

Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies



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Choices for the treatment of type 2 diabetes mellitus (T2DM) have multiplied as our understanding of the underlying pathophysiologic defects has evolved. Treatment should target multiple defects in T2DM and follow a patient-centered approach that considers factors beyond glycemic control, including cardiovascular risk reduction. The American Association of Clinical Endocrinologists/American College of Endocrinology and the American Diabetes Association recommend an initial approach consisting of lifestyle changes and monotherapy, preferably with metformin. Therapy choices are guided by glycemic efficacy, safety profiles, particularly effects on weight and hypoglycemia risk, tolerability, patient comorbidities, route of administration, patient preference, and cost. Balancing management of hyperglycemia with the risk of hypoglycemia and consideration of the effects of pharmacotherapy on weight figure prominently in US-based T2DM recommendations, whereas less emphasis has been placed on the ability of specific medications to affect cardiovascular outcomes. This is likely because, until recently, specific glucose-lowering agents have not been shown to affect cardiorenal outcomes. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes 6 (SUSTAIN-6) recently showed a reduction in overall cardiovascular risk with empagliflozin, liraglutide, and semaglutide treatment, respectively. Moreover, empagliflozin has become the first glucose-lowering agent indicated to reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease. Results from cardiovascular outcomes trials have prompted an update to the 2017 American Diabetes Association standards of care, which now recommend consideration of empagliflozin or liraglutide for patients with suboptimally controlled longstanding T2DM and established atherosclerotic cardiovascular disease because these agents have been shown to reduce cardiovascular and all-cause mortality when added to standard care. © 2017 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (Am J Cardiol 2017;120[suppl]:S4–S16)

Eight core defects, collectively known as “the ominous octet,” contribute to the pathophysiology of type 2 diabetes mellitus (T2DM).^{1,2} These include decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic glucose

production, and increased glucagon secretion (Figure 1).^{1–3} Therapy choices should target these established pathophysiologic defects in T2DM,^{1,2} as well as follow a patient-centered approach that considers factors beyond glycemic control, including reduction of overall cardiovascular risk.^{4–6} This review discusses current consensus

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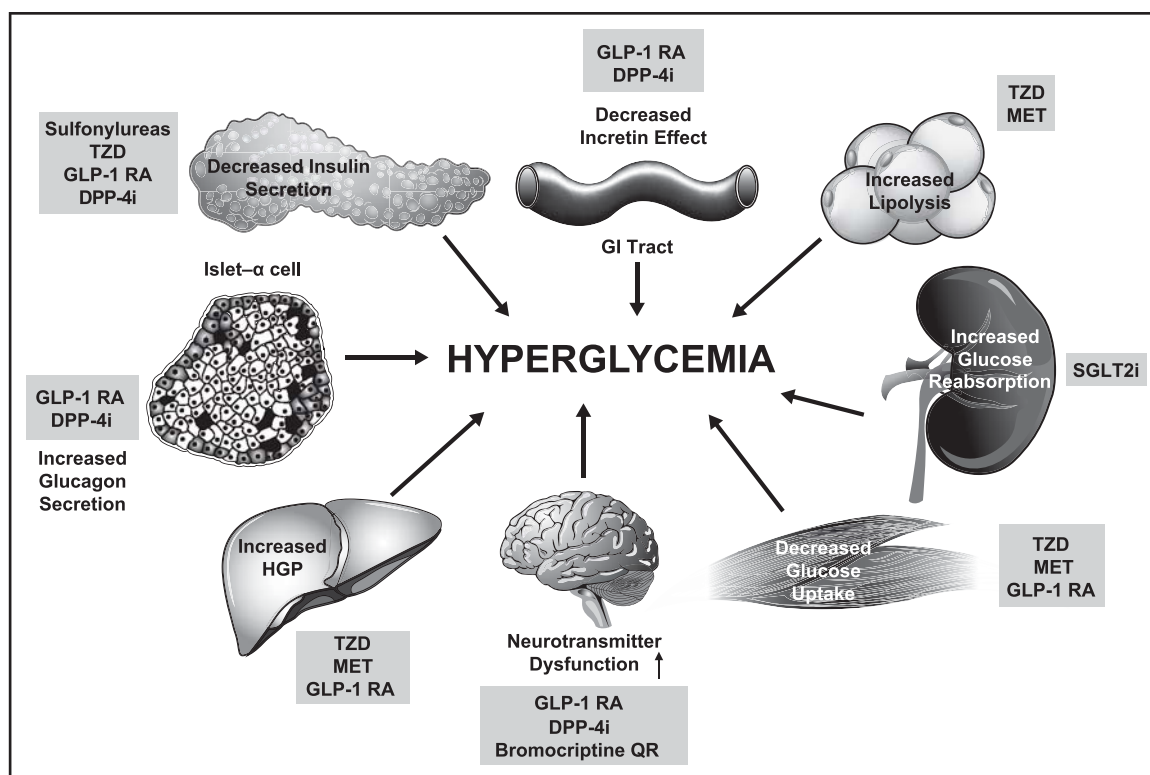


Figure 1. The ominous octet showing the mechanism and site of action of glucose-lowering medications based on pathophysiologic disturbances present in T2DM.^{1–3} DPP-4i = dipeptidyl peptidase-4 inhibitor; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HGP = hepatic glucose production; MET = metformin; QR = quick release; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione. Adapted from DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. American Diabetes Association. 2013 Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Available at: http://care.diabetesjournals.org/content/36/Supplement_2/S127.

recommendations for the management of hyperglycemia in patients with T2DM, focusing on major drug classes, their mechanisms of action, efficacy, and key safety points for appropriate use.

