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CLINICAL GUIDELINE

Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Clinical Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this clinical guideline to update recommendations on newer pharmacologic treatments of type 2 diabetes. This clinical guideline is based on the best available evidence for effectiveness, comparative benefits and harms, consideration of patients' values and preferences, and costs.

Methods: This clinical guideline is based on a systematic review of the effectiveness and harms of newer pharmacologic treatments of type 2 diabetes, including glucagon-like peptide-1 (GLP-1) agonists, a GLP-1 agonist and glucose-dependent insulinotropic polypeptide agonist, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and long-acting insulins, used either as monotherapy or in combination with other medications. The Clinical Guidelines Committee prioritized the following outcomes, which were evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach: all-cause mortality, major adverse cardiovascular events, myocardial infarction, stroke, hospitalization for congestive heart failure, progression of chronic kidney disease, serious adverse events, and severe hypoglycemia. Weight loss, as measured by percentage of participants who achieved at least 10% total body weight loss, was a prioritized outcome, but data were insufficient for network meta-analysis and were not rated with GRADE.

Audience and Patient Population: The audience for this clinical guideline is physicians and other clinicians. The population is nonpregnant adults with type 2 diabetes.

Recommendation 1: *ACP recommends adding a sodium–glucose cotransporter-2 (SGLT-2) inhibitor or glucagon-like peptide-1 (GLP-1) agonist to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control (strong recommendation; high-certainty evidence).*

- *Use an SGLT-2 inhibitor to reduce the risk for all-cause mortality, major adverse cardiovascular events, progression of chronic kidney disease, and hospitalization due to congestive heart failure.*
- *Use a GLP-1 agonist to reduce the risk for all-cause mortality, major adverse cardiovascular events, and stroke.*

Recommendation 2: *ACP recommends against adding a dipeptidyl peptidase-4 (DPP-4) inhibitor to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control to reduce morbidity and all-cause mortality (strong recommendation; high-certainty evidence).*

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The age-adjusted prevalence of type 2 diabetes in adults is 14.8% in the United States (1) and 10.5% globally (2). The age-adjusted incidence of type 2 diabetes in U.S. adults is 5.8 per 1000 persons; however, an estimated 23% of the U.S. adults with type 2 diabetes are undiagnosed (3).

Type 2 diabetes is associated with higher risk for mortality and morbidity, greater health care use, and greater costs when adults with diabetes are compared with those without diabetes (4). The economic burden of type 2 diabetes in the United States is substantial, with an annual estimated cost of $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity (5).

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Type 2 diabetes disproportionately affects adults with obesity and racial and ethnic minorities (6). For example, the age-adjusted prevalence of type 2 diabetes is higher in Black (19%) and Hispanic (21%) adults than in White adults (12%) (7). People with type 2 diabetes and social risk factors are more likely to die prematurely and to have health-related complications, poor access to high-quality health care, and difficulty with adherence to treatments than people with type 2 diabetes who do not have adverse social risk factors (8–15). In the United States, the excess risk for premature deaths attributed to type 2 diabetes decreased between 1997 and 2011 among Hispanic and White adults, but not among Black adults (16). Access to high-quality health care in people with type 2 diabetes differs by race and ethnicity even after adjustment for socioeconomic, lifestyle, and health factors (17). It is important to note that race and ethnicity are social constructs rather than biological risk factors. Differences in risk for diabetes and outcomes in people with diabetes may be mediated by such factors as social determinants of health.

Major treatment goals for patients with type 2 diabetes include adequate glycemic control and primary and secondary prevention of atherosclerotic cardiovascular and kidney diseases, which account for nearly half of all deaths among adults with type 2 diabetes (18). Despite multiple treatment options, 16% of adults with type 2 diabetes have inadequate glycemic control, with hemoglobin A_{1c} (HbA_{1c}) levels of 9% or higher (7). Inadequate glycemic control is more prevalent among Black (24%) and Hispanic (29%) adults than among White adults (9%) with type 2 diabetes (7).

In 2017, the American College of Physicians (ACP) published a clinical guideline on oral pharmacologic treatments of type 2 diabetes focused on glycemic control (19). The ACP Clinical Guidelines Committee (CGC) recommended that clinicians prescribe metformin, in addition to lifestyle treatments, when pharmacologic therapy is needed to improve glycemic control in adults with type 2 diabetes (19).

