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REVIEW ARTICLE

Pharmacologic Therapies for Type 2 Diabetes

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Abstract

Type 2 diabetes (T2D) is a complex chronic disorder with an increasing prevalence. Treatment of T2D involves both lifestyle and pharmacologic interventions aimed at lowering blood glucose levels to help counteract the negative effects of long-term hyperglycemia. The range of pharmacologic treatments for T2D has grown substantially, with newer agents demonstrating not only glucose-lowering efficacy, but also reductions in long-term cardiometabolic complications. This review discusses the newest pharmacologic agents for the treatment of T2D and the evidence regarding their cardiometabolic benefits. We highlight key considerations for their use based on patient characteristics and clinical context. In addition, we discuss emerging pharmacologic therapies that target the underlying pathogenesis of T2D, underscoring ongoing advances in diabetes care.

C. Corey Hardin, M.D. Ph.D., Editor

Introduction

Type 2 diabetes (T2D) is a chronic and progressive metabolic disease that is among the most common conditions seen by primary care physicians and endocrinologists alike. As of 2021, approximately 537 million people worldwide were living with diabetes, the majority of whom had T2D, with projections reaching 783 million by 2045.[1] The rising prevalence of T2D can be attributed to several factors, including increased rates of obesity, sedentary lifestyles, aging populations, and diets rich in processed foods and low in fiber.[2] In addition, genetic predisposition can contribute to susceptibility to T2D.[3] A major concern in the management of T2D is the development of both microvascular and macrovascular complications, which can lead to conditions such as atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD). People with T2D have a two-to-fourfold increased risk of cardiovascular events, including myocardial infarction, stroke, and heart failure, compared with the general population, and CKD develops in 20 to 40% of individuals with diabetes.[4-6]

The treatment of T2D is complex and multifactorial. The American Diabetes Association (ADA) recommends a target hemoglobin A1c (HbA1c) of less than 7% for most adults to decrease the risk for microvascular complications.[7] T2D treatment should be patient centered, considering the patient's glycemic and weight goals, medication side effects, and relevant clinical factors. These include comorbidities (e.g., cardiovascular disease) and baseline kidney and liver function, which may influence medication choice and dosing.[7] Lifestyle management is considered first-line treatment in the management of T2D. Core lifestyle interventions recommended by the ADA include a diet that follows one of several identified healthy patterns, such as a Mediterranean diet, at least 150 minutes of weekly aerobic activity, and

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weight loss.[8-10] In conjunction with lifestyle interventions, pharmacologic therapy is often needed to reach glycemic targets. This review provides an overview of the latest T2D pharmacologic therapies, their safety considerations and adverse effects, and the evidence supporting their effectiveness in addressing diabetes-related comorbidities.

Pharmacologic Selection

The selection of pharmacologic agents for the treatment of T2D has expanded over the last several decades. Table 1 summarizes current classes of pharmacologic agents, including the newest agents, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is), as well as older drug classes, including metformin, sulfonylureas, meglitinides, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones, and alpha-glucosidase inhibitors. Metformin has historically been recommended as the first-line agent for T2D due to its efficacy, low cost, and safety.[7] However, the development of GLP-1 RAs and SGLT2is has shifted practice in T2D management by providing proven cardiorenal benefits in addition to glycemic control. In view of growing evidence, current guidelines no longer strictly recommend metformin as the preferred first-line treatment, instead recommending an individualized approach that often favors the selection of newer pharmacologic agents based on cardiovascular risk and comorbidities[7,11] (Fig. 1). In the following sections, the available evidence supporting the cardiovascular benefits, renal benefits, and glycemic efficacy of GLP-1 RAs and SGLTis is reviewed.

Cardiovascular Risk Reduction

Cardiovascular safety data for new T2D medications became a requirement after a 2007 meta-analysis linked the thiazolidinedione rosiglitazone to an increased risk of myocardial infarction and cardiovascular death.[12,13] Although rosiglitazone was later shown to be neutral for major adverse cardiovascular events (MACE) in a randomized open-label trial, the controversy spurred public and regulatory concern about the cardiovascular safety of glucose-lowering medications.[12,14] In response, the U.S. Food and Drug Administration (FDA) issued guidance in 2008 mandating that all new glucose-lowering agents demonstrate cardiovascular safety through long-term cardiovascular outcomes trials before approval.[15] This mandate led to a series of cardiovascular outcomes trials for newer T2D agents, including GLP-1 RAs and SGLT2is, which not only demonstrated the cardiovascular safety of these agents, but also revealed cardiovascular benefits.[16]

