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GUIDELINES

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline 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 the comparative effectiveness and safety of type 2 diabetes medications.

Methods: This guideline is based on a systematic evidence review evaluating literature published on this topic from 1966 through April 2010 that was identified by using MEDLINE (updated through December 2010), EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline included all-cause mortality, cardiovascular morbidity and mortality, cerebrovascular morbidity, neuropathy, nephropathy, and retinopathy. This guideline grades the evidence and recommendations by using the American College of Physicians clinical practice guidelines grading system.

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).

Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).

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Diabetes mellitus is the seventh leading cause of death in the United States. In addition, it is a leading cause of morbidity and leads to 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 25.8 million people in the United States (1). Type 2 diabetes increases with age, and nearly 27% of people in the United States older than 65 years have diabetes (1). In addition, because of increasing rates of obesity in the United States, the incidence and prevalence of diabetes mellitus are increasing substantially (1). The costs associated with diabetes in the United States alone reached $174 billion in 2007 (2).

See also:

Print
Summary for Patients I-36

Web-Only
Appendix Tables
Conversion of graphics into slides

Good management of type 2 diabetes with pharmacologic and nonpharmacologic therapies is important and includes patient education, evaluation for microvascular and macrovascular complications, treatment of glycemia, and minimization of cardiovascular and other long-term risks. In the United States, 11 unique classes of drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of hyperglycemia in type 2 diabetes; all of these medications vary in cost and risk (3). Among people diagnosed with diabetes, most will receive more than 1 class of diabetes medication: 14% take both insulin and oral medication and 58% take oral medications only (2).

The purpose of this American College of Physicians (ACP) guideline is to address the pharmacologic management of type 2 diabetes by comparing the effectiveness and safety of currently available oral pharmacologic treatment for type 2 diabetes. The target audience for this guideline includes all clinicians, and the target patient population comprises all adults with type 2 diabetes. These recommendations are based on a systematic evidence review by Bennett and colleagues (4) and an evidence report spon-

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sored by the Agency for Healthcare Research and Quality (AHRQ) (5). The 2011 review expands on a 2007 AHRQ evidence report (6), which discussed mortality, microvascular and macrovascular outcomes, intermediate outcomes, and adverse effects for drugs available until 2006. The 2011 report focuses on head-to-head comparisons and includes direct comparisons for monotherapy and dual-therapy regimens. Combination therapies with more than 2 agents were not included in the review. The 2011 report also includes evidence for more recently approved diabetes medications and excludes data on α-glucosidase inhibitors, such as acarbose (5).

Methods

The evidence report informing this guideline reviewed data for 11 FDA-approved, unique classes of drugs for the treatment of hyperglycemia in type 2 diabetes (**Appendix Table 1**, available at www.annals.org). This guideline is based on a systematic evidence review that addressed the following key questions:

Key question 1: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options for the intermediate outcomes of glycemic control (in terms of hemoglobin A_{1c} [HbA_{1c}]), weight, or lipids?

Key question 2: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (for example, myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy?

Key question 3: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of these treatment options in terms of the following adverse events and side effects: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal side effects?

Key question 4: Do safety and effectiveness of these treatment options differ across subgroups of adults with type 2 diabetes, in particular for adults aged 65 years or older, in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes?

The systematic evidence review was conducted by the Johns Hopkins Evidence-based Practice Center. This review updates a 2007 systematic review on the same topic and focuses on head-to-head comparisons rather than placebo-controlled trials (6, 7). The literature search included studies identified by using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The studies that were selected included observational studies and trials published in the English language from 1966 through April 2010. In addition, the MEDLINE search was updated to December 2010 for long-term clinical outcomes (all-cause mortality, cardiovascular morbidity and mortality, nephropathy, neuropathy, and retinopathy). Reference lists, FDA medical reviews, European Public Assessment Reports, Health Canada Product Monographs, unpublished data from pharmaceutical companies, and public registries of clinical trials were also reviewed. Standardized forms were used for data abstraction, and each article underwent double review. Quality of randomized, controlled trials (RCTs) was assessed by using the Jadad criteria, and quality of observational studies was assessed as recommended in the Guide for Conducting Comparative Effectiveness Reviews (8, 9). The I^2 statistic was used to determine study heterogeneity (10). Further details about the methods and inclusion and exclusion criteria applied in the evidence review are available in the full AHRQ report (5).

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.

This guideline rates the recommendations by using the American College of Physicians guideline grading system, which is based on the GRADE system (**Table 1**). Details of the ACP guideline development process can be found in ACP's methods paper (11). This guideline focuses on results that were statistically significant, and details on non–statistically significant results are available in the full AHRQ report (5).

Comparative Effectiveness of Type 2 Diabetes Medications on Intermediate Outcomes

Table 2 summarizes the key findings and strength of evidence for intermediate outcomes comparing various diabetes medications as monotherapy or as combination therapy.

HbA_{1c} Levels

Evidence was gathered from 104 head-to-head RCTs that varied from low to high quality and offered direct evidence from comparisons among various type 2 diabetes medications (5).

