

## CLINICAL PRACTICE

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# Glucose-Lowering Drugs to Reduce Cardiovascular Risk in Type 2 Diabetes

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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A 64-year-old woman with a 10-year history of type 2 diabetes presents for a routine wellness visit. She had a myocardial infarction 4 years ago and has well-controlled hypertension and dyslipidemia. Her medications include 2000 mg of metformin daily, losartan, hydrochlorothiazide, high-intensity atorvastatin, and aspirin. She does not monitor her blood glucose levels routinely at home. On examination, her blood pressure is 128/75 mm Hg and her body-mass index (the weight in kilograms divided by the square of the height in meters) is 33. Her glycated hemoglobin level is 7.9%, total cholesterol level 155 mg per deciliter (4.0 mmol per liter), high-density lipoprotein cholesterol level 52 mg per deciliter (1.34 mmol per liter), triglyceride level 126 mg per deciliter (1.4 mmol per liter), and low-density lipoprotein cholesterol level 78 mg per deciliter (2.0 mmol per liter). The estimated glomerular filtration rate is 76 ml per minute per 1.73 m<sup>2</sup> of body-surface area, and the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine in grams) is 25. She has no retinopathy or neuropathy. She has heard that certain medications for diabetes can reduce her risk of cardiovascular disease. What would you advise?

## THE CLINICAL PROBLEM

**D**IABETES AFFECTS MORE THAN 450 MILLION PEOPLE WORLDWIDE AND has a global prevalence of 9.3%.<sup>1</sup> Type 2 diabetes accounts for 90 to 95% of cases and is characterized by the progressive loss of adequate insulin secretion, usually in persons with insulin resistance.<sup>2</sup> The main complications of diabetes are microvascular disease (retinopathy, neuropathy, and nephropathy) and macrovascular disease (coronary heart disease, peripheral vascular disease, and cerebrovascular disease).

Atherosclerotic cardiovascular disease and heart failure, which are major causes of illness and death in patients with type 2 diabetes, have various pathophysiological mechanisms.<sup>3-5</sup> The prevalence of atherosclerotic cardiovascular disease is more than two times as high in patients who have diabetes as in those who do not, and the relative risk of coronary heart disease is higher among women than among men.<sup>6</sup> Although early studies suggested that death from coronary heart disease in patients with diabetes and no prior myocardial infarction was as high as that in nondiabetic patients with prior myocardial infarction,<sup>7</sup> many other factors (e.g., age, sex, race, hypertension, dyslipidemia, and smoking) and diabetes-



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## KEY CLINICAL POINTS

**GLUCOSE-LOWERING DRUGS TO REDUCE CARDIOVASCULAR RISK IN TYPE 2 DIABETES**

- The attainment of glycemic targets and comprehensive reduction in risk factors for cardiovascular disease are important to the reduction in microvascular and macrovascular diabetic complications, respectively.
- In men and nonpregnant women with diabetes who are otherwise healthy, most professional societies recommend a glycosylated hemoglobin level below 6.5% or 7.0%. However, glycemic targets should be individualized according to other factors (e.g., risk of hypoglycemia, coexisting conditions, and patient preferences).
- Along with lifestyle recommendations, the standard initial pharmacologic treatment used in patients with type 2 diabetes is metformin. Assessment of cardiovascular disease status and risk factors is critical in guiding the selection of additional glucose-lowering therapy to reduce the risk of cardiovascular events.
- The treatment of patients with diabetes and established cardiovascular disease (and in selected patients at high risk for cardiovascular disease) should include a glucose-lowering medication with demonstrated cardiovascular benefit, including specific agents from the glucagon-like peptide-1 (GLP-1) receptor agonist or sodium–glucose cotransporter type 2 (SGLT2) inhibitor classes.
- For patients with type 2 diabetes who have a history of heart failure with reduced ejection fraction, SGLT2 inhibitors with demonstrated benefit in heart failure are recommended.

specific characteristics (e.g., the duration of disease, presence of microvascular complications, and use of specific glucose-lowering drugs) affect the magnitude of cardiovascular risk among patients with diabetes.<sup>8</sup>

Multiple agents are currently approved for the management of hyperglycemia in patients with type 2 diabetes. Their benefits and adverse effects are summarized in Tables 1 and 2.

## STRATEGIES AND EVIDENCE

**EVALUATION**

The evaluation of cardiovascular risk among patients with type 2 diabetes includes assessment of lifestyle behaviors, the presence of cardiovascular risk factors and the extent to which they are controlled, the use of diabetes medications and the achievement of glycemic targets, the presence of coexisting conditions, the history of microvascular or macrovascular complications, and the stratification of the risks of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease (CKD). A detailed history should be obtained and physical examination performed, and an assessment of cardiac function should be completed in patients with symptoms or signs of vascular disease or heart failure (e.g., chest pain on exertion, claudication, carotid bruits, and edema) or atypical cardiac symptoms (e.g., unexplained dyspnea). A patient-centered approach, with shared decision making regarding the de-

velopment of a treatment plan, should be emphasized.

