	NR	NR	NR
	Metformin, 79	59.5	66	NR	29 81 kg	NR	NR	NR
	Metformin + glyburide, 253	60.7	66	NR	27 75 kg	NR	NR	NR
Amador-Licona, 2000[66]	Glibenclamide, 23	48.2	30.4	NR	30.4 73.2 kg	8.4	4	NR
	Metformin, 28	49.3	39.3	NR	26.8 70.7 kg	8.5	4.5	NR
Fonseca, 2000[90]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, Other: 12.7	29.8 NR	8.9	8.3	18
	Placebo + Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, Other: 12.9	30.2 NR	8.9	7.5	18
Nakamura, 2000[103]	Pioglitazone, 15	60	46.7	NR	NR NR	7.7	16	NR
	Glibenclamide, 15	61	53.3	NR	NR NR	7.8	14	NR
Horton, 2000[79]	Nateglinide, 179	58.6	61.5	AA: 9.5, C: 82.1, Asian: 2.8, H: 0, Other: 5.6	29.6 NR	8.3	4.7	NR

Table 7. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on long-term outcomes (KQ2) (continued)

Author, year	Group, N	Mean age (age range), Age categories(n;) in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin, 178	56.8	68	AA: 9.6, C: 79.2, Asian: 2.2, H: 0, Other: 9	29.6 NR	8.4	7.5	NR
	Metformin + nateglinide, 172	58.4	58.7	AA: 11.6, C: 82.6, Asian: 0.6, H: 0, Other: 5.2	30 NR	8.4	4.5	NR
Wolffenbuttel, 1999[116]	Repaglinide, 286	61	62	NR	28.4 81.5 kg	7.1	Median 6	NR
	Placebo + glyburide, 139	61	68	NR	28 81.3 kg	7	Median 6	NR
DeFronzo, 1995[70]	Metformin, 143	53	43.4	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46.0	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49.3	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + Metformin, 210	55	45.7	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[68]	Diet + Metformin, 25	60	63	NR	NR 78.6 kg	6.9	4	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	NR
	Diet + Metformin + glibenclamide + Other, 54	NR	80.2	NR	NR NR	NR	NR	NR
Marbury, 1999[117]	Repaglinide, 362	58.3	67	AA: 9, C: 77, Asian: 0, H: 0, Other: 14	29.4 NR	8.7	7.2	NR
	Placebo + glyburide, 182	58.7	66	AA: 9, C: 79, Asian: 0, H: 0, Other: 12	29.1 NR	8.9	8.3	NR

AA= African American; C= Caucasian; H=Hispanic; Kg=kilogram; Met=Metformin; NR=Not reported; Repa=Repaglinide; Rosi=Rosiglitazone; Sita=Sitagliptin; SU=Sulfonylurea

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin versus thiazolidinedione						
Hsiao, 2009[173]	Cohort	Grp1: Metformin NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 22 (4.51) HR: 1.15 (CI: 0.6 to 2.21) p: 0.6753 Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 44 (8.89) HR: 1.0 (CI: 0.26 to 3.89) p: 0.9954	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 5 (1.03)
Hsiao, 2009[173]	Cohort	Grp1: Metformin NS Grp2: Rosiglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 154 (7.52) HR: 1.79 (CI: 1.39 to 2.3) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 266 (12.71) HR: 2.09 (CI: 1.36 to 3.24) p: 0.0007	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 16 (0.8) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 23 (1.14)
Brownstein, 2010[182]	Cohort	Grp1: Metformin NS Grp2: Rosiglitazone NS			Def: Hospitalization for acute MI Grp1: ref Grp2: HR: 3.0 (CI: 2.4-3.7)	
Tzoulaki, 2009[171]	Cohort	Grp1: Metformin NS Grp2: Rosiglitazone NS	Grp1: ref Grp2: 34 (<1) HR: 1.07 (CI: 0.77 to 1.49) p: 0.74		Def: Incident MI Grp1: ref Grp2: 9 (<1) HR: 0.79 (CI: 0.41 to 1.53) p: 0.485	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR	Grp1: ref Grp2: HR: 1.33 (CI: 0.93 to 1.91) p: 0.11		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 0.96 (CI: 0.76 to 1.21) p: 0.74	
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 1.08 (CI: 0.78 to 1.51) p: 0.64		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.11 (CI: 0.91 to 1.34) p: 0.32	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: 149 (2) Grp2: 152 (2)	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 62 (1) Grp2: 70 (1)	
Lawrence, 2004[53]	RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1: 1 (5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (5) Grp2: 0 (0)	Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 0 (0)	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Rosenstock, 2006[49]	RCT	Grp1: Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1847 mg, Max: 2000 mg D: 32 wks Grp2: Rosiglitazone Varied, glucose: 6.1 mmol/l Start: 4 mg, Mean: 7.7 mg, Max: 8 mg D: 32 wks	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease Grp1: 2 (1) Grp2: 2 (1)	
Kahn, 2006[38]	RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg	Grp1: 31 (2) Grp2: 34 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 2 (0.1)	Grp1: 21 (1.4) Grp2: 25 (1.7)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 16 (1.1)
Schernthaner, 2004[52]	RCT	Grp1: Metformin Varied Max: 850 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1: 2 (0.3) Grp2: 3 (0.5)			
Metformin versus sulfonylurea						
Hsiao, 2009[173]	Cohort	Grp1: Metformin NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 940 (0.99)
Tzoulaki, 2009[171]	Cohort	Grp1: Metformin NS Grp2: Sulfonylurea NS	Grp1: ref Grp2: 1379 (2) HR: 1.24 (CI: 1.14 to 1.35) p: <0.001		Def: Incident MI Grp1: ref Grp2: 365 (1) HR: 1.09 (CI: 0.94 to 1.27) p: 2.66	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: HR: 0.54 (CI: 0.46 to 0.64) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.94 (CI: 0.85 to 1.05) p: 0.23 Grp2: ref	
Simpson, 2006[166]	Cohort	Grp1: Metformin NR Grp2: Glyburide NR	Grp1: 39.6/1000 person-years Grp2: 61.4/1000 person-years	Def: Fatal MI Grp1: 11.5/1000 person-years Grp2: 17.6/1000 person-years		
Eurich, 2005[169]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 69 (33) Adjusted HR 0.70 Grp2: 404 (52)			
Fisman, 2001[177]	Cohort	Grp1: Metformin NR Grp2: Glyburide NR	Grp1: 25 (32) Grp2: 324 (34)	Def: CVD mortality/CVD mortality + ICD-9 codes 410-414 + matched the patients ID number with their life status in the population registry + ischemic heart disease Grp1: Age-adjusted IR 30/1000 person-years Grp2: Age-adjusted IR 24.5/1000 person-years		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Johnson, 2005[167]	Cohort	Grp1: Metformin Varied Min: 250 mg Grp2: Sulfonylurea Varied		Def: CVD mortality/CVD mortality registry + CVD mortality + ICD-9 codes 410, 411-414, 420-427, 429, 428, 430-432, 433-434, 436-438, 440 Grp1: 14.4/1000 patient-years Grp2: 25.5/1000 patient-years	Def: Non-fatal cardiovascular hospitalization/used ICD-9 codes 410-414, 420-427, 429, 428, 440, 430-432, 433-434, 436-438 Grp1: 53.7/1000 patient-years Grp2: 75.3/1000 patient-years	
Johnson, 2002[168]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 159 (14) Grp2: 750 (25)	Def: CVD mortality/Fatal MI + fatal stroke + CVD mortality + ICD-9 codes 390-398, 401-417, 420-438, 440-444, 446-448, 451-459 Grp1: 80 (7) Grp2: 351 (11.6)		
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: 149 (2) Grp2: 152 (2)	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 62 (1) Grp2: 94 (1)	
Evans, 2006[176]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: (4.7) Adjusted RR: 1.43 Grp2: (17.9)	Grp1: Adjusted HR: 1.7 Grp2: ref		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Kahler, 2007[175]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 82 (2.7) Grp2: 1005 (5.3)			
Hermann, 1994[68]	RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg			Def: CVD morbidity/unclear CHD Grp1: 2 (5) Grp2: 3 (9)	
Goldstein, 2003[62]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed Start: 15mg bid	Grp1: 0 (0) Grp2: 0 (0)			
Garber, 2003[61]	RCT	Grp1: Metformin Varied Start: 500 mg, max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, max: 10 mg	Grp1: 0 (0) Grp2: 0 (0)			
DeFronzo, 1995[70]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1: 1 (0.5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (0.5) Grp2: 0 (0)		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Chien, 2007[59]	RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 1000mg, Mean: 1910 mg, Max: 2000 mg D: 4 wks Grp2: Glyburide Varied, glucose: 140 Start: 10 mg, Mean: 19 mg, Max: 20 mg D: 4 wks	Grp1: 0 (0) Grp2: 0 (0)			
Kahn, 2006[38]	RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: 140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: 31 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Not defined Grp1: 21 (1.4) Grp2: 15 (1)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 17 (1.2)
Gulliford, 2004[170]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 144 (7) Grp2: 1030 (16)			
Fisman, 1999[178]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 78 (26) Grp2: 234 (23)			
Metformin versus DPP-4 inhibitors						
Aschner, 2010[77]	RCT	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 weeks Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1: 0 (0) Grp2: 1 (<1)			
Jadzinsky, 2009[78]	RCT	Grp1: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week Gpr2: Saxagliptin Fixed	Grp1: 3 (1) Grp2: 0 (0)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin versus meglitinide						
Horton, 2000[179]	RCT	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Nateglinide Fixed Start: 120 mg tid	Grp1: 1 (0.6) Grp2: 0 (0)	Def: CVD mortality/due to arteriolosclerotic and hypertensive heart disease + unclear CHD Grp1: 1 (0.6) Grp2: 0 (0)	Def: CVD morbidity/electrocardio-gram abnormalities Grp1: 0 (0) Grp2: 0 (0)	
Metformin versus metformin + thiazolidinedione						
Hsiao, 2009[173]	Cohort	Grp1: Metformin NS Grp2: Metformin + rosiglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 103 (4.26) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 25 (1.03)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 12 (0.49) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 11 (0.45)
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Metformin + rosiglitazone NR			Def: Composite outcome Grp1: 149 (2) Grp2: 24 (2)	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Metformin + rosiglitazone NR			Def: Non-fatal MI Grp1: 62 (1) Grp2: 6 (<1)	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Metformin + rosiglitazone NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: OR: 6.1 Grp2: ref	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Weissman, 2005[86]	RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)		Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 2 (1)	
Weissman, 2005[86]	RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg			Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 3 + 1 withdrew (1) Grp2: 5 (1)	
Gomez-Perez, 2002[88]	RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 1 (3)	
Gomez-Perez, 2002[88]	RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 2 (5)	
Fonseca, 2000[90]	RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1: 0 (0) Grp2: 1 (1)	Def: CVD mortality/unclear mortality + Fatal MI Grp1: 0 (0) Grp2: 0 (0)		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Bailey, 2005[87]	RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2500mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD mortality/sudden cardiac death Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 0 (0) Grp2: 1 (<1)	
Stewart, 2006[156]	RCT	Grp1: Metformin Varied Start: 500 mg, Mean: 2627.9 mg, Max: 3000 mg D: 20wks Grp2: Metformin + rosiglitazone Varied Start: 500 mg, Mean: 1812.9 mg, Max: 2000 mg D: 18 wks			Def: MI, angina pectoris, myocardial ischemic, coronary artery insufficiency Grp1: 0 (0) Grp2: 4 (2)	
Rosenstock, 2006[49]	RCT	Grp1: Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1799 mg, Max: 2000 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2mg D: 32 wks	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease Grp1: 2 (1) Grp2: 1 (1)	
Jones, 2003[179]	RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, NS Start: 2.5 g; Max: 8 mg	Grp1: 0 (0) Grp2: 1 (1)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin versus metformin + sulfonylurea						
Hsiao, 2009[173]	Cohort	Grp1: Metformin NS Grp2: Metformin + sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 11435 (4.27)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 1637 (0.61)
Fisman, 1999[178]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 20 (26) Grp2: 84 (32)	Def: Fatal MI Grp1: 39.3/1000 person-years Grp2: 35.3/1000 person-years	Def: CVD mortality/CVD mortality + ICD-9 codes 410-414 + matched the patients ID number with their life status in the population registry + ischemic heart disease Grp1: IR: 30/1000 person-years Grp2: IR: 31.2/1000 person-years	
Gulliford, 2004[170]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 144 (5) Grp2: 159 (6)			
Kahler, 2007[175]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 82 (2.7) Grp2: 468 (3.4)			
Evans, 2006[176]	Cohort	Grp1: Metformin NR Grp2: Metformin + later addition of sulfonylurea NR		Def: Cardiovascular mortality Grp1: Adjusted RR 2.29 (CI: 1.45-3.61) Grp2: ref		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Evans, 2006[176]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea + later addition of metformin NR		Def: Cardiovascular mortality Grp1: Adjusted RR 2.43 (CI: 1.61-3.66) Grp2: ref		
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: 149 (2) Grp2: 36 (3)	
McAfee, 2007[181]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR			Def: MI based on ICD-9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 62 (1) Grp2: 17 (1)	
Garber, 2003[61]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 2 (1)			
Goldstein, 2003[62]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 0 (0)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
DeFronzo, 1995[70]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	Grp1: 1 (1)) Grp2: 0 (0)			
Hermann, 1994[68]	RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75mg, Max: 5.25 mg			Def: CVD morbidity/unclear CHD Grp1: 2(5) Grp2: 10 (14)	
Chien, 2007[59]	RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5 mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks	Grp1: 0 (0) Grp2: 0 (0)			
Johnson, 2002[168]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 159 (14) Grp2: 635 (14)			
Eurich, 2005[169]	Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 69 (33) Grp2: 263 (31)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Fisman, 2001[177]	Cohort	Grp1: Metformin NR Grp2: Metformin + Glyburide NR	Grp1: 25 (32) Grp2: 111 (44)			
Metformin versus metformin + DPP-IV inhibitor						
Raz, 2008[93]	RCT	Grp1: Metformin Fixed Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1: 1 (1) Grp2: 0 (0)	Def: Fatal MI Grp1: 1 (1) Grp2: 0 (0)		
Jadzinsky, 2009[78]	RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 week Grp2: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week	Grp1: 0 (0) Grp2: 3 (1)			
Jadzinsky, 2009[78]	RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 5 mg Grp2: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week	Grp1: 0 (0) Grp2: 3 (1)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Thiazolidinedione versus thiazolidinedione						
Juurlink, 2009[210]	Cohort	Grp1: Rosiglitazone Varied, NS Grp2: Pioglitazone Varied, NS	Grp1: 645 (3) Grp2: 377 (2) HR: 0.86 (CI: 0.75 to 0.98)	Def: Death or admission to hospital Grp1: 1563 events Grp2: 895 events HR: 0.83 (CI: 0.76 to 0.9)	Def: Acute MI Grp1: 425 events Grp2: 273 events HR: 0.95 (CI: 0.81 to 1.11) Def: Hospitalization Grp1: 869 events Grp2: 461 events HR: 0.77 (CI: 0.69 to 0.87)	
Hsiao, 2009[173]	Cohort	Grp1: Rosiglitazone NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52) Grp2: 22 (4.51) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71) Grp2: 44 (8.89)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 5 (1.03)
Pantalone, 2009[174]	Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 0.81 (CI: 0.52 to 1.27) p: 0.36		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.15 (CI: 0.87 to 1.53) p: 0.32	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Thiazolidinedione versus sulfonylurea						
Hsiao, 2009[173]	Cohort	Grp1: Pioglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 22 (4.51) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 44 (8.89) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 2 (0.41) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 5 (1.03) Grp2: 940 (0.99)
Hsiao, 2009[173]	Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 940 (0.99)
Brownstein, 2010[182]	Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea			Def: Hospitalization for acute MI Grp1: HR: 1.3 (CI: 1.0-1.7) Grp2: ref	
Tzoulaki, 2009[174]	Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea NS	Grp1: 34 (<1) Grp2: 1379 (2)		Def: Incident MI Grp1: 9 (<1) Grp2: 365 (1)	
Pantalone, 2009[174]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.73 (CI: 0.51 to 1.02) p: 0.08 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.90 (CI: 0.71 to 1.14) p: 0.41 Grp2: ref	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pantalone, 2009[174]	Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.59 (CI: 0.43 to 0.81) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 1.04 (CI: 0.86 to 1.26) p: 0.69 Grp2: ref	
McAfee, 2007[181]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: 152 (2) Grp2: 191 (2)	
McAfee, 2007[181]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 70 (1) Grp2: 94 (1)	
Hanefeld, 2007[100]	RCT	Grp1: Rosiglitazone Fixed Start: 4 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hanefeld, 2007[100]	RCT	Grp1: Rosiglitazone Fixed Start: 8 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			
Kahn, 2006[38]	RCT	Grp1: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: 140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: 34 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Non-fatal MI Grp1: 25 (1.7) Grp2: 15 (1)	Def: Stroke not defined Grp1: 16 (1.1) Grp2: 17 (1.2)
Jain, 2006[101]	RCT	Grp1: Pioglitazone Varied, glucose: 69-141 mg/dL Start: 15 mg, Median: 45 mg, Max: 45 mg D: 12 wks Grp2: Glyburide Varied, glucose: 69-141 mg/dL Start: 5 mg, Median: 10 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 2 (0.8)		Def: Non-fatal MI Grp1: 2 (0.8) Grp2: 2 (0.8)	
St John Sutton, 2002[149]	RCT	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Max: 20 mg			Def: CVD morbidity/heart disease Grp1: 9 (9) Grp2: 5 (5)	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Sulfonylurea versus meglitinide						
Marbury, 1999[117]	RCT	Grp1: Glyburide Varied Start: 2.5 mg, Max: 4 mg bid Grp2: Repaglinide Varied Start: 0.5 mg, Max: 12 mg	Grp1: 1 (1) Grp2: 3 (1)		Def: CVD morbidity/unclear CHD Grp1: 4 (2) Grp2: 19 (5)	
Wolffenbuttel, 1999[116]	RCT	Grp1: Glyburide Varied Start: 1.75 mg, Max: 10.5 mg bid Grp2: Repaglinide Varied Start: 1.5 mg, Max: 12 mg			Def: Cardiac events NOS Authors stated similar frequencies in each group but no data given	
Sulfonylurea versus GLP-1 agonists						
Seino, 2010[121]	RCT	Grp1: Glibenclamide Varied, prespecified target dose Start: 1.25 mg, Max: 2.5 mg D: 4 weeks Grp2: Liraglutide Varied, prespecified target dose Start: 0.3 mg, Max: 0.9 mg D: 2 weeks	Grp1: 0 (0) Grp2: 1 (<1)		Grp1: 9 (6.8) Grp2: 9 (3.4)	
Metformin + thiazolidinedione versus metformin + sulfonylurea						
Hsiao, 2009[173]	Cohort	Grp1: Metformin + rosiglitazone NS Grp2: Metformin + sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 103 (4.26) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 25 (1.03) Grp2: 11435 (4.27)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 12 (0.49) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 11 (0.45) Grp2: 1637 (0.61)

