

VINNI MAKIN, MBBS, MD, FACE

Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Clinical Assistant Professor, Ohio Heritage College of Osteopathic Medicine, Cleveland, OH

M. CECILIA LANSANG MD, MPH

Director, Inpatient Diabetes Service; Chair, Cleveland Clinic Health Systems Diabetes Care Committee; Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Diabetes management: Beyond hemoglobin A_{1c}

ABSTRACT

Diabetes management is a tailored affair. Patients live with the disease for decades and need increasingly complicated treatment regimens to attain glycemic goals. But other goals such as cardiovascular risk reduction, weight control, and avoidance of hypoglycemia also need consideration.

KEY POINTS

Some glucagon-like peptide 1 (GLP-1) receptor agonists have been shown to reduce cardiovascular risk, and liraglutide carries an indication for this use.

The sodium-glucose cotransporter 2 inhibitors empaglifozin and canaglifozin carry indications to prevent cardiovascular death in patients with diabetes with established cardiovascular disease.

Metformin, GLP-1 receptor agonists, and dipeptidyl peptidase 4 inhibitors are beneficial in terms of promoting weight loss—or at least not causing weight gain.

Disadvantages and adverse effects of various drugs must also be considered.

WHEN SCIENTISTS DISCOVERED the band of hemoglobin A_{1c} during electrophoresis in the 1950s and 1960s and discerned it was elevated in patients with diabetes, little did they know the important role it would play in the diagnosis and treatment of diabetes in the decades to come.¹⁻³ Despite some caveats, a hemoglobin A_{1c} level of 6.5% or higher is diagnostic of diabetes across most populations, and hemoglobin A_{1c} goals ranging from 6.5% to 7.5% have been set for different subsets of patients depending on comorbidities, complications, risk of hypoglycemia, life expectancy, disease duration, patient preferences, and available resources.⁴

With a growing number of medications for diabetes—insulin in its various formulations and 11 other classes—hemoglobin A_{1c} targets can now be tailored to fit individual patient profiles. Although helping patients attain their glycemic goals is paramount, other factors should be considered when prescribing or changing a drug treatment regimen, such as cardiovascular risk reduction, weight control, avoidance of hypoglycemia, and minimizing out-of-pocket drug costs (Table 1).

■ CARDIOVASCULAR BENEFIT

Patients with type 2 diabetes have a 2 to 3 times higher risk of clinical atherosclerotic disease, according to 20 years of surveillance data from the Framingham cohort.⁵

Mixed results with intensive treatment

Reducing cardiovascular risk remains an important goal in diabetes management, but unfortunately, data from the long-term clinical trials aimed at reducing macrovascular risk with intensive glycemic management have been conflicting.

TABLE 1

Advantages of selected type 2 diabetes drugs

Drug	Cardiovascular benefit	Weight loss	Low risk of hypoglycemia	Low cost
Metformin		Yes	Yes	Yes
Sulfonylureas				Yes
Meglitinides				
GLP-1 agonists	Yes	Yes	Yes	
DPP-4 inhibitors			Yes	Yes
SGLT2 inhibitors	Yes	Yes	Yes	
Thiazolidinediones			Yes	
Colesevelam			Yes	
Alpha-glucosidase inhibitors			Yes	
Pramlintide		Yes		
Bromocriptine			Yes	
Insulin				Varies by formulation

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose cotransporter 2

Patients with type 2 diabetes have a 2 to 3 times higher risk of clinical atherosclerotic disease

The United Kingdom Prospective Diabetes Study (UKPDS),⁶ which enrolled more than 4,000 patients with newly diagnosed type 2 diabetes, did not initially show a statistically significant difference in the incidence of myocardial infarction with intensive control vs conventional control, although intensive treatment did reduce the incidence of microvascular disease. However, 10 years after the trial ended, the incidence was 15% lower in the intensive-treatment group than in the conventional-treatment group, and the difference was statistically significant.⁷

A 10-year follow-up analysis of the Veterans Affairs Diabetes Trial (VADT)⁸ showed that patients who had been randomly assigned to intensive glucose control for 5.6 years had 8.6 fewer major cardiovascular events per 1,000 person-years than those assigned to standard therapy, but no improvement in median overall survival. The hemoglobin A_{1c} levels achieved during the trial were 6.9% and 8.4%, respectively.

In 2008, the US Food and Drug Administration (FDA)⁹ mandated that all new applications for diabetes drugs must include cardio-

vascular outcome studies. Therefore, we now have data on the cardiovascular benefits of two antihyperglycemic drug classes—cretins and sodium-glucose cotransporter 2 (SGLT2) inhibitors, making them attractive medications to target both cardiac and glucose concerns.

Incretins

The incretin drugs comprise 2 classes, glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors.