The 10-year risk of atherosclerotic cardiovascular disease can be calculated with the use of pooled cohort equations.<sup>8</sup> The risk estimate can help to inform clinical decisions regarding preventive therapies, with the exception of statins, which are routinely recommended irrespective of the calculated risk of atherosclerotic cardiovascular disease among patients with diabetes.<sup>3,8</sup>

**TREATMENT**

The aim of treatment for type 2 diabetes is the prevention or delay of the progression of complications and improvement in quality of life. A comprehensive approach, including lifestyle management and pharmacologic treatment, has proved to be effective. This section reviews several approaches to treatment, including the use of glycemic targets, modification of lifestyle and cardiovascular risk factors, and the use of glucose-lowering medication.

*Glycemic Targets*

Hallmark trials in which more and less intensive glucose-lowering treatments have been compared with respect to microvascular and macrovascular outcomes have informed glycemic targets. In the United Kingdom Prospective Diabetes Study (UKPDS 33), 3867 patients who were 25 through 65 years of age with newly diagnosed type 2 diabetes were randomly assigned to receive in-

**Table 1. Injectable Glucose-Lowering Medications Available for the Treatment of Type 2 Diabetes in the United States.\***

Medications	Decrease in Glycated Hemoglobin Level†‡	Mechanism	Selected Adverse Effects	Benefits and Considerations
<b>Insulins: basal</b> Human: NPH (isophane) Analogues: glargine, detemir, degludec <b>Insulins: bolus</b> Human: regular Analogues: lispro, aspart, glulisine Insulin human inhalation powder	In theory, no limit	Activate insulin receptors, which stimulate peripheral glucose uptake by skeletal muscle and fat and inhibit hepatic glucose production	Weight gain Hypoglycemia Allergic reactions, injection-site reactions, lipodystrophy, rash, edema Inhaled insulin only: contraindicated in chronic lung disease	Basal insulins are long- or intermediate-acting; usually administered once or twice daily Bolus insulins are short- or rapid-acting; administered before meals or to correct high blood glucose levels Inhaled insulin is ultra-rapid-acting and administered before meals Many insulins are available in different concentrations Administered with use of vials and syringes or pen devices Some premixed basal and bolus formulations are available High cost for analogue insulins
<b>Amylin agonist</b> Pramlintide	Up to 0.5%	Mimics action of hormone amylin; decreases release of glucagon, slows gastric emptying, and suppresses appetite	Nausea Hypoglycemia Contraindicated in patients with gastroparesis	Weight loss Use recommended only in patients who take insulin (at a reduced dose) at mealtime Administered before meals High cost
<b>GLP-1 receptor agonists</b> Shorter acting: exenatide, lixisenatide Longer acting: exenatide extended release, liraglutide, dulaglutide, semaglutide (subcutaneous), semaglutide (oral)‡§	Up to 1.5%	Are also known as incretin mimetics; mimic action of GLP-1 hormone, which increases glucose-dependent pancreatic insulin release, suppresses glucagon secretion, slows gastric emptying, and suppresses appetite	Nausea, vomiting, abdominal pain, diarrhea Possible pancreatitis§ Acute gallbladder disease (liraglutide, exenatide extended release) Not usually recommended in patients with severe gastroparesis Diabetic retinopathy complications (semaglutide, dulaglutide) Long-acting GLP-1 receptor agonists: warning for C-cell hyperplasia and medullary thyroid tumors; contraindicated with MEN2, medullary thyroid cancer	Weight loss¶ Low risk of hypoglycemia High cost Both injectable and oral formulations (semaglutide) <b>Indications in patients with established CVD or heart failure or with multiple risk factors for CVD, according to FDA:</b> Decrease in MACE in type 2 diabetes and established CVD (liraglutide, semaglutide) and in type 2 diabetes and established CVD or multiple risk factors for CVD (dulaglutide)

\* CVD denotes cardiovascular disease, FDA Food and Drug Administration, GLP glucagon-like peptide, MACE death from cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke, and MEN2 multiple endocrine neoplasia 2.

† The change in glycated hemoglobin level is based on lowering of the placebo-subtracted glycated hemoglobin level as reported in clinical trials cited in the FDA label. Efficacy in lowering the glycated hemoglobin level is usually greater when agents are used as monotherapy, at higher doses, and with higher baseline glycated hemoglobin levels. Combination oral and fixed-dosed therapies are not shown.

‡ Exenatide extended release, dulaglutide, and injectable semaglutide are taken weekly, the other GLP-1 receptor agonists are taken once or twice daily.

§ There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal pancreatitis.