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
McAfee, 2007[181]	Cohort	Grp1: Metformin + rosiglitazone NR Grp2: Metformin + sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD-9 and CPT codes Grp1: 24 (2) HR: 0.61 (0.37 to 1.03) Grp2: 36 (3)	
McAfee, 2007[181]	Cohort	Grp1: Metformin + rosiglitazone NR Grp2: Metformin + sulfonylurea NR			Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 6 (<1) Grp2: 17 (1)	
Hamann, 2008[123]	RCT	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 4 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 5 mg D: 12 wks	Grp1: 2 (1) Grp2: 2 (1)			
Bakris, 2006[125]	RCT	Grp1: Metformin + rosiglitazone Varied, NS; Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 4mg D: 3 wks Grp2: Metformin + glyburide Varied, NS; Varied, glucose: ≤ 6.6mmol/L Unclear; Start: 5 mg D: 3 wks	Grp1: 1 (1) Grp2: 0 (0)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin + thiazolidinediones versus metformin + DPP-4 inhibitors						
Rigby, 2009[130]	RCT	Grp1: Metformin + rosiglitazone Fixed NS; Mean: 4 mg Grp2: Metformin + sitagliptin NS: Mean: 100 mg			Def: Transient ischemic cerebrovascular accident Grp1: 1 (2) Grp2: 0 (0)	
Metformin + thiazolidinediones versus metformin + meglitinides						
Raskin, 2009[131]	RCT	Grp1: Metformin + rosiglitazone Varied, prespecified target dose Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 8 mg D: 4 wks Grp2: Metformin + repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 10 mg D: 4 wks	Grp1: 0 (0) Grp2: 1 (1)	Def: Sudden cardiac death Grp1: 0 (0) Grp2: 1 (1)		
Metformin + thiazolidinedione versus thiazolidinedione + sulfonylurea						
McAfee, 2007[181]	Cohort	Grp1: Metformin + rosiglitazone NR Grp2: Rosiglitazone + sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD -9 and CPT codes Grp1: 24 (2) HR: 0.61 (0.37 to 1.03) Grp2: 6 (<1)	
McAfee, 2007[181]	Cohort	Grp1: Metformin + rosiglitazone NR Grp2: Rosiglitazone + sulfonylurea NR			Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 6 (<1) Grp2: 21 (2)	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Rosak, 2006[183]	RCT	Grp1: Metformin + rosiglitazone Varied Grp2: Rosiglitazone + sulfonylurea Varied NS; Start: 4 mg, Max: 8 mg			Def: Not defined Grp1: 0.08/100 patient-years (0.04) Grp2: 0.22/100 patient-years (0.11)	Def: Not defined Grp1: 0.03/100 patient years (0.36) Grp2: 0.01/100 patient-years (0.18)
Metformin + sulfonylurea versus metformin + meglitinide						
Monami, 2008[180]	Cohort	Grp1: Metformin + sulfonylurea NR Grp2: Metformin + repaglinide NR	Grp1: 35/6344 person-months Grp2: 5/2013 person-months			
Schwarz, 2008[152]	RCT	Grp1: Metformin + glyburide Varied, glucose: 6.7mmol/l Start: 500 mg, Max: 2000 mg D: 12 wks Grp2: Metformin + nateglinide Varied, glucose: 6.7mmol/l Start: 500 mg; Max: 2000 mg D: 12 wks	Grp1: 1 (3) Grp2: 0 (0)			
Gerich, 2005[136]	RCT	Grp1: Metformin + glyburide Varied, glucose: 6.7 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1105mg D: 12 wks Grp2: Metformin + nateglinide Varied, glucose: 6.7 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1459 mg D: 12 wks	Grp1: 1 (1) Grp2: 1 (1)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin + sulfonylurea versus metformin + DPP-IV inhibitors						
Seck, 2010[134]	RCT	Grp1: Metformin + sitagliptin Fixed Grp2: Metformin + glipizide Fixed; Varied, glucose > 110 mg/dl NR; Start: 5 mg, Max: 20 mg, Mean: 9.2 mg	Grp1: 8 (1.4) Grp2: 1 (0.2)	Def: Sudden cardiac death Grp1: 2 (<1) Grp2: 0 (0)		
Nauck, 2007[133]	RCT	Grp1: Metformin + glipizide NR Grp2: Metformin + sitagliptin NR	Grp1: 2 (0.3) Grp2: 1 (0.2)	Def: Fatal MI Grp1: 1 (0.2) Grp2: 0 (0)		
Metformin + sulfonylurea versus metformin + GLP-1 agonists						
Pratley, 2010[143]	RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.8 mg		Def: Fatal cardiac arrest Grp1: 1 (<1) Grp2: 0 (0)		
Pratley, 2010[143]	RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.2 mg		Def: Fatal cardiac arrest Grp1: 1 (<1) Grp2: 0 (0)		
Metformin + sulfonylurea versus thiazolidinedione + sulfonylurea						
McAfee, 2007[181]	Cohort	Grp1: Metformin + sulfonylurea NR Grp2: Rosiglitazone + sulfonylurea NR			Def: Inpatient MI and coronary revascularization using ICD -9 and CPT codes Grp1: 36/1852 person-years Grp2: 39/1474 person-years	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
McAfee, 2007[181]	Cohort	Grp1: Metformin + sulfonylurea NR Grp2: Rosiglitazone + sulfonylurea NR			Def: MI based on ICD -9 diagnosis codes (could be fatal or nonfatal MI since not specified but likely nonfatal mostly) Grp1: 17/1865 person-years Grp2: 21/1495 person-years	
Hanefeld, 2004[140]	RCT	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	Grp1: 2 (1) Grp2: 1 (<1)		Def: Coronary heart diseases/cardiac disorders Grp1: (3.1) Grp2: (4.1)	
van der Meer, 2009[141]	RCT	Grp1: Metformin + glimepiride Fixed Start: 1000 mg, Max: 2000 mg; Start: 15 mg, Max: 30 mg D: 8 wks Grp2: Pioglitazone + glimepiride Varied Not specified D: 8 weeks		Def: CVD event Grp1: 0 (0) Grp2: 0 (0)		

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin + sulfonylurea versus metformin + premixed insulin						
Kvapil, 2006[138]	RCT	Grp1: Metformin + sulfonylurea Fixed; Varied Start: 1660 mg; Start: 1.75 mg, Max: 10.5, Mean: 6.58 Grp2: Metformin + aspart 70/30 Fixed; Varied Start: 1660 mg; Start: 0.2 U/kg BID, Mean: 0.3 BID	Grp1: 0 (0) Grp2: 1	Def: Fatal MI Grp1: 0 (0) Grp2: 1		
Malone, 2003[137]	RCT	Grp1: Metformin + glibenclamide Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; 16 wks Grp2: Metformin + lispro 75/25 Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg; Mean: 0.19 U/kg in am and 0.14 U/kg in evening D: 4 wks; 16 wks	Grp1: 0 (0) Grp2: 1 (<1)			

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Metformin + sulfonylureas versus metformin or sulfonylureas + thiazolidinediones						
Home, 2009[16]	RCT	Grp1: Metformin + sulfonylurea Varied, HgbA1c: ≤7.0% Max: 2550 mg; Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks Grp2: Rosiglitazone + metformin or sulfonylurea Varied, HgbA1c: ≤7.0% Start: 4 mg, Max: 8 mg; Metformin, Max: 2550 mg, Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks	Grp1: 157 Grp2: 136 HR: 0.86 (CI: 0.68 to 1.08), p: 0.19	Grp1: 71 Grp2: 60 HR: 0.84 (CI: 0.59 to 1·18), p: 0.32	Def: Fatal and non-fatal MI Grp1: 56 Grp2: 64 HR: 1.14 (CI: 0.80 to 1·63), p: 0.47	Def: Fatal and nonfatal stroke Grp1: 63 Grp2: 46 HR: 0.72 (CI: 0.49 to 1·06), p: 0.10
Metformin + basal insulin versus metformin + premixed insulin						
Malone, 2005[165]	RCT	Grp1: Metformin + lispro 75/25 Varied, premeal glucose 90-126 mg/dL; 2-hr postprandial 144-180 mg/dL Start: 1500 mg, Max: 2550 mg, Mean: 2146 mg; Mean: 0.42 U/kg BID D: 4 wks, 16 wks Grp2: Metformin + glargine Varied, pre-meal glucose 90-126 mg/dL Start: 1500 mg, Max: 2500 mg, Mean: 2146 mg; Mean: 0.36 U/Kg QD D: 4 wks, 16 wks	Grp1: 1 (2) Grp2: 1 (2)	Grp1: 1 (2) Grp2: 0 (0)		

bid= twice; CHD= coronary heart disease; CPT=current procedural terminology; CVD=cardiovascular disease; Def=definition; D=duration of titration; g = grams per day; Grp= group; HbA1c = hemoglobin A1c; HR= hazard ratio; ICD=International Classification of Diseases; ID= identification; IR= incidence ratio; Met= metformin; mg = milligram; MI= myocardial infarction; mmol/l = millimoles/liter; NOS= not otherwise specified; NR= not reported; OR= odds ratio; RCT= randomized controlled trial; RR=risk ratio; SU= sulfonylurea; tid = thrice; U/kg = unit per kilogram; wks = weeks

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2)

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Metformin versus thiazolidinedione				
Schernthaner, 2004[52]	RCT		Def: urinary albumin/creatinine ratio	
		Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg	Grp1: 1%	
		Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp2: 19%, p: 0.002 vs. Grp2	
Metformin versus sulfonylurea				
Amador-Licona, 2000[66]	RCT		Def: change in glomerular filtration rate	
		Grp1: Metformin Varied Start: 850mg, Max: NR	Grp1: B: 138 mL/min F: 134 mL/min, p=0.46 vs. baseline	
		Grp2: Glibenclamide Varied Start: 5mg, Max: NR	Grp2: B: 136 mL/min F: 151 mL/min, p=0.04 vs. baseline	
Amador-Licona, 2000[66]	RCT		Def: change in microalbumin (mg/d)	
		Grp1: Metformin Varied Start: 850 mg, Max: NR	Grp1: B: 74 mg/d F: 49 mg/d, p=0.008 vs. baseline	
		Grp2: Glibenclamide Varied Start: 5 mg, Max: NR	Grp2: B: 83 mg/d F: 102 mg/d, p=0.09 vs. baseline	
Metformin versus metformin + thiazolidinedione				
Gomez-Perez, 2002[88]	RCT			Def: Unclear neuropathy
		Grp1: Metformin Fixed Start: 2500 mg		Grp1: 1
		Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid		Grp2: 0 (0)

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Gomez-Perez, 2002[88]	RCT			Def: Unclear neuropathy
		Grp1: Metformin Fixed Start: 2500 mg		Grp1: 1
		Grp2: Metformin + rosiglitazone Fixed Start: 2500mg; Start: 4mg bid		Grp2: 0 (0)
Metformin versus metformin + DPP-IV inhibitors				
Raz, 2008[93]	RCT			Def: NR
		Grp1: Metformin Fixed NR		Grp1: 2 (2.1)
		Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg		Grp2: 4 (4.2)
Thiazolidinedione versus sulfonylurea				
Nakamura, 2006[108]	RCT		Def: Urine albumin excretion (microgram/min), mean (SD)	
		Grp1: Pioglitazone Fixed Mean: 30 mg	Grp1: Baseline: 142.5 (46.5); 12 mos: 40.5 (20.5) p<0.001	
		Grp2: Glibenclamide Fixed Mean: 5 mg	Grp2: Baseline: 136.5 (40.8); 12 mos: 146.0 (48.8)	
			Grp1-Grp2: -111.5	
Nakamura, 2004[102]	RCT		Def: Urine albumin excretion (microgram/min), mean (SD)	
		Grp1: Pioglitazone Fixed Start: 30 mg	Grp1: 6 mos: 86.5 (24.5); 12 mos: 44.5 (16.4)	
		Grp2: Glibenclamide Fixed Start: 5 mg	Grp2: 6 mos: 142.5 (42.5); 12 mos: 146.8 (38.5)	
			Grp1-Grp2: 6 mos, p: <0.05; 12 mos: <0.01	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Agarwal, 2005[184]	RCT		Def: Proteinuria	
		Grp1: Pioglitazone Varied, glucose: 140 mg/dL, HgbA1c: 8% Start: 15 mg, Mean: 33 mg, Max: 41 mg D: 3.8 mos	Grp1: % mean reduction: 7.2, CI: -24.9 - 10.6	
		Grp2: Glipizide Varied, glucose: 140 mg/dL, HgbA1c: 8% Start: 5 mg, Mean: 16 mg, Max: 19 mg D: 3.7 mos	Grp2: % mean increase: 6.1, CI: -11.7-23.8	
			Grp1-Grp2: % reduction: 13.2, CI: -38.4 -11.9, p: 0.294	
Bakris, 2003[104]	RCT		Def: n (%) with normal albuminuria at baseline who progressed to microalbuminuria by study end	
		Grp1: Rosiglitazone Fixed Start: 4 mg bid	Grp1: 3 (7)	
		Grp2: Glyburide Varied Start: NR, Max: 20 mg	Grp2: 5 (10.6)	
Bakris, 2003[104]	RCT		Def: albumin/creatinine ratio	
		Grp1: Rosiglitazone Fixed Start: 4 mg bid	Grp1: (-45 to -4) p: NSG vs. Grp2	
		Grp2: Glyburide Varied Start: NR, Max: 20 mg	Grp2: (-22 to 4)	
Nakamura, 2000[103]	RCT		Def: urinary albumin excretion	
		Grp1: Pioglitazone Fixed Start: 30 mg bid	Grp1: B: 142.8 ug/min F: 48.4 ug/min, p: < 0.05	
		Grp2: Glibenclamide Fixed Start: 5 mg	Grp2: B: NR F: NR, p: > 0.05	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Thiazolidinedione versus meglitinide				
Nakamura, 2006[108]	RCT		Def: Urine albumin excretion (microgram/min), mean (SD)	
		Grp1: Pioglitazone Fixed Mean: 30 mg	Grp1: Baseline: 142.5 (46.5); 12 mos: 40.5 (20.5) p<0.001	
		Grp2: Nateglinide Fixed Mean: 270 mg	Grp2: Baseline: 134.6 (42.8); 12 mos: 140.8 (44.4)	
			Grp1-Grp2: -108.2	
Metformin + thiazolidinedione versus metformin + sulfonylurea				
Bakris, 2006[125]	RCT		Def: % change in UACR (urine albumin: creatinine ratio >=30), Mean (SD)	
		Grp1: Metformin + rosiglitazone Varied; Varied, glucose: ≤ 6.6 mmol/L NS; Start: 4mg D: 3 wks	Grp1: -22.7 (15), p: <0.01	
		Grp2: Metformin + Glyburide Varied; Varied, glucose: ≤6.6 NR; Start: 5 mg D: 3 wks	Grp2: -5.5 (14.5), p: NSG	
			Grp1-Grp2: -15.5%, p: 0.07	
Comaschi, 2007[129]	RCT	Grp1: Metformin + pioglitazone Varied, NR Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks		Grp1: 1
		Grp2: Metformin + glibenclamide Varied, HgbA1c: 7.50% Start: 400mg, Max: 3g; Start: 2.5mg D: 22 wks		Grp2: 0 (0)
Metformin + sulfonylurea versus thiazolidinedione + sulfonylurea				
Hanefeld, 2004[140]	RCT		Def: albumin/ creatinine ratio	
		Grp1: Metformin + unspecified sulfonylurea + placebo Varied Start: 850 mg, Max: 2550 mg; NR	Grp1:	
		Grp2: Pioglitazone + unspecified sulfonylurea + placebo Varied Start: 15 mg, Max: 45 mg; NR	Grp2: CI: 0.73-0.97, p: 0.017 vs. Grp1	

Table 8. Comparative effectiveness of diabetes medications on long-term clinical outcomes (KQ2) (continued)

Author, year	Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Hanefeld, 2004[140]	RCT		Def: microalbuminuria resolved	
		Grp1: Metformin + unspecified sulfonylurea + placebo Varied Start: 850 mg, Max: 2550 mg; NR	Grp1: 7.7%	
		Grp2: Pioglitazone + unspecified sulfonylurea + placebo Varied Start: 15 mg, Max: 45 mg; NR	Grp2: 10.2%	

B=Baseline; bid=twice; CI= Confidence interval; Def=Definition; D= Duration of titration; F=Final; Grp=Group; HgbA1c = hemoglobin A1c; mos=Months; mg = milligram; mL/min = milliliter per minute; mmol/l = millimoles/liter; NR=Not reported; NSG=Not significant; RCT = Randomized controlled trial; ug/min= micrograms per minute; UACR= Urine albumin: creatinine ratio; wks=weeks

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Hypoglycemia

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. TZD							
1 trial	2910	Medium	Unknown	Direct	Precise	Small, No favorite	Moderate
Met vs. SU							
11 RCTs	6679	Medium	Consistent	Direct	Precise	Large, Favors metformin	High
Met vs. DPP-4 Inhibitor							
3 RCTs	1918	Medium	Consistent	Direct	Precise	Small, No favorite	High
Met vs. Meg							
5 RCTs	914	Medium	Consistent	Direct	Imprecise	Small, Favors Met	Moderate
Met vs. Met + TZD							
8 RCTs	3073	Medium	Consistent	Direct	Precise	Small, Favors Met alone	Moderate
Met vs. Met + SU							
9 RCTs	2141	Medium	Consistent	Direct	Imprecise	Large, Favors Met alone	Moderate
Met vs. Met + DPP-4 Inhibitor							
4 RCTs (in 5 reports)	1448	High	Consistent	Direct	Precise	Small, No favorite	Moderate
Met vs. Met + Meg							
3 RCTs	559	Medium	Inconsistent	Direct	Imprecise	Large, Favors Met alone	Low
Rosi vs. Pio							
1 obs.	202	High	Unknown	Direct	Imprecise	Small, Favors Rosi	Low
TZD vs. SU							
8 RCTs, 1 obs	10680	Medium	Consistent	Direct	Precise	Large, Favors TZD	High
TZD vs. Meg							
2 RCTs	248	High	Consistent	Direct	Precise	Small, Favors TZD	Low
SU vs. DPP-4 Inhibitor							
1 RCT	245	Low	Unknown	Direct	Precise	Large, Favors DPP-4 inhibitor	Moderate
SU vs. Meg							
8 RCTs	1846	Medium	Consistent	Direct	Precise	Small Favors Meg	Low
SU vs. GLP-1 Agonist							
3 RCTs	1310	Low	Consistent	Direct	Precise	Medium, Favors liraglutide	High
Met + TZD vs. Met + Another Agent (mostly SU)							
6 RCTs, 1 obs	2543	Medium	Consistent	Direct	Precise	Large, Favors Met + TZD	High
Met + TZD vs. TZD + SU							
1 obs	22808	High	Unknown	Direct	Precise	Large, Favors Met + TZD	Low
Met + SU vs. Met + Another Agent							
9 RCTs	3409	Low	Inconsistent	Direct	Imprecise	Small, Unclear, Depends on “other agent”	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Hypoglycemia

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met + SU vs. TZD + SU							
1 RCT	441	High	Unknown	Direct	Precise	Small, Favors TZD + SU	Low
Met + GLP-1 Agonist vs. Met + Basal Insulin							
1 RCT	69	Low	Unknown	Direct	Imprecise	Large, Favors Met + exenatide`	Low
Met + Basal Insulin vs. Met + Another Insulin							
5 RCTs	826	Medium	Consistent	Direct	Precise	Medium, Favors Met + basal insulin	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; obs = observational study; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Liver injury

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and direction of effect	
Met vs. TZD							
1 RCt 1 Obs	1194	Low	Consistent	Direct	Precise	Small, no favorite	Moderate
Met vs. SU							
1 RCT	1194	Low	Unknown	Direct	Imprecise	Unclear.	Low
Rosi vs. Pio							
1 Obs	3694	Low	Unknown	Direct	Precise	Unclear	Low
TZD vs. SU							
1 Obs, 2 RCT	7764	Moderate	Consistent	Direct	Precise	Small, no favorite	High
Met + TZD vs. Met + Another agent							
1 RCT	95	Low	Unknown	Direct	Imprecise	No difference	Low
Met + SU vs. TZD + SU							
2 RCT	837	High	Unknown	Direct	Precise	No difference	Low

Met = metformin; obs = observational study; Pio = pioglitazone; RCT = randomized controlled trial; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Congestive heart failure

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
3 RCTS 4 Obs	178691	Medium	Inconsistent	Direct	Imprecise	Small. No favorite	Moderate
Met vs. SU							
5 Obs	189610	Medium	Consistent	Direct	Precise	Small. Increase risk with SU	Moderate
Rosi vs. Pio							
4 Obs	45114	High	Unknown	Direct	Imprecise	Unclear.	Low
TZD vs. SU							
4 RCTs 5 Obs	274880	Medium	Consistent	Direct	Imprecise	Small. Increase risk with TZD	Moderate
Met + TZD vs. TZD + SU							
1 Obs	12193	High	Unknown	Direct	Imprecise	Small. Increase risk with TZD + SU combination	Low
Met + SU vs. TZD + other							
1 RCT	2200	Low	Unknown	Direct	Imprecise	Favors SU + Met	Low
Met + Basal Insulin vs. Met + Another Insulin							
1 RCT	67	Low	Inconsistent	Direct	Imprecise	Unclear	Low

Met = metformin; obs = observational study; Pio = pioglitazone; RCT = randomized controlled trial; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Lactic acidosis

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. SU							
2 RCTs	160	Low	Consistent	Direct	Imprecise	Weak; no increased risk with Metformin	Moderate
Met vs. Met +SU							
2 RCTs	163	Low	Consistent	Direct	Imprecise	Weak; no favorite	Moderate

Met = metformin; RCT = randomized controlled trial; SU = sulfonylurea. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cancer

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. SU							
1 Obs	38860	High	Unknown	Direct	Imprecise	Weak; favors Met	Low
Met vs. Meg							
1 RCT	96	Low	Unknown	Direct	Imprecise	Weak; favors Meg	Low
Met vs. Met + SU							
1 Obs	45303	High	Unknown	Direct	Imprecise	Weak; favors Met	Low
Met vs. Met +DPP-4 Inhibitor							
1 RCT	190	Low	Unknown	Direct	Imprecise	Weak; favors Met + DPP-4 inhibitor	Low
TZD vs. SU							
1 RCT	502	Low	Unknown	Direct	Imprecise	Weak; favors TZDs	Low

DPP-4 = dipeptidyl peptidase-4; Meg = meglitinides; Met = metformin; obs = observational study; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Fractures

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
1 RCT 1 Obs	79533	Medium	Unknown	Direct	Precise	Small. Favors metformin	High
Met vs. SU							
2 RCTs 1 Obs	135258	Medium	Consistent	Direct	Imprecise	Unclear	Low
Met vs. Met+ TZD							
1 RCT 2 Obs	78275	Medium	Unknown	Direct	Imprecise	Small, favors metformin	Low
Met vs. Met + SU							
1 RCT	59	Medium	Unknown	Direct	Imprecise	Unclear	Low
Met vs. Met + DPP-4 Inhibitor							
1 RCT	190	Medium	Unknown	Direct	Imprecise	Unclear	Low
TZD vs. SU							
2 RCT 1 Obs	87738	Medium	Unknown	Direct	Imprecise	Small, favors SU	High
Met + SU vs. TZD + Another agent							
1 RCT	3325	Low	Unknown	Direct	Precise	Small. Favors metformin + SU	High