The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)⁴ and the American Diabetes Association (ADA)⁶ support a stepwise, progressive approach to pharmacotherapy. This includes the individualization of glycated hemoglobin (HbA1c) goals based on patient-specific variables (eg, comorbidities) and the adverse effects of therapy, especially hypoglycemia. The AACE/ACE recommends an initial HbA1c goal $\leq 6.5\%$ for most patients on the basis of the trial results comparing intensive with standard glucose-lowering strategies.⁴ They stress the importance of individualizing therapy; thus, a goal of $>6.5\%$, even 7% to 8%, may be appropriate for some patients, such as those with limited life expectancy, a history of severe hypoglycemia, or advanced comorbid disease.⁴ Likewise, the ADA recommends an HbA1c goal $<7\%$ for most nonpregnant adults.⁷ The ADA suggests that more stringent goals ($<6.5\%$) be considered if this can be achieved without unduly increasing the risk of hypoglycemia or adverse therapy outcomes, and less stringent goals ($<8\%$) may be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbidity, or long-standing T2DM.

The recommended initial T2DM management approach includes lifestyle changes and monotherapy (usually with metformin).^{4,6} If the HbA1c goal has not been met within approximately 3 months of starting initial therapy, treatment should be intensified by adding a second agent. Glycemic control should be reassessed again in approximately 3 months, and triple therapy should be considered if the HbA1c target is not achieved. If the HbA1c target is still not achieved, combination injectable therapy including basal insulin may be considered to obtain glycemic control. In patients with high baseline HbA1c levels, initial treatment with dual-combination therapy can be considered. The AACE/ACE suggests initial dual therapy (ie, metformin plus another agent in addition to lifestyle therapy) for patients with an entry HbA1c level $\geq 7.5\%$,⁴ whereas the ADA suggests considering initial dual therapy if the entry HbA1c level is $\geq 9\%$.⁶

The AACE/ACE algorithm (Figure 2)⁴ suggests a preferred hierarchy of use for add-on therapy.⁴ In contrast, the ADA (Figure 3)⁶ does not list a specific order for adding individual agents after metformin and lists 4 oral options (sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitor, sodium glucose cotransporter 2 [SGLT2] inhibitor) and 2 injectable agents (glucagon-like peptide-1 receptor agonist [GLP-1 RA] or basal insulin) as appropriate choices based on patient, disease, and drug characteristics (including cost), with the aim of decreasing blood

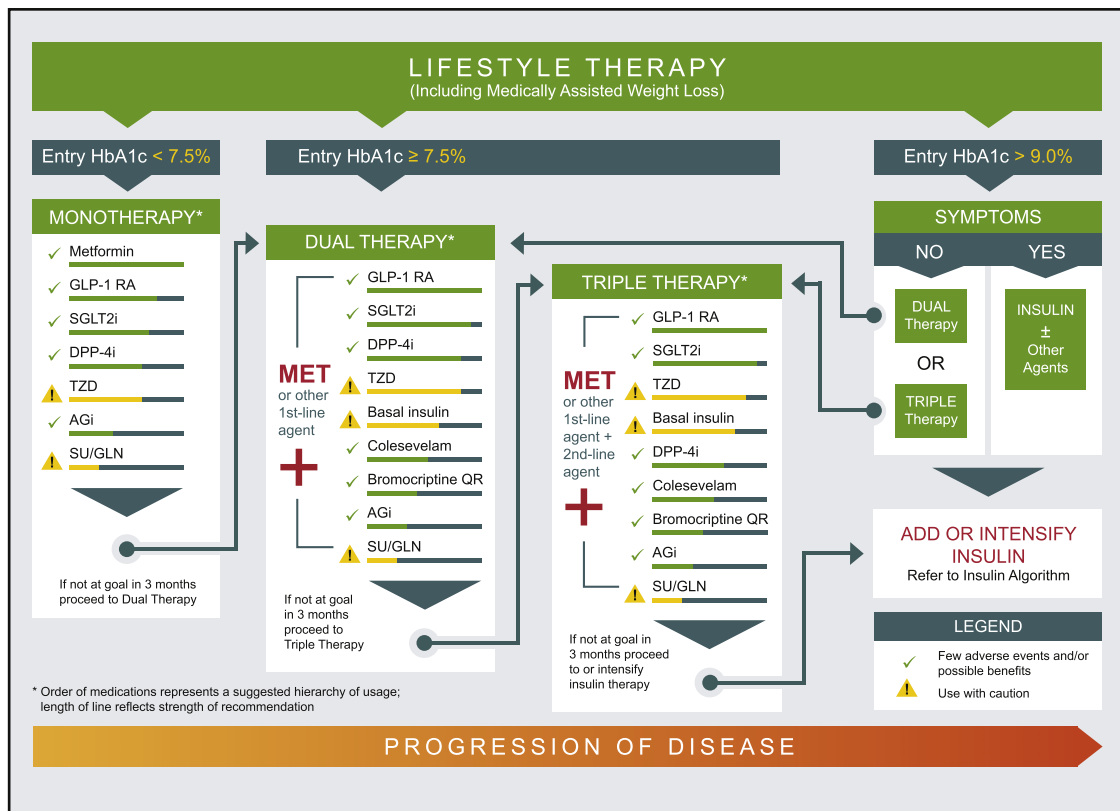


Figure 2. Glycemic control algorithm from the AACE/ACE.⁴ AACE/ACE = American Association of Clinical Endocrinologists/American College of Endocrinology; AGi = alpha-glucosidase inhibitor; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLN = glinide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; MET = metformin; QR = quick release; SGLT2i = sodium glucose cotransporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione. Reprinted with permission from American Association of Clinical Endocrinologists. ©2017 AACE. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive type 2 diabetes management algorithm. 2017. *Endocr Pract*. 2017;23:207-238.

glucose levels while minimizing adverse events, particularly hypoglycemia. The 6 classes of preferred noninsulin glucose-lowering agents common to the ADA and AACE/ACE are listed in Table 1⁶ in order of recommended use in the AACE/ACE hierarchy.⁴ A brief discussion of therapeutic classes is presented in Table 1 in this order.