Scope and Purpose

This ACP clinical guideline is an update to the 2017 version (19) with evidence about the effectiveness and harms of newer pharmacologic treatments to reduce the risk for all-cause mortality, cardiovascular morbidity, and progression of chronic kidney disease (CKD) in adults with type 2 diabetes. In addition to incorporating network meta-analyses (NMAs), this clinical guideline adds key questions on patient values and preferences and economic evidence.

Newer pharmacologic treatments include glucagon-like peptide-1 (GLP-1) agonists (dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide), a GLP-1 agonist and glucose-dependent insulinotropic polypeptide agonist (tirzepatide), sodium–glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin), dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin), and long-acting insulins (insulin glargine and insulin degludec). The CGC did not consider studies of hospitalized adults with type 2 diabetes; type 2 diabetes management in adults with acute comorbid conditions, including acute stroke and myocardial infarction (MI); or adults with type 2 diabetes undergoing surgery or active cancer treatment.

Population

The patient population is nonpregnant adults with type 2 diabetes.

Intended Audience

The intended audience is physicians and other clinicians caring for adults with type 2 diabetes.

Guideline Development Process

The CGC developed this clinical guideline according to ACP's guideline development methods (20) and its policy on disclosure of interests and management of conflicts of interest (21). The CGC used the Evidence-to-Decision framework when reporting evidence (**Supplement Tables 1** to **5**, available at Annals.org) and rated the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (22) (**Figure 1**). The Appendix (available at Annals.org) lists the key questions for the supporting systematic reviews (**Appendix Table 1**, available at Annals.org), describes the selection and definition of critical and important clinical outcomes, and details the methods used for the clinical guideline and systematic reviews. **Supplement Tables 1** to **5** incorporate evidence from systematic reviews alongside interpretation and judgements made by the CGC, which are briefly summarized in **Figures 2** and **3**. ACP completes a Guidelines International Network Guideline Standards (23) reporting form for each clinical guideline it publishes, which can be found in the Network's International Guidelines Library or on ACP's website (www.acponline.org/clinical-information/guidelines/guideline-process).

Systematic Review of Benefits and Harms and Summary of the Evidence

This clinical guideline is based on an accompanying systematic review and NMA of randomized controlled trials (RCTs) with at least 12 months of treatment and follow-up that examined the benefits and harms of newer pharmacologic treatments in adults with type 2 diabetes (24). The systematic review and NMA was completed by the ACP Center for Evidence Reviews at Minnesota and funded by ACP.

Figure 1. Grading the certainty of evidence and strength of recommendations in ACP clinical guidelines using GRADE.

Grading Certainty of Evidence			
High	Confident that the true effect lies close to the estimate of the effect (the intervention "results in" the effect).		
Moderate	Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a sizeable possibility that it is substantially different (the intervention "probably results in" the effect).		
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect (the intervention "may result in" the effect).		
Grading Strength of Recommendations			
Strength	**Balance of Benefits and Harms**	**Applicable Patient Population**	**Policy Implications**
Strong (ACP recommends)	Confidence that the benefits clearly outweigh risks and burden or vice versa.	Applies to most patients in most circumstances.	Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs.
Conditional (ACP suggests)	Benefits probably outweigh the risks and burden, or vice versa, but there is appreciable uncertainty.	Applies to many patients but may differ depending on circumstances or patients' values and preferences.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

ACP = American College of Physicians; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Although the systematic review was not limited to add-on therapy in which a newer pharmacologic treatment of type 2 diabetes was added to usual care in adults with inadequate glycemic control, that is how most included studies were designed. The most common usual care medication in the included trials was metformin. In assessing the applicability of the evidence, the CGC considered glycemic control and lifestyle modifications directed by study investigators and physicians, prior treatments, risk for cardiovascular diseases (CVDs), presence of CKD, and comorbid conditions at baseline.

Outcomes of Interest

Benefits and Harms

The CGC, CGC Public Panel, and members of the topic expert panel for the systematic review independently rated the importance of clinical outcomes as "critical," "important," or "less important" for decision making (**Appendix Table 2**, available at Annals.org). The CGC prioritized the following outcomes for decision making: all-cause mortality, congestive heart failure (CHF) requiring hospitalization, major adverse cardiovascular events (MACE; generally defined as the occurrence of cardiovascular death, a nonfatal MI, or a nonfatal stroke), MI alone, progression of CKD, serious adverse events (SAEs), severe hypoglycemia, stroke alone, and weight change (as measured by achieving ≥10% total body weight loss). However, the Center for Evidence Reviews did not appraise the certainty of evidence for total body weight loss of 10% or more because data were heterogeneous and insufficient to include in the NMA. Glycemic control was not a prioritized outcome because all eligible medications have been shown to improve this surrogate measure.