DPP-4 = dipeptidyl peptidase-4; Met = metformin; obs = observational study; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Pancreatitis

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. Met +SU							
1 RCT	366	Low	Unknown	Direct	Imprecise	Small, favors metformin	Low
DPP-4 Inhibitors vs. GLP-1 Agonists							
1 RCT	665	Low	Unknown	Direct	Imprecise	Unclear, no favorite	Low
Sulfonylureas vs. GLP-1 Agonists							
2 RCT	1156	Low	Unknown	Direct	Imprecise	Small, favors SU	Low

DPP-4 = dipeptidyl peptidase-4; GLP-1 agonist = glucagon-like peptide-1 agonist; Met = metformin; RCT = randomized controlled trial; SU = sulfonylurea. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Cholecystitis

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
1 RCT	205	Low	Unknown	Direct	Imprecise	Small, favors metformin	Low
Met vs. Met + TZD							
1 RCT	569	Low	Unknown	Direct	Imprecise	Small, favors TZD	Low
TZD vs. SU							
1 RCT	2120	Low	Unknown	Direct	Imprecise	Small, no favorite	Low

Met = metformin; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Macular edema

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met + TZD vs. Met + Another agent							
1 RCT	561	Low	Unknown	Direct	Imprecise	Small, increased risk with metformin + TZD	Low

Met = metformin; RCT = randomized controlled trial; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Gastrointestinal effects

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met vs. TZD							
5-RCTs	5021	Low	Consistent	Direct	Precise	Large; Favors TZD	High
Met vs. SU							
11 RCTs, 1 Obs.	10666	Medium	Consistent	Direct	Precise	Large; Favors SU	Moderate
Met vs. DPP-4 Inhibitor							
2 RCTs	1028	High	Unknown	Direct	Imprecise	Large; Favors Sitagliptin	Low
Met vs. Meg							
4 RCTs	776	Medium	Inconsistent	Direct	Imprecise	Small; Unclear for “any GI effect”; favors MEG for diarrhea	Low
Met vs. Met + TZD							
8 RCTs	2977	Medium	Consistent	Direct	Imprecise	Small; Unclear for “any GI effect”; favors Met+TZD for diarrhea	Moderate
Met vs. Met + SU							
10 RCTs	2786	Medium	Consistent	Direct	Imprecise	Small; Unclear favorite; favors combination arm when combination dose of metformin lower	Moderate
Met vs. Met + DPP-4 Inhibitor							
6 RCTs	3355	Medium	Consistent	Direct	Precise	Small; Unclear favorite	Low
Met vs. Met + Meg							
1 RCT	193	Low	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
TZD vs. SU							
4 RCTs	6083	Low	Consistent	Direct	Precise	Small; Unclear favorite	High
TZD vs. Meg							
1 RCT	123	Medium	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
SU vs. GLP-1 Agonist							
						Favors SU	Low
Met + TZD vs. Met + SU							
4 RCTs	1212	Low	Inconsistent	Direct	Imprecise	Small; Favors neither	Low
Met + TZD vs. Met + DPP-4 Inhibitor							
1 RCT	181	Low	Unknown	Direct	Imprecise	Small; Favors neither	Low
Met + TZD vs. Met + GLP-1 Agonist							
						Favors met + TZD	Low

Table 9. Number of studies, strength of evidence domains, magnitude of effect, and strength of evidence. Outcome: Gastrointestinal effects (continued)

Number of Studies	Total N	Domains Pertaining to Strength of Evidence					Strength of Evidence
		Risk of Bias Design/ Quality	Consistency	Directness*	Precision	Magnitude and Direction of Effect	
Met + SU vs. Met + DPP-4 Inhibitor							
1 RCT	1172	Low	Unknown	Direct	Imprecise	Small; Favors neither	Low
Met + SU vs. Met + MEG							
1 RCT	66	Low	Unknown	Direct	Imprecise	Small; Unclear favorite for "any GI side effects"; Favors Met + MEG for abdominal dyspepsia	Low
Met + basal insulin vs. Met + another insulin							
1 RCT	317	Low	Unknown	Direct	Imprecise	Small; Unclear favorite	Low
Met + SU vs. TZD + SU							
2 RCTs	1591	Medium	Consistent	Direct	Precise	Small; Favors TZD combination arm	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinides; Met = metformin; NA = not applicable; Nateg = nateglinide; obs = observational study; Pio = pioglitazone; RCT = randomized controlled trial; Repag = repaglinide; Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione. All other comparisons were graded as insufficient since there were no studies of those comparisons. 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. N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2010[121] Japan	RCT	Neither year reported 24 weeks	Yes	< 6 months	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 weeks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or reccurent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 weeks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Derosa, 2010[44] Italy	RCT	Neither year reported 12 months	No run-in period	< 6 months	No	128/128	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Defronzo, 2010[132] United States	RCT	Start year: 2006 End year: 2008 20 weeks	None	< 6 months	Yes	NR/137 NR	Age <18 or >75 years, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 weeks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other antidiabetic medication (other than metformin)
Aschner, 2010[77] Multicontinent	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	2068/1050 NR	Age <18 and > 78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 mg/dL or >250 mg/dL, triglycerides >600 mg/dL, CK > 2 times normal upper limit
Seck, 2010[134] NR	RCT	Neither year reported 2 years	Run-in period but number of participants excluded was NR	< 6 months	Yes	2141/1172 NR	Age <17 years or >78 years

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Komajda, 2010[292] Multicontinent	RCT	Start year: 2001 End year: 2003 5.5 years	None	NR	Yes	NR/4447	Age <40 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c ≤7% or > 9%, BMI ≤25 kg/m^2, planned cardiovascular intervention, uncontrolled hypertension, no Type 2 DM, current use of other anti-DM medications, hospitalization within last 3 months for CVD event, heart failure
Pratley, 2010[143] Multi-continent, Europe, USA and Canada	RCT	Start year: 2008 End year: 2009 26 months	None	>= 6 months	Yes	1302/665	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7.5% or >10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Pantalone, 2009[174] United States	Prospective or retrospective cohort	Start year: 1998 End year: 2006 8 years	NA	NA	Yes	NR/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Currie, 2009[173] Taiwan	Prospective or retrospective cohort	Start year: 2000 End year: 2005 6 years	NA	NA	NR	1432850/473483 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period
Currie, 2009[212] United Kingdom	Prospective or retrospective cohort	Start year: 2000 5 years	NA	NA	No	170000/62809 Outpatient: primary care, General Practices	Age <40 years at diabetes onset, <6 sequential prescriptions of ODM, secondary causes of DM
Tzoulaki, 2009[171] United Kingdom	Prospective or retrospective cohort	Start year: 1990 End year: 2005 Mean 7.1 years	NA	NA	No	NR/91,521 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age < 35 or > 90 years, no DM, multiple or missing dates of death, missing information, no treatment with medications

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Perez, 2009[56] United States, Multinational Europe	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	1436/600 NR	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglyceride level 500, if they were NOT discontinued metformin and TZD therapy due to lack of efficacy
Juurlink, 2009[210] Canada	Prospective or retrospective cohort	Start year: 2002 End year: 2008 3 years	NA	NA	No	NA/ 39736 Outpatient: primary care	Age <66 years, patients on rosiglitazone or pioglitazone before the index date, patients on insulin before the index date
Dormuth, 2009[215] Canada	Prospective or retrospective cohort	Start year: 1998 End year: 2007 11 years	NA	NR	No	127581/ 84339 Community	Had received insulin or other ODMs besides metformin, SU or TZD, gestational DM, fractures, admitted to long term facility

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009[130] United States, Multicontinent	RCT	Start year: 2007 End year: 2008	NA	< 6 months	Yes	169/356 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c <7% (6.5% if on metformin combination therapy), BMI> 40 kg/m^2, LDL<50mg/dl or TG ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 weeks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Mancini, 2009[214] Italy	Cross-sectional study	Neither year reported NR	NA	NA	Yes	65/65 Outpatient: primary care, Outpatient: subspecialty care setting	History of significant trauma, neoplastic disorder or diseases affecting the bone, prolonged immobilization, use of anti-osteoporotic drug
Tolman, 2009[150] United States	RCT	Start year: 2000 End year: 2005 3 years	None	< 6 months	Yes	NR/2120 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7%, BMI <20kg/m^2 or >48 kg/m^2, not taking metformin and/or SU, history of ketoacidosis, history of TZD use other than troglitazone before 4/00
Dimic, 2009[199] Serbia	Non-randomized trial	Neither year reported 12 weeks	None	< 6 months	NR	NR/60 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c <7.5%, glucocorticoids

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jadzinsky, 2009[78] Multi-continent	RCT	Start year: 2006 End year: 2007 24 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	2936/1394 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c< 8% >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
DeFronzo, 2009[95] NR	RCT	Neither year reported 24 weeks	Yes	< 6 months	Yes	1462/743 NR	Age >18 and <77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BM >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bunck, 2009[144] Sweden, Finland, Netherlands	RCT	Start year: 2004 End year: 2007 56 weeks	None	< 6 months	Yes	150/69 NR	Age <30 and >75 years, HbA1c<6.5% or >9.5%, BMI <25 kg/m^2 or BMI >40 kg/m^2, metformin treatment not at a stable dose for at least 2 months, no other blood glucose lowering medications allowed in 3 months prior to study, no changes in other medications known to affect B cell function (ACEI, B Blockers)
Garber, 2009[122] United States, Mexico	RCT	Start year: 2006 End year: 2007 52 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/746 NR	Age <18 or >80 years, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of ODM monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Derosa, 2009[46] Italy	RCT	Neither year reported 15 months	Fewer than 10% of participants were excluded during run-in	< 6 months	NR	271/252 Outpatient: primary care, computerized clinic registry	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 6.5%, BMI <25 kg/m2 or >30 kg/m2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Williams-Herman, 2009[76] NR	RCT	Neither year reported 54 weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 years, HbA1c ≤7.5% or ≥11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (≥75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM
Kaku, 2009[84] Japan	RCT	Start year: 2005 40 weeks	Yes	< 6 months	Yes	NR/236 NR	Age ≤20 or ≥65 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, gastrointestinal, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre coma within the preceding 26 weeks, if on any medications that might affect glycemic control, drug or alcohol dependency
Nauck, 2009[92] Multi-continent	RCT	Neither year reported 26 weeks	Run-in period but number of participants excluded was NR	>= 6 months	Yes	1662/1087 NR	Age <18 or >80 years, HbA1c > 11% if on monotherapy; 10% if on combination therapy (both greater than 3 months), HbA1c < 7%, BMI >40 kg/m^2, used insulin in last 3 months

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Raskin, 2009[131] NR	RCT	Neither year reported 26 weeks	No run-in period	< 6 months	Yes	1093/383 Outpatient: primary care	Age <18 years, pregnant, nursing, currently not under monotherapy at least 2 months or dual therapy, FBG >260 mg/dL, any disease of abnormality as judged by the investigator, treatment with the investigational drug for 4 weeks, allergy to study drugs or related compounds, history of hypoglycemia unawareness or recurrent severe hyperglycemia
van der Meer, 2009[141] Netherlands	RCT	Neither year reported 24 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	173/80 NR	Age <45 or >65 years, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mm Hg, DBP <85 mm Hg, prior TZD or insulin use
Scott, 2008[85] Multi-continent	RCT	Neither year reported 18 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 weeks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Raz, 2008[93] Multicontinent	RCT	Neither year reported 30 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	544/190 NR	Age <18 or >78 years, HbA1c <8% after run-in, HbA1c >11% after run-in, BMI <20 or >43 kg/m^2, pregnant, nursing, insulin within 8 weeks prior to screening, PPAR-G or incretin mimetics within 12 weeks prior to screening, Type 1 DM, FPG <7.2 or >15.6 mmol/L consistently during run-in, no Type 2 DM

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[123] Multinational Europe, Mexico	RCT	Neither year reported 52 weeks	Yes	< 6 months	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 weeks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/ dl for men and < 10.0 g/ dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg
Seufert, 2008[142] Multicontinent	randomized but does not no control; comparative study	Neither year reported 104 weeks	No run-in period	NR	Yes	NR/1269 NR	Age < 35 or >75 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c < 7.5% or > 11%, pregnant, nursing, fasting c-peptide >1.5, ketoacidosis, symptomatic heart failure, acute malabsorption, chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Schwarz, 2008[152] US	RCT	Neither year reported 104 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	75/69 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0% or >11.0%, BMI <22 or >45 kg/m^2, FBG >270 mg/dL, history of lactic acidosis, congestive cardiac failure requiring pharmacologic treatment, Type 1 DM or secondary forms of DM
Asche, 2008[200] US	Cohort	Start year: 1996 End year: 2005 395 days NA	NA	NA	Yes	1129573/5438 General Electric Research Database	Age <65 years, took any ODM within 395 days prior to first prescription for monotherapy with metformin, SU, or TZD, less than two HbA1c levels (first recorded within 90 days prior to index date or 30 days post-index date and the second level drawn either (longer of the two) 90 days after index date or baseline A1c), no Type 2 DM (defined by ICD-9 , FBG ≥125 mg/dL, on ODM, or prescription for injectable incretic mimetic)
McAlister, 2008[208] Canada	Cohort	Start year: 1991 End year: 1996 9 years	NA	NA	No	NR/5631 Saskatchewan Health database	Age <30 years, treatment with insulin, did not receive at least one new prescription for an oral antidiabetic medication (metformin or SU) between 01/01/1991 and 12/31/96, not eligible for prescription drug benefits, less than one year of coverage in the provincial health plan, history of heart failure (by ICD-9 for hospitalization for heart failure) in last 3 years prior to starting first ODM, receipt of more than one ODM at any time (concurrently or not)

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kahn, 2008[213] U.S., Multinational Europe	RCT	Neither year reported 4 years	No run-in period	NR	Yes	4360/4351 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), history of lactic acidosis, uncontrolled hypertension, corticosteroid use
Davies, 2007[147] United Kingdom	RCT	Neither year reported 4 months	Run-in period but number of participants excluded was NR	< 6 months	NR	82/NR NR	Age <30 or >80 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2weeks, duration of Type 2 DM <12 months, C-peptide levels <0.33, severe concurrent disease, serum creatine >150umol/l

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Chien, 2007[59] Taiwan, Multi-center	RCT	Neither year reported 16 weeks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c >12% and FPG>250 mg/dL at screening visit, HbA1c <7% and FPG<140 mg/dL at screening visit, BMI <18.5 or >35 kg/m^2, current significant GI disorder, hyperosmolar nonketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 weeks, history of cancer in 5 years, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or glicazide<10 mg/day, glimepiride<4mg/d, glicazide<160mg/d)

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2007[75] Multicontinent	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with < 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose > 280 mg/dl after run-in period, no Type 1 DM or Type 2 DM
Hanefeld, 2007[100] Multinational Europe	RCT	Neither year reported 52 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG <7mmol/l or > 15mmol/l, C-peptide <0.27 nmol/l

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Scott, 2007[111] U.S.	RCT	Neither year reported 12 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	2186/743 NR	Age <21 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Comaschi, 2007[129] Italy	RCT	Neither year reported 6 months	Run-in period but number of participants excluded was NR	< 6 months	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33nmol/L
Nauck, 2007[133] U.S., Multinational Europe, Multi-continent	RCT	Neither year reported 52 weeks	Yes	< 6 months	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 weeks of screening, history of Type 1 DM, other treatments for hypoglycemia

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Robbins, 2007[145] US, Multinational Europe, Multi-continent, India, Australia	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	433/317 NR	Age <35 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)
Raskin, 2007[146] US	RCT	Neither year reported 28 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	N:/NR NR	Age <18 or >75 years, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275 lbs.), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Lund, 2007[197] Denmark	RCT	Start year: 2001 End year: 2002 8 months	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	127/96 Outpatient: subspecialty care setting	Age <40 years for onset of diabetes diagnosis, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >9.5% with ongoing ODMs prior to study start; 10.5 on 2 visits with >1 month interval, HbA1c <6.5% after run in period, BMI >27 kg/m^2, pregnant, insulin treated Type 2 DM, secondary DM, Factor II, VII, X <0.7, ongoing co-existing illness with life shortening prognosis, mental retardation or reduced intellectual behavior, history of drug abuse, weight loss of >5 kg in past 6 months prior to study start, fasting C peptide <300 of non fasting glucagon stimulated C peptide <600, ketonuria; ketoacidosis
Kahn, 2006[38] Multi-continent	RCT	Start year: 2000 End year: 2006 6 years	No run-in period	NR	Yes	6676/4360 NR	Age < 30 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, fasting plasma glucose <126 or > 180 mg/dL, history of lactic acidosis

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2006[49] Multi-continent	RCT	Start year: 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis
Charbonnel, 2006[94] Multi-continent	RCT	Neither year reported 24 weeks	Run-in period but number of participants excluded was NR	NR	Yes	1464/701 NR	Age < 18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 weeks of screening, FPG > 14.4mmol/l

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[101] US, Puerto Rico	RCT	Neither year reported 56 weeks	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c < 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to rosiglitazone, pioglitazone or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin , SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin > 250 mg/day, ODM, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria, anemia(< 10g/dl women, < 12g/dl men, BMI <20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Jibran, 2006[112] Pakistan	Randomized, open-label, 2 arm parallel prospective study	Start year: 2000 End year: 2001 12 months	NA	< 6 months	NR	NR/100 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g. failed initial treatment), no Type 2 DM, on insulin

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Bakris, 2006[125] U.S., Multi-continent, South America, Europe	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Umpierrez, 2006[126] U.S.	RCT	Neither year reported 28 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	538/210 Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >79 years, HbA1c <7.5% or >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2 months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3 months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis
Garber, 2006[128] U.S.	RCT	24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >78 years, any liver disease, any kidney disease, history of CVD, HbA1c ≤7.0% or ≥12.0%, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kvapil, 2006[138] Multinational Europe	RCT	Neither year reported 16 weeks	No run-in period	< 6 months	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, adequately controlled on metformin
Stewart, 2006[156] Multinational Europe	RCT	Start year: 2003 to 2004 32 weeks	Yes	< 6 months	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >9%, drug naive patients with FPG <7 mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Rosak, 2006[183] Germany	Cohort	Neither year reported 6 months	NA	< 6 months	Yes	NR/22808 Outpatient: primary care, Outpatient: subspecialty care setting	Not all treated with rosiglitazone

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Wright, 2006[198] U.K.	RCT	Start year: 1977 End year: 1991 6 years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	7616/4191 23 clinical Center	Age <25 or >65 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG ≤6 mmol/l x2 after being diagnosed with diabetes, ketonuria> 3 mmol/l, mixed ethnicity, severe previous illness that would limit life expectancy or require systemic treatment, serum creatinine>175 umol/l, if on same treatment for <6 years
Hanefeld, 2006[201] Germany	Cohort	Neither year reported 42 months	NA	>= 6 months	Yes	NR/500 Outpatient: primary care	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pregnant, known hypersensitivity to pioglitazone, glibenclamide, or their metabolites, ketoacidosis, diabetic coma, pre-coma, Type 1 DM, serious impairment of adrenocortical function
Malone, 2005[165] Multinational Europe	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	97/119 NR	Age <30 or>75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control
Yamanouchi, 2005[50] Japan	RCT	12 months (Planned duration)	Not extracted	Not extracted	No	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Leiter, 2005[83] Canada	RCT	Neither year reported 32 weeks	No run-in period	< 6 months	Yes	720/613 Outpatient: primary care	Age <20 or >80 years, HbA1c < 9.5%, no Type 2 DM, FBG <7 but >14mmol/L
Weissman, 2005[86] U.S.	RCT	Neither year reported 24 weeks (Planned duration)	Run-in period but number of participants excluded was NR	< 6 months	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5% for subjects having received prior combination treatment (metformin + SU), HbA1c < 7% or > 10% for drug naive or prior monotherapy subjects, BMI <27 kg/m2, FPG < 126mg/dL or >270mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non-compliant patient with metformin up-titration
Bailey, 2005[87] U.K., 14 European Countries	RCT	24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other
Feinglos, 2005[91] U.S.	RCT	16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >81 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2005[127] Italy	RCT	Neither year reported 12 months	No run-in period	< 6 months	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Gerich, 2005[136] US	RCT	Neither year reported 2 years	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	908/428 NR	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), neuropathy, retinopathy, HbA1c <7% or >11%, BMI < 22 kg/m2 or >45 kg/m2, not using adequate contraception, FPG ≥15mmol/L, if Type 1 DM, symptomatic hypoglycemia with >10% weight loss in previous 8 weeks, history of lactic acidosis or CHF requiring meds, other medical conditions that could interfere with interpretation of results or pose sign risk to the subject, had to be drug naive