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial in 2016 was the first cardiovascular outcome trial to show that GLP-1 RAs have cardiovascular benefit. The trial demonstrated that patients with T2D randomly assigned to liraglutide versus placebo had a significantly lower occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke over a median follow-up of 3.8 years.[17] Similarly, dulaglutide and subcutaneous semaglutide were also shown to lead to significant reductions in MACE compared with placebo in randomized controlled trials.[18,19] More recently, the Semaglutide Cardiovascular Outcomes (SOUL) trial demonstrated that 14 mg of oral semaglutide reduced the incidence of MACE from 13.8 to 12% among individuals with T2D, ASCVD, and/or CKD over a mean follow-up of 47.5 months.[20] With regard to stroke prevention, findings from several meta-analyses have shown that GLP-1 RAs are associated with a more pronounced effect on stroke risk reduction than SGLT2is.[21,22]

In addition, the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial demonstrated that semaglutide reduced the incidence of MACE in patients with preexisting cardiovascular disease and overweight or obesity but without diabetes from 8.0 to 6.5% over a mean follow-up of 40 months, with a number needed to treat of 65.[23,24] Notably, the cardiovascular risk reduction of semaglutide demonstrated in this trial is comparable to the risk reduction seen with statins, which is approximately 20% per 1 mmol/l reduction in low-density lipoprotein cholesterol.[25,26] These results suggest that the cardiovascular benefits of semaglutide extend beyond the population with T2D to those with other comorbid conditions, such as obesity and atherosclerotic disease.

SGLT2is have shown cardiovascular benefits in those with T2D as well. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients — Removing Excess Glucose (EMPA-REG OUTCOME) showed that patients with T2D and high ASCVD risk who were randomly assigned to receive empagliflozin for a median observation of 3.1 years had a significant reduction in composite cardiovascular outcomes compared with placebo (10.5% vs. 12.1%).[27] In contrast, in the Dapagliflozin Effect on Cardiovascular Events — Thrombolysis In Myocardial Infarction (DECLARE-TIMI) 58 trial, patients with T2D who had or were at risk for ASCVD did not have

Table 1. Summary of Glucose-Lowering Agents for T2D and Their Associated Effects.*

Drug Class	Example Agents	Mechanism	Glycemic Efficacy†	Advantages‡	Disadvantages‡	Neutral Effects	Safety Considerations
GLP-1 RA	Dulaglutide Liraglutide Semaglutide	• ↑ Glucose-dependent insulin secretion • ↓ Glucagon • Delays gastric emptying, promotes satiety	↑↑↑	• MACE risk reduction • Renal risk reduction • Weight reduction • Hepatic benefit in MASH • No hypoglycemia risk	• High cost • Gastrointestinal AEs	• Neutral HF effect	• Contraindicated if personal or family history of medullary thyroid cancer or MEN 2 • Caution if history of biliary disease, pancreatitis, and diabetic retinopathy
GIP/GLP-1 RA	Tirzepatide	• ↑ Glucose-dependent insulin secretion • ↓ Glucagon • Delays gastric emptying, promotes satiety	↑↑↑	• Weight reduction • No hypoglycemia risk	• High cost • Gastrointestinal AEs	• MACE, renal, and HF benefit TBD	• Same as GLP-1 RAs
SGLT2i	Empagliflozin Dapagliflozin Canagliflozin	• ↑ Urinary excretion of glucose	↑	• MACE risk reduction • Renal risk reduction • HF risk reduction • No hypoglycemia risk	• Intermediate cost • Euglycemic DKA risk	• Only modest weight loss	• Contraindicated with eGFR <20 ml/min/1.73 m^2, volume depletion, and prior history of euglycemic DKA • Caution if history of amputation, and mycotic or urinary infections
Biguanide	Metformin	• ↓ Hepatic gluconeogenesis • ↑ Insulin sensitivity	↑↑	• Low cost • No hypoglycemia risk	• Gastrointestinal AEs	• Neutral MACE, HF, and renal effect • Neutral weight effect	• Contraindicated with eGFR <30 ml/min/1.73 m^2, severe hepatic impairment, and acute or chronic metabolic acidosis
DPP-4 inhibitor	Sitagliptin Linagliptin	• ↑ Glucose-dependent insulin secretion • ↓ Glucagon	↑	• Minimal AEs • No hypoglycemia risk	• Intermediate cost	• Neutral MACE, HF, and renal effect • Neutral weight effect	• Caution if history of pancreatitis and heart failure • Do not use in conjunction with GLP-1 RA
Sulfonylurea	Glipizide Glimepiride	• ↑ Glucose-independent insulin secretion	↑↑	• Low cost	• Weight gain • Hypoglycemia risk	• Neutral MACE, HF, and renal effect	• Cautionary use in those at risk for hypoglycemia
Meglitinide	Repaglinide	• ↑ Glucose-independent insulin secretion • Shorter duration of action than sulfonylureas	↑	• Low cost	• Weight gain • Hypoglycemia risk, though less than that of sulfonylureas	• Neutral MACE, HF, and renal effect	• Caution in those at risk for hypoglycemia
Thiazolidinedione	Pioglitazone Rosiglitazone	• ↑ Insulin sensitivity	↑↑	• Low cost • Hepatic benefit in MASH (pioglitazone) • Possible MACE benefit (pioglitazone)	• Weight gain • Increases HF risk and fluid retention	• Neutral renal effect	• Contraindicated in NYHA class III or IV heart failure
Alpha-glucosidase inhibitor	Acarbose	• Delays carbohydrate digestion and absorption	↑	• Low cost • Weight reduction • No hypoglycemia risk	• Gastrointestinal AEs	• Neutral MACE, HF, and renal effect	• Contraindicated in cirrhosis, inflammatory bowel disease, colonic ulceration, and intestinal obstruction
Insulin	Glargine (long-acting) Lispro (rapid-acting)	• ↑ Insulin receptor activation, glucose utilization, and cellular uptake • ↓ Gluconeogenesis	↑↑↑	• Glycemic efficacy • Rapid onset of action	• Intermediate cost • Hypoglycemia risk • Weight gain	• Neutral MACE, HF, and renal effect	• May need lower insulin doses with progressing renal impairment

