Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations

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Background: Given the increase in medications for type 2 diabetes mellitus, clinicians and patients need information about their effectiveness and safety to make informed choices.

Purpose: To summarize the benefits and harms of metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 receptor agonists, as monotherapy and in combination, to treat adults with type 2 diabetes.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from inception through April 2010 for English-language observational studies and trials. The MEDLINE search was updated to December 2010 for long-term clinical outcomes.

Study Selection: Two reviewers independently screened reports and identified 140 trials and 26 observational studies of head-to-head comparisons of monotherapy or combination therapy that reported intermediate or long-term clinical outcomes or harms.

Data Extraction: Two reviewers following standardized protocols serially extracted data, assessed applicability, and independently evaluated study quality.

Data Synthesis: Evidence on long-term clinical outcomes (all-cause mortality, cardiovascular disease, nephropathy, and neuropathy) was of low strength or insufficient. Most medications decreased the hemoglobin A_{1c} level by about 1 percentage point and most 2-drug combinations produced similar reductions. Metformin was more efficacious than the DPP-4 inhibitors, and compared with thiazolidinediones or sulfonylureas, the mean differences in body weight were about −2.5 kg. Metformin decreased low-density lipoprotein cholesterol levels compared with pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylureas had a 4-fold higher risk for mild or moderate hypoglycemia than metformin alone and, in combination with metformin, had more than a 5-fold increased risk compared with metformin plus thiazolidinediones. Thiazolidinediones increased risk for congestive heart failure compared with sulfonylureas and increased risk for bone fractures compared with metformin. Diarrhea occurred more often with metformin than with thiazolidinediones.

Limitations: Only English-language publications were reviewed. Some studies may have selectively reported outcomes. Many studies were small, were of short duration, and had limited ability to assess clinically important harms and benefits.

Conclusion: Evidence supports metformin as a first-line agent to treat type 2 diabetes. Most 2-drug combinations similarly reduce hemoglobin A_{1c} levels, but some increased risk for hypoglycemia and other adverse events.

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In the United States, 11 unique classes of medication are approved to treat hyperglycemia in type 2 diabetes mellitus; remarkably, 9 of these classes became available since 1995 (1). Most adults with type 2 diabetes will receive more than 1 class of diabetes medication concurrently to achieve adequate glycemic control (2).

The goals of pharmacologic therapy are to reduce symptoms of hyperglycemia and the long-term complications of diabetes. Glycemic control is known to reduce the risk for microvascular complications, including retinopathy and neuropathy (3–5). The risk for death from cardiovascular disease is increased in adults with type 2 diabetes (6); however, it is unclear whether intensive glycemic control reduces that risk (7, 8). To make well-informed choices among the options for achieving glucose control, clinicians and patients need comprehensive information about the effectiveness and safety of therapies, with attention to patient-relevant outcomes (4, 9, 10).

The Agency for Healthcare Research and Quality (AHRQ) published its first systematic review on the comparative effectiveness and safety of oral hypoglycemic medications for type 2 diabetes in 2007 (11, 12). The agency requested an update of this review to include medication classes newly approved by the U.S. Food and Drug Administration (FDA) and evidence on combinations of medications, including oral medications combined with insulin. This review focuses on head-to-head comparisons relevant to clinicians and patients and provides both an update and an expansion of the previous comprehensive review (11).

See also:

Print
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Web-Only
Appendix Figures
CME quiz
Conversion of graphics into slides

Methods

When we formulated the key questions for this systematic review, we incorporated input from experts in diabetes care, policy, and research about the drug comparisons of greatest clinical interest. The key questions, protocol, and draft report were posted for public comment and then refined accordingly. The full evidence report (13) contains a detailed description of the methods and results, including search strategies and evidence tables.

Data Sources and Search Strategy

We searched for original articles in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to April 2010. After manuscript submission, we updated the MEDLINE search to December 2010 for long-term clinical outcomes (all-cause mortality, cardiovascular morbidity and mortality, nephropathy, and neuropathy). We reviewed reference lists of relevant review articles and each included article, handsearched the 15 medical journals most likely to publish articles on this topic, and invited peer reviewers and public reviewers to provide additional citations. We obtained medical reviews from the FDA, the European Public Assessment Reports, and Health Canada Product Monographs and unpublished data from several pharmaceutical companies. We also reviewed public registries of clinical trials. Our search strategy for the bibliographic databases combined terms for type 2 diabetes and the specific diabetes agents and was limited to English-language reports of studies in adults.

Study Selection

Two authors independently reviewed titles and abstracts to identify eligible articles. We selected original studies in nonpregnant persons aged 18 years or older with type 2 diabetes that assessed the benefits and harms of medications in a head-to-head comparison of interest (13). We included FDA-approved oral diabetes medications used as monotherapy or in 2-drug combinations with either metformin or a thiazolidinedione, and insulin therapies in combination with selected oral medications. We excluded studies of α-glucosidase inhibitors (for example, acarbose) because they are infrequently prescribed in the United States; have lower efficacy for glycemic control; and have high rates of gastrointestinal adverse effects, limiting their tolerability (11). We also excluded colesevelam, which was only recently approved by the FDA.

We selected studies that reported on major long-term clinical outcomes or any of the following intermediate end points or adverse events: hemoglobin A_{1c} (HbA_{1c}) level, body weight, lipid levels (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides), hypoglycemia (mild, moderate, or severe), liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal adverse effects and other serious adverse events. We included only randomized, controlled trials (RCTs) for intermediate end points and both trials and observational studies for major clinical outcomes and adverse events.

We excluded studies that followed patients for less than 3 months, had fewer than 40 patients, did not have a drug comparison of interest, or used background medications for diabetes without stratification of the outcomes by the combination of medications. The eligibility criteria for this review differed from those for the initial review (11). The most important differences were the inclusion of newly FDA-approved drug classes (dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists), a focus on 2-drug combinations (some of which contained an insulin product), the inclusion of several additional safety outcomes (fractures, cholecystitis, pancreatitis, and macular edema), and the exclusion of placebo-controlled trials.

The search, selection process, and description of articles newly included since the 2007 review are shown in **Appendix Figures 1** and **2** (available at www.annals.org).

Data Abstraction, Quality, and Applicability Assessments

One investigator used standardized forms to abstract data on general study characteristics (for example, study design and duration); study participants (for example, age, sex, race, and duration of diabetes); eligibility criteria; interventions (for example, drugs and dosing); outcome measures; and results for each outcome, along with their measures of variability. A second investigator confirmed the

Context

There are numerous treatment regimens for type 2 diabetes.

Contribution

This review found little evidence about the relative effects of various antihyperglycemic therapies on long-term clinical outcomes. Most monotherapies reduced hemoglobin A_{1c} levels by similar amounts. Metformin therapy reduced body weight compared with thiazolidinediones and sulfonylureas; decreased low-density lipoprotein cholesterol levels compared with pioglitazone, sulfonylureas, and dipeptidyl peptidase-4 inhibitors; caused less hypoglycemia than sulfonylureas; and caused more diarrhea than thiazolidinediones.

Caution

Evidence on the comparative effects of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, and different drug combinations was scant.

Implication

Consider metformin the initial drug of choice for treating type 2 diabetes.