Biguanide: Metformin

Metformin is the first choice for the treatment of T2DM, unless contraindicated or not tolerated, based on its well-defined efficacy and safety profile^{4,6} and low cost.⁶ Metformin suppresses hepatic glucose production and improves insulin sensitivity.^{15,16} Its place in therapy was solidified with the landmark United Kingdom Prospective Diabetes Study (UKPDS).^{8,9} In the UKPDS, overweight patients with newly diagnosed T2DM were randomized to an intensive glycemic control strategy with metformin versus conventional therapy with diet alone. As discussed by Lüscher and Paneni¹⁷ in this Supplement, patients receiving metformin therapy experienced a significantly decreased risk of any diabetes-related endpoint, mortality, and myocardial infarction. These effects were maintained at the 10-year follow up: patients in the metformin arm had a significantly lower risk for any diabetes-related endpoint (hazard ratio [HR], 0.79; $P = .01$), diabetes-related death (HR, 0.70;

$P = .01$), all-cause mortality (HR, 0.73; $P = .002$), and myocardial infarction (HR, 0.67; $P = .005$).⁸

In a meta-analysis of 35 clinical trials, metformin demonstrated robust glycemic control as monotherapy, providing an HbA1c reduction of -1.12% (95% confidence interval [CI], -0.92 to -1.32) versus placebo.¹⁸ In addition to glycemic control, metformin leads to improvements in endothelial dysfunction, hemostasis, oxidative stress, insulin resistance, lipid profiles, and fat redistribution.¹⁹ Metformin is associated with minimal risk of hypoglycemia and can be used with any of the other available glucose-lowering agents.^{4,6} Metformin and/or metformin extended release is available as a single-pill (ie, fixed-dose) combination with multiple other glucose-lowering agents, including sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors.²⁰ Although gastric tolerability with metformin can be a problem for some patients, this can be improved with appropriate dose up-titration over time or by changing to an extended-release formulation of metformin.¹⁹

Although stringent restrictions regarding the use of metformin had been in place for patients with T2DM and chronic kidney disease because of an increased risk of lactic acidosis, the US Food and Drug Administration (FDA) recommended an update to the labeling of metformin-containing products in 2016.²¹ It is now recommended to assess renal function on

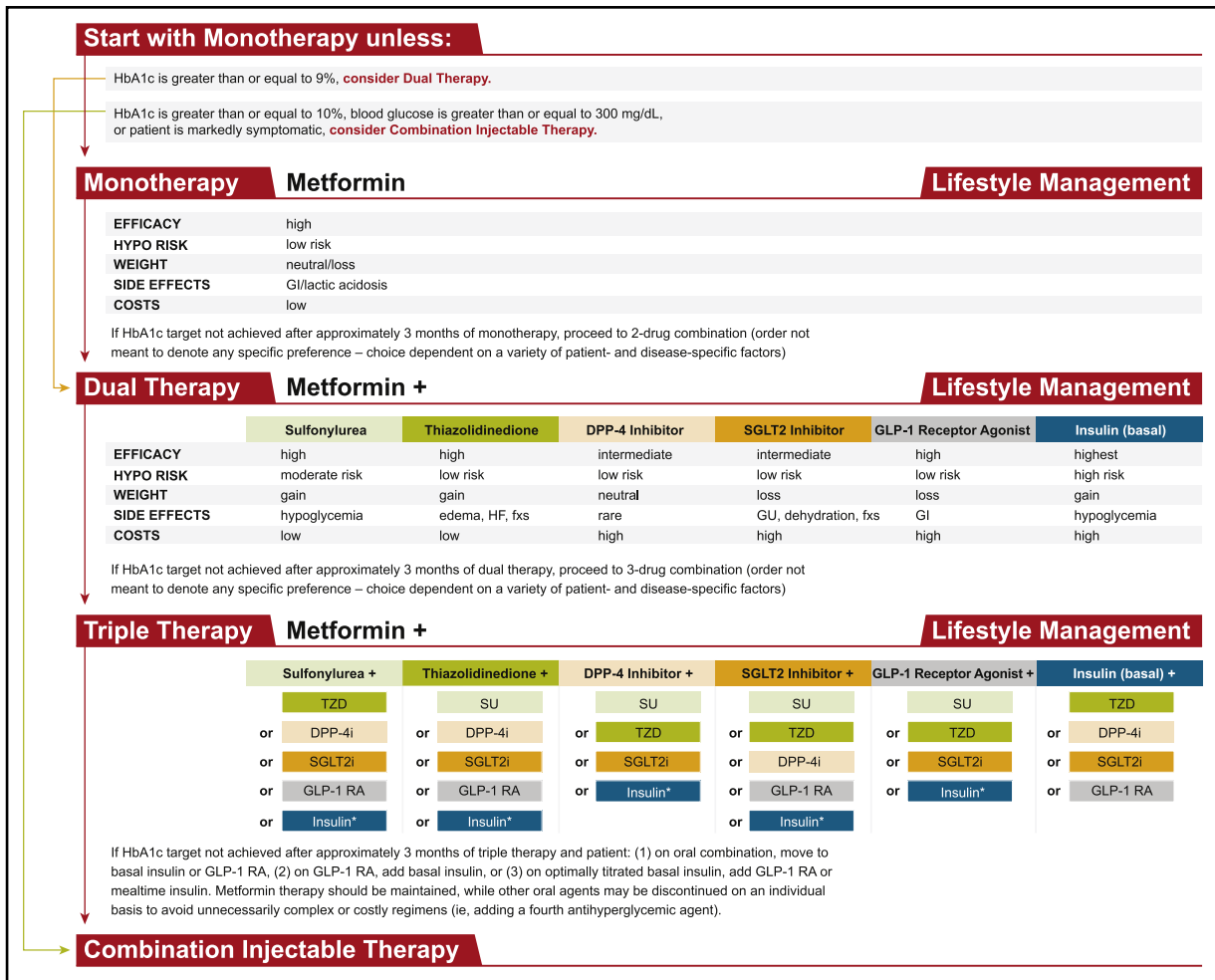


Figure 3. Glucose-lowering therapy in T2DM: general recommendations from the ADA.⁶ The order in the chart was determined by historical availability and route of administration, with injectables to the *right*; it is not meant to denote any specific preference. Potential sequences of glucose-lowering therapy for patients with T2DM are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is possible, depending on the circumstances). *Usually a basal insulin (neutral protamine Hagedorn, glargine, detemir, degludec). ADA = American Diabetes Association; DPP-4i = dipeptidyl peptidase-4 inhibitor; fxs = fractures; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HbA1c = glycated hemoglobin; HF = heart failure; HYPO = hypoglycemia; SGLT2i = sodium glucose cotransporter 2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione. Reprinted from the American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment, 2017. American Diabetes Association. 2017 Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Available at: <http://professional.diabetes.org/content/clinical-practice-recommendations>.

the basis of the estimated glomerular filtration rate (eGFR) instead of serum creatinine, which is how renal dosing had been historically labeled. Metformin can be used in those with an eGFR <60 mL/min/1.73 m², but it should not be initiated in those with an eGFR 30 to 45 mL/min/1.73 m², and the risks versus benefits of therapy continuation should be considered if eGFR decreases to <45 mL/min/1.73 m². Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m².