Table 2. **Key Findings and Strength of Evidence for Intermediate Outcomes***

Comparison	HbA_{1c}	Weight/BMI	LDL Cholesterol	HDL Cholesterol	Triglycerides
Monotherapy vs. monotherapy					
Metformin vs.					
TZD	Neither favored, moderate	Favors metformin, high	Favors metformin, moderate† Favors metformin, high‡	Neither favored, moderate† Favors pioglitazone, high‡	Favors metformin, moderate† Favors pioglitazone, high‡
Sulfonylurea	Neither favored, high	Favors metformin, high	Favors metformin, high	Neither favored, high	Favors metformin, moderate
DPP-4 inhibitor	Favors metformin, moderate	Favors metformin, moderate	Favors metformin, moderate	Neither favored, low	Neither favored, low
Meglitinide	Neither favored, low§ Favors metformin, low§	Unclear, low	Unclear, low	Unclear, low	Unclear, low
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
TZD vs.					
TZD	Neither favored, moderate	Neither favored, low	Favors pioglitazone, low	Favors pioglitazone, moderate	Neither favored, low
Sulfonylurea	Neither favored, moderate	Favors sulfonylurea, low	Favors sulfonylurea, low†‡	Favors rosiglitazone, low† Favors pioglitazone, moderate‡	Unclear, low† Favors pioglitazone, low‡
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear, low§ Neither favored, low‖	Unclear, low	Unclear, low†‡	Unclear, low† Favors pioglitazone, low§	Unclear, low† Favors pioglitazone, low§
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfonylurea vs.					
DPP-4 inhibitor	Neither favored, low	Unclear, low	Neither favored, low	Neither favored, low	Neither favored, low
Meglitinide	Neither favored, high§ Neither favored, low‖	Neither favored, high	Neither favored, low	Neither favored, high	Neither favored, moderate
GLP-1 agonist	Unclear, low	Favors GLP-1 agonist, moderate	Unclear, low	Insufficient	Unclear, low
DPP-4 inhibitor vs.					
Meglitinide	Insufficient	Insufficient	Insufficient	Unclear, low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Monotherapy vs. combination therapy					
Metformin vs.					
Metformin + TZD	Favors metformin + TZD, high	Favors metformin, high	Favors metformin, high† Unclear, low‡	Favors metformin + rosiglitazone, high† Favors metformin + pioglitazone, low‡	Favors metformin, high† Unclear, low‡
Metformin + sulfonylurea	Favors metformin + sulfonylurea, high	Favors metformin, high	Neither favored, low	Neither favored, low	Neither favored, low
Metformin + DPP-4 inhibitor	Favors metformin + DPP-4 inhibitor, moderate	Neither favored, moderate	Neither favored, low	Neither favored, moderate	Favors metformin + DPP-4 inhibitor, low
Metformin + meglitinide	Favors metformin + meglitinides, low	Favors metformin, low	Unclear, low	Neither favored, low	Favors metformin + meglitinides, low
Combination therapy vs. combination therapy					
Metformin + TZD vs.					
Metformin + sulfonylurea	Neither favored, moderate	Favors metformin + sulfonylurea, moderate	Favors metformin + sulfonylurea, moderate† Favors metformin + sulfonylurea, low‡	Favors metformin + rosiglitazone, moderate† Favors metformin + pioglitazone, low‡	Neither favored, moderate† Favors metformin + pioglitazone, moderate‡
Metformin + meglitinide	Neither favored, low§ Insufficient‖	Unclear, low	Favors metformin + meglitinides, low† Insufficient‡	Favors metformin + rosiglitazone, low† Insufficient‡	Neither favored, low† Insufficient‡
Metformin + DPP-4 inhibitor	Neither favored, low	Favors metformin + DPP-4 inhibitor, low	Insufficient†‡	Unclear, low† Insufficient‡	Favors metformin + sitagliptin, low† Insufficient‡

Continued on following page

Table 2—**Continued**

Comparison	HbA_{1c}	Weight/BMI	LDL Cholesterol	HDL Cholesterol	Triglycerides
Metformin + GLP-1 agonist	Neither favored, low	Favors metformin + GLP-1 agonist, low	Unclear, low†‡	Favors metformin + rosiglitazone, low† Insufficient‡	Favors metformin + GLP-1 agonist, low† Insufficient‡
TZD + sulfonylurea	Favors TZD + sulfonylurea, low	Insufficient	Insufficient† Neither favored, low‡	Insufficient† Favors metformin + pioglitazone, low‡	Insufficient* Favors metformin + pioglitazone, low‡
Metformin + sulfonylurea vs.					
Metformin + meglitinide	Insufficient§ Unclear, low‖	Unclear, low	Unclear, low	Neither favored, low	Unclear, low
Metformin + DPP-4 inhibitor	Neither favored, low	Favors metformin + DPP-4 inhibitor, low	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Unclear, low	Favors metformin + GLP-1 agonist, low	Insufficient	Insufficient	Insufficient
TZD + sulfonylurea	Favors metformin + sulfonylurea, low	Favors metformin + sulfonylurea, moderate	Unclear, low† Favors metformin + sulfonylurea, low‡	Unclear, low† Favors pioglitazone + sulfonylurea, low‡	Unclear, low† Favors pioglitazone + sulfonylurea, low‡
Metformin + premixed insulin	Unclear, low	Favors metformin + basal insulin, low	Insufficient	Insufficient	Insufficient
Metformin + basal insulin vs.					
Metformin + premixed insulin	Neither favored, low	Neither favored, low	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Neither favored, low	Favors metformin + GLP-1 agonist, low	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor vs.					
Metformin + GLP-1 agonist	Favors metformin + GLP-1 agonist, low	Favors metformin + GLP-1 agonist, low	Unclear, low	Neither favored, low	Unclear, low

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TZD = thiazolidinedione.
* Unless otherwise noted, comparisons and intermediate outcomes were graded as insufficient because there were no studies.
† For comparisons with rosiglitazone.
‡ For comparisons with pioglitazone.
§ For comparisons with repaglinide.
‖ For comparisons with nateglinide.

Monotherapy vs. Monotherapy

Most diabetes medications had similar efficacy and reduced HbA_{1c} levels by an average of 1 percentage point (4). However, pooled results from 3 studies (reported in 4 papers) showed that metformin decreased HbA_{1c} levels more than did dipeptidyl peptidase-4 (DPP-4) inhibitors (mean difference, −0.37 percentage point [95% CI, −0.54 to −0.20 percentage point]; $I^2 = 0\%$; moderate-quality evidence) (12–15).

Monotherapy vs. Combination Therapy

All dual-regimen combination therapies were more efficacious than monotherapy and reduced HbA_{1c} levels by an average of 1 additional percentage point compared with monotherapy (4). Pooled data for the combination of metformin with another agent compared with metformin monotherapy showed a greater decrease in HbA_{1c} levels: metformin plus a sulfonylurea (mean difference, 1.00 percentage point [CI, 0.75 to 1.25 percentage point]; $I^2 = 85\%$; high-quality evidence), metformin plus a DPP-4 inhibitor (mean difference, 0.69 percentage point [CI, 0.56 to 0.82 percentage point]; $I^2 = 97\%$; moderate-quality evidence), metformin plus a thiazolidinedione (mean difference, 0.66 percentage point [CI, 0.45 to 0.86 percentage point]; $I^2 = 84\%$; high-quality evidence). Comparisons between different combinations of drugs showed similar effects, although few trials were available. Evidence from trials that included glucagon-like peptide-1 (GLP-1) agonists was graded as insufficient or low.