* AE denotes adverse event; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; MEN 2, multiple endocrine neoplasia type 2; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; and TBD, to be determined.

† Arrows correspond to average hemoglobin A1c lowering: ↑, 0.5 to 1.0 percentage point; ↑↑, 1.0 to 1.5 percentage point; ↑↑↑, 1.0 to 2.0 percentage point.

‡ Cost is indicated by the following scale corresponding to median National Average Drug Acquisition Costs data for a 30-day supply or 1000 units of insulin dosage: low (US$2 to US$30); intermediate (US$100 to US$600); and high (US$700 to US$1000).

a significantly lower rate of MACE, cardiovascular death, or all-cause mortality when treated with dapagliflozin versus placebo.[28] The differences in MACE and cardiovascular death in these trials may have been due to the inclusion of a large number of patients without established ASCVD in the DECLARE-TIMI 58 trial. This evidence suggests that the cardiovascular protective benefits of SGLT2is may not be as impactful in patients who do not have established clinical ASCVD. Nonetheless, for patients with T2D who have established clinical ASCVD, either an SGLT2i or GLP-1 RA is an appropriate first-line pharmacologic agent (Fig. 1).

Heart Failure

The role of SGLT2is in improving cardiovascular outcomes in those with existing heart failure has also been investigated.[29-31] The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) found that in patients with class II, III, or IV heart failure with reduced ejection fraction (HFrEF) of less than 40%, those who were randomly assigned to receive 10 mg of empagliflozin daily during a