Glucagon-Like Peptide-1 Receptor Agonists

The term “incretin effect” is derived from the observation that insulin release from the pancreas is greater after oral than intravenous glucose administration.²² GLP-1 and glucose-dependent insulintropic polypeptide are both incretin hormones released from the gut after a meal.

Stimulation of the GLP-1 receptor enhances insulin release and decreases glucagon secretion from the pancreas. Gastric emptying also may be delayed (particularly with shorter-acting pharmacologic compounds),²³ which may lead to appetite suppression.²²

The GLP-1 RAs are synthetic analogues of the native human GLP-1 with improved pharmacokinetic properties and more stable pharmacodynamic profiles than the native peptide.²⁴ Exenatide and lixisenatide are approximately 50% identical to the native GLP-1 molecule, whereas albiglutide, dulaglutide, and liraglutide are ≥90% identical to native GLP-1.²³ Exenatide twice daily and lixisenatide once daily are short-acting compounds, and thus do not provide continuous receptor activation; in contrast, once-daily liraglutide and the once-weekly formulations of albiglutide, dulaglutide, and exenatide extended release provide ongoing receptor activation.²³

Table 1
Properties of select noninsulin glucose-lowering agents in the United States that may guide individualized treatment choices in patients with T2DM⁶

Class	Agents (Route of Administration)	Cellular Mechanism(s)	Primary Physiologic Action(s)	Advantages	Disadvantages*	Cost
Biguanides	Metformin Metformin XR (oral)	Activates AMP-kinase (? Other)	• ↓ Hepatic glucose production	<ul style="list-style-type: none"> • Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS)^{8,9} • Relatively higher HbA1c efficacy 	<ul style="list-style-type: none"> • GI side effects (diarrhea, abdominal cramping, nausea) • Vitamin B₁₂ deficiency • Contraindications: eGFR <30 mL/min/1.73 m², acidosis, hypoxia, dehydration, etc. • Lactic acidosis (rare) 	Low
GLP-1 RAs	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide Lixisenatide (SC injection)	Activates GLP-1 receptors	<ul style="list-style-type: none"> • ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some CV risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide, LEADER)¹⁰ 	<ul style="list-style-type: none"> • GI side effects (nausea, vomiting, diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements 	High
SGLT2 inhibitors	Canagliflozin Dapagliflozin [†] Empagliflozin (oral)	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption in the kidney, increasing glucosuria	<ul style="list-style-type: none"> • Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin, EMPA-REG OUTCOME)¹¹ 	<ul style="list-style-type: none"> • Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis 	High
DPP-4 inhibitors	Alogliptin Linagliptin Sitagliptin Saxagliptin (oral)	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	<ul style="list-style-type: none"> • ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) 	<ul style="list-style-type: none"> • Rare hypoglycemia • Well tolerated 	<ul style="list-style-type: none"> • Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin, ? alogliptin) 	High
SUs	Second generation Glimepiride Glipizide Glyburide (oral)	Closes K _{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	<ul style="list-style-type: none"> • Extensive experience • ↓ Microvascular risk (UKPDS)¹² • Relatively higher HbA1c efficacy 	<ul style="list-style-type: none"> • Hypoglycemia • ↑ Weight 	Low

Table 1
(continued)

Class	Agents (Route of Administration)	Cellular Mechanism(s)	Primary Physiologic Action(s)	Advantages	Disadvantages*	Cost
TZDs	Pioglitazone [†] Rosiglitazone (oral)	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	<ul style="list-style-type: none"> • Rare hypoglycemia • Relatively higher HbA1c efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone)¹³ • ↓ Risk of stroke and MI in patients without diabetes and with insulin resistance and history of recent stroke or TIA (IRIS study,¹⁴ pioglitazone) 	<ul style="list-style-type: none"> • ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) 	Low

AMP = adenosine monophosphate; CV = cardiovascular; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose; GI = gastrointestinal; GIP = glucose-dependent insulintropic polypeptide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; IRIS = Insulin Resistance Intervention after Stroke; LDL-C = low-density lipoprotein cholesterol; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI = myocardial infarction; PPAR = peroxisome proliferator-activated receptor; PROactive = PROspective pioglitAZone Clinical Trial In macroVascular Events; SC = subcutaneous; SGLT2 = sodium glucose cotransporter 2; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; TZD = thiazolidinedione; UKPDS = United Kingdom Prospective Diabetes Study; XR = extended release.

* Please refer to prescribing information for a full list of contraindications, warnings, precautions, and adverse events.

[†] Initial concerns regarding bladder cancer risk are decreasing after subsequent study.