Public and Patient Values and Preferences

The CGC assessed the evidence in the systematic review about values and preferences for newer pharmacologic treatments in adults with type 2 diabetes (**Supplement Table 6**, available at Annals.org). Evidence about public and patient values and preferences was identified through 2 sources, the accompanying review of research evidence conducted by the Center for Evidence Reviews and consultation with the CGC Public Panel. The CGC Public Panel was engaged in rating the importance of clinical outcomes, as well as providing their views on the findings from the systematic review about the benefits and harms of treatment options. In addition, the CGC Public Panel provided feedback on treatment selection preferences and guideline recommendations.

Costs

The CGC considered costs and the economic burden of care when assessing the value of the treatments. The Center for Evidence Reviews completed a separate systematic review (funded by ACP) (25) on the economic value of treatments based on willingness-to-pay thresholds for incremental cost-effectiveness ratio per quality-adjusted life-year gained reported in high-quality cost-effectiveness analyses applicable to the United States (26, 27). Average annual Medicare spending per beneficiary for type 2 diabetes medications is reported in **Supplement Tables 7** and **8** (available at Annals.org). A summary of findings for the systematic review on cost-effectiveness analyses is in **Supplement Table 9** (available at Annals.org).

Recommendations

A visual clinical guideline for this topic displaying a visual summary of the recommendations, rationales, and clinical considerations, alongside an interactive data visualization, is available at Annals.org (28).

Figure 2. Summary of CGC interpretation of evidence for newer diabetes medications compared with usual care or placebo.

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
Compared with usual care or placebo								
DPP-4 inhibitors	No difference	No difference	No difference	No difference	No difference	No difference	No difference	No difference
GLP-1 agonists	*Reduce all-cause mortality by 12% or 10 fewer events*	*Reduce MACE by 9% or 11 fewer events*	No difference	*Reduce stroke by 14% or 5 fewer events*	No difference	No data	No difference	Probably no difference
Long-acting insulins	May be no difference	May be no difference	No data	No data	May be no difference	No data	Probably no difference	Insufficient evidence
SGLT-2 inhibitors	*Reduce all-cause mortality by 14% or 9 fewer events*	*Probably reduce MACE by 10% or 12 fewer events*	No difference	No difference	*Reduce hospitalization due to CHF by 36% or 19 fewer events*	*Reduce progression of CKD by 34% or 12 fewer events*	*Reduce SAEs by 7% or 23 fewer events*	*Reduce severe hypoglycemia by 15% or 3 fewer events*
Tirzepatide	May be no difference	Insufficient evidence	No data	No data	No data	No data	No difference	Probably no difference

Favors intervention (*green*) or favors comparator (*red*; not present in this figure) indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., ≥25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper (1.25) bounds. Italicized interpretation text indicates statistically significant findings. Statistics are from the American College of Physicians (ACP)–funded systematic review and network meta-analysis (24) available in **Supplement Tables 1** to **4** (available at Annals.org). Interpretation of findings was done by the CGC. CGC = Clinical Guidelines Committee; CHF = congestive heart failure; CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MACE = major adverse cardiovascular events; MI = myocardial infarction; SAE = serious adverse event; SGLT-2 = sodium–glucose cotransporter-2.

* SAEs were defined by investigators, varied, and were not always fully reported. In general, these SAEs included events considered fatal or life-threatening and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (24). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

Figures 2 and **3** provide an overview of the CGC's interpretation of the summary of findings from the systematic review. Full summary of findings tables can be found in **Supplement Tables 1** to **5**.

Recommendation 1

ACP recommends adding a sodium–glucose cotransporter-2 (SGLT-2) inhibitor or glucagon-like peptide-1 (GLP-1) agonist to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control (strong recommendation; high-certainty evidence).

