Pharmacological Agents Utilized in Patients With Type-2 Diabetes: Beyond Lowering A1c

Joanna W. Chung, PharmD, BCPS; Melody L. Hartzler, PharmD, AE-C, BCACP, BC-ADM; Ashley Smith, PharmD; Jessica Hatton, PharmD; and Kristi Kelley, PharmD, FCCP, BCPS, CDE, BC-ADM

INTRODUCTION

According to the Centers for Disease Control and Prevention, the diagnosis of diabetes increased approximately 9.3% from 1980 to 2014, with type-2 diabetes mellitus (T2DM) accounting for more than 90% of cases.[1] Diabetes is newly diagnosed in 1.5 million Americans each year, while 86 million Americans 20 years of age and older have prediabetes.[1] With the increased rate of diabetes comes increased costs associated with the long-term complications of the disease and related comorbidities, in part because patients are living longer due to advances in screening, pharmacotherapy, and technology. The costs are staggering at a total of $245 billion in 2012: $176 billion for direct medical costs and $69 billion in reduced productivity.[2]

It is increasingly difficult for practitioners to navigate the wide range of individualized pharmacotherapy options available for T2DM. Staying up to date with evolving T2DM pharmacotherapies is important for providers so they can offer optimal evidence-based therapies to their patients. The objective of this article is to discuss available evidence to support the role of novel and existing pharmacological agents in treating T2DM.

PATHOPHYSIOLOGY

A variety of etiologies result in elevated glucose, including genetic defects in beta-cell function or insulin activity, pancreatic diseases, or medication-related adverse effects. Type-1 diabetes mellitus (T1DM) and its subtypes are attributed to cell-mediated beta-cell destruction that leads to a deficiency in insulin. Typically diagnosed in childhood or early adulthood, T1DM accounts for 5% to 10% of patients with diabetes. The majority of patients with diabetes are diagnosed with T2DM, which involves insulin resistance in muscle and liver cells that results in a defect in pancreatic insulin secretion. Despite the existence of multiple subtypes of diabetes, a diagnosis of diabetes in nonpregnant patients occurs when the criteria listed in Table 1 are met.[3,4]

T2DM is more than just hyperglycemia. Ralph A. DeFronzo, MD, first published research regarding the "ominous octet" in 2009 to describe the eight pathophysiological changes that lead to hyperglycemia.[5] With insulin resistance and beta-cell dysfunction playing a critical role, impaired neurotransmitters in the brain also fail to provide correct signaling to the pancreas and the gut during digestion. Impaired signaling results in defects within the negative feedback mechanisms to and from the brain, liver, kidneys, pancreas, and gut, leading to hyperglycemia. While the metabolism of glucose is impaired via dysregulated insulin and glucagon secretion, the liver continues to produce glucose via gluconeogenesis. The ominous octet also includes increased reabsorption of glucose in the kidneys as well as increased lipolysis and reduced muscle uptake of glucose, leading to reduced insulin sensitivity and hyperglycemia.[6] Hormones in the stomach and small intestine, including glucagon-like peptide-1 (GLP-1) and glucose insulinotropic peptide that naturally decrease glucose absorption, are also impaired.

Table 1 Type-2 Diabetes Diagnostic Criteria[3,4]

Fasting plasma glucose	≥ 126 mg/dL
Two hours after oral glucose tolerance test	≥ 200 mg/dL
A_{1c} test (%)	≥ 6.5
Random plasma glucose	≥ 200 mg/dL + symptoms

Another proposed classification system, the "egregious 11," assumes the beta-cell–centric model involves insulin resistance due to multiple genetic factors, environmental factors, immune dysfunction, and inflammation of beta cells. In addition to the ominous octet, this classification system includes dysregulated pathways in the stomach/small intestine, colon/biome, and immune system plus inflammation.[7] Each of these proposed pathophysiological deficits identifies pharmacological targets for therapy. New medication classes have mechanisms that directly interact with single or multiple pathways leading to hyperglycemia. It is important for clinicians to understand differences in various mechanisms in order to provide individualized therapy while reducing health care costs.