¶ A higher dose of liraglutide than indicated for glycemic management has also been approved by the FDA for long-term weight management in obese or overweight adults who have at least one weight-related condition, with or without diabetes.

tensive glucose-lowering treatment with insulin or a sulfonylurea (chlorpropamide, glipizide, or glibenclamide [also referred to as glyburide]) or conventional treatment with diet (median glycated hemoglobin level in the two groups during the trial period, 7.0% and 7.9%, respectively).<sup>9</sup> As compared with conventional treatment, intensive glucose-lowering treatment significantly reduced the risk of microvascular complications but not myocardial infarction (defined as nonfatal or fatal myocardial infarction or sudden death) over 10 years of study follow-up. The between-group differences in risk reduction persisted for most microvascular complications during subsequent long-term observation,<sup>10</sup> and the risks of myocardial infarction (15%) and diabetes-related death (27%) that emerged were significantly lower in the group that had been allocated to intensive treatment than in the group allocated to conventional treatment.

Three subsequent trials investigated the effects of intensive glucose-lowering treatment with a combination of oral agents plus insulin, if needed, as compared with the standard of care in older patients (average age,  $\geq 60$  years) with long-standing type 2 diabetes who had established or high-risk cardiovascular disease.<sup>11-13</sup> These trials, conducted over 3.5 to 5.6 years, showed that the incidence and progression of some microvascular complications was lower, with near normalization of blood glucose levels (mean glycated hemoglobin level, 6.4 to 6.9%), than with standard care (mean glycated hemoglobin level, 7.0 to 8.4%). However, the incidence of cardiovascular outcomes was not significantly lower with the intensive treatment than with standard care during the trial period or in long-term observational follow-up.<sup>14-16</sup> Instead, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive lowering of glucose levels (i.e., with a goal of lowering glycated hemoglobin levels below 6%) as compared with standard care resulted in increases in death from cardiovascular disease and from any cause during the trial period.<sup>11</sup> Consequently, most professional societies recommend an initial glycated hemoglobin target below 6.5% or 7.0% for men and nonpregnant women if the target is achievable without the development of clinically significant hypoglycemia or other adverse effects, as well as establishment of individualized glycemic goals.<sup>17-21</sup> Additional information is pro-

vided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

#### *Modification of Lifestyle and Cardiovascular Risk Factors*

Lifestyle management is emphasized at the time that diabetes is diagnosed and throughout the disease course, as is the management of cardiovascular risk factors (e.g., obesity, diet, physical inactivity, hypertension, dyslipidemia, and smoking) and the use of preventive medications (e.g., statins and antiplatelet agents), in accordance with current clinical guidelines for patients with diabetes.<sup>3,8</sup> A large, randomized trial involving overweight or obese participants with type 2 diabetes showed that intensive lifestyle interventions that promote weight loss, as compared with usual diabetes education and support, reduced several risk factors for cardiovascular disease but did not significantly reduce the rate of cardiovascular events.<sup>22</sup> In one small trial involving patients with type 2 diabetes, the risk of cardiovascular events was significantly lower with intensive multifactorial intervention (changes in lifestyle followed by pharmacologic treatment targeting cardiovascular risk factors) than with conventional therapy.<sup>23</sup>

#### *Glucose-Lowering Medications*

Since the 1990s, the Food and Drug Administration (FDA) has approved new drugs for the treatment of diabetes on the basis of their safety and efficacy in lowering levels of glycated hemoglobin, a surrogate end point for long-term diabetic complications (data on cardiovascular outcomes were not initially required). In 2008, the FDA issued a guidance for industry stating that no glucose-lowering drug approved for type 2 diabetes could be associated with an unacceptable level of cardiovascular risk in postmarketing trials involving cardiovascular outcomes.<sup>24</sup> A more recent proposed guidance emphasizes a broader range of safety concerns.<sup>25</sup> Postmarketing cardiovascular outcome trials have been conducted for agents in the dipeptidylpeptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, and sodium-glucose cotransporter type 2 (SGLT2) inhibitor classes. In order to accrue a sufficient number of events over a median of 2 to 5 years of follow-up, each of these trials enrolled approximately 5000 to 15,000 participants, the majority of whom had

