REVIEW

Annals of Internal Medicine

Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes

A Systematic Review and Meta-analysis

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Background: Clinicians and patients need updated evidence on the comparative effectiveness and safety of diabetes medications to make informed treatment choices.

Purpose: To evaluate the comparative effectiveness and safety of monotherapy (thiazolidinediones, metformin, sulfonylureas, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium–glucose cotransporter 2 [SGLT-2] inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists) and selected metformin-based combinations in adults with type 2 diabetes.

Data Sources: English-language studies from MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, indexed from inception through March 2015 (MEDLINE search updated through December 2015).

Study Selection: Paired reviewers independently identified 179 trials and 25 observational studies of head-to-head monotherapy or metformin-based combinations.

Data Extraction: Two reviewers independently assessed study quality and serially extracted data and graded the strength of evidence.

Data Synthesis: Cardiovascular mortality was lower for metformin versus sulfonylureas; the evidence on all-cause mortality, cardiovascular morbidity, and microvascular complications was insufficient or of low strength. Reductions in hemoglobin A_{1c} values were similar across monotherapies and metformin-based combinations, except that DPP-4 inhibitors had smaller effects. Body weight was reduced or maintained with metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors and increased with sulfonylureas, thiazolidinediones, and insulin (between-group differences up to 5 kg). Hypoglycemia was more frequent with sulfonylureas. Gastrointestinal adverse events were highest with metformin and GLP-1 receptor agonists. Genital mycotic infections were increased with SGLT-2 inhibitors.

Limitation: Most studies were short, with limited ability to assess rare safety and long-term clinical outcomes.

Conclusion: The evidence supports metformin as first-line therapy for type 2 diabetes, given its relative safety and beneficial effects on hemoglobin A_{1c}, weight, and cardiovascular mortality (compared with sulfonylureas). On the basis of less evidence, results for add-on therapies to metformin were similar to those for monotherapies.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2016;164:740-751. doi:10.7326/M15-2650 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 19 April 2016.

Type 2 diabetes and its complications are a substantial public health burden, affecting 9.3% of the U.S. adult population (1, 2). Most patients with type 2 diabetes eventually require glucose-lowering pharmacologic therapy, with a goal of reducing long-term complications. More than 7 classes of diabetes medications, which differ in their effects on glucose-lowering, safety, and other important outcomes, are recommended as first- or second-line therapy (3, 4).

The Agency for Healthcare Research and Quality (AHRQ) published 2 detailed reports comparing monotherapies and medication combinations for adults with type 2 diabetes (5, 6), but many new medications have been approved by the U.S. Food and Drug Administration (FDA) since then. These include medications in a new class, the sodium–glucose cotransporter 2 (SGLT-2) inhibitors, and several new dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

Evidence on the newer versus older diabetes medications continues to amass, and we performed an updated systematic review of the comparative effectiveness and safety of medications for type 2 diabetes in terms of intermediate, long-term, and safety outcomes. This review focused on monotherapy comparisons and combination comparisons that include metformin, with the aim of providing the range of stakeholders, including patients and clinicians, a synthesis of the current evidence on the most common monotherapies and combination therapies used to treat type 2 diabetes.

See also:

Web-Only
CME quiz

Methods

With input from a technical expert panel and representatives from AHRQ, we developed a protocol (available at www.effectivehealthcare.ahrq.gov). The full evidence report (7) has additional details on the methods and results, including search strategies and evidence tables.

Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The search strategy included terms for the diabetes medications of interest and terms for type 2 diabetes (Appendix Table 1, available at www.annals.org, provides the MEDLINE search strategy).

We ran the search developed for the prior review with the date restrictions of April 2009 through March 2015. We ran an additional search that included the Medical Subject Heading terms and text words for all of the new medications included in this update, without any date restrictions. After completion of the evidence report (7), we searched MEDLINE through December 2015, and updated our findings where the strength of evidence changed from low or insufficient to moderate or high.

We hand-searched the reference lists of all newly included articles and relevant systematic reviews. In addition, we searched ClinicalTrials.gov to identify relevant registered trials and reviewed the FDA Web site for any unpublished additional studies relevant to the topic as part of our gray-literature search.

Study Selection

Two reviewers independently screened titles, abstracts, and full-text articles for inclusion and resolved differences through consensus. We included English-language studies of nonpregnant adults with type 2 diabetes that evaluated at least 3 months of use of a diabetes medication or drug combination of interest. We included head-to-head monotherapy comparisons of metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists; comparisons of metformin alone with a metformin-based combination; and comparisons of metformin-based combinations where the second medication was one of the monotherapies described above or a basal or premixed insulin (Appendix Table 2, available at www.annals.org). We excluded studies that did not specify adjunctive medications. We excluded acarbose because of its infrequent use and the absence of new key studies that would substantially change the conclusions from our original report (5, 8).

We included randomized, controlled trials (RCTs) that evaluated all-cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety (7). We also included observational studies that adequately accounted for confounding, although not for the intermediate outcomes.

Data Extraction, Quality, and Applicability Assessment

Using standardized forms, reviewers extracted information on the general study and participant characteristics, interventions, comparisons, and the outcome results. A second reviewer confirmed the abstracted data.

Two independent reviewers assessed risk of bias in individual RCTs by using the criteria of Jadad and colleagues (9), as in our prior review (6). We used the Downs and Black tool for assessment of the risk of bias for the nonrandomized trials and observational studies (10). 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 created a set of detailed evidence tables. We conducted meta-analyses when data were sufficient (from at least 3 trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and medication dosing). When a trial had more than 1 study group, we included in the quantitative pooling the study group with drug doses and study durations most similar to the other studies for that comparison and outcome.

We pooled the mean difference between groups for continuous outcomes and calculated pooled odds ratios for the dichotomous outcomes using the intention-to-treat denominator. We evaluated the heterogeneity among the trials by using the I^2 statistic (11). We generated summary treatment effects with the random-effects model estimated by using the DerSimonian and Laird method in settings of low heterogeneity ($I^2 < 50\%$) (12) and the profile likelihood estimate in settings of high heterogeneity ($I^2 \geq 50\%$) (13).

Grading of the Evidence

Adapting an evidence grading scheme recommended in the AHRQ guide for conducting comparative effectiveness reviews (14), 2 reviewers sequentially graded the studies' limitations, consistency, directness, precision, and potential reporting bias for the evidence on each outcome and comparison. We graded the evidence separately for RCTs and observational studies. The final evidence grade and conclusion were based on the RCTs and could be strengthened by evidence from observational studies with few study limitations. 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 evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding a conclusion.

Role of the Funding Source

The AHRQ reviewed the protocol and report but did not participate in the literature search, determination of study eligibility, analysis, interpretation of findings, or preparation, review, or approval of the manuscript for publication.

RESULTS

Study and Quality Characteristics

We included 204 studies, 116 of which are newly identified, in this updated review (Appendix Figure, available at www.annals.org). Eighty-one percent were RCTs. Appendix Table 3 (available at www.annals.org)

Table 1. Effects of Metformin Compared With Sulfonylurea Monotherapy on Long-Term All-Cause Mortality and Cardiovascular Mortality and Morbidity

Outcome	Range in RR From RCTs	Range in RD From RCTs	Adjusted HR From Observational Studies	Strength of Evidence
All-cause mortality	0.5 to 1.0 (2 studies [15, 16])	−5.0% to −0.1% (2 studies [15, 16])	0.5 to 0.8 (7 studies* [17–23])	Low
CVD mortality	0.6 to 0.7 (2 studies [15, 16])	−2.9% to −0.1% (2 studies [15, 16])	0.6 to 0.9 (3 studies [19, 21, 24])	Moderate
CVD morbidity	0.7 to 1.6 (2 studies [15, 16])	−0.4% to 10.1% (2 studies [15, 16])	0.3 to 0.9 (5 studies† [19, 20, 22, 25, 26])	Low

CVD = cardiovascular disease; HR = hazard ratio; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk.
* One additional retrospective cohort study reported an odds ratio of 0.9 (27).
† One additional case–control study reported an odds ratio of 0.8 (28).

shows the number and design of studies, by outcome. Fifty studies were multicontinental; the others were conducted in Europe (55 studies), Asia (39 studies), and the United States (34 studies). Study durations ranged from 3 months to 8 years, but only 22 studies (7 RCTs) lasted longer than 2 years. Only 1 RCT specified a cardiovascular outcome as a primary outcome (15).