—The Editors

Table 1. **Strength of Evidence for the Comparative Effectiveness and Safety of Diabetes Medications as Monotherapy and Combination Therapy on Long-Term Clinical Outcomes**

Outcome	Strength of Evidence	Conclusions
All-cause mortality	Low	All-cause mortality was slightly lower with metformin than with a sulfonylurea in observational studies, but results differed between trials and observational studies. Risk for bias in the studies was moderate.
	Low	Many RCTs were short (<1 y) and few deaths occurred, limiting precision.
	Insufficient	Several comparisons did not address all-cause mortality; these included most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone vs. rosiglitazone, comparisons with an insulin preparation, and most combination therapy comparisons.
Cardiovascular disease mortality	Low	Cardiovascular mortality was slightly lower with metformin than with a sulfonylurea, but results were imprecise and had moderate risk for bias.
	Low	Risk for cardiovascular mortality was similar between metformin and the thiazolidinediones as monotherapy, with high imprecision of results, inconsistencies, and moderate risk for bias.
	Insufficient	Several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone vs. rosiglitazone, and most combination therapy comparisons, did not address this outcome.
Cardiovascular disease morbidity	Low	Results were inconclusive for comparison of metformin with a thiazolidinedione, with high imprecision and inconsistency of direction of findings.
	Low	Metformin decreased risk for fatal and nonfatal ischemic heart disease events (odds ratio, 0.43 [95% CI, 0.17 to 1.10]) compared with the combination of metformin and rosiglitazone, with a consistent direction of results but high imprecision and lack of statistical significance.
	Insufficient	Several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone vs. rosiglitazone, and most combination therapy comparisons, did not address this outcome.
Nephropathy, neuropathy, or retinopathy	Moderate	Pioglitazone reduced the urinary albumin–creatinine ratio in 2 trials (by 15% and 19%) over metformin, suggesting less nephropathy.
	Low	Three comparisons were included for the outcome of neuropathy; studies had high risk for bias, small sample sizes, and poorly defined outcomes.
	Insufficient	No studies addressed the outcome of retinopathy.

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RCT = randomized, controlled trial.

abstracted data. Two investigators used items based on the Jadad criteria to independently assess the quality of trials and used items for selection bias, treatments, outcome measurement, statistical methods, and losses to follow-up to assess the quality of observational studies. For all studies, we rated overall quality as good (low risk for bias), fair, or low (high risk for bias) (14, 15). To assess study applicability, we evaluated whether the study population, interventions, outcomes, and settings were similar to usual care for people with type 2 diabetes in the United States.

Data Synthesis and Analysis

We conducted qualitative and quantitative (where possible) syntheses for each outcome, by comparison of interest. We conducted meta-analyses when at least 3 trials were available that were sufficiently homogenous in terms of population characteristics, study duration, and drug dosages. We combined medications by class, except for thiazolidinediones, which were considered as individual drugs (rosiglitazone and pioglitazone) because of their differences in effects.

For continuous outcomes, we used a random-effects model with the DerSimonian and Laird formula to derive pooled posttreatment weighted mean differences (16). For the dichotomous outcomes of congestive heart failure and ischemic heart disease, we calculated pooled fixed-effects odds ratios by using the treatment-group continuity correction (reciprocal of the sample size in the opposite treatment group in cells with 0 events) (17). For the outcome of hypoglycemia, we calculated pooled odds ratios by using the Peto method because sample sizes were balanced (18). We tested for heterogeneity among trials by using a chi-square test with a significance threshold for α of 0.10 or less and an I^2 statistic greater than 50% (19). If we found heterogeneity, we either did not pool the studies or attempted to determine the potential reasons for the heterogeneity by doing metaregression using study-level characteristics, such as baseline values, study duration, and dose ratio (dose given in the study divided by the maximum approved dose of drug). We conducted sensitivity analyses by omitting 1 study at a time to assess the influence of any single study on the pooled estimate. We tested for publication bias by using the Begg and Mazumdar test (20) and the Egger test (21). All statistical analyses were performed by using STATA, version 9.0 or higher (StataCorp, College Station, Texas).

Grading of the Evidence

Three or more investigators graded the quantity, quality, and consistency of the results; the directness of the measures used for each outcome; the precision of the results; and the magnitude of the effect on the basis of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group criteria (22). "High" strength of evidence indicates that the evidence probably reflects the true effect; "moderate" strength indicates that further research may change the result; and "low" strength indicates low confidence that the evidence reflects the true effect and further research is very likely to change the result. "Insufficient" evidence indicates that no studies

met our inclusion criteria for the comparison for a given outcome.

Role of the Funding Source

AHRQ reviewed the work plan before the project was started and provided copyright release for this manuscript; however, AHRQ had no role in the literature search, data analysis, or interpretation of the results.

RESULTS

Study Characteristics

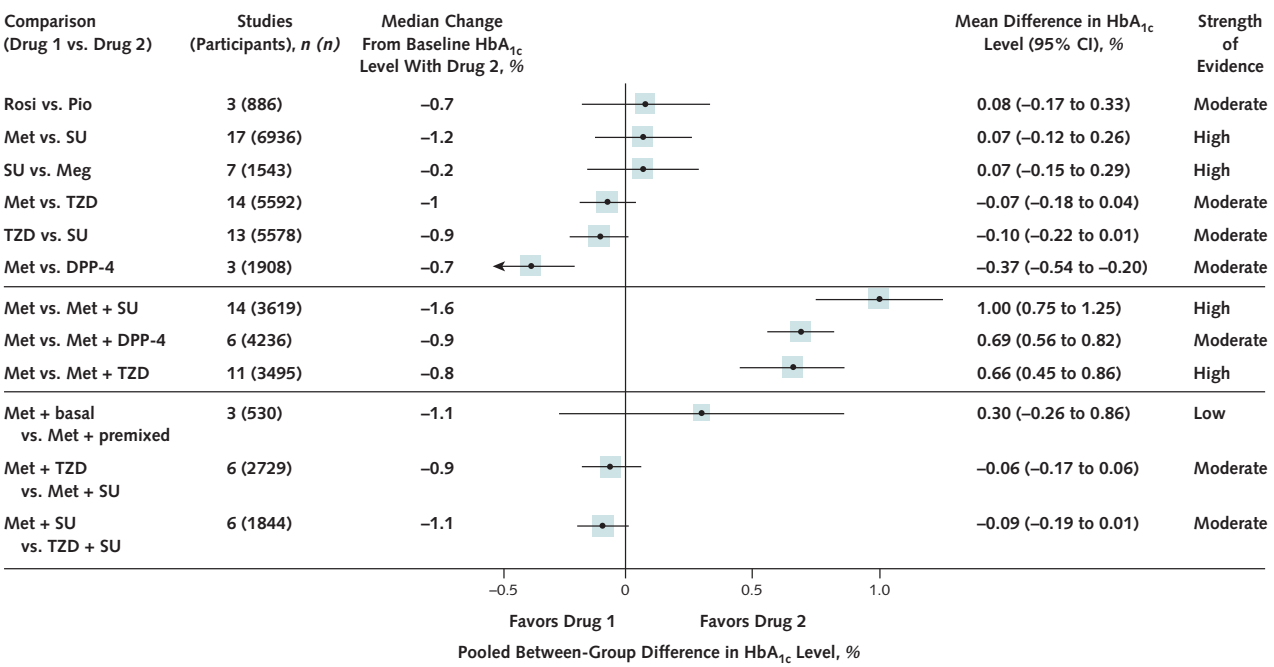
From our primary searches, we identified 140 RCTs and 26 observational studies in 166 articles that met inclusion criteria. Seventy-seven articles reported on either metformin or a thiazolidinedione in combination with another medication, 8 articles had comparisons that included insulin in combination with oral medications, and 19 articles included the new GLP-1 receptor agonists or DPP-4 inhibitors as monotherapy or combination therapy. Sixty-four articles evaluated long-term clinical outcomes, 116 evaluated intermediate outcomes, and 107 evaluated safety. Thirty-three studies were done exclusively in the United States, 59 in Europe, 19 in Asia, and 25 on multiple continents. Study duration ranged from 12 weeks to 11 years, but only 25 studies (5 of which were RCTs) lasted longer than 2 years. No article focused on safety as the primary outcome. Pharmaceutical company support was reported in 95 articles. Most studies excluded participants with type 1 diabetes mellitus, those with significant comorbid conditions (including liver, kidney, and cardiovascular disease), and older persons.

Comparative Effectiveness for Long-Term Clinical Outcomes

Although we included 2 additional large RCTs (23, 24) and 39 other studies since the 2007 review, studies were generally short (less than 1 year) and few events occurred, making estimates of risk very imprecise. Thus, the strength of evidence was low or insufficient to support conclusions about the comparative effectiveness of diabetes medications on all-cause mortality, cardiovascular morbidity and mortality, and microvascular outcomes (**Table 1**). In the search updated to December 2010, we screened 805 records and identified 4 articles that addressed long-term clinical outcomes. Two of these articles reported on RCTs, and 1 of the RCTs was an extension of a study in a previously included article (25). Results of these studies were consistent with the findings from our review and did not change the strength of evidence grades (13).