Combination Therapy vs. Combination Therapy

One RCT showed that the combination of metformin plus a GLP-1 agonist (liraglutide) statistically significantly decreased HbA_{1c} levels by 0.34 to 0.60 percentage points in low- and high-dose combinations compared with metformin plus a DPP-4 inhibitor (sitagliptin) (low-quality evidence) (16). A post hoc analysis of a small RCT showed that the combination of a thiazolidinedione plus a sulfonylurea decreased HbA_{1c} levels by 0.03 percentage point

($P = 0.04$) more than did the combination of metformin plus a thiazolidinedione (low-quality evidence) (17). All other combinations had similar efficacy in reducing HbA_{1c} levels (5).

Body Weight

Evidence was gathered from 79 head-to-head RCTs that varied from low to high quality and offered direct evidence from comparisons among various type 2 diabetes medications (5).

Monotherapy vs. Monotherapy

Pooled results showed that monotherapy with metformin resulted in more weight loss compared with thiazolidinediones (mean difference, −2.6 kg [CI, −4.1 to −1.2 kg]; $I^2 = 85\%$; high-quality evidence) (18–25), sulfonylureas (mean difference, −2.7 kg [CI, −3.5 to −1.9 kg]; $I^2 = 51\%$; high-quality evidence) (23, 26–36), and DPP-4 inhibitors (mean difference, −1.4 kg [CI, −1.8 to −1.0; $I^2 = 5\%$; moderate-quality evidence) (12, 14, 15). Monotherapy with a thiazolidinedione compared with a sulfonylurea resulted in more weight loss (mean difference, 1.2 kg [CI, 0.6 to 1.9 kg]; $I^2 = 0\%$; low-quality evidence) (23, 37–40). Compared with GLP-1 agonists, sulfonylureas showed more weight gain (mean difference, 2.5 kg [CI, 1.2 to 3.8 kg]; $I^2 = 93\%$; moderate-quality evidence), although the studies were very heterogeneous (41–43).

Monotherapy vs. Combination Therapy

Pooled data showed that metformin monotherapy was more effective in decreasing body weight than metformin plus a thiazolidinedione (mean difference, −2.2 kg [CI, −2.6 to −1.9 kg]; $I^2 = 0\%$; high-quality evidence) (24, 44–47) or metformin plus a sulfonylurea (mean difference, −2.3 kg [CI, −3.3 to −1.2 kg]; $I^2 = 83\%$; high-quality evidence) (29–36, 48, 49). Metformin was also favored when compared with metformin plus meglitinides in 2 RCTs (50, 51).

Combination Therapy vs. Combination Therapy

Pooled data showed that the combination of metformin plus a sulfonylurea was favored for weight compared with metformin plus a thiazolidinedione (mean difference, 0.9 kg [CI, 0.4 to 1.3 kg]; $I^2 = 0\%$; moderate-quality evidence) (52–56). Pooled data also showed that the combination of metformin plus a sulfonylurea is favored over the combination of a thiazolidinedione and sulfonylurea (mean difference, −3.17 [CI, −5.21 to −1.13 kg]; $I^2 = 83\%$; moderate-quality evidence). Compared with the combination of metformin plus a sulfonylurea (glipizide), metformin plus a DPP-4 inhibitor (sitagliptin) statistically significantly reduced weight in 1 RCT (mean difference, −2.5 kg [CI, −3.1 to −2.0 kg]) (57), and the trend continued when the study was extended for another year (mean difference, −2.3 kg [CI, −3.0 to −1.6 kg]) (low-quality evidence) (58). Combination of metformin plus a GLP-1 agonist also resulted in greater weight loss compared with the combination of metformin plus a sulfonylurea, as shown in 2 RCTs (low-quality evidence) (49, 59).

Plasma Lipid Levels

Evidence was gathered from 74 head-to-head RCTs that varied from low to high quality and offered direct evidence from comparisons among various type 2 diabetes medications. Most diabetes medications had a small to moderate effect on lipid levels: 5 to 10 mg/dL for low-density lipoprotein (LDL) cholesterol, 3 to 5 mg/dL for high-density lipoprotein (HDL) cholesterol, and 10 to 30 mg/dL for triglycerides (5).

LDL Cholesterol Levels

Monotherapy vs. Monotherapy. Monotherapy with metformin decreased LDL more than did thiazolidinedione monotherapy with pioglitazone (mean difference, −14.21 mg/dL [CI, −15.29 to −13.13 mg/dL]; $I^2 = 0\%$; high-quality evidence) (18, 22, 25, 60–62) or rosiglitazone (mean difference, −12.76 mg/dL [CI, −23.96 to −1.56 mg/dL]; $I^2 = 56\%$; moderate-quality evidence) (20, 21, 24, 63–65). Metformin was also favored over both sulfonylureas (mean difference, −10.1 mg/dL [CI, −13.3 to −7.0 mg/dL]; $I^2 = 85\%$; high-quality evidence) (28, 30, 31, 33, 35, 36, 66, 67) and DPP-4 inhibitors (mean difference, −5.9 mg/dL [CI, −9.7 to −2.0 mg/dL]; $I^2 = 28\%$; moderate-quality evidence) (12, 14, 15). Pooled data showed that monotherapy with sulfonylureas more effectively reduced LDL cholesterol than did pioglitazone (mean difference, 7.12 mg/dL [CI, 5.26 to 8.98 mg/dL]; $I^2 = 4\%$; low-quality evidence) (40, 68, 69), and 2 RCTs showed that rosiglitazone increased LDL cholesterol compared with sulfonylurea monotherapy (low-quality evidence) (37, 39).

Monotherapy vs. Combination Therapy. Compared with metformin monotherapy, combination of metformin with other agents did not show any benefit (5).

Combination Therapy vs. Combination Therapy. The combination of metformin plus a sulfonylurea was favored over metformin plus a thiazolidinedione, as pooled data showed for rosiglitazone (mean difference, 13.5 mg/dL [CI, 9.1 to 17.9 mg/dL]; $I^2 = 0\%$; moderate-quality evidence) (54, 55, 70, 71) and a single RCT showed for pioglitazone (mean difference, 8.5 mg/dL; $P = 0.03$; low-quality evidence) (56). The combination of metformin plus a sulfonylurea was also favored over the combination of pioglitazone plus a sulfonylurea, as reported in 2 RCTs (low-quality evidence) (72, 73).