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2005[159] Italy	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <18 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other
Agarwal, 2005[184] US	RCT	Start year: 2001 End year: 2003 16 weeks	No run-in period	< 6 months	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2 <7.5 kg/m^2, class III or IV heart failure, NSAID use
Rajagopalan, 2005[194] US	Cohort		Not extracted	Not extracted	Yes	Not extracted	Age <18 years, any liver disease, no Type 2 DM, other
Maru, 2005[195] UK	Cohort	130 (mean followup)	Not extracted	Not extracted	Yes	Not extracted	Age <35, treatment experienced, no Type 2 DM, other
Nichols, 2005[196] US	Cohort		Not extracted	Not extracted	Yes	Not extracted	Other
Rajagopalan, 2005[206] US	Cohort	Start year: 1999 End year: 2001 Duration: NA	NA	NA	Yes	NA (for cohort studies, claims data, etc)/1123645 pharmacy database	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), use of troglitazone, in cohort <12 months prior to study, follow up <3 months after study started, prior treated with rosiglitazone, metformin, pioglitazone, or SU, not continuously having insurance or medication coverage
Karter, 2005[207] US	Cohort	Start year: 1999 End year: 2001 10 months	NA	NA	No	NA (for cohort studies, claims data, etc)/23440 managed care organization	CHF, no pharmacy benefit, Type 1 DM, >80% pill adherence, filled a refill of index medication, member of health plan >1 year, any utilization of the index therapy in the 12 months prior to initiation of the study

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Madsbad, 2004[120] Multinational Europe	RCT	Start year: 2000 End year: 2001 12 weeks	No run-in period	< 6 months	Yes	311/193 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs
Schernthaner, 2004[52] Europe	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Derosa, 2004[60] Italy	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <46 or >67 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Horton, 2004[80] NR	RCT	Neither year reported 24 weeks	Yes	< 6 months	Yes	701/401 NR	Age >30 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), neuropathy, retinopathy, HbA1c < 6.8% or >11%, Type 1 or 2 DM, diabetes> 3 months duration, FPG <15mmol/L, diabetic complication, on corticosteroids, non treatment naive

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tan, 2004[106] Denmark, Finland, Norway, and Sweden.	RCT	52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5% or > 9.5% for patients receiving ODM, no Type 2 DM, other
Raskin, 2004[109] U.S.	RCT	12 titration and 12 maintenance weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 years, HbA1c <7% or >12% during previous monotherapy with SU or metformin at 50% or more of maximal recommended dose for at least 3 months, no Type 2 DM, other
Jovanovic, 2004[110] U.S.	RCT	12 week titration then 12 week maintenance (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 years, HbA1c <7% or >12%, no Type 2 DM, other
Hanefeld, 2004[140] Canada, U.K., Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands	RCT	NR	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Malone, 2004[164] US	RCT	Neither year reported 32 weeks	Yes	< 6 months	Yes	145/111 NR	Age <30 OR >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Hussein, 2004[202] Australia	Cohort	Start year: 2000 End year: 2002 30 months	NA	NA	No	2500/203 Outpatient: subspecialty care setting	HbA1c < 8%, treated at Melbourne Hospital, treated with rosiglitazone or pioglitazone >2 months
Tosi, 2003[36] Italy	RCT, cross-over	6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Pavo, 2003[54] Russia and Hungary	RCT	32 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other
Garber, 2003[61] US	RCT	16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	NR
Goldstein, 2003[62] US	RCT	18 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5 and >12.0, other
Derosa, 2003[81] Italy	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Any kidney disease, history of CVD, treatment experienced, HbA1c < 7%, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Yang, 2003[139] China	RCT	Neither year reported 12 weeks	Run-in period but number of participants excluded was NR	< 6 months	Yes	NR/211 NR	Age <35 or >70 years, poorly controlled on prior treatments (e.g. failed initial treatment), no Type 2 DM as defined by WHO, not treated with diet and sulfonylurea for 6-months
Malone, 2003[137] 14 countries not specified	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 weeks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test meals	Age < 30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 weeks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at max clinically effective dose for previous 30 days
Jones, 2003[179] US	RCT	Neither year reported 6 months	Run-in period but number of participants excluded was NR	< 6 months	NR	NR/N: NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history of chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days
Blonde, 2002[63] US	RCT	16 weeks (planned duration)	Not extracted	Not extracted	Yes		Age <30 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other
Marre, 2002[64] Netherlands, Denmark, Portugal, France, Belgium	RCT	4 months (planned duration)	Not extracted	Not extracted	Yes		Age <18 years, any liver disease, any kidney disease, history of CVD, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2002[65] US	RCT	20 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Gomez-Perez, 2002[88] Mexico	RCT	26 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Marre, 2002[96] Multi-continent	RCT	Neither year reported 24 weeks	Yes	< 6 months	Yes	680/467 NR	Age < 30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 6.8% or >11%, BMI <20 kg/m2 or >35 kg/m2, DM at least 6 months, FPG>15mmol/l, gastroparesis, change in body weight during run-in, treated with diabetes meds other than metformin 3 months before study
Vakkilainen, 2002[119] Finland	RCT	12 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >75 years, any liver disease, any kidney disease, HbA1c <6.5% or >10%, no Type 2 DM, other
St John Sutton, 2002[149] US	RCT	52 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, no type 2 DM, other
Charpentier, 2001[71] France	RCT	20 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 years, any kidney disease, history of CVD, no Type 2 DM, other

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Madsbad, 2001[114] Denmark, Scandinavia	RCT	12 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤39 or ≥76 years, any liver disease, any kidney disease, HbA1c <6.5% or >10%, no Type 2 DM, other
Amador-Licona, 2000[66] Mexico	RCT	12 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other
Horton, 2000[79] US	RCT	24 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 years, any kidney disease, HbA1c <6.8% or >11%, no Type 2 DM, other
Einhorn, 2000[89] US	RCT	16 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Fonseca, 2000[90] US	RCT	26 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no type 2 DM, other
Moses, 1999[82] Australia	RCT	Neither year reported 4 to 5 months	No run-in period	NR	NR	108/83 NR	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c < 7.1%, BMI <21 kg/m^2, no Type 2 DM, not on metformin for more than 6 months, alcohol abuse, drug use, intention to become pregnant, history of lactic acidosis, vitamin B12 <150 pmol/l with anemia

Table 10. Study design characteristics of studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year Country	Study design	Enrollment period Followup duration	Run-in period	Planned interval of follow-up	Pharmaceutical support	Number screened/ enrolled Source population	Exclusion criteria
Landgraf, 1999[115] Germany, Austria, and Netherlands	RCT	14 weeks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Wolffenbuttel, 1999[116] Germany, Austria, Netherlands	RCT	12 months (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.5% if treated with diet only, >12% if treated with diet plus oral, other
Marbury, 1999[117] US, Canada	RCT	12 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age >37 or <75 years, any liver disease, any kidney disease, history of CVD, treatment experienced, retinopathy, HbA1c <6.5% or 14.6%, no Type 2 DM, other
DeFronzo, 1995[70] +US	RCT	29 weeks (planned duration)	Not extracted	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Hermann, 1994[68] Sweden	RCT	6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	No Type 2 DM, other
Wolffenbuttel, 1993[118] Netherlands	RCT	12 (4 week titration, 8 week treatment) (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, HbA1c <7.0% or >12.0%, no Type 2 DM, other

ACEI = angiotensin-converting enzyme inhibitors; ALT = alanine aminotransferase; AST = asparate aminotransferase; BID = twice a day; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine kinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DKA = diabetic ketoacidosis; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; GFR = glomerular filtration rate; GI = gastrointestinal; HbA1c = hemoglobin A1c; HONK = hyper osmolar non ketotic; HTN = hypertension; ICD = International classification disease;kg/m2 = kilograms per meters squared; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; mg/d = milligrams per day; mg/dl = milligrams/deciliter; MHS = Military health system; mmHg = millimeters of mercury; mmol = millimoles; mmol/L = millimoles per liter; NA = not applicable; NPH = neutral protamine Hagedorn; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; NYHA = New York

Health Association; OAD = oral antidiabetic; OAM = oral antihyperglycemic medications; PPAR-G = peroxisome proliferator-activated receptors-gamma; PPG = postprandial glucose; QD = once a day; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TG = triglycerides; TZD = thiazolidinedione; U/kg = unit per kilogram; y = years

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[121]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Derosa, 2010[44]	Metformin + glibenclamide, 65	56	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 63	57	48	NR	28.7 NR	8.8	NR	4
Defronzo, 2010[132]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Aschner, 2010[77]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[134]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, Other: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, other: 3.1	31.3 90.3 kg	7.3	5.7	328
Komajda, 2010[292]	Metformin + rosiglitazone, 2220	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 2227	NR	NR	NR	NR NR	NR	NR	NR
Pratley, 2010[143]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, Other: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, Other: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, Other: 4	33.1 94.6 kg	8.4	6.4	52

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Raskin, 2009[131]	Metformin + repaglinide, 187	54.8	58	AA: 16, Asian: 4, C: 75, American Indian/Alaska Native: 1, Other: 4	32.9 NR	8.45	7.4	62
	Metformin + repaglinide, 187	54.5	59	AA: 13, Asian: 5, C: 80, American Indian/Alaska Native: 1, Other: 2	32.5 NR	8.29	7.3	58
	Metformin + rosiglitazone, 187	55.5 (28 to 83)	51	AA: 13, Asian: 2, C: 79, American Indian/Alaska Native: 1, Other: 4	32.2 NR	8.46	7.1	58
Derosa, 2009[46]	Metformin, 67	55	51	C: 100	27.2 77.7 kg	9.1	NR	7
	Metformin + glimepiride, 66	57.7	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57	49	C: 100	27.4 76.4	9.3	NR	9
	Pioglitazone, 69	54	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[141]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5
Kaku, 2009[84]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Williams-Herman, 2009[76]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Pantalone, 2009[174]	Rosiglitazone, 1079	61.4	45.5	C: 86.8, Non-Caucasian: 13.2	32.7 NR	7.3	NR	NR
	Any in the SU class, 7427	66.1	49.5	C: 78, Non-Caucasian: 22	31.1 NR	7.6	NR	NR
	Pioglitazone, 1508	61.6	48.3	C: 83.5, Non-Caucasian: 16.5	33 NR	7.3	NR	NR
	Metformin, 10436	56.8	41.8	C: 76.9, Non-Caucasian: 23.1	33.8 NR	7.7	NR	NR
Nauck, 2009[92]	Metformin, 122	56	60	AA: 3, Asian: 7, C: 88, other: 3	31.6 NR	8.4	8	48
	Metformin + glimepiride, 244	57	57	AA: 2, Asian: 9, C: 89, other: 1	31.2 NR	8.4	8	34
	Metformin + liraglutide, 242	57	59	AA: 2, Asian: 7, C: 88, Other: 2	30.9 NR	8.4	8	51
	Metformin + liraglutide, 241	57	54	AA: 4, Asian: 8, C: 88, Other:1	31.1 NR	8.3	7	44

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Hsiao, 2009[173]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the SU class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Currie, 2009[212]	Metformin + sulfonylurea, 13882	64.4	57.9	NR	NR 90.9 kg for men 79.7 kg for women	8.6	4.4	NA
	Metformin, 31421	58.6	51.1	NR	NR 95.9 kg for men 86.2 kg for women	8.4	1.5	NA
	Any in the SU class, 7439	70	54.9	NR	NR 80.4 kg for men 68 kg for women	8.4	1.9	NA
Tzoulaki, 2009[171]	Metformin, 68181	66.3	50.6	NR	31.47 NR	8.13	5.59	NR
	Rosiglitazone, 8442	65.7	50.5	NR	31.7 NR	8.4	6.7	NR
	Any in the SU class, 58095	70.4	52.6	NR	28.5 NR	8.2	6.6	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Perez, 2009[56]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[130]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, other: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, unspecified: 1.8	NR 79.6 kg	8.17	8.35	11
Juurlink, 2009[210]	Rosiglitazone, 22785	NR	53.1	NR	NR NR	NR	(<2 years: 6%, 2-5 years: 11%, >5 years: 83%)	NR
	Pioglitazone, 16951	NR	52.1	NR	NR NR	NR	(<2 years: 7%, 2-5 years: 11%, >5 years: 82%)	NR
Dormuth, 2009[215]	TZD, 10476	56	48	NR NR	NR NR	NR	4.6	NR
	Rosiglitazone, 6880	56	48	NR NR	NR NR	NR	4.6	NR
	Pioglitazone, 3596	57	48	NR NR	NR NR	NR	4.7	NR
	Any in the SU class, 73863	60	47	NR NR	NR NR	NR	4	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Mancini, 2009[214]	Metformin, 22	Median: 73 (61-78)	100	NR	Median: 30 (Range: 25-38) NR	Median: 7.2 (Range: 6.0-9.3)	Median: 15 (Range: 4-30)	NA
	Metformin + rosiglitazone, 21	Median: 69 (47-77)	100	NR	Median: 34 (Range: 27-40) NR	Median: 7.4 (Range: 5.8-10)	Median: 14 (Range: 5-30)	NA
Tolman, 2009[150]	Pioglitazone, 1063	54 (20-82)	57.2	AA: 14.5, Asian: 3.4, C: 59.8, H: 19.1	32.5 NR	9.5	5.86	649
	Glibenclamide, 1057	55 (19-81)	55.5	AA: 13.2, Asian: 2.5, C: 62.1, H: 18.7	32.5 NR	9.5	5.61	641
Dimic, 2009[199]	Metformin + glimepiride, 30	59	47	NR	29.21 NR	8.63	3.21	0
	Metformin + repaglinide, 30	57	43	NR	29.63 NR	8.67	3.63	0
Jadzinsky, 2009[78]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, other: 5	29.9 NR	9.4	2	58
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, other: 5.9	30.3 NR	9.5	1.4	62
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, other: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, other: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[95]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, other: 12	31.7 86 kg	8.1	6.7	44
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, other: 9.4	31.2 87.3 kg	8.1	6.4	48
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, other: 9.9	31.1 87.8 kg	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, other: 10.1	31.6 87.1 kg	8.1	6.7	40
Bunck, 2009[144]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	6
	Metformin + glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	3

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Garber, 2009[122]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, other: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, other: 7	32.8 92.8 kg	8.3	5.3	74
	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, Other: 5	33.2 92.5 kg	8.3	5.2	NR
Asche, 2008[200]	Any in the sulfonylurea class, 2117	NR	NR	NR	NR NR	NR	NR	NA
	Metformin, 2138	NR	NR	NR	NR NR	NR	NR	NA
	Thiazolidinedione, 702	NR	NR	NR	NR NR	NR	NR	NA
McAlister, 2008[208]	Any in the sulfonylurea class, 4162	66.59	58.1	NR	NR NR	NR	NR	0
	Metformin, 1469	63.37	53.8	NR	NR NR	NR	NR	0
Kahn, 2008[213]	Glyburide, 1441	NR	58	NR	NR NR	NR	NR	0
	Metformin, 1454	NR	59.4	NR	NR NR	NR	NR	0
	Rosiglitazone, 1456	NR	56	NR	NR NR	NR	NR	0
Scott, 2008[85]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Other: 3	30.4 84.9 kg	7.7	4.6	2
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Other: 1	30.3 83.1	7.8	4.9	9
Raz, 2008[93]	Metformin, 94	56.1 (36 to 77)	41	AA: 1, C: 47, H: 25, multiracial: 25, not specified: 2	30.4 81.2 kg	9.1	7.3	16
	Metformin + sitagliptin, 96	53.6 (29 to 73)	51	AA: 3, C: 42, H: 32, multiracial: 22, not specified: 1	30.1 81.5 kg	9.3	8.4	18

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seufert, 2008[142]	Metformin + sulfonylurea, 320	60	54.7	NR	30 NR	8.8	7.1	58
	Pioglitazone + sulfonylurea, 319	60	53.6	NR	30.2 NR	8.81	7	38
Robbins, 2007[145]	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[123]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[59]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
Schwarz, 2008[152]	Metformin + glyburide, 40	70.4	50	AA: 11.1, C: 77.8, Other: 11	33.5 NR	7.7	2.5	18
	Metformin + nateglinide, 35	70.1	51.5	AA: 9.1, C: 78.8, Other: 12.1	30.4 NR	7.8	1.7	14
Comaschi, 2007[129]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2007[75]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4NR	182
	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
Davies, 2007[147]	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Lund, 2007[197]	Metformin, 48	59.45	77	C: 100	24.71 74.81 kg	7.34	(Median: 3 years)	12*
	Repaglinide, 48	63.31	75	C: 100	24.82 75.57 kg	7.57	(Median: 5 years)	8†
Nauck, 2007[133]	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, other: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, other: 3.7	NR NR	7.7	6.5	202
Raskin, 2007[146]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, Other: 1	31.2 88.7 kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, other: 1	30.8 86.2 kg	9.9	NR	6

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Hanefeld, 2007[100]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, other: <1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, other: 3	28.8 NR	8.2	6	9
	Rosiglitazone, 195	60.4	68	AA: 0, C: 98, other: 2	28.7 NR	8.1	5.9	12
Scott, 2007[111]	Glipizide, 123	54.7 (21 to 76)	56.9	AA: 3.3, Asian: 4.9, C: 61, other: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, other: 21.1	30.5 NR	7.9	4.9	7
	Sitagliptin, 123	55.6 (34 to 76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, Other: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, Other: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	62 49.6	AA: 6.4, Asian: 5.6, C: 68.8, multiracial: 6.4, other: 12.8	30.8 NR	7.9	4.3	18
Kahn, 2006[38]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, Other: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, Other: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, other: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Charbonnel, 2006[94]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, other: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Wright, 2006[198]	Any in the sulfonylurea class, 1687	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 336	NR	NR	NR	NR NR	NR	NR	NR
	Total, 5063	52.4	59	AA: 8, Asian: 9, C: 83	27.5 NR	6.9	NR	NR
Rosenstock, 2006[49]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, other: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, Other: 3	32.8 NR	8.8	2.7	22
Jain, 2006[101]	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, Other: 0.4	32.8 94.3kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, Other: 0.4, Native American: 0.4	32.5 93.9kg	9.2	0.8	117
Stewart, 2006[156]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bakris, 2006[125]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Rosak, 2006[183]	Metformin + rosiglitazone, 7705	60	50.2	NR	29.3 87.2	8.1 (median)	3.9	545
	Rosiglitazone, 1559	62	47.7	NR	28.7 83.8	8.1 (median)	4.5	542
	Rosiglitazone + sulfonylurea, 5511	65	48.2	NR	27.7 81.3kg	8.3 (median)	5.3	478
Hanefeld, 2006[201]	Metformin + glibenclamide, 250	61	55	NR	32 91.8kg	8.6	4.6	138
	Metformin + pioglitazone, 250	61	54	NR	32 90.2kg	8.5	4.8	55
Umpierrez, 2006[126]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, Other: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, Other: 0	33.81 NR	8.31	5.9	17
Kvapil, 2006[138]	Metformin + aspart 70/30, 116	56.4	46	NR	30.4 85.1 kg	9.3	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30. 84.0 kg	9.4	8.1	5
Gerich, 2005[136]	Metformin + glyburide, 209	53.5	48	AA: 16.7, Asian: 0.5, C: 65.2, other: 17.7	33.5 NR	8.3	2.0	87
	Metformin + nateglinide, 219	52.6	51	AA: 13, Asian: 2.4, C: 64.4, other: 20.2	33.3 NR	8.4	1.5	78
Karter, 2005[207]	Any in the sulfonylurea class, 5921	59.9	54.8	NR	NR NR	8.9	NR	0
	Metformin, 11937	59.9	52.5	NR	NR NR	9.6	NR	0
	Pioglitazone, 3556	60.2	51.1	NR	NR NR	9.6	NR	0