Study participants were overweight or obese men and women with baseline hemoglobin A_{1c} levels between 7% and 9%. About 45% of the RCTs did not report race/ethnicity. When reported, only 10% to 30% of the enrolled population was of nonwhite race. Most studies excluded older persons and those with clinically significant comorbid conditions.

Of the randomized trials, approximately one half reported on their randomization scheme. Sixty-five percent reported double-blinding, but most did not report steps taken to ensure double-blinding. Of the newly included RCTs, losses to follow-up exceeded 20% in the majority (>70%) of trials lasting 1 year or more and in 24% of those lasting less than 1 year. Most studies used the last-observation-carried-forward approach for analysis of intermediate outcomes. Of the newly included trials, use of rescue therapy was reported in 35%, but 42% did not report on this. All included observational studies were at low risk of bias. Sixty-seven percent of studies reported receiving funding from pharmaceutical companies. We did not identify substantive reporting bias that would have affected our findings.

All-Cause Mortality and Macrovascular and Microvascular Outcomes

Although we included 65 new studies (52 RCTs and 13 observational studies) for these outcomes in this review, the trials were largely 1 year or less in duration, with few or no events; the evidence was insufficient or of low strength for almost all comparisons for these outcomes. However, we found moderate strength of evidence that metformin monotherapy was associated with lower long-term (≥2 years) cardiovascular mortality compared with sulfonylurea monotherapy (Table 1), on the basis of consistent findings from 2 RCTs (3199 total participants) (15, 16) and 3 observational studies (115 105 total participants) (19, 21, 24) at low risk of bias.

Both RCTs showed a lower risk for cardiovascular mortality with metformin versus a sulfonylurea (Appendix Table 4, available at www.annals.org). The first, ADOPT (A Diabetes Outcome Progression Trial) (16), was conducted among patients with newly diagnosed, untreated diabetes. The incidence of fatal myocardial infarction was slightly lower in the metformin group (2 of 1454 participants [0.1%]; median follow-up, 4.0 years) than the glyburide group [3 of 1441 participants [0.2%]; median follow-up, 3.3 years); losses to follow-up were greater in the glyburide group than in the metformin group (44% vs. 38%, respectively) (16). The second, SPREAD-DIMCAD (Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease) (15), was a smaller RCT conducted in China among patients with known coronary heart disease (clinical evidence of acute myocardial infarction or coronary stenosis >50% on angiography) and also reported a lower risk for cardiovascular mortality for metformin compared with a sulfonylurea (7 of 156 participants [4.5%] vs. 11 of 148 participants [7.4%], respectively) over 5.0 years (15). Losses to follow-up were 5% in both groups of SPREAD-DIMCAD (15, 29). Cardiovascular mortality was part of the composite primary outcome for SPREAD-DIMCAD (15), whereas cardiovascular outcomes were considered adverse events and not actively ascertained in ADOPT (16). The 3 high-quality observational studies supported the findings of lower cardiovascular mortality with metformin compared with a sulfonylurea (Appendix Table 5, available at www.annals.org).

Findings were less consistent across studies of this comparison for all-cause mortality and cardiovascular morbidity. On the basis of the same set of RCTs and additional observational studies, metformin was associated with lower risk compared with sulfonylureas, but the evidence was of low strength for these outcomes (Table 1).

All other evidence on these outcomes for all of the other drug comparisons was of low strength or insufficient.

Comparative Effectiveness for Intermediate Outcomes

Hemoglobin A_{1c}

Most diabetes medications used as monotherapy (metformin, thiazolidinediones, and sulfonylureas) reduced hemoglobin A_{1c} to a similar degree in the short term, except for DPP-4 inhibitors, which were less effective than metformin or sulfonylureas (Figure 1). In the 2011 report (6), there were no significant between-group differences in hemoglobin A_{1c} with metformin versus sulfonylureas, and the strength of evidence was

graded as high; therefore, this comparison was not updated in this report. In this update, 2-drug combination therapies with metformin were more effective than metformin monotherapy in reducing hemoglobin A_{1c} (Figure 1). For the combination comparisons, the combination of metformin plus a GLP-1 receptor agonist reduced hemoglobin A_{1c} more than metformin plus DPP-4 inhibitors (Figure 1). Otherwise, most combination therapy comparisons with moderate strength of evidence had no clinically meaningful between-group differences (≥0.3%) in hemoglobin A_{1c} (Figure 1). Although we included comparisons with the GLP-1 receptor agonists and comparisons with metformin plus injectables (that is, GLP-1 receptor agonists, premixed insulin, and basal insulin), most of the evidence for these comparisons was insufficient or of low strength.

Body Weight

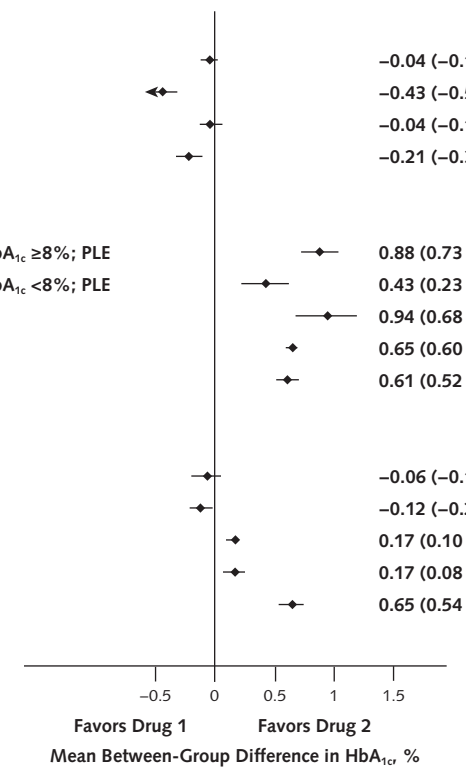
Medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) were favored compared with medications expected to increase weight (sulfonylureas, thiazolidinediones, and insulin) (Figure 2 and Appendix Table 6, available at www.annals.org). Metformin decreased body weight more than DPP-4 inhibitors, whereas sulfonylureas caused slightly less weight gain than thiazolidinediones (Figure 2). The SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors (Appendix Table 6). The combinations of metformin plus a GLP-1 receptor agonist and metformin plus an SGLT-2 inhibitor were both favored over the combination of metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 receptor agonist was favored over metformin plus a premixed insulin (Figure 2 and Appendix Table 6). Metformin plus a sulfonylurea had more favorable weight effects than metformin plus a premixed or basal insulin (Appendix Table 6). In the 2011 report (6), metformin reduced weight by about 2.5 kg versus thiazolidinedione and sulfonylurea monotherapy, with high strength of evidence; therefore, we did not update this evidence in the current review.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were evaluated for SGLT-2 inhibitors and GLP-1 receptor agonists only. We found moderate strength of evidence that the

Figure 1. Pooled between-group differences in the change in HbA_{1c} for comparisons of monotherapies and metformin-based combination therapies.