HDL Cholesterol Levels

Monotherapy vs. Monotherapy. Monotherapy with metformin was less effective than a thiazolidinedione (pioglitazone) at increasing HDL cholesterol levels (mean differ-

ence, −3.2 mg/dL [CI, −4.3 to −2.1 mg/dL]; I^2 = 93%; high-quality evidence) (18, 22, 23, 25, 60–62, 74). Monotherapy with a thiazolidinedione more effectively increased HDL cholesterol levels compared with a sulfonylurea, as shown by pooled data for pioglitazone (mean difference, 4.27 mg/dL [CI, 1.93 to 6.61 mg/dL]; I^2 = 99%; moderate-quality evidence) (23, 40, 59, 68, 74, 75) and data from 2 RCTs for rosiglitazone (range in median between-group difference, 3.5 to 7.7 mg/dL; low-quality evidence) (37, 39). Two RCTs also showed that monotherapy with pioglitazone was favored over meglitinides (mean difference, 7 mg/dL; low-quality evidence) (75, 76). When thiazolidinediones were compared, pioglitazone increased HDL cholesterol levels more than did rosiglitazone (mean difference, −2.33 mg/dL [CI, −3.46 to −1.20 mg/dL]; I^2 = 0%; moderate-quality evidence) (77–79).

Monotherapy vs. Combination Therapy. The combination of metformin with a thiazolidinedione was better than monotherapy with metformin, as shown by pooled data for rosiglitazone (mean difference, −2.8 mg/dL [CI, −3.5 to −2.2 mg/dL]; I^2 = 83%; high-quality evidence) (24, 44, 45, 47, 80–82), and 2 RCTs favored the combination of metformin plus pioglitazone over metformin monotherapy (46, 83).

Combination Therapy vs. Combination Therapy. The combination of metformin plus a thiazolidinedione was favored over the combination of metformin and a sulfonylurea, as shown by pooled data for rosiglitazone (mean difference, 2.7 mg/dL [CI, 1.4 to 4.1 mg/dL]; I^2 = 0%; moderate-quality evidence) (54, 55, 70, 71), data from 2 RCTs for pioglitazone (between-group differences ranged from 5.1 mg/dL [$P < 0.001$] to 5.8 mg/dL [$P < 0.001$]; low-quality evidence) (56, 84). Post hoc analysis in 1 RCT showed that the combination of metformin plus pioglitazone increased HDL cholesterol levels (2.3 mg/dL; $P = 0.009$) compared with pioglitazone plus sulfonylurea (0.4 mg/dL; $P = 0.62$) (low-quality evidence) (84). Three RCTs found an increase in HDL cholesterol levels with the combination of pioglitazone plus a sulfonylurea compared with metformin plus a sulfonylurea (low-quality evidence) (72, 73, 84).

Triglyceride Levels

Monotherapy vs. Monotherapy. Metformin monotherapy decreased triglyceride levels compared with sulfonylureas (mean difference, −8.6 mg/dL [CI, −15.6 to −1.6 mg/dL]; I^2 = 92%; moderate-quality evidence) (23, 26, 28–31, 33, 35, 36, 66, 74) and rosiglitazone (mean difference, −26.86 mg/dL [CI, −49.26 to −4.47 mg/dL]; I^2 = 70%; moderate-quality evidence) (20, 21, 24, 63–65). However, pooled data from other studies showed that pioglitazone decreased triglyceride levels more than did metformin (mean difference, 27.2 mg/dL [CI, 24.4 to 30.0 mg/dL]; I^2 = 0%; high-quality evidence) (18, 22, 23, 25, 60–62, 74) and sulfonylureas (mean difference, −31.62 mg/dL [CI, −49.15 to −14.10 mg/dL]; I^2 = 91%; low-quality evidence) (23, 40, 68, 69, 74, 75). Two RCTs also favor pioglitazone over meglitinides for reducing triglyceride levels (75, 76).

Monotherapy vs. Combination Therapy. Metformin monotherapy decreased triglyceride levels more than metformin plus a thiazolidinedione (rosiglitazone) (mean difference, −14.5 mg/dL [CI, −15.8 to −13.3 mg/dL]; I^2 = 0%; high-quality evidence) (24, 44, 45, 47, 80–82). However, than with metformin monotherapy, combination therapy consisting of metformin plus a DPP-4 inhibitor (mean difference, 20.68 mg/dL [CI, −0.79 to 42.14 mg/dL]; low-quality evidence; $P > 0.05$) (14, 15, 47, 85) or metformin plus meglitinides (data from a single RCT: range of between-group differences, −17.8 to 8.9 mg/dL; $P < 0.05$ for the higher-dose nateglinide; low-quality evidence) (50) decreased triglyceride levels more than did metformin alone.

Combination Therapy vs. Combination Therapy. Two RCTs showed that the combination of metformin plus pioglitazone decreased triglyceride levels more than did metformin plus a sulfonylurea (between-group differences ranged from −10 mg/dL [$P = 0.30$] to −24.9 mg/dL [$P = 0.045$]; moderate-quality evidence) (56, 84). One small RCT found that metformin plus a GLP-1 agonist fared better than the combination of metformin plus rosiglitazone (between-group mean difference in triglyceride levels, 36.3 mg/dL; significance not reported; low-quality evidence) (86). In addition, data from 4 RCTs showed that the combination of a thiazolidinedione (pioglitazone) plus a sulfonylurea decreased triglyceride levels more or increased triglyceride levels less than the combination of metformin plus a sulfonylurea (low-quality evidence) (72, 73, 84, 87).

Comparative Effectiveness of Type 2 Diabetes Medications on Long-Term Clinical Outcomes

A total of 66 studies (46 RCTs; duration, 12 weeks to 6 years) reported comparative effectiveness of oral diabetes medications on long-term outcomes. The mean age of participants ranged from 48 years to 75 years (5). It was difficult to draw conclusions about the comparative effectiveness of type 2 diabetes medications on all-cause mortality, cardiovascular morbidity and mortality, and microvascular outcomes because of low quality or insufficient evidence (4). **Appendix Table 2** (available at www.annals.org) summarizes the findings and strength of evidence for long-term outcomes comparing various diabetes medications as monotherapy or combination therapy.