GOALS OF THERAPY

The goals for optimizing diabetes management are to reduce the risk of developing microvascular complications (i.e., retinopathy, nephropathy, neuropathy) and macrovascular complications (i.e., cardiovascular disease [CVD], myocardial infarction [MI], stroke). The 2018 American Diabetes Association (ADA) guidelines propose glycemic targets that are individualized to patients' needs by considering factors such as duration of diabetes, presence of macro/microvascular complications, comorbid disease states, and risk of hypoglycemia.[3] The ADA

Dr. Chung is a Clinical Pharmacy Specialist at the Veterans Affairs Medical Center (VAMC) in Bedford, Massachusetts. Dr. Hartzler is an Associate Professor at Cedarville University School of Pharmacy in Cedarville, Ohio, and a Clinical Pharmacist in Western Medicine Family Physicians in Fairborn, Ohio. Dr. Smith is a Pharmacist at the VAMC in Mountain Home, Tennessee. Dr. Hatton is a Pharmacy Market Liaison at Caresource in Dayton, Ohio. Dr. Kelley is an Associate Clinical Professor and Clinical Pharmacist at Auburn University Harrison School of Pharmacy in Birmingham, Alabama.

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recommends a glycemic goal (hemoglobin A1c [HbA_{1c}]) of less than 7% for otherwise healthy nonpregnant adults, whereas the American Association of Clinical Endocrinologists (AACE) recommends a stricter goal of less than 6.5%. Table 2 outlines differences in glycemic targets according to ADA guidelines and AACE consensus statements.[3,4] Both recommend that goals of therapy be individualized to patient-specific needs and risk factors. For example, children, pregnant women, and the elderly may have differing glycemic targets.

Both the ADA and AACE recommend lifestyle modifications as first-line therapy while concurrently optimizing these lifestyle changes with the initiation of therapeutic treatment. Pharmacological treatment includes metformin as the preferred initial glucose-lowering therapy for T2DM unless contraindicated.[3,7] The recommendations differ largely due to patient-specific characteristics, with the ADA recognizing oral and noninsulin injectable agents' effectiveness in HbA_{1c}-lowering ranges upwards from 0.5% to 1%. The 2018 ADA Standards of Care recommend tailoring synergistic effects when combining dual noninsulin agents for patients with uncontrolled glucose after three months of monotherapy while assessing a patient-centered approach that considers efficacy, side effect profile, hypoglycemia, and other comorbidities, such as established CVD. In patients with established CVD, the ADA recommends use of empagliflozin (Jardiance, Boehringer Ingelheim) or liraglutide (Victoza, Novo Nordisk) given their reductions in cardiovascular (CV) death risk and all-cause mortality when used with standards of care (rated class A evidence). Alternatively, canagliflozin may be considered to reduce major adverse cardiovascular events based on patient-specific factors (rated class C evidence).[3] For patients with an HbA_{1c} greater than 10% or those with suboptimal glycemic control despite oral agents, the initiation of insulin should not be delayed.

In contrast, the 2018 AACE consensus statements recommend a hierarchy of therapy based on efficacy and safety in order of consensus recommendations: metformin, GLP-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 inhibitors (SGLT2s), dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, insulin secretagogues, and miscellaneous noninsulin agents.[8] AACE consensus statements recommend initiating combination therapy in patients who have an HbA_{1c} greater than 7.5%, and for patients with an HbA_{1c} greater than 9%, initiation of insulin with or without other agents is recommended unless asymptomatic to decrease beta-cell impairment from glucose toxicity.[8]

Because multiple noninsulin agents typically result in an average HbA_{1c} reduction of 1% to 1.5%, a patient-centered approach is recommended by both the ADA and AACE to individualize optimal therapies. Factors should include patient comorbidities, adverse effect profiles, and preference of formulations with regard to improved adherence. New and ongoing evidence from CV outcomes data have opened an area of clinical practice that supports utilization of preferred agents, resulting in a potential for cost-savings from diabetes-associated complications, such as macrovascular events and other long-term effects. Agents that lack long-term efficacy, positive CV outcomes, and reductions in all-cause mortality are no longer preferred as initial second-line monotherapy or dual therapy; they should be used with caution.[8]

Table 2 Glycemic Targets

Glycemic Targets	ADA[3]	AACE[4]
A1c (%)	< 7.0	≤ 6.5
Fasting plasma glucose	80–130 mg/dL	< 110 mg/dL
Two-hour postprandial glucose	< 180 mg/dL	< 140 mg/dL

AACE = American Association of Clinical Endocrinologists;
ADA = American Diabetes Association.