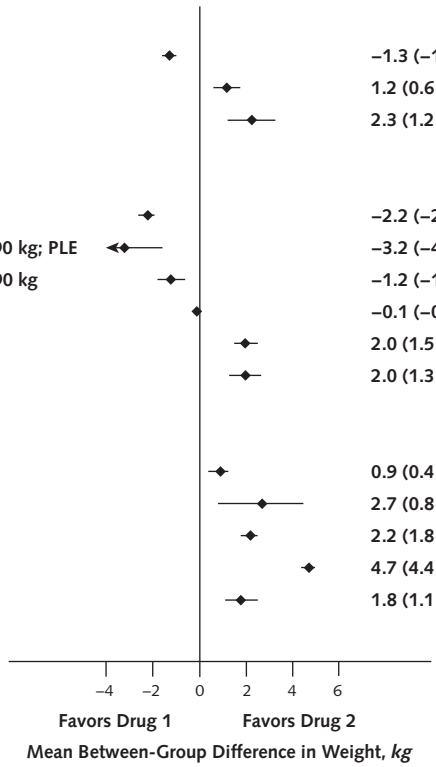
Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Participants, *n*	Study Characteristics	Effect Size (95% CI)	Strength of Evidence
Monotherapies					
Met vs. TZD	23	6733	≤52 wk	−0.04 (−0.11 to 0.03)	High
Met vs. DPP-4	6	2813	≤52 wk	−0.43 (−0.55 to −0.31)	High
TZD vs. SU	15	5986	≤52 wk	−0.04 (−0.13 to 0.06)	High
SU vs. DPP-4	3	769	≤52 wk	−0.21 (−0.32 to −0.09)	Moderate
Metformin vs. metformin-based combinations					
Met vs. Met + TZD	7	1718	≤52 wk; BL HbA_{1c} ≥8%; PLE	0.88 (0.73 to 1.04)	High
Met vs. Met + TZD	7	2022	≤52 wk; BL HbA_{1c} <8%; PLE	0.43 (0.23 to 0.63)	High
Met vs. Met + SU	15	3756	≤52 wk	0.94 (0.68 to 1.19)	High
Met vs. Met + DPP-4	26	11 285	≤52 wk	0.65 (0.60 to 0.70)	High
Met vs. Met + SGLT-2	9	2399	≤52 wk	0.61 (0.52 to 0.71)	High
Metformin-based combinations					
Met + TZD vs. Met + SU	8	3063	≤52 wk	−0.06 (−0.19 to 0.06)	Moderate
Met + TZD vs. Met + DPP-4	5	926	≤52 wk	−0.12 (−0.21 to −0.02)	Moderate
Met + SU vs. Met + SGLT-2	3	2933	104 wk	0.17 (0.10 to 0.20)	Moderate
Met + DPP4 vs. Met + SGLT-2	4	1278	≤52 wk	0.17 (0.08 to 0.26)	Moderate
Met + DPP4 vs. Met + GLP-1	3	1385	≤52 wk	0.65 (0.54 to 0.75)	Moderate



All differences for HbA_{1c} are absolute percentage-point differences. BL = baseline; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; Met = metformin; PLE = profile likelihood estimate; SGLT-2 = sodium–glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

Figure 2. Pooled between-group differences in the change in weight for comparisons of monotherapies and metformin-based combination therapies.

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Participants, *n*	Study Characteristics	Effect Size (95% CI)	Strength of Evidence
Monotherapies					
Met vs. DPP-4	6	2774	≤52 wk	−1.3 (−1.6 to −1.0)	High
TZD vs. SU	7	664	≤52 wk	1.2 (0.6 to 1.8)	High
SU vs. GLP-1	4	1710	≤52 wk; PLE	2.3 (1.2 to 3.3)	Moderate
Metformin vs. metformin-based combinations					
Met vs. Met + TZD	6	2860	≤52 wk	−2.2 (−2.6 to −1.9)	High
Met vs. Met + SU	5	1169	≤52 wk; BL wt ≥90 kg; PLE	−3.2 (−4.6 to −1.6)	High
Met vs. Met + SU	5	846	≤52 wk; BL wt <90 kg	−1.2 (−1.6 to −0.6)	High
Met vs. Met + DPP-4	20	10 564	≤52 wk	−0.1 (−0.3 to 0.01)	High
Met vs. Met + SGLT-2	7	2297	≤52 wk	2.0 (1.5 to 2.5)	High
Met vs. Met + GLP-1	5	1013	≤52 wk	2.0 (1.3 to 2.7)	Moderate
Metformin-based combinations					
Met + TZD vs. Met + SU	6	2572	≤52 wk	0.9 (0.4 to 1.3)	Moderate
Met + TZD vs. Met + DPP-4	4	674	≤52 wk	2.7 (0.8 to 4.5)	Moderate
Met + SU vs. Met + DPP-4	4	2373	≤52 wk	2.2 (1.8 to 2.5)	High
Met + DPP4 vs. Met + SGLT-2	3	2948	52–104 wk	4.7 (4.4 to 5.0)	High
Met + DPP4 vs. Met + GLP-1	3	1382	≤52 wk	1.8 (1.1 to 2.5)	Moderate



BL = baseline; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; PLE = profile likelihood estimate; SGLT-2 = sodium–glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione; wt = weight.

SGLT-2 inhibitors reduced systolic blood pressure by 3 to 5 mm Hg compared with other monotherapy when there were sufficient studies for pooling (Appendix Table 7, available at www.annals.org). For the metformin-based combinations, metformin plus an SGLT-2 inhibitor and metformin plus a GLP-1 receptor agonist reduced systolic blood pressure by 3 to 5 mm Hg more than metformin alone, with moderate to high strength of evidence (Appendix Table 7).

For heart rate, only 2 comparisons had sufficient data to grade the evidence as more than insufficient or low. Metformin plus an SGLT-2 inhibitor decreased heart rate more than metformin plus a sulfonylurea (pooled between-group difference in heart rate, 1.5 beats/min [95% CI, 0.6 to 2.3 beats/min]). The GLP-1 receptor agonists showed no between-group differences in heart rate compared with metformin monotherapy (Appendix Table 7).

Safety Outcomes

Hypoglycemia

Sulfonylureas were associated with increased risk for severe hypoglycemia as monotherapy (compared with metformin or thiazolidinedione) and in combination with metformin (compared with metformin plus a DPP-4 inhibitor or metformin plus an SGLT-2 inhibitor) (Table 2).

Sulfonylureas alone and in combination with metformin increased the risk for mild, moderate, or total hypoglycemia compared with all other monotherapies and metformin-based combinations for which we identified evidence (Figure 3 and Table 2). Metformin plus a basal or premixed insulin increased the risk for hypoglycemia over metformin plus a GLP-1 receptor agonist (Table 2), and metformin plus a basal insulin conferred a lower risk for hypoglycemia compared with the combination of metformin plus premixed insulin (Table 2).

Gastrointestinal Side Effects

Metformin and GLP-1 receptor agonists, as monotherapy or in combination, were associated with more gastrointestinal side effects (typically nausea, vomiting, or diarrhea) than were all other medications with sufficient studies for comparison (Figure 4 and Table 2). Metformin plus a GLP-1 receptor agonist yielded more gastrointestinal side effects than metformin plus DPP-4 inhibitors and metformin plus thiazolidinediones (Table 2). Nausea and vomiting were more common with GLP-1 receptor agonists than with metformin

(Figure 4). Metformin resulted in more diarrhea than metformin plus a thiazolidinedione (Figure 4).

Adverse Events Specific to SGLT-2 Inhibitors

We found moderate or high strength of evidence that SGLT-2 inhibitors, alone and in combination with metformin, increased the risk for genital mycotic infections compared with all other monotherapies and metformin-based combinations for which we identified evidence (Table 2). Evidence on the risk for fracture for SGLT-2 inhibitors as monotherapy or in combination with metformin was of low or insufficient strength (Appendix Tables 8 to 10, available at www.annals.org). Evidence on the comparative safety of SGLT-2 inhibitor–based comparisons regarding renal impairment, urinary tract infection, and volume depletion was also insufficient or of low strength.