Mortality (All-Cause and Cardiovascular)

Five RCTs (30, 31, 33, 88, 89) and 11 observational studies (90–100) were examined for all-cause mortality between metformin monotherapy and sulfonylurea monotherapy. These studies indicate that metformin was associated with lower all-cause mortality compared with

sulfonylureas (low-quality evidence). Metformin was also favored over sulfonylureas for cardiovascular mortality (low-quality evidence), as evidenced by ADOPT (A Diabetes Outcome Progression Trial) (89) and 4 cohort studies (92, 94, 96, 101), although 1 prospective cohort study showed a slightly higher cardiovascular mortality rate for metformin than for sulfonylurea monotherapy (94).

Morbidity (Cardiovascular and Cerebrovascular)

Monotherapy with metformin was linked to lower cardiovascular morbidity than combination therapy for metformin plus sulfonylureas (low-quality evidence), as shown by 1 RCT (5% vs. 14% adverse cardiovascular events) (35) and 1 cohort study (adjusted incidence of hospitalization for myocardial infarction or coronary revascularization, 13.90 vs. 19.44 per 1000 person-years) (102). Evidence for all other comparisons was insufficient or unclear (**Appendix Table 2**) (5).

Retinopathy, Nephropathy, and Neuropathy

There was moderate-quality evidence for nephropathy only for the comparison between pioglitazone and metformin. In the 2 studies that addressed this comparison, pioglitazone significantly reduced the urinary albumin–creatinine ratio by 19% (25) and 15% (72), whereas the ratio was unchanged in patients treated with metformin.

Comparative Safety of Type 2 Diabetes Medications

Appendix Table 3 (available at www.annals.org) summarizes the findings and strength of evidence for adverse effects among various diabetes medications as monotherapy or combination therapy.

Hypoglycemia

No particular monotherapy or combination therapy increased severe hypoglycemia (generally defined as hypoglycemia requiring assistance for resolution) compared with the other treatments (4).

Monotherapy vs. Monotherapy

Pooled results from monotherapy trials show that sulfonylureas increase the risk for mild to moderate hypoglycemia compared with metformin (odds ratio [OR], 4.60 [CI, 3.20 to 6.50]; $I^2 = 68\%$; high-quality evidence) (27, 29–32, 36, 66, 74, 88), thiazolidinediones (OR, 3.88 [CI, 3.05 to 4.94]; $I^2 = 41\%$; high-quality evidence) (37–40, 74, 89, 103–105), and meglitinides (OR, 0.78 [CI, 0.55 to 1.12]; $I^2 = 18\%$; low-quality evidence) (106–113). Data from RCTs also indicate that other agents were favored over sulfonylureas for hypoglycemia: DPP-4 inhibitors (data from 1 RCT showed that 21 of 123 patients treated with a sulfonylurea had mild or moderate hypoglycemia compared with no patients treated with a DPP-4 inhibitor; moderate-quality evidence) (114) and GLP-1 agonists (data from 3 RCTs; high-quality evidence) (41–43). Monotherapy with meglitinides resulted in more hypoglycemia compared with metformin (OR, 3.00 [CI, 1.80 to 5.20]; $I^2 = 0\%$; moderate-quality evidence) (51, 115–118) or thiazolidinediones (2 RCTs: relative risk [RR], 1.2 [CI, 0.8 to 1.8] [76]; RR, 1.6 [CI, 1.0 to 2.6] [119]; low-quality evidence).

Monotherapy vs. Combination Therapy

Compared with metformin monotherapy, the combination of metformin plus a thiazolidinedione (OR, 1.57 [CI, 1.01 to 2.43]; $I^2 = 0\%$; moderate-quality evidence) (24, 44–47, 81–83), metformin plus a sulfonylurea (RR, 1.6 to 25 in 9 RCTs; moderate-quality evidence) (27, 29–31, 35, 36, 48, 49, 88), and metformin plus meglitinides (OR, 2.75 [CI, 0.98 to 7.71]; $I^2 = 21\%$; low-quality evidence; $P > 0.05$) (49–51) resulted in an increase in hypoglycemia.

Combination Therapy vs. Combination Therapy

The combination of metformin plus a sulfonylurea increased the risk for hypoglycemia by about 6 times compared with the combination of metformin plus a thiazolidinedione (OR, 5.80 [CI, 4.30 to 7.70]; $I^2 = 0\%$; high-quality evidence) (17, 52, 54, 56, 71). One large RCT reported that metformin plus a thiazolidinedione resulted in fewer hypoglycemic events compared with a thiazolidinedione plus a sulfonylurea (0.05 vs. 0.47 event per 100 person-years of follow-up; low-quality evidence) (120). Another study found more hypoglycemic symptoms in patients treated with the combination of metformin plus a sulfonylurea than with the combination of a thiazolidinedione plus a sulfonylurea (RR, 1.3 [CI, 0.9 to 2]; low-quality evidence) (121).

Other Adverse Effects

Evidence was insufficient to show any difference among the various type 2 diabetes medications on liver injury.

Evidence from 51 studies was evaluated to determine gastrointestinal effects (5). Evidence examined from studies addressing these effects that compared metformin monotherapy with thiazolidinediones (high-quality evidence) (22, 24, 25, 89, 122), sulfonylureas (moderate-quality evidence) (26, 27, 29–33, 35, 66, 88, 89), DPP-4 inhibitors (moderate-quality evidence) (12, 14, 15), or meglitinides (low-quality evidence) (115–118) report more gastrointestinal adverse effects with metformin. Trials comparing metformin monotherapy with combination metformin plus thiazolidinedione therapy (moderate-quality evidence) (24, 44–47, 80–82) or metformin plus sulfonylurea therapy (moderate-quality evidence) (27, 29–33, 35, 49, 66, 88, 123) generally favored the combination therapy, although the metformin dosage was typically lower in the combination group, possibly accounting for this difference. One RCT reported more dyspepsia with a combination of metformin plus a meglitinide than with metformin plus a sulfonylurea (13% vs. 3%; low-quality evidence) (124).

Two RCTs reported more diarrhea in combination treatment with metformin plus a sulfonylurea than with a thiazolidinedione plus a sulfonylurea (moderate-quality evidence) (72, 121).