The AACE treatment algorithm and the ADA's general recommendations for antihyperglycemic therapy in type-2 diabetes have been summarized in graphic form and are available at: https://tinyurl.com/AACE-alg and https://tinyurl.com/ADA-2018rec.

PREFERRED THERAPIES

Biguanides (Metformin)

Phenformin, metformin's predecessor, was discovered in the 1950s, and metformin received Food and Drug Administration (FDA) approval in 1994. Since then, multiple formulations and combinations have been developed using metformin, which is now available as a generic. Metformin has been recommended as the drug of choice for initial pharmacotherapy in T2DM in both adolescents and adults if glycemic goals are not achievable with diet and lifestyle modification (unless contraindicated).[3,8] Metformin is a biguanide antihyperglycemic agent that primarily decreases hepatic gluconeogenesis and decreases intestinal absorption of glucose. Furthermore, recent studies have concluded that metformin increases GLP-1 secretion, inhibits DPP-4 activity, and upregulates GLP-1 receptors.[9] In the presence of weight loss, metformin may improve peripheral insulin sensitivity; however, this is more likely a result of the reduction in adipose tissue than a specific effect of the compound itself.[10] Metformin is found to be efficacious for patients with residual pancreatic islet-cell function. Metformin rarely causes hypoglycemia as monotherapy because it does not significantly change insulin concentrations.[11]

Clinically, metformin lowers fasting and postprandial glucose by decreasing fasting plasma glucose by 25% to 30% and reducing overall HbA_{1c} by approximately 2%.[12] Metformin as initial treatment may reduce mortality and risk of MI in overweight adults with T2DM.[13,14] It is, however, notable for its adverse effects of diarrhea and epigastric pain, which can be reduced by administration with food and gradual titration to the maximum effective dose of 2,000 mg daily. Transitioning to extended-release formulations can also help alleviate gastrointestinal (GI) side effects.[15] Additional common adverse effects include vitamin B_{12} deficiency and subsequently worse neuropathy, which can be treated with supplementation and frequent monitoring. Unlike other antihyperglycemic medications, metformin does not cause weight gain and may provide a modest decrease in low-density lipoprotein-cholesterol (LDL-C) and total cholesterol.[16,17]

Metformin labeling has been updated for patients with renal dysfunction to minimize underutilization of the drug. The FDA has removed the serum creatinine concentrations of 1.5 mg/dL and 1.4 mg/dL in males and females, respectively. This allows metformin use in patients with mild-to-moderate chronic kidney disease (CKD) given its benefit in improving CV outcomes that outweighs the risk of lactic acidosis.[18] Use of metformin remains

contraindicated in patients with an estimated glomular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2. Metformin may be used in patients with stable heart failure (HF) and normal renal function; however, its use is advised with caution in patients with unstable and acute HF and should be avoided in patients with unstable HF who are hospitalized. Furthermore, risk of lactic acidosis may increase in patients who are elderly, renally impaired, in a hypoxic state, hepatically impaired, or at increased risk of nephrotoxicity with concurrent use with contrast media.[18]

GLP-1 RAs

Incretins are responsible for up to 70% of insulin secretion after oral glucose intake.[19] As incretin mimetics, GLP-1 RAs bind and activate GLP-1 receptors, which increases glucose-dependent insulin synthesis and secretion from pancreatic beta cells, and suppresses glucagon secretion. GLP-1 RAs further slow gastric emptying, and they promote satiety and beta-cell proliferation.[20] Seven GLP-1 RAs are currently on in the U.S. market, including exenatide immediate-release (Byetta, AstraZeneca), exenatide extended-release (Bydureon, AstraZeneca), albiglutide (Tanzeum, GlaxoSmithKline), dulaglutide (Trulicity, Eli Lilly), liraglutide, lixisenatide (Adlyxin, Sanofi-Aventis US), and semaglutide (Ozempic, Novo Nordisk). They differ in preparation of the injection device, reconstitution, frequency of administration, severity of side effects, and dosing requirements for renally impaired patients. All GLP-1 RAs are subcutaneous injections that lower HbA_{1c} by up to 1.5%. The effects on postprandial hyperglycemia with GLP-1 RAs are more pronounced with the once- or twice-daily formulations, whereas once-weekly formulations cause a greater reduction in fasting glucose levels.[20]