Congestive Heart Failure

We found low strength of evidence that the risk for congestive heart failure was 1.2- to 1.6-fold greater with thiazolidinediones than with sulfonylureas (pooled odds ratio [OR], 1.6 [CI, 0.96 to 2.8]; range in risk dif-

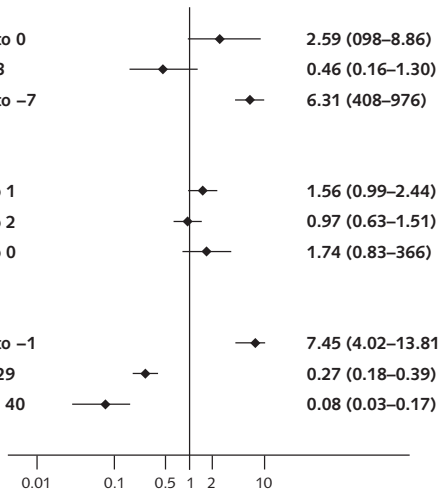
Table 2. Summary of the Moderate- to High-Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combination Therapy for Selected Safety Outcomes

Comparison	Study Type (Participants), *n (n)*	Range in OR; Range in RD*	Conclusion	Strength of Evidence
Severe hypoglycemia				
Met vs. SU	RCT: 2 (376) Observational: 1 (1789)	OR, 1.4 to 2; RD, 0.8% to 14% OR in normal renal function, 9.0 (95% CI, 4.9 to 16.4), and in impaired renal function, 6.0 (CI, 3.8 to 9.5)	Met favored	Moderate
SU vs. TZD	RCT: 2† (3304)	OR, 8; RD, 0.5%	TZD favored	Moderate
Met + SU vs. Met + DPP-4	RCT: 7 (8345)	Pooled OR for studies <52 wk: 0.2 (95% CI, 0.1 to 0.6) Pooled OR for studies ≥52 wk: 0.1 (CI, 0.03 to 0.3)	Met + DPP-4 favored	High
Met + SU vs. Met + SGLT-2	RCT: 2 (1779)	OR, 7; RD, 1% to 3%	Met + SGLT-2 favored‡	Moderate
Mild, moderate, or total hypoglycemia§				
SU vs. GLP-1	RCT: 5 (2467)	OR, 3.1 to 5.3; RD, 12% to 21%	GLP-1 favored for mild-moderate hypoglycemia	Moderate
SU vs. DPP-4	RCT: 4 (1065)	OR, 3.8 to 12.4; RD, 6% to 15%	DPP-4 favored	Moderate
Met + SU vs. Met	RCT: 10 (3732)	OR, 2 to 17; RD, 0% to 35%	Met favored	Moderate
Met + SU vs. Met + GLP-1	RCT: 3 (2557)	OR, 3.4 to 7.1; RD, 15% to 30%	Met + GLP-1 inhibitors favored†	Moderate
Met + GLP-1 vs. Met + basal or premixed insulin	RCT: 3 (460)	OR, 0.18 to 0.35; RD, –3% to –13%	Met + GLP-1 agonist favored‖	Moderate
Met + basal insulin vs. Met + premixed insulin	RCT: 5 (530)	OR, 0.23 to 0.89; RD, –5% to –28%	Met + basal insulin favored	Moderate
GI side effects¶				
GLP-1 vs. SU	RCT: 3 (1568)	OR, 1.4 to 2.4; RD, 3% to 9%	SU favored	Moderate
Met + GLP-1 vs. Met + DPP-4	RCT: 4 (2891)	OR, 1.0 to 7.7; RD, 0% to 23%	Met + DPP-4 favored	Moderate
Met + GLP-1 vs. Met + TZD	RCT: 1** (514)	OR, 2.9 to 6.3; RD, 8% to 19%	Met + TZD favored	Moderate
TZD vs. SU	RCT: 5 (6432)	OR, 0.78 to 2.02; RD, –1.2% to 1.7%	Neither favored	High
Met + SU vs. Met + TZD	RCT: 5 (1382)	OR, 0.5 to 2.0; RD, –5.0% to 2.1%	Neither favored	Moderate
Genital mycotic infections				
Metformin + SGLT-2 vs. Met	RCT: 9 (4035)	Pooled OR, 3.0 (CI, 1.2 to 7.2) for women Pooled OR, 2.7 (CI, 0.8 to 9.0) for men RD, –2.3% to 9.9%	Met favored	High
Met + SGLT-2 vs. Met + SU	RCT: 3 (3815)	Pooled OR, 5.2 (CI, 3.4 to 8.0) for women Pooled OR, 7.6 (CI, 4.0 to 14.4) for men RD, 7.1% to 17.4%	Met + SU favored	High
SGLT-2 vs. Met	RCT: 4 (2292)	Pooled OR, 4.1 (CI, 2.0 to 8.3) RD, –0.04% to 15.7%	Met favored	Moderate
Met + SGLT-2 vs. Met + DPP-4	RCT: 5 (3423)	RD, –2.8% to 8.8%	Met + DPP-4 favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; Met = metformin; OR = odds ratio; RCT = randomized, controlled trial; RD = risk difference; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* We present the range in ORs and RDs, unless otherwise specified.
† One study reported 2 severe events in the SU group and did not report on the outcome in the TZD group.
‡ Evidence is for studies lasting 1 to 2 y.
§ Only results where meta-analyses could not be performed. For meta-analysis results, see Figure 3.
‖ Evidence is for studies lasting 26 to 84 wk.
¶ Only results where meta-analyses could not be performed. For meta-analysis results, see Figure 4. Typical GI side effects were nausea, vomiting, or diarrhea.
** Reported on 3 GI outcomes: diarrhea, nausea, and vomiting.

Figure 3. Pooled odds ratios for mild and moderate hypoglycemia for comparisons of monotherapies and metformin-based combination therapies.

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Events/Participants, *n/N* Drug 1	Drug 2	Study Characteristics	Range in RD, %	Effect Size (95% CI)	Strength of Evidence
Monotherapies							
Met vs. SU	5	16/542	54/617	≤52 wk; PLE	−16 to 0	2.59 (098–8.86)	High
Met vs. SGLT-2	4	12/545	5/550	≤52 wk	0 to 3	0.46 (0.16–1.30)	Moderate
TZD vs. SU	5	26/763	148/784	≤52 wk	−25 to −7	6.31 (408–976)	High
Metformin vs. metformin-based combinations							
Met vs. Met + TZD	8	34/1543	51/1530	≤52 wk	−3 to 1	1.56 (0.99–2.44)	High
Met vs. Met + DPP-4	14	45/2204	56/3041	≤52 wk	−4 to 2	0.97 (0.63–1.51)	High
Met vs. Met + SGLT-2	7	11/946	23/949	≤52 wk	−3 to 0	1.74 (0.83–366)	Moderate
Metformin-based combinations							
Met + TZD vs. Met + SU	6	34/999	203/958	≤52 wk	−32 to −1	7.45 (4.02–13.81)	High
Met + SU vs. Met + DPP-4	4	244/967	58/966	<52 wk	4 to 29	0.27 (0.18–0.39)	High
Met + SU vs. Met + SGLT-2	3	559/1670	69/1656	104 wk; PLE	22 to 40	0.08 (0.03–0.17)	High



Relative risk for hypoglycemia shown by ranges in absolute RDs across study groups and as pooled odds ratios. DPP-4 = dipeptidyl peptidase-4; Met = metformin; PLE = profile likelihood estimate; RD = risk difference; SGLT-2 = sodium–glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

ference, 0% to 2%) or metformin (2 short RCTs with no events and one 4-year RCT with a risk difference of 3%; range in hazards ratios, 1.2 to 1.5 in 2 observational studies with 6 to 8 years of follow-up). We found low or insufficient strength of evidence on the comparative safety of DPP-4 inhibitors regarding congestive heart failure in mainly short studies (5 short RCTs reporting no events in the DPP-4 inhibitor groups, and 1 short RCT with 1 event in the metformin plus DPP-4 inhibitor group and none in the comparator group).

