



Effective Health Care Program

Diabetes Medications for Adults With Type 2 Diabetes: An Update Executive Summary

Condition and Therapeutic Strategies

Type 2 diabetes affects more than 9.3 percent of the U.S. population, or 29.1 million people.¹ Diabetes and its complications are a substantial public health burden, as they contribute significantly to mortality, morbidity, and health care costs.¹ Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. Diabetes also contributes importantly to macrovascular complications, including coronary artery disease, peripheral arterial disease, and carotid artery disease, and increases the risk of cardiovascular-related death nearly twofold.² Lifestyle modification and pharmacologic therapy are the cornerstones of the management of hyperglycemia for type 2 diabetes to reduce diabetes complications.³⁻⁵

When beginning medical treatment, patients usually begin with a medication from one of six drug classes that have been approved by the Food and Drug Administration (FDA) for use as monotherapy, although several guidelines recommend use of metformin when not contraindicated as the first therapy after lifestyle modifications.^{3,4} The approved drug classes are metformin (alone in

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

the biguanide class), sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose cotransporter-2 (SGLT-2)

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inhibitors. Clinical guidelines, including those of the American Diabetes Association, recommend monitoring hemoglobin A1c (HbA1c) to determine the need for changing the medication dose or adding another agent to improve glycemic control.⁴ Clinicians also monitor other intermediate outcomes, including body weight, and short-term and long-term safety and adverse effects of the drugs, which vary by drug class, with the goal of improving long-term clinical outcomes.

The Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) has published two prior systematic reviews comparing monotherapies and medication combinations for adults with type 2 diabetes.^{6,7} Since January 2010, the month of the last publications included in the past review, the FDA has approved one new medication class (SGLT-2 inhibitors, with 3 new medications) and several new DPP-4 inhibitors and GLP-1 receptor agonists. Additional data on previously approved medications have also emerged, which could change the balance of benefit and risk attributable to these drugs or could alter the strength of evidence about some of the drug comparisons previously reviewed.⁸⁻¹¹ Given the ever-increasing literature about type 2 diabetes medications and the recent approval of many new medications, an updated systematic review evaluating the effects of these medications on intermediate and long-term effectiveness and safety outcomes will be valuable to clinicians, patients, investigators, guideline developers, and payers.

Scope and Key Questions

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.⁷ We are focusing on priority head-to-head drug class comparisons identified, a priori, as clinically relevant comparisons for which there are evidence gaps (Table A). Given the unique and emerging potential benefits and harms of some of these medications, we have included additional intermediate and safety outcomes in the review: for studies including either SGLT-2 inhibitors or GLP-1 receptor agonists, systolic blood pressure and heart rate, and for studies that include a comparison with SGLT-2 inhibitors, impaired renal function, urinary tract infections, genital infections, volume depletion, and bone fractures.

The Key Questions that we address in this review are as follows:

Key Question 1a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness

of the specified monotherapy FDA-approved diabetes medications for the intermediate outcomes of HbA1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 1b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of metformin-based combinations of FDA-approved diabetes medications for the intermediate outcomes of HbA1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 2a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the monotherapy FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 2b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the metformin-based combinations of FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative safety of the monotherapy FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 3b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative safety of metformin-based combinations of FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4: Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index of adults with type 2 diabetes?

Table A. Priority medication comparisons included for each Key Question

Intervention	Main Intervention Class (Generic Individual Drug Names)	Comparisons
Monotherapy as main intervention	Biguanides (metformin)	<ul style="list-style-type: none"> • Thiazolidinediones* • Sulfonylureas† • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists‡ • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT-2 inhibitor • Combination of metformin plus GLP-1 receptor agonist
	Thiazolidinediones (rosiglitazone or pioglitazone)	<ul style="list-style-type: none"> • Sulfonylureas • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	Sulfonylureas (glimepiride, glyburide,§ glibenclamide,§ or glipizide)	<ul style="list-style-type: none"> • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, or sitagliptin)	<ul style="list-style-type: none"> • SGLT-2 inhibitors • GLP-1 receptor agonists
	SGLT-2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin)	<ul style="list-style-type: none"> • GLP-1 receptor agonists
Combination therapy as main intervention	Combination of metformin plus thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin	<ul style="list-style-type: none"> • Combination of metformin plus sulfonylurea 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; HbA1c = hemoglobin A1c; SGLT-2 = sodium-glucose cotransporter 2.

*For studies comparing thiazolidinediones with metformin, we reviewed only HbA1c, long-term outcomes, and selected safety outcomes, given the high strength of evidence from our prior Comparative Effectiveness Review for other outcomes (specifically fracture and weight).⁷

† For studies comparing sulfonylureas with metformin, we reviewed only long-term outcomes and cancer, given the high strength of evidence on the other outcomes from our prior Comparative Effectiveness Review.⁷

‡ 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.

Methods

Topic Refinement and Review Protocol

This review updates the 2011 Comparative Effectiveness Review on diabetes medications for adults with type 2 diabetes.⁷ We recruited a Technical Expert Panel (TEP) to review a draft of the protocol and a summary of the revisions from the 2011 review. The TEP included endocrinologists, general internists, biostatisticians, and representatives from government agencies. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the Key Questions. With the feedback from the TEP and the AHRQ representatives, we finalized and posted the protocol (www.effectivehealthcare.ahrq.gov).

Literature Search Strategy

Search Strategy

We searched MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). We ran the search developed for the 2011 review with the date restrictions of April 2009 through April 2015. (See Appendix A.) The expanded search included medical subject headings (MeSH) and text words for all of the new medications included in this updated report, without date restrictions.

Additionally, we searched ClinicalTrials.gov to identify relevant registered trials. We reviewed the FDA Web site for any unpublished additional studies relevant to the topic as part of our gray literature search. We also provided an opportunity for manufacturers of interventions to submit unpublished data.

Study Selection

Two independent reviewers conducted title scans and advanced articles if either one thought them relevant. The abstract review phase was designed to identify studies reporting the effectiveness or safety of the medications and medication combinations of interest. Two investigators independently reviewed abstracts. Differences between investigators regarding the inclusion or exclusion of abstracts were resolved through consensus adjudication. Full articles underwent another independent parallel review regarding their appropriateness for inclusion. Selection criteria for studies are provided in Table B.

Table B. Study inclusion criteria

PICOTS	Inclusion Criteria
Population	<ul style="list-style-type: none"> We included studies of adult humans with type 2 diabetes, non–insulin-dependent diabetes mellitus, or adult-onset diabetes.
Interventions	<ul style="list-style-type: none"> We included studies that evaluated a diabetes medication of interest or drug combination of interest. (See Table A.)
Comparisons	<ul style="list-style-type: none"> We included studies that evaluated a comparison of interest. (See Table A.)
Outcomes*	<ul style="list-style-type: none"> We included studies addressing the following intermediate outcomes for KQ1: <ul style="list-style-type: none"> Hemoglobin A1c Weight Systolic blood pressure Heart rate We included studies addressing the following microvascular, macrovascular, and mortality outcomes for KQ2: <ul style="list-style-type: none"> All-cause mortality Cardiovascular and cerebrovascular morbidity and mortality Retinopathy Nephropathy Neuropathy We included studies addressing the following safety outcomes for KQ3: <ul style="list-style-type: none"> Liver injury Impaired renal function Lactic acidosis Pancreatitis Hypoglycemia Gastrointestinal side effects Congestive heart failure Cancer Macular edema or decreased vision Fractures Urinary tract infections Genital mycotic infections Volume depletion KQ4 included studies considering any of the above outcomes.
Type of study	<ul style="list-style-type: none"> For KQ1, we included only RCTs. For KQ2 and KQ3, we included RCTs, nonrandomized experimental studies with a comparison group, and high-quality observational studies with a comparison group. We included randomized trials that used a crossover design, with some exceptions. Only studies published in English were included.
Timing and setting	<ul style="list-style-type: none"> We included studies in which the observed intervention or exposure period was more than 3 months.

KQ = Key Question; PICOTS = populations, interventions, comparisons, outcomes, timing, and settings; RCT = randomized controlled trial.

*Not every outcome was assessed for each comparison.

Data Extraction

Reviewers extracted information on the general study characteristics, study participant characteristics, interventions, comparisons, method of ascertainment of safety outcomes, and outcome results, including measures of variability. We also collected data on outcomes for the subgroups of interest, which were defined by age, sex, race/ethnicity, and body mass index.

Risk-of-Bias Assessment of Individual Studies

Two independent reviewers assessed risk of bias. We assessed the risk of bias in individual randomized controlled trials (RCTs) using the Jadad criteria, consistent with the prior report.¹² We used the Downs and Black tool for assessment of internal validity for nonrandomized trials and observational studies.¹³ We included only medium- or high-quality observational studies, as determined by assessment of each study's risk of bias. The Downs and Black tool was also applied to the observational studies that had been included in the prior report;⁷ some of the previously included observational studies were excluded owing to methodological deficiencies.

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies, including those from the prior Comparative Effectiveness Reviews. We conducted meta-analyses when there were sufficient data (at least 3 trials) and studies were sufficiently homogeneous with respect to key variables (population characteristics, study duration, and drug dose). We included in the quantitative pooling those study arms with drug doses and study durations most commonly reported. We tested the heterogeneity among the trials considered for quantitative pooling using a chi-squared test with a significance level of alpha less than or equal to 0.10, and we also examined heterogeneity among studies with an I² statistic.¹⁴ We pooled the mean difference between groups using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (I² <50%)¹⁵ or the profile likelihood estimate when statistical heterogeneity was high.¹⁶ For dichotomous outcomes, we calculated pooled odds ratios using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity¹⁵ or the profile likelihood estimate in settings of high heterogeneity (I² >50%).¹⁶ Sensitivity analyses included sequential study elimination to assess for influential studies. Stratification and metaregression (only if 10 or more studies were included in the meta-analysis) were done to identify and

describe sources of heterogeneity and their effects on outcomes when substantial heterogeneity was identified.