Common adverse effects include nausea, vomiting, and diarrhea but can subside or cease over time. Post-marketing data suggest that pancreatitis and acute renal impairment or failure can occur. Thus, patients who have a history of pancreatitis, severe GI disorders such as gastroparesis, a familial/personal history of medullary thyroid carcinoma, or unstable renal dysfunction should use these agents with extreme caution or avoid them. In particular, patients with a creatinine clearance (CrCL) of less than 30 mL/min should avoid exenatide and lixisenatide; however, no renal impairment dosage adjustment is necessary with albiglutide, liraglutide, dulaglutide, or semaglutide.[21–26] When patients develop severe vomiting, gastroesophageal reflux disease, or significant unintentional weight loss, alternative regimens should be considered because there have been reports of intestinal obstruction, according to the European Medicines Agency.[27]

Liraglutide was shown to provide CV benefits in the LEADER trial, published in 2016.[28] In the trial, 9,340 patients with T2DM, including patients with high CV risk, were randomized to receive liraglutide or placebo, with a median follow-up of 3.8 years. Liraglutide was associated with a significant reduction in CV mortality. The trial also found lower rates, although nonsignificant, for nonfatal MI and nonfatal stroke.[28] An earlier trial, ELIXA, focused on lixisenatide in the first CV outcome trial reported with a GLP-1 RA.[29] The trial found no increased risk of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. However, there was no indication of any particular CV benefit. Additional details on the use of GLP-1 RAs and the impact on CVD can be found in the *Cardiovascular Outcomes* section below.

As a brand-only pharmacological class with per-unit costs ranging upwards of $600 (Table 3), GLP-1 RAs offer effective HbA_{1c} lowering, CV benefits with specific agents, and modest weight loss due to effective slowing of gastric emptying and improved insulin activity.[30,31] The FDA continues to approve new agents in this class (most recently semaglutide), along with improved devices intended to ease preparation and administration.[32–34] A once-monthly GLP-1 RA may also be in the pipeline.[35] As competition in this class continues to grow, one manufacturer has announced that albiglutide (Tanzeum) will be discontinued by July 2018.[36] GLP-1 RAs may be practical for patients who have maximized oral regimens and/or insulin to help reduce pill burden and insulin requirements, and who prefer the possibility of administering once-weekly regimens.

DPP-4 Inhibitors

DPP-4 inhibitors prolong the activity of endogenous GLP-1 and gastric inhibitory peptide in the GI tract to slow gastric emptying and stimulate insulin release from pancreatic cells in response to glucose. Sitagliptin (Januvia, Merck), saxagliptin (Onglyza, AstraZeneca), linagliptin (Tradjenta, Boehringer Ingelheim), and alogliptin are available as individual agents and in combination with other T2DM treatments. Studies show these medications can lower HbA_{1c} by approximately 0.75%.[12] Common side effects include headache, sinus infections, nasopharyngitis, upper respiratory tract infections, and GI upset. Rare side effects include pancreatitis, hepatic dysfunction, skin rash, and musculoskeletal effects.[37–40]

In 2016, the FDA recommended against the use of saxagliptin and alogliptin in patients with HF.[41] The SAVOR-TIMI 53 trial found an increased risk of HF hospitalization with saxagliptin versus placebo.[42] This was noted in patients with risk of or pre-existing HF and CKD. However, two cohort studies showed that HF risk with DPP-4 inhibitors is not greater than other medication classes linked to HF (thiazolidinediones, sulfonylureas).[43,44] Based on available evidence, caution is recommended in the use of DPP-4 inhibitors (saxagliptin and alogliptin) in patients with pre-existing HF.

In patients with CKD, linagliptin is the recommended DPP-4 inhibitor because it is not eliminated renally.[45] In one study, patients 18 to 80 years of age with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) had significantly improved HbA_{1c} levels after 12 weeks and continued improvements over one year. This finding makes linagliptin an option for clinicians to treat patients with diabetes and CKD initially and after other treatment options have failed.[46] In addition, DPP-4 inhibitors can be used as monotherapy in patients intolerant of metformin or with high risk of hypoglycemia.