- *Use an SGLT-2 inhibitor to reduce the risk for all-cause mortality, major adverse cardiovascular events, progression of chronic kidney disease, and hospitalization due to congestive heart failure.*
- *Use a GLP-1 agonist to reduce the risk for all-cause mortality, major adverse cardiovascular events, and stroke.*

The only newer pharmacologic treatments of type 2 diabetes that reduced all-cause mortality compared with placebo or usual care were SGLT-2 inhibitors and GLP-1 agonists. However, after evaluating the benefits and harms of these pharmacologic classes, the CGC could not determine the superiority of one over the other. In addition, the most common usual care medication in the included trials was metformin. High-certainty evidence indicates that adding an SGLT-2 inhibitor to usual care reduces the risk for all-cause mortality, hospitalization due to CHF, and progression of CKD, and moderate-certainty evidence indicates that it probably reduces the risk for MACE compared with usual care (that is, background pharmacologic treatment and lifestyle modifications) (**Supplement Table 1**) (24). High-certainty evidence indicates that adding a GLP-1 agonist to usual care reduces the risk for all-cause mortality, MACE, and stroke (**Supplement Table 1**) (24). The CGC Public Panel considered the benefits and harms of SGLT-2 inhibitors and GLP-1 agonists and supported their use, which was consistent with the conclusions in the systematic review of studies on patient values and preferences (24).

When SGLT-2 inhibitors and GLP-1 agonists are compared indirectly (NMA), SGLT-2 inhibitors probably reduce the risk for hospitalization due to CHF, whereas GLP-1 agonists probably reduce the risk for stroke (**Supplement Table 3**) (24). Neither pharmacologic class causes severe hypoglycemia, but both are associated with various harms and carry specific warnings (24). Sodium–glucose cotransporter-2 inhibitors are associated with bone fractures, lower-limb amputations, urogenital mycotic infections, Fournier gangrene, orthostatic hypotension, euglycemic ketoacidosis, and other harms (24). Glucagon-like peptide-1 agonists are

Figure 3. Summary of CGC interpretation of evidence for DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors compared with other active treatments.

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
DPP-4 inhibitors (head-to-head)								
Compared with GLP-1 agonists	*DPP-4s probably increase all-cause mortality by 64% or 7 more events*	DPP-4s increase MACE by 42% or 16 more events	Probably no difference	Probably no difference	*DPP-4s probably increase hospitalization due to CHF by 112% or 13 more events*	No data	No difference	No difference
Compared with long-acting insulins	No difference	No difference	No data	No data	No difference	No data	*DPP-4s may reduce SAEs by 18%*	Probably no difference
Compared with SGLT-2 inhibitors	May be no difference	*DPP-4s probably increase MACE by 13%*	Probably no difference	Probably no difference	*DPP-4s may increase hospitalization due to CHF by 68%*	*DPP-4s probably increase progression of CKD by 62%*	No difference	May be no difference
Compared with sulfonylureas	No difference	No difference	No difference	No difference	No difference	No data	*DPP-4s probably reduce SAEs by 5% or 12 fewer events*	*DPP-4s reduce severe hypoglycemia by 86% or 44 fewer events*
Compared with tirzepatide	May be no difference	May be no difference	No data	No data	No data	No data	Probably no difference	Insufficient evidence
GLP-1 agonists (head-to-head)								
Compared with DPP-4 inhibitors	*GLP-1s probably reduce all-cause mortality by 39% or 9 fewer events*	GLP-1s reduce MACE by 30% or 16 fewer events	Probably no difference	Probably no difference	*GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events*	No data	No difference	No difference
Compared with long-acting insulins	*GLP-1s probably reduce all-cause mortality by 38% or 10 fewer events*	GLP-1s reduce MACE by 26% or 13 fewer events	No data	No data	GLP-1s probably reduce hospitalization due to CHF by 46% or 10 fewer events	No data	May be no difference	*GLP-1s probably reduce severe hypoglycemia by 77% or 38 fewer events*
Compared with SGLT-2 inhibitors	Probably no difference	Probably no difference	Probably no difference	*GLP-1s probably reduce stroke by 23%*	*GLP-1s probably increase hospitalization due to CHF by 44%*	No data	Probably no difference	Probably no difference
Compared with sulfonylureas	GLP-1s reduce all-cause mortality by 33% or 8 fewer events	No difference	Insufficient evidence	Insufficient evidence	*GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events*	No data	Probably no difference	*GLP-1s probably reduce severe hypoglycemia by 51% or 7 fewer events*
Compared with tirzepatide	May be no difference	May be no difference	No data	No data	No data	No data	*GLP-1s probably reduce SAEs by 43% or 24 fewer events*	May be no difference

Favors intervention (*green*) or favors comparator (*red*) indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., ≥25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper (1.25) bounds. Italicized interpretation text indicates statistically significant findings. Statistics are from the American College of Physicians–funded systematic review and network meta-analysis (24) available in **Supplement Tables 1** to **4** (available at Annals.org). Interpretation of findings was done by the CGC. CGC = Clinical Guidelines Committee; CHF = congestive heart failure; CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MACE = major adverse cardiovascular events; MI = myocardial infarction; SAE = serious adverse event; SGLT-2, sodium–glucose cotransporter-2.