Strength of the Body of Evidence

At the completion of the review, two reviewers sequentially graded the evidence addressing the Key Questions by adapting an evidence grading scheme recommended in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹⁷ We generated evidence grades about each intervention comparison for each outcome (Table A) for which there was at least one RCT or three observational studies. We graded the evidence separately for the RCTs and the observational studies.¹⁷ The final evidence grade and conclusion were typically based on the RCT grade and could be strengthened by evidence from the observational studies. We separately assessed the strength of evidence for shorter and longer studies (≥ 2 years); however, we assessed strength of evidence only for longer studies from which we could draw a conclusion.

We assessed the study limitations, consistency, directness, precision, and reporting bias. If we conducted a meta-analysis for a body of evidence, we relied on the results of the meta-analysis to rate precision and used the designated minimally important differences as a point of reference for precision. (See full report for details.)

We classified evidence pertaining to the Key Questions into four categories: (1) high grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); (2) moderate grade (indicating moderate confidence that the evidence reflects the true effect, but further research could change our confidence in the estimate of the effect and may change the estimate); (3) low grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) insufficient (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion).

Applicability

We assessed the applicability of the evidence in terms of the degree to which the study populations, interventions, outcomes, timing, and settings were typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting, such as outpatient treatment by internists, family physicians, and endocrinologists.

Results

In this Executive Summary, results are presented by Key Question and focus on moderate- or high-strength evidence. We also highlight some key areas for which there was low-strength or insufficient evidence. The full results of this synthesis, including detailed results on all evidence, are in the full report.

Results of Literature Searches

We included 166 publications in our previous review. After excluding studies that no longer had a comparison or an outcome of interest and cohort studies that did not meet our quality criteria, we included 105 of these studies from the prior review (published in 107 articles) in the update.

We also retrieved 19,171 unique citations from our updated literature search. After reviewing titles, abstracts, and full text, we included 114 new studies (published in 142 new articles). Ten of the new publications were either

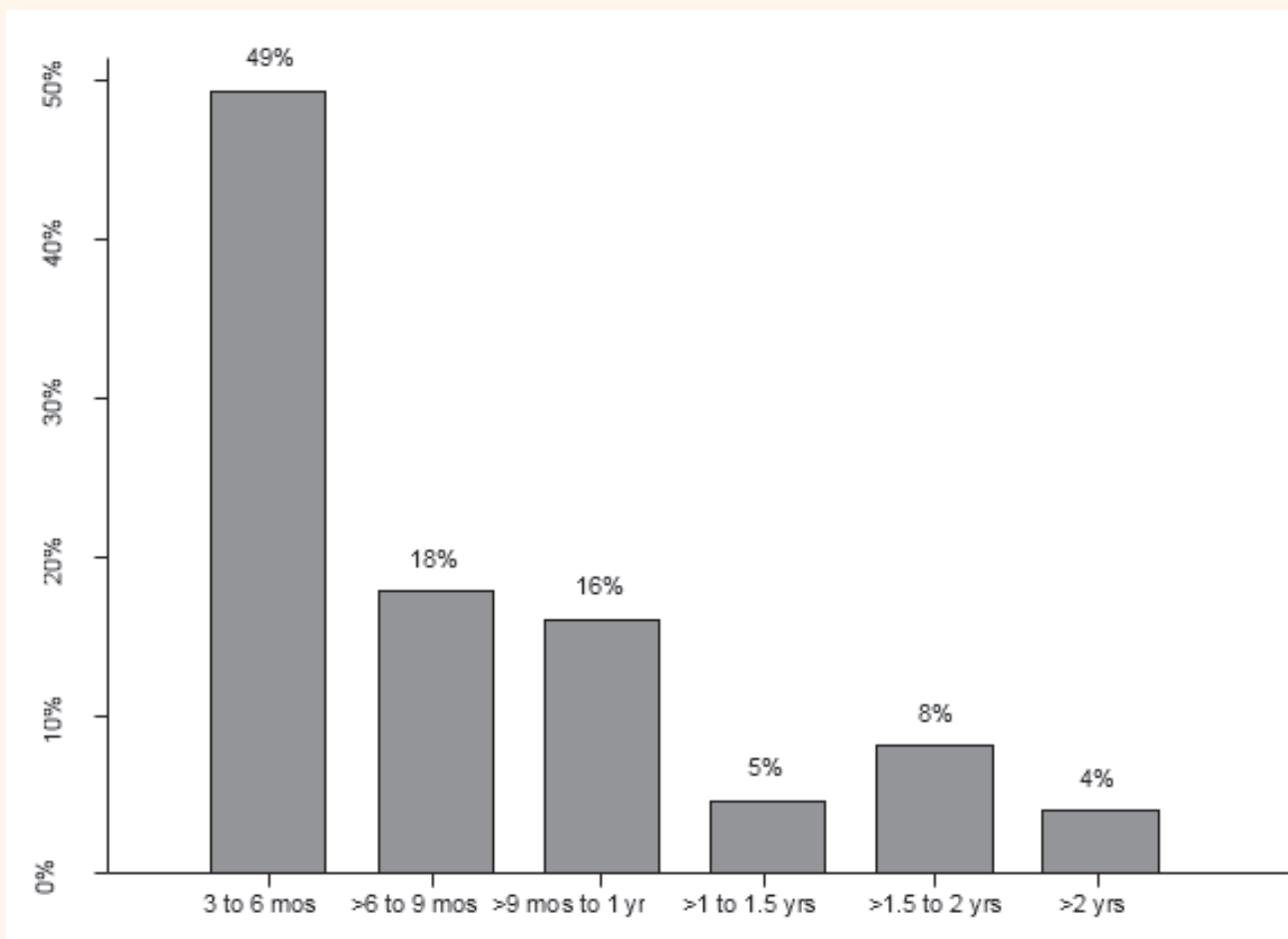
extensions or additional analyses of studies included in the previous review. Overall, we included 219 studies, published in 249 articles.

Study Duration for All Key Questions (KQ1–KQ4)

Of the 177 included RCTs for all Key Questions combined, most studies were less than 1 year in duration (Figure A). Only 4 percent of studies lasted longer than 2 years, making it difficult to draw any firm conclusions about long-term outcomes. Unless stated otherwise in the text or figures, results and conclusions for all the Key Questions are for short-term outcomes.

Followup among the 25 observational studies lasted between 3 months and 8 years. Five of the included observational studies lasted 1 year or less. Most (64%) of the cohorts had at least 2 years of followup.

Figure A. Duration of followup for randomized controlled trials comparing the effects of diabetes medications among adults with type 2 diabetes (N = 177)



Key Questions 1a and 1b: Intermediate Outcomes

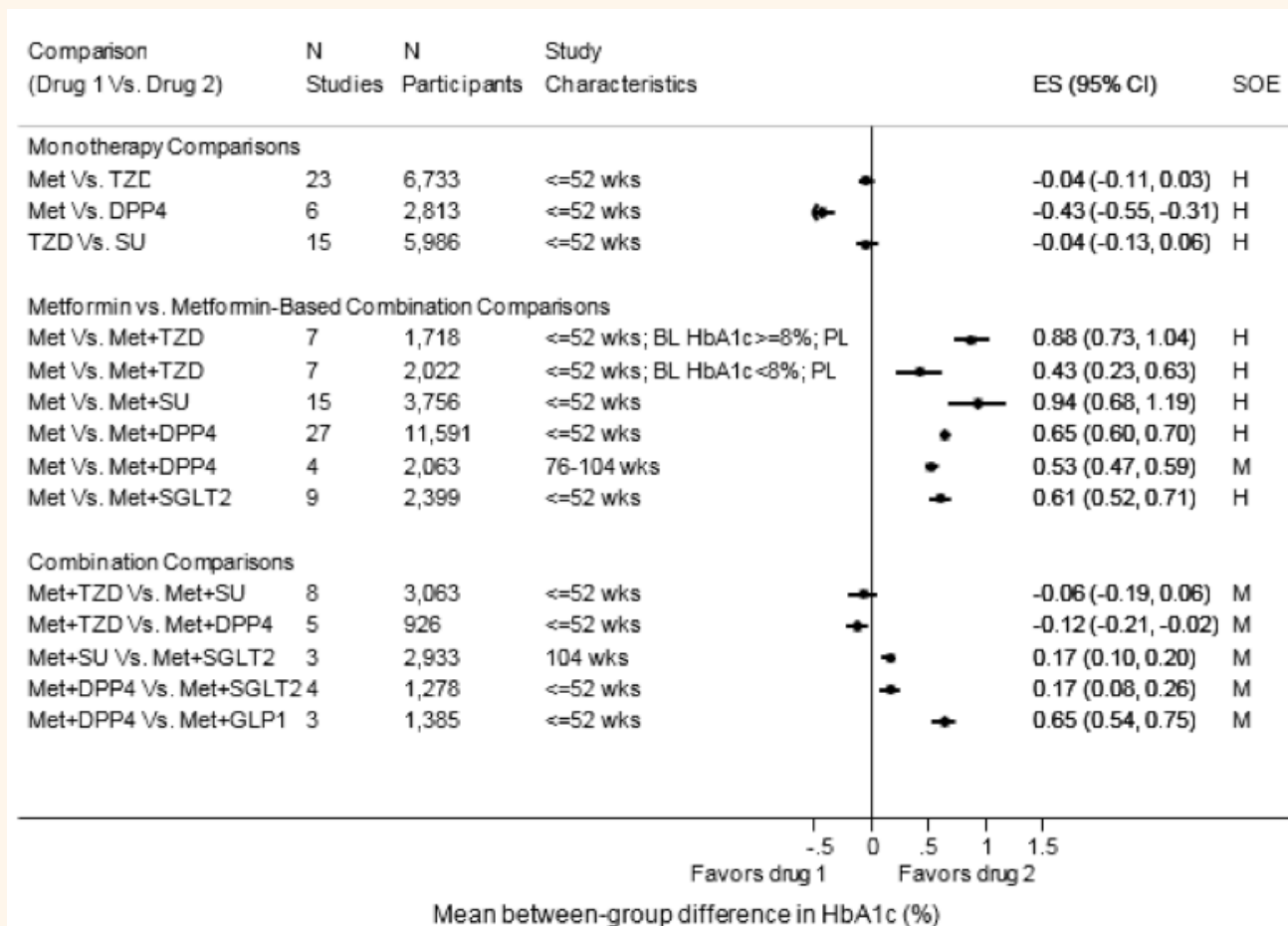
Of the 162 RCTs (reported in 189 articles) identified for Key Question 1, 81 percent were less than 1 year long. Only 12 percent of these trials reported having received no industry support, and 14 percent did not report on this at all. Study participants were generally overweight or obese and had a baseline HbA1c between 7 and 9 percent. The exclusion criteria were generally similar for most trials: significant renal, cardiovascular, and hepatic disease. About half of the trials (58%) excluded older subjects (generally older than 75 to 80 years of age). Almost all of the studies reported a diverse male-female mix among the participants. Of the few studies that evaluated longer timeframes (>2 years), most were consistent with the shorter term results. While an occasional longer study conflicted with the shorter study results, the high losses to followup (generally >20%) and frequent use of last observation carried forward analyses made it difficult to draw conclusions about longer term effects. Therefore, results discussed here are for the short term unless otherwise specified in the figures or text.