Other Safety Outcomes

The evidence on the outcomes of liver injury, lactic acidosis, pancreatitis, cancer, severe allergic reactions, and macular edema and decreased vision was of low strength or insufficient.

Applicability

Older patients and patients with comorbid conditions (who were often explicitly excluded) and racial and ethnic minorities were underrepresented in studies. The short duration of studies limited the applicability of results to the long-term care of patients with diabetes.

DISCUSSION

A major goal of glucose-lowering treatment in diabetes is to reduce long-term complications and death. Previously, no firm evidence supported the benefit of any one medication class over another for micro- or macrovascular outcomes or death (6, 30, 31). In this updated review of direct comparisons of monotherapies and metformin-based combination therapies for type 2 diabetes (with over 100 newly included articles), we found moderate-strength evidence that metformin monotherapy was associated with a lower risk for cardiovascular mortality compared with sulfonylurea monotherapy. This finding is consistent with results of the 10-year follow-up of the United Kingdom Prospective Diabetes Study, which provided indirect evidence (results for metformin vs. diet and sulfonylureas/insulin vs. diet) on the relative benefits of metformin and sulfonylureas for the spectrum of long-term outcomes important in diabetes (32). We could not draw substantive conclusions for any other comparisons for mortality or micro- or macrovascular outcomes, and we did not find substantive evidence on rare safety outcomes. In the absence of conclusive evidence on other long-term outcomes, this review provides detailed comparative evidence on intermediate and more frequent adverse events.

Most of the diabetes medications studied—including the newest class, the SGLT-2 inhibitors—reduced hemoglobin A_{1c} similarly, but DPP-4 inhibitors reduced hemoglobin A_{1c} less than metformin and sulfonylureas. Results for the comparative effects of GLP-1 receptor agonists on hemoglobin A_{1c} were inconsistent, raising the possibility of intraclass differences for this class of medications.

Obesity is common among patients with diabetes, and body weight is a treatment-related outcome that is important to patients (33). Our results show the clinically significant differential effects of the diabetes medications on weight (up to 5 kg): Thiazolidinediones, sulfonylureas, and insulin were associated with weight gain compared with medications that maintain or reduce weight (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors). We also found that SGLT-2 inhibitors and GLP-1 receptor agonists reduced systolic blood pressure by 3 to 5 mm Hg without concomitant increases in heart rate. However, whether these small differences in weight and blood pressure translate to differences in cardiovascular morbidity and mortality is unclear.

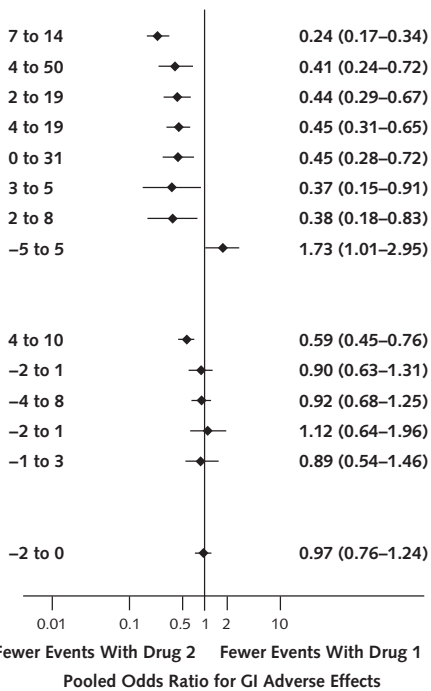
For monotherapies, we concluded the following for adverse events: Sulfonylureas increased hypoglycemia risk; metformin and GLP-1 receptor agonists increased gastrointestinal side effects; thiazolidinediones increased risk for congestive heart failure; and SGLT-2 inhibitors increased risk for genital mycotic infections. We had low-strength or insufficient evidence on the comparative effects of specific medication classes and outcomes that have been highlighted by recent FDA warnings regarding GLP-1 receptor agonists and pancreatitis (34, 35), GLP-1 receptor agonists and cancer (36–38), DPP-4 inhibitors and congestive heart failure (39), and SGLT-2 inhibitors and fracture (40).

Although we found less evidence on comparisons of add-on therapy to metformin, results for intermediate and safety outcomes were generally consistent with those for monotherapy. Notably, our review included several clinically relevant combinations of injectables (GLP-1 receptor agonists, basal insulin, and premixed insulins) with metformin, but we found conclusive evidence only for hypoglycemia and weight. The combination of metformin plus a GLP-1 receptor agonist was associated with a lower risk for hypoglycemia than metformin plus either premixed or basal insulin and was favored for its weight effects versus metformin plus premixed insulin. We also found that metformin plus basal insulin was associated with a lower risk for hypoglycemia than metformin plus premixed insulin.

Consistent with the prior report (6) and a Cochrane review on this topic (41), we did not find an increased risk for lactic acidosis with metformin, on the basis of limited evidence. A recent systematic review of predominantly observational studies (42) reported that the incidence of lactic acidosis among adults with mild to moderate chronic kidney disease receiving metformin was similar to that among persons with diabetes who are not receiving metformin (41). The FDA is currently reviewing 2 citizen petitions (43, 44) to expand the use of metformin to adults with diabetes and mild to moderate chronic kidney disease, with potential dose reductions to increase safety in these populations.

Figure 4. Pooled odds ratios for GI side effects for monotherapies and metformin-based combination therapies.

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Events/Participants, *n/N*		Outcome Type	Range in RD, %	Effect Size (95% CI)	Strength of Evidence
		Drug 1	Drug 2				
Monotherapies							
Met vs. TZD	6	187/1421	47/1330	Diarrhea	7 to 14	0.24 (0.17–0.34)	Moderate
Met vs. SU	6	146/625	73/697	Diarrhea	4 to 50	0.41 (0.24–0.72)	Moderate
Met vs. SU	3	86/361	47/345	Abdominal pain	2 to 19	0.44 (0.29–0.67)	Moderate
Met vs. SU	3	105/476	58/475	Nausea and vomiting	4 to 19	0.45 (0.31–0.65)	Moderate
Met vs. SU	4	111/336	63/315	Any GI adverse event	0 to 31	0.45 (0.28–0.72)	Moderate
Met vs. DPP-4	3	28/504	7/417	Nausea	3 to 5	0.37 (0.15–0.91)	High
Met vs. DPP-4	3	49/504	15/417	Diarrhea	2 to 8	0.38 (0.18–0.83)	High
Met vs. GLP-1	3	23/540	39/550	Vomiting	–5 to 5	1.73 (1.01–2.95)	Moderate
Metformin vs. metformin-based combinations							
Met vs. Met + TZD	6	269/1273	174/1262	Diarrhea	4 to 10	0.59 (0.45–0.76)	Moderate
Met vs. Met + DPP-4	8	64/1496	59/1495	Nausea	–2 to 1	0.90 (0.63–1.31)	Moderate
Met vs. Met + DPP-4	8	139/1056	192/1515	Any GI adverse event	–4 to 8	0.92 (0.68–1.25)	Moderate
Met vs. Met + DPP-4	7	22/1404	28/1588	Vomiting	–2 to 1	1.12 (0.64–1.96)	Moderate
Met vs. Met + SGLT-2	3	36/474	32/472	Diarrhea	–1 to 3	0.89 (0.54–1.46)	Moderate
Metformin-based combinations							
Met + SU vs. Met + DPP-4	4	141/2381	139/2379	Diarrhea	–2 to 0	0.97 (0.76–1.24)	High



DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; Met = metformin; RD = risk difference; SGLT-2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

Our findings are consistent with those of prior, less comprehensive systematic reviews that focused only on selected medication comparisons and outcomes (45–50), and this review fills many gaps left by prior work. Most reviews have not evaluated head-to-head comparisons and usually have evaluated one medication class against placebo or multiple medication classes for a limited number of outcomes. In this review, we include more recent articles, focus squarely on comparative effectiveness with direct medication comparisons, and provide a comprehensive synthesis of the range of outcomes important to clinicians and patients.