* SAEs were defined by investigators, varied, and were not always fully reported. In general, these SAEs included events considered fatal or life-threatening and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (24). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

Continued on following page

Figure 3–Continued.

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
SGLT-2 inhibitors (head-to-head)								
Compared with DPP-4 inhibitors	May be no difference	*SGLT-2s probably reduce MACE by 12%*	Probably no difference	Probably no difference	*SGLT-2s may reduce hospitalization due to CHF by 40%*	*SGLT-2s probably reduce progression of CKD by 38%*	No difference	May be no difference
Compared with GLP-1 agonists	Probably no difference	Probably no difference	Probably no difference	*SGLT-2s probably increase stroke by 30%*	*SGLT-2s probably reduce hospitalization due to CHF by 31%*	No data	Probably no difference	Probably no difference
Compared with long-acting insulins	*SGLT-2s may reduce all-cause mortality by 30%*	May be no difference	No data	No data	*SGLT-2s may reduce hospitalization due to CHF by 36%*	No data	*SGLT-2s may reduce SAEs by 21%*	*SGLT-2s may reduce severe hypoglycemia by 78%*
Compared with sulfonylureas	Probably no difference	*SGLT-2s reduce MACE by 43% or 14 fewer events*	Insufficient evidence	Insufficient evidence	May be no difference	No data	No difference	*SGLT-2s reduce severe hypoglycemia by 90% or 83 fewer events*
Compared with tirzepatide	Insufficient evidence	Insufficient evidence	No data	No data	No data	No data	May be no difference	May be no difference

associated with thyroid C-cell tumors (in rodents), pancreatitis, acute gallbladder disease, diabetic retinopathy, and other harms (24). The analysis of SAEs was limited by variation in definition across studies, but it also included events that could be considered effectiveness outcomes (such as stroke and MI). As a result, newer therapies, such as SGLT-2 inhibitors, resulted in a reduction in SAEs compared with usual care (24), but this was likely attributable to how the outcome was measured as opposed to the treatment actually reducing SAEs.

Over study periods, SGLT-2 inhibitors and GLP-1 agonists resulted in total body weight loss (24). Inconsistent reporting of clinically important total body weight loss of 10% or more precluded accurate comparative assessment of this outcome by pharmacologic class (24). However, individual RCTs suggested that a higher percentage of participants had total body weight loss exceeding 10% with GLP-1 agonists than with usual care or long-acting insulins (24). Although all examined medications are indicated for improvement in glycemic control, primary study designs allowing postrandomization treatments in response to inadequate glycemic control, at the discretion of study investigators and physicians, precluded accurate assessment of comparative glycemic control by pharmacologic class (24).

The comparative evidence among all evaluated pharmacologic classes suggests that the most favorable net benefit is derived from an add-on SGLT-2 inhibitor or GLP-1 agonist (**Supplement Tables 2** to **5**) (24). Compared with long-acting insulins, SGLT-2 inhibitors may reduce and GLP-1 agonists probably reduce all-cause mortality (24). Compared with DPP-4 inhibitors, GLP-1 agonists probably reduce all-cause mortality. Sodium–glucose cotransporter-2 inhibitors probably reduce MACE compared with DPP-4 inhibitors and reduce MACE compared with sulfonylureas (24). The risk for severe hypoglycemia is lower with SGLT-2 inhibitors and GLP-1 agonists than with sulfonylureas and long-acting insulins (**Supplement Tables 2** to **5**) (24).

Beyond benefits and harms, a systematic review of cost-effectiveness analyses (25) did not demonstrate substantial enough differences between SGLT-2 inhibitors and GLP-1 agonists to warrant prioritizing one pharmacologic class over the other (**Supplement Table 9**). The systematic review found low-certainty evidence that both drug classes may have intermediate value (that is, an incremental cost-effectiveness ratio of $50 000 to $150 000 per quality-adjusted life-year gained) compared with usual care consisting of metformin (25). Low-certainty evidence also suggests that a GLP-1 agonist (oral semaglutide) may be of low value (incremental cost-effectiveness ratio, >$150 000 per quality-adjusted life-year gained) compared with an SGLT-2 inhibitor (empagliflozin) (**Supplement Table 9**) (25).