Liraglutide. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial¹⁰ compared liraglutide (a GLP-1 receptor agonist) and placebo in 9,000 patients with diabetes who either had or were at high risk of cardiovascular disease. Patients in the liraglutide group had a lower risk of the primary composite end point of death from cardiovascular causes or the first episode of nonfatal (including silent) myocardial infarction or nonfatal stroke, and a lower risk of cardiovascular death, all-cause mortality, and microvascular events than those in the placebo group. The number of patients who would need to be treated to pre-

vent 1 event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause.⁹

Lixisenatide. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial¹¹ studied the effect of the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in 6,000 patients with type 2 diabetes with a recent coronary event. In contrast to LEADER, ELIXA did not show a cardiovascular benefit over placebo.

Exenatide. The Exenatide Study of Cardiovascular Event Lowering (EXSCCEL)¹² assessed another GLP-1 extended-release drug, exenatide, in 14,000 patients, 73% of whom had established cardiovascular disease. In those patients, the drug had a modest benefit in terms of first occurrence of any component of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (3-component major adverse cardiac event [MACE] outcome) in a time-to-event analysis, but the results were not statistically significant. However, the drug did significantly reduce all-cause mortality.

Semaglutide, another GLP-1 receptor agonist recently approved by the FDA, also showed benefit in patients who had cardiovascular disease or were at high risk, with significant reduction in the primary composite end point of death from cardiovascular causes or the first occurrence of nonfatal myocardial infarction (including silent) or nonfatal stroke.¹³

Dulaglutide, a newer GLP-1 drug, was associated with significantly reduced major adverse cardiovascular events (a composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in about 9,900 patients with diabetes, with a median follow-up of more than 5 years. Only 31% of the patients in the trial had established cardiovascular disease.¹⁴

Comment. GLP-1 drugs as a class are a good option for patients with diabetes who require weight loss, and liraglutide is now FDA-approved for reduction of cardiovascular events in patients with type 2 diabetes with established cardiovascular disease. However, other factors should be considered when prescribing these drugs: they have adverse gastrointestinal effects, the cardiovascular benefit was not a class effect, they are relatively ex-

pensive, and they must be injected. Also, they should not be prescribed concurrently with a DPP-4 inhibitor because they target the same pathway.

SGLT2 inhibitors

The other class of diabetes drugs that have shown cardiovascular benefit are the SGLT2 inhibitors.

Empagliflozin. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG)¹⁵ compared the efficacy of empagliflozin vs placebo in 7,000 patients with diabetes and cardiovascular disease and showed relative risk reductions of 38% in death from cardiovascular death, 31% in sudden death, and 35% in heart failure hospitalizations. Empagliflozin also showed benefit in terms of progression of kidney disease and occurrence of clinically relevant renal events in this population.¹⁶

Canagliflozin also has cardiovascular outcome data and showed significant benefit when compared with placebo in the primary outcome of the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, but no significant effects on cardiovascular death or all-cause mortality.¹⁷ Data from this trial also suggested a nonsignificant benefit of canagliflozin in decreasing progression of albuminuria and in the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate (eGFR), the need for renal replacement therapy, or death from renal causes.

The above data led to an additional indication from the FDA for empagliflozin—and recently, canagliflozin—to prevent cardiovascular death in patients with diabetes with established disease, but other factors should be considered when prescribing them. Patients taking canagliflozin showed a significantly increased risk of amputation. SGLT2 inhibitors as a class also increase the risk of genital infections in men and women; this is an important consideration since patients with diabetes complain of vaginal fungal and urinary tract infections even without the use of these drugs. A higher incidence of fractures with canagliflozin should also be considered when using these medications in elderly and osteoporosis-prone patients at high risk of falling.

Consider:
side effects,
hypoglycemia
risk, cost, heart
benefit, effect
on weight

Dapagliflozin, the third drug in this class, was associated with a lower rate of hospitalization for heart failure in about 17,160 patients—including 10,186 without atherosclerotic cardiovascular disease—who were followed for a median of 4.2 years.¹⁸ It did not show benefit for the primary safety outcome, a composite of major adverse cardiovascular events defined as cardiovascular death, myocardial infarction, or ischemic stroke.

■ WEIGHT MANAGEMENT

Weight loss can help overweight patients reach their hemoglobin A_{1c} target.

Metformin should be continued as other drugs are added because it does not induce weight gain and may help with weight loss of up to 2 kg as shown in the Diabetes Prevention Program Outcomes Study.¹⁹

GLP-1 receptor agonists and SGLT2 inhibitors help with weight loss and are good additions to a basal insulin regimen to minimize weight gain.

Liraglutide was associated with a mean weight loss of 2.3 kg over 36 months of treatment compared with placebo in the LEADER trial.¹⁰

In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6),²⁰ the mean body weight in the semaglutide group, compared with the placebo group, was 2.9 kg lower in the group receiving a lower dose and 4.3 kg lower in the group receiving a higher dose of the drug.

In a 24-week trial in 182 patients with type 2 diabetes inadequately controlled on metformin, dapagliflozin produced a statistically significant weight reduction of 2.08 kg (95% confidence interval 2.84–1.31; $P < .0001$) compared with placebo.²¹

Lifestyle changes aimed at weight management should be emphasized and discussed at every visit.