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The efficacy and safety of 6 GLP-1 RAs have been assessed in head-to-head trials; these include 2 short-acting agents (twice-daily exenatide and once-daily lixisenatide) and 4 long-acting agents (once-daily liraglutide and the once-weekly formulations of exenatide, albiglutide, and dulaglutide).²³ Key results from these are summarized next (for a more comprehensive review, refer to Madsbad²³). In all trials, patients were receiving background therapy, and GLP-1 RAs led to reductions in HbA1c ranging from -0.3% to -1.9% .²³

Exenatide once weekly resulted in greater HbA1c reductions than exenatide twice daily ($P < .0023$) in several trials.^{25–27} In addition, HbA1c reductions were significantly greater with liraglutide once daily versus exenatide once weekly (-1.48 vs -1.28% ; $P = .02$) in the 26-week Diabetes Therapy Utilization: Researching Changes in A1C, Weight, and Other Factors Through Intervention With Exenatide Once Weekly 6 (DURATION-6) trial²⁸ and versus exenatide twice daily (-1.12% vs -0.79% ; 95% CI, -0.47 to -0.18 ; $P < .0001$) in the 26-week Liraglutide Effect and Action In Diabetes 6 (LEAD-6) trial.²⁹ Several trials have compared the older agents with newer once-weekly GLP-1 RAs. In the GLP-1 agonist AVE0010 in patients with type 2 diabetes mellitus for Glycemic cOntrol and sAfety evaluation (GetGOAL-X) study, reductions in HbA1c were similar between lixisenatide once weekly and exenatide twice daily.³⁰ In the HARMONY-7 study, liraglutide resulted in greater HbA1c reductions than albiglutide.³¹ Finally, in the Assessment of Weekly Administration of LY2189265 (dulaglutide) in Diabetes-6 (AWARD-6) study, there was no significant difference in glucose-lowering efficacy between liraglutide and dulaglutide.³² Most trials also assessed fasting and postprandial plasma glucose concentrations. Because delayed gastric emptying is more closely associated with the short-acting GLP-1 RAs, these agents have a greater effect on postprandial glucose, whereas the longer-acting agents result in greater improvements in fasting plasma glucose.²³ In addition to their robust effects on HbA1c, the GLP-1 RAs are associated with significant reductions in body weight (>2.0 kg).³³

Cardiovascular outcomes trials in T2DM are reviewed by Lüscher and Paneni¹⁷ in this Supplement. Briefly, results from the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) cardiovascular outcome trial of patients with T2DM and acute coronary syndrome demonstrated cardiovascular safety for lixisenatide versus placebo based on a major adverse cardiovascular event (MACE) endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina).³⁴ No reduction in overall cardiovascular risk and no between-group difference in heart failure were observed. In contrast, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial with the long-acting GLP-1 RA liraglutide demonstrated a reduced risk of MACE and cardiovascular mortality,¹⁰ and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) with the long-acting GLP-1 RA semaglutide (not currently marketed in the United States or elsewhere) demonstrated a reduced risk in MACE.³⁵

Neither trial demonstrated a significant reduction in the risk of hospitalizations for heart failure. Of note, in SUSTAIN-6, diabetic retinopathy complications occurred significantly more frequently in the semaglutide group than in the placebo group, whereas the incidence of retinopathy events was nonsignificantly higher with liraglutide versus placebo in the LEADER trial. These findings require further investigation.

The GLP-1 RAs are associated with a low risk of hypoglycemia except when used with insulin or agents that stimulate insulin secretion (eg, sulfonylureas).^{36–41} Gastrointestinal disorders are the most frequently reported adverse events associated with GLP-1 RA therapy (Table 1). Gastrointestinal adverse events tend to diminish as treatment progresses.⁴² These adverse events may vary by formulation; nausea was reported less frequently with once-weekly exenatide and once-weekly albiglutide than with twice-daily exenatide and once-daily liraglutide.²³ GLP-1 RA therapy has not been studied in and is not recommended for patients with preexisting severe gastrointestinal disease, including severe gastroparesis.^{36–41}

The GLP-1 RAs (except exenatide twice daily³⁹ and lixisenatide⁴¹) are contraindicated in those with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.⁴² This is due to reports of benign and malignant thyroid C-cell tumors in preclinical studies of GLP-1 RAs administered at clinically relevant concentrations^{36–38,40}; however, in humans, no clear association between the use of GLP-1 RAs and the emergence of thyroid C-cell tumors, including medullary thyroid carcinoma, has been established.^{36–38,40} Postmarketing cases of pancreatitis have been reported; however, a causal relationship has not been established.⁴² Other agents should be considered in patients with a history of pancreatitis; if acute pancreatitis develops in patients receiving GLP-1 RA therapy, treatment should be discontinued.^{36–41}

Acute kidney injury, sometimes requiring hemodialysis or renal transplant, has been reported in patients treated with GLP-1 RAs.^{36–41} These events have occurred in patients who do not have underlying renal disease, and nausea, vomiting, and diarrhea have been identified as precipitating factors. Recommendations for GLP-1 RA use in patients with T2DM and chronic kidney disease vary among the agents. Both twice-daily and once-weekly exenatide, as well as lixisenatide, should not be used in patients with end-stage renal disease.^{36,39,41} The exenatide products are not recommended for use in patients with severe renal impairment and should be used with caution in patients who have had a renal transplantation and in patients with moderate renal impairment.^{36,39} Caution should be exercised when initiating or escalating the exenatide dose in patients with moderate renal failure.³⁹ No dose adjustment in patients with renal impairment is recommended for albiglutide, dulaglutide, liraglutide, or lixisenatide; however, renal function should be monitored if these patients experience severe adverse gastrointestinal reactions.^{37,38,40,41}

Sodium Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors target the kidney to promote urinary glucose excretion and decrease hyperglycemia.^{43,44} Under

normal conditions, the kidney reabsorbs nearly all of the filtered glucose, so that virtually no glucose is excreted into the urine. Renal glucose reabsorption occurs in the proximal tubule, primarily by the glucose transport protein SGLT2, and to a lesser extent by sodium glucose cotransporter 1. Evidence suggests that SGLT2 expression is increased in patients with T2DM, resulting in increased glucose reabsorption and preservation of elevated blood glucose levels.⁴³ SGLT2 inhibition reduces the renal capacity for glucose reabsorption by approximately 30% to 50% by promoting urinary glucose excretion, which then decreases hyperglycemia.⁴⁴ Because of their noninsulin-dependent mode of action, SGLT2 inhibitors can be used in combination with any class of glucose-lowering agent and at any stage of disease, including in patients with long-standing T2DM who have minimal insulin secretion. Single-pill combinations of SGLT2 inhibitors and metformin are available, as are SGLT2 inhibitor/DPP-4 inhibitor single-pill combinations: empagliflozin/linagliptin⁴⁵ and dapagliflozin/saxagliptin.⁴⁶