Annual Medicare spending for brand formulations differs among individual treatments within and between pharmacologic classes (**Supplement Tables 7** and **8**). The cheapest brand formulation of an SGLT-2 inhibitor had lower annual per beneficiary spending in 2021 than the cheapest brand formulation of a GLP-1 agonist ($1480 vs. $2313) (**Supplement Table 7**). The CGC considered only Medicare annual spending data on each drug and recognized that injectable formulations may have additional costs.

In the systematic review of values and preferences and feedback from the CGC Public Panel, medication

cost was also an important consideration for patients when making choices about pharmacologic treatments of type 2 diabetes. No generic SGLT-2 inhibitors or GLP-1 agonists currently exist, but these formulations may become available (**Supplement Table 7**).

Recommendation 2

ACP recommends against adding a dipeptidyl peptidase-4 (DPP-4) inhibitor to metformin and lifestyle modifications in adults with type 2 diabetes and inadequate glycemic control to reduce morbidity and all-cause mortality (strong recommendation; high-certainty evidence).

High-certainty evidence showed that add-on DPP-4 inhibitors, compared with usual care, result in no differences in all-cause mortality, MACE, MI, stroke, CHF hospitalization, CKD progression, or severe hypoglycemia (**Supplement Table 1**) (24). Evidence from the NMA suggests that DPP-4 inhibitors may increase hospitalization due to CHF and probably increase the risk for MACE and progression of CKD compared with SGLT-2 inhibitors (**Figure 3**). Compared with GLP-1 agonists, DPP-4 inhibitors probably increase all-cause mortality and hospitalization due to CHF and the risk for MACE (**Figure 3**) (24). The most common usual care medication in the included trials was metformin. In addition, the CGC Public Panel expressed a preference for not using DPP-4 inhibitors primarily because of a lack of benefits compared with SGLT-2 inhibitors or GLP-1 agonists. Low-certainty evidence from a cost-effectiveness analysis also suggested that DPP-4 inhibitors may be more expensive and less effective than sulfonylureas when added to metformin to treat type 2 diabetes (**Supplement Table 9**) (25).

Applicability

These recommendations apply to adults who have long-standing type 2 diabetes with an HbA_{1c} level around 8% (mean range in included primary RCTs, 7.2% to 9.5%) despite use of usual care with such treatments as metformin and lifestyle modifications (24). The most common usual care medication in the included trials was metformin. Social risk factor data were infrequently reported (24). Limited data were reported in specific subgroup populations. Three RCTs required participants to have CKD, 4 required existing CVD or acute coronary syndrome, 3 required overweight or obesity, and 11 required participants to be "at risk for CVD" with varying definitions (24). Most individuals with type 2 diabetes had additional CVD risk factors, including obesity, hypertension, or a history of tobacco use (24). Evidence ultimately did not allow evaluation of differences in treatment effects in patients with established CVD or CKD (secondary prevention) compared with those who did not have these diseases (primary prevention) (24). Therefore, our recommendations apply to patients with type 2 diabetes with and without established CVD or CKD.