Hemoglobin A1c

We found that most diabetes medications as monotherapy (metformin, thiazolidinediones, and sulfonylureas) reduced HbA1c to a similar degree in the short term (Figure B). In the 2011 report,⁷ the evidence on metformin versus

sulfonylurea, which showed no significant between-group differences in HbA1c, was graded as high; therefore, the comparison was not updated in this report. In this report, metformin was more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy by about 0.4 percent. (All differences for HbA1c represent absolute percentage points.) Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, metformin plus SGLT-2 inhibitors, and metformin plus DPP-4 inhibitors) were generally more effective in reducing HbA1c than metformin monotherapy by about 1 percent (Figure B). For the combination comparisons, metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus DPP-4 inhibitors by 0.65 percent. Otherwise, most combination therapy comparisons with moderate strength of evidence had either no significant or no clinically meaningful between-group differences (<0.3%) in HbA1c between arms (Figure B). Although we included comparisons with the GLP-1 receptor agonists, we graded the evidence for most of these comparisons as insufficient or low; therefore, we were limited in our ability to draw conclusions about their effectiveness. Despite the clinical interest in comparing metformin plus injectables, there was insufficient or low strength of evidence on glycemic control for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Figure B. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in HbA1c); GLP1 = glucagon-like peptide-1 agonists; H = high; HbA1c = hemoglobin A1c; M = moderate; Met = metformin; PL = profile likelihood estimate; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinedione.

The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Weight

Monotherapy and combination medication comparisons generally showed significant between-group differences when comparing medications expected to increase weight (sulfonylureas, thiazolidinediones, and insulin) with medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors). Figure C shows the data from the meta-analyses that could feasibly be conducted. We report between-group differences in the text regarding results where meta-analyses could not be done. DPP-4

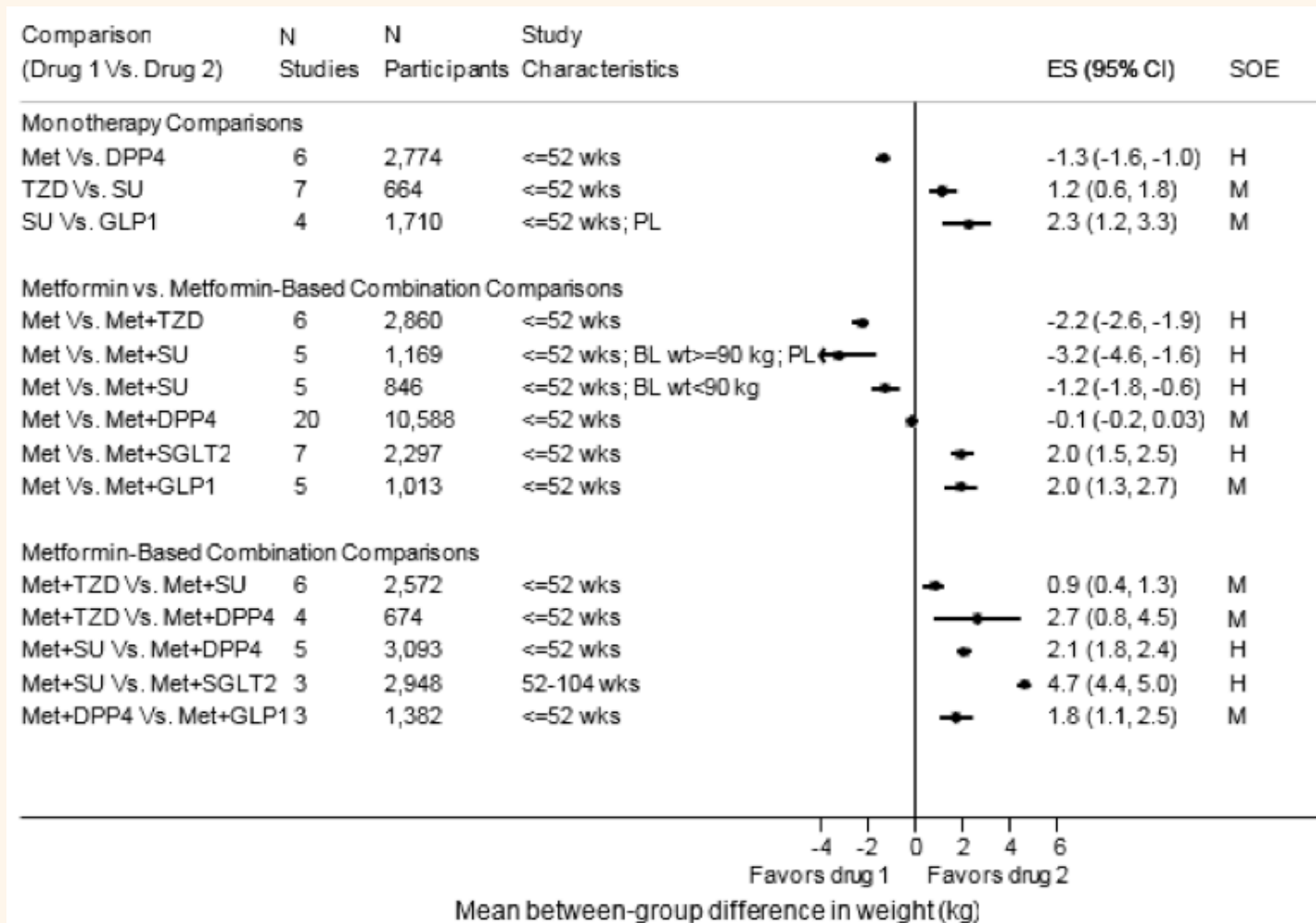
inhibitors and GLP-1 receptor agonists both decreased weight more than thiazolidinediones (between-group differences ranging from -2.3 kg to -3.5 kg). In the 2011 report, comparisons of metformin versus thiazolidinedione and metformin versus sulfonylurea were found to favor metformin by about -2.5 kg, with high strength of evidence; therefore, these comparisons were not updated.

In this report, several monotherapy and metformin-based combination medications were compared where both arms had medications expected to maintain or decrease weight, or both arms had medications expected to increase weight, with varying effects. Metformin decreased weight more than DPP-4 inhibitors, whereas sulfonylureas caused slightly less weight gain than thiazolidinediones (Figure C). There was moderate strength of evidence that SGLT-

2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors (between-group differences ranging from -1.3 kg to -2.7 kg). The combinations of metformin plus a GLP-1 receptor agonist (Figure C) and metformin plus an SGLT-2 inhibitor (range in between-group differences of -1.8 to -3.6 kg) were both favored over the combination of metformin plus a DPP-4 inhibitor. Metformin plus a sulfonylurea had more favorable weight effects than the combination of metformin plus a premixed

or basal insulin (range in mean between-group differences of -0.5 kg to -1.7 kg), with moderate strength of evidence. Despite the clinical interest in comparing metformin plus injectables, there was low strength of evidence about weight for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Figure C. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in weight); GLP1 = glucagon-like peptide-1 agonists; H = high; M = moderate; Met = metformin; PL = profile likelihood estimate; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinedione.