A recent meta-analysis of 34 randomized, controlled trials demonstrated that SGLT2 inhibitor therapy leads to a mean reduction in HbA1c of -0.69% (95% CI, -0.75 to -0.62), body weight of -2.1 kg (95% CI, -2.3 to -2.0), and systolic blood pressure of -3.9 mm Hg (95% CI, -4.6 to -3.3) versus placebo.⁴⁷

The effect of SGLT2 inhibitors on cardiovascular outcomes was largely unknown until data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial were reported in 2015.^{11,48} Briefly, significant reductions in the risks of MACE, cardiovascular mortality, all-cause mortality, and hospitalization for heart failure were demonstrated with empagliflozin treatment compared with placebo in patients with T2DM and cardiovascular disease. On the basis of the results of this study, the FDA granted a new indication for empagliflozin to reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease.⁴⁹ Cardiovascular outcomes trials for canagliflozin (CANagliflozin cardiovascular Assessment Study [CANVAS]) and dapagliflozin (Dapagliflozin Effect on CardiovascuLAR Events—Thrombolysis in Myocardial Infarction 58) are ongoing. Cardiovascular death and total mortality data from CANVAS are expected to be combined with data from the CANVAS renal endpoint study (CANVAS-R) and reported in 2017⁵⁰; final data from DECLARE-TIMI 58 are due in 2019.⁵¹

The EMPA-REG OUTCOME trial also investigated renal outcomes,⁵² as discussed by Wanner⁵³ in this Supplement. In summary, empagliflozin treatment was associated with significant reductions in the risk of incident or worsening nephropathy, progression to macroalbuminuria (a component of incident or worsening nephropathy), and developing clinically relevant renal outcomes (including doubling of serum creatinine levels and initiation of replacement therapy) when compared with placebo. However, it should be noted that the efficacy of SGLT2 inhibitors is dependent on renal function; in the United States, these agents are not recommended for use when eGFR is <45 mL/min/1.73 m² (empagliflozin or canagliflozin) or <60 mL/min/1.73 m² (dapagliflozin).^{49,54,55}

SGLT2 inhibitors are generally well tolerated, and treatment is associated with a low risk of hypoglycemia, unless taken in combination with insulin or insulin secretagogues.^{49,54,55} This class is associated with an increased risk of genital mycotic infection, which occurred more frequently in women and patients with a history of genital mycotic infections. Osmotic diuresis and intravascular volume reduction caused by SGLT2 inhibition may increase the risk of volume-related adverse events, such as orthostatic hypotension and postural dizziness, in susceptible patients (eg, elderly, renal impairment, low systolic blood pressure, receiving diuretics). Volume status should be assessed, and hypovolemia corrected in these at-risk individuals. Although the risk of SGLT2 inhibitor–associated urinary tract infection is small and clinical trials data on these events are inconsistent,⁵⁶ postmarketing cases of potentially fatal urosepsis and pyelonephritis that developed from urinary tract infections in patients receiving SGLT2 inhibitors have been reported.⁵⁷ There also have been postmarketing reports of acute kidney injury requiring hospitalization and dialysis in patients treated with SGLT2 inhibitors.^{49,54,55} Predisposing factors for acute kidney injury include decreased blood volume, chronic kidney insufficiency, congestive heart failure, and use of medications such as diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs.⁵⁸ Temporary discontinuation of SGLT2 inhibitors in settings of reduced oral intake or fluid losses should be considered; if acute kidney injury occurs, SGLT2 inhibitor therapy should be discontinued and treatment for acute kidney injury should be promptly initiated.^{49,54,55}

As the newest class of agents used for diabetes, the fewest long-term safety data are available for SGLT2 inhibitors relative to the other classes discussed. However, safety information has been obtained from postmarketing surveillance and pooled analyses of data from extensive clinical trial programs. For example, a small number of postmarketing cases of serious diabetic ketoacidosis were reported for patients treated with SGLT2 inhibitors, some of which occurred with off-label use in patients with type 1 diabetes mellitus.⁵⁹ A number of cases of diabetic ketoacidosis occurred in patients without significant hyperglycemia, known as “euglycemic ketoacidosis.”⁵⁹ Predisposing factors for diabetic ketoacidosis include reduced food and fluid intake, reduced insulin doses, or recent alcohol intake,^{59,60} as well as other metabolically stressful conditions (eg, concurrent illness, surgical procedures). Subsequent analyses of manufacturer clinical trial databases showed that the incidence of diabetic ketoacidosis with SGLT2 inhibitor treatment was rare.^{50,61,62}

Finally, a pooled analysis of clinical trial data reported a small increase in the frequency of bone fractures with canagliflozin (100 mg and 300 mg) versus comparator (1.4 and 1.5 vs 1.1 per 100 patient-years, respectively).⁵⁴ An increased frequency of bladder cancers was observed for patients treated with dapagliflozin (0.17%) versus comparator (0.03%; placebo or active) groups in a pooled analysis of clinical trial data; the numbers were too small to permit any formal conclusions.⁵⁵

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors reduce the enzymatic degradation of the incretin hormones, GLP-1, and glucose-dependent insulinotropic polypeptide by reducing the activity of serum DPP-4 by $\geq 80\%$.²² This leads to an increased availability of endogenous incretins,²² stimulating insulin secretion from pancreatic β -cells and inhibiting glucagon release from pancreatic α -cells in a glucose-dependent manner.²² These agents may be used as monotherapy or combination therapy and are available as single-pill combinations with metformin or metformin extended release. In addition, the DPP-4 inhibitor alogliptin is available in combination with a thiazolidinedione (alogliptin/pioglitazone).⁶³

In a meta-analysis of 80 randomized controlled trials, DPP-4 inhibitors were associated with mean changes from baseline in HbA1c of -0.6% to -1.1% (without adjustment for background therapies, blinding, or placebo comparators).³³ Another meta-analysis of 15 randomized controlled trials reported that DPP-4 inhibitors had modest systolic and diastolic blood pressure-lowering effects compared with placebo or nontreatment.⁶⁴ These agents are neutral with regard to changes in body weight.⁶⁵

Prospective cardiovascular outcomes trials of saxagliptin, alogliptin, and sitagliptin have shown no increase in the risk of MACE; no cardiovascular outcome benefits were observed.^{66–68} These trials produced conflicting results regarding the risk of hospitalization for heart failure associated with DPP-4 inhibitor treatment, and this is discussed in the review by Lehrke and Marx⁶⁹ in this Supplement. Studies with linagliptin are still ongoing.