**Table 2.** Oral Glucose-Lowering Medications Available for Treatment of Type 2 Diabetes in the United States.\*

Class and Drug	Decrease in Glycated Hemoglobin Level	Mechanism	Selected Adverse Effects	Benefits and Considerations
<b>Sulfonylureas</b> Glyburide Glipizide Glimepiride	Up to 2.0%	Stimulate pancreas to release insulin over hours, activating sulfonylurea receptors on beta cells	Hypoglycemia Weight gain	High rate of secondary failure Low cost
<b>Biguanide</b> Metformin	Up to 2.0%	Inhibits hepatic glucose production through multiple mechanisms; also increases insulin-mediated glucose uptake in muscle, increases intestinal glucose uptake, and alters gut microbiota	Nausea, diarrhea, abdominal pain Vitamin B <sub>12</sub> deficiency Rare lactic acidosis (i.e., in severe chronic kidney disease, liver failure, hypoxic states)	Often considered first-line therapy Weight neutral (or potential weight loss) Low risk of hypoglycemia Low cost
<b><math>\alpha</math>-Glucosidase inhibitors</b> Acarbose Miglitol	Up to 1.0%	Inhibit intestinal $\alpha$ -glucosidase, slowing digestion and absorption of carbohydrates	Flatulence, diarrhea, abdominal pain Contraindicated with cirrhosis, chronic intestinal disease, inflammatory bowel disease	Weight neutral Low risk of hypoglycemia Taken before meals Low cost
<b>Meglitinides</b> Repaglinide Nateglinide	Up to 2.0%	Short-acting secretagogues that stimulate pancreas to release insulin, activating sulfonylurea receptors on beta cells	Hypoglycemia (less than with sulfonylureas) Weight gain	Taken before meals Low cost
<b>Thiazolidinediones</b> Pioglitazone Rosiglitazone	Up to 1.5%	Decrease insulin resistance in muscle, liver, and adipocytes, which results in increased insulin-dependent glucose disposal through activation of peroxisome proliferator–receptor gamma	Weight gain, edema Can cause or exacerbate heart failure in some patients Contraindicated in heart failure, NYHA class III or IV Fractures, macular edema, liver failure Warnings regarding bladder cancer (pioglitazone) or myocardial infarction (rosiglitazone)	Low risk of hypoglycemia Durability Increase in HDL cholesterol level Low cost
<b>DPP-4 inhibitors</b> Sitagliptin Saxagliptin Linagliptin Alogliptin	Up to 1.0%	Inhibit the enzyme that breaks down incretins, leading to increase in glucose-dependent pancreatic insulin release, decrease in glucagon release	Nausea, diarrhea Upper respiratory symptoms Possible pancreatitis† Rare severe joint pains Warning regarding heart failure (saxagliptin, alogliptin)	Weight neutral Low risk of hypoglycemia High cost

<b>SGLT2 inhibitors</b> Canagliflozin Empagliflozin Dapagliflozin Ertugliflozin	Up to 1.0%	Block reabsorption of glucose from urine by inhibiting SGLT2 in proximal tubules of kidney, resulting in glucosuria	Increased urination Volume depletion Acute kidney injury Genital mycotic and urinary tract infections Euglycemic diabetic ketoacidosis Increased LDL cholesterol level (empagliflozin, ertugliflozin) Fracture (canagliflozin) Warning regarding leg amputation (canagliflozin, ertugliflozin) Rare Fournier's gangrene	Weight loss, reduced blood pressure Should be discontinued before major surgery due to risk of diabetic ketoacidosis Low risk of hypoglycemia Additional benefits in chronic kidney disease‡ High cost <b>Indications in patients with established CVD or heart failure or with multiple risk factors for CVD, according to FDA:</b> Decrease in MACE (canagliflozin) or CVD death (empagliflozin) in type 2 diabetes and established CVD Decrease in hospitalization for heart failure in type 2 diabetes and established CVD or multiple CVD risk factors (dapagliflozin) Decrease in hospitalization for heart failure and CVD-related death in heart failure and reduced ejection fraction, with or without diabetes (dapagliflozin)§
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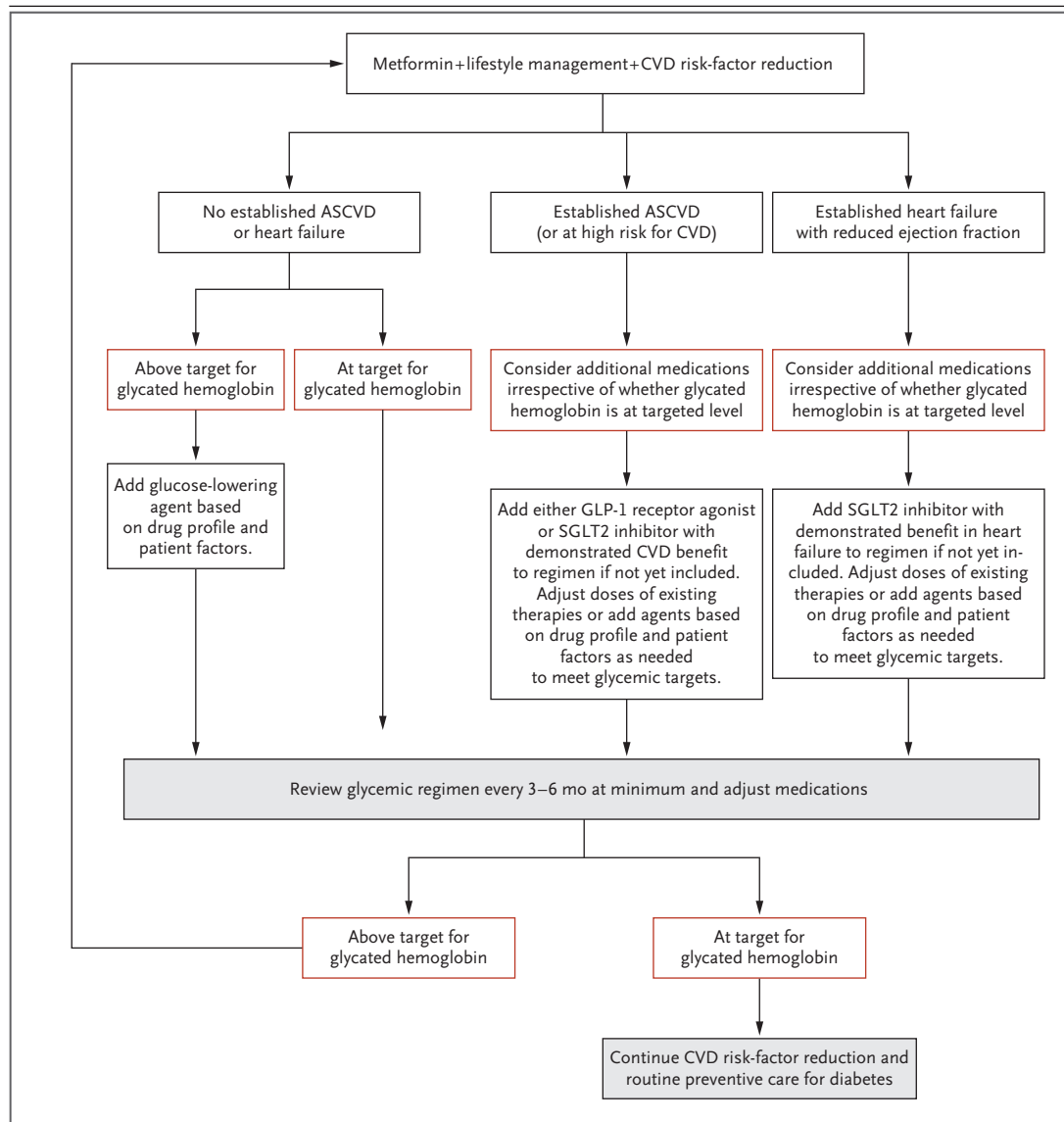
\* Drug classes are listed in order of approval. Colesevelam and bromocriptine have also been approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes but are not commonly used for this indication and are not included here. CVD denotes cardiovascular disease, DPP dipeptidylpeptidase-4, HDL high-density lipoprotein, LDL low-density lipoprotein, and MACE death from major adverse cardiovascular events (cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke), NYHA New York Heart Association, and SGLT2 sodium–glucose cotransporter type 2.