The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were evaluated only for the newer medications, SGLT-2 inhibitors and GLP-1 receptor agonists, owing to the suspected effects of these newer medications on these clinical outcomes based on prior literature.^{18,19} The SGLT-2 inhibitors consistently reduced systolic blood pressure by 3 to 5 mmHg in all comparisons for which there were sufficient numbers of

studies (Table C). Also, metformin plus a GLP-1 receptor agonist yielded a greater reduction in systolic blood pressure, about 3 mmHg, compared with metformin alone (Table C).

For heart rate, only two comparisons had sufficient data to grade the evidence as more than insufficient or low. These comparisons had no or small differences (<2 beats per minute) between groups (Table C). When there were differences in outcomes among comparisons rated as having low strength of evidence, they were less than three beats per minute.

Table C. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for systolic blood pressure and heart rate

Outcome	Conclusions	Strength of Evidence
Systolic blood pressure	Metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than— <ul style="list-style-type: none"> • Metformin alone: pooled between-group difference for shorter studies, 4.4 mmHg (95% CI, 2.9 to 6.0 mmHg) • Metformin plus SU: pooled between-group difference, 5.1 mmHg (95% CI, 4.2 mmHg to 6.0 mmHg) 	High
	Metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than metformin plus a DPP-4 inhibitor: pooled between-group difference, 4.1 mmHg (95% CI, 3.6 mmHg to 4.6 mmHg).	Moderate
	SGLT-2 inhibitors reduced systolic blood pressure more than metformin: pooled between-group difference, 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg).	Moderate
	Metformin plus a GLP-1 receptor agonist reduced systolic blood pressure more than metformin: pooled between-group difference, 3.1 mmHg (95% CI, 1.4 to 4.9 mmHg).	Moderate
Heart rate	Increases in heart rate were minimal and similar for metformin and GLP-1 receptor agonist monotherapy.	Moderate
	Combination therapy with metformin plus an SGLT-2 inhibitor resulted in less increase in heart rate than metformin plus an SU: pooled between-group difference in heart rate, 1.5 bpm; 95% CI, 0.6 bpm to 2.3 bpm.	Moderate

bpm = beats per minute; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Key Questions 2a and 2b: All-Cause Mortality and Macrovascular and Microvascular Outcomes

Of 118 studies (reported in 141 publications) identified for Key Question 2, 96 were RCTs and 21 were observational (mainly retrospective cohort) studies. Most studies evaluated all-cause or cardiovascular mortality or cardiovascular morbidity. Of the 96 trials, 33 were at least 1 year in duration. Only 11 had 2 years or more of followup time, and 10 of these had over 20-percent losses to followup. No trial specified mortality or a macrovascular or microvascular outcome as its primary outcome. Mean/median followup of the observational studies ranged from 6 months to 5 years, with 12 lasting at least 2 years. Seven of the observational studies were designed to evaluate cardiovascular outcomes. Because of low event rates and sample size, the pooled studies for most comparisons on these outcomes were underpowered.

All-Cause Mortality, Cardiovascular Mortality, and Cardiovascular Morbidity

Only one comparison had moderate strength of evidence for any of these outcomes. The rest of the outcomes were rated as low strength of evidence or insufficient. We found moderate strength of evidence that sulfonylurea monotherapy was associated with a 50-percent to 70-percent higher relative risk (absolute risk difference,

0.1% to 2.9% in RCTs; number needed to treat, 20 to 1,000) of cardiovascular mortality compared with metformin monotherapy (Table D). This conclusion was supported by consistent findings from two high-quality RCTs (N = 4,664), with a range in mean/median followup of 2.8 to 4.0 years, and three high-quality observational studies (N = 115,105) that used propensity score methodology (2 studies) and multivariate regression (1 study) to account for confounding. Our findings on all cause-mortality and cardiovascular morbidity, drawn from the same RCTs plus additional observational studies (noted in Table D), also favored metformin over sulfonylureas; however, the strength of evidence was low for these outcomes because of less consistency in results across studies. It is of note that losses to followup were greater than 20 percent in both RCTs. Losses to followup were the same (20%) across arms in the study by Hong and colleagues (2013) and therefore not anticipated to bias the comparison of arms.²⁰ In A Diabetes Outcome Progression Trial (ADOPT), losses to followup were higher in the sulfonylurea (44%) than the metformin (38%) arm, with median followup of 3.3 years for the sulfonylurea arm versus 4.0 years for the metformin arm.²¹ Therefore, study results were likely biased to the null, lending further support to the inference that metformin was favored over sulfonylurea monotherapy.

Table D. Comparative effectiveness of sulfonylureas compared with metformin for long-term all-cause mortality and cardiovascular mortality and morbidity—moderate strength of evidence or consistent low-strength evidence

Outcome	Range in RR From RCTs	Range in RD From RCTs	Adjusted HR From Observational Studies	SOE
All-cause mortality	1.0 to 2.1 (N = 2)	0.1% to 5.0% (N = 2)	1.2 to 1.9 (N = 7*)	Low
CVD mortality	1.5 to 1.7 (N = 2)	0.1% to 2.9% (N = 2)	1.1 to 1.6 (N = 3)	Moderate
CVD morbidity	0.7 to 1.4 (N = 2)	-10.1% to 0.4% (N = 2)	1.1 to 3.3 (N = 5†)	Low

CVD = cardiovascular disease; HR = hazard ratio; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SOE = strength of evidence.

*One additional retrospective cohort study reported an odds ratio of 1.1.

†Additionally, 1 case-control study reported an odds ratio of 1.2.

Retinopathy, Nephropathy, and Neuropathy

While we found more evidence than in the prior report, there were still too few studies to reach firm conclusions; all evidence for these outcomes was of low strength or insufficient.

Key Questions 3a and 3b: Comparative Safety

Of 145 studies identified for Key Question 3, 137 were RCTs and 8 were observational (mainly retrospective cohort) studies. Most RCTs lasted a year or less, with only about 5 percent lasting more than 2 years. Mean or median followup of the eight observational studies ranged from 3 months to 5 years. The few longer studies were generally consistent with the shorter term results; however, the losses to followup were often high (>20% in the majority of the longer studies), making it difficult to draw firm long-term conclusions. Therefore, most safety comparisons represent shorter term results unless specifically stated in the text or a figure.

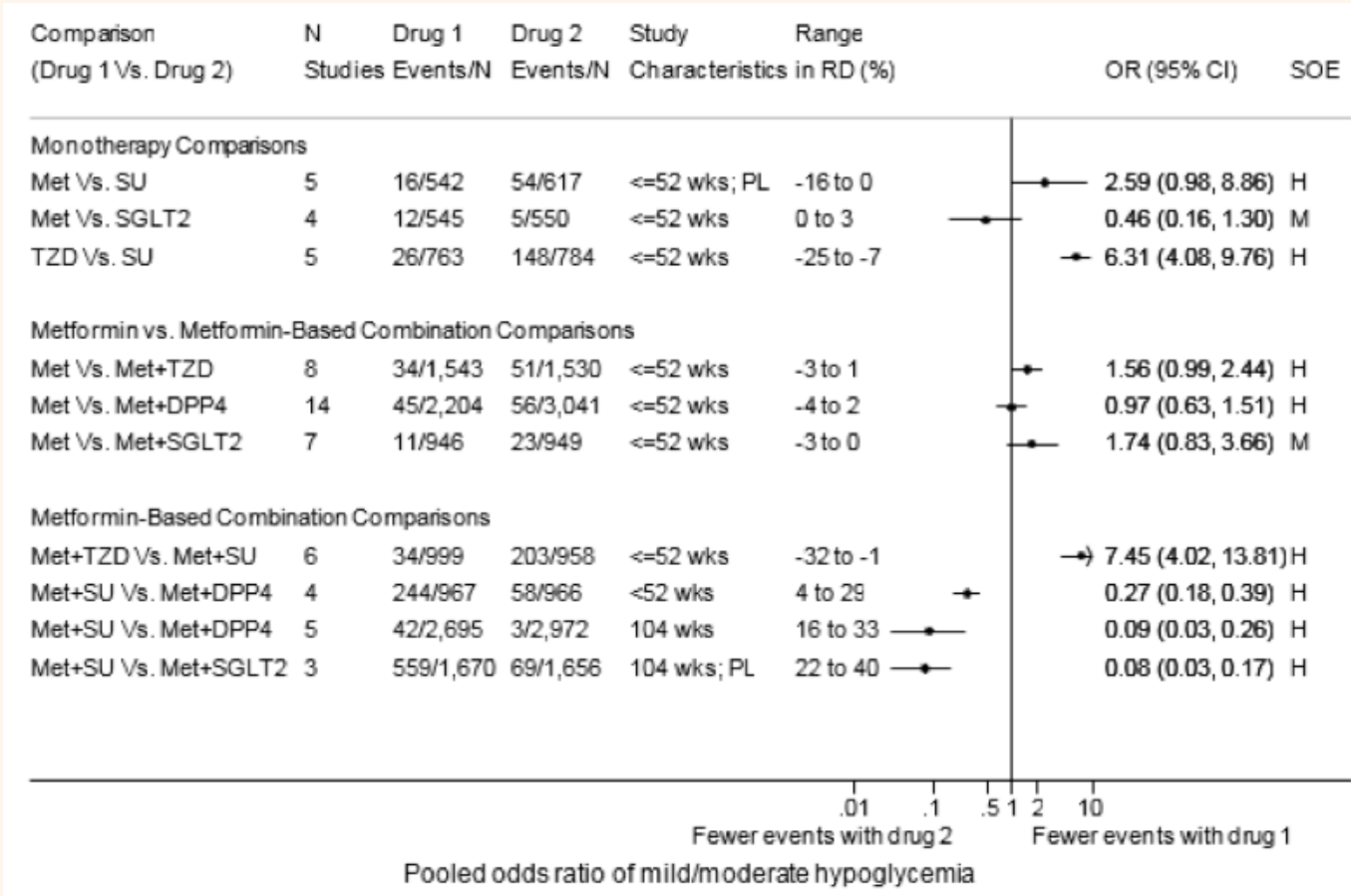
Hypoglycemia

Sulfonylureas alone and in combination with metformin had a higher risk of mild, moderate, or total hypoglycemia than any other monotherapies and metformin-based combinations for which we identified evidence (Figure D). While studies were too heterogeneous for a meta-analysis, sulfonylureas also had greater risk of hypoglycemia than GLP-1 receptor agonists (range in odds ratio [OR], 3.1 to 5.3; range in risk difference [RD], 12% to 21%) and DPP-4 inhibitors (range in OR, 3.8 to 12.4; range in RD, 6%