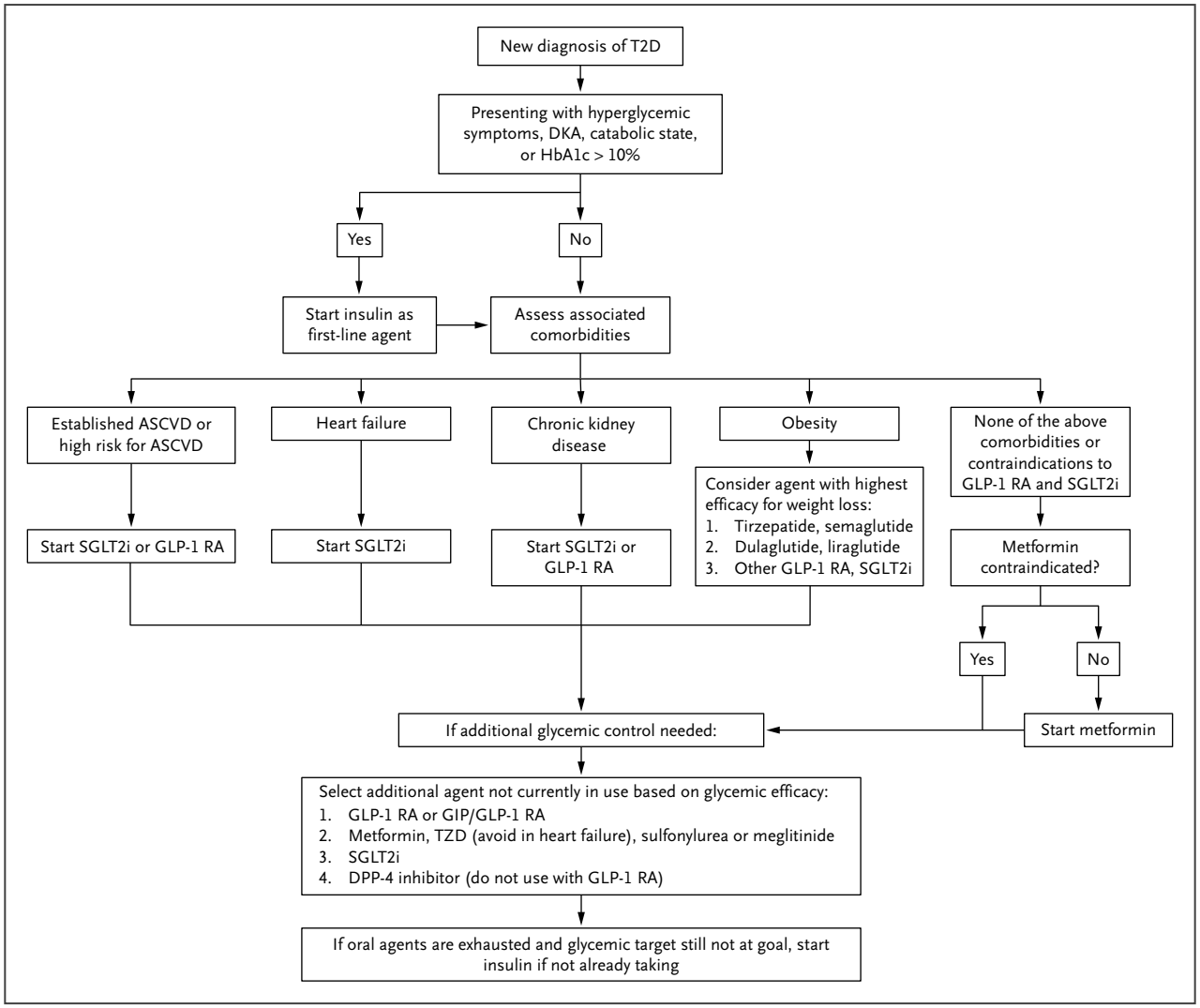

Figure 1. Selection of Pharmacologic Agents for Treatment of T2D.

ASCVD denotes atherosclerotic cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; and TZD, thiazolidinedione.

median follow-up of 16 months had a significantly lower incidence of cardiovascular death or hospitalization for worsening heart failure than those assigned to placebo (19.4% vs. 24.7%), regardless of the presence of diabetes.[29] Similarly, in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin was shown to significantly lower the incidence of worsening heart failure or cardiovascular death than placebo in those with HFrEF over a median follow-up of 18.2 months (16.3% vs. 21.2%).[30] In the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, dapagliflozin significantly reduced the incidence of worsening heart failure outcomes compared with placebo in patients with heart failure with preserved ejection fraction (HFpEF), regardless of T2D status (16.4% vs. 19.5%).[31] Contrary to SGLT2is, GLP-1 RAs have not shown significant benefit in improving heart failure outcomes in randomized controlled trials in patients with T2D.[6,32] However, in patients with obesity and HFpEF but without diabetes, the Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial demonstrated that semaglutide significantly improved heart failure–related symptoms and exercise capacity compared with placebo.[33] Thus, in patients with T2D and heart failure, an SGLT2i should be initiated to reduce the risk of heart failure hospitalization and cardiovascular death.

Renal Protection

With regard to renal outcomes, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial found that in individuals with CKD (as defined as an estimated glomerular filtration rate [eGFR] of 25 to 75 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of at least 200 mg/g), treatment with SGLT2is improved renal outcomes regardless of the presence of T2D.[34] Those who were randomly assigned to receive 10 mg of dapagliflozin daily over a median follow-up of over 2.4 years had a significantly lower incidence of a composite primary outcome of sustained decline in eGFR of at least 50%, development of end-stage renal disease, or death from renal or cardiovascular causes (9.2% vs. 14.5%).[34] Similarly, the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial investigated the renal and cardiovascular effects of empagliflozin on a broader population of patients with CKD, including 2282 (34.5%) patients with an eGFR of less than 30 ml/min/1.73 m^2. Over a median follow-up of 2 years, the primary renal outcome occurred in a significantly lower percentage of the empagliflozin group than in the placebo (13.1% vs. 16.9%).[35]

Recently, the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial showed that semaglutide significantly reduced the risk of major kidney events in those with T2D and CKD when compared with placebo (18.7% vs. 23.2%).[36] The composite primary outcome included kidney failure, a decline of 50% or more in eGFR from baseline, or death from kidney-related causes.[36] A meta-analysis of 10 randomized controlled trials, including the FLOW and SOUL trials, demonstrated consistent reductions in MACE and composite kidney outcomes with both subcutaneous and oral long-acting GLP-1 RAs, supporting a class effect rather than one limited to individual agents.[37] In addition, when patients in the FLOW trial were stratified by whether or not they were being treated with SGLT2is at baseline, SGLT2i use did not result in a significant difference in the primary outcome of major kidney disease events, suggesting that GLP-1 RA benefits on kidney and cardiovascular outcomes are independent of SGLT2i use.[38] Therefore, either drug class can provide renal protection in patients with T2D and CKD.