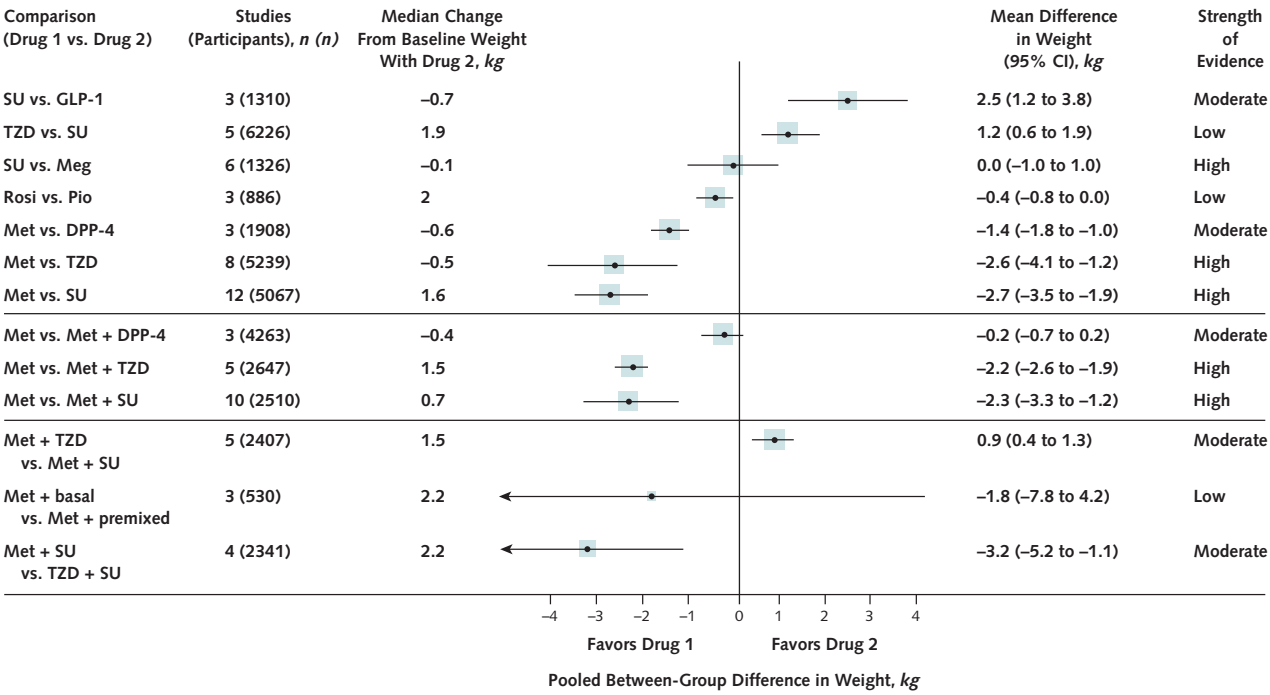
ADOPT (A Diabetes Outcome Progression Trial) was a large, double-blind RCT involving 4360 patients followed for a median of 4 years, in which patients were randomly assigned to receive metformin, rosiglitazone, or glyburide (23). The primary outcome of the trial was time to monotherapy failure. The authors reported similar rates

Figure 1. **Pooled between-group differences in HbA_{1c} level with monotherapy and combination therapies.**



Error bars represent 95% CIs. basal = basal insulin; DPP-4 = dipeptidyl peptidase-4 inhibitor; HbA_{1c} = hemoglobin A_{1c}; Meg = meglitinide; Met = metformin; Pio = pioglitazone; premixed = premixed insulin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione.

Figure 2. **Pooled between-group differences in body weight with monotherapy and combination therapies.**



Error bars represent 95% CIs. basal = basal insulin; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1; Meg = meglitinide; Met = metformin; Pio = pioglitazone; premixed = premixed insulin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione.

of all-cause mortality, cardiovascular disease mortality and morbidity, and stroke in the 3 study groups. Trials of short duration also reported no differences; however, the small trials had few, if any, events. Observational studies had conflicting results compared with the trial data: Metformin was typically associated with a lower risk for all-cause mortality and cardiovascular disease mortality and morbidity than were sulfonylureas (13).

Seven short-duration RCTs reported a lower risk for fatal and nonfatal ischemic heart disease with metformin than with the combination of metformin and rosiglitazone (pooled odds ratio, 0.43 [95% CI, 0.17 to 1.10]), but event rates were low and the confidence bounds were wide and overlapped 1.0 (26–32) (**Appendix Figure 3**, available at www.annals.org). RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), the only study with cardiovascular mortality as its primary outcome, reported that the combined groups of rosiglitazone plus metformin and rosiglitazone plus sulfonylurea were noninferior to metformin plus a sulfonylurea for the primary end point of hospitalization or death from cardiovascular disease (hazard ratio, 1.08 [CI, 0.89 to 1.31]) over a mean follow-up of 5.5 years (24). No RCTs directly compared rosiglitazone with pioglitazone for cardiovascular outcomes, but 3 cohort studies presented conflicting results (13).

Comparative Effectiveness for Intermediate Outcomes

HbA_{1c} Level

Figure 1 shows the comparative effectiveness of diabetes medications for HbA_{1c}. Most diabetes medications were similarly efficacious when used as monotherapy and decreased HbA_{1c} levels by 1 absolute percentage point on average over the course of a study. An exception was metformin, which reduced HbA_{1c} levels more than the DPP-4 inhibitors did as monotherapy. Combination therapy (including the combination of metformin and a DPP-4 inhibitor) decreased HbA_{1c} levels more than monotherapy did, by about 1 absolute percentage point.

Low strength of evidence suggested that metformin plus a GLP-1 agonist decreased HbA_{1c} levels more than metformin plus a DPP-4 inhibitor. No other combination reduced HbA_{1c} levels more than another combination, including metformin plus a thiazolidinedione compared with metformin plus a sulfonylurea.

Body Weight

Figure 2 shows the comparative effectiveness of diabetes medications in terms of body weight. Metformin decreased weight compared with thiazolidinediones and sulfonylureas. Sulfonylureas and meglitinides increased weight similarly, sulfonylureas increased weight less than thiazolidinediones, and GLP-1 agonists decreased weight

compared with sulfonylureas. Combinations of metformin plus a thiazolidinedione or metformin plus a sulfonylurea increased weight more than metformin monotherapy. The combination of metformin plus a DPP-4 inhibitor compared with metformin alone affected weight similarly. Weight gain was slightly less with metformin plus sulfonylurea than with either metformin plus a thiazolidinedione or a thiazolidinedione plus a sulfonylurea. Reduction in weight was greater with metformin plus a GLP-1 agonist than with most standard combinations, although fewer studies used the same comparators and therefore the strength of evidence was low.

Plasma Lipid Levels

Effects on lipid levels varied across medication type, but most effects were small to moderate. In general, metformin had favorable effects on all the lipid classes; it decreased LDL-C and triglyceride levels and modestly increased HDL-C levels.

Figure 3 shows the comparative effectiveness of diabetes medications in terms of LDL-C levels. Rosiglitazone and pioglitazone increased LDL-C levels, whereas the sulfonylureas and DPP-4 inhibitors had little effect on them. Metformin decreased LDL-C levels significantly compared with pioglitazone, sulfonylureas, and DPP-4 inhibitors. Similarly, the combination of metformin and rosiglitazone increased LDL-C levels compared with metformin monotherapy, and the combination of metformin and rosiglitazone increased LDL-C levels compared with combination therapy with metformin and sulfonylureas.