Although there have been no active-comparator studies among the DPP-4 inhibitors, HbA_{1c} lowering is relatively comparable among them. Alogliptin became the first generic available in this class in 2016. The cost savings (approximately half the price of DPP-4 brands) may help increase its market share with improved cost-effectiveness. The three brand-only products have average wholesale prices (AWPs) around $440, while generic alogliptin costs around $230 (Table 3).[31]

Table 3 Summary of FDA-Approved Medications for Use in Patients With Type-2 Diabetes[31]

Class	Generic Name	Trade Name	Formulation Availability	Unit (Package Size)	AWP/Unit†
Biguanide	Metformin*	Glucophage (Bristol-Myers Squibb)/ Fortamet (Andrx Labs LLC)	IR/XR tablets	500, 750, 850, 1,000 mg (100)	$0.70–2.44
		Riomet	Suspension	500 mg/5 mL (473 mL)	$1.56
GLP-1 Agonists	Exenatide	Byetta/Bydureon Pen/Bcise (AstraZeneca), single-dose tray	IR/XR SQ pen/vial	250 mcg, 2 mg, (1.2–2.4 mL) (4s)	$198.05–708.38
	Liraglutide	Victoza (Novo Nordisk)	SQ pen	6 mg/mL, 3 mL (3s)	$107.56
	Dulaglutide	Trulicity (Eli Lilly and Co.)	SQ pen	0.75, 1.5 mg/0.5 mL (4s)	$438.12
	Abiglutide	Tanzeum (GlaxoSmithKline)	SQ pen	30, 50 mg (4s)	$156.60
	Lixisenatide	Adlyxin (Sanofi-Aventis US)	SQ pen	100 mcg/mL, 3 mL (2s)	$117.90
	Semaglutide	Ozempic (Novo Nordisk)	SQ Pen	2 mg, 1.5 mL (2s)	$270.4–540.80
DPP-4 Inhibitors	Alogliptin*	Nesina (Takeda)	Tablets	6.25, 12.5, 25 mg (30)	$7.80
	Linagliptin	Tradjenta (Boehringer Ingelheim)	Tablets	5 mg (30)	$16.46
	Saxagliptin	Onglyza (AstraZeneca)	Tablets	2.5, 5 mg (30)	$16.33
	Sitagliptin	Januvia (Merck)	Tablets	25, 50, 100 mg (30)	$17.18
SGLT2s	Canagliflozin	Invokana (Janssen)	Tablets	100, 300 mg (30)	$18.58
	Dapagliflozin	Farxiga (AstraZeneca)	Tablets	5, 10 mg (30)	$18.58
	Empagliflozin	Jardiance (Boehringer Ingelheim)	Tablets	10, 25 mg (30)	$18.60
	Ertugliflozin	Steglatro (Merck)	Tablets	5, 15 mg (30)	$10.73
Secretagogues	Glipizide*	Glucotrol (Pfizer)	IR/XR tablets	2.5, 5, 10 mg (100)	$0.41–0.81
	Glyburide*	Glynase (Pharmacia and Upjohn)	IR/micronized	1.25, 1.5, 2.5, 3, 5, 6 mg (100)	$0.28–1.08
	Glimeperide*	Amaryl (Sanofi-Aventis US)	Tablets	1, 2, 4 mg (100)	$0.40–1.23
	Nateglinide*	Starlix (Novartis)	Tablets	60, 120 mg (100)	$1.66–1.73
	Repaglinide*	Prandin (Gemini Labs)	Tablets	0.5, 1, 2 mg (100)	$3.33–3.66
	Pramlintide	SymlinPen (AstraZeneca)	SQ pen	1,000 mcg/mL, 1.5–2.7 mL (2s)	$235.81–$357.44
Thiazolidinediones	Rosiglitazone	Avandia (GlaxoSmithKline)	Tablets	2, 4 mg (30)	$6.78
	Pioglitazone*	Actos (Takeda)	Tablets	15, 30, 45 mg (30)	$7.01–11.62
Insulin	Glargine	Basaglar (Eli Lilly and Co.)	SQ pen	100 units/mL, 3mL (5s)	$26.11
	Inhaled human insulin	Afrezza (MannKind)	Aerosol	4, 8, 12 units (90)	$3.64–10.93
	Lispro	Humalog/Junior (Lilly)	SQ vial/pen	100, 200 units/mL, 3–10 mL (3–5s)	$32.96–84.86
	Lispro	Admelog (Sanofi-Aventis US)	SQ vial/pen	100 units/mL, 3–10 mL (5s)	$28.02–36.07
	Lispro protamine/lispro	