Comparative Effectiveness Review
Number 27

Effective Health Care

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

Executive Summary

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

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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)

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?

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

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

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

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.

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.

1. 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%.
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.

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 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? (contined)		
Body weight (continued)	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 (continued) 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
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? (contined)		
HDL cholesterol	High	Metformin increased HDL to a lesser extent than did pioglita zone, 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 rosiglita zone, 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).

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 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? (contined)		
Triglycerides (continued)	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).
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 cardiovas cular 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 met formin 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.

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? (continued)		
Cardiovascular and cerebrovascular morbidity (nonfatal myocardialinfarction 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.
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%.

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? (continued)		
Hypoglycemia (continued)	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.

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? (continued)		
Gastrointestinal (GI) side effects (continued)	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
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.

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? (continued)		
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%.

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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Full Report

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