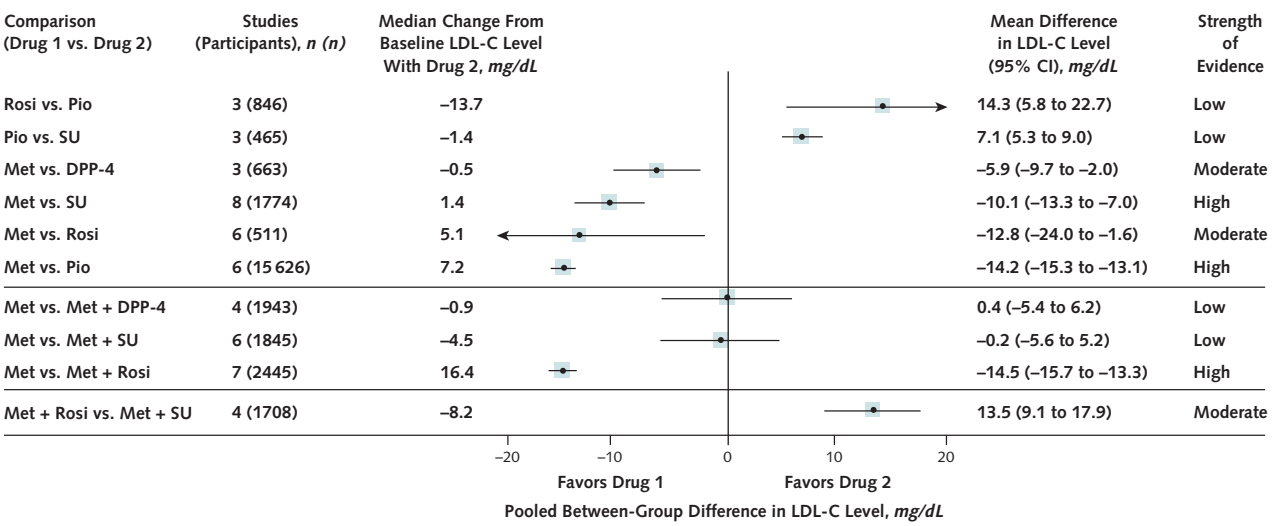
Pioglitazone increased HDL-C levels more than rosiglitazone, metformin, or sulfonylureas. The effects of monotherapy with rosiglitazone or sulfonylureas on HDL-C levels were similar to those of metformin. Compared with metformin monotherapy, metformin plus rosiglitazone increased HDL-C levels, whereas metformin plus DPP-4 inhibitors affected these levels similarly. Metformin plus either pioglitazone or rosiglitazone increased HDL-C levels more than the combination of metformin and a sulfonylurea. Combination therapy containing pioglitazone plus either metformin or a sulfonylurea tended to increase HDL-C levels more than therapies that did not contain pioglitazone (metformin monotherapy and metformin plus sulfonylurea) (**Appendix Figure 4**, available at www.annals.org).

Pioglitazone decreased triglyceride levels compared with metformin, whereas metformin decreased triglyceride levels compared with rosiglitazone. Metformin monotherapy decreased triglyceride levels compared with the combination of metformin and rosiglitazone. Metformin decreased triglyceride levels compared with sulfonylureas, and sulfonylureas and meglitinides had similar effects on triglyceride levels. The combination of metformin and pioglitazone decreased triglyceride levels compared with the combination of metformin and a sulfonylurea, whereas the combination of metformin and rosiglitazone and that of metformin and a sulfonylurea did not differ (**Appendix Figure 5**, available at www.annals.org).

Applicability of Evidence and Publication Bias

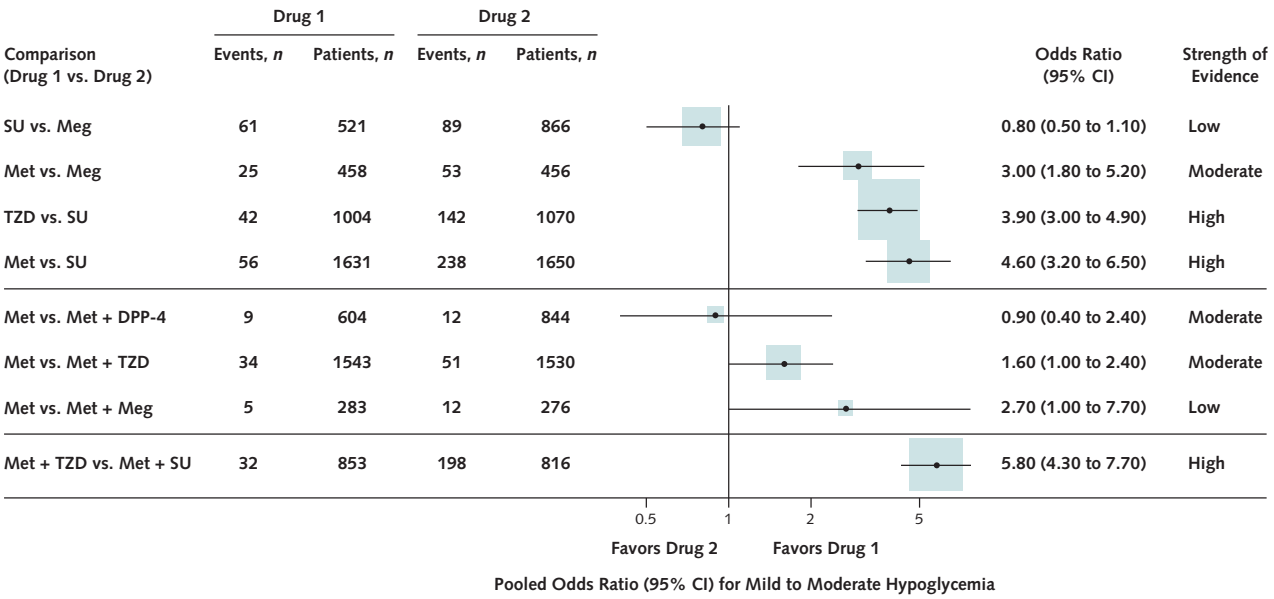
Participants included in studies of intermediate outcomes were generally younger, healthier, and less racially and ethnically diverse than the general population of adults with type 2 diabetes in the United States. Participants typically received diabetes medications for less than 2 years, a much shorter duration than for the average patient.

Figure 3. **Pooled between-group differences in LDL-C levels with monotherapy and combination therapies.**



Error bars represent 95% CIs. To convert LDL-C values to mmol/L, multiply by 0.0259. DPP-4 = dipeptidyl peptidase-4 inhibitor; LDL-C = low-density lipoprotein cholesterol; Met = metformin; Pio = pioglitazone; Rosi = rosiglitazone; SU = sulfonylurea.

Figure 4. **Pooled odds of mild or moderate hypoglycemia with monotherapy and combination therapies.**



Error bars represent 95% CIs. DPP-4 = dipeptidyl peptidase-4 inhibitor; Meg = meglitinide; Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione.

The Egger test ($P < 0.05$) suggested that publication bias may have caused overestimation of the effect on HbA_{1c} of metformin plus a thiazolidinedione compared with metformin, because large studies with small effects and small studies with large effects were included. The Egger test also suggested overestimation of the effect of metformin compared with rosiglitazone on triglyceride levels.

Comparative Safety

Hypoglycemia

Severe hypoglycemia did not seem to occur more often with any particular monotherapy or combination therapy. **Figure 4** shows the comparative safety of diabetes medications in terms of mild or moderate hypoglycemia. Sulfonylureas consistently increased the risk for hypoglycemia more than monotherapy with metformin, thiazolidinediones, DPP-4 inhibitors, or liraglutide. Sulfonylureas compared with metformin alone had a greater than 4-fold higher risk for hypoglycemia, and metformin plus a sulfonylurea compared with metformin plus a thiazolidinedione had almost a 6-fold higher risk. The DPP-4 inhibitors had a lower risk for hypoglycemia than sulfonylureas that was similar to that of metformin. Moderate strength of evidence showed that metformin plus basal insulin had lower risk for hypoglycemia than the combination of metformin plus a premixed insulin.

Other Adverse Effects

Table 2 summarizes the comparative safety of diabetes medications in terms of congestive heart failure, fractures, and gastrointestinal adverse effects. Few RCTs provided risk estimates for congestive heart failure. Thiazolidinediones increased the risk for congestive heart failure compared with sulfonylureas, with moderate strength of evidence, but the pooled odds ratio overlapped 1.0 (pooled odds ratio, 1.68 [CI, 0.99 to 2.85]) (**Appendix Figure 6**, available at www.annals.org).