Extensive clinical experience with the DPP-4 inhibitors has shown that these drugs generally have a good safety profile and are well tolerated, with a low risk of hypoglycemia (except when used in combination with insulin or insulin secretagogues).⁶⁵ Nasopharyngitis is a frequently reported adverse event. Serious hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin reactions, have been reported with this class of agents.^{70–73} In addition, severe and disabling arthralgia has been reported; the DPP-4 inhibitor should be considered as a cause of severe joint pain and discontinued if appropriate.^{70–73} There have been postmarketing reports of acute pancreatitis in patients treated with DPP-4 inhibitors; however, no clear causal association has been established.⁷⁴ Prompt discontinuation of DPP-4 inhibitor treatment is recommended if pancreatitis is suspected.^{70–73}

Because most DPP-4 inhibitors are eliminated from the body by renal pathways, dose adjustment is required for patients with moderate or severe renal impairment when treated with sitagliptin, saxagliptin, or alogliptin.^{70,72,73} Linagliptin is primarily cleared by nonrenal mechanisms and therefore does not require dosage adjustment in patients with renal impairment.⁷¹

Other Oral Glucose-Lowering Therapies

The sulfonylureas and thiazolidinediones may be considered as an alternative to metformin for monotherapy or as an add-on option for dual- or triple-combination therapy.^{4,6} These agents have a lower priority in the AACE/ACE treatment algorithm, due in part to their

propensity for hypoglycemia (sulfonylureas), heart failure (thiazolidinediones), and weight gain (sulfonylureas and thiazolidinediones), among other adverse events.⁴ In the ADA algorithm, these classes are among 6 treatment options that can be added to metformin (the preferred background therapy).⁶ Although not preferred, these agents may be useful in select clinical settings. For example, thiazolidinediones may be useful for patients who require an insulin sensitizing agent, but in whom metformin is contraindicated. The thiazolidinediones also may be useful for patients with T2DM whose occupations preclude the use of insulin and in whom the risk of a hypoglycemic episode could have severe consequences; in such circumstances, a thiazolidinedione could be used as part of a triple-therapy regimen.

Thiazolidinediones stimulate peroxisome proliferator-activated receptors, nuclear receptors that alter the transcription of several genes involved in glucose and lipid metabolism, thereby promoting insulin sensitivity in adipocytes, muscle, and liver.⁷⁵ In a report analyzing data from 20 clinical trials, treatment with thiazolidinediones resulted in significant HbA1c reductions of -0.5% to -1.5% .⁷⁶ However, thiazolidinediones are associated with fluid retention, which can lead to weight gain, peripheral edema, and heart failure,^{4,6} and are thus contraindicated in patients with established New York Heart Association Class III or IV heart failure.^{77,78} Pioglitazone has been associated with decreased risk of stroke,^{13,14,79} whereas there has been controversy surrounding a potential increased risk of ischemic cardiovascular events with rosiglitazone. The FDA restricted the use of rosiglitazone on the basis of initial concerns about a signal for increased cardiovascular risk in a published meta-analysis⁸⁰; however, the restrictions were later eased after data were re-reviewed.⁸¹ Thiazolidinediones decrease bone mineral density, which can lead to an increased risk of nonosteoporotic bone fractures,^{27,28} particularly in postmenopausal women and elderly men.⁴

The sulfonylureas stimulate insulin release from the pancreas by binding to the sulfonylurea receptor on the adenosine triphosphate-sensitive potassium channel on the β -cell membrane.⁸² In an analysis of data from 61 clinical trials, sulfonylureas reduced HbA1c levels in patients with T2DM by approximately -1.0% to -1.25% .⁸³ However, adverse effects of sulfonylureas include increases in body weight and hypoglycemia. The cardiovascular safety of this class is discussed by Lüscher and Paneni¹⁷ in this Supplement.

Other oral glucose-lowering agents, such as the α -glucosidase inhibitors, colesevelam (a bile acid sequestrant), and bromocriptine (a quick-release dopamine receptor agonist), may be considered in a combination therapy regimen for selected patients.^{4,6} The α -glucosidase inhibitors slow intestinal absorption of carbohydrates and have modest HbA1c-lowering efficacy^{4,6}; the need for frequent dosing⁶ and gastrointestinal adverse events (flatulence and diarrhea)^{4,6} may limit use. Colesevelam provides modest reductions in HbA1c,^{4,6} rarely causes hypoglycemia,^{4,6} and decreases low-density lipoprotein cholesterol^{4,6}; however, it may increase triglycerides,^{4,6} cause constipation,⁶ and affect the absorption of other medications.⁶ Bromocriptine rarely causes hypoglycemia,^{4,6} has slight HbA1c-lowering efficacy, and may cause nausea and orthostatic events.⁴ Although data from a small 1-year,

placebo-controlled safety trial and a subsequent post hoc analysis suggested overall decreased cardiovascular event rates with bromocriptine treatment, the trial was not powered or designed to the standards of recent prospective cardiovascular outcomes trials.^{84,85}