Glycemic Efficacy

With regard to glycemic efficacy, GLP-1 RAs have been shown to achieve the largest reductions in HbA1c compared with other glucose-lowering agents, apart from insulin.[7,39] The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study (GRADE) trial demonstrated that both insulin glargine and liraglutide, when added to metformin, were significantly more effective at achieving and maintaining target HbA1c levels below 7.0% than glimepiride and sitagliptin.[39] Although SGLT2is were not included in the GRADE trial due to their relatively recent introduction to the market at the time of the trial's initiation in 2013, results from several meta-analyses have suggested that GLP-1 RAs are associated with greater HbA1c reduction than SGLT2is.[40,41] The comparative effectiveness of these agents in reducing HbA1c (Table 1) should be considered alongside cardiovascular risk factors and comorbidities when targeting glycemic goals for individuals with T2D.

Combination Therapy

No cardiovascular outcome trials have directly compared GLP-1 RAs and SGLT2is. However, there is comparative evidence that offers insight into their complementary benefits. A meta-analysis of 12 randomized trials demonstrated that in patients with T2D, SGLT2is were associated with a reduced risk of MACE in patients regardless of whether or not they were also receiving GLP-1 RAs.[42] The effects on hospitalization for heart failure or cardiovascular death and CKD progression were also consistent, irrespective of GLP-1 RA use.[42] In a comparative effectiveness study comparing newly initiated SGLT2i or GLP-1 RA therapy in patients with T2D over a median follow-up of 1.6 years, there was no significant difference in the risk of MACE between new users of SGLT2is and GLP-1 RAs.[43] Thus, evidence suggests that these therapies have independent cardiovascular effects, and their combined use could be beneficial in improving cardiovascular and renal outcomes in patients with T2D. The drug classes can be used in combination for greater glycemic reduction as well. However, despite the clinical benefits of both drug classes, cost is a major consideration (Table 1). GLP-1 RAs are generally more expensive than SGLT2is, and the high cost of both classes compared with older glucose-lowering medications may limit their use.[7] Therefore, cost-effectiveness and affordability are crucial considerations in selecting appropriate glucose-lowering agents.

Impact on Weight

When selecting medications for T2D, the impact on weight should be considered as well, especially in patients with overweight or obesity. Newer dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RAs have emerged as a promising treatment option for T2D and obesity. The combined incretin effect of GIP and GLP-1 receptor stimulation has been postulated to have a greater effect on glucose and weight reduction than GLP-1 receptor stimulation alone. Tirzepatide, a GLP-1 and GIP RA, has been shown to be slightly more effective than 1 mg of semaglutide at reducing HbA1c in patients with T2D over a 40-week period at doses of 5 mg, 10 mg, and 15 mg (−2.0 to −2.3 percentage point reduction with tirzepatide vs. −1.9 percentage point reduction with 1 mg of semaglutide).[44] However, no comparisons have been made between tirzepatide and 2 mg of semaglutide thus far. Tirzepatide has also demonstrated greater weight loss than placebo and 1 mg of semaglutide in individuals with and without T2D,[44-46] indicating that it may be preferred over single-agent agonists for patients needing larger reductions in HbA1c and weight. After tirzepatide, weight loss is greatest with the maximum dose of semaglutide, followed by liraglutide and dulaglutide.[19,47]

Safety Considerations and Adverse Effects

SGLT2is should be avoided in those with severe renal impairment and an eGFR lower than 20 ml/min/1.73 m^2 or who are on dialysis, as the glucose-lowering efficacy is reduced with worsening renal impairment.[4] Most common adverse effects include genital mycotic infections and urinary tract infections, which are typically mild, along with volume depletion and orthostatic hypotension.[48] An increased risk of lower-limb amputations was also reported in the Canagliflozin Cardiovascular Assessment Study (CANVAS), which led to a boxed warning by the FDA.[49] However, subsequent data on SGLT2is have been conflicting, leading to the removal of the warning in 2020.[50,51] Nonetheless, caution is advised when considering SGLT2is for individuals at higher risk for foot ulcers or amputation.