Thiazolidinediones, either in combination with another medication or as monotherapy, were associated with a higher risk for bone fractures than was metformin alone or combined with a sulfonylurea. Fractures were mainly in the limbs and not the hips. Both ADOPT and RECORD, which were larger studies, reported elevated fracture risk among women receiving rosiglitazone compared with regimens containing sulfonylureas or metformin (24, 33).

The incidence of gastrointestinal adverse effects was higher for metformin than the thiazolidinediones and was similar for the thiazolidinediones and the sulfonylureas. Rates of liver injury were similarly low with thiazolidinediones and sulfonylureas. Moderate strength of evidence indicated no increased risk for lactic acidosis in metformin recipients than in persons receiving a sulfonylurea or a combination of metformin and a sulfonylurea. Few studies reported on the outcome of cancer, and definitive conclusions about the comparative risk could not be made.

Applicability of Evidence and Publication Bias

Studies tended to include younger patients; thus, the applicability of safety results to older patients is uncertain. Short study duration (≤2 years) and exclusion of participants with comorbid conditions limited the applicability of

study results regarding congestive heart failure and fractures, outcomes that are probably related to duration of exposure. We found no evidence of publication bias.

Discussion

To our knowledge, this systematic review is the first to address the comparative effectiveness of newer diabetes medication classes as monotherapy and in combination therapies for a wide range of clinical outcomes in patients with type 2 diabetes. The inclusion of additional trials and drug comparisons since the 2007 review did not provide sufficient evidence to definitively support one drug or combination of drugs over another for long-term clinical outcomes of mortality and macrovascular and microvascular complications of diabetes. When intermediate outcomes were evaluated, most diabetes medications reduced HbA_{1c}

Table 2. **Congestive Heart Failure, Fractures, and Gastrointestinal Adverse Effects Related to Monotherapy and Combinations of Medications for Type 2 Diabetes**

Comparison	Type and Number of Studies*	Participants, *n*	Range in Risk Estimates†	Strength of Evidence; Conclusion
Congestive heart failure				
Met vs. TZD	RCT: 3	5026	Met, 0%–1.3%; Rosi, 0.7%–1.5%; Pio, 0%	Moderate; neither drug favored
	Observational: 4	173 665	HR, 0.65–1.63	
Met vs. SU	Observational: 5	189 610	HR, 0.7–0.85	Moderate; favors Met
Rosi vs. Pio	Observational: 4	45 114	HR, 1.30 in 1 study; event rates for Rosi and Pio similar in 3 other studies	Low; unclear
TZD vs. SU	RCT: 4	6727	Pooled OR, 1.68 (95% CI, 0.99–2.85)	Moderate; favors SU
	Observational: 4	123 042	HR, 0.88–1.37	
TZD + SU vs. Met + TZD	Observational: 1	12 193	Met + TZD: 0.13/100 person-years; TZD + SU: 0.47/100 person-years	Low; favors Met + TZD
TZD + SU or Met vs. Met + SU	RCT: 1	4450	RR, 2.1	Low; favors Met + SU
Met + basal insulin vs. Met + another insulin	RCT: 1	67	0 or 1 event in each study group	Insufficient
Fractures				
Met vs. TZD	RCT: 2	4750	HR, 0.64; HR for women, 0.55 (CI, 0.36–0.85) (Met vs. Rosi)	High; favors Met
	Observational: 1	1 097 404	No statistical difference	
Met vs. SU	RCT: 2	2929	Met, 0%–4.1%; glyburide, 3.4%–5%	Low; unclear
	Observational: 1	91 521	No statistical difference between groups	
Met vs. Met + TZD	RCT: 1	411	0.5% in each group	Low; favors Met
	Observational: 2	77 864	HR, 0.65; OR, 0.15	
Met vs. Met + SU	RCT: 1	59	0 or 1 fracture in each study group	Low; unclear
Met vs. Met + DPP-4	RCT: 1	190	0 or 1 fracture in each study group	Low; unclear
TZD vs. SU	RCT: 2	4862	HR, 2.13 in 1 subanalysis; other RCT: Pio, 0%, and glyburide, 0.2%	High; favors SU
TZD + SU or Met vs. Met + SU	RCT: 1	4450	RR, 1.57; higher among women than men (RR, 1.82 vs. 1.23)	High; favors Met + SU
Gastrointestinal adverse effects				
Met vs. TZD	RCT: 5	5021	Diarrhea: Met, 15%–24%; TZD, 3%–8%	High; favors TZD
Met vs. SU	RCT: 11	5745	Diarrhea: Met, 2.4%–50%; SU, 0%–13%	Moderate; favors SU
Met vs. DPP-4	RCT: 2	1028	Overall rate: Met, 21%–31%; DPP-4, 12%–20%	Moderate; favors DPP-4
Met vs. Meg	RCT: 4	776	Overall rate (1 study): Met, 70%; Meg, 47%	Low; favors Meg
Met vs. Met + TZD	RCT: 8	2977	Overall rate: Met, 9%–15%; Met + TZD: 7%–17%	Moderate; favors Met + TZD
Met vs. Met + SU	RCT: 10	2786	Overall rate (1 study): Met, 32%; Met‡ + SU, 8%	Moderate; favors Met + SU
Met vs. Met + DPP-4	RCT: 6	3355	Overall rate: Met, 9%–31%; Met + DPP-4, 1%–29%	Low; unclear
Met vs. Met + Meg	RCT: 1	193	Abdominal pain: Met, 7%; Met + Meg, 12%	Low; unclear
TZD vs. SU	RCT: 4	6083	Diarrhea: TZD, 6%–9%; SU, 6%–10%	High; neither favored
TZD vs. Meg	RCT: 1	123	Overall rate: TZD, 3%; Meg: 5%	Low; unclear
SU vs. GLP-1	RCT: 2	895	Diarrhea: SU, 3.8%–9%; GLP-1, 6%–19% Overall rate (1 study): SU, 26%; GLP-1, 51%	Low; favors SU
Met + TZD vs. Met + SU	RCT: 4	1212	Overall rate: Met + TZD, 10%–13%; Met + SU, 11%–18%	Low; unclear
Met + TZD vs. Met + DPP-4	RCT: 1	181	Overall rate: Met + TZD, 7%; Met + DPP-4, 9%	Low; neither favored
Met + TZD vs. Met + GLP-1	RCT: 1	137	Vomiting: Met + TZD, 0%; Met + GLP-1, 22%	Low; unclear
Met + SU vs. Met + DPP-4	RCT: 1	1172	Nausea/vomiting: Met + SU, 4.2; Met + DPP-4, 3.5%	Low; neither favored

DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 agonist; HR = hazard ratio; Meg = meglitinide; Met = metformin; OR = odds ratio; Pio = pioglitazone; RCT = randomized, controlled trial; Rosi = rosiglitazone; RR = relative risk; SU = sulfonylurea; TZD = thiazolidinedione.
* Studies for which data on risk estimates were available.
† Absolute event rates are listed if RRs, HRs, or risk differences were not provided.
‡ A lower dose of metformin was used in the combination therapy group.

levels similarly, by about 1 absolute percentage point (consistent with the 2007 review). Metformin was consistently associated with weight reduction or neutrality compared with most other diabetes medications, which generally increased weight. Overall, medication effects on lipid levels were small to moderate and of uncertain clinical importance. Conclusions on comparative risk for adverse events were clearest for sulfonylureas and meglitinides, which increased the risk for hypoglycemia; for metformin, which was associated with increased gastrointestinal adverse effects; and for thiazolidinediones, which increased risk for heart failure.

Overall, combinations of 2 drugs compared with monotherapy had additive effects, in terms of not only improved glycemic control but also risk for adverse events and weight gain. The comparative benefit of one 2-drug combination over another was not clear. For example, metformin plus a sulfonylurea had efficacy similar to that of metformin plus a thiazolidinedione in reducing HbA_{1c} level and had a lower risk for heart failure, but the risk for hypoglycemia was increased 6-fold.