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Agarwal, 2005[184]	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1
Derosa, 2005[127]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2
Malone, 2004[164]	Metformin + glargine,	NR	NR	NR	NR NR	NR	NR	7
	Metformin + lispro 75/25,	NR	NR	NR	NR NR	NR	NR	3
	Pooled arms	NR	63	NR	30.9 91.5kg	8.7	9	NR
Malone, 2005[165]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Madsbad, 2004[120]	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0
	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3
	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Rajagopalan, 2005[206]	Any in the sulfonylurea class, 1474	54.5	52.9	NR	NR NR	NR	NR	NR
	Metformin, 1137	52.5	49.6	NR	NR NR	NR	NR	NR
	Pioglitazone, 1137	52.7	50	NR	NR NR	NR	NR	NR
	Pioglitazone, 1474	54.6	54.3	NR	NR NR	NR	NR	0
	Pioglitazone, 1847	54.3	52.4	NR	NR NR	NR	NR	0
	Rosiglitazone, 1847	54.3	51.8	NR	NR NR	NR	NR	0
Hussein, 2004[202]	Pioglitazone, 107	64.4 (36 to 86)	48	NR	NR 84.3	9.5	17	0
	Rosiglitazone, 96	64.6 (41 to 82)	55	NR	NR 82.3	9.6	14.5	0
Horton, 2004[80]	Metformin, 104	55.4	67.3	NR	29.9 NR	8.3	3.7	NR
	Metformin + nateglinide, 89	57.7	65.2	NR	30.6 NR	8.2	3.4	NR
	Nateglinide, 104	57.9	56.7	NR	29.9 NR	8.1	4.7	NR
Malone, 2003[137]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, other: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, other: 3	29.8 83.0 kg	9.17	8.0	25
Yang, 2003[139]	Metformin + sulfonylurea	NR	NR	NR	NR NR	8.59	NR	NR
	Rosiglitazone + sulfonylurea	NR	NR	NR	NR NR	8.61	NR	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Jones, 2003[179]	Metformin, 121	58 (38 to 78)	70	NR	34 NR	8.7	5	0
	Metformin, 22	64 (46 to 81)	9	NR	23 NR	8.6	6.5	NR
	Metformin, 82	60 (40 to 81)	74	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 141	58 (36 to 82)	69	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 142	57 (39 to 80)	57	NR	34 NR	8.8	5	NR
	Metformin + rosiglitazone, 35	62 (42 to 78)	71	NR	23 NR	9.3	8	NR
Marre, 2002[96]	Metformin, 152	56.4	55.3	AA: 3.3, Asian: 2.6, C: 30.8	29.6 NR	8.25	6.5	16
	Metformin + nateglinide, 155	57.9	61.3	AA: 4.5, Asian: 3.2, C: 90.3	29.4 NR	7.99	7.2	18
	Metformin + nateglinide, 160	57.3	61.3	AA: 3.8, Asian: 3.1, C: 91.3	29.3 NR	8.18	6.8	15
Moses, 1999[82]	Metformin, 27	57.8	63	Asian: 7, C: 85, not specified: 7	31.8 NR	8.6	8	0
	Metformin + repaglinide, 27	57.2	67	C: 96, not specified: 4	33.2 NR	8.3	5.9	0
	Repaglinide, 28	60.3	54	Asian: 7, C: 93	31.3 NR	8.6	7	0
Jibran, 2006[112]	Glibenclamide, 50	45.8	10	NR	30.4 72.7 kg	10.2	0	0
	Repaglinide, 50	46.6	16	NR	27.1 65.8 kg	9.9	0	0
Leiter, 2005[83]	Metformin, 78	60	56	C: 86, Others: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Others: 24	33 NR	7.5	5.3	18
Garber, 2006[128]	Diet + metformin + glibenclamide, 160	56 (31-78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	NR
	Diet + metformin + rosiglitazone, 158	56 (24-78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Weissman, 2005[86]	Metformin, 384	55.7	NR	NR	33.8 96.7kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2kg	8.05	NR	76
	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2kg	8.05	NR	95
	Metformin, 351	55.7	NR	NR	33.8 96.7kg	7.97	NR	76
Bailey, 2005[87]	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, Other: 1	32.1 89.5kg	7.5	6.1	44
	Metformin + rosiglitazone, 289	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9kg	7.4	6	30
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, Asian: 1, C: 97, other: 1	32.2 90.9kg	7.4	6	30
Yamanouchi, 2005[50]	Diet + exercise + glimepiride, 37	55.6 (46.3 - 64.9)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	3
	Diet + exercise + metformin, 39	54.7 (44.9 - 64.5)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	2
	Diet + exercise + pioglitazone, 38	55.2 (46 - 64.4)	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	2
	Glimepiride, 37	55.6	51	NR	25.6 NR	9.8	3.3	3
	Metformin, 39	54.7	51	NR	26.2 NR	9.9	3	2
	Pioglitazone, 38	55.2	47	NR	25.8 NR	10.2	3.2	3
Derosa, 2005[159]	Diet + exercise + behavioral therapy + metformin + glimepiride, 47	52 (47 -57)	49	NR	26.8 NR	7.9	4	NR
	Diet + exercise + behavioral therapy + metformin + rosiglitazone, 48	54 (50 -58)	52	NR	26.6 NR	8	5	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Rajagopalan, 2005[194]	Metformin, 1137	52.5 (19-88)	49.6	NR	NR NR	NR	NR	NR
	Pioglitazone, 1847	54.3 (18-91)	52.4	NR	NR NR	NR	NR	NR
	Unspecified sulfonylurea, 1474	54.5 (19-94)	52.9	NR	NR NR	NR	NR	NR
	Pioglitazone, 1137	52.7 (18-90)	50	NR	NR NR	NR	NR	NR
	Pioglitazone, 1474	54.6 (18-91)	54.3	NR	NR NR	NR	NR	NR
	Rosiglitazone, 1847	54.3 (18-92)	51.8	NR	NR NR	NR	NR	NR
Feinglos, 2005[91]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	NR
	Placebo + metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	NR
Maru, 2005[195]	Unspecified sulfonylurea, 11350	64	52.5	NR	(BMI>=30: 21%) NR	NR	NR	NR
	Metformin, 4579	59	48.2	NR	(BMI>=30: 48%) NR	NR	NR	NR
Schernthaner, 2004[52]	Metformin, 597	56 (35 to 75)	58	NR	31.4 89.7kg	8.7	3.1	96
	Pioglitazone, 597	57 (35 to 75)	53	NR	31.2 88.2kg	8.7	3.4	98
	Placebo + diet + metformin, 597	56	57.8	NR	31.4 89.7kg	8.7	3.1	NR
	Placebo + diet + pioglitazone, 597	57	52.6	NR	31.2 88.2kg	8.7	3.4	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nichols, 2005[196]	Unspecified sulfonylurea, 1085	62	55.9	NR	NR NR	8	4	NR
	Metformin + unspecified sulfonylurea, 1834	61.1	52.4	NR	NR NR	8.3	5.8	NR
	Metformin, 272	60	51.1	NR	NR NR	7.8	4.3	NR
Derosa, 2004[60]	Placebo + diet + exercise + glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	NR
	Placebo + diet + exercise + metformin, 83	58	51	NR	28.1 NR	8.4	NR	NR
Tan, 2004[106]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	5.22	41
	Pioglitazone, 91	60	62	C: 99, Unspecified: 1	30.2 88.4 kg	8.4	4.76	36
Raskin, 2004[109]	Repaglinide, 63	58.5	62	AA: 16, C: 63, H: 2, Unspecified: 19	30.4 NR	9.3	7.2	25
	Rosiglitazone, 62	56.6	53	AA: 13, C: 68, H: 0, Unspecified: 19	31.4 NR	9	7.4	25
Jovanovic, 2004[110]	Pioglitazone, 62	56.2	50	AA: 11, C: 82, H: 3, other: 3	32.1 NR	9.1	6.1	36
	Pioglitazone + repaglinide, 123	58.9	68.3	AA: 15, C: 82, H: 1, others: 2.4	32.3 NR	9.3	7.1	18
	Repaglinide, 61	57.8	58	AA: 11, C: 75, H: 4.9, other: 8.1	31.2 NR	9	6.9	25
Hanefeld, 2004[140]	Metformin + sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, other: 0.6	30 84.9 kg	8.8	7.1	279
	Pioglitazone + sulfonylurea, 319	60 (36 to 75)	53,6	AA: 0.6, C: 99.4, other: 0	30.2 85.3 kg	8.82	60	259
	Placebo + metformin + unspecified sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	NR
	Placebo + unspecified sulfonylurea + pioglitazone, 31	60 (36 to 75)	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Garber, 2003[61]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	NR
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	NR
Tosi, 2003[36]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	NR
Goldstein, 2003[62]	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	NR
	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	NR
Derosa, 2003[81]	Diet + exercise + metformin, 56	52	48	NR	24.7 72.3 kg	7.4	5	NR
	Diet + exercise + repaglinide, 56	55	52	NR	25.2 70.2 kg	7.6	4	NR
Pavo, 2003[54]	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	6.3	9
	Pioglitazone, 105	54.2	56.2	NR	31.3 86.6 kg	8.6	5.6	5
Vakkilainen, 2002[119]	Placebo + glibenclamide, 20	63	NR	AA: 0, C: 100, Asian: 0, H: 0, O: 0	28.8 NR	7.6	NR	NR
	Placebo + nateglinide, 23	63	NR	AA: 0, C: 100, Asian: 0, H: 0, O: 0	27.8 NR	7.6	NR	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Blonde, 2002[63]	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	NR
	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	NR
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	NR
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	NR
St John Sutton, 2002[149]	Glyburide, 99	56.1	72	AA: 3, C: 76, others: 21	NR 85.1 kg	9.5	6.2	NR
	Rosiglitazone, 104	55.1	72	AA: 5, C: 73, others: 22	NR 82.6 kg	9.1	5.3	NR
Marre, 2002[64]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	NR
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	NR
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	NR
	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	NR
Garber, 2002[65]	Metformin + glyburide, 165	58.1	58	AA: 6, C: 79, Asian: 0, H: 10, O: 5	29.6 86.7 kg	8.18	3.3	NR
	Glyburide, 161	56.5	51	AA: 9, C: 78, Asian: 0, H: 9, O: 4	30.3 87.2 kg	8.21	2.81	NR
	Metformin + glyburide, 158	56.9	58	AA: 13, C: 74, Asian: 0, H: 11, O: 2	30.1 88.8 kg	8.25	3.52	NR
	Metformin, 161	56	58	AA: 4, C: 81, Asian: 0, H: 12, O: 2	30.4 88.6 kg	8.26	2.98	NR
Gomez-Perez, 2002[88]	Metformin, 34	53.4 (40 - 68)	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7 (40 - 73)	28.6	C: 0, H: 80, Mestizo: 20	28.0 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2 (42-76)	40	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Charpentier, 2001[71]	Metformin + glimepiride, 147	56.8 (36-70)	59	NR	29.5 81.2 kg	6.4	5.6	NR
	Placebo + glimepiride, 150	55.4 (35-70)	58	NR	29.3 81 kg	6.5	5.3	NR
	Placebo + metformin, 75	56.7 (36-69)	60	NR	29.2 82.2 kg	6.8	7	NR
Madsbad, 2001[114]	Repaglinide, 175	60.2	61	NR	28 82.9 kg	7.3	8.1	NR
	Placebo + glipizide, 81	62	64	NR	28 83.6 kg	7.2	7	NR
Amador-Licona, 2000[66]	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	NR
	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	NR
Einhorn, 2000[89]	Diet + metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	NR
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, H: 3.8, Others: 3.1	32.12 NR	9.75	NR	37
	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, H: 10.1, Others: 0.6	32.11 NR	9.86	NR	21
	Placebo + diet + metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	NR
Fonseca, 2000[90]	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, other: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, others: 12.7	29.8 NR	8.9	8.3	18
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, others: 12.9	30.2 NR	8.9	7.5	18
Horton, 2000[79]	Metformin, 178	56.8	68	AA: 9.6, C: 79.2, Asian: 2.2, H: 0, O: 9	29.6 NR	8.4	7.5	NR
	Nateglinide, 179	58.6	61	AA: 9.5, C: 82.1, Asian: 2.8, H: 0, O: 5.6	29.6 NR	8.3	4.7	NR

Table 11. Population characteristics of the studies reporting on the comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m^2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Landgraf, 1999[115]	Repaglinide, 94	61	60	AA: 0, C: 96, Asian: 0, H: 0, O: 4	27.6 80 kg	7.8	10	NR
	Placebo + glibenclamide, 100	63	57	AA: 6, C: 93, Asian: 0, H: 0, O: 1	27.5 79 kg	8	10	NR
Marbury, 1999[117]	Placebo + glyburide, 182	58.7	66	AA: 9, C: 79, Asian: 0, H: 0, O: 12	29.1 NR	8.9	8.3	NR
	Repaglinide, 362	58.3	67	AA: 9, C: 77, Asian: 0, H: 0, O: 14	29.4 NR	8.7	7.2	NR
Wolffenbuttel, 1999[116]	Placebo + glyburide, 139	61	68	NR	28 81.3 kg	7	Median: 6	NR
	Repaglinide, 286	61	62	NR	28.4 81.5 kg	7.1	Median: 6	NR
DeFronzo, 1995[70]	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[68]	Diet + metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	NR
	Diet + metformin, 25	NR	NR	NR	NR 78.6 kg	6.9	NR	NR
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	NR
Wolffenbuttel, 1993[118]	Glibenclamide, 15	62 (45-75)	25	NR	26.1 70.9 kg	Range 7.0-12.0	9	NR
	Repaglinide, 29	62 (45-75)	25	NR	26.1 74 kg	Range 7.0-12.0	9	NR

AA=African American; C=Caucasian; H=Hispanic; kg=kilogram; NR=not reported; O = other
* 5 while on metformin prior to second crossover; 2 during washout period; and 5 while on repaglinide after crossover
† 2 excluded on repaglinide prior to first crossover; 1 during washout, and 5 after first crossover while on metformin

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin versus thiazolidinediones								
Tzoulaki, 2009[171]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: First episode of CHF Grp1: ref Grp2: 0.61 (CI: 0.33 to 1.15)	Non-hip fractures Grp1: ref Grp2: HR: 1.09 (CI: 0.72 to 1.68)		
Tzoulaki, 2009[171]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: First episode of CHF Grp1: ref Grp2: 1.17 (CI: 0.77 to 1.77)	Non-hip fractures Grp1: ref Grp2: HR: 1.28 (CI: 0.93 to 1.77)		
Perez, 2009[56]	RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 0 (0)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (2.6)	
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.16 (CI: 0.78 to 1.73)			
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.38 (CI: 1.00 to 1.90)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hsiao, 2009[173]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 67 (3.33); HR: 1.30 (CI: 0.89 to 1.89)			
Hsiao, 2009[173]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 13 (2.66); HR: 1.54 (CI: 0.65 to 3.64)			
Karter, 2005[207]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9-CM codes for primary discharge diagnosis (HR relative to sulfonylurea use) Coll: Passive Timing: Unspecified ITT: NR Grp1: HR: 0.7 (CI: 0.49 - 0.99), p: 0.05 Grp2: HR: 1.28 (CI: 0.85 - 1.92), p: 0.2			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Asche, 2008[200]	Cohort	Grp1: Metformin NR Grp2: Thiazolidinediones NR			Def: NR Coll: NR Timing: Unspecified ITT: NR Grp1: NR Grp2: 18 (2.6)		Def: Nausea & vomiting; diarrhea; dyspepsia Coll: NR Timing: NR ITT: NR Grp1: (1.3%; 1.6%; 2.8%) Grp2: NR	Def: Lactic acidosis Coll: NR Timing: Unspecified ITT: NR Grp1: 6 (0.3) Grp2: NR
Kawai, 2008[221]	Non-randomized	Grp1: Metformin NR Start: 500-750mg, Max: 750mg Grp2: Pioglitazone Fixed NR	Def: Mild, moderate and severe Coll: NR Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)					
Rosenstock, 2006[49]	RCT	Grp1: Metformin Varied, mean daily glucose ≤ 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone Varied, mean daily glucose ≤ 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 13 (8)				Def: Diarrhea, nausea, vomiting, dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (35)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2006[38]	RCT	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Def: Self reported Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 142 (9.8), Severe: 1 (0.1)		Def: Investigator reported Grp1: 19 (1.3) Grp2: 22 (1.5)		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified ITT: Yes Grp1: (38.3) Grp2: (23)	
Yamanouchi, 2005[50]	RCT	Grp1: Metformin Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg women, 45 mg men	Def: NR Grp1: 0 (0) Grp2: 0 (0)					
Pavo, 2003[54]	RCT	Grp1: Metformin Varied, glucose: < 126 mg/dl Start: 850 mg, Max: 2550 mg, Mean: 2292 mg D: 8 wks Grp2: Pioglitazone Varied, glucose: < 126 mg/dl Start: 35 mg, Max: 45 mg, Mean: 41.5 mg D: 8 wks					Def: Diarrhea Grp1: (16) Grp2: (3)	Def: Cholecystitis Coll: Active Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 1 (1)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Schernthaner, 2004[52]	RCT	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied Start: 35 mg, Max: 45 mg					Def: Diarrhea; Nausea Grp1: (11.1); (4.2) Grp2: (3.2); (2.3)	
Leiter 2005[83]	RCT	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Rosiglitazone Varied, glucose: <7.0 mmol/L Start: 4 mg, Max: 8 mg D: 8 wks			Grp1: 0 (0) Grp2: 3 (1)			
Rajagopalan, 2005[206]	Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR		Def: ICD9 code liver failure or hepatitis Coll: Passive Timing: Unspecified ITT: NR Grp1: 0.8% incidence Grp2: 0.5% incidence HR: 1.139 (CI: 0.439 - 2.96)				

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rajagopalan, 2005[206]	Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR		Def: ICD9 code 'liver failure' or 'hepatitis' Coll: Passive Timing: Unspecified ITT: NR Grp1: 0.8% incidence Grp2: 0.4% incidence				
Kahn, 2008[213]	RCT	Grp1: Metformin Varied, glucose: < 140 Start dose: 500g, Max: 2g Grp2: Rosiglitazone Varied, glucose: < 140 Start dose: 4mg, Max: 8mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/ 100 patient-years Grp2: 1.86/ 100 patient-years HR: 1.57 (CI: 1.13 - 2.17), p: 0.0073		
Metformin versus sulfonylurea								
Pantalone, 2009[174]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 0.76 (CI: 0.64 to 0.91) Grp2: ref			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Tzoulaki, 2009[171]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: First episode of CHF Grp1: ref Grp2: 1.18 (CI: 1.04 to 1.34)	Non-hip fractures Grp1: ref Grp2: HR: 1.09 (CI: 0.97 to 1.23)		
Currie, 2009[212]	Cohort	Grp1: Metformin NR Grp1: Sulfonylurea						Def: Cancer Coll: Passive Timing: Unspecified ITT: NA Grp1: ref Grp2: HR: 1.36 (CI: 1.19 to 1.54)
Asche, 2008[200]	Cohort	Grp1: Metformin NR Grp2: Any drug in the sulfonylurea class NR					Def: Nausea/ vomiting; Diarrhea; Dyspepsia Coll: NR Timing: No ITT: NR Grp1: (1.3; 1.6; 2.8) Grp2: NR	Def: Lactic acidosis Coll: NR Timing: Unspecified ITT: NR Grp1: 6 (0.3) Grp2: NR
McAlister, 2008[208]	Cohort	Grp1: Metformin NR Median: 726 mg Grp2: Any sulfonylurea Varied Median: 4 mg for glyburide, 198 mg for chlorpropamide, 425 mg for tolbutamide			Def: Primary, secondary or most responsible diagnosis of HF using ICD-9 codes Coll: Passive ITT: NR Grp1: 3.3 cases/100yrs Grp2: 4.4 cases/100 yrs, aHR: 1.16 (CI: 0.96-1.41)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Karter, 2005[207]	Cohort	Grp1: Metformin NR Grp2: Any sulfonylurea NR			Def: ICD-9-CM codes for primary discharge diagnosis Coll: Passive Timing: Unspecified ITT: NR Grp1: HR: 0.7 (CI: 0.49-0.99), p: 0.05 Grp2: ref			
Chien, 2007[59]	RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Mean: 19 mg D: 4 wks	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)				Def: Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing: Unspecified ITT: Yes Grp1: (32) Grp2: (13)	
Kahn, 2006[38]	RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 557 (38.7), Severe: 8 (0.6)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 19 (1.3), Serious: 12 (0.8) Grp2: All: 9 (0.6), Serious: 3 (0.2)		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified ITT: Yes Grp1: (38.3) Grp2: (21.9)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Wright, 2006[198]	RCT	Grp1: Metformin Varied, glucose: <6 mmol/L Max: 2550 mg Grp2: Sulfonylurea Varied, glucose: <6 mmol/L Max: glipizide 40 mg, chlorpropramide 500 mg, glibenclamide 20 mg	Def: Mean annual % Coll: Active Timing: Specified ITT: NR Grp1: Substantive hypo: 0.3, (CI: 0.1-1.1); Any: 1.7, (CI: 1-3) Grp2: Substantive hypo: 1.2, (CI: 0.4-3.4); Any: 7.9, (CI: 5.1-11.9)					
Yamanouchi, 2005[50]	RCT	Grp1: Metformin Fixed 750 mg Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 after 1 month in 8 cases. Rest on 1 mg	Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 1 (2.7)					
Derosa, 2004[60]	RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 4 mg	Grp1: 0 (0) Grp2: 0 (0)				Def: Nausea + diarrhea Grp1: 2 (2.4) Grp2: NR	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Garber, 2003[61]	RCT	Grp1: Metformin Varied Start: 500 mg (adjusted to patient response), Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 (adjusted to patient response), Max: 10 mg	Def: Mild or moderate Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 98 (57.6), Fingerstick: 16 (10.6)				Def: Abdominal pain; Nausea & Vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4; 6.6; 5.3)	
Blonde, 2002[63]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg	Def: Mild or moderate, Fsg≤60mg/dl + symptomatic Grp1: 1 (<1) Grp2: 3 (1.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6); (12.4); (2) Grp2: (3); (5.5); (0)	
Marre, 2002[64]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 (0) Grp2: Serious: 1 (1.0), Mild or moderate: 7 (7)					
Garber, 2002[65]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10mg	Def: Mild or moderate Grp1: 0 (0) Grp2: 10 (6)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: (43) Grp2: (24)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Charpentier, 2001[71]	RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Fixed or Varied 1 mg (either fixed or increased stepwise to 2, 4, 6 mg od depending on clinical symptoms of hypoglycemia)	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 3 (2), Mild or moderate: 17 (11)				Def: Diarrhea Grp1: (7) Grp2: (1)	
DeFronzo, 1995[70]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 10 mg, Max: 20 mg	Def: Mild or moderate Grp1: 4 (2) Grp2: 6 (3)				Def: Nausea + diarrhea Grp1: (1.4) Grp2: (1)	
Hermann, 1994[68]	RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Def: Serious Grp1: 8 (21) Grp2: 12 (35)				Def: Nausea + diarrhea + dyspepsia and digestive Grp1: (63) Grp2: (32)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Maru, 2005[195]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: CHF/clinical diagnosis + validated a small sample via questionnaires to Grp to confirm the diagnosis + oxmis and read codes similar to ICD-9 codes Grp1: IR: 18.8/1000 person-years Grp2: IR: 26.6/1000 person-years			
Nichols, 2005[196]	Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: Medical record for CHF + ICD-9 code for CHF + clinical diagnosis + first record Grp1: IR: 10.5 (6.7-16.2) Grp2: IR: 13.8 (11.4-16.6)			
Rajagopalan, 2005[206]	Cohort	Grp1: Metformin NR Grp2: Any drug in SU class NR		Def: ICD9 code liver failure or hepatitis Coll: Passive Timing: Unspecified ITT: NR Grp1: (0.8) Grp2: (1)				