† There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal pancreatitis. If pancreatitis is suspected, discontinue drug.

‡ Canagliflozin has an FDA-approved indication for reductions in the risk of end-stage kidney disease, worsening of kidney function, death from cardiovascular disease, and hospitalization for heart failure among adults with type 2 diabetes and diabetic kidney disease. Placebo-controlled trials have also shown benefit in slowing the progression of kidney disease with dapagliflozin (primary outcome) and empagliflozin (secondary outcome).<sup>30,36,37</sup>

§ Placebo-controlled trials of dapagliflozin and empagliflozin in patients with heart failure and reduced ejection fraction have shown that these drugs are associated with a reduced risk of hospitalization for heart failure and of CVD-related death (primary outcome).<sup>34,35</sup> Trials of canagliflozin in patients with or at high risk for CVD have also shown benefit in reducing hospitalization for heart failure (secondary outcome).<sup>31</sup>





established atherosclerotic cardiovascular disease, with the remainder being at high risk. The primary outcome was a major adverse cardiovascular event, including nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease, with or without hospitalization for unstable angina. By the end of the follow-up period, between-group differences in the glycated hemoglobin level were minimal, since adjustment of background glucose-lowering therapy was allowed. Findings from these trials not only indicated cardiovascular safety but also showed superiority of specific agents in the GLP-1 receptor agonist and SGLT2 inhibitor classes with respect

to cardiovascular outcomes. Consequently, most professional societies now recommend use of these drugs for cardiovascular risk reduction in patients with type 2 diabetes who have established atherosclerotic cardiovascular disease and in specified patients at high risk for cardiovascular disease, irrespective of their glycemic targets (Fig. 1).<sup>3,4,17,18,20,26</sup> The effects of different glucose-lowering drugs on the risk of cardiovascular disease are described below and reviewed in Table 3.

#### Insulin

The results of studies of the effects of insulin on cardiovascular outcomes have been inconsis-

**Figure 1 (facing page). Approach to the Use of Glucose-Lowering Medications in Patients with Type 2 Diabetes and Established Cardiovascular Disease (CVD).**