Although we did not perform a comprehensive review of the addition of insulin to oral medications, we include several clinically relevant comparisons. The addition of premixed insulin to metformin seemed to produce greater reduction in HbA_{1c} level, slightly greater weight gain, and higher risk for hypoglycemia than metformin plus basal insulin.

Two other recent systematic reviews compared add-on treatments with metformin in terms of HbA_{1c} level (34, 35). One review identified 16 placebo-controlled trials and 11 active-comparator trials of metformin combination therapy and concluded that sulfonylureas plus metformin were superior to thiazolidinediones plus metformin in reducing HbA_{1c} levels (34). In our analyses using direct comparisons, we did not detect a significant difference between these combinations, which was confirmed in a recent network meta-analysis (35). Our review adds to these recently published reviews by assessing combinations with thiazolidinediones and including more articles and additional meta-analyses.

The American Diabetes Association/European Association for the Study of Diabetes consensus statement has suggested consideration of a GLP-1 receptor agonist as an add-on treatment to metformin if weight gain is a concern (36), but no explicit recommendations were made regarding DPP-4 inhibitors. The American Association of Clinical Endocrinologists/American College of Endocrinology consensus algorithm recommends use of a DPP-4 inhibitor as one of several options for either initial monotherapy or second-line therapy and a GLP-1 agonist as one of several options for initial combination therapy with metformin when the HbA_{1c} level is 7.6% or greater (37). Overall, we found that the DPP-4 inhibitors improved HbA_{1c} to a lesser extent than metformin as monotherapy, but when added to metformin they reduced HbA_{1c} levels without additional risk for hypoglycemia. The GLP-1 agonists were associated with weight loss compared with sulfonylureas. We could not draw firm conclusions about most other comparisons for intermediate outcomes, safety, or long-term effects of GLP-1 agonists or DPP-4 inhibitors because few studies were available per drug comparison, but our findings were consistent with those of other recent systematic reviews (38–40).

In September 2010, the FDA placed restrictions on the use of rosiglitazone through a Risk Evaluation and Mitigation Strategy; in part, this will require clinicians to attest to and document that the benefits of the drug outweigh its 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 (41). Their conclusion was based on recent observational data (42, 43) and 2 meta-analyses by Nissen and Wolski (44, 45), as well as on increased understanding of the pharmacology of rosiglitazone (46). Other analyses, including the original 2007 review (11, 12, 47, 48), did not show an elevated risk for myocardial ischemia but had very imprecise point estimates. A notable addition to this update was RECORD, which reported that the combined study groups of rosiglitazone plus metformin and rosiglitazone plus sulfonylurea were noninferior to metformin plus sulfonylurea for the primary end point of hospitalization or death from cardiovascular disease. However, these findings were inconclusive for myocardial infarction, for which a non–statistically significant, slight increase in risk was seen in the 2 combined rosiglitazone (metformin or sulfonylurea plus rosiglitazone) groups (24). As the FDA acknowledged, RECORD was open-label with a noninferiority design, which may have limited its ability to ascertain the cardiovascular effects of rosiglitazone (49).

Our updated review informs the debate about rosiglitazone by providing a comprehensive comparative risk and benefit assessment relative 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. Overall, other than the risk for 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 (44, 45). We included studies that were done only in people with type 2 diabetes and had active comparators, whereas Nissen and Wolski included studies in people with other chronic diseases as well as placebo-controlled trials (44, 45). 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.

Our systematic review has limitations. First, because this was an update of a comprehensive review performed 2 years ago, we focused a priori on studies with active-control comparators, which are most relevant for clinical practice. The exclusion of placebo-controlled trials may have implications for the review, including missed rare adverse events. 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 and is known to be more effective than placebo. Because the current review is an update of a review that had included placebo-controlled trials, this was probably true for most drug comparisons (50). However, this assumption may be less valid for the newer medications saxagliptin, sitagliptin, nateglinide, exenatide, and liraglutide; evidence from other systematic reviews, such as Cochrane reviews, will be helpful in making conclusions about these agents (38, 39, 51).

Second, our inclusion criteria required that all studies meet 1 or more of the prespecified comparisons of interest; thus, studies with any number of "background medications" were excluded. Our goal was to avoid contamination with the intervention medications and to clearly identify combinations of medications. This criterion resulted in exclusion of several larger trials (4, 5, 7, 8, 52–57), some of which compared HbA_{1c}-lowering strategies rather than individual medications, and exclusion of some smaller trials and observational studies.

Third, we may have missed some studies and outcomes because our search was limited to English-language articles or because studies selectively reported results. Fourth, limitations of reporting in the included studies limited our ability to combine them in meta-analyses. For example, several studies did not report the significance of reported between-group differences and the measures of dispersion, thereby hindering our efforts to estimate effect size across trials. In addition, some trials underdosed comparison medications, limiting our ability to draw conclusions about efficacy.

Fifth, many included trials were industry-sponsored, raising the possibility of publication bias and other forms of bias, such as selective reporting of outcomes. Although we generally did not find publication bias, the tests had limited power to detect this owing to the small number of studies for many comparisons. Finally, most included studies were small and short with limited ability to detect clinically important harms and benefits most important to patients.

This updated comprehensive systematic review confirms the finding from the 2007 review that metformin, both as monotherapy and in combination with other medications, has the highest benefit–risk profile in most comparisons. Overall, we could not draw firm conclusions about the safety and long-term clinical outcomes of the newest agents, the DPP-4 inhibitors and the GLP-1 agonists, because studies were short-term and had few common comparators. Most 2-drug combinations had similar effects on glycemic control, but some combinations had lower comparative risk for hypoglycemia, weight gain, congestive heart failure, and fractures, which may affect the choice of a second agent. The comprehensiveness of this review allowed us to identify deficiencies in the published literature: most important, the need for future research to evaluate long-term clinical outcomes in higher risk subpopulations, such as different ethnic groups; older adults; and patients with underlying comorbid conditions, who may also have higher event rates.

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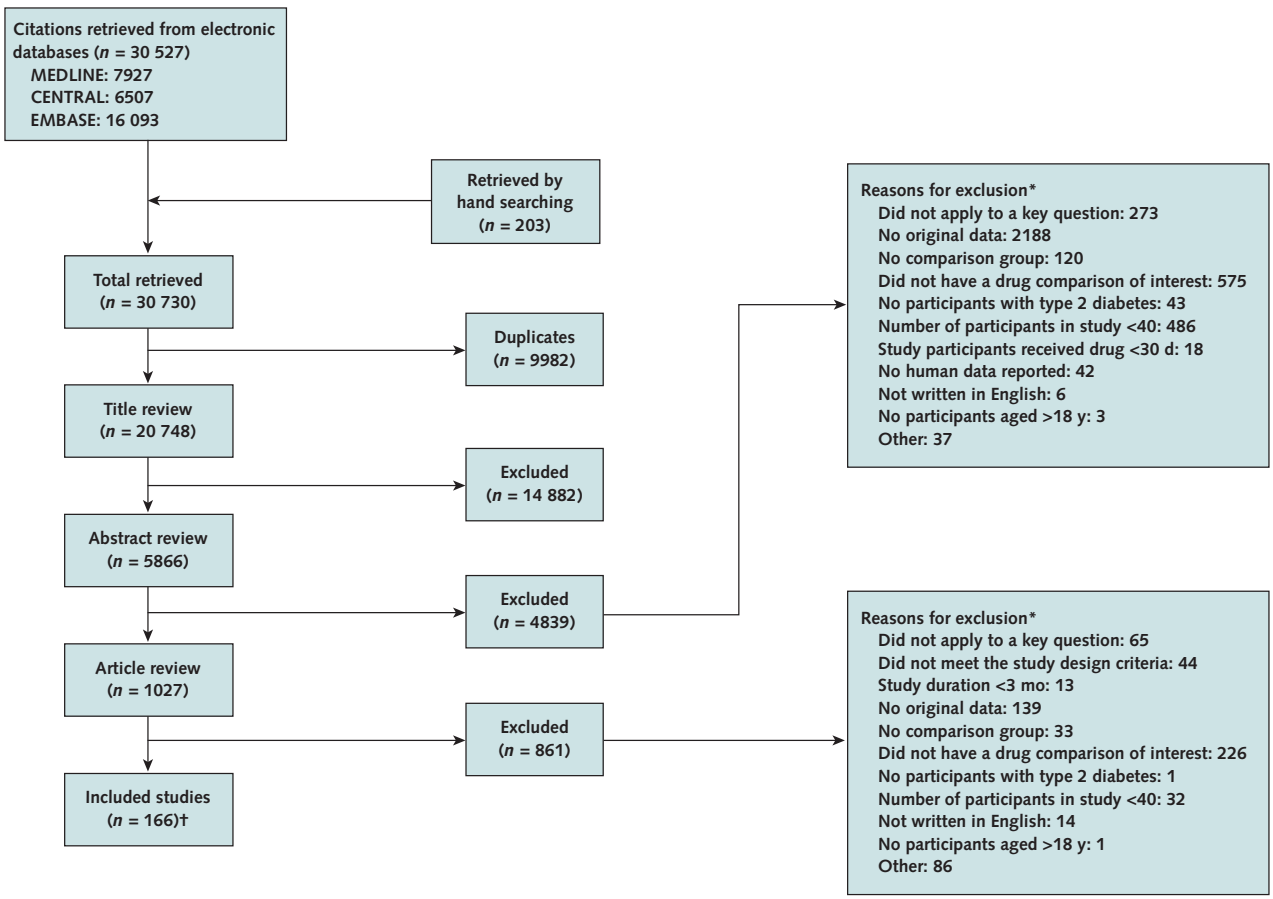
58. **Agarwal R, Saha C, Battiwala M, Vasavada N, Curley T, Chase SD, et al.** A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy. Kidney Int. 2005;68:285-92. [PMID: 15954919]