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2008[213]	RCT	Grp1: Metformin Varied, glucose: < 140 mg/dL Start dose: 500 mg, Max: 2 g Grp2: Glyburide Varied, glucose: < 140 mg/dL Start dose: 2.5 mg, Max: 15 mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/100 patient-years Grp2: 1.15/100 patient-years		
Chien, 2007[59]	RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start dose: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start dose: 10 mg, Max: 20 mg, Mean: 19 mg D: 4 wks				Def: Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes Grp1: 0 Grp2: 1 (6)		
Amador-Licona, 2000[66]	RCT	Grp1: Metformin Varied Start: 850 mg Grp2: Glibenclamide Varied Start: 5 mg					Def: Diarrhea + Diffuse abdominal pain Grp1: 4 (14.3) Grp2: NR	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2003[62]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Varied Start: 30 mg, Max: 30 mg					Def: Diarrhea Grp1: (17.3) Grp2: (13.1)	
Metformin versus DPP-IV inhibitors								
Aschner, 2010[77]	RCT	Grp1: Metformin Varied, prespecified dose Start: 500 mg, Max: 2000 mg; Mean: 1903 mg D: 5 weeks Grp2: Sitagliptin Fixed Mean: 100 mg	Coll: Passive Timing: Unspecified ITT: No Grp1: Severe: 0 (0) Mild/moderate: 17 (3.3); 23 events Grp2: Severe: 2 (<1) Mild/moderate: 9 (1.7); 17 events				Def: Combined GI events; Nausea; Diarrhea; Vomiting; Abdominal pain Coll: NR Timing: Unspecified ITT: No Grp1: (20.7, 3.1, 10.9, 1.3, 3.8) Grp2: (11.6, 1.1, 3.6, 0.4, 2.1)	
Jadzinsky, 2009[78]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Saxagliptin Fixed Mean: 10 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 5 (1)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 10 (3)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Williams-Herman, 2009[76]	RCT	Grp1: Metformin Fixed Mean: 1000 mg or 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Def: Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 2 (1)				Def: Nausea; Diarrhea; Abdominal pain; Vomiting; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 7; 4; 0; 20 for 1000 mg and 10; 12; 6; 3; 31 for 2000 mg) Grp2: (1; 4; 5; 1; 20)	
Goldstein, 2007[75]	RCT	Grp1: Metformin Varied, prespecified target Start: 500 mg, Max: 2000 mg Grp2: Sitagliptin Varied, prespecified target Start: 50 mg, Max: 100 mg	Grp1: 3 (2) Grp2: 1 (1)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin versus meglitinides								
Lund, 2007[197]	RCT	Grp1: Metformin Varied, prespecified target Start: 500 mg, Max: 2000 mg, Mean: 1629 mg D: 12 days Grp2: Repaglinide Varied, prespecified target Start: 1 mg, Max: 6 mg, Mean: 4.72 mg D: 12 days	Coll: Active Timing: Specified ITT: Yes Grp1: Serious: 1 (1), Mild or moderate: 22 (23) Grp2: Serious: 1 (1), Mild or moderate: 45 (47)				Def: NR Coll: Active Timing: Specified ITT: Yes Grp1: (65.7) Grp2: (42.7)	Def: Cancer Grp1: 2 (2) Grp2: 0 (0)
Horton, 2004[80]		Grp1: Metformin Fixed Start: 500 mg Grp2: Nateglinide Fixed Start: 120 qac	Def: Mild/ moderate, plasma glucose <2.8 mmol/l Coll: Active Timing: Specified ITT: Yes Grp1: 1 (1) Grp2: 2 (2)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (20.2) Grp2: (3.8)	
Moses, 1999[82]	RCT	Grp1: Metformin NR Grp2: Repaglinide Fixed Start: 0.5 mg, Max: 4.0 mg D: 12-28 days	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: No Grp1: 1 (4) Grp2: 3 (11)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Derosa, 2003[81]	RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 2500 mg D: 8 weeks Grp2: Repaglinide Varied Start: 0.5 mg bid, Max: 4 mg tid D: 8 weeks	Def: Mild or moderate Grp1: 0 (0) Grp2: 0 (0)				Def: Nausea + diarrhea (withdrawn due to) Grp1: (3.6) Grp2: (0)	
Horton, 2000[79]	RCT	Grp1: Metformin Fixed Start: 500 mg Grp2: Nateglinide Fixed Start: 120 mg tid	Def: Mild or moderate Grp1: 19 (11) Grp2: 22 (12)				Def: Nausea + diarrhea (withdrawn due to) Grp1: (3.4) Grp2: (0.6)	
Metformin versus metformin + thiazolidinedione								
Mancini, 2009[214]	Cross-sectional	Grp1: Metformin Median: 1700 mg Grp2: Metformin + rosiglitazone Median: 1850 mg; Median: 8 mg				Def: Vertebral fractures Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: OR: 6.5 (CI: 1.3 to 38.1)		
Perez, 2009[56]	RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Metformin + pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 1 (<1)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (9)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kawai, 2008[221]	Non-randomized	Grp1: Metformin NR Start: 500-750 mg, Max: 750 mg Grp2: Metformin + pioglitazone NR; Fixed Start: 500-750 mg, Max: 750 mg; NR	Def: Mild, moderate and severe Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)					
Kaku, 2009[84]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: NR; 16 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)				Def: abdominal pain and constipation Grp1: (2.3) Grp2: (2.4)	
Scott, 2008[85]	RCT	Grp1: Metformin Fixed Start: >1500 mg D: 10 wks Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg D: 10 wks	Def: Mild or moderate Coll: NR Timing: Unspecified Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (9) Grp2: (7)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rosenstock, 2006[49]	RCT	Grp1: Metformin Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks	Def: Self reported mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 19 (12)				Def: Diarrhea, nausea, vomiting Dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (47)	
Stewart, 2006[156]	RCT	Grp1: Metformin Varied, prespecified Start: 500 mg, Max: 3000 mg, Mean: 2627.9 mg D: 20 wks Grp2: Metformin + rosiglitazone Varied, prespecified Start: 500 mg, Max: 2000 mg, Mean: 1812.2 mg; Start: 4 mg, Max: 8 mg, Mean: 6.8 mg D: 18 wks; 16 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (4) Grp2: 17 (7)				Def: Diarrhea Grp1: (18) Grp2: (8)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Jones, 2003[179]	RCT	Grp1: Metformin Fixed Max: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, prespecified target Max: 2.5 g; Max: 8 mg	Def: Symptomatic hypoglycemia Grp1: All: (0.4), Obese: (1.7) Grp2: All: (2.1), Obese: (1.9)					
Weissman, 2005[86]	RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 12 mg	Def: Mild or moderate Grp1: 4 (1) Grp2: 4 (1)				Def: Withdrawn due to GI Grp1: (6.8) Grp2: (3.1)	
Bailey, 2005[87]	RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg D: 24 wks Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg D: 24 wks	Grp1: Serious: 0, Mild or moderate: 1 (<1) Grp2: Serious: 0, Mild or moderate: 3 (1)				Def: diarrhea and abdominal pain Grp1: (5.4) Grp2: (3.2)	Def: acute cholecystitis, serious cholelithiasis and cholestatic jaundice Coll: Active Timing: Specified ITT: Yes Grp1: 1 (<1) Grp2: 0 (0)
Fonseca, 2000[90]	RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4-8 mg	Def: mild or moderate Grp1: 2 (2) Grp2: 5 (4)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Einhorn, 2000[89]	RCT	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; 30 mg	Grp1: 1 (0.6) Grp2: 1 (0.6)					
Gomez-Perez, 2002[88]	RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed Start: 2.5 g; Start: 2-4 mg bid					Def: Nausea + vomiting + diarrhea + flatulence and abdominal pain Grp1: (15.4) Grp2: (16.8)	
Metformin versus metformin + sulfonylurea								
Currie, 2009[212]	Cohort	Grp1: Metformin NR Grp1: Metformin + sulfonylurea						Def: Cancer Coll: Passive Timing: Unspecified ITT: NA Grp1: ref Grp2: HR: 1.8 (CI: 0.96 to 1.21)
Nauck, 2009[92]	RCT	Grp1: Metformin Varied Start: 2000 mg, Max: 2000 mg Grp2: Metformin + glimepiride Varied; Fixed Start: 2000 mg, Max: 2000 mg; Start: 1 mg, Max: 4 mg D: NR; 3 wks	Def: Serious Coll: NR Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 0 (0)				Def: nausea, vomiting, and diarrhea Coll: NR Timing: NR ITT: NR Grp1: (17) Grp2: (17)	Def: acute pancreatitis Coll: NR Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 1 (<1)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Feinglos, 2005[91]	RCT	Grp1: Metformin Fixed Start: ≥1000 mg Grp2: Metformin + glipizide Fixed Start: ≥1000 mg; 2.5 mg	Def: FSG <60 mg/dl w/ symptoms or FSG <50 mg/dl w/o symptoms or FPG<55 mg/dl w/o symptoms Grp1: Serious: 0, Mild or moderate: 2 (3.3) Grp2: Serious: 0, Mild or moderate: 9 (14.8)					
Garber, 2003[61]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Def: Mild or moderate Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 59 (39.1), Fingerstick: 19 (11.2)				Def: Abdominal pain; nausea + vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4.1; 4.7; 7.6)	
Tosi, 2003[36]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000; Start: 2.5 mg, Max: 10mg	Grp1: Severe: 2 (10.5), Mild or moderate: 1 (5) Grp2: NR				Def: Diarrhea + constipation + discomfort and abdominal pain and anorexia Grp1: (10.5) Grp2: (2.6)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Blonde, 2002[63]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Def: FSG≤60mg/dl + symptomatic Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (3.7; 6.8; 2.5)	
Blonde, 2002[63]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: FSG≤60mg/dl + symptomatic Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (5; 10; 6.3)	
Marre, 2002[64]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 0, Mild or moderate: 11 (10.9)				Def: Not specified Grp1: (14.4) Grp2: (6.9)	
Marre, 2002[64]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 2 (1.9), Mild or moderate: 12 (11.4)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Garber, 2002[65]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg; Start: 1.25 mg	Def: Mild or moderate Grp1: NR Grp2: 18 (11.4)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43 Grp2: IR - 32	
Garber, 2002[65]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg; Start: 2.5 mg	Def: Mild or moderate Grp1: NR Grp2: 61 (37.7)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43 Grp2: IR - 38	
Charpentier, 2001[71]	RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed Start: 850 mg tid; Start: 1 mg	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 2 (1.4), Mild or moderate: 30 (21)				Def: diarrhea Grp1: (7) Grp2: (3)	
DeFronzo, 1995[70]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20mg	Def: Mild or moderate Grp1: 4 (2) Grp2: 38 (18)				Def: Nausea + diarrhea Grp1: (1.4) Grp2: (0.9)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hermann, 1994[68]	RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 3000 mg; Start: 1.75 mg, Max: 14 mg	Def: Mild or moderate Grp1: 8 (21) Grp2: 24 (33)					
Chien, 2007[59]	RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1680 mg; Start: 5 mg, Max: 10 mg, Mean: 8.4 mg D: 4 wks	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)			Def: Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)	Def: Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing: Unspecified ITT: NR Grp1: (32) Grp2: (13)	
Nichols, 2005[196]	Cohort	Grp1: Metformin NR Grp2: Metformin + unspecified sulfonylurea NR			Def: Medical record for CHF + ICD-9 code for CHF + clinical diagnosis + first record Grp1: IR: 10.5 (CI: 6.7-16.2) Grp2: IR: 13.4 (CI: 11.6-15.5)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2003[62]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg					Def: Diarrhea Grp1: (17.3) Grp2: (13.1)	
Metformin versus metformin + DPP-IV inhibitors								
Jadzinsky, 2009[78]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 5 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 11 (3)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 22 (7)	
Jadzinsky, 2009[78]	RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 10 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 2 (1) Mild/moderate: 16 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 31 (10)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
DeFronzo, 2009[95]	RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 10 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 7 (4)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 10 (6)	
DeFronzo, 2009[95]	RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 5 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 10 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 11 (6)	
DeFronzo, 2009[95]	RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 2.5 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 15 (8)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 19 (10)	
Williams-Herman, 2009[76]	RCT	Grp1: Metformin Fixed Mean: 1000 mg bid Grp2: Metformin + sitagliptin Fixed Mean: 500 mg bid; Mean: 50 mg bid	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 4 (2)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (5; 2; 9; 3; 26)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Williams-Herman, 2009[76]	RCT	Grp1: Metformin Fixed Mean: 1000 mg bid Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg bid; Mean: 50 mg bid	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 5 (3)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (NR; 4; 13; 4; 29)	
Scott, 2008[85]	RCT	Grp1: Metformin Fixed Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥1500 mg; Start: 100 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (9) Grp2: (1)	
Raz, 2008[93]	RCT	Grp1: Metformin Fixed Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥ 1500 mg; Start: 100 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (1)			Def: Limb fracture Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 0 (0)	Def: abdominal pain, nausea, vomiting, or diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (7.4) Grp2: (10.4)	Def: Neoplasms Coll: NR Timing: Unspecified ITT: No Grp1: 3 (3) Grp2: 0 (0)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Goldstein, 2007[75]	RCT	Grp1: Metformin Fixed Start: 500 mg or 1000 mg bid Grp2: Metformin + sitagliptin Fixed Start: 500 mg or 1000 mg bid; Start: 50 mg bid	Def: Mild or moderate Grp1: 3 (2) Grp2: 6 (3)					
Charbonnel, 2006[94]	RCT	Grp1: Metformin Varied, HbA1c: 7 - 10% Start: ≥1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: ≥1500 mg; Mean: 100 mg D: 19 wks	Def: Mild or moderate Grp1: 5 (2.1) Grp2: 6 (1.3)				Def: Abdominal pain, nausea, vomiting, or diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (10.5) Grp2: (11.9)	
Metformin versus metformin + meglitinides								
Horton, 2004[80]	RCT	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Metformin + nateglinide Fixed Start: 500 mg tid; Start: 120 mg ac	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: Symptomatic: 11 (0.6), Confirmed ≤2.8 mmol/l: 1 (1.0) Grp2: Symptomatic: 26 (29.2), Confirmed ≤ 2.8mmol/l: 3 (3.4)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (20.2) Grp2: (16.9)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Marre, 2002[96]	RCT	Grp1: Metformin Fixed Start: 1000 mg bid Grp2: Metformin + nateglinide Fixed Start: 1000 mg bid; Start: 60 mg ac	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: Symptomatic: 6 (3.9), Confirmed: 1 (0.7) Grp2: Symptomatic: 13 (8.4), Confirmed: 0					
Marre, 2002[96]	RCT	Grp1: Metformin Fixed Start: 1000 mg bid Grp2: Metformin + nateglinide Fixed Start: 1000 mg bid; Start: 120 mg ac	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: Symptomatic: 6 (3.9), Confirmed: 1 (0.7) Grp2: Symptomatic: 25 (15.6), Confirmed: 5 (3.1)					
Moses, 1999[82]	RCT	Grp1: Metformin NR Grp2: Metformin + repaglinide NR; Varied, glucose: 4.4-7.8 mmol/l NR; Start: 0.5 mg, Max: 4 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: NR Grp1: 0 Grp2: 9 (33.3)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Thiazolidinedione versus thiazolidinedione								
Pantalone, 2009[174]	Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.19 (CI: 0.74to 1.91)			
Hsiao, 2009[173]	Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 67 (3.33) Grp2: 13 (2.66)			
Juurlink, 2009[210]	Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: Congestive cardiac failure or heart failure hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: ref Grp2: HR: 0.77 (CI: 0.69 to 0.87)			
Hussein, 2004[202]	Cohort	Grp1: Rosiglitazone Fixed Start: 15-45 mg Grp2: Pioglitazone Fixed Start: 4-8 mg	Def: Mild or moderate Coll: Passive Timing: Unspecified Grp1: 11 (11) Grp2: 18 (17) Grp1-Grp2: p: NSG		Def: Pulmonary edema Coll: Passive Timing: Unspecified ITT: NR Grp1: 3 (3) Grp2: 2 (2)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rajagopalan, 2005[206]	Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR		Def: ICD9 code liver failure or hepatitis Coll: Passive Timing: Unspecified ITT: NR Grp1: (0.4) Grp2: (0.5)				
Thiazolidinedione versus sulfonylurea								
Pantalone, 2009[174]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 0.88 (CI: 0.60 to 1.31) Grp2: ref			
Pantalone, 2009[174]	Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 1.05 (95% CI 0.77 to 1.43) Grp2: ref			
Hsiao, 2009[173]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 67 (3.33); Grp2: 1872 (1.97)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hsiao, 2009[173]	Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 13 (2.66) Grp2: 1872 (1.97)			
Dormuth, 2009[215]	Cohort	Grp1: Thiazolidinedione NR Grp2: Sulfonylurea NR				Def: Hip fractures Coll: Passive Timing: Unspecified ITT: NA Grp1: HR: 1.28 (CI: 1.12 to 1.45) Grp2: ref		
Tolman, 2009[150]	RCT	Grp1: Pioglitazone Varied, HbA1c < 7.5% Max: 45 mg Grp2: Glibenclamide Max: 15 mg	Coll: Active Timing: Specified ITT: Yes Grp1: 40 (4) Grp2: 119 (11)	Def: ALT > 3x ULN with repeat confirmation Coll: Active Timing: Specified ITT: Yes Grp1: 0 (0) Grp2: 4 (<1)	Coll: Active Timing: Specified ITT: Yes Grp1: 12 (1) Grp2: 11 (1)		Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: 93 (9) Grp2: 80 (8)	Def: Cholecystitis Coll: Active Timing: Specified ITT: Yes Grp1: 4 (<1) Grp2: 4 (<1)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Jain, 2006[101]	RCT	Grp1: Pioglitazone Varied, glucose: FPG (69-141 mg/dl) Start: 15 mg, Max: 45 mg, Median: 45 mg Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dl Start: 5 mg, Max: 15 mg, Median: 10 mg	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: Yes Grp1: 11 (4.4) Grp2: 61 (24.3)			Def: Ankle Coll: Active Timing: No ITT: Yes Grp1: (0) Grp2: (0.8)	Def: diarrhea Coll: active Timing: Unspecified ITT: Yes Grp1: (6) Grp2: (6.4)	Def: stage IV colon ca Coll: active Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 2 (0.8)
Yamanouchi, 2005[50]	RCT	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0	Grp1: Serious: 0 (0), Mild or moderate: 0 (0) Grp2: Serious: 0 (0), Mild or moderate: 1 (2.7)					
Tan, 2004[106]	RCT	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5 mg	Def: Symptoms or SMBG < 50 mg/dl Grp1: 4 (4) Grp2: 32 (29)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hanefeld, 2007[100]	RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg	Coll: NR Timing: Unspecified ITT: Yes Grp1: 1 (0.5) Grp2: Serious: 2 (<1), Mild or moderate: 23 (11)				Def: Unspecified Coll: NR Timing: Unspecified ITT: Yes Grp1: 11 (5.5) Grp2: 7 (3.4)	
Hanefeld, 2007[100]	RCT	Grp1: Rosiglitazone Fixed Start: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Coll: NR Timing: Unspecified ITT: Yes Grp1: 3 (1.6) Grp2: Serious: 2 (<1), Mild or moderate: 23 (11)				Def: Unspecified Coll: NR Timing: Unspecified ITT: Yes Grp1: 5 (2.6) Grp2: 7 (3.4)	
St John Sutton, 2002[149]	RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glyburide Varied Start: NR, Max: 20 mg D: 8 weeks	Def: Signs and symptoms Grp1: (1.9) Grp2: (7.1)		Def: NR Grp1: 1 (1.0) Grp2: 0 (0)			
Asche, 2008[200]	Cohort	Grp1: Thiazolidinedione NR Grp2: Any in the Sulfonylurea class NR	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: NR Grp1: 12 (1.7) Grp2: 55 (2.6)		Coll: NR Timing: Unspecified ITT: NR Grp1: 18 (2.6) Grp2: NR			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kahn, 2006[38]	RCT	Grp1: Rosiglitazone Varied, glucose: <140 mg/dl Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dl Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: Serious events: 1 (0.1), Mild or moderate events: 142 (9.8) Grp2: Serious events: 8 (0.6), Mild or moderate events: 557 (38.7)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 22 (1.5), Serious: 12 (0.8) Grp2: All: 9 (0.6), Serious: 3 (0.2), p: ≤ 0.05		Def: Nausea, vomiting, diarrhea, abdominal discomfort Grp1: (23) Grp2: (21.9)	
Agarwal, 2005[184]	RCT	Grp1: Pioglitazone Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 15 mg D: 16 wks Grp2: Glipizide Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 5 mg D: 16 wks	Grp1: 2 events Grp2: 3 events		Grp1: 2 (2) Grp2: 2 (2)			
Karter, 2005[207]	Cohort	Grp1: Pioglitazone NR Grp2: Any sulfonylurea NR			Def: ICD-9-CM codes for primary discharge diagnosis Coll: Passive Timing: Unspecified ITT: NR Grp1: HR: 1.28 (CI: 0.85-1.92), p: 0.2 Grp2: ref			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rajagopalan, 2005[206]	Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR		Def: ICD9 code liver failure or hepatitis Coll: Passive Timing: Unspecified ITT: NR Grp1: (0.4) Grp2: (1)				
Rajagopalan, 2005[206]	Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR		Def: visit with ICD9 code liver failure or hepatitis Coll: Passive Timing: Unspecified ITT: NR Grp1: (0.5) Grp2: (1)				
Thiazolidinedione versus meglitinides								
Jovanovic, 2004[110]	RCT	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Repaglinide Varied Start: 0.5 mg if HbA1c<8% or 1 mg if HbA1c >8%, Max: 4 mg per meal D: 12 weeks	Def: Severe: needed assistance, Mild or moderate: <50mg/dl Grp1: Severe: 0, Mild or moderate: 2 (3) Grp2: Severe: 0, Mild or moderate: 5 (8)				Def: Diarrhea Grp1: (3) Grp2: (5)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Raskin, 2004[109]	RCT	Grp1: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid D: 12 weeks Grp2: Repaglinide Varied Start: 0.5 mg per meal if HbA1c≤8% or 1 mg if >8%, Max: 4 mg per meal D: 12 weeks	Grp1: Severe: 0, Mild or moderate: 1 (2) Grp2: Severe: 0, Mild or moderate: 4 (6)					
Kahn, 2008[213]	RCT	Grp1: Rosiglitazone Varied, glucose: <140 mg/dL Start dose: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start dose: 2.5 mg, Max: 15 mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.86/100 patient-years HR: 1.61 (CI: 1.14-2.28), p: 0.0069 Grp2: 1.15/100 patient-years		