CLINICAL CONSIDERATIONS

- Metformin (unless contraindicated) and lifestyle modifications are the first steps in managing type 2 diabetes in most patients (19, 29). When selecting an additional therapy, clinicians should consider the evidence of benefits, harms, patient burden, and cost of medications in addition to performing an individualized assessment of each patient's preferences, glycemic control target, comorbid conditions, and risk for symptomatic hypoglycemia.
  - Clinicians should prioritize adding SGLT-2 inhibitors in patients with type 2 diabetes and CHF or CKD.
  - Clinicians should prioritize adding GLP-1 agonists in patients with type 2 diabetes and an increased risk for stroke or for whom total body weight loss is an important treatment goal.
- Clinicians should aim to achieve HbA_{1c} levels between 7% and 8% in most adults with type 2 diabetes and deintensify pharmacologic treatments in adults with HbA_{1c} levels less than 6.5% (29). An individualized glycemic goal should be based on risk for hypoglycemia, life expectancy, diabetes duration, established vascular complications, major comorbidities, patient preferences and access to resources, capacity for adequate monitoring of hypoglycemia, and other harms.
- Self-monitoring of blood glucose might be unnecessary in patients receiving metformin combined with either an SGLT-2 inhibitor or a GLP-1 agonist.
- When adding an SGLT-2 inhibitor or a GLP-1 agonist results in adequate glycemic control, clinicians should reduce or discontinue existing treatment with sulfonylureas or long-acting insulins due to increased risk for severe hypoglycemia.
- Sulfonylureas and long-acting insulins are inferior to SGLT-2 inhibitors and GLP-1 agonists in reducing all-cause mortality and morbidity but may still have some limited value for glycemic control.
- Benefits and harms of additional pharmacologic treatment beyond the initial add-on treatment are unknown (for example, a patient who receives metformin plus an SGLT-2 inhibitor but in the future receives an additional GLP-1 agonist). Further, clinical evidence on patient mortality, morbidity, and hospitalizations and economic evidence are lacking for use of SGLT-2 inhibitors and GLP-1 agonists as initial treatment for patients with type 2 diabetes.
- Collaborative care plans should include integrated efforts with dietary improvement and weight management, sleep health, physical activity, stress management, and management of comorbidities and concomitant medications.
- Type 2 diabetes management should be based on collaborative communication and goal setting among all team members, including clinical pharmacists, to reduce the risk for polypharmacy and associated harms.
- Health systems should have a process in place to assess social risk factors. All relevant entities and stakeholders should intervene to connect adults with type 2 diabetes

and adverse social risk factors to social and community services.
- There are currently no generic SGLT-2 inhibitors or GLP-1 agonists, but these formulations may become available. Clinicians should prescribe generic medications when they are available rather than more expensive brand-name medications (30).
- Clinicians and patients should discuss the cost of an add-on SGLT-2 inhibitor or GLP-1 agonist when selecting a medication from either drug class.
- Clinicians should be attentive to patient race and ethnicity as a social risk factor for diabetes. Worse health outcomes for type 2 diabetes may be mediated by such factors as social determinants of health.

Interventions With No Recommendations

Evidence was inconclusive to develop recommendations for both add-on tirzepatide and add-on long-acting insulins to metformin and lifestyle modifications.

Evidence Gaps and Research Needs

Areas of Insufficient Evidence

Most included studies had shorter-term follow-up (treatment and follow-up range, 52 to 329 weeks), highlighting the need for longer-term studies to better understand the benefits and harms of newer treatments of type 2 diabetes. The evidence was very uncertain regarding predefined subgroups of interest, including demographic subgroups, treatment-naive patients, and patients with established CVD or CKD (24).

Evidence was insufficient or had low certainty regarding cost-effectiveness analyses directly comparing newer type 2 diabetes medications or pharmacologic classes (Supplement Table 9) (25).

Areas of No Evidence

For newer type 2 diabetes medications compared with usual care, evidence was not available on the effects of GLP-1 agonists for the progression of CKD and effects of tirzepatide on MI, stroke, hospitalizations for CHF, and progression of CKD. Evidence was not available on the effects of tirzepatide compared with other medications on MI, stroke, hospitalizations for CHF, and progression of CKD.

Evidence from RCTs was lacking for examined newer diabetes pharmacologic classes in patients with type 2 diabetes who have not been previously treated (24). The net benefit and cost-effectiveness of combined formulations or combined treatments with newer pharmacologic classes beyond glycemic control are currently unknown.

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Note: Clinical guidelines are meant to guide care based on the best available evidence and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a guideline is not intended as an endorsement of any specific commercial product. All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Appendix: Additional Details of Guideline Methods

Details of the ACP guideline development process can be found in ACP's methods articles (20, 21).

Panel Composition and Stakeholder Involvement

The CGC is a multidisciplinary group of 14 members. Twelve of these members are internal medicine physicians representing various clinical areas of expertise across hospital and ambulatory medicine, including internal medicine subspecialties (for example, geriatrics, nephrology, rheumatology, and pulmonology). The development of this guideline also included perspectives, values, and preferences of nonphysician CGC members who represent the public and a CGC Public Panel. The CGC convened a topic expert panel made up of clinical topic experts, clinicians, and epidemiologists to inform the systematic review and assist in refining the scope and key questions.

Disclosures of Interests and Management of Conflicts of Interest

All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed in accordance with CGC policy (21). Disclosure of interests and management of any conflicts can be found on ACP's website (31).