59. **Tolman KG, Freston JW, Kupfer S, Perez A.** Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. Drug Saf. 2009;32:787-800. [PMID: 19670918]

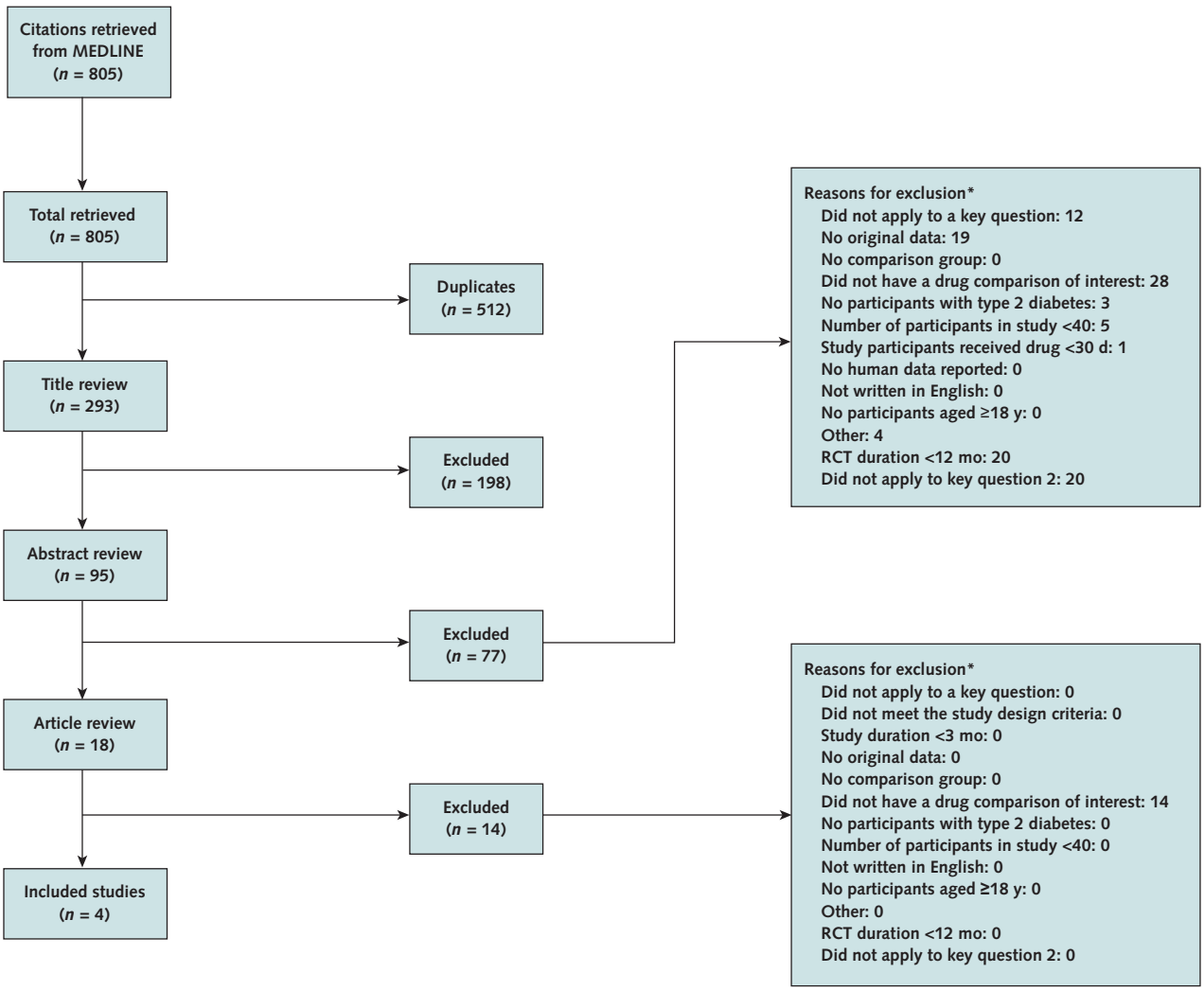
60. **St John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, et al.** A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care. 2002;25:2058-64. [PMID: 12401757]

Appendix Figure 1. **Summary of evidence search and selection.**



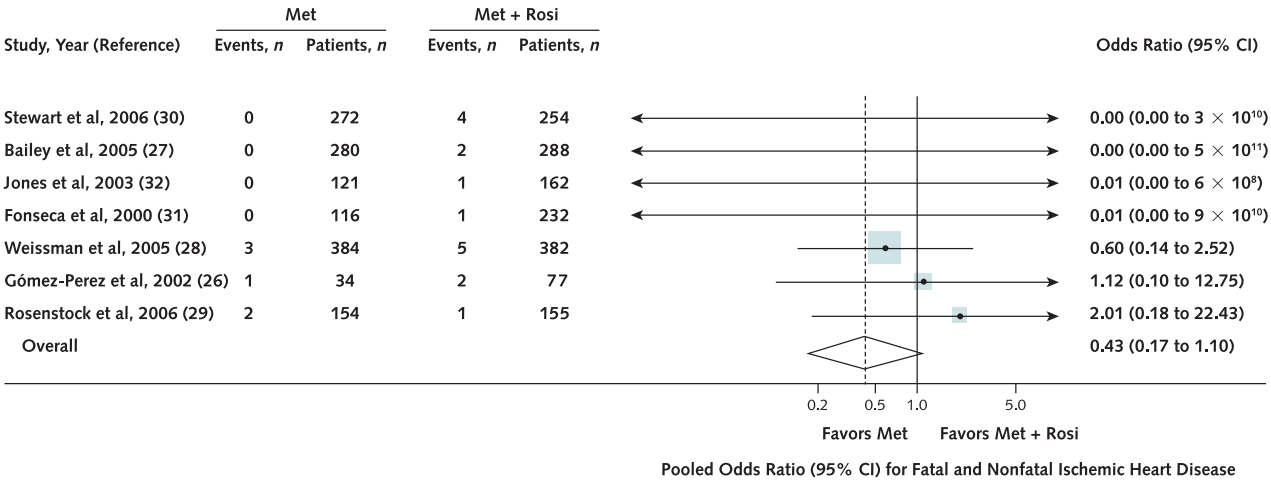
Searches were done through April 2010. CENTRAL = Cochrane Central Database of Controlled Trials.
* Total may exceed the number in the corresponding box because articles could be excluded for more than 1 reason at this level.
† 71 studies were included in the 2007 review.