to 15%), with moderate strength of evidence. In addition to the increased risk of hypoglycemia with metformin plus sulfonylurea versus several comparators (Figure D), the combination of metformin plus sulfonylurea also had greater risk of hypoglycemia compared with metformin monotherapy (range in OR, 2 to 17; range in RD, 0% to 35%) and compared with the combination of metformin plus a GLP-1 receptor agonist (for studies lasting 104 to 234 weeks: range in OR, 3.4 to 7.1; range in RD, 15% to 30%). When compared with metformin plus a basal or premixed insulin, metformin plus a GLP-1 receptor agonist had less hypoglycemia risk (range in OR, 0.18 to 0.35; range in RD, -3% to -13%), with moderate strength of evidence. The combination of metformin plus basal insulin had a lower risk of hypoglycemia than the combination of metformin plus premixed insulin (range in OR, 0.23 to 0.89; range in RD, -5% to -28%), with moderate strength of evidence. We did not pool these studies owing to high heterogeneity.

We found moderate strength of evidence that sulfonylureas had an increased risk of severe hypoglycemia compared with metformin or thiazolidinedione monotherapy (range in OR, 1.4 to 8; range in RD, 0.5% to 23%). Similarly, sulfonylureas in combination with metformin had a greater risk of severe hypoglycemia than the combination of metformin plus DPP-4 inhibitors (range in OR, 6 to 14; range in RD, 0% to 3%) or metformin plus SGLT-2 inhibitors (OR, 7; range in RD, 1% to 3%), with moderate strength of evidence for both comparisons.

Figure D. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; H = high; M = moderate; Met = metformin; OR = odds ratio; PL = profile likelihood estimate; RD = absolute risk difference; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinediones.

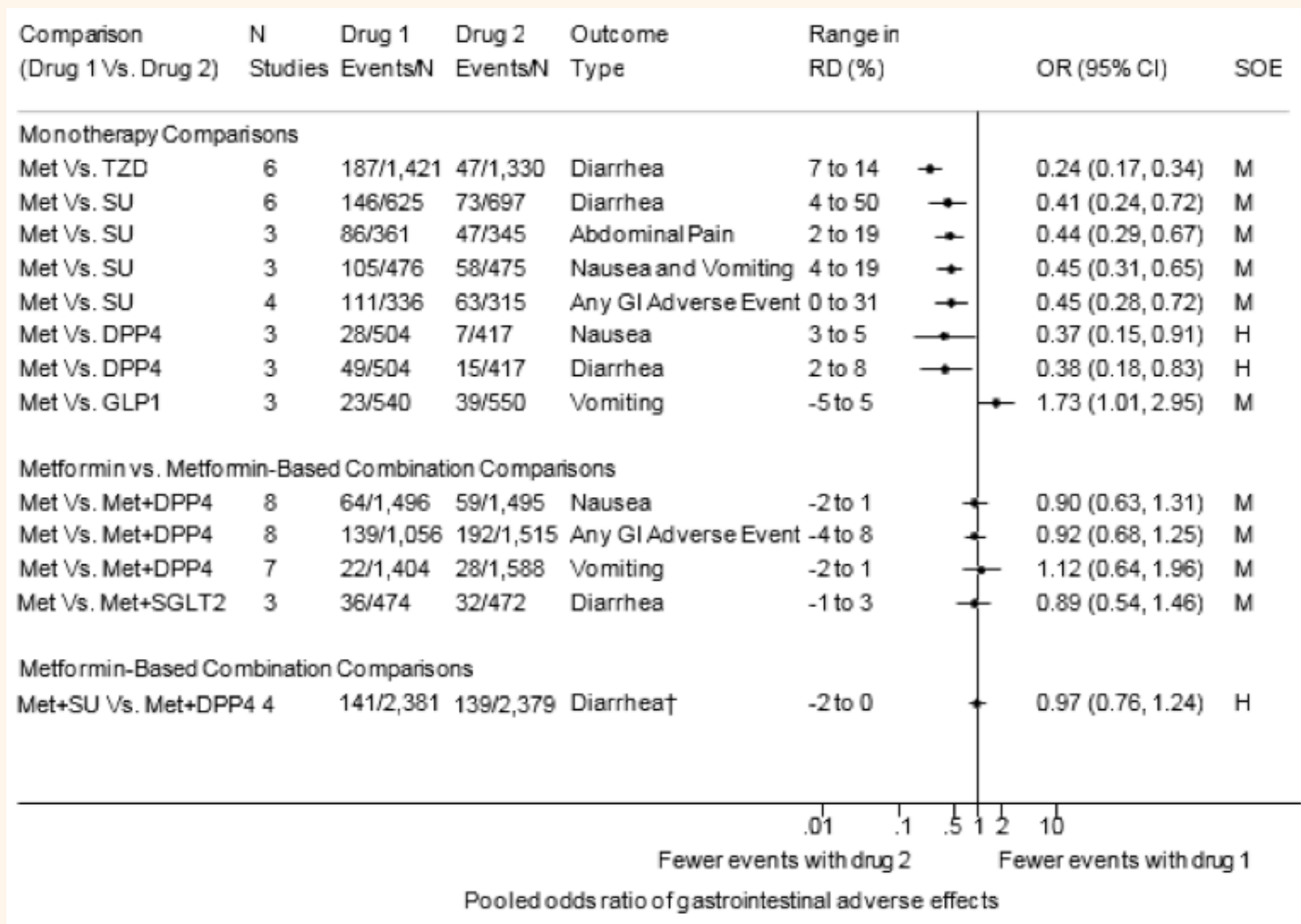
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Gastrointestinal Side Effects

Metformin and GLP-1 receptor agonists were associated with more gastrointestinal side effects (typically nausea, vomiting, or diarrhea) than any other medications with sufficient studies for comparison, regardless of whether they were used as monotherapy or in combination (Figure E). Although there were insufficient studies for a meta-analysis, GLP-1 receptor agonists had greater gastrointestinal side effects than sulfonylureas, with moderate strength of evidence (range in OR, 1.4 to 2.4; range in RD, 3% to 9%). Metformin plus a GLP-1 receptor agonist had more gastrointestinal side effects than metformin plus DPP-4 inhibitors (range in OR, 1.0 to 7.7; range in RD, 0% to 23%) and metformin plus

thiazolidinediones (range in OR, 2.9 to 6.3; range in RD, 8% to 19%), with moderate strength of evidence. Nausea and vomiting were more common with GLP-1 receptor agonists than with metformin (Figure E), but rates of diarrhea were similar between the groups. The rates of gastrointestinal side effects were similar for metformin monotherapy compared with metformin plus a DPP-4 inhibitor or metformin plus SGLT-2 inhibitors (Figure E). We found high strength of evidence that the rates of gastrointestinal adverse events were similar for thiazolidinediones (range, 2% to 9%) and sulfonylureas (range, 3% to 10%), with a range in RD of -1.2% to 1.7%. The combination of metformin plus a sulfonylurea (range, 1% to 18%) was also similar to the combination of metformin plus a thiazolidinedione (range, 1% to 13%), with a range in RD of -5.0% to 2.1% (moderate strength of evidence).

Figure E. Pooled odds ratios of gastrointestinal adverse events and strength of evidence for monotherapy and metformin-based combination comparisons*



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1 receptor agonists; H = high; M = moderate; Met = metformin; OR = odds ratio; RD = absolute risk difference; SGLT-2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinediones.

The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

*All results presented in this graph are based on short-term (less than 52 weeks) studies unless otherwise specified.

†Based on studies with 104 weeks of followup.

Congestive Heart Failure

There was only one long-term trial, which lasted 4 years, and only a few observational studies of medium quality with 6 to 8 years of followup that allow an assessment of the comparative safety of diabetes medications regarding congestive heart failure. We found low strength of evidence that the risk of congestive heart failure was 1.2 to 1.6 times as great with thiazolidinediones as with sulfonylureas (pooled OR, 1.6; 95% CI, 0.96 to 2.8; range in RD, 0% to 2%) or metformin (2 RCTs lasting less than a year with no events; 1 4-year RCT with an RD of 3%;

and range in hazard ratio of 1.2 to 1.5 in 2 observational studies). Despite recent concerns about congestive heart failure with specific DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative safety of this drug class for this outcome in studies lasting less than 2 years (5 RCTs reporting no events in the DPP-4 inhibitor arms; 1 RCT with 1 event in the metformin plus DPP-4 inhibitor arm and none in the comparator arm; and 1 RCT of metformin plus DPP-4 inhibitor vs. metformin plus sulfonylurea reporting fewer events in the DPP-4 combination arm compared with the sulfonylurea combination arm [3 vs. 6 events]).