A major shift has occurred in the past few years that extends beyond the use of glucose-lowering drugs solely to meet glycemic targets, favoring the use of glucose-lowering agents that are also associated with demonstrated cardiovascular benefit (i.e., a label from the Food and Drug Administration stating that the agent is indicated to reduce CVD events) in patients with type 2 diabetes who also have established atherosclerotic CVD (ASCVD) or heart failure with reduced ejection fraction (i.e., New York Heart Association Class II–IV). In most trials, established ASCVD has been defined as a history of coronary heart disease, cerebrovascular disease, or peripheral vascular disease. Some of these agents also have demonstrated cardiovascular benefit in patients with type 2 diabetes who are at high-risk for cardiovascular disease. Factors indicating high risk have been variably defined in different clinical trials either by an age of 55 years or older with the presence of subclinical vascular disease on imaging (i.e., vascular stenosis >50% in the coronary or carotid arteries or the arteries in the legs) or by an age of 60 years or older and the presence of additional risk factors for CVD (e.g., hypertension with or without left ventricular hypertrophy, dyslipidemia, current smoking, retinopathy, abdominal obesity, an estimated glomerular filtration rate of <60 ml per minute per 1.73 m<sup>2</sup> of body-surface area, albuminuria, or ankle–brachial index <0.9). Different approaches may be used by the clinician to stratify the extent of CVD risk, such as tabulating the number of cardiovascular risk factors or calculating the 10-year risk of ASCVD to determine which patients are at high risk. Drug profile and patient factors to consider when choosing a glucose-lowering medication include efficacy in lowering the glycated hemoglobin level; the risk of hypoglycemia; the effects on weight, cost, and route and frequency of administration; side effects; and clinical benefits.

tent.<sup>38</sup> No increased risk of myocardial infarction or diabetes-related death was observed among participants assigned to insulin therapy as compared with conventional treatment in UKPDS 33.<sup>9</sup> In a large trial involving patients with risk factors for cardiovascular disease and either prediabetes or type 2 diabetes, the use of insulin glargine as compared with standard care (with no drug treatment or with metformin or a sulfonylurea) had a neutral effect on cardiovascular outcomes over 6 years.<sup>39</sup> The results of another trial involving patients with type 2 diabetes (85% with established cardiovascular disease or moderate chronic kidney disease) showed no significant differences between ultra-long-act-

ing insulin degludec and glargine in the incidence of cardiovascular outcomes over 2 years.<sup>40</sup>

#### Sulfonylureas

Although there have been concerns regarding the association of an increased risk of cardiovascular disease with use of the first-generation sulfonylurea tolbutamide, prompting a classwide warning regarding the risk of death from cardiovascular causes that remains on the package insert to this day, no increased risk of myocardial infarction or diabetes-related death was reported in UKPDS 33 participants assigned to a sulfonylurea (chlorpropamide or glyburide) as compared with conventional treatment.<sup>9,41</sup> A meta-analysis that included trials of second- and third-generation sulfonylureas (glipizide, glyburide, and glimepiride) did not suggest an overall increased risk of myocardial infarction or death from cardiovascular disease.<sup>42</sup>

#### Biguanides

Metformin is widely considered to be the drug of choice for most patients with type 2 diabetes. The findings in UKPDS 34 suggested cardiovascular benefits.<sup>43</sup> Among 753 overweight participants with newly diagnosed type 2 diabetes assigned to receive intensive treatment with metformin or conventional treatment (mean glycated hemoglobin level, 7.4% and 8.0%, respectively), those randomly assigned to receive metformin had significant reductions in the risk of myocardial infarction (39%) and diabetes-related death (42%) during the 10-year trial period, and the benefits persisted during subsequent long-term observation.<sup>10</sup> However, a meta-analysis that included the results of this trial and other, smaller trials concluded that owing to limited data, there was uncertainty as to whether metformin reduces the risk of cardiovascular disease.<sup>44</sup>

#### Thiazolidinediones

Although rosiglitazone, a thiazolidinedione, was reported to result in significantly increased risks of myocardial infarction and death from cardiovascular disease in a large meta-analysis of 42 trials (prompting guidance from the FDA in 2008 regarding trials assessing cardiovascular outcomes), many of the trials included were small and of short duration,<sup>45</sup> and the findings were not confirmed in a later analysis in which alternative meta-analytic approaches were used.<sup>46</sup> Moreover, a large trial in which rosiglitazone (with metformin or a sulfonylurea) was compared with the control treatment (metformin plus a



**Table 3. Clinical Trials Showing Cardiovascular Benefit of Glucose-Lowering Agents in Patients with Type 2 Diabetes.\***

Class and Drug with CVD Benefit in Specific Study Populations	Clinical Trial	Primary and Secondary Outcomes with Significant Risk Reductions	
		Major Adverse Cardiovascular Events†	Hospitalization for Heart Failure
Established CVD			
GLP-1 receptor agonists			
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) <sup>27</sup>	Primary outcome‡	
Semaglutide§	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) <sup>28</sup>	Primary outcome‡	
Dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) <sup>29</sup>	Primary outcome‡	
SGLT2 inhibitors			
Empagliflozin	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) <sup>30</sup>	Primary outcome‡	Secondary outcome
Canagliflozin	Canagliflozin Cardiovascular Assessment Study (CANVAS) <sup>31</sup>	Primary outcome‡	Secondary outcome
Dapagliflozin	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) <sup>32</sup>		Primary outcome‡¶
Ertugliflozin	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) <sup>33</sup>		Secondary outcome
Multiple CVD risk factors			
GLP-1 receptor agonist, dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) <sup>29</sup>	Primary outcome‡	
SGLT2 inhibitor, dapagliflozin	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) <sup>32</sup>		Primary outcome‡¶
Heart failure with reduced ejection fraction¶			
SGLT2 inhibitors			
Dapagliflozin	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) <sup>34</sup> ‡		Primary outcome‡¶
Empagliflozin	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) <sup>35</sup>		Primary outcome¶
Albuminuric chronic kidney disease**			
SGLT2 inhibitors			
Canagliflozin	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) <sup>36</sup>	Secondary outcome	Secondary outcome‡
Dapagliflozin	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) <sup>37</sup>	Secondary outcome	Secondary outcome