Key Questions and Clinical Outcomes of Interest

The CGC identified the key questions (Appendix Table 1). Members of the CGC (clinicians and nonclinician public members) and CGC Public Panel members were asked a priori to independently rate the importance of evaluated outcomes. All critical and important outcomes were considered in developing recommendations (Appendix Table 2).

Systematic Review

The ACP Center for Evidence Reviews at Minnesota conducted the supporting systematic review (24), which was funded by ACP. The evidence review team and the CGC used GRADE tables to summarize the review findings and to rate the certainty of evidence for clinical outcomes, to develop the recommendations. The ACP Center for Evidence Reviews used the following categories: high, moderate, low, or insufficient.

Appendix Table 1. Key Questions for the Systematic Review

Key question 1: In adults with type 2 diabetes, what are the effectiveness, comparative effectiveness, and harms of SGLT-2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, or long-acting insulins used either as a monotherapy or in combination with other diabetes medications?
- Do treatment benefit and harms vary by:
  - Demographic characteristics: age, sex, race/ethnicity, SDoH
  - Diabetes severity and control
    - HbA_{1c} levels
    - Duration of diabetes
  - Comorbidities
    - Baseline CVD: definitions included previous history of acute MI, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization, occlusive peripheral arterial disease
    - CHF
    - Obesity (i.e., BMI >30 kg/m^2)
    - CKD (stage 3 or greater)

Key question 2: What are patients' values and preferences regarding diabetes medications for type 2 diabetes management?
- How do patients weigh the benefits and harms of the pharmacologic combination therapies for type 2 diabetes?
- How do they use this valuation in their decision making to undergo treatment?
- What patient factors are associated with treatment preferences (e.g., age, sex, race/ethnicity, insurance status, sociodemographic factors, and comorbid conditions)?

Key question 3: What are the costs and cost-effectiveness of diabetes medications alone or in combination for the management of adults with type 2 diabetes?
- The CGC's value thresholds for economic evidence were used by the CER in its ACP-funded systematic review of cost-effectiveness analyses (25).

ACP = American College of Physicians; BMI = body mass index; CGC = Clinical Guidelines Committee; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; MI = myocardial infarction; SDoH = social determinants of health; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 2. Outcome Ratings*

Outcomes rated as critical
All-cause mortality
Amputations
Congestive heart failure requiring hospitalization
Diabetic ketoacidosis
Discontinuation due to adverse events
Lactic acidosis
Major adverse cardiovascular events
Myocardial infarction
Progression of chronic kidney disease
Serious adverse events
Severe hypoglycemia
Stroke
Outcomes rated as important
All-cause hospitalizations
Glucosuria
Glycemic control
Perineal infection
Urinary tract infection
Weight change†

* Outcomes in boldface were prioritized by the Clinical Guidelines Committee (CGC) to be evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and in evidence-to-decision tables.
† The CGC prioritized weight change, but data were too infrequently reported and heterogeneous for total body weight loss ≥10% to be analyzed and evaluated with GRADE.

Values and Preferences

The accompanying systematic review (24) included systematic reviews with a U.S. perspective of the studies aimed at patient values and preferences. In addition, ACP staff surveyed the CGC Public Panel through 2 ad hoc surveys to collect their opinions on findings from the supporting systematic review, including preferences regarding the treatment options, and to ask for their feedback on the draft recommendations.

Costs

The accompanying systematic review (25) included cost-effectiveness analyses that were applicable to the United States, were recent (that is, input data from the past 10 years), were not industry-sponsored, met validity criteria, and reported incremental cost-effectiveness ratios per gained quality-adjusted life-year (32, 33). The ACP staff obtained the data from the validated U.S. Centers for Medicare & Medicaid Services databases (34) and incorporated average Medicare Part D spending per beneficiary in 2021 on medications that were eligible for the review. The CGC developed a consensus about value thresholds for economic evidence that were used in ACP-funded systematic reviews of cost-effectiveness analyses (35, 36). The CGC adapted value thresholds from the World Health Organization's CHOICE (Choosing Interventions That Are Cost-Effective) program (36).

Peer Review

The supporting systematic review and guideline each had a peer-review process through the journal. The guideline was posted online for comments from ACP Regents and ACP Governors, who represent internal medicine and its subspecialty physician members at the national and international level. The CGC considered any comments before finalizing the guideline.

Guideline Expiration or Living Guideline Process

All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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