Cancer

Evidence was generally lacking or of low strength for cancer outcomes. We found low strength of evidence that the combination of metformin plus a sulfonylurea was favored over the combination of metformin plus a DPP-4 inhibitor for cancer risk (3 RCTs with 104 weeks of followup). An unpublished study (104 weeks of followup) and an unpublished longer term (156 weeks) followup of one of the included published studies²² were consistent with this finding and might have increased the evidence to moderate strength had they been included. A recent RCT with only 52 weeks of followup also found a higher risk of cancer in the DPP-4 inhibitor combination arm compared with the sulfonylurea combination arm.²³

Adverse Events Specific to SGLT-2 Inhibitors

We evaluated the comparative effectiveness of SGLT-2 inhibitors for specific adverse events of interest: urinary tract infections, genital mycotic infections, renal function impairment, fractures, and volume depletion. We found

high strength of evidence that the combination of metformin plus an SGLT-2 inhibitor increased the odds of a genital mycotic infection approximately threefold compared with metformin monotherapy and sixfold compared with the combination of metformin plus a sulfonylurea (Table E). We also found moderate strength of evidence that SGLT-2 inhibitors increased the odds of genital mycotic infection fourfold compared with metformin monotherapy. The evidence was of low strength or insufficient for the other safety outcomes specific to SGLT-2 inhibitors.

Other Outcomes

The evidence on the outcomes of liver injury, pancreatitis, lactic acidosis, severe allergic reactions, and macular edema and decreased vision was of low strength or insufficient. We could not make any conclusions about these outcomes.

Table E. Summary of the moderate- to high-strength evidence on the comparative safety of diabetes medications as monotherapy and metformin-based combination therapy for genital mycotic infections

Conclusions	Strength of Evidence
<p>The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with—</p> <ul style="list-style-type: none"> • Metformin monotherapy: <ul style="list-style-type: none"> – Pooled OR, 3.0; 95% CI, 1.2 to 7.2 for females – Pooled OR, 2.7; 95% CI, 0.8 to 9.0 for males – Range in between-group risk difference, -2.3% to 9.9% • Metformin plus SU: <ul style="list-style-type: none"> – Pooled OR, 5.2; 95% CI, 3.4 to 8.0 for females – Pooled OR, 7.6; 95% CI, 4.0 to 14.4 for males – Range in between-group risk difference, 7.1% to 17.4% 	High
<p>The rates of genital mycotic infections were higher with SGLT-2 inhibitors compared with metformin monotherapy</p> <ul style="list-style-type: none"> – Pooled OR, 4.1; 95% CI, 2.0 to 8.3 – Range in between-group risk difference, -0.04% to 15.7% 	Moderate
<p>The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with metformin plus DPP-4 inhibitors</p> <ul style="list-style-type: none"> – Range in between-group risk difference, -2.8% to 8.8% 	Moderate

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; OR=odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Key Question 4: Subgroups

We found little evidence on the comparative effectiveness and safety of diabetes medications in predefined subgroups of age, sex, race/ethnicity, or body mass index. Most of the evidence on subgroups was for the outcome of HbA1c and did not show differential effects of the included comparisons by age, sex, race/ethnicity, or body mass index.

Discussion

Key Findings in Context

Intermediate Outcomes

This report builds on prior work by adding more information for HbA1c and weight regarding the metformin-based combination comparisons and comparisons with the newer medications. It also adds new comparative information for the SGLT-2 inhibitors and GLP-1 agonists on both heart rate and blood pressure.

While there is controversy about HbA1c targets, better glycemic control (measured by HbA1c levels) is strongly associated with lower risk of microvascular disease,²⁴⁻²⁶ making it a good proximal outcome to measure. Consistent with the 2011 Comparative Effectiveness Review, most monotherapies were found to be similarly effective in reducing HbA1c, with the exception of DPP-4 inhibitors, which had a smaller effect relative to metformin (Figure B).⁷ While metformin versus GLP-1 receptor agonists and metformin versus SGLT-2 inhibitors also showed no clear between-group differences in HbA1c, the evidence was graded as low strength because the three studies in each comparison were imprecise and inconsistent. In this update, we found inconsistent findings in the studies of GLP-1 receptor agonists. It may be that the individual GLP-1 receptor agonists have different effects on HbA1c. A 2011 Cochrane systematic review showed small between-group differences in HbA1c, around 0.3 percent, favoring liraglutide and weekly exenatide over daily exenatide.¹⁹

Combination therapy with metformin generally reduced HbA1c by 0.7 to 1 absolute percentage points compared with metformin monotherapy. While we found moderate strength of evidence that some combination comparisons were more effective than others, most between-group differences were small (<0.3 percentage points), with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by greater than 0.3 percentage points over any

other combination comparison: the combination of metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor by 0.65 percentage points. Two prior network meta-analyses^{27, 28} showed that most metformin combination comparisons had similar reductions in HbA1c. However, the results of the direct comparisons evaluated in this report are more precise, allowing us to detect smaller between-group differences than the indirect comparisons in the network meta-analyses.

Weight gain was small to moderate in the trials in which participants gained weight; even in the longest trials, weight gain was less than 5 kg. However, even small to moderate weight gain (5% to 10% of body weight) may be associated with increased insulin resistance.²⁹ In addition, weight loss and glycemic control were reported as the primary drivers of patient preferences for diabetes medications when compared with treatment burden and side effects in a recent systematic review.³⁰ Drug effects on weight, therefore, have a strong impact on the choice of the drug for second-line combination therapy in a patient not well controlled on a single agent. Our systematic review builds on prior work by adding more direct comparative data about metformin combination comparisons that further confirm the known weight effects of the individual medications. As monotherapy and in combination with metformin, thiazolidinediones, sulfonylureas, and insulin are associated with weight gain, DPP-4 inhibitors with weight maintenance, and SGLT-2 inhibitors and GLP-1 receptor agonists with weight loss.^{7, 18, 19, 31}

We evaluated systolic blood pressure and heart rate for the newer classes of medications, the SGLT-2 inhibitors and GLP-1 receptor agonists, because of suspected effects of these medications based on prior literature.^{18, 19} Blood pressure control is essential in adults with diabetes.³²⁻³⁵ The United Kingdom Prospective Diabetes Study showed that for every 10 mmHg decrease in systolic blood pressure, there is a 15-percent decrease in diabetes-related deaths.³³ Our findings of modest systolic blood pressure reductions of 3 to 5 mmHg with SGLT-2 inhibitors compared with many other agents are consistent with other reviews¹⁸ on these agents, and our review builds on prior work by evaluating direct comparisons of specific medication classes. This is important because thiazolidinediones and GLP-1 receptor agonists have been associated previously with decreases in systolic blood pressure of 3 to 5 mmHg.^{6, 19} We also found moderate strength of evidence that metformin plus a GLP-1 receptor agonist had a greater reduction in systolic blood pressure than metformin alone (pooled between-

group difference, 3.1 mmHg; 95% CI, 1.4 to 4.9 mmHg). While the clinical relevance of these small differences is unclear, a change of 3 to 5 mmHg is about half the effect of a low-sodium diet (around 7 to 11 mmHg) and about one-third the effect of blood pressure medications (around 10 to 15 mmHg).^{36,37} Future research should determine if there are any links between these small differences in blood pressure and micro- and macrovascular outcomes, especially given the prevalent use of effective medications to reduce cardiovascular risk (e.g., aspirin, blood pressure and cholesterol medications).

Increased heart rate is associated with increased mortality.³⁸ However, whether heart rate is an independent predictor of long-term clinical outcomes, such as mortality, is less clear.³⁹ We wanted to determine if the potential benefits from blood pressure reduction might be offset by a concomitant increase in heart rate. We did not identify any prior systematic reviews that evaluated this outcome for the diabetes comparisons of interest. Only two comparisons had sufficient data to grade the evidence as more than insufficient or low. The SGLT-2 inhibitors in combination with metformin were found to decrease heart rate by 1.5 beats per minute (bpm) (95% CI, 0.6 bpm to 2.3 bpm) when compared with metformin plus a sulfonylurea; metformin and GLP-1 receptor agonists showed no differences in heart rate between groups. Therefore, these early findings support minimal to no effects on heart rate and no increase in heart rate for the newer medications.

All-Cause Mortality and Macrovascular and Microvascular Outcomes

Additional evidence allowed this report to include firm conclusions regarding metformin versus sulfonylurea monotherapy for cardiovascular mortality. Sulfonylurea monotherapy was associated with a 50-percent to 70-percent higher relative risk of cardiovascular mortality than metformin monotherapy (for sulfonylurea vs. metformin: absolute risk difference, 0.1% to 2.9%; number needed to harm, 34 to 1,000 in RCTs). The low-strength evidence regarding all-cause mortality and cardiovascular morbidity was consistent with this conclusion, also favoring metformin over sulfonylureas. Our results augment findings from prior meta-analyses published in 2012 and 2013, which relied more heavily on observational data or did not report on explicit head-to-head comparisons of metformin and sulfonylurea monotherapy.^{40, 41} Importantly, we do not know if metformin actually decreases cardiovascular disease mortality or just increases cardiovascular disease mortality less than sulfonylureas; likewise, we do not know if sulfonylureas actually increase cardiovascular disease mortality or just decrease cardiovascular disease mortality less than metformin.