■ HYPOGLYCEMIA RISK

Hypoglycemia is a major consideration when tailoring hemoglobin A_{1c} targets. In the Action to Control Cardiovascular Risk (ACCORD) trial,²² severe, symptomatic hypoglycemia increased the risk of death in both the

intensive and conventional treatment groups. In VADT, the occurrence of a recent severe hypoglycemic event was the strongest independent predictor of death within 90 days. Further analysis showed that even though serious hypoglycemia occurred more often in the intensive therapy group, it was associated with progression of coronary artery calcification in the standard therapy group.²³ Hence, it is imperative that tight glycemic control not be achieved at the cost of severe or recurrent hypoglycemia.

In terms of hypoglycemia, metformin is an excellent medication. The American Diabetes Association²⁴ recommends metformin as the first-line therapy for newly diagnosed diabetes. Long-term follow-up data from UKPDS showed that metformin decreased mortality and the incidence of myocardial infarction and lowered treatment costs as well as the overall risk of hypoglycemia.²⁵ When prescribed, it should be titrated to the highest dose.

The FDA²⁶ has changed the prescribing information for metformin in patients with renal impairment. Metformin should not be started if the eGFR is less than 45 mL/min/1.73 m², but it can be continued if the patient is already receiving it and the eGFR is between 30 and 45. Previously, creatinine levels were used to define renal impairment and suitability for metformin. This change has increased the number of patients who can benefit from this medication.

In patients who have a contraindication to metformin, DPP-4 inhibitors can be considered, as they carry a low risk of hypoglycemia as well. Sulfonylureas should be used with caution in these patients, especially if their oral intake is variable. When sulfonylureas were compared to the DPP-4 inhibitor sitagliptin as an add-on to metformin, the rate of hypoglycemia was 32% in the sulfonylurea group vs 5% in the sitagliptin group.²⁷

Of the sulfonylureas, glipizide and glimepiride are better than glyburide because of a comparatively lower risk of hypoglycemia and a higher selectivity for binding the K_{ATP} channel on the pancreatic beta cell.²⁸

Meglitinides can be a good option for patients who skip meals, but they are more expensive than other generic oral hypoglycemic agents and require multiple daily dosing.

Tight glycemic control should not be achieved at the cost of severe or recurrent hypoglycemia

GLP-1 analogues also have a low risk of hypoglycemia but are only available in injectable formulations. Patients must be willing and able to perform the injections themselves.²⁹

■ **LOOSER TARGETS FOR OLDER PATIENTS**

In 2010, among US residents age 65 and older, 10.9 million (about 27%) had diabetes,³⁰ and this number is projected to increase to 26.7 million by 2050.³¹ This population is prone to hypoglycemia when treated with insulin and sulfonylureas. An injury sustained by a fall induced by hypoglycemia can be life-altering. In addition, no randomized clinical trials show the effect of tight glycemic control on complications in older patients with diabetes because patients older than 80 are often excluded.

A reasonable goal suggested by the European Diabetes Working Party for Older People 2011³² and reiterated by the American Geriatrics Society in 2013³³ is a hemoglobin A_{1c} between 7% and 7.5% for relatively healthy older patients and 7.5% to 8% or 8.5% in frail elderly patients with diabetes.

Consider prescribing medications that carry a low risk of hypoglycemia, can be dose-adjusted for kidney function, and do not rely on manual dexterity for administration (ie, do not require patients to give themselves injections). These include metformin and DPP-4 inhibitors.

■ **DRUG COMBINATIONS**

Polypharmacy is a concern for all patients with diabetes, especially since it increases the

risk of drug interactions and adverse effects, increases out-of-pocket costs, and decreases the likelihood that patients will remain adherent to their treatment regimen. The use of combination medications can reduce the number of pills or injections required, as well as copayments.

Due to concern for multiple drug-drug interactions (and also due to the progressive nature of diabetes), many people with type 2 diabetes are given insulin in lieu of pills to lower their blood glucose. In addition to premixed insulin combinations (such as combinations of neutral protamine Hagedorn and regular insulin or combinations of insulin analogues), long-acting basal insulins can now be prescribed with a GLP-1 drug in fixed-dose combinations such as insulin glargine plus lixisenatide and insulin degludec plus liraglutide.

■ **COST CONSIDERATIONS**

It is important to discuss medication cost with patients, because many newer diabetic drugs are expensive and add to the financial burden of patients already paying for multiple medications, such as antihypertensives and statins.

Metformin and sulfonylureas are less expensive alternatives for patients who cannot afford GLP-1 analogues or SGLT2 inhibitors. Even within the same drug class, the formulary-preferred drug may be cheaper than the nonformulary alternative. Thus, it is helpful to research formulary alternatives before discussing treatment regimens with patients. ■

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ADDRESS: Vinni Makin, MBBS, MD, FACE, Department of Endocrinology, Diabetes, and Metabolism, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; makinv@ccf.org

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