Appendix Figure 2. **Summary of evidence search and selection for systematic reviews.**



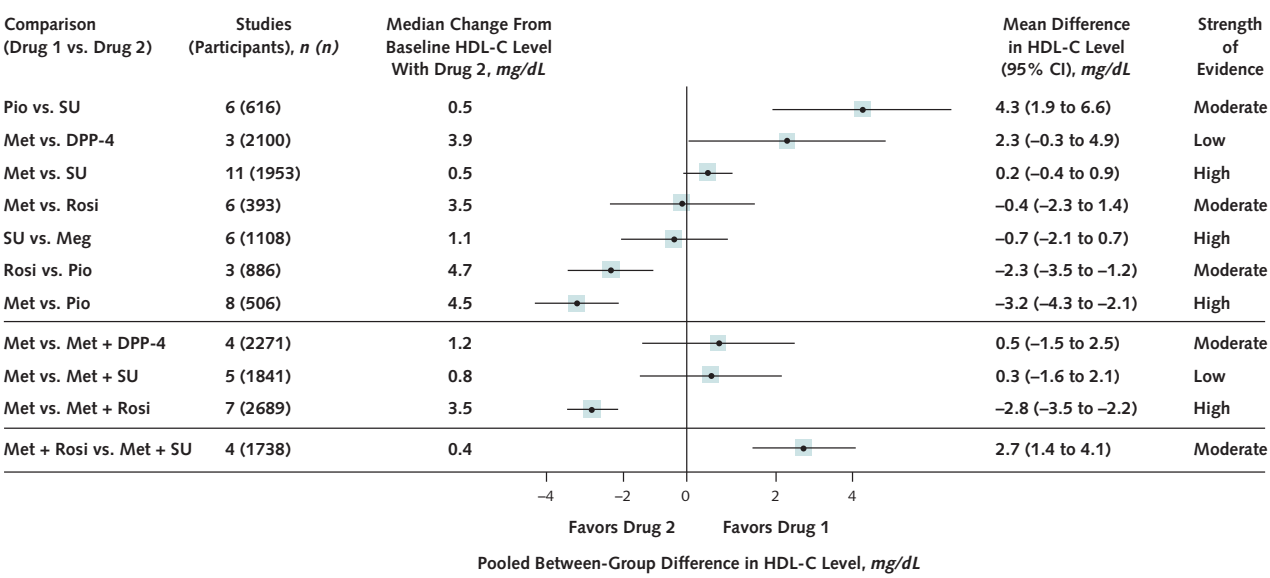
RCT = randomized, controlled trial.
* Total may exceed the number in the corresponding box because articles could be excluded for more than 1 reason at this level.

Appendix Figure 3. **Odds of fatal and nonfatal ischemic heart disease with metformin monotherapy and metformin plus rosiglitazone.**



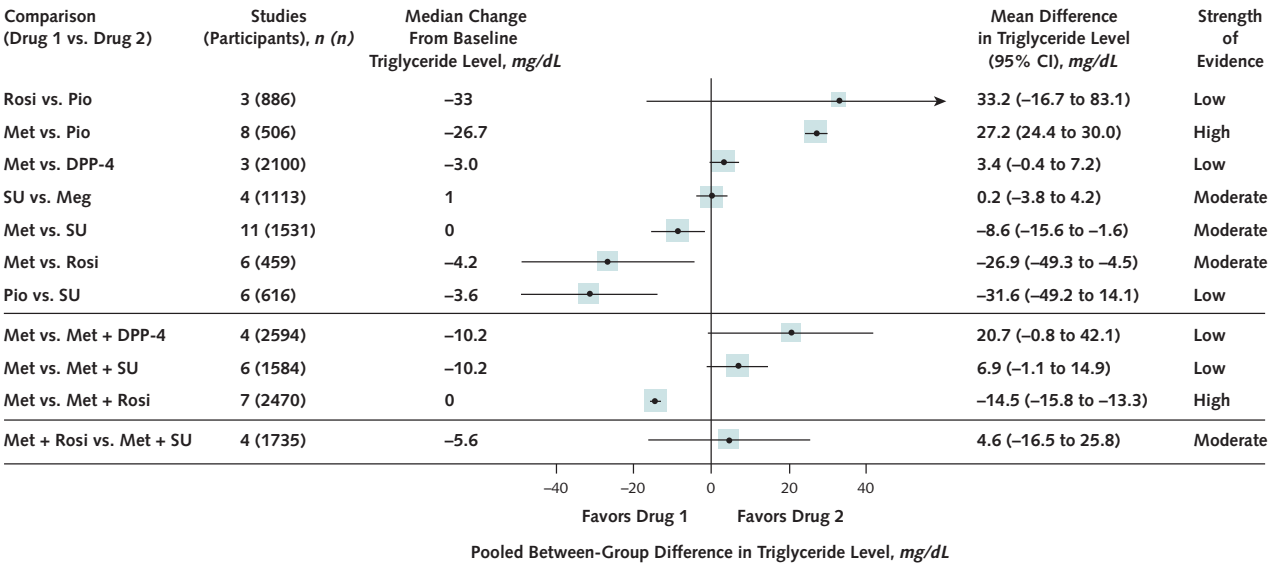
Error bars represent 95% CIs. Met = metformin; Rosi = rosiglitazone.

Appendix Figure 4. **Pooled between-group differences in HDL-C levels with monotherapy and combination therapies.**



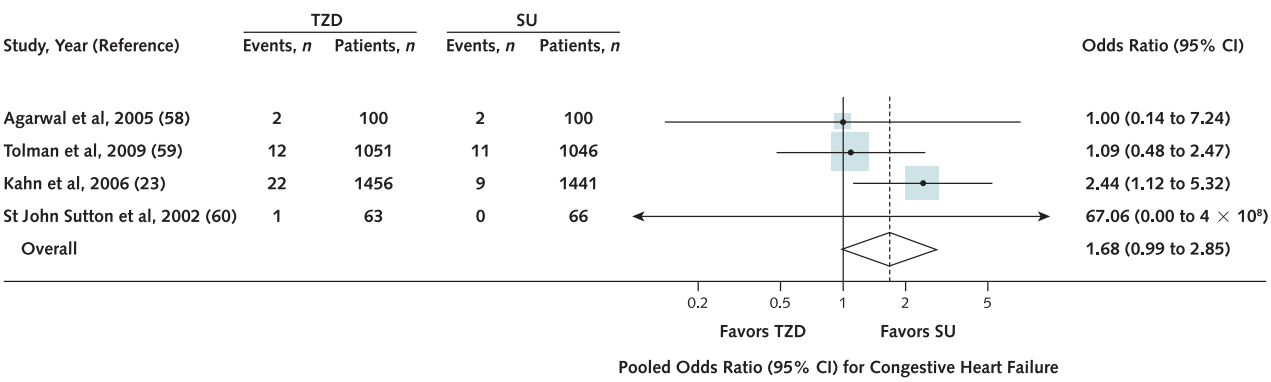
Error bars represent 95% CIs. To convert HDL-C values to mmol/L, multiply by 0.0259. DPP-4 = dipeptidyl peptidase-4 inhibitor; HDL-C = high-density lipoprotein cholesterol; Meg = meglitinide; Met = metformin; Pio = pioglitazone; Rosi = rosiglitazone; SU = sulfonylurea.

Appendix Figure 5. **Pooled between-group differences in triglyceride levels with monotherapy and combination therapies.**



Error bars represent 95% CIs. To convert triglyceride values to mmol/L, multiply by 0.0113. DPP-4 = dipeptidyl peptidase-4 inhibitor; Meg = meglitinide; Met = metformin; Pio = pioglitazone; Rosi = rosiglitazone; SU = sulfonylurea.

Appendix Figure 6. **Odds of congestive heart failure with thiazolidinediones and sulfonylureas.**



Error bars represent 95% CIs. SU = sulfonylurea; TZD = thiazolidinedione.