We did not find evidence to support substantive conclusions about the comparative effectiveness of thiazolidinediones on long-term cardiovascular risk and therefore could not address the issues raised previously about rosiglitazone and cardiovascular outcomes.⁴² We did not include the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) Trial here because it did not report on macrovascular outcomes stratified by specific medication combinations of interest; however, a reanalysis of data from this study led the FDA to lift its restrictions on the use of rosiglitazone.⁴³

We found little evidence supporting conclusions regarding the comparative effectiveness of most of the newer classes of drugs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) and these clinical outcomes. However, three recent large placebo-controlled RCTs not meeting our inclusion criteria (because they did not evaluate direct head-to-head comparisons of interest) evaluated the effects of DPP-4 inhibitors on cardiovascular outcomes: SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction) 53, EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care), and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin). These studies reported noninferiority for DPP-4 inhibitors relative to standard care,⁴⁴⁻⁴⁶ but several limitations prevent conclusions based on these studies: (1) differential diabetes medication use across arms; (2) low power to demonstrate noninferiority; and (3) mixed inconsistent findings on cardiovascular outcomes across trials (N >35,000).⁴⁴⁻⁴⁶

Otherwise, most of the evidence on all-cause mortality and macrovascular and microvascular outcomes came from RCTs that were generally 12 months or shorter in duration with rare or no events; this evidence was of low strength or insufficient, precluding conclusions on the comparative effectiveness of the comparisons of interest for short-term harms. The scant evidence on the comparative effectiveness of diabetes medications and microvascular outcomes (retinopathy, nephropathy, and neuropathy) precluded any substantive conclusions.

Safety Outcomes

Severe hypoglycemia is associated with increased morbidity (e.g., reduced cognition), increased avoidable health care use (e.g., emergency room visits for hypoglycemia), and increased mortality.⁴⁷⁻⁵⁰ In this report, we confirmed the elevated risk for severe hypoglycemia and nonsevere hypoglycemia with sulfonylureas compared with other drug classes (Figure D). We added to the

literature base on SGLT-2 inhibitors by providing more evidence showing that SGLT-2 inhibitors may have less risk of hypoglycemia than metformin, although both medications had low absolute rates of hypoglycemia. We also found that, when compared with metformin plus basal or premixed insulin, metformin plus a GLP-1 receptor agonist had less hypoglycemia risk.

For the outcome of gastrointestinal side effects, we also confirmed findings from our 2011 report⁷ and a prior Cochrane systematic review¹⁹ that both metformin and GLP-1 receptor agonists induce more gastrointestinal side effects than most comparators. Our data add information about specific combination comparisons and specific types of gastrointestinal adverse events. The combinations of metformin plus DPP-4 inhibitors did not have worse gastrointestinal side effects than metformin monotherapy or metformin plus a sulfonylurea. We identified new evidence about GLP-1 receptor agonists and SGLT-2 inhibitors: metformin plus a GLP-1 receptor agonist was associated with more gastrointestinal side effects than metformin plus a thiazolidinedione or metformin plus a sulfonylurea. GLP-1 receptor agonists were associated with more vomiting, but similar rates of diarrhea, when compared with metformin monotherapy. SGLT-2 inhibitors did not increase gastrointestinal side effects when added to metformin.

There was only one long-term trial lasting 4 years (the rest, less than 2 years) and only a few observational studies of medium quality with 6 to 8 years of followup that assessed the effect of diabetes medications on congestive heart failure. We found 1.2 to 1.6 times increased odds of heart failure with the thiazolidinedione class of medications (low strength of evidence) when compared with metformin or sulfonylureas, a finding also reported in two recent meta-analyses.^{51, 52} We excluded the RECORD study for this outcome because the active comparator in the analysis was either sulfonylurea or metformin instead of a single active comparator. Consistent with our findings, RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure compared with the combination of sulfonylurea and metformin.⁵³ Both thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4) according to product labels.^{54, 55}

We had low or insufficient strength of evidence for most other medication comparisons for heart failure, including the newer agents. Despite recent concerns about congestive heart failure with DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative

safety of this drug class for this outcome in mainly short studies. Several large double-blind placebo-controlled RCTs evaluating DPP-4 inhibitors on cardiovascular outcomes in adults with moderate to high cardiovascular risk were excluded from our systematic review of head-to-head comparisons but deserve mention because of recent controversy.⁴⁴⁻⁴⁶ Two of these RCTs (comparing either saxagliptin or alogliptin with placebo) reported an increased risk of hospitalization for congestive heart failure in adults at moderate to high cardiovascular risk (range in RD of 0.7% and 0.9%).^{44, 46} The EXAMINE trial with alogliptin reported these differences solely for the outcome of first hospitalization for heart failure in adults without preexisting congestive heart failure as part of a post hoc subgroup analysis.⁴⁶ The third placebo-controlled RCT⁴⁵ compared sitagliptin with placebo on cardiovascular outcomes in adults at elevated risk for these outcomes, and reported no between-group differences in hospitalization for congestive heart failure (3.1% in each arm). It is unclear if differences in these trials result from differences in drug type, chance alone, or other causes. Because of these findings, however, the FDA has requested additional labeling for saxagliptin and alogliptin to reflect concerns about the potential increased risk of hospitalization for congestive heart failure.⁵⁶ Further research directly comparing specific DPP-4 inhibitors with other active comparators and placebo will be useful in determining the comparative safety of these medications on heart failure risk. Two RCTs of linagliptin are in progress: the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) and the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) studies.^{57, 58}

As in the 2011 report,⁷ we found little evidence about cancer risk. While animal studies have raised concerns about medullary thyroid cancer with GLP-1 receptor agonists⁵⁹⁻⁶² and in vitro studies have raised concern about pancreatic cancer risk with incretin mimetic therapies,⁶³ we found no evidence allowing for substantive conclusions on the association between GLP-1 receptor agonists or DPP-4 inhibitors and cancer. We found low strength of evidence from published RCTs with 104 weeks of followup that the combination of metformin plus a sulfonylurea was favored over the combination of metformin plus a DPP-4 inhibitor for cancer risk; unpublished studies that supported these findings may have strengthened this evidence if they had been included in our review. A newer study with only 52 weeks of followup also corroborated the findings from the longer RCTs. The SAVOR-TIMI 53, TECOS, and EXAMINE trials, mentioned earlier, did not find differences in the risk of pancreatic cancer for DPP-

4 inhibitors added to current treatment versus standard care, but other diabetes medication use was differential across arms, thus limiting inferences about effects specific to DPP-4 inhibitors.⁴⁴⁻⁴⁶ Reviews and meta-analyses suggest that metformin decreases the risk of many types of cancer^{64, 65} and that pioglitazone⁶⁶ increases the risk of bladder cancer slightly, but we could not include many of the studies supporting those conclusions in our review because of our stringent inclusion criteria for observational studies.

We found little evidence from comparative effectiveness studies to substantiate firm conclusions about the risk of pancreatitis for DPP-4 inhibitors and GLP-1 receptor agonists, since we excluded placebo-controlled trials and studies that did not include the specific diabetes medication comparisons of interest for this review. SAVOR-TIMI 53, TECOS, and EXAMINE all reported increased incidence of acute pancreatitis with DPP-4 inhibitors added to standard therapy versus standard therapy alone, with a consistent risk difference of 0.1 percent (number needed to harm for DPP-4 inhibitors, 1,000).⁴⁴⁻⁴⁶ Data across the Liraglutide Effect and Action in Diabetes (LEAD) RCTs also found more pancreatitis with DPP-4 inhibitors.⁶⁷

We have added additional evidence on specific comparisons based on SGLT-2 inhibitors, confirming the increased risk of genital mycotic infections with this class, which has been described in prior reviews.^{18, 68} The evidence on SGLT-2 inhibitor comparisons regarding fractures, renal impairment, urinary tract infections, and volume depletion was not conclusive. However, in late 2015, the FDA strengthened its warning of an increased risk of fractures with canagliflozin based on pooled data from nine clinical trials (mean followup, 85 weeks) that showed incidences of fracture of 1.4 and 1.5 per 100 patient-years for canagliflozin 100 mg daily and canagliflozin 300 mg daily, respectively, versus 1.1 per 100 patient-years for the active/placebo combined comparators.⁶⁹ The labeling for canagliflozin notes that factors that increase fracture risk should be considered when starting canagliflozin.⁷⁰

The FDA issued a warning on the possible risk of ketoacidosis associated with SGLT-2 inhibitors on May 15, 2015.⁷¹ We did not evaluate this outcome, because it was not a concern at the time of the selection of outcomes for this report; the FDA has not changed the labeling for SGLT-2 inhibitors and is currently evaluating emerging data on this issue. A separate analysis of

17,596 participants in canagliflozin trials showed a dose-dependent increased risk of ketoacidosis in participants receiving SGLT-2 inhibitors versus other therapy/placebo; the authors noted that a number of patients with ketoacidosis had evidence of autoimmune diabetes.⁷²

Evidence on other adverse events, including liver injury, lactic acidosis, macular edema or decreased vision, and severe allergic reactions, does not support conclusions. Similarly, the evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and body mass index was generally insufficient for conclusions.

Implications

This update provides additional evidence supporting metformin as the firstline medication therapy to treat type 2 diabetes when tolerated, and it supports a number of treatment options that might be added to metformin based on patient preferences. Not only is metformin favored on many intermediate outcomes, including HbA1c and weight, but also we found more conclusive evidence that cardiovascular mortality is higher with sulfonylureas than metformin. This is consistent with several guidelines, such as those of the American College of Physicians and American Diabetes Association, which recommend metformin as a firstline treatment choice.