Our review has limitations. First, we excluded studies in which participants took nonstudy drugs for diabetes if the results were not stratified by medication. Owing to this exclusion, we did not include several large trials (51–65) because results did not allow evaluation of the head-to-head comparisons of interest in this review. For example, we found low strength of evidence on heart failure risk because of imprecision when comparing thiazolidinediones with metformin and sulfonylureas, but we excluded the large RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes) trial from assessment of the heart failure outcome because it compared thiazolidinediones with metformin or sulfonylureas without stratifying results (66).

In addition, although we identified short RCTs that could not substantiate any conclusions, 2 placebo-controlled studies (62, 64) and a recent systematic review that included placebo-controlled trials have raised concerns about increased risk for hospitalization for heart failure with DPP-4 inhibitors (67, 68).

Finally, we focused on interclass (and not intraclass) comparisons in this review. Although we did not combine studies where individual drugs were found to be a clinical or statistical source of heterogeneity, we may not have identified smaller intraclass differences.

Future research on the comparative effects of diabetes medications on long-term mortality; cardiovascular mortality and morbidity; microvascular outcomes; and rare, serious adverse events should be prioritized. Because of the low frequency of and long time frame needed for events, RCTs are not feasible as the primary study design to obtain substantive evidence on these outcomes. Thus, high-quality observational studies are needed to address the large evidence gap on the long-term comparative effectiveness and safety of diabetes medications in a timely fashion. In particular, future observational studies should 1) include samples of sufficient size, with longitudinal follow-up and detailed data on treatments and confounding variables; and 2) address major sources of bias (confounding by indication, immortal time bias, time- and cumulative exposure-varying incidence of outcomes, reverse causation, informative censoring, time-varying drug exposure, and time-dependent confounding) (69).

In summary, the evidence from this systematic review supports current guidelines (31, 70) with metformin as the recommended first-line agent to treat adults with type 2 diabetes, given its beneficial effects on hemoglobin A_{1c}, weight, and cardiovascular mortality (versus sulfonylureas) and relative safety profile. All of the medications have specific side effects, and the newer medications are not necessarily safer than the older medications. In the absence of more evidence on the effects of glucose-lowering medications on long-term diabetes complications, patient factors (such as comorbid conditions) and preferences regarding the known comparative effects (for example, hemoglobin A_{1c}, weight, hypoglycemia, and gastrointestinal side effects), tolerance of uncertainty in risk, and logistical considerations (including administration and cost) should continue to drive the selection of a second or alternative agent to metformin in the treatment of type 2 diabetes.

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Acknowledgment: The authors thank their Task Order Officers at AHRQ, Drs. Karen Lee and Elisabeth Kato, and their Associate Editor at the RAND Corporation, Dr. Margaret A. Maglione, for their guidance on this review, as well as Jessica Gayleard for her help in reviewing articles.

Financial Support: This project was funded under contract 290-2012-00007-I from AHRQ, U.S. Department of Health and Human Services.

Disclosures: Dr. Maruthur reports a contract with AHRQ during the conduct of the study. Ms. Wilson reports a contract with AHRQ during the conduct of the study. Dr. Berger reports a contract with AHRQ during the conduct of the study. Dr. Segal reports a contract with AHRQ during the conduct of the study. Dr. Bolen reports a contract with AHRQ during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2650.

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Appendix Table 1. MEDLINE Search String

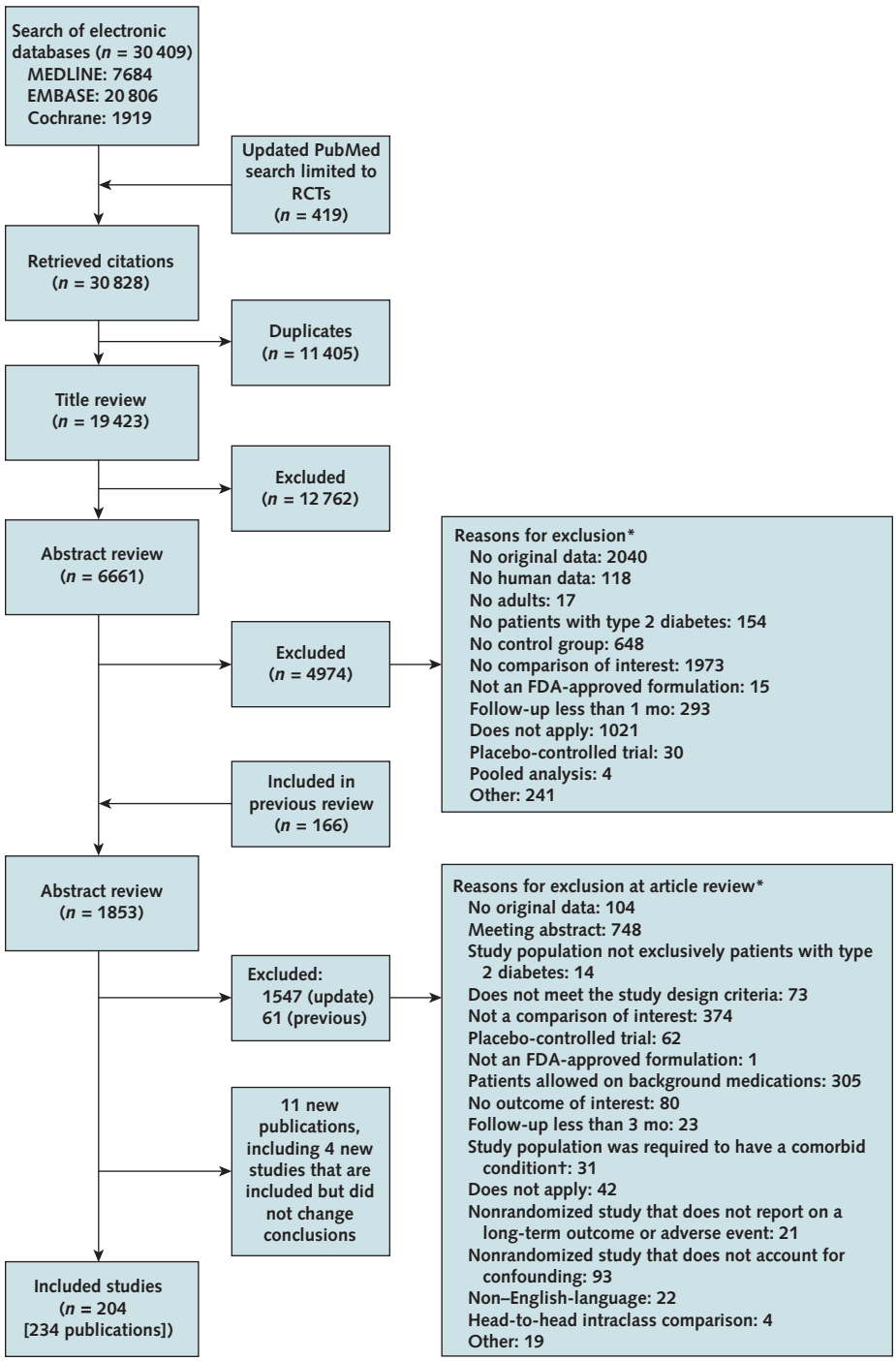
Search	String
1	("diabetes mellitus, type 2"[mh] or (diabet*[tiab] and ("non-insulin dependent"[tiab] or type-2[tiab] or "type II"[tiab] or "type 2"[tiab]))) AND ("metformin"[mh] or "thiazolidinediones"[mh] or "glipizide"[mh] or "glyburide"[mh] or "Dipeptidyl-Peptidase IV Inhibitors"[mh] or "Glucagon-Like Peptide 1"[mh] or biguanide*[tiab] or metformin[tiab] or thiazolidinedione*[tiab] or pioglitazone[tiab] or rosiglitazone[tiab] or sulfonylurea*[tiab] or sulphonylurea*[tiab] or glipizide[tiab] or glyburide[tiab] or glimepiride[tiab] or glibenclamide[tiab] or "insulin secretagogues"[tiab] or sitagliptin*[tiab] or saxagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or liraglutide[tiab] or exenatide[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt]) AND (("2009/04/01"[edat] : "2014/07/11"[edat]))
2	("diabetes mellitus, type 2"[mh] or (diabet*[tiab] and ("non-insulin dependent"[tiab] or type-2[tiab] or "type II"[tiab] or "type 2"[tiab]))) AND (linagliptin*[tiab] or alogliptin*[tiab] or albiglutide*[tiab] or dulaglutide*[tiab] or "sodium–glucose cotransporter 2 inhibitors"[tiab] or "sodium–glucose cotransporter 2 inhibitor" [tiab] or "SGLT-2" [tiab] or "canagliflozin"[tiab] or "dapagliflozin"[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])
3	("diabetes mellitus, type 2"[mh] or (diabet*[tiab] and ("non-insulin dependent"[tiab] or type-2[tiab] or "type II"[tiab] or "type 2"[tiab]))) AND (empagliflozin*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])