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Sulfonylurea versus DPP-IV inhibitors								
Scott, 2007[111]	RCT	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 5 mg bid to 50 mg bid	Def: Mild or moderate Grp1: 21 (17.1) Grp2: 0 (0)					
Sulfonylurea versus meglitinides								
Jibran, 2006[112]	RCT	Grp1: Glibenclamide Varied, FPG < 130 mg/dl, PPG < 175 mg/dl Start: 5 mg, Max: 15 mg Grp2: Repaglinide Varied, FPG < 130 mg/dl, PPG < 175 mg/dl Start: 0.5 mg TDS, Max: 1.5 mg TDS	Def: Mild, moderate or severe Grp1: 0 (0) Grp2: 0 (0)					
Vakkilainen, 2002[119]	RCT	Grp1: Glibenclamide Varied Start: 5 mg, Max: 10 mg Grp2: Nateglinide Fixed Start: 120 mg tid	Grp1: 3 (12.5) Grp2: 0 (0)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Madsbad, 2001[114]	RCT	Grp1: Glipizide Varied Start: 5 mg, Max: 15 mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 4.0 mg tid	Def: Severe Grp1: 0 (0) Grp2: 0 (0)					
Landgraf, 1999[115]	RCT	Grp1: Glibenclamide Varied Max: 10.5 mg Grp2: Repaglinide Varied Max: 4.0 mg tid	Def: Mild or moderate Grp1: 9 (9.0) Grp2: 9 (9.6)					
Marbury, 1999[117]	RCT	Grp1: Glyburide Varied Start: 2.5 mg, Max: 15mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 12 mg	Grp1: Severe: 2 (1), Mild or moderate: 35 (18) Grp2: Severe: 5 (1), Mild or moderate: 54 (14)					
Wolffenbuttel, 1999[116]	RCT	Grp1: Glyburide Varied Start: 1.75 mg, Max: 10.5 mg D: 6-8 weeks Grp2: Repaglinide Varied Start: 1.5 mg, Max: 12.0 mg D: 6-8 weeks	Def: Mild or moderate Grp1: 13 (9) Grp2: 26 (9)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Wolffenbuttel, 1993[118]	RCT	Grp1: Glibenclamide Varied Start: 5 mg, Max: 15 mg Grp2: Repaglinide Varied Start: 0.5 mg, Max: 4 mg tid	Grp1: Severe: 0 (0), Mild or moderate: 1 (7) Grp2: Severe: 0 (0), Mild or moderate: 0 (0)					
Sulfonylurea versus GLP-1 agonists								
Seino, 2010[121]	RCT	Grp1: Glibenclamide Varied, prespecified dose Start: 1.25 mg; Max: 2.5 mg D: 4 weeks Grp2: Liraglutide Varied, prespecified dose Start: 0.3 mg; Max: 0.9 mg D: 2 weeks	Coll: Passive Timing: Unspecified ITT: No Grp1: Symptoms: 45 (34.1); 228 events; IR: 3.927/year Severe: 0 (0) Grp2: Symptoms: 36 (13.4) 61 events; IR: 0.525/year Severe: 0 (0)				Def: Diarrhea; Constipation Coll: NR Timing: Unspecified ITT: No Grp1: (3.8; 3.8) Grp2: (6.3; 5.6)	Def: Pancreatitis Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)
Garber, 2009[122]	RCT	Grp1: Glimepiride Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 weeks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.8 mg D: 2 weeks	Def: Not requiring assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 8 events				Def: Total GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 51) Grp2: (12, 38)	Def: Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Garber, 2009[122]	RCT	Grp1: Glimepiride Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 weeks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.2 mg D: 2 weeks	Def: Not requiring assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 12 events				Def: Total GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 49) Grp2: (12, 39)	Def: Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)
Madsbad, 2004[120]	RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.75 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[120]	RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.60 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 1 (3)					
Madsbad, 2004[120]	RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.45 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Madsbad, 2004[120]	RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.225 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[120]	RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 weeks Grp2: Liraglutide Fixed Mean: 0.045 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Metformin + thiazolidinedione versus metformin + sulfonylurea								
Hamann, 2008[123]	RCT	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 4 mg, Max: 8 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 5 mg, Max: 15 mg D: 12 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 18 (6) Grp2: 90 (30)				Coll: Active Timing: Specified ITT: Yes Grp1: (13) Grp2: (18)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Comaschi, 2007[129]	RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR, 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg D: 22 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)					
Bakris, 2006[125]	RCT	Grp1: Metformin + rosiglitazone Varied, glucose: ≤6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 5 mg D: 3 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 2 (1) Grp2: 22 (12)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Umpierrez, 2006[126]	RCT	Grp1: Metformin + pioglitazone Varied, glucose: <120 mg/dl, HbA1c: <8.0% Start: 1.54 g, Max: 1.57 g; Start: 30 mg, Max: 45 mg Grp2: Metformin + glimepiride Varied, glucose: <120 mg/dL Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR, 6 wks	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (9) Grp2: 32 (33)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (4.7) Grp2: (6)	
Garber, 2006[128]	RCT	Grp1: Metformin + rosiglitazone Varied Start: 1500 or 2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000; Start: 5 mg , Max: 10 mg	Grp1: Severe: 0 (0), Mild or moderate: 2 (1) Grp2: Severe: 7 (4), Mild or moderate: 53 (33)				Def: Diarrhea + abdominal pain + other GI symptoms; Diarrhea; Abdominal pain Grp1: (10; 3; 4) Grp2: (11; 6; 6)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hanefeld, 2006[201]	RCT	Grp1: Metformin + pioglitazone Fixed; Varied Mean: 1900 mg; Start: 30 mg, Max: 45 mg Grp2: Metformin + glibenclamide NR; Varied Mean: 1900 mg; Start: 3.5 mg, Max: 5 mg	Def: Severe Coll: NR Timing: Unspecified ITT: NR Grp1: 5 (2) Grp2: 34 (14)					
Yang, 2003[139]	RCT	Grp1: Metformin + sulfonylurea Fixed Grp2: Rosiglitazone + sulfonylurea Fixed		Def: AST or ALT 3 x ULN Coll: NR Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 0 (0)				
Derosa, 2005[159]	RCT	Grp1: Metformin + rosiglitazone Fixed Start: 1500 mg; Start: 4 mg Grp2: Metformin + glimepiride Fixed Start: 1500 mg; Start: 2 mg					Def: Transient flatulence Grp1: (4.2) Grp2: (2.1)	
Metformin + thiazolidinedione versus metformin + meglitinides								

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Raskin, 2009[131]	RCT	Grp1: Metformin + rosiglitazone Varied, prespecified target dose Start: 1000 mg, Max: 2500 mg; Start: 4, Max: 8 mg D: 4 wks Grp2: Metformin + repaglinide Varied Start: 1000 mg, Max: 2500 mg; Start: 4 mg, Max: 10 mg D: 4 wks	Coll: Active Timing: Specified ITT: NR Grp1: Severe: 0 (0), Mild or moderate: 1 (1) Grp2: Severe: 0 (0), Mild or moderate: 8 (4)					Def: Macular edema Grp1: 2 (1) Grp2: 0 (0)
Metformin + thiazolidinedione versus metformin + DPP-IV inhibitors								
Scott, 2008[85]	RCT	Grp1: Metformin + rosiglitazone Fixed Start: > 1500 mg; Mean: 8 mg D: 10 wks Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Mean: 100 mg D: 10 wks	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (7) Grp2: (1)	
Metformin + thiazolidinedione versus metformin + GLP-1 agonists								

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Defronzo, 2010[132]	RCT	Grp1: Metformin + rosiglitazone Varied, prespecified dose NR: Start: 4 mg; Max: 8 mg Grp2: Metformin + exenatide Varied, prespecified dose NR: Start: 0.010 mg; Max: 0.02 mg BID D: 2 months	Coll: NR Timing: Unspecified ITT: No Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 2 (4)				Def: Vomiting; Diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (0; 9) Grp2: (49; 16)	
Metformin + thiazolidinedione versus thiazolidinedione + sulfonylurea								
Comaschi, 2007[129]	RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50% Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR	Def: Mild or moderate Grp1: 0 (0) Grp2: 0 (0)					
Rosak, 2006[183]	Cohort	Grp1: Metformin + rosiglitazone NR Unclear; Start: 4mg, Max: 8mg Grp2: Rosiglitazone + sulfonylurea Varied Start: 4mg, Max: 8mg; NR	Def: Hypoglycemic events Coll: Active Timing: Specified ITT: Yes Grp1: 0.05/100 patient-years Grp2: 0.47/100 patient-years		Def: Investigator reported Coll: Active Timing: Specified ITT: Yes Grp1: 0.13/100 patient-years Grp2: 0.47/100 patient-years			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Derosa, 2005[127]	RCT	Grp1: Metformin + rosiglitazone Fixed Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 4mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 2 mg, Max: 2 mg		Def: Transiently elevated LFT to 1.5 times upper limit of normal Coll: NR Timing: Unspecified ITT: NR Grp1: 3 events out of 48 participants Grp2: NR				

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + sulfonylurea versus metformin + meglitinides								
Dimic, 2009[199]	Non-randomized trial	Grp1: Metformin + glimepiride Fixed NR Grp2: Metformin + repaglinide Fixed Mean: 2000 mg; Mean: 6 mg	Coll: Active Timing: Specified ITT: NR Grp1: 7 (23) Grp2: 5 (17)					
Schwarz, 2008[152]	RCT	Grp1: Metformin + glyburide Varied, glucose: <120 mg/dL Start: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 10 mg D: 12 wks Grp2: Metformin + nateglinide Varied, glucose: <120 mg/dL Start: 500 mg, Max: 2000 mg; Start: 360 mg, Max: 360 mg D: 12 wks	Def: Severe Coll: Active Timing: Specified ITT: Yes Grp1: 1 (3) Grp2: 0 (0)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (20) Grp2: (22.9)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Gerich, 2005[136]	RCT	Grp1: Metformin + glyburide Varied, glucose: FPG ≥6.7 mmol/L Start: 500 mg, Max: 2000 mg, Mean: 1105 mg; Start: 1.25 mg, Max: 10 mg, Mean: 5.1 mg D: 12 wks Grp2: Metformin + nateglinide Varied, glucose: FPG ≥6.7 mmol/L; Fixed Start: 500 mg, Max: 2000 mg, Mean: 1459 mg; Start: 120 mg, Mean: 357 mg D: 12 wks	Def: Severe Coll: NR Timing: Unspecified ITT: Yes Grp1: Mild or moderate:38 (18); Severe: 2 (1) Grp2: Mild or moderate:18 (8); Severe: 0 (0)					
Metformin + sulfonylurea versus metformin + DPP-IV inhibitors								
Seck, 2010[134]	RCT	Grp1: Metformin + sitagliptin Fixed NR Grp2: Metformin + glipizide Fixed; Varied NR; Start: 5 mg, Max: 20 mg; Mean: 9.2 mg	Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 18 (3) Mild/moderate: 31 (5.3) Grp2: Severe: 2 (<1) Mild/moderate: 199 (34.1)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Nauck, 2007[133]	RCT	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: NR, 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Def: Severe Coll: Active Timing: Specified ITT: Yes Grp1: 7 (1) Grp2: 1 (<1)				Def: Diarrhea, abdominal pains, nausea, vomiting Coll: Active Timing: Specified ITT: Yes Grp1: 69 (12) Grp2: 70 (12)	
Metformin + sulfonylurea versus metformin + GLP-1 agonists								
Derosa, 2010[44]	RCT	Grp1: Metformin + glibenclamide NR Mean: 1500 mg; Start: 7.5 mg; Max: 15 mg Grp2: Metformin + exenatide NR NR; Start: 10 mcg; Max: 20 mcg	Def: FPG < 60 mg/dL Coll: Active Timing: Specified ITT: No Grp1: 3 (5) Grp2: 0 (0)				Def: Vomiting; Diarrhea Coll: Active Timing: Specified ITT: No Grp1: (2; 2) Grp2: (2; 3)	
Nauck, 2009[92]	RCT	Grp1: Metformin + glimepiride Fixed; Varied Mean: 2000 mg; Start: 1 mg; Max: 4 mg Grp2: Metformin + liraglutide Fixed; Varied Start: 0.6 mg; Max: 1.8 mg	Coll: Passive Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: (17) Grp2: Grp1: Severe: 0 (0) Mild/moderate: (3)				Def: Nausea, vomiting, and diarrhea Coll: Passive Timing: Unspecified ITT: Yes Grp1: (17) Grp2: (44)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Nauck, 2009[92]	RCT	Grp1: Metformin + glimepiride Fixed; Varied Mean: 2000 mg; Start: 1 mg; Max: 4 mg Grp2: Metformin + liraglutide Fixed; Varied Start: 0.6 mg; Max: 1.2 mg	Coll: Passive Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: (17) Grp2: Grp1: Severe: 0 (0) Mild/moderate: (3)				Def: Nausea, vomiting, and diarrhea Coll: Passive Timing: Unspecified ITT: Yes Grp1: (17) Grp2: (40)	
Metformin + sulfonylurea versus metformin + premixed insulin								
Malone, 2003[137]	RCT	Grp1: Metformin + glibenclamide Varied, glucose: fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks Grp2: Metformin + lispro 75/25 fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks	Def: Symptomatic or BG <3.5mmol/l Timing: Unspecified ITT: NR Grp1: (1) Grp2: (1.3)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Kvapil, 2006[138]	RCT	Grp1: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg bid, Mean: 0.30 U/kg bid	Coll: NR Timing: Unspecified ITT: Yes Grp1: Severe: 0, Mild or moderate: 9 (8) Grp2: Severe: 0, Mild or moderate: 13 (12)					
Metformin + sulfonylurea versus thiazolidinedione + sulfonylurea								
van der Meer, 2009[141]	RCT	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed, Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR			Grp1: 0 (0) Grp2: 0 (0)			

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Seufert, 2008[142]	RCT	Grp1: Metformin + sulfonylurea Fixed Max: 2550 mg, Mean: 2081 mg; NR D: 12 wks Grp2: Pioglitazone + sulfonylurea Fixed Max: 45 mg, Mean: 37 mg; NR D: 12 wks	Coll: NR Timing: Unspecified ITT: NR Grp1: 50 (22) Grp2: 36 (17)				Def: Diarrhea Coll: NR Timing: Unspecified ITT: NR Grp1: (14.4) Grp2: (3.4)	
Hanefeld, 2004[140]	RCT	Grp1: Metformin + sulfonylurea Varied; Fixed Start: 850 mg, Max: 2550 mg; NR D: 12 wks Grp2: Pioglitazone + sulfonylurea Varied; Fixed Start: 15 mg (, Max: 45 mg; NR D: 12 wks	Def: Serious Grp1: 0 (0) Grp2: 0 (0)				Def: Diarrhea Grp1: (12.2) Grp2: (23.4)	
Yang, 2003[139]	RCT	Grp1: Metformin + sulfonylurea Fixed Start: 1000 mg; NR Grp2: Rosiglitazone + sulfonylurea Fixed Start: 4mg; NR					Def: Diarrhea Grp1: NR Grp2: 2 cases	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + DPP-IV inhibitor versus metformin + GLP-1 agonist								
Pratley, 2010[143]	RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.2 mg					Def: GI events Coll: NR Timing: Unspecified ITT: No Grp1: 4 (2) Grp2: 3 (1)	Def: Neoplasm Coll: NR Timing: Unspecified ITT: No Grp1: 1 (<1) Grp2: 0 (0) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)
Pratley, 2010[143]	RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.8 mg					Def: GI events Coll: NR Timing: Unspecified ITT: No Grp1: 4 (2) Grp2: 3 (1)	Def: Neoplasm Coll: NR Timing: Unspecified ITT: No Grp1: 1 (<1) Grp2: 1 (<1) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Metformin + GLP-1 agonist versus metformin + basal insulin								
Bunck, 2009[144]	RCT	Grp1: Metformin + exenatide Fixed; Varied, HbA1c: 7.1%-7.5% Mean: 2058 mg; Start: 5 ug bid, 20 ug tid Grp2: Metformin + glargine Fixed; Varied, SMBG: 4.5-5.5 mmol/L Mean: 1798 mg; Start: 10 U, Mean: 33.6 U qd	Def: <3.3mmol/L Coll: Active Timing: Unspecified ITT: NR Grp1: (8.3) Grp2: (24.2)				Def: Mild to moderate nausea, vomiting, diarrhea Grp1: NR Grp2: (50)	Def: Pancreatitis Grp1: 1 (3) Grp2: 0 (0)
Metformin + basal insulin versus metformin + premixed insulin								
Davies, 2007[147]	RCT	Grp1: Metformin + NPH Varied, glucose < 6.0 mmol/L NR; Start: 10 IU/kg; Mean: 0.58 IU/kg D: 6 weeks Grp2: Metformin + BHI 70/30 Varied, glucose < 6.0 mmol/L NR; Start: 10 IU bid, Mean: 0.63 IU bid	Def: Clinical hypoglycemia Coll: Active Timing: Specified ITT: NR Grp1: (25) Grp2: (29.6)					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Raskin, 2007[146]	RCT	Grp1: Metformin + glargine Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 U/kg QD, Mean: 0.57 IU/kg QD Grp2: Metformin + aspart 70/30 Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 IU/kg BID, Mean: 0.91 IU/kg	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 11 (14) Grp2: 33 (42)					
Robbins, 2007[145]	RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg bid, Max: 1000 mg bid, Mean: 1636 mg; Mean: 0.6 U/kg QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg bid, Max: 1000 mg bid, Mean: 1641 mg; Mean: 0.7 U/kg tid	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 2 (1), Mild or moderate: 75 (47) Grp2: Severe: 3 (2), Mild or moderate: 79 (50)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1: (5.7) Grp2: (6.4)	