A complication of SGLT2is is the development of euglycemic diabetic ketoacidosis (eDKA). Although the absolute risk of eDKA during hospitalization in patients treated with SGLT2is has been reported to be low (0.2% in one large cohort, with a mean onset of 5 days after the first SGLT2i dose),[52] it has become increasingly recognized in the perioperative setting as use of SGLT2is has grown.[53] eDKA is more likely to occur during acute illness, surgery, periods of fasting or low carbohydrate intake, endogenous insulin deficiency, or reductions or omission of insulin doses, many of which can occur in the preoperative setting.[54] Presenting symptoms include nausea, abdominal pain, and malaise, along with acidosis and ketosis. Serum glucose is typically lower than in traditional DKA due to increased renal clearance of glucose caused by the medication.[54] Current FDA guidelines recommend holding SGLT2is at least 3 days before an elective surgical or invasive procedure.[55] In addition, patients should be educated on eDKA signs and symptoms, maintaining adequate hydration, and pausing the medication during illness or low carbohydrate intake.[53,54] For patients who develop eDKA while taking an SGLT2i, the medication should not be restarted due to high recurrence risk.[4,56]

The most common adverse effects of GLP-1 RAs are gastrointestinal, including nausea, vomiting, and diarrhea.

However, these symptoms can be mitigated by starting with the lowest dose for the first 4 weeks of use and gradually titrating upward.[11] The GLP-1 and GIP RA tirzepatide is associated with similar gastrointestinal side effects that are dose dependent, and data from a network meta-analysis show that the odds of tirzepatide causing gastrointestinal events are comparable to those associated with GLP-1 RAs.[57] GLP-1 RAs are also associated with an increased risk of biliary and gallbladder disease, including cholelithiasis and cholecystitis.[58] This risk appears to be more pronounced when GLP-1 RAs are used for weight loss, and at higher doses and longer durations of use.[58] Thus, these agents should be used with caution in patients who are at higher risk for biliary disease. There have been concerns about possible associations between GLP-1 RA use and pancreatitis; however, large trials have not demonstrated a significant increase in these risks, although patients with a history of pancreatitis have generally not been included in these trials.[17] Nonetheless, alternative agents should be considered for patients who are at high risk for pancreatitis or have a history of pancreatitis due to the potential risk of recurrence.[11] Diabetic retinopathy has been shown to be associated with GLP-1 RA use in meta-analyses of randomized trials.[59,60] Patients with a prior history of proliferative diabetic retinopathy or long-standing T2D for more than 10 years appear to be at higher risk of worsening diabetic retinopathy when using GLP-1 RAs, particularly if they experience a rapid reduction in HbA1c.[60,61] As such, these patient populations should receive regular ophthalmologic consultation prior to starting GLP-1 RAs, and alternative pharmacologic agents could be considered.

GLP-1 RAs are contraindicated in those with a personal or family history of medullary thyroid cancer or medullary endocrine neoplasia type 2, although new evidence regarding the risk of thyroid cancer with GLP-1 RAs is emerging. A French nested case–control study showed that use of GLP-1 RA for 1 to 3 years was associated with an increased risk of all thyroid cancer subtypes.[62] Conversely, a large multisite cohort study found no increased risk of thyroid cancer with GLP-1 RA use compared with DPP-4 inhibitors for up to 3 years of use.[63] Further research is needed to clarify the long-term risk of thyroid cancer with GLP-1 RA use.

Periprocedural recommendations regarding GLP-1 RAs have stemmed from concerns that GLP-1 RAs are associated with increased gastric residual content, which may raise aspiration risk under anesthesia.[64] However, given the limited evidence linking GLP-1 RA use to aspiration, a multisociety guideline in 2024 recommended that patients without an elevated risk of delayed gastric emptying may continue GLP-1 RAs prior to surgery.[65,66] For patients at higher risk, such as those on higher doses of the drug, a 24-hour liquid-only diet prior to surgery may help mitigate this risk.[66]