The alternative to initial therapy with metformin in type 2 diabetes is an important consideration, given that metformin is not currently recommended for use in patients with kidney disease⁷³ (approximately 22% of people with diabetes in the United States)⁷⁴ or may not be tolerated because of side effects. In addition, the “best” second-line therapy after metformin is still unclear. We evaluated non-metformin-based monotherapy comparisons in this report and demonstrated that the other monotherapies, with the exception of DPP-4 inhibitors, which are not as effective in reducing HbA1c as metformin, generally decrease HbA1c to a similar extent (and comparably to metformin). These other monotherapies’ effects on body weight vary, as do their risks, such as congestive heart failure (increased risk for thiazolidinediones), hypoglycemia (highest risk with sulfonylureas, including for severe hypoglycemia for many comparisons), gastrointestinal side effects (nausea and vomiting with GLP-1 receptor agonists), and genital mycotic infections (increased risk for SGLT-2 inhibitors). Most importantly, we do not have conclusive evidence on

the relative long-term effects of non-metformin-based monotherapy comparisons on all-cause mortality or cardiovascular outcomes, microvascular outcomes, and rare serious adverse events (e.g., pancreatitis risk with GLP-1 receptor agonists). The evidence we present on metformin-based combination therapies provides some insight into the selection of add-on therapy to metformin, but it is not definitive because of the uncertainty of long-term outcomes and differential effects on weight and adverse effects. Comparisons of the metformin-based combinations yielded effectiveness and safety results consistent with the metformin monotherapy comparisons described in detail previously. Therefore, the “best” alternative to metformin initial therapy or the “best” second-line therapy choice after metformin remains unclear and should be based on individual patient factors, as suggested in recent guidelines.⁴ These include clinical factors such as patient age and weight as well as preferences related to differential effects of medications on weight, hypoglycemia, and gastrointestinal and other side effects; tolerance of unknown risks; treatment burden (e.g., oral vs. parenteral administration); and cost.

Limitations of the Review Process

A few key limitations to our review deserve mention. To focus on comparative effectiveness, we did not include placebo-controlled studies and instead evaluated head-to-head comparisons. We also excluded studies in which participants could take nonstudy drugs for treating diabetes (“background” medications) and the results were not stratified by medication. We used this exclusion to avoid interactions between medications. This was especially important because of our goal of evaluating two-drug combinations. Using these criteria, we excluded several large trials,^{26, 47, 75-83} because investigators did not stratify their results to allow reporting on the head-to-head comparisons of interest. We also used strict selection criteria for observational studies, mainly based on the control of confounding factors. In this way, we included observational studies with the most valid results to support conclusions. Also, we focused on interclass (and not intraclass) comparisons in this report. While we did not combine studies in which individual drugs were found to be a clinical or statistical source of heterogeneity, we may have missed smaller intraclass differences. In our 2007 report,⁶ we found that glyburide/glibenclamide had a higher absolute risk difference of mild, moderate, or total hypoglycemia than other sulfonylureas (pooled RD, 3%; 95% CI, 0.5% to 5%). In this update, which focused on interclass comparisons, the studies that included glyburide/glibenclamide as the sulfonylurea did not consistently have larger between-group differences in hypoglycemia risk

than the other sulfonylurea studies. Therefore, these studies were combined with the other sulfonylurea comparisons for hypoglycemia evaluation. For microvascular outcomes, we included studies evaluating more proximal measures, such as change in retinal exam or changes in microalbuminuria, which may be less relevant than other included clinical outcomes of blindness and changes in estimated glomerular filtration rate. However, we were unable to conclude anything about comparative effects on the microvascular outcomes because of lack of sufficient evidence. These distinctions may become more important as more evidence accrues on the different microvascular outcomes. Finally, we did not evaluate patient-reported outcomes, such as quality of life; future research is needed to identify ideal measures to assess treatment-sensitive patient-reported outcomes in diabetes.

Applicability

Using the PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) framework, the evidence in this report is generally applicable to the population of U.S. adults with type 2 diabetes, with a few notable concerns. Compared with the general population with type 2 diabetes,⁸⁴ populations in the included studies had fewer elderly adults (e.g., often excluded persons ≥ 75 years of age), had fewer significant comorbid conditions, and were less racially and ethnically diverse. Regarding the interventions, the majority of studies were less than 2 years long, while patients with diabetes are typically on medications for decades. While many of the longer duration studies were consistent with the short-term findings, more studies lasting longer than 2 years are needed to better understand the durability of the differences reported in shorter term studies.

Research Gaps

Based on the limitations of the evidence base, we highlight several major gaps in the evidence using the PICOTS framework and provide corresponding recommendations for future research (Table F).

The most important gap is the lack of conclusive evidence on the comparative effectiveness and safety of the diabetes medications for all-cause mortality, macrovascular complications, microvascular complications, and rare serious adverse events. Based on the relatively low frequency of these outcomes and long timeframe for development, RCTs are simply not feasible to address this gap because of both cost and the need for evidence now (and not in 5 to 10 years). Therefore, supplementing the rare RCT that can be conducted for these outcomes with high-quality observational studies is paramount.

Database requirements for such observational studies include sufficient sample size, followup of patients over time, detailed data on treatments (including doses and duration), and detailed data on confounding variables (e.g., duration of diabetes, comorbid conditions). Study

designs will need to handle the following 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 confounders.⁸⁵

Table F. Evidence gaps and future research needs for the comparative effectiveness and safety of diabetes medications for adults with type 2 diabetes

Category	Evidence Gap	Future Research Needs
Population	<ul style="list-style-type: none"> Lack of study of older adults, racial/ethnic minorities, and people with comorbid conditions, such as significant renal, cardiovascular, and hepatic impairment Limited evidence on a priori subgroups of interest, such as older adults, racial/ethnic minorities, and subgroups by sex and BMI 	<ul style="list-style-type: none"> Studies that include diverse populations Studies with an a priori plan to investigate differences by important subgroups of interest
Interventions and comparators (HbA1c, weight, hypoglycemia, and GI adverse events)	<ul style="list-style-type: none"> Limited information on GLP-1 receptor agonist comparisons as monotherapy and in combination with metformin Limited information on metformin plus insulin vs. other metformin-based combinations 	<ul style="list-style-type: none"> RCTs evaluating the GLP-1 receptor agonists as monotherapy and in combination with metformin RCTs evaluating metformin plus insulin with other metformin-based combinations, especially metformin plus GLP-1 receptor agonist as injectable add-on therapy to metformin
Outcomes		
All-cause mortality and macrovascular and microvascular outcomes	<ul style="list-style-type: none"> Limited information on macrovascular outcomes and death Underpowered existing evidence Limited number of high-quality observational studies No conclusive evidence on microvascular outcomes No RCTs evaluating these outcomes as a primary outcome Inconsistent outcome definitions, ascertainment, and reporting in each study arm 	<ul style="list-style-type: none"> High-quality observational studies* for all comparisons Longer duration RCTs (>2 years) for all comparisons evaluating macrovascular and microvascular events as primary outcomes Standardized definitions for macrovascular and microvascular outcomes Reporting on outcomes in all arms of RCTs
Rare safety outcomes	<ul style="list-style-type: none"> Limited evidence on rare safety outcomes Underpowered existing evidence Lack of high-quality observational studies Inconsistent outcome definitions, ascertainment, and reporting in each study arm, especially for pancreatitis and cancer 	<ul style="list-style-type: none"> High-quality observational studies* RCTs— <ul style="list-style-type: none"> Active ascertainment of all safety outcomes Standardized definitions for all safety outcomes Reporting on safety outcomes in all arms Responsiveness to incorporating evaluation of new safety concerns
Timing	<ul style="list-style-type: none"> Most evidence is for short-term outcomes, as few studies lasted more than 2 years 	<ul style="list-style-type: none"> Longer duration studies (>2 years) to— <ul style="list-style-type: none"> Determine durability of short-term comparative effects on HbA1c and weight Determine long-term clinical effectiveness and safety

Table F. Evidence gaps and future research needs for the comparative effectiveness and safety of diabetes medications for adults with type 2 diabetes (continued)

Category	Evidence Gap	Future Research Needs
Methodological	<ul style="list-style-type: none"> • High, and often differential, losses to followup in RCTs • Lack of reporting on randomization methods for RCTs • Lack of reporting on allocation concealment, blinding, and withdrawals for all studies • Lack of appropriate accounting for bias in observational studies • Lack of reporting on treatments in observational studies 	<ul style="list-style-type: none"> • Complete or near-complete followup in RCTs • Appropriate methods to account for losses to followup in RCTs • Reporting on methods for randomization, allocation concealment, and blinding in RCTs • High-quality observational studies* for long-term comparative effectiveness and safety of diabetes medications

BMI = body mass index; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; RCT = randomized controlled trial.

*See text for more detail.

Conclusions

The evidence supports metformin as a firstline therapy, given its beneficial effects on HbA1c, weight, cardiovascular mortality (vs. sulfonylureas), and relative safety profile. The comparative long-term benefits and harms of other diabetes medications remain unclear. In this report, we provide comprehensive information comparing the benefits and common and serious harms of diabetes medications. In the absence of conclusive findings on long-term clinical and safety outcomes for most medication comparisons, this evidence synthesis can facilitate personalized treatment choices for clinicians and their patients, as well as support decisionmaking by payers and regulators.

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Errata

This Executive Summary states that metformin and GLP-1 receptor agonists were similar for diarrhea, but this was of low and not moderate or high strength and therefore should have not appeared.

Full Report

This executive summary is part of the following document: Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, Wilson LM, Chu Y, Iyoha E, Maruthur NM. Diabetes Medications for Adults With Type 2 Diabetes: An Updated. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 16-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