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Malone, 2005[165]	RCT	Grp1: Metformin + lispro 75/25 Varied, pre-meal glucose 90-126 mg/dL 2-hr PPG 144-180 mg/dL Start: 1500 mg; Max: 2550 mg; Mean: 2146 mg; Mean: 0.42 U/kg bid D: 4 weeks; 16 weeks Grp2: Metformin + glargine Varied, glucose 90-126 mg/dL Start: 1500 mg; Max: 2550 mg; Mean: 2146 mg; Mean: 0.36 U/kg qd D: 4 weeks; 16 weeks	Def: Overall Coll: Active Timing: Specified ITT: NR Grp1: 0.61 episodes/ patient/30 days Grp2: 0.44 episodes/ patient/30 days					

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3) (continued)

Author, year	Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Malone, 2004[164]	RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.57 U/kg qd Grp2: Metformin + lispro 75/25 Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.62 U/kg bid	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 0 (0), Mild or moderate: 40 (40) Grp2: Severe: 0 (0), Mild or moderate: 57 (57)		Coll: Active Timing: Specified ITT: Yes Grp1: 0 (0) Grp2: 1 (1)			

Abbreviations: D = duration; Def = definition; DPP-4 = dipeptidyl peptidase-4; dys = days; fsg = fasting serum glucose; GLP-1 = glucagon-like peptidase-1; Grp = group; HR = hazard ratio; ICD = International Classification Disease; IR = incident rates; ITT = intention to treat; mg/day = milligram per day; mg/dl = milligrams/deciliter; mg = milligram; mmol/l = millimoles per liter; NR = not reported; NSG = non significant; od = once a day; SU = sulfonylurea; tid = twice a day; wks = weeks

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Agarwal, 2005[184]	Yes	Yes	No	Not described	Yes	Good
Amador-Licona, 2000[66]	Yes	Not described	No	No	Yes	
Aschner, 2010[77]	Yes	Yes	Yes	Not described	Yes	Fair
Bailey, 2005[87]	Yes	Yes	Yes	Not described	Yes	
Bakris, 2003[104]	Yes	Not described	No	No	No	
Bakris, 2006[125]	Yes	Not described	Yes	Not described	Yes	Good
Betteridge, 2005[289]	Yes	Not described	Yes	Yes	No	
Blonde, 2002[63]	Yes	Not described	Yes	Not described	Yes	
Bunck, 2009[144]	Yes	Yes	No	Not described	Yes	Good
Campbell, 1994[67]	Yes	Yes	No	No	Yes	
Charbonnel, 2006[94]	Yes	Not described	Yes	Not described	Yes	Fair
Charpentier, 2001[71]	Yes	Not described	Yes	Not described	Yes	
Chien, 2007[59]	Yes	Not described	Yes	Yes	Yes	Fair
Comaschi, 2007[129]	Yes	Not described	No	Not described	Yes	Fair
Comaschi, 2008[158]	Yes	Not described	No	Not described	No	Fair
Davies, 2007[147]	Yes	No	No	Not described	Yes	Poor
DeFronzo, 1995[70]	Yes	Not described	Yes	Yes	Yes	
DeFronzo, 2009[95]	Yes	Not described	Yes	Not described	No	Poor
Defronzo, 2010[132]	Yes	Yes	No	Not described	Yes	Fair
Derosa, 2003[81]	Yes	Not described	No	No	Yes	
Derosa, 2003[113]	Yes	Yes	Yes	Yes	Yes	
Derosa, 2004[60]	Yes	Not described	No	No	Yes	
Derosa, 2005[159]	Yes	Yes	Yes	Yes	Yes	
Derosa, 2005[151]	Yes	Yes	Yes	Yes	Yes	Good
Derosa, 2005[127]	Yes	Yes	Yes	Yes	Yes	Good
Derosa, 2006[157]	Yes	Yes	Yes	Yes	Yes	Good
Derosa, 2007[40]	Yes	Yes	Yes	Yes	No	Good

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications (continued)

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Derosa, 2007[288]	Yes	Not described	Yes	Not described	Yes	Fair
Derosa, 2009[135]	Yes	Yes	Yes	Yes	Yes	Good
Derosa, 2009[46]	Yes	Yes	Yes	Yes	Yes	Good
Derosa, 2010[44]	Yes	Yes	No	Not described	Yes	Fair
Dimic, 2009[199]	No	Not described	No	Not described	No	Poor
Einhorn, 2000[89]	Yes	Not described	Yes	Not described	Yes	
Erdem, 2008[39]	Yes	Not described	Not reported/Can't tell	Not described	No	Fair
Feinglos, 2005[91]	Yes	Not described	Yes	Not described	Yes	
Fonseca, 2000[90]	Yes	Yes	Yes	Yes	Yes	
Garber, 2002[65]	Yes	Not described	Yes	Yes	Yes	
Garber, 2003[61]	Yes	Yes	Yes	Yes	Yes	
Garber, 2006[128]	Yes	Not described	Yes	Yes	Yes	
Garber, 2009[122]	Yes	Yes	Yes	Not described	Yes	Good
Gerich, 2005[136]	Yes	Yes	Yes	Yes	Yes	Good
Goldberg, 2005[98]	Yes	Not described	Nr	Not described	No	
Goldstein, 2003[62]	Yes	Yes	No	No	Yes	
Goldstein, 2007[75]	Yes	Not described	Yes	Not described	Yes	Poor
Gomez-Perez, 2002[88]	Yes	Not described	Yes	Not described	Yes	
Gupta, 2009[47]	Yes	Yes	No	Not described	Yes	Fair
Hallsten, 2002[55]	Yes	Not described	No	No	Yes	
Hallsten, 2004[153]	Yes	Not described	Yes	Not described	Yes	Good
Hamann, 2008[123]	Yes	Yes	Yes	Not described	Yes	Fair
Hanefeld, 2004[140]	Yes	Not described	Yes	Yes	No	
Hanefeld, 2007[100]	Yes	Not described	Yes	Not described	Yes	Good
Hermann, 1991[69]	Yes	Yes	Yes	Yes	No	
Hermann, 1991[155]	Yes	Not described	Yes	Not described	Yes	

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications (continued)

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Hermann, 1994[68]	Yes	Yes	Yes	Yes	No	
Home, 2007[124]	Yes	Yes	No	Not described	Yes	Good
Home, 2009[16]	Yes	Yes	Yes	Yes	Yes	Good
Horton, 2000[79]	Yes	Not described	Yes	Yes	Yes	
Horton, 2004[80]	Yes	Not described	Yes	Not described	Yes	Good
Iliadis, 2007[48]	Yes	Not described	Not reported/ Can't tell	Not described	Yes	Fair
Jadzinsky, 2009[78]	Yes	Yes	Yes	Yes	Yes	Good
Jain, 2006[101]	Yes	Not described	Yes	Not described	Yes	Fair
Jones, 2003[179]	Yes	Not described	Yes	Not described	No	Fair
Jonker, 2009[160]	Yes	Not described	Yes	Not described	No	Fair
Jovanovic, 2004[110]	Yes	Not described	No	No	Yes	
Kahn, 2006[38]	Yes	Yes	Yes	Yes	Yes	Good
Kaku, 2009[84]	Yes	Not described	Yes	Not described	Yes	Fair
Kato, 2009[57]	Yes	Yes	Yes	Not described	No	Fair
Kawai, 2008[221]	No	Not described	No	Not described	Yes	Poor
Khan, 2002[97]	Yes	Not described	No	No	Yes	
Kim, 2007[42]	Yes	Not described	No	Not described	Yes	Poor
Kiyici, 2009[45]	Yes	Not described	No	Not described	No	Fair
Komajda, 2010[292]	Yes	Yes	No	Not described	No	Fair
Kvapil, 2006[138]	Yes	Yes	No	Not described	Yes	Good
Landgraf, 1999[115]	Yes	Not described	Yes	Yes	Yes	
Langenfeld, 2005[290]	Yes	Inappropriate	No	No	Yes	
Lawrence, 2004[53]	Yes	Not described	No	No	Yes	
Leiter, 2005[83]	Yes	Not described	No	Not described	Yes	Fair
Lester, 2005[228]	Yes	Not described	Yes	Not described	No	
Lund, 2007[197]	Yes	Yes	Yes	Yes	Yes	Fair

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications (continued)

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Madsbad, 2001[114]	Yes	Not described	Yes	Not described	Yes	
Madsbad, 2004[120]	Yes	Not described	Yes	Not described	Yes	Fair
Mafauzy, 2002[203]	Yes	Not described	No	Not described	Yes	Good
Malone, 2003[137]	Yes	Not described	No	Not described	Yes	Good
Malone, 2004[164]	Yes	Yes	No	Not described	Yes	Poor
Malone, 2005[165]	Yes	Not described	No	Not described	Yes	Poor
Marbury, 1999[117]	Yes	Not described	Yes	Not described	Yes	
Marre, 2002[64]	Yes	Not described	Yes	Not described	Yes	
Marre, 2002[96]	Yes	Not described	Yes	Yes	Yes	Good
Moses, 1999[82]	Yes	Not described	Yes	Yes	Yes	Fair
Nagasaka, 2004[43]	Yes	Not described	No	Not described	Yes	Fair
Nakamura, 2000[103]	Yes	Not described	No	No	No	
Nakamura, 2004[102]	Yes	Not described	No	Not described	Yes	Fair
Nakamura, 2006[108]	Yes	Not described	No	Not described	No	Fair
Natali, 2004[148]	Yes	Not described	Yes	Yes	Yes	
Nauck, 2007[133]	Yes	Not described	Yes	Not described	Yes	Good
Nauck, 2009[92]	Yes	Yes	Yes	Not described	No	Fair
Pavo, 2003[54]	Yes	Not described	Yes	Not described	Yes	
Perez, 2009[56]	Yes	Not described	Yes	Not described	Yes	Fair
Pfutzner, 2005[105]	Yes	Not described	No	No	No	
Pratley, 2010[143]	Yes	Yes	No	Not described	Yes	Good
Ramachandran, 2004[51]	Yes	Not described	No	No	No	
Raskin, 2004[109]	Yes	Not described	Nr	No	Yes	
Raskin, 2007[146]	Yes	Yes	No	Not described	Yes	Good
Raskin, 2009[131]	Yes	Not described	Not reported/ Can't tell	Not described	No	
Raz, 2008[93]	Yes	Yes	Yes	Not described	Yes	Poor

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications (continued)

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Rigby, 2009[130]	Yes	Not described	No	Not described	No	Fair
Robbins, 2007[145]	Yes	Yes	No	Not described	Yes	Good
Rosak, 2006[183]	No	Not described	No	Not described	No	Fair
Rosenstock, 2006[49]	Yes	Not described	Yes	Not described	Yes	Good
Schernthaner, 2004[52]	Yes	Yes	Yes	Yes	Yes	
Schwarz, 2008[152]	Yes	Not described	Yes	Not described	Yes	Good
Scott, 2007[111]	Yes	Yes	Yes	Yes	Yes	Good
Scott, 2008[85]	Yes	Not described	Yes	Not described	Yes	Fair
Seck, 2010[134]	Yes	Not described	Yes	Not described	Yes	Poor
Seino, 2010[121]	Yes	Not described	Yes	Not described	Yes	Poor
Seufert, 2008[142]	No	Not described	No	Not described	Yes	Fair
Smith, 2004[291]	Yes	Not described	Yes	Not described	No	Poor
St John Sutton, 2002[149]	Yes	Not described	No	No	Yes	
Stewart, 2006[156]	Yes	Not described	Yes	Yes	Yes	Good
Tan, 2004[106]	Yes	Not described	NR	Not described	Yes	
Tan, 2004[107]	Yes	Not described	Yes	Not described	Yes	
Teramoto, 2007[41]	Yes	Not described	No	Not described	Yes	Fair
Tolman, 2009[150]	Yes	Yes	Yes	Yes	Yes	Fair
Tosi, 2003[36]	Yes	Not described	Yes	Yes	Yes	
Turkmen Kemal, 2007[58]	Yes	Not described	No	Not described	Yes	Fair
Turner, 1999[37]	Yes	Yes	Not reported/ Can't tell	Not described	Yes	Fair
Umpierrez, 2006[126]	Yes	Yes	Not reported/ Can't tell	Not described	Yes	Good
Vakkilainen, 2002[119]	Yes	Not described	Yes	Not described	Yes	Fair
van der Meer, 2009[141]	Yes	Yes	Yes	Yes	Yes	Good
Vijay, 2009[99]	Yes	Yes	No	Not described	No	Fair
Virtanen, 2003[154]	Yes	Not described	Nr	Not described	Yes	

Table 13. Study quality of randomized controlled trials reporting of the comparative effectiveness and safety of diabetes medications (continued)

Author, year	Randomized	Randomization scheme	Study described as double blind	Double blind described	Withdrawals and dropouts	Overall quality*
Weissman, 2005[86]	Yes	Not described	Yes	Yes	Yes	
Williams-Herman, 2009[76]	Yes	Yes	Yes	Not described	No	Poor
Wolffenbuttel, 1993[118]	Yes	Yes	No	No	Yes	
Wolffenbuttel, 1999[116]	Yes	Not described	Yes	Yes	Yes	
Wright, 2006[198]	Yes	Not described	Not reported/Can't tell	Not described	No	Fair
Yamanouchi, 2005[50]	Yes	Yes	No	No	Yes	
Yang, 2003[139]	No	Not described	Yes	Not described	No	Poor

* Overall study quality was not evaluated for studies included in the original review. For studies included in the updated review, 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 the reporting.

Table 14. Study quality of observational studies reporting of the comparative safety of diabetes medications

Author, year	Setting or population	Inclusion/ exclusion	Key characteristics	Detail about treatment	Detail about outcomes	Statistical analysis	Results adjusted	Loss to followup	% lost to followup	Overall quality*
Pantalone, 2009[174]	Yes (incomplete)	Yes	Some description	No	Yes	Yes	Yes	Not applicable	Not reported	Fair
Hsiao, 2009[173]	Yes (complete)	Yes	Yes	No	Some description	Yes	Yes	No	Not reported	Fair
Currie, 2009[212]	Yes (complete)	Yes	Yes	No	Some description	Yes	Yes	No	Not reported	Fair
Tzoulaki, 2009[171]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Fair
Jonker, 2009[160]	Yes (incomplete)	Yes	Yes	No	Yes	Yes	Yes	Yes	10-20% in any group	Fair
Juurlink, 2009[210]	Yes (complete)	Yes	Some description	Yes	Yes	Yes	Yes	Unclear	Not reported	Fair
Dormuth, 2009[215]	Yes (incomplete)	Yes	Some description	No	Yes	Yes	Yes	No	Not reported	Fair
Mancini, 2009[214]	Yes (incomplete)	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not reported	Fair
Dimic, 2009[199]	No	No	Some description	No	Some description	Yes	No	No	Not reported	Poor
Jadzinsky, 2009[78]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	Yes	>20%	Fair
DeFronzo, 2009[95]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	Yes	>20%	Fair
Brownstein, 2010[182]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	No	Not reported	Good
Asche, 2008[200]	Yes (incomplete)	Yes	Yes	No	Some description	No	No	Not applicable	<10% in any group	Fair
McAlister, 2008[208]	Yes (incomplete)	Yes	Some description	No	Yes	Yes	Yes	Not applicable	<10% in any group	Fair
McAfee, 2007[181]	Yes (complete)	Yes	Some description	No	Yes	Yes	Yes	No	Not reported	Fair
Monami, 2008[180]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	Yes	<10% in any group	Fair
Kahler, 2007[175]	Yes (complete)	Yes	Yes	No	Yes	Yes	Yes	Not applicable	<10% in any group	Fair
Rosak, 2006[183]	Yes (incomplete)	No	Yes	No	Yes	Yes	Yes	No	Not reported	Fair
Hanefeld, 2006[201]	Yes (incomplete)	Yes	Yes	Yes	Some description	Yes	Yes	No	Not reported	Fair

Table 14. Study quality of observational studies reporting of the comparative safety of diabetes medications (continued)

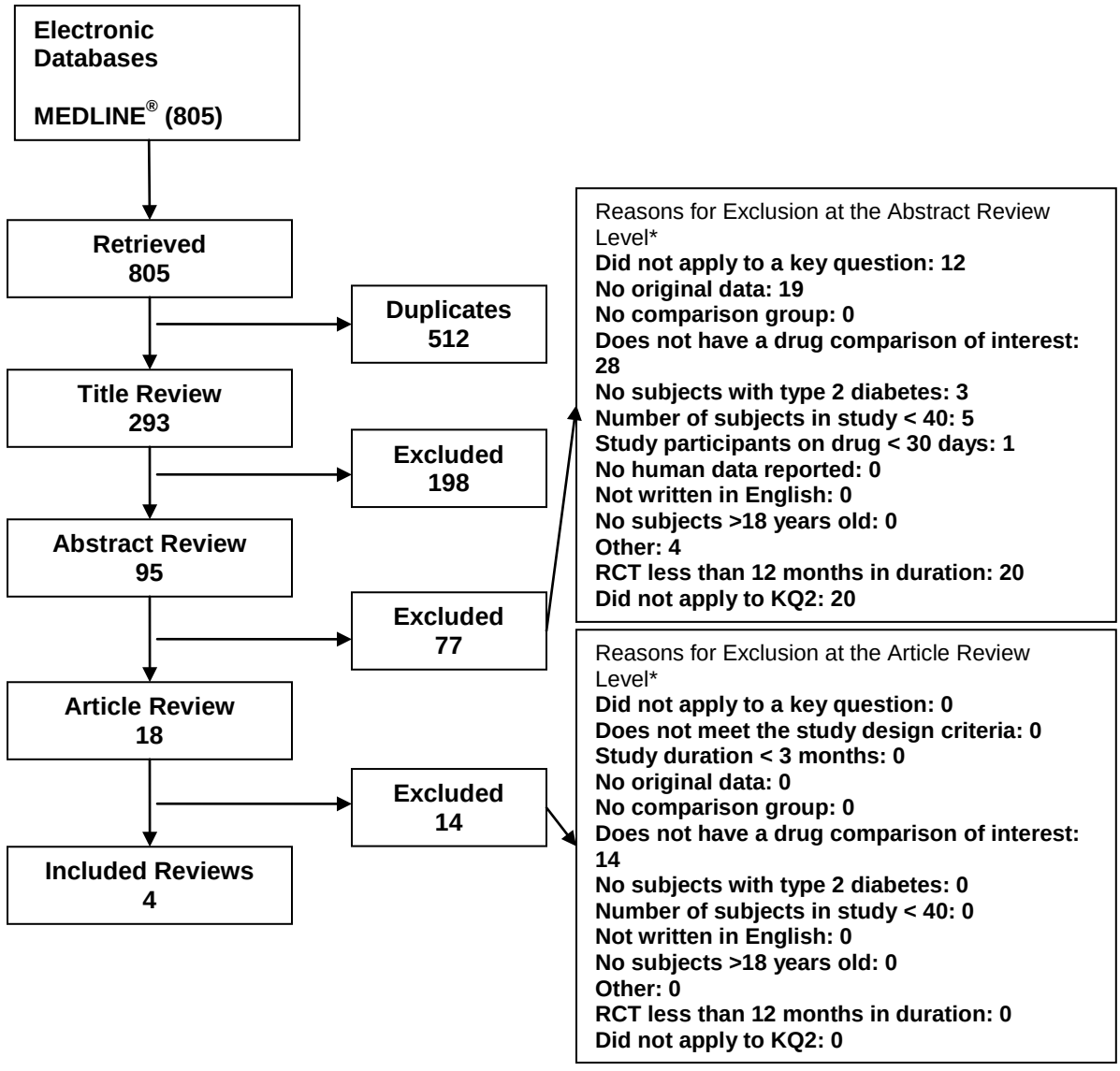
Author, year	Setting or population	Inclusion/ exclusion	Key characteristics	Detail about treatment	Detail about outcomes	Statistical analysis	Results adjusted	Loss to followup	% lost to followup	Overall quality*
Simpson, 2006[166]	Yes (incomplete)	Yes	Some description	Yes	Yes	Yes	Yes	No	Not reported	Fair
Karter, 2005[207]	Yes (incomplete)	Yes	Some description	No	Yes	Yes	Yes	No	Not reported	Fair
Rajagopalan, 2005[206]	Yes (incomplete)	Yes	Yes	Yes	Yes	Yes	Yes	No	Not reported	Fair
Hussein, 2004[202]	Yes (incomplete)	Yes	Some description	Yes	Yes	Yes	No	No	Not reported	Fair
Fisman, 1999[178]	Yes (incomplete)	Yes	Yes	No	Some description	Yes	Yes	No	Not reported	Fair
Jibran, 2006[112]	Yes (complete)	Yes	Some description	Yes	Yes	Yes	No	No	Not reported	Fair

* Overall study quality was not evaluated for studies included in the original review. For studies included in the updated review, 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.

Appendix H. Summary of Updated Literature Search for Long-Term Clinical Trials (Number of Articles)

Table 12. Comparative effectiveness of diabetes medications on adverse events (KQ3)



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
CENTRAL = Central Register of Controlled Trials; CINAHL = Cumulative Index to Allied Health and Nursing Literature; FDA = U.S. Food and Drug Administration