Insulin Therapy

Insulin should be initiated as first-line therapy for T2D if patients have evidence of glucotoxicity at diagnosis, such as symptomatic hyperglycemia, HbA1c greater than 10%, or catabolic features including weight loss and ketosis[11] (Fig. 1). Many patients with T2D who do not require insulin initially may ultimately require it if adequate glycemic control is not achieved with lifestyle interventions and other pharmacologic therapies. Insulin is an effective glucose-lowering agent, but it is associated with increased risk of hypoglycemia and weight gain. It is most conveniently initiated as once-daily long-acting basal insulin. The addition of rapid-acting prandial insulin should be considered if total daily requirements exceed 0.5 units/kg/day and glycemic targets are unmet.[7] Regardless of the insulin regimen utilized, additional pharmacologic agents with cardiovascular and renal benefits should still be maintained in the treatment regimen. In particular, GLP-1 RAs or GIP and GLP-1 RAs should be considered prior to insulin initiation in the majority of patients, provided there are no contraindications, as they allow for effective glucose lowering with less weight gain, minimal risk of hypoglycemia, and a reduced injection burden compared with multiple daily insulin injections.[7,67] However, given the relatively recent adoption of these recommendations in clinical practice, many patients may already be on insulin by the time pharmacologic agents with cardiovascular or renal benefit are introduced. Depending on glycemic control at the time of initiating an SGLT2i or GLP-1 RA, adjustments to insulin doses should be considered to mitigate the risk of hypoglycemia.[68-70] A proposed framework for these adjustments when initiating these agents is presented in Figure 2.

Future Treatment Landscape

A primary weakness of the current pharmacologic options for T2D is that they primarily focus on reducing hyperglycemia that develops as the disease progresses. Few existing agents adequately target the insulin resistance and defective insulin secretion that drive the pathogenesis of T2D.

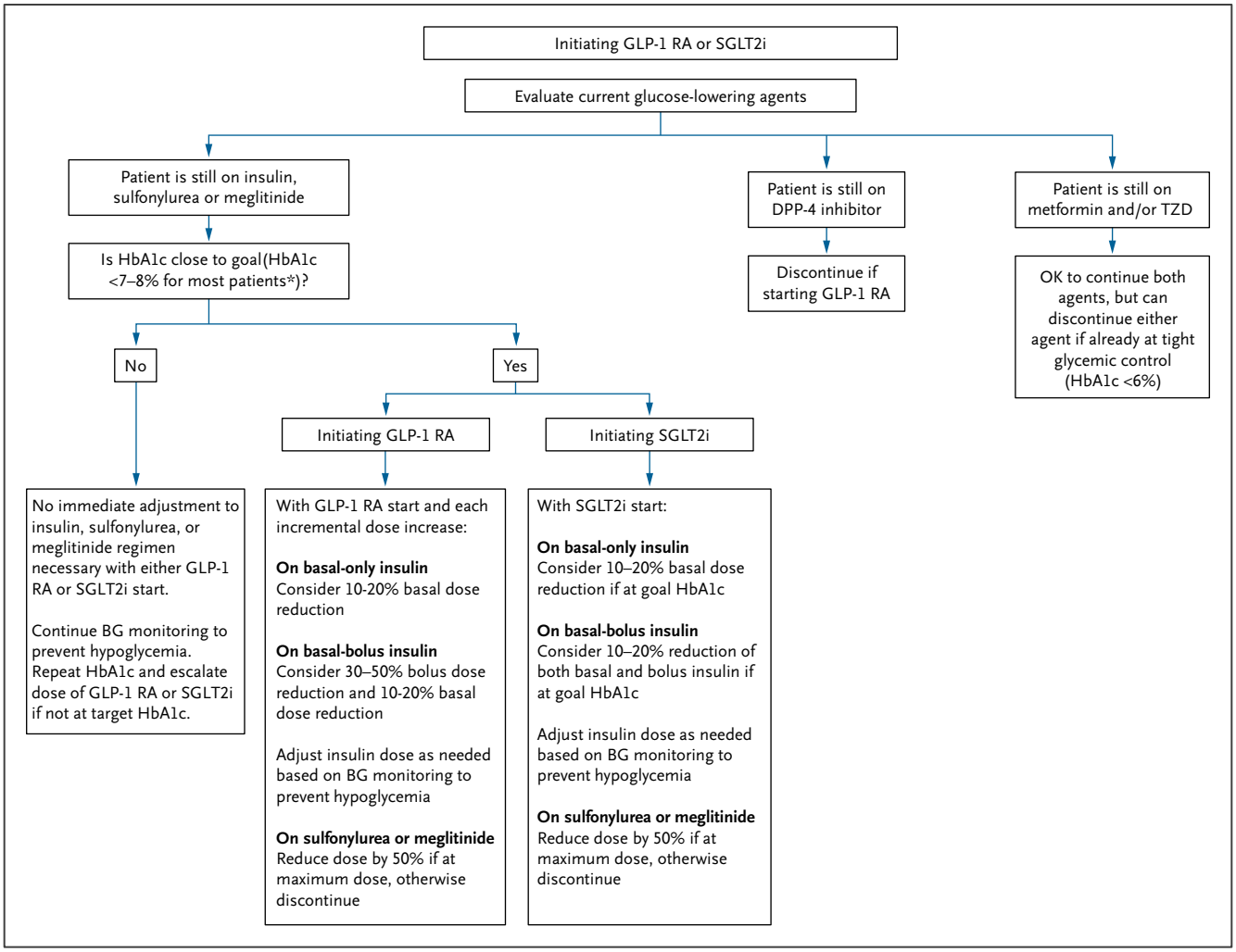

Figure 2. Proposed Adjustments to Insulin and Other Glucose-Lowering Agents When Initiating a GLP-1 RA or SGLT2i in Patients with T2D.