Appendix Table 2. Priority Medication Comparisons Included for Each Key Question

Therapy	Main Intervention Class (Generic Individual Drug)	Comparison
Monotherapy as main intervention	Biguanides (metformin)	TZD* SU† DPP-4 inhibitors SGLT-2 inhibitors GLP-1 receptor agonists‡ Combination of metformin + TZD Combination of metformin + SU Combination of metformin + DPP-4 inhibitor Combination of metformin + SGLT-2 inhibitor Combination of metformin + GLP-1 receptor agonist
	TZD (rosiglitazone or pioglitazone)	SU DPP-4 inhibitors SGLT-2 inhibitors GLP-1 receptor agonists
	SU (glimepiride, glyburide¶, glibenclamide¶, or glipizide)	DPP-4 inhibitors SGLT-2 inhibitors GLP-1 receptor agonists
	DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, or sitagliptin)	SGLT-2 inhibitors GLP-1 receptor agonists
	SGLT-2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin)	GLP-1 receptor agonists
Combination therapy as main intervention	Combination of metformin plus (TZD or SU or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin)	Combination of metformin + (SU or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin‡ or premixed insulin‡)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium–glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.
* For studies comparing TZD with metformin, we review only the outcomes of hemoglobin A_{1c}, long-term outcomes, and selected safety outcomes, given the high strength of evidence from our prior evidence report for other outcomes (specifically, fracture and body weight) (6).
† For studies comparing SU with metformin, we review only the long-term outcomes and cancer, given the high strength of evidence on the other outcomes from the prior comparative effectiveness review (6).
‡ The generic individual drug names for the GLP-1 receptor agonists are exenatide, liraglutide, dulaglutide, and albiglutide. The generic individual drug names for basal insulin are insulin glargine, insulin detemir, and neutral protamine Hagedorn (NPH) insulin. The generic individual drug names for premixed insulin are NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, and insulin aspart 70/30.
¶ Glyburide and glibenclamide are the same drug.

Appendix Figure. Summary of evidence search and selection.



FDA = U.S. Food and Drug Administration; RCT = randomized, controlled trial.
* Total may exceed the number in the corresponding box because articles could be excluded for >1 reason at this level.
† Comorbid condition restrictions were end-stage renal disease, end-stage liver disease, cancer, new-onset diabetes after transplant, or a cardiovascular event within 3 mo (such as acute coronary syndrome, acute myocardial infarction, post–coronary artery bypass graft surgery, or drug-eluting stents).

Appendix Table 3. Number of Studies for Each Type of Outcome*

Type of Study	All-Cause Mortality and Macro- and Microvascular Outcomes	Intermediate Outcomes	Safety Outcomes
Randomized, controlled trials	98	167	142
Observational studies	22	Not applicable	8
Total	120	167	150

* A detailed list of outcomes provided in the full report (7).

Appendix Table 4. Randomized, Controlled Trials Comparing the Effects of Metformin and Sulfonylurea Monotherapy on Cardiovascular Mortality Among Patients With T2DM

Study, Year (Reference)	Population	Primary Outcome	Ascertainment of CVD	Metformin				Sulfonylurea			
				Daily Dose, *mg*	Loss to Follow-up, %	Median Follow-up, *y*	Events/Patients, *n/N* (%)	Daily Dose, *mg*	Loss to Follow-up, %	Median Follow-up, *y*	Events/Patients, *n/N* (%)
ADOPT, 2006 (16)	Recent* diagnosis of T2DM + no prior pharmacotherapy	Time to monotherapy failure	Collected through adverse event reporting	2000 (maximum)	38	4.0	Fatal MI: 2/1454 (0.1)	Glyburide: 15 mg (maximum)	44	3.3	Fatal MI: 3/1441 (0.2)
SPREAD-DIMCAD, 2013 (15)	T2DM + CAD†	Composite CVD‡	Active; confirmed by medical records and death certificates	1400 (mean)	5	5.0	CVD death: 7/156 (4.5)	Glipizide: 28.3 (mean)	5	5.0	CVD death: 11/148 (7.4)

ADOPT = A Diabetes Outcome Progression Trial; CAD = coronary artery disease; CVD = cardiovascular disease; MI = myocardial infarction; SPREAD-DIMCAD = Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease; T2DM = type 2 diabetes mellitus.
* Diagnosed in the past 3 y.
† Documented acute MI (by cardiac enzymes, electrocardiography, and symptoms) or >50% stenosis of coronary artery on angiography.
‡ Nonfatal MI or stroke; percutaneous transluminal coronary angioplasty or coronary artery bypass graft, death from CVD, or death from any cause.

Appendix Table 5. Observational Studies Comparing the Effects of Sulfonylurea and Metformin Monotherapy on Cardiovascular Mortality

Study, Year (Reference)	Cohort	Population	Outcome Ascertainment	Confounding	Metformin Group		Sulfonylurea Group		Adjusted HR (95% CI) for CVD Mortality
					Events/Patients, *n/N* (%)	Median Follow-up, *y*	Events/Patients, *n/N* (%)	Median Follow-up, *y*	
Johnson et al, 2005 (24)	Saskatchewan Health database*	New, exclusive users of sulfonylurea or metformin (1991–1999) using sufficient medication†	ICD-9 codes for cardiovascular-related death from vital statistics	Propensity-score adjustment	61/923 (6.6)	4.3	254/2138 (11.9)	4.5	0.76 (0.58–1.00) Reference: sulfonylurea
Andersson et al, 2010 (21)	Danish National Patient Register‡	Use of sulfonylurea or metformin 90 d prior to hospitalization for new heart failure§ (1997-2006)	ICD-10 codes for cardiovascular death	Multivariate adjustment	103/688 (15)	2.3‖	1378/3615 (38.1)	2.3‖	0.79 (0.65–0.96) Reference: sulfonylurea
Schramm et al, 2011 (19)	Danish National Patient Register‡	New users of sulfonylurea or metformin (1997–2006)	ICD-10 codes for cardiovascular death from National Causes of Death Register	Propensity matching					
					Prior MI				
					2906	1.76	Glibenclamide: 1168	2.28	Glibenclamide: 1.50 (1.22–1.84)
							Glipizide: 660	2.19	Glipizide: 1.63 (1.28–2.07)
							Glimepiride: 3894	1.98	Glimepiride: 1.32 (1.11–1.57)
									Reference: metformin
					No Prior MI				
					43 340	1.67	Glibenclamide: 12 495	2.35	Glibenclamide: 1.14 (1.03–1.25)
							Glipizide: 6965	2.35	Glipizide: 1.25 (1.12–1.40)
							Glimepiride: 36 313	2.11	Glimepiride: 1.28 (1.18–1.38)
									Reference: metformin