\* Some agents are beneficial in reducing the risk of worsening nephropathy as a secondary outcome, but only cardiovascular benefits are shown. GLP1 denotes glucagon-like peptide-1 and SGLT2 sodium–glucose transporter type 2.

† Major adverse cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular disease (CVD).

‡ These agents have a label indication from the Food and Drug Administration indicating a reduction in this cardiovascular outcome in the specific population of patients listed with type 2 diabetes.

§ Only the injectable version of semaglutide has demonstrated CVD benefit.

¶ The primary outcome included hospitalization for heart failure and cardiovascular death (and, in DAPA-HF, an urgent visit for heart failure).

|| Ongoing placebo-controlled trials are investigating the use of dapagliflozin (ClinicalTrials.gov number, NCT03619213) and empagliflozin (ClinicalTrials.gov number, NCT03057951) in the treatment of heart failure with preserved ejection fraction.

\*\* Ongoing placebo-controlled trials are investigating the use of empagliflozin (ClinicalTrials.gov number, NCT03594110) and semaglutide, (ClinicalTrials.gov number, NCT03819153) in patients with chronic kidney disease.

sulfonylurea) did not support the association of increased cardiovascular risk with rosiglitazone.<sup>47</sup> In a placebo-controlled trial of pioglitazone in patients with type 2 diabetes and macrovascular disease, there was no significant difference in the risk of primary composite end-point events in the two groups, but pioglitazone was found to reduce the risk of secondary composite end-point events, which included death from any cause, nonfatal myocardial infarction, and stroke over 3 years.<sup>48</sup> Pioglitazone also lowered the risk of cardiovascular events among patients with insulin resistance (but without diabetes) and a recent history of ischemic stroke.<sup>49</sup>

#### $\alpha$ -Glucosidase Inhibitors

Large trials to investigate the cardiovascular effects of  $\alpha$ -glucosidase inhibitors in patients with type 2 diabetes have not been conducted. However, in a large, randomized trial involving patients with coronary heart disease and impaired glucose tolerance, the risk of a primary composite cardiovascular end-point event was similar in the groups receiving acarbose, an  $\alpha$ -glucosidase inhibitor, and placebo over 5 years.<sup>50</sup>

#### DPP-4 Inhibitors

DPP-4 inhibitors were shown to be noninferior or safe as compared with placebo in cardiovascular outcome trials, with the exception of saxagliptin, which was associated with a significantly increased risk of hospitalization for heart failure.<sup>51</sup> In one large, randomized trial, linagliptin was found to be noninferior to the sulfonylurea glimepiride with respect to the risk of major adverse cardiovascular outcomes over 6 years.<sup>52</sup>

#### GLP-1 Receptor Agonists

Specific GLP-1 receptor agonists have shown superiority as compared with placebo in reducing the incidence of the primary three-point composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes in trials that mostly included participants with type 2 diabetes and established cardiovascular disease (Table 3). In these trials, significant reductions in risk were reported for liraglutide (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97) and injectable semaglutide (hazard ratio, 0.74; 95% CI, 0.58 to 0.95).<sup>27,28</sup> In a trial including largely patients at high risk for cardiovascular disease (only 32% with established cardiovascular disease), use of dulaglutide resulted in a significant reduction in the composite cardiovascular outcome (hazard ratio, 0.88; 95% CI, 0.79 to 0.99).<sup>29</sup> In a trial largely involv-

ing patients with established cardiovascular disease or chronic kidney disease, oral semaglutide was reported to be noninferior to placebo for the primary three-point composite cardiovascular outcome over a median follow-up of 16 months.<sup>53</sup>