* Consider more aggressive reductions in pharmacotherapy in older adults to avoid hypoglycemia. BG denotes blood glucose; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes mellitus; and TZD, thiazolidinedione.

This approach can lead to suboptimal long-term outcomes and does not fully mitigate the progression of the disease.[71] There are ongoing efforts to develop new pharmacologic agents aimed at improving insulin sensitivity and secretion (Table 2). Several of these potential treatment agents currently being investigated include fibroblast growth factor 21 and adiponectin, which have the potential to improve insulin sensitivity and lipoprotein metabolism.[72,73] Glucokinase activators (GKAs) lower glucose by promoting insulin secretion and hepatic glycogen synthesis.[72] While early trials showed HbA1c reduction with GKAs, concerns about waning efficacy and adverse effects, including hyperlipidemia and hepatic steatosis, have limited their progress.[74,75] Ongoing studies aim to address these issues. Imeglimin is a novel agent recently approved for the treatment of T2D in Japan and China. It targets mitochondrial function in pancreatic beta cells and the liver, improving insulin secretion and action while also suppressing hepatic glucose output.[73] Specific G-protein–coupled receptors GPR40, GPR119, and GPR120 located in pancreatic beta cells are also being explored for their ability to increase glucose-dependent insulin and incretin secretion upon stimulation.[72] Triple agonist therapies targeting GLP-1, GIP, and glucagon receptors are being investigated due to their potential synergistic effects on metabolic regulation. Although glucagon receptor agonism can raise plasma

Table 2. Novel Pharmacologic Agents for T2D Currently under Development that Target Insulin Resistance and Secretion.*

Drug Class	Mechanism	Potential Glycemic Efficacy	Additional Benefits and Drawbacks	Clinical Trial Stage
FGF21 analogs	• Stimulates adiponectin secretion • ↑ Insulin sensitivity • ↑ Lipoprotein metabolism	Mild	• Improvement in dyslipidemia and hepatic steatosis • Potential weight loss	Phase 2
Imeglimin	• ↑ Insulin secretion • ↑ Insulin sensitivity • ↓ Hepatic gluconeogenesis • Improves mitochondrial function	Moderate	• Potential weight loss	Phase 3 Approved in Japan and China
Glucokinase activators	• ↑ Insulin secretion • ↑ Hepatic glycogen synthesis	Moderate	• Associated with hypertriglyceridemia, hepatic steatosis, and hypertension	Phase 1–3
GLP-1/GIP/glucagon receptor triple agonist	• ↑ Glucose-dependent insulin secretion • Delays gastric emptying, promotes satiety • ↑ Energy expenditure	High	• Weight loss	Phase 2
G-protein–coupled receptor ligands	• ↑ Incretin secretion • ↑ Insulin secretion	High	• Associated with hepatotoxicity	Phase 1–2

*FGF21 denotes fibroblast growth factor 21; GIP, glucose-dependent insulinotropic polypeptide GLP-1, glucagon-like peptide 1; and T2D, type 2 diabetes.

glucose, it also enhances insulin sensitivity, improves lipid metabolism, and increases energy expenditure.[76,77] These effects, when combined with those of GLP-1 and GIP, can potentially reduce body weight and improve metabolic parameters to a greater degree.

Conclusion

The pharmacologic treatment options for T2D have expanded substantially over the last several decades, resulting in multiple approaches for lowering glucose levels that can be used in combination to help patients achieve their glycemic goals. The safety data of newer agents have brought forth evidence that GLP-1 RAs and SGLT2is are not only effective at lowering glucose, but demonstrate reductions in MACE, heart failure hospitalizations, and progression of CKD. This has led to a paradigm shift in the treatment of T2D that emphasizes the improvement of cardiovascular and renal health, as well as obesity, to achieve better overall health outcomes for patients rather than solely blood sugar control. Building on the positive outcomes seen with these agents, future research endeavors in T2D treatment will likely explore combination therapies and novel molecular targets that provide cardiorenal benefits while addressing the pathogenesis of diabetes as well.

Disclosures

Author disclosures are available at evidence.nejm.org.

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