Insulin

Insulin remains the most potent glucose-lowering agent, particularly for patients with high HbA1c levels. There are multiple barriers to initiating insulin therapy, including time constraints, patient discomfort with self-injections, and limited knowledge regarding new insulin formulations.^{86–88} These barriers may explain why data from a retrospective cohort study of more than 81,000 people in the United Kingdom Clinical Practice Research database showed that the median time to treatment intensification with insulin was >7.1, >6.1, or 6.0 years for those taking 1, 2, or 3 oral glucose-lowering therapies, respectively.⁸⁹ The decision to add insulin will require discussion between the prescribing physician and the patient; this decision should be a mutual one, taking into consideration the patient's motivation, general health, age, risk of hypoglycemia, and cardiorenal complications.⁴

The AACE/ACE guidelines recommend basal insulin, in combination with metformin or other glucose-lowering agents, as initial therapy for patients with an entry HbA1c level >9% who have symptoms of hyperglycemia and in other patients as an add-on option for dual- or triple-combination therapy.⁴ Specifically, basal insulin is suggested for use in patients with T2DM receiving 2 oral glucose-lowering agents who have an HbA1c >8% or long-standing T2DM.⁴ Likewise, the ADA recommends basal insulin as 1 of 6 options for dual-combination therapy (ie, step-up from monotherapy or initial dual therapy if HbA1c is $\geq 9\%$).⁶ For patients with newly diagnosed T2DM, the ADA suggests initiating combination injectable therapy (ie, basal insulin plus prandial insulin, basal insulin plus a GLP-1 RA, or a premixed insulin) in patients who have an HbA1c $\geq 10\%$, a blood glucose level ≥ 300 mg/dL, or marked symptoms.⁶

Insulin is available in rapid-acting/prandial (eg, lispro, aspart, glulisine), short-acting (eg, human regular), intermediate-acting (eg, human isophane [neutral protamine Hagedorn]), and premixed formulations. The addition of prandial insulin based on postprandial glucose levels may be necessary for patients who remain hyperglycemic despite basal insulin intensification. Clinical studies have shown that the stepwise addition of prandial insulin is effective in lowering HbA1c levels, with a low risk of hypoglycemia.^{4,6} Alternatively, guidelines support combining basal insulin with a GLP-1 RA in lieu of prandial insulin, with data showing similar efficacy and the advantage of weight loss and less hypoglycemia with GLP-1 RA therapy compared with prandial insulin therapy.^{4,6} The FDA has recently approved 2 fixed-dose combinations of a long-acting basal insulin and a GLP-1 RA in an injectable pen formulation for once-daily subcutaneous use. These include the fixed-dose combination of insulin glargine/lixisenatide 100 U/33 μ g/mL, as well as insulin degludec/liraglutide 100 U/3.6 mg/mL.^{90,91} Compared with other glucose-lowering therapies, there is a substantial risk of hypoglycemia with insulin therapy,

especially combination regimens that include prandial insulin. Frequent monitoring of blood glucose levels in patients on multiple daily injections of insulin helps guide patient decisions regarding prandial insulin dosing and clinician decisions regarding adjustments to the prescribed insulin regimen. For a more detailed discussion of the relative roles of basal and prandial insulin in clinical practice, the reader is referred to the AACE/ACE position statement⁴ and ADA standards of care.⁶

Impact of Recent Cardiovascular Outcomes Trials on Treatment Algorithms

Until the results of EMPA-REG OUTCOME, LEADER, and SUSTAIN-6, specific glucose-lowering agents had not been shown to affect cardiorenal outcomes. Consideration of the effects of pharmacotherapy on HbA1c, weight, and the risk of hypoglycemia were key attributes for US-based T2DM recommendations, whereas the effects on cardiovascular outcomes were not prioritized.

The results of these recent cardiovascular outcomes trials have informed modifications to the diabetes management guidelines.^{6,92} For example, in 2016, the ADA standards of care first made mention of the cardiovascular benefits of empagliflozin as a potential advantage of the SGLT2 inhibitors.⁹² Also in 2016, the Canadian Diabetes Association was the first group to revise its algorithm for the management of hyperglycemia in T2DM to include a category for cardiovascular outcomes trials stating, “the presence of clinical cardiovascular disease and the effect of anti-hyperglycemic agents on cardiovascular outcomes should be considered the top priority in choosing add-on treatment regimens for patients with type 2 diabetes.”⁹³ They recognized that patients in these trials were already receiving standard care that included cardiovascular therapies and glucose-lowering agents discussed in this article (mostly metformin) and had at least one preexisting cardiovascular disease or cardiovascular disease risk factor.

The Canadian guidelines also were the first to recommend the addition of a glucose-lowering agent with a demonstrated cardiovascular benefit in adults with T2DM and clinical cardiovascular disease in whom glycemic targets are not met, namely, empagliflozin (Grade 1 evidence) or liraglutide (aged ≥ 50 years [Grade 1 evidence] or < 50 years [Grade D evidence/consensus]).⁹³ Results from cardiovascular outcomes trials have prompted a further update to ADA standards of care; the 2017 document recommends consideration of empagliflozin or liraglutide for patients with long-standing suboptimally controlled T2DM and established atherosclerotic cardiovascular disease because these agents have been shown to reduce cardiovascular and all-cause mortality when added to standard care.⁶

What the US and Canadian groups have not separately considered is the impact of heart failure on pharmacotherapy choices. In 2013, inpatient hospitalizations due to non-hypertensive congestive heart failure were associated with related costs of more than \$10.2 billion,⁹⁴ suggesting the importance of this outcome. Trials of glucose-lowering agents in patients with heart failure are being initiated and may serve to inform the development of future guidelines.

Conclusions

A range of therapies is available for the management of patients with T2DM, and each class has advantages and disadvantages based on their mechanisms of action and evidence from clinical experience. Glycemic efficacy, safety profiles, particularly effects on weight and hypoglycemia risk, tolerability, patient comorbidities, route of administration, patient preference, and cost are used to guide therapy choices. Although all of these factors are important, patients may have preferences for specific therapy attributes. For example, some patients may prefer agents that are administered orally over those that require self-injection, others may prioritize low prescription costs, and still others may be most concerned about limiting weight gain. Patients and physicians alike will strive to avoid adverse drug reactions (eg, severe hypoglycemia) and long-term complications of T2DM, particularly microvascular and macrovascular disease.

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