#### SGLT2 Inhibitors

Placebo-controlled trials largely involving participants with type 2 diabetes and established cardiovascular disease have shown reductions in the incidence of the primary three-point composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease with specific SGLT2 inhibitors, including empagliflozin (hazard ratio, 0.86; 95% CI, 0.74 to 0.99) and canagliflozin (hazard ratio, 0.86; 95% CI, 0.75 to 0.97).<sup>30,31</sup> In a trial that largely included patients at high risk for cardiovascular disease (only 40% with established cardiovascular disease), dapagliflozin was shown to significantly reduce the incidence of the primary outcome of death from cardiovascular disease or hospitalization for heart failure (hazard ratio, 0.83; 95% CI, 0.73 to 0.95).<sup>32</sup> Moreover, significant reductions of 27 to 35% have been observed in the incidence of the secondary outcome of hospitalization for heart failure for all SGLT2 inhibitors currently available.<sup>30-33</sup> In addition, the risk of death from cardiovascular causes or hospitalization for heart failure was significantly lower with dapagliflozin or empagliflozin than with placebo among patients with heart failure with reduced ejection fraction, with or without diabetes.<sup>34,35</sup> Although detailed discussion of renal outcomes is beyond the scope of this article, canagliflozin and dapagliflozin have also been shown to significantly reduce the risk of kidney failure and cardiovascular or renal death in placebo-controlled trials involving patients with albuminuric chronic kidney disease and type 2 diabetes (dapagliflozin has also been effective in patients with chronic kidney disease who did not have diabetes).<sup>36,37</sup> A placebo-controlled trial of a dual SGLT1–SGLT2 inhibitor in patients with type 2 diabetes and recent worsening of heart failure also showed cardiovascular benefits.<sup>54</sup>

#### AREAS OF UNCERTAINTY

Several mechanisms have been proposed for the cardiovascular effects of SGLT2 inhibitors and GLP-1 receptor agonists, and it remains uncertain whether the benefits are drug-specific or

classwide.<sup>3,4</sup> With some exceptions,<sup>29,32</sup> more than two thirds of all participants in cardiovascular outcome trials had established atherosclerotic cardiovascular disease or heart failure.<sup>27,28,30,31,33-35</sup> Various definitions have been used to classify the remaining participants at high risk for atherosclerotic cardiovascular disease (Fig. 1). Subgroup analyses in some trials suggest similar cardiovascular effects in patients at high risk,<sup>28,29,31,32</sup> but the evidence of benefit in this population is less definitive, and both the number needed to treat and the cost of treatment would be greater than with patients who have established cardiovascular disease. Since patients with glycated hemoglobin targets of less than 6.5% or 7.0% and those with no or minimal cardiovascular risk factors were not enrolled in the cardiovascular outcome trials, it remains unclear whether the results can be generalized to these patients. Also, it is not known whether the combination of a GLP-1 receptor agonist and an SGLT2 inhibitor would confer more cardiovascular benefit than either alone.

The long-term adverse effects of most GLP-1 receptor agonists and SGLT2 inhibitors require further study, and these drugs are expensive in many countries. Since large trials of older and less costly agents were never mandated, their cardiovascular effects remain less certain. Although approximately three quarters of the participants in cardiovascular outcome trials were taking metformin, post hoc analyses suggest similar cardiovascular benefits with or without background therapy with metformin,<sup>55</sup> and there is controversy regarding its position in the treatment algorithm for patients with established atherosclerotic cardiovascular disease. A trial is under way to determine cardiovascular outcomes with metformin or placebo in participants with prediabetes and established atherosclerotic cardiovascular disease (ClinicalTrials.gov number NCT02915198).

#### GUIDELINES

Guidelines published by multiple professional organizations in the United States, Canada, and Europe recommend the preferential use of glucose-lowering agents in the SGLT2 inhibitor and GLP-1 receptor agonist classes with demonstrated cardiovascular benefit for patients

who meet criteria consistent with those in the aforementioned randomized trials, which includes patients with established cardiovascular disease and in some cases those at high risk for cardiovascular disease.<sup>3,4,17,18,20,26</sup> The guidelines are generally concordant with each other, with relatively minor differences with respect to guidance for high-risk patients, the specific glucose-lowering agents recommended, and glycemic targets. Most organizations and societies endorse the use of metformin as first-line therapy for type 2 diabetes,<sup>3,4,17-21</sup> although there are exceptions.<sup>26</sup> The recommendations presented here are in general agreement with these guidelines.

#### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has type 2 diabetes of long duration and established atherosclerotic cardiovascular disease. In addition to advising the patient on diet, recommending a gradual increase in exercise, and addressing other risk factors for cardiovascular disease, it would be beneficial to prescribe a glucose-lowering agent that has been shown to have cardiovascular benefit. Currently, this would include agents in the GLP-1 receptor agonist and SGLT2 inhibitor classes. Factors that may guide the choice of agent include the route of administration and frequency, the presence of coexisting conditions, and patient preferences. In patients with diabetes and heart failure with reduced ejection fraction or those with chronic kidney disease, SGLT2 inhibitors with proven cardiovascular or renal benefit should be considered. For the obese patient described, a GLP-1 receptor agonist with demonstrated cardiovascular benefit would be favored over an SGLT2 inhibitor, given the generally greater magnitude of weight loss that has been reported with this drug class. Either class would facilitate the achievement of the patient's individualized glycemic target; a glycated hemoglobin goal of less than 7.0% or 7.5% for this patient would be in accordance with various clinical guidelines. An assessment of the patient's ability to manage the diabetes and the need for further education or support would be critical. She should be encouraged to monitor her blood glucose levels at home, and clinical follow-up

## and reassessment of the glycated hemoglobin level in 3 months are recommended.

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