Although few studies reported on congestive heart failure, moderate-quality evidence from 5 observational studies favors metformin over sulfonylureas (98, 100, 125–127), and moderate-quality evidence from 4 RCTs (39, 89, 103, 105) and 4 observational studies (98, 104, 125, 127, 128) favors sulfonylureas over thiazolidinediones. One 6-month observational study reported higher rates of heart failure with the combination of a thiazolidinedione plus a sulfonylurea (0.47 per 100 person-years) than with a thiazolidinedione plus metformin (0.13 per 100 person-years) (low-quality evidence) (120). One RCT reported that the combination of a thiazolidinedione plus a sulfonylurea or metformin doubled the risk for heart failure compared with a sulfonylurea plus metformin (RR, 2.1 [CI, 1.35 to 3.27]; low-quality evidence) (129).

Evidence was insufficient to show any difference among the various type 2 diabetes medications on macular edema.

One RCT identified 1 person with cholecystitis out of 105 patients treated with a thiazolidinedione compared with none of 100 patients treated with metformin (low-quality evidence) (22). Another RCT identified 1 person with cholecystitis ($n = 280$) treated with metformin monotherapy compared with no patients ($n = 288$) treated with a combination of metformin plus a thiazolidinedione (low-quality evidence) (44). Low-quality evidence for pancreatitis came from 1 trial that reported 1 patient ($n = 242$) with acute pancreatitis treated with a combination of metformin plus a sulfonylurea compared with no patients receiving metformin monotherapy ($n = 121$) (49). The evidence was insufficient to show any difference in cholecystitis or pancreatitis with other monotherapies or combination therapies.

For bone fractures, high-quality evidence from 1 RCT showed more bone fractures with thiazolidinedione monotherapy than with metformin monotherapy (hazard ratio [HR], 1.57 [CI, 1.13 to 2.17]), and subgroup analysis showed that the risk is higher for women (HR, 1.81 [CI, 1.17 to 2.80]; $P = 0.008$) (130). Data were assessed from 2 RCTs and 1 observational study, and results showed fewer fractures with sulfonylureas than with thiazolidinediones (high-quality evidence) (38, 130, 131). One RCT found an increase in fractures for patients treated with rosiglitazone compared with a sulfonylurea (HR, 2.13 [CI, 1.30 to 3.51]) (130), whereas another study reported 2 ankle fractures ($n = 251$) with pioglitazone monotherapy and no fractures with sulfonylurea monotherapy ($n = 251$) (38). The observational study found statistically significantly more fractures in women treated with pioglitazone (HR, 1.70 [CI, 1.30 to 2.23]; $P < 0.001$) and rosiglitazone (HR, 1.29 [CI, 1.04 to 1.59]; $P = 0.02$) than with sulfonylurea (131). The combination of metformin plus a sulfonylurea was favored over the combination of thiazolidinediones plus a sulfonylurea or thiazolidinediones plus metformin (RR, 1.57 [CI, 1.26 to 1.97]; $P < 0.001$; high-quality evidence), and the RR for fractures was higher for women than men (1.82 [CI, 1.37 to 2.41] vs. 1.23 [CI, 0.85 to 1.77]) (129).

Comparative Effectiveness of Type 2 Diabetes Medications Across Subgroups of Adults Aged 65 Years or Older

Evidence was gathered from 28 studies (21 RCTs) that reported comparative effectiveness and safety data for subpopulations (defined by age, sex, or race; obesity, duration of diabetes, or geographic region; required medication dose; previous comorbid conditions) (5). The evidence favoring one medication over another across subgroups is not clear because of lack of sufficient power in the included studies.

Summary

The evidence shows that most diabetes medications reduced HbA_{1c} levels to a similar degree. Metformin was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases). It was difficult to draw conclusions about the comparative effectiveness of type 2 diabetes medications on all-cause and cardiovascular mortality, cardiovascular and cerebrovascular morbidity, and microvascular outcomes because of low-quality or insufficient evidence.

High-quality evidence shows that the risk for hypoglycemia with sulfonylureas exceeds the risk with metformin or thiazolidinediones and that the combination of metformin plus sulfonylureas is associated with 6 times more risk for hypoglycemia than the combination of metformin plus thiazolidinediones. Moderate-quality evidence shows that the risk for hypoglycemia with metformin and thiazolidinediones is similar. Metformin is associated with an increased risk for gastrointestinal side effects. Thiazolidinediones are associated with an increased risk for heart failure, and both rosiglitazone and pioglitazone are contraindicated in patients with serious heart failure (132, 133).

The current evidence was not sufficient to show any difference in effectiveness among various medications across subgroups of adults.

Recommendations

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

Figure 1. **The American College of Physicians guideline on oral medications for type 2 diabetes.**

ACP Clinical Practice®
American College of Physicians
GUIDELINES

The American College of Physicians Guideline on Oral Medications for Type 2 Diabetes	
Disease or condition	Type 2 diabetes
Target audience	Internists, family physicians, other clinicians
Target patient population	Adults with type 2 diabetes
Interventions	Oral pharmacologic treatment for hyperglycemia in type 2 diabetes
Outcomes	All-cause mortality Cardiovascular morbidity and mortality Cerebrovascular morbidity Neuropathy, nephropathy, retinopathy Hemoglobin A_{1c} levels Weight Plasma lipid levels Adverse effects
Recommendations	*Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).* *Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).* *Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).*
Clinical Considerations	• Good management of type 2 diabetes with pharmacologic and nonpharmacologic therapies is important and includes patient education, evaluation, and self-management, for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. • Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. • Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss and/or lifestyle modification fails. • Metformin monotherapy was more effective in decreasing glycemic levels than other monotherapies, as well as in combination therapy with a second agent. In addition, metformin has the advantage of reducing body weight and improving plasma lipid profiles (in most cases). • Although combination therapy more effectively reduces hemoglobin A_{1c} levels, it is also associated with more adverse events.

Initiation of oral pharmacologic therapy is an important approach to effective management of type 2 diabetes. There are no data on the best time to add oral therapies to lifestyle modifications; thus, to avoid an unacceptable burden on patients, other complicating factors should be considered, such as life expectancy of the patient, presence or absence of microvascular and macrovascular complications, risk for adverse events related to glucose control, and patient preferences (134). The goal for HbA_{1c} should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences. An HbA_{1c} level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.

Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).

The effectiveness, adverse effect profiles, and costs of various oral pharmacologic treatments vary. Metformin is more effective than other pharmacologic agents in reducing glycemic levels and is not associated with weight gain. In addition, metformin aids in decreasing weight and reduces LDL cholesterol and triglyceride levels. Metformin was also associated with slightly lower all-cause mortality and cardiovascular mortality compared with sulfonylureas. Finally, metformin is associated with fewer hypoglycemic episodes and is cheaper than most other pharmacologic agents. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis.

Figure 2. **The American College of Physicians best practice advice: oral medications for type 2 diabetes.**

ACP
American College of Physicians
Best Practice Advice

The American College of Physicians Best Practice Advice: Oral Medications for Type 2 Diabetes	
Disease or condition	Type 2 diabetes
Target audience	Internists, family physicians, other clinicians
Target patient population	Adults with type 2 diabetes
Interventions	Oral pharmacologic treatment for hyperglycemia in type 2 diabetes
Evidence on comparative effectiveness of oral pharmacologic agents	• Metformin was more effective than other agents as monotherapy as well as in combination therapy with a second agent in reducing hemoglobin A_{1c} levels, body weight, and plasma lipid levels (in most cases). • Risk for hypoglycemia is higher when sulfonylureas are given as monotherapy or as combination therapy with a second agent, including metformin. • Metformin is associated with fewer adverse events than sulfonylureas.
High-value, cost-conscious care	• Metformin is the effective initial management strategy in patients with type 2 diabetes (unless contraindicated) when lifestyle modifications fail to adequately control hyperglycemia. • Clinicians should prescribe generic medications, if possible, rather than expensive branded medications for pharmacologic management of type 2 diabetes.

Physicians and patients should discuss adverse event profiles before selecting a medication. Compared with baseline values, most diabetes medications (metformin, thiazolidinediones, and sulfonylureas) reduced baseline HbA_{1c} by about 1 percentage point 3 or more months after the initiation of treatment. For adverse effects, metformin is associated with an increased risk for gastrointestinal side effects, sulfonylureas and meglitinides are associated with an increased risk for hypoglycemia, and thiazolidinediones are associated with an increased risk for heart failure (with no conclusive evidence for an increase in ischemic cardiovascular risk). However, in comparing the effectiveness of various agents, the evidence shows that metformin is the most efficacious agent as monotherapy and in combination therapy.

Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).

All dual-therapy regimens were more efficacious than monotherapies in reducing the HbA_{1c} level in patients with type 2 diabetes by about 1 additional percentage point. Combination therapies with more than 2 agents were not included in the evidence review. No good evidence supports one combination therapy over another, even though some evidence shows that the combination of metformin with another agent generally tends to have better efficacy than any other monotherapy or combination therapy. However, combination therapies are also associated with an increased risk for adverse effects compared with monotherapy. Generic sulfonylureas are the cheapest second-line therapy; however, adverse effects are generally worse with combination therapies that include a sulfonylurea.

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

See **Figure 1** for a summary of the recommendations and clinical considerations.

ACP Best Practice Advice

On the basis of the evidence reviewed in this paper, ACP has found strong evidence that in most patients with type 2 diabetes in whom lifestyle modifications have failed to adequately improve hyperglycemia, oral pharmacologic therapy with metformin (unless contraindicated) is an effective management strategy. It is cheaper than most other pharmacologic agents, has better effectiveness, and is associated with fewer adverse effects; of note, it does not result in weight gain (**Figure 2**).

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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Appendix Table 1. Type 2 Diabetes Medications, Dosages, and Wholesale Price Range*

Drug Type and Dosage	Price for 1-Month Supply	
	Generic	Brand
Metformin		
500 mg once daily	$	$$
500 mg twice daily	$$	$$
500 mg 3 times daily	$$	$$$
850 mg once daily	$$	$$
850 mg twice daily	$$$	$$$
850 mg 3 times daily	$$$	$$$$
1000 mg once daily	$$	$$
1000 mg twice daily	$$$	$$$$
Metformin (extended release)		
500 mg once daily	$	$$
1000 mg once daily	$$	$$
1500 mg once daily	$$	$$$
2000 mg once daily	$$$	$$$$
Second-generation sulfonylureas		
Glimepiride		
1 mg once daily	$	$
2 mg once daily	$	$$
4 mg once daily	$$	$$
8 mg once daily	$$$	$$$
Glipizide		
5 mg once daily	$	$$
10 mg once daily	$$	$$
10 mg twice daily	$$$	$$$$
20 mg twice daily	$$	$$$
Glipizide (extended release)		
5 mg once daily	$	$
20 mg once daily	$$	$$$
Glyburide		
2.5 mg twice daily	$$	$$
5 mg once daily	$$	$$
5 mg twice daily	$$	$$$
Micronized glyburide		
1.5 mg once daily	$	$$
3 mg once daily	$	$$
6 mg twice daily	$$	$$$$
Meglitinides		
Repaglinide		
0.5 mg 3 times daily	NA	$$$$$
1 mg 3 times daily	NA	$$$$$
4 mg 3 times daily	NA	$$$$$
Nateglinide		
60 mg 3 times daily	NA	$$$$
120 mg 3 times daily	NA	$$$$
Thiazolidinedione		
Pioglitazone		
15 mg once daily	NA	$$$$
30 mg once daily	NA	$$$$$
45 mg once daily	NA	$$$$$
DPP-4 inhibitors		
Sitagliptin		
100 mg once daily	NA	$$$$$
Saxagliptin		
2.5–5 mg once daily	NA	$$$$$

Appendix Table 1—Continued

Drug Type and Dosage	Price for 1-Month Supply	
	Generic	Brand
GLP-1 agonists		
Exenatide		
Injection of 5 mcg twice daily	NA	$$$$$
Injection of 10 mcg twice daily	NA	$$$$$
Liraglutide		
Injection of 0.6 mcg twice daily	NA	$$$$
Injection of 1.2 mcg twice daily	NA	$$$$$
Injection of 1.8 mcg twice daily	NA	$$$$$

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not available.

* Adapted from the Agency for Healthcare Research and Quality Clinician Research Summary. $ = $5 to $25; $$ = $26 to $75; $$$ = $76 to $125; $$$$ = $126 to $200; $$$$$ = >$200.