CVD = cardiovascular disease; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction.
* Saskatchewan Health covers >90% of residents of Saskatchewan (excluding Indians, inmates, military, and police).
† Dispensed minimum daily dose for at least 6 mo during follow-up.
‡ Information on all dispensed drugs available for Danish residents since 1995, and all hospitalizations since 1978 registered with discharge diagnosis or diagnoses.
§ Unclear whether this population was included in Schramm and colleagues' study (19).
‖ Follow-up time by treatment not reported.

Appendix Table 6. Summary of the Moderate- to High-Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combination Therapy Where Meta-analyses Could Not Be Conducted for Weight

Comparison	RCTs (Participants), *n (n)*	Range in Mean Between-Group Differences	Conclusion	Strength of Evidence
SU vs. DPP-4 inhibitors	4 (1659)	0.7 to 1.8 kg	DPP-4 inhibitors favored	Moderate
DPP-4 inhibitors vs. TZD	2 (1475)	−2.3 to −2.5 kg	DPP-4 inhibitors favored	Moderate
GLP-1 receptor agonists vs. TZD	2 (1048)	Both studies: −3.5 kg	GLP-1 receptor agonists favored	Moderate
SGLT-2 inhibitors vs. Met	3 (1903)	−1.3 to −1.4 kg	SGLT-2 inhibitors favored	Moderate
SGLT-2 inhibitor vs. DPP-4 inhibitors	1 (899)	−2.5 to −2.7 kg	SGLT-2 inhibitors favored	Moderate
Met + SGLT-2 inhibitors vs. Met + DPP-4 inhibitors	5 (3423)	−1.8 to −3.6 kg	Met + SGLT-2 inhibitors favored	Moderate
Met + SU vs. Met + premixed or basal insulin	3 (894)	−1.7 to −0.6 kg	Met + SU favored	Moderate
Met + GLP-1 receptor agonists vs. Met + premixed insulin	2 (426)	−1.9 to −5.1 kg	Met + GLP-1 receptor agonists favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; RCT = randomized, controlled trial; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylureas; TZD= thiazolidinedione.

Appendix Table 7. Summary of the Moderate- to High-Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combination Therapy for Systolic Blood Pressure and Heart Rate

Comparison	RCTs (Participants, *n (n)*	Pooled Mean Between-Group Differences (95% CI)	Conclusion	Strength of Evidence
Systolic blood pressure				
SGLT-2 inhibitors vs. Met	4 (1651)	2.8 mm Hg (2.6–3.0 mm Hg)	SGLT-2 inhibitors favored	Moderate
Met + SGLT-2 inhibitors vs. Met	7 (3988)	4.4 mm Hg (2.9–6.0 mm Hg)	Met + SGLT-2 inhibitors favored	High
Met + GLP-1 receptor agonists vs. Met	5 (2688)	3.1 mm Hg (1.4–4.9 mm Hg)	Met + GLP-1 agonists favored	Moderate
Met + SGLT-2 inhibitors vs. Met + SU	3 (3815)	5.1 mm Hg (4.2–6.0 mm Hg)	Met + SGLT-2 inhibitors favored	High
Met + SGLT-2 inhibitors vs. Met + DPP-4 inhibitors	4 (3423)	4.1 mm Hg (3.6–4.6 mm Hg)	Met + SGLT-2 inhibitors favored	Moderate
Heart rate				
Met vs. GLP-1 receptor agonists	2 (820)	0.5–1.2 (range in between-group differences)	Neither drug favored	Moderate
Met + SGLT-2 inhibitors vs. Met + SU	3 (3815)	1.5 beats/min (0.6–2.3 beats/min)	Met + SGLT-2 inhibitor favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; RCT = randomized, controlled trial; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea.

Appendix Table 8. Randomized, Controlled Trials Comparing Metformin With Metformin Plus an SGLT-2 Inhibitor for Fracture Risk

Study, Year (Reference)	Follow-up, *wk*	Definition of Fracture	Ascertainment of Fracture	Loss to Follow-up, %*	Events/Patients, *n/N (%)*	
					Met	Met + SGLT-2 Inhibitor
Yang et al, 2015 (71)	24	Ankle and lower limb (nonhip) fracture	NR	7–12	1/145 (0.7)	Met + dapagliflozin, 5 mg: 0/147 (0) Met + dapagliflozin, 10 mg: 2/152 (1.3)
Schumm-Draeger et al, 2015 (72)	16	Hip fracture	NR	6–9	0/101 (0)	Met + dapagliflozin, 5 mg: 0/100 (0) Met + dapagliflozin, 10 mg: 0/99 (0)
Bailey et al, 2013 (73)	102	Nonhip fracture	NR	30–47	2/137 (1.5)	Met + dapagliflozin, 2.5 mg: 2/137 (1.5) Met + dapagliflozin, 5 mg: 2/137 (1.5) Met + dapagliflozin, 10 mg: 3/135 (2.2)
Bolinder et al, 2014 (74)	102	Nonhip fracture	NR	23.1	1/91 (1.1)	Met + dapagliflozin, 10 mg: 1/91 (1.1)

Met = metformin; NR = not reported; SGLT-2 = sodium–glucose cotransporter-2.
* Range in loss to follow-up across groups.

Appendix Table 9. Randomized, Controlled Trials Comparing Metformin Plus an SU With Metformin Plus an SGLT-2 Inhibitor for Fracture Risk

Study, Year (Reference)	Follow-up, *wk*	Definition of Fracture	Ascertainment of Fracture	Loss to Follow-up, %*	Events/Patients, *n/N (%)*	
					Met + SU	**Met + SGLT-2 Inhibitor**
Nauck et al, 2014 (75)	104	Nonhip fracture	NR	23	Met + glipizide: 9/408 (2.2)	Met + dapagliflozin, 10 mg: 6/406 (1.5)
Ridderstråle et al, 2014 (76)	104	Nonhip fracture	NR	8–9	Met + glimepiride: 17/780 (2)	Met + empagliflozin, 25 mg: 19/765 (2)

Met = metformin; NR = not reported; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea.
* Range in loss to follow-up across groups.

Appendix Table 10. Randomized, Controlled Trials Comparing Metformin Plus a DPP-4 Inhibitor With Metformin Plus an SGLT-2 Inhibitor for Fracture Risk

Study, Year (Reference)	Follow-up, *wk*	Definition of Fracture	Ascertainment of Fracture	Loss to Follow-up, %*	Events/Patients, *n/N (%)*	
					Met + DPP-4 Inhibitor	**Met + SGLT-2 Inhibitor**
Rosenstock et al, 2015 (77)	24	Nonhip fracture	NR	89	Met + saxagliptin, 5 mg: 2/176 (1.0)	Met + dapagliflozin, 10 mg: 1/179 (0.6)

DPP-4 = dipeptidyl peptidase-4; Met = metformin; NR = not reported; SGLT-2 = sodium–glucose cotransporter-2.
* Range in loss to follow-up across groups.