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CLINICAL GUIDELINE

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians.

Methods: This guideline is based on a systematic review of randomized, controlled trials and observational studies published through December 2015 on the comparative effectiveness of oral medications for type 2 diabetes. Evaluated interventions included metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. Study quality was assessed, data were extracted, and results were summarized qualitatively on the basis of the totality of evidence identified by using several databases. Evaluated outcomes included intermediate outcomes of hemoglobin A_{1c}, weight, systolic blood pressure, and heart rate; all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms. This guideline grades the recommendations by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes.

Recommendation 1: *ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.*

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Diabetes mellitus is the seventh leading cause of death in the United States. It also is a leading cause of morbidity, resulting in both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery, cerebrovascular, and peripheral vascular disease) complications. Type 2 diabetes mellitus is the most common form of the disease (affecting 90% to 95% of persons with diabetes), with a prevalence of approximately 29.1 million people in the United States (1). The risk for type 2 diabetes increases with age, and nearly 26% of people in the United States older than 65 years have diabetes (1). In addition, because of the rising obesity rate in the United States, the incidence and prevalence of diabetes mellitus are increasing substantially (2). The total direct and indirect costs associated with diabetes in the United States alone reached $245 billion in 2012 (1).

Management of type 2 diabetes often includes lifestyle modification and pharmacologic therapy. In the United States, several unique classes of drugs are approved by the U.S. Food and Drug Administration (FDA) to treat hyperglycemia in type 2 diabetes, all of which vary regarding cost and harms. Most adults diagnosed with type 2 diabetes receive treatment with oral medications only rather than injection medications, such as insulin or glucagon-like peptide-1 (GLP-1) receptor agonists (3).

Guideline Focus and Target Population

Since the publication of the 2012 American College of Physicians (ACP) guideline on the comparative effectiveness and safety of oral medications for the treatment of type 2 diabetes, several new studies evaluated medications for this disease, and the FDA approved several new agents. New information in the up-

See also:

Editorial comment 1
Summary for Patients 2

Web-Only
CME quiz

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dated review includes evidence on the FDA-approved sodium–glucose cotransporter-2 (SGLT-2) inhibitor class of drugs and on additional dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as further evidence on other drugs included in the 2011 review. The purpose of this ACP guideline is to present the updated evidence regarding the oral pharmacologic treatment of type 2 diabetes; it replaces the 2012 ACP guideline on the same topic (4). The target audience for this guideline includes all clinicians, and the target patient population includes all adults with type 2 diabetes. These recommendations are based on a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (5) as well as a recently published update of the review (6). Although the focus of this guideline is oral pharmacologic therapy, lifestyle modifications are an important management strategy for type 2 diabetes. Injectable medications, including insulin, also are important treatments, although most patients prefer oral agents as initial therapy. This guideline is endorsed by the American Academy of Family Physicians.

METHODS

Systematic Review of the Evidence

The evidence review was conducted by the AHRQ Johns Hopkins Evidence-based Practice Center. Additional methodological details can be found in the Appendix (available at www.annals.org), the full report (5), and the published article (6). Reviewers searched several databases for studies published in English from April 2009 through March 2015. An updated search through December 2015 found evidence that changed from low or insufficient quality to high or moderate quality. Reviewers combined data when possible by using meta-analysis and assessed risk of bias and study quality according to established methodology. The study population included adults (aged ≥18 years) with type 2 diabetes.

The review evaluated head-to-head comparisons of oral monotherapy with metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors; comparisons of metformin monotherapy with a metformin-based combination; and comparisons of metformin-based combinations in which the second medication was one of the monotherapies described earlier. The review contains additional information on injectables, including GLP-1 receptor agonists and insulin, which is not considered in the guideline. Evaluated outcomes included intermediate outcomes of hemoglobin A_{1c} (HbA_{1c}) levels, weight, systolic blood pressure (for SGLT-2 inhibitors only), and heart rate (for SGLT-2 inhibitors only); all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee (CGC) according to ACP's guideline development process, details of which can be found in the methods paper (7). This guideline rates the evidence and recommendations by using ACP's guideline grading system (Table 1).

Table 1. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments, and the published review article was peer reviewed through the journal. The guideline was peer reviewed through the journal and posted online for comments from ACP Regents and Governors, who represent physician members at the regional level.

COMPARATIVE BENEFITS OF ORAL MEDICATIONS FOR TYPE 2 DIABETES

Long-Term All-Cause Mortality, Microvascular, and Macrovascular Outcomes

Evidence from new studies (52 randomized, controlled trials and 13 observational studies, mostly 1 year or less in duration) was either low quality or insufficient for evaluating clinical outcomes, such as mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy, and neuropathy.

All-Cause Mortality

Low-quality evidence comparing metformin monotherapy with sulfonylurea monotherapy showed that metformin was associated with lower all-cause mortality; however, results were inconsistent across studies (8–16). Generally, if low-quality evidence was available for all-cause mortality, it showed no difference between monotherapies and combination therapies.

Cardiovascular Mortality

The review found moderate-quality evidence that metformin was associated with lower cardiovascular mortality (≥2 years) than sulfonylureas, on the basis of 2 randomized, controlled trials (8, 9) and 3 nonexperimental studies (10, 11, 17). The CGC reviewed the individual studies and found the 2 trials to be underpowered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

The committee also noted that in 2 of the nonexperimental studies, the combination of metformin and a sulfonylurea significantly reduced overall (9) and cardiovascular (16) mortality compared with a sulfonylurea alone.

Evidence for all other comparisons was insufficient or low quality.

Cardiovascular and Cerebrovascular Morbidity

Low-quality evidence showed that metformin monotherapy was associated with lower cardiovascular morbidity than sulfonylurea monotherapy, although results were inconsistent across studies (8–16). Evidence for all other comparisons was insufficient or low quality, thus inconclusive for this outcome.

Retinopathy, Nephropathy, and Neuropathy

All randomized, controlled trials were short term, and evidence for all comparisons was insufficient or low quality, thus inconclusive for these outcomes.

Intermediate Outcomes

HbA_{1c} Levels

Monotherapy Versus Monotherapy. As in the 2012 guideline, most diabetes medications had similar efficacy in reducing HbA_{1c} levels. High-quality evidence from the 2011 review showed no difference between metformin and sulfonylureas regarding their effect on HbA_{1c} levels (hence, evidence was not updated) (18). High-quality evidence also showed no difference between metformin and thiazolidinediones (19–41) or between thiazolidinediones and sulfonylureas in reducing HbA_{1c} levels (32, 35, 40–52). High-quality evidence showed that metformin reduced HbA_{1c} levels to a greater extent than DPP-4 inhibitors (mean between-group difference, −0.43% [CI, −0.55% to −0.31%]) (37, 53–60), and moderate-quality evidence favored sulfonylureas over DPP-4 inhibitors (mean between-group difference, −0.21% [CI, −0.32% to −0.09%]) (61–63). Low-quality evidence showed no difference between metformin and SGLT-2 inhibitors (64–66).

Monotherapy Versus Combination Therapy. High-quality evidence showed that all combination therapies that included metformin were superior to metformin monotherapy in reducing HbA_{1c} levels (thiazolidinediones: pooled between-group difference in HbA_{1c} for baseline HbA_{1c} >8%, 0.88% [CI, 0.73% to 1.04%], and for baseline HbA1c <8%, 0.43% [CI, 0.23% to 0.63%]; sulfonylureas: 0.94% [CI, 0.68% to 1.19%]; DPP-4 inhibitors: 0.65% [CI, 0.60% to 0.70%]; SGLT-2 inhibitors: 0.61% [CI, 0.52% to 0.71%]) (5, 6).

Combination Therapy Versus Combination Therapy. Moderate-quality evidence showed that the combination of metformin plus an SGLT-2 inhibitor was superior to metformin plus a DPP-4 inhibitor (pooled between-group difference in HbA_{1c}, 0.17% [CI, 0.08% to 0.26%]) (67–70) and to metformin plus a sulfonylurea (pooled between-group difference in HbA_{1c}, 0.17% [CI, 0.10% to 0.20%]) (71–75). Moderate-quality evidence showed that metformin plus a thiazolidinedione was superior to metformin plus a DPP-4 inhibitor (pooled between-group difference in HbA_{1c}, −0.12% [CI, −0.21% to −0.02%]) (63, 76–79). Moderate-quality evidence showed no difference between metformin plus a thiazolidinedione and metformin plus a sulfonylurea (80–87). Moderate-quality evidence also showed no substantial differences regarding most other comparisons.

Weight

Monotherapy Versus Monotherapy. According to high-quality evidence from the 2011 review, metformin reduced weight more than thiazolidinediones (pooled mean between-group difference, −2.6 kg [CI, −4.1 to −1.2 kg]) or sulfonylureas (pooled mean between-group difference, −2.7 kg [CI, −3.5 to −1.9 kg]) (hence, evidence was not updated) (18). High-quality evidence also showed that metformin was more favorable than DPP-4 inhibitors for weight reduction (pooled mean between-group difference, −1.3 kg [CI, −1.6 to −1.0 kg]) (37, 53–60). Moderate-quality evidence showed that SGLT-2 inhibitors reduced weight more than metformin (range of between-group differences, −1.3 to −1.4 kg) (64, 66) or DPP-4 inhibitors (between-group difference, −2.5 to −2.7 kg) (88) and that DPP-4 inhibitors reduced weight more than thiazolidinediones (range of between-group differences, −2.3 to −2.5 kg) (37, 89). High-quality evidence showed that sulfonylureas caused less weight gain than thiazolidinediones (pooled mean between-group difference, 1.2 kg [CI, 0.6 to 1.8 kg]) (35, 41, 43, 44, 50, 52, 90). Moderate-quality evidence indicated that DPP-4 inhibitors were favored over sulfonylureas (range of between-group differences, 0.7 to 1.8 kg) (61–63).

Monotherapy Versus Combination Therapy. High-quality evidence showed that metformin monotherapy reduced weight more than metformin plus a thiazolidinedione (pooled between-group difference, −2.2 kg [CI, −2.6 to −1.9 kg]) (26, 36, 63, 91–93) or metformin plus a sulfonylurea (pooled between-group difference, −2.2 kg [CI, −3.4 to −1.0 kg]) (94–103). High-quality evidence showed no difference in mean weight between metformin monotherapy and metformin plus a DPP-4 inhibitor (53, 56, 57, 59, 63, 67, 69, 103–115). Metformin plus an SGLT-2 inhibitor was superior to metformin monotherapy for weight reduction (high-quality evidence; pooled between-group difference, 2.0 kg [CI, 1.5 to 2.5 kg]) (64, 67, 69, 116, 117).

Combination Therapy Versus Combination Therapy. The combination of metformin plus a DPP-4 inhibitor was superior for weight reduction compared with metformin plus a thiazolidinedione (moderate-quality evidence; pooled mean between-group difference, 2.7 kg [CI, 0.8 to 4.5 kg]) (63, 76–78) and compared with metformin plus a sulfonylurea (high-quality evidence; pooled mean between-group difference, 2.2 kg [CI, 1.8 to 2.5 kg]) (103, 118–121). High-quality evidence showed that the combination of metformin plus an SGLT-2 inhibitor was superior to metformin plus a sulfonylurea (pooled mean between-group difference, 4.7 kg [CI, 4.4 to 5.0 kg]) (72–74).

Systolic Blood Pressure and Heart Rate

Monotherapy Versus Monotherapy. Moderate-quality evidence showed that SGLT-2 inhibitors reduced systolic blood pressure more than metformin (pooled between-group difference, 2.8 mm Hg [CI, 2.6 to 3.0 mm Hg]) (64, 65). The evidence was insufficient to draw conclusions regarding the effects on heart rate of any monotherapy comparisons.

Monotherapy Versus Combination Therapy. High-quality evidence showed that metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than metformin alone (pooled between-group difference, 4.4 mm Hg [CI, 2.9 to 6.0 mm Hg]) (64, 67–69, 111, 116, 117, 122–124).

The evidence was insufficient to draw conclusions regarding the effects on heart rate of any metformin combination therapy compared with metformin alone.

Combination Therapy Versus Combination Therapy. The combination of metformin and an SGLT-2 inhibitor reduced systolic blood pressure more than that of metformin and a sulfonylurea (high-quality evidence; pooled between-group difference, 5.1 mm Hg [CI, 4.2 to 6.0 mm Hg]) (74, 75, 114) or metformin and a DPP-4 inhibitor (moderate-quality evidence; pooled between-group difference, 4.1 mm Hg [CI, 3.6 to 4.6 mm Hg]) (67–70).

Moderate-quality evidence indicated that the combination of metformin and an SGLT-2 inhibitor increased heart rate less than metformin plus a sulfonylurea (pooled between-group difference, 1.5 beats/min [CI, 0.6 to 2.3 beats/min]) (72–74).

Comparative Harms of Oral Medications for Type 2 Diabetes

Hypoglycemia

Moderate-quality evidence showed that metformin monotherapy was associated with a lower risk for mild, moderate, or total hypoglycemia than metformin plus a sulfonylurea (94, 95, 97, 101–103, 125–128). Moderate-quality evidence also showed that monotherapy with either metformin (37) or a thiazolidinedione (9, 43) was associated with a lower risk for severe hypoglycemia than sulfonylureas. Moderate-quality evidence also showed that monotherapy with a DPP-4 inhibitor (61–63, 129) was associated with a lower risk for mild, moderate, or total hypoglycemia than sulfonylureas.

The combination of metformin and a DPP-4 inhibitor was associated with a lower risk for severe hypoglycemia than metformin plus a sulfonylurea (high-quality evidence) (118–120, 130–133). Moderate-quality evidence showed that metformin plus an SGLT-2 inhibitor was associated with a lower risk for severe hypoglycemia than metformin plus a sulfonylurea (74, 75, 114).

Gastrointestinal Side Effects

High-quality evidence showed no difference between thiazolidinediones and sulfonylureas for gastrointestinal side effects (9, 41, 43, 44, 134). Moderate-quality evidence indicated no difference between metformin plus a thiazolidinedione and metformin plus a sulfonylurea (82–85, 87).

Genital Mycotic Infections

The SGLT-2 inhibitors, used alone or combined with metformin, increased the risk for genital mycotic infections compared with all other monotherapies or combination therapies. Metformin was associated with fewer genital mycotic infections than SGLT-2 inhibitors (moderate-quality evidence) (64, 65).

High-quality evidence showed that metformin monotherapy was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (64, 67, 68, 116, 117, 122, 135, 136). The combination of metformin and a DPP-4 inhibitor was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (moderate-quality evidence) (66–70). High-quality evidence showed that metformin plus a sulfonylurea was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (71, 74, 75, 114).

Multiple Chronic Conditions

Patients with multiple chronic conditions often were excluded from the studies included in the systematic review.

Summary

Although all oral diabetes medications reduced HbA_{1c} levels, the DPP-4 inhibitors were inferior to metformin and sulfonylureas for this outcome. Metformin had a greater benefit on weight than all agents except the SGLT-2 inhibitors, and SGLT-2 inhibitors were more effective than metformin in reducing blood pressure. Combination therapies with metformin and an SGLT-2 or a DPP-4 inhibitor were superior to metformin alone in reducing HbA_{1c} levels, weight, and blood pressure. Head-to-head comparisons of various combination therapies showed that metformin plus an SGLT-2 inhibitor was superior to metformin plus a DPP-4 inhibitor or metformin plus a sulfonylurea in reducing HbA_{1c} levels, although the CGC felt that these differences were of dubious clinical importance. Metformin monotherapy was associated with a low risk for hypoglycemia compared with other monotherapies. Evidence showed that sulfonylureas increased the risk for hypoglycemia, thiazolidinediones for congestive heart failure, and SGLT-2 inhibitors for genital mycotic infections. Thiazolidinediones and sulfonylureas were associated with weight gain when compared with metformin, DPP-4 inhibitors, and SGLT-2 inhibitors.

The CGC generally agreed with the evidence review that all evidence from comparisons of monotherapies and combination therapies with respect to overall and cardiovascular mortality, as well as cardiovascular morbidity, was of low quality. However, the committee felt that the evidence showing greater cardiovascular mortality with sulfonylureas than metformin mono-

Figure. Summary of the American College of Physicians guideline on oral medications for type 2 diabetes.

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	Summary of the American College of Physicians Guideline on Oral Medications for Type 2 Diabetes
Disease/Condition	Type 2 diabetes
Target Audience	Internists, family physicians, other clinicians
Target Patient Population	Adults with type 2 diabetes
Interventions Evaluated	Oral pharmacologic treatments: metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors
Outcomes Evaluated	Clinical outcomes: all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy Intermediate outcomes: HbA_{1c}; weight; systolic blood pressure; harms: hypoglycemia, gastrointestinal side effects, genital mycotic infections
Benefits	Clinical Outcomes Metformin monotherapy was associated with a lower risk for cardiovascular mortality than sulfonylurea monotherapy. HbA_{1c} Most drugs reduced HbA_{1c} to similar levels. DPP-4 inhibitors reduced HbA_{1c} levels less than metformin or sulfonylureas. All combination therapies with metformin were superior to metformin monotherapy. Weight Metformin was better than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors for weight. Combinations of metformin and SGLT-2 inhibitor agonists reduced weight more than metformin monotherapy. Thiazolidinediones and sulfonylureas, either alone or in combination therapy, were associated with worse weight outcomes. Systolic Blood Pressure SGLT-2 inhibitors, as monotherapy or combined with metformin, reduced systolic blood pressure compared with metformin monotherapy.
Harms	Metformin: increased risk for gastrointestinal side effects Sulfonylureas: increased risk for hypoglycemia compared with other drugs Thiazolidinediones: increased risk for heart failure SGLT-2 inhibitors: increased genital mycotic infections
Recommendations	*Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)* *Recommendation 2: ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.*
Clinical Considerations	Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails. Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight. Although combination therapy reduces HbA_{1c} levels more effectively than monotherapy, it is associated with more adverse events. The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease. Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2).

DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = hemoglobin A_{1c}; SGLT-2 = sodium–glucose cotransporter-2.

Table 2. Comparative Efficacy, Adverse Effects, and Costs for Add-on Oral Therapies to Metformin

Comparative Efficacy vs. Other Combinations With Metformin (Quality of Evidence)	Comparative Harms vs. Other Combinations With Metformin/Class Adverse Effects and FDA Warnings	Agents	Fair Price for a 60-d Supply, $*	Adverse Effects
SUs				
SU + metformin favored for weight vs. TZD + metformin (moderate)	Higher risk for hypoglycemia than with metformin combinations with TZD, DPP-4 inhibitor, or SGLT-2 inhibitor	Glipizide, 5 mg	9	Diarrhea, gas, jitteriness, dizziness, uncontrollable shaking, red or itchy skin, rash, hives, and blisters
		Glimepiride, 4 mg	14	Dizziness and nausea
		Glyburide (DiaBeta, Sanofi-Aventis), 5 mg	111	Nausea and upper abdominal fullness
		Glyburide (Glynase, Pfizer), 6 mg	226	Nausea and upper abdominal fullness
TZDs				
TZD + metformin favored for short-term CVD mortality (rosiglitazone only) (low) and HbA_{1c} vs. DPP-4 inhibitor + metformin (moderate)	TZDs increase risk for congestive heart failure May also be associated with increased risk for fracture or bladder cancer	Pioglitazone, 30 mg	24	Headache; muscle, arm, or leg pain; sore throat; and gas
		Rosiglitazone (Avandia, GlaxoSmithKline), 2 mg	178	Headache, runny nose and other cold symptoms, sore throat, and back pain
DPP-4 inhibitors				
DPP-4 inhibitor + metformin favored for long-term all-cause mortality, long-term CVD mortality, and CVD morbidity vs. SU + metformin (low) DPP-4 inhibitor + metformin favored for short-term CVD morbidity vs. pioglitazone + metformin (low) DPP-4 inhibitor + metformin favored for weight vs. SU + metformin (high) or TZD + metformin (moderate)	FDA warns that sitagliptin, saxagliptin, linagliptin, and alogliptin may be associated with potentially severe and disabling joint pain	Alogliptin, 25 mg	335	Headache, stuffy or runny nose, sore throat, and joint pain
		Linagliptin (Tradjenta, Boehringer Ingelheim), 5 mg	734	Headache and joint pain
		Saxagliptin (Onglyza, AstraZeneca), 5 mg	752	Sore throat, headache, and joint pain
		Sitagliptin (Januvia, Merck), 100 mg	746	Stuffed or runny nose, sore throat, headache, diarrhea, nausea, and joint pain
SGLT-2 inhibitors				
SGLT-2 inhibitor + metformin favored for CVD mortality (low), HbA_{1c} (moderate), weight (high), systolic blood pressure (high), and heart rate (moderate) vs. SU + metformin SGLT-2 inhibitor + metformin favored for weight and systolic blood pressure (moderate) vs. DPP-4 inhibitor + metformin	Higher risk for genital mycotic infection than metformin alone or metformin combinations with SU or DPP-4 inhibitor FDA warns that canagliflozin may be associated with increased risk for bone fracture and risk for decreased bone mineral density	Canagliflozin (Invokana, Janssen), 300 mg	808	Excessive urination, including at night; increased thirst; constipation; and dry mouth
		Dapagliflozin (Farxiga, AstraZeneca), 10 mg	812	Excessive urination, including at night, and increased thirst
		Empagliflozin (Jardiance, Boehringer Ingelheim), 25 mg	812	Excessive urination, including at night, and increased thirst

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; FDA = U.S. Food and Drug Administration; HbA_{1c} = hemoglobin A_{1c}; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Data obtained from https://healthcarebluebook.com.

therapy was of low rather than moderate quality. The committee also noted that the comparisons between metformin and metformin plus a sulfonylurea did not suggest greater cardiovascular mortality as the result of adding a sulfonylurea to metformin.

See the **Figure** for a summary of the recommendations and clinical considerations. **Appendix Tables 1** to **3** (available at www.annals.org) contain further details about the comparative effectiveness and safety evidence.

RECOMMENDATIONS

Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)

Metformin is effective in reducing glycemic levels, is associated with weight loss and fewer hypoglycemic episodes, and is cheaper than most other pharmacologic agents. Although the evidence was considered low quality, metformin may have an advantage over sulfonylurea monotherapy in terms of cardiovascular mortality. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification.

As defined by the FDA, metformin is contraindicated in patients with decreased tissue perfusion or hemodynamic instability, advanced liver disease, alcohol abuse, acute unstable congestive heart failure, or any

condition that might lead to lactic acidosis. However, the FDA recently concluded that metformin is safe in patients with mild kidney impairment and in some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2) (137).

Recommendation 2: ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.

Combination therapies with metformin were more effective than metformin monotherapy in reducing HbA_{1c} levels, weight, and blood pressure in patients with type 2 diabetes. This recommendation is graded as weak because of the fine balance between benefits and harms for the various drug combinations. See Table 2 for a summary of the comparative benefits and harms of metformin combination therapies as well as the adverse effects and cost of each medication. The evidence review did not include therapies combining more than 2 agents. Combination therapies also were associated with an increased risk for adverse effects compared with monotherapy.

Sulfonylureas have been used for many years and are the least expensive oral agent to add to metformin. However, sulfonylureas, both alone and combined with other agents, are associated with an increased risk for mild, moderate, or severe hypoglycemia as well as weight gain. The evidence review did not address medication switching for patients currently taking sulfonylureas. Regarding patients whose glycemic levels are adequately controlled and who do not have adverse effects with sulfonylureas, keeping them on this drug may be reasonable.

The SGLT-2 inhibitors are favored over sulfonylureas as an add-on to metformin therapy in terms of cardiovascular mortality, HbA_{1c}, weight, systolic blood pressure, and heart rate and are favored over DPP-4 inhibitors as an add-on to metformin therapy in terms of weight and systolic blood pressure. As an add-on to metformin therapy, DPP-4 inhibitors are favored over sulfonylureas for long-term all-cause mortality, long-term cardiovascular mortality, and cardiovascular morbidity; over pioglitazone for short-term cardiovascular morbidity; and over sulfonylureas or thiazolidinediones for weight.

Each class of drugs is associated with adverse effects, which are summarized in Table 2. The FDA warned that the DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease (138). The SGLT-2 inhibitors are associated with an increased risk for genital mycotic infections. Sulfonylureas are associated with an increased risk for hypoglycemia.

Although this guideline addresses only oral pharmacologic therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.

HIGH-VALUE CARE

Oral pharmacologic therapy with metformin (unless contraindicated) is an effective management strategy. It is cheaper and more effective than most other pharmacologic agents and is associated with fewer adverse effects; of note, it does not result in weight gain. Adding a second agent to metformin may provide additional benefits; however, the increased cost may not always support the added benefit, particularly for the more expensive, newer medications.

INSUFFICIENT AREAS OF EVIDENCE

Insufficient evidence exists for clinical outcomes, including mortality, cardiovascular morbidity, and micro- or macrovascular outcomes, for most drugs and drug comparisons. The evidence review did not address whether patients who are already taking sulfonylureas and have stable HbA_{1c} levels should switch to another medication. No data exist regarding the best time to add oral therapies to lifestyle modifications.

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Appendix: Methods

Key Questions Addressed

Key Question 1

a. In adults aged 18 years 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 HbA_{1c}, weight, systolic blood pressure, and heart rate?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications for the intermediate outcomes of HbA_{1c}, weight, systolic blood pressure, and heart rate?

Key Question 2

a. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified 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?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified 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 3

a. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of the specified 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; 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?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of the specified 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; 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?

Search Strategy

To update the 2011 systematic review (18), the reviewers searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for English-language studies published from April 2009 through March 2015 and updated through December 2015. Studies were limited to randomized, controlled trials for key question 1; high-quality observational studies also were considered for key questions 2 and 3.

Meta-analysis

The reviewers conducted a meta-analysis when data were sufficient and studies were sufficiently homogeneous with respect to study population characteristics, study duration, and medication dosing.

Quality Assessment

The reviewers used the Jadad criteria (139) to assess risk of bias in randomized, controlled trials and the Downs and Black tool (140) to assess nonrandomized trials and observational studies.

Population Studied

The study population included adults with type 2 diabetes, non–insulin-dependent diabetes mellitus, or adult-onset diabetes.

Interventions Evaluated

Evaluated pharmacologic interventions included metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors. Although the GLP-1 receptor agonists were not evaluated in the guideline, they were included in the full evidence review (5).

Comparators

Monotherapies were compared with one another, metformin was compared with combination therapies including metformin, and metformin-based combination therapies were compared with one another.

Outcomes

Outcomes evaluated included all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy, HbA_{1c}, weight, systolic blood pressure, heart rate, and harms.

Timing

In the studies evaluated, oral pharmacologic interventions were used for more than 3 months.

Setting

The setting was outpatient as well as inpatient.

Target Audience

The target audience for this guideline includes all clinicians.

Target Patient Population

The target patient population includes all adults with type 2 diabetes.

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments, and the published review article was peer reviewed through the journal. The guideline was peer reviewed through the journal and posted online for comments from ACP Regents and ACP Governors, who represent physician members at the regional level.

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Appendix Table 1. Summary of Clinical Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
All-cause mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	5	Neither treatment favored for short-term mortality
Metformin vs. rosiglitazone	Low	4	Metformin favored
Metformin vs. SU (shorter-duration studies)	Low	4	Neither favored for short-term mortality
Metformin vs. SU (longer-duration studies)	Low	9	Metformin favored for long-term mortality
Metformin vs. DPP-4 inhibitors	Low	6	Neither treatment favored for short-term mortality
Metformin vs. SGLT-2 inhibitors	Low	4	Neither treatment favored
Pioglitazone vs. DPP-4 inhibitors	Low	2	Neither treatment favored
SU vs. DPP-4 inhibitors	Low	1	DPP-4 inhibitors favored for short-term mortality
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	6	Metformin monotherapy favored; OR, 2.51 (95% CI, 0.66–9.52) ‡
Metformin vs. metformin + SU	Low	5	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (<2 y)	Low	14	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	Low	6	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (long-duration studies)	Low	2	Neither treatment favored
Combination vs. combination			
Metformin + rosiglitazone vs. metformin + SU	Low	3	Neither treatment favored for short-term mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration)	Low	6	Metformin + DPP-4 inhibitors favored for long-term mortality; OR, 0.64 (CI, 0.27–1.52) ‡
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Low	3	Neither treatment favored for long-term mortality
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	Neither favored for short-term mortality
Cardiovascular mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	2	Neither treatment favored
Metformin vs. rosiglitazone	Low	1	Neither treatment favored
Metformin vs. SU (longer-duration studies)	Moderate§	5	Metformin favored; range in RR from RCTs, 0.6–0.7; adjusted HR from observational studies, 0.6–0.9
Metformin vs. DPP-4 inhibitors	Low	3	DPP-4 inhibitors favored for short-term mortality
Rosiglitazone vs. SU (longer-duration studies)	Low	1	Rosiglitazone favored
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	5	Metformin favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitor	Low	7	Metformin + DPP-4 inhibitors favored for short-term mortality
Combination vs. combination			
Metformin + SU vs. metformin + DPP-4 inhibitors (104 wk follow-up)	Low	5	Metformin + DPP-4 inhibitors favored for long-term CVD mortality
Metformin + SU vs. metformin + SGLT-2 inhibitor (longer-duration studies)	Low	2	Metformin + SGLT-2 inhibitors favored
Cardiovascular morbidity			
Monotherapy vs. monotherapy			
Metformin vs. rosiglitazone	Low	5	Metformin favored for long-term CVD morbidity
Metformin vs. pioglitazone	Low	5	Neither treatment favored
Metformin vs. SU	Low	7	Metformin favored for long-term CVD morbidity; range in RR from RCTs, 0.7–1.6; adjusted HR from observational studies, 0.3–0.9
Rosiglitazone vs. SU	Low	4	SU favored for long-term CVD morbidity
Pioglitazone vs. SU	Low	3	Pioglitazone favored for short-term CVD morbidity
SU vs. DPP-4 inhibitors	Low	2	DPP-4 inhibitor favored for short-term CVD morbidity
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone (shorter duration)	Low	6	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SU (shorter duration)	Low	1	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SGLT-2 inhibitor (shorter duration)	Low	1	Metformin favored for short-term CVD
Combination vs. combination			
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + DPP-4 inhibitor favored for short-term cardiovascular morbidity
Metformin + rosiglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + rosiglitazone favored for short-term CVD morbidity
Metformin + SU vs. metformin + DPP-4 inhibitor (long-term nonfatal MI)	Low	2	Metformin + DPP-4 inhibitor favored for long-term nonfatal MI
Metformin + SU vs. metformin + SGLT-2 inhibitor (long-term)	Low	1	Neither favored

(*Continued on following page*)

Appendix Table 1–Continued

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
Nephropathy			
Monotherapy vs. monotherapy			
Metformin vs. SU (shorter-duration studies)	Low	4	Metformin favored
TZD vs. SU (mainly shorter-duration studies)	Low	7	TZD favored for short-term nephropathy outcomes
SU vs. DPP-4 inhibitors (shorter-duration study)	Low	1	Neither treatment favored
Metformin vs. metformin combination			
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	2	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 (shorter-duration study)	Low	1	Neither treatment favored
Neuropathy			
Metformin vs. metformin + DPP-4 inhibitor (shorter-duration study)	Low	1	Metformin favored
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	1	Neither treatment favored

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Only comparisons that were evaluated by at least 1 randomized controlled trial are listed. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short term (1 y or shorter), because few longer-duration studies evaluated this outcome.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).
‡ Effect is not statistically significant.
§ Grade given by the evidence reviewers. The Clinical Guidelines Committee reviewed the individual studies and found the 2 trials to be underpowered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

Appendix Table 2. Summary of Intermediate Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention, by Outcome	Strength of Evidence*	Studies, *n*	Summary†
HbA_{1c}			
Monotherapy vs. monotherapy			
Metformin vs. TZD	High	23	Neither drug favored; −0.04% (95% CI, −0.11 to 0.03%)
Metformin vs. SU	High	NA	No significant between-group differences (not updated for this report)
Metformin vs. DPP-4 inhibitors	High	6	Metformin favored; −0.43% (CI, −0.55 to −0.31%)
TZD vs. SU	High	15	Neither drug favored; −0.04% (CI, −0.13 to 0.06%)
SU vs. DPP-4 inhibitors	Moderate	3	SU favored; −0.21% (CI, −0.32 to −0.09%)
Metformin vs. metformin combination			
Metformin vs. metformin + TZD (HbA_{1c} ≥8%)	High	7	Metformin +TZD favored; 0.88% (CI, 0.73 to 1.04%)
Metformin vs. metformin + TZD (HbA_{1c} <8%)	High	7	Metformin + TZD favored; 0.43% (CI, 0.23 to 0.63%)
Metformin vs. metformin + SU	High	15	Metformin + SU favored; 0.94% (CI, 0.68 to 1.19%)
Metformin vs. metformin + DPP-4 inhibitors (shorter duration)	High	26	Metformin + DPP-4 inhibitor favored; 0.65% (CI, 0.60 to 0.70%)
Metformin vs. metformin + DPP-4 inhibitors (longer duration)	Moderate	4	Metformin + DPP-4 inhibitor favored; 0.5% (CI, 0.47 to 0.6%)
Metformin vs. metformin + SGLT-2 inhibitors	High	9	Metformin + SGLT-2 inhibitor favored; 0.61% (CI, 0.52 to 0.71%)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	8	Neither drug combination favored; −0.06% (CI, −0.19 to 0.06)
Metformin + TZD vs. metformin +DPP-4 inhibitors	Moderate	5	Metformin + TZD favored; −0.12% (CI, −0.21 to −0.02%)
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Moderate	3	Metformin + SGLT-2 inhibitor favored; 0.17% (CI, 0.10 to 0.20%)
Metformin + DPP-4 inhibitors vs. metformin +SGLT-2 inhibitors	Moderate	4	Metformin + SGLT-2 inhibitor favored; 0.17% (CI, 0.08 to 0.26%)
Weight			
Monotherapy vs. monotherapy			
Metformin vs. TZD	High	NA	Metformin favored; −2.6 kg (CI, −4.1 to −1.2 kg) (did not update for this report)
Metformin vs. SU	High	NA	Metformin favored; −2.7 kg (CI, −3.5 to −1.9 kg) (did not update for this report)
Metformin vs. DPP-4 inhibitors	High	6	Metformin favored; −1.3 kg (CI, −1.6 to −1.0 kg)
Metformin vs. SGLT-2 inhibitors	Moderate	3	SGLT-2 inhibitors favored; range of between-group differences, −1.3 to −1.4 kg
TZD vs. SU	High	7	SU favored; 1.2 kg (CI, 0.6 to 1.8 kg)
TZD vs. DPP-4 inhibitors	Moderate	2	DPP-4 inhibitors favored; range in between-group differences, −2.3 to −2.5 kg
DPP-4 inhibitors vs. SGLT-2 inhibitors	Moderate	1	SGLT-2 inhibitors favored; between-group difference, −2.5 to −2.7 kg
SU vs. DPP-4 inhibitors	Moderate	4	DPP-4 inhibitors favored; between-group difference, 0.7 to 1.8 kg
Metformin vs. metformin combination			
Metformin vs. metformin + TZD	High	6	Metformin favored; −2.2 kg (CI, −2.6 to −1.9 kg)
Metformin vs. metformin + SU	High	10	Metformin favored Baseline weight ≥90 kg; profile likelihood estimate: −3.2 kg (CI, −4.6 to −1.6 kg) Baseline weight <90 kg: −1.2 kg (CI, −1.6 to −0.6 kg)
Metformin vs. metformin + DPP-4 inhibitors (duration ≤1 y)	High	20	Neither treatment favored; −0.10 kg (CI, −0.30 to 0.01 kg)
Metformin vs. metformin + SGLT-2 inhibitors	High	7	Metformin + SGLT-2 inhibitors favored; 2.0 kg (CI, 1.5 to 2.5 kg)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	6	Metformin + SU favored; 0.9 kg (CI, 0.4 to 1.3 kg)
Metformin + TZD vs. metformin + DPP-4 inhibitors	Moderate	4	Metformin + DPP-4 inhibitors favored; 2.7 kg (CI, 0.8 to 4.5 kg)
Metformin + SU vs. metformin + DPP-4 inhibitors (duration <1 y)	High	4	Metformin + DPP-4 inhibitors favored; 2.2 kg (CI, 1.8 to 2.5 kg)
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	High	3	Metformin + SGLT-2 inhibitors favored; 4.7 kg (CI, 4.4 to 5.0 kg)
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	5	Metformin + SGLT-2 inhibitors favored; range in between-group differences, −1.8 to −3.6 kg

(*Continued on following page*)

Appendix Table 2–Continued

Intervention, by Outcome	Strength of Evidence*	Studies, *n*	Summary†
Systolic blood pressure			
Monotherapy vs. monotherapy			
Metformin vs. SGLT-2 inhibitors	Moderate	4	SGLT-2 inhibitors favored; 2.8 mm Hg (CI, 2.6 to 3.0 mm Hg)
Metformin vs. metformin combination			
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	High	7	Metformin + SGLT-2 inhibitors favored; 4.4 mm Hg (CI, 2.9 to 6.0 mm Hg)
Combination vs. combination			
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	High	3	Metformin + SGLT-2 inhibitors favored; 5.1 mm Hg (CI, 4.2 to 6.0 mm Hg)
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	4	Metformin + SGLT-2 inhibitors favored; 4.1 mm Hg (CI, 3.6 to 4.6 mm Hg)
Heart rate			
Combination vs. combination			
Metformin + SU vs. metformin +SGLT-2 inhibitors (longer duration)	Moderate	3	Metformin + SGLT-2 inhibitor favored; mean between-group difference, 1.5 beats/min (CI, 0.6 to 2.3 beats/min)

DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* This table summarizes only high- and moderate-quality evidence.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).

Appendix Table 3. Summary of Harms for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention, by Outcome	Strength of Evidence	Studies, *n*	Summary*
Hypoglycemia			
Monotherapy vs. monotherapy			
Metformin vs. TZD			
Mild, moderate, total symptoms	Low	5	Metformin favored
Severe symptoms	Low	1	Neither favored
Metformin vs. SU			
Mild, moderate symptoms	High	5	Metformin favored; OR, 2.59 (95% CI, 0.98 to 8.86)†
Severe symptoms	Moderate	3	Metformin favored; OR, 1.4 to 2; RD, 0.8% to 14% OR in normal renal function, 9.0 (CI, 4.9 to 16.4), and in impaired renal function, 6.0 (CI, 3.8 to 9.5)
Metformin vs. DPP-4 inhibitors			
Mild, moderate, total symptoms	Low	6	DPP-4 inhibitor favored
Severe symptoms	Low	6	Neither favored
Metformin vs. SGLT-2 inhibitors			
Mild, moderate symptoms	Moderate	4	SGLT-2 inhibitors favored; OR, 0.46 (CI, 0.16 to 1.30)†
Severe symptoms	Moderate	3	Neither favored
TZD vs. SU			
Mild, moderate symptoms	High	5	TZD favored; OR, 6.31 (CI, 4.08 to 9.76)
Severe symptoms	Moderate	2	TZD favored; OR, 8.0; RD, 0.5%
TZD vs. DPP-4 inhibitors			
Severe symptoms	Low	2	Neither favored
SU vs. DPP-4 inhibitors			
Mild, moderate, total symptoms	Moderate	4	DPP-4 favored; range in OR, 3.8 to 12.4; range in RD, 6% to 15%
Severe symptoms	Moderate	2	DPP-4 favored
DPP-4 inhibitors vs. SGLT-2 inhibitors			
Mild, moderate, total symptoms	Low	1	Neither favored
Severe symptoms	Low	1	Neither favored
Metformin vs. metformin combination			
Metformin vs. metformin + TZD			
Mild, moderate, total symptoms	High	8	Metformin favored; OR, 1.56 (CI, 0.99 to 2.44)†
Metformin vs. metformin + SU			
Mild, moderate, total symptoms	Moderate	10	Metformin favored, range in OR, 2 to 17; range in RD, 0% to 35%
Severe symptoms	Moderate	2	Neither favored
Metformin vs. metformin + DPP-4 inhibitors			
Mild, moderate symptoms	High	14	Neither favored; pooled OR for mild–moderate, 0.97 (CI, 0.6 to 1.5)
Severe symptoms	High	12	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors (<2 y)			
Mild, moderate symptoms	Moderate	7	Metformin favored; OR, 1.74 (CI, 0.83 to 3.66)†
Severe symptoms	Moderate	7	Neither favored; no events
Combination vs. combination			
Metformin + TZD vs. metformin + SU			
Mild, moderate symptoms	High	6	Metformin + TZD favored; OR, 7.45 (CI, 4.02 to 13.81)
Severe symptoms	Low	1	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 inhibitors			
Mild, moderate, total symptoms	Low	2	Neither drug combination favored
Severe symptoms	Low	3	Neither favored
Metformin + SU vs. metformin + DPP-4 inhibitors			
Mild, moderate symptoms	High	4	Metformin + DPP4-inhibitors favored; OR, 0.27 (CI, 0.18 to 0.39)
Severe symptoms	High	7	Met + DPP-4 favored <52 wk: OR, 0.2 (CI, 0.1 to 0.6) ≥52 wk: OR, 0.1 (CI, 0.03 to 0.3)
Metformin + SU vs. metformin + SGLT-2 inhibitors (<2 y)			
Mild, moderate, total symptoms	High	3	Metformin + SGLT-2 inhibitors favored; OR, 0.08 (CI, 0.03 to 0.17)
Severe symptoms	Moderate	2	Metformin + SGLT-2 inhibitors OR, 7; range in RD, 1% to 13%
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors			
Mild, moderate, total symptoms	Low	4	Neither group favored in studies lasting 12–78 wk
Severe symptoms	Low	2	Neither group favored

(*Continued on following page*)

Appendix Table 3–Continued

Intervention, by Outcome	Strength of Evidence	Studies, *n*	Summary*
GI side effects			
Monotherapy vs. monotherapy			
Metformin vs. TZD	Moderate	6	TZD favored for diarrhea: OR, 0.24 (CI, 0.17 to 0.34)
Metformin vs. SU	Moderate	12	SU favored for diarrhea: OR, 0.41 (CI, 0.24 to 0.72); abdominal pain: OR, 0.44 (CI, 0.29 to 0.67); nausea and vomiting: OR, 0.45 (CI, 0.31 to 0.65); and any GI adverse events: OR, 0.45 (CI, 0.28 to 0.72)
Metformin vs. DPP-4 inhibitors	High	6	DPP-4 inhibitors favored for nausea: OR, 0.37 (CI, 0.15 to 0.91), and diarrhea: OR, 0.38 (CI, 0.18 to 0.83)
Metformin vs. SGLT-2 inhibitors	Low	4	SGLT-2 inhibitors favored for diarrhea and nausea
TZD vs. SU	High	5	Neither favored; range in OR, 0.78 to 2.0; range in RD, −1.2% to 1.7%
TZD vs. DPP-4 inhibitors	Low	2	Neither favored
SU vs. DPP-4 inhibitors	Low	2	Neither favored
Metformin vs. metformin combination			
Metformin vs. metformin + TZD	Moderate	6	Metformin + TZD favored for diarrhea; OR, 0.59 (CI, 0.45 to 0.76)
Metformin vs. metformin + SU	Low	12	Neither drug favored for diarrhea or any GI adverse events
Metformin vs. metformin + DPP-4 inhibitors	Moderate	7	Neither favored; OR, 0.90 (CI, 0.63 to 1.31) for nausea; OR, 0.92 (CI, 0.68 to 1.25) for any GI adverse event; OR, 1.12 (CI, 0.64 to 1.96) for vomiting
Metformin vs. metformin + SGLT-2 inhibitors	Moderate	3	Neither favored for diarrhea; OR, 0.89 (CI, 0.54 to 1.46)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	5	Neither favored; range in OR, 0.5 to 2.0; range in RD, −5.0% to 2.1%
Metformin + TZD vs. metformin + DPP-4 inhibitors	Low	3	Neither favored
Metformin + SU vs. metformin + DPP-4 inhibitors (long-term studies)	High	4	Neither favored for diarrhea at 104 wk; OR, 0.97 (CI, 0.76 to 1.24)
Metformin + SU vs. metformin + SGLT-2 inhibitors	Low	3	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	No difference
Genital mycotic infections			
Monotherapy vs. monotherapy			
Metformin vs. SGLT-2 inhibitors	Moderate	4	Metformin favored; OR, 4.1 (CI, 2.0 to 8.3)
DPP-4 inhibitors vs. SGLT-2 inhibitors	Low	2	DPP-4 inhibitors favored
Metformin vs. metformin combination			
Metformin vs. metformin + SGLT-2 inhibitors	High	9	Metformin favored; OR, 3.0 (CI, 1.2 to 7.2) for females, and OR, 2.7 (CI, 0.8 to 9.0)† for males; RD, −2.3% to 9.9%
Combination vs. combination			
Metformin + SU vs. metformin + SGLT-2 inhibitors	High	3	Metformin + SU favored; OR, 5.2 (CI, 3.4 to 8.0) for females and 7.6 (CI, 4.0 to 14.4) for males; RD 7.1% to 17.4%
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	5	Metformin + DPP-4 inhibitors favored; RD, −2.8% to 8.8%

DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; OR = odds ratio; RD = risk difference; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Includes only estimates for comparisons with high or moderate strength of evidence.
† Effect is not statistically significant.