Appendix Table 2. Key Findings and Strength of Evidence for Long-Term Outcomes

Comparison	All-Cause Mortality	Cardiovascular Mortality	Cardiovascular and Cerebrovascular Morbidity	Nephropathy and Neuropathy
Monotherapy vs. monotherapy				
Metformin vs.				
TZD	Neither favored, low	Neither favored, low	Unclear, low	Favors pioglitazone*, moderate
Sulfonylurea	Favors metformin, low	Favors metformin, low	Unclear, low	Unclear, low* Insufficient†
DPP-4 inhibitor	Unclear, low	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
TZD vs.				
TZD	Insufficient	Insufficient	Unclear, low	Insufficient
Sulfonylurea	Neither favored, low	Unclear, low	Unclear, low	Unclear, low*
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Insufficient	Insufficient	Insufficient	Unclear, low*
GLP-1 agonist	Unclear, low	Insufficient	Unclear, low	Insufficient
Sulfonylurea vs.				
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor vs.				
Meglitinide	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Monotherapy vs. combination therapy				
Metformin vs.				
Metformin + TZD	Unclear, low	Unclear, low	Unclear, low	Insufficient* Unclear, low†
Metformin + sulfonylurea	Neither favored, low	Unclear, low	Favors Met, low	Insufficient
Metformin + DPP-4 inhibitor	Unclear, low	Unclear, low	Unclear, low	Insufficient* unclear, low†
Metformin + meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient
Combination therapy vs. combination therapy				
Metformin + another agent vs.				
Metformin + TZD	Unclear, low	Unclear, low	Unclear, low	Conclusion unclear for nephropathy and neuropathy, low
Metformin + sulfonylurea	Unclear, low	Unclear, low	Unclear, low	Insufficient
Metformin + meglitinide	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Unclear, low	Unclear, low	Unclear, low	Insufficient
Metformin + GLP-1 agonist	Insufficient	Unclear, low	Insufficient	Insufficient
Metformin + basal insulin	Insufficient	Unclear, low	Unclear, low	Insufficient
Metformin + premixed insulin	Unclear, low	Unclear, low	Insufficient	Insufficient
TZD + another agent vs.				
Metformin + TZD	Insufficient	Insufficient	Unclear, low	Insufficient
Metformin + sulfonylurea	Unclear, low	Insufficient	Unclear, low	Insufficient
Metformin + meglitinide	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Unclear, low	Insufficient	Unclear, low	Insufficient

DPP-4 inhibitor = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione.
* Key finding for nephropathy.
† Key finding for neuropathy.

Appendix Table 3. **Key Findings and Strength of Evidence for Adverse Events***

Comparison	Hypoglycemia	Liver Injury	GI Event	CHF	Macular Edema	Pancreatitis or Cholecystis	Fractures
Monotherapy vs. monotherapy							
Metformin vs.							
TZD	Neither favored, moderate	Neither favored, moderate	Favors TZD, high	Neither favored, moderate	Insufficient	Favors metformin, low† Insufficient‡	Favors metformin, high
Sulfonylurea	Favors metformin, high	Unclear, low	Favors sulfonylurea, moderate	Favors metformin, moderate	Insufficient	Insufficient	Unclear, low
DPP-4 inhibitor	Neither favored, high	Insufficient	Favors DPP-4 inhibitor, moderate	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Favors metformin, moderate	Insufficient	Favors meglitinides, low§	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
TZD vs.							
TZD	Favors rosiglitazone, low	Unclear, low	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient
Sulfonylurea	Favors TZD, high	Neither favored, high	Neither favored, high	Favors sulfonylurea, moderate	Insufficient	Neither favored, low† Insufficient‡	Favors sulfonylurea, high
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Favors TZD, low	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfonylurea vs.							
DPP-4 inhibitor	Favors DPP-4 inhibitor, moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Favors meglitinides, low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Favors GLP-1 agonist, high	Insufficient	Favors sulfonylurea, low	Insufficient	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor vs.							
Meglitinide	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient† Neither favored, low‡	Insufficient
Monotherapy vs. combination therapy							
Metformin vs.							
Metformin + TZD	Favors metformin, moderate	Insufficient	Favors metformin + TZD, moderate§	Insufficient	Insufficient	Favors metformin + TZD, low†	Favors metformin, low
Metformin + sulfonylurea	Favors metformin, moderate	Insufficient	Favors metformin + sulfonylurea, moderate‖	Insufficient	Insufficient	Insufficient† Favors metformin, low‡	Unclear, low
Metformin + DPP-4 inhibitor	Neither favored, moderate	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Unclear, low
Metformin + meglitinide	Favors metformin, low	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Insufficient

Continued on following page

Appendix Table 3—**Continued**

Comparison	Hypoglycemia	Liver Injury	GI Event	CHF	Macular Edema	Pancreatitis or Cholecystis	Fractures
Combination therapy vs. combination therapy							
Metformin + another agent vs.							
Metformin + TZD	Favors metformin + TZD, high	Neither favored, low	Neither favored, low	Insufficient	Favors metformin + other, low	Insufficient	Favors metformin + other, high
Metformin + sulfonylurea	Unclear, low	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + meglitinide	Insufficient	Insufficient	Favors metformin + sulfonylurea, low¶	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Insufficient	Insufficient	Neither favored, low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Insufficient	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Favors metformin + basal insulin, moderate	Insufficient	Unclear, low	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
TZD + another agent vs.							
Metformin + TZD	Favors metformin + TZD, low	Insufficient	Insufficient	Favors metformin + TZD, low	Insufficient	Insufficient	Insufficient
Metformin + sulfonylurea	Favors TZD + sulfonylurea, low	Neither favored, low	Favors TZD + other, moderate	Favors metformin + sulfonylurea, low	Insufficient	Insufficient	Favors metformin + sulfonylurea, high
Metformin + meglitinide	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + basal insulin	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Metformin + premixed insulin	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CHF = congestive heart failure; DPP-4 inhibitor = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione.
* Unless otherwise noted, comparisons and intermediate outcomes were graded as insufficient because there were no studies.
† Key finding and evidence grade for cholecystitis.
‡ Key finding and evidence grade for pancreatitis.
§ For diarrhea only.
‖ With lower dose of metformin.
¶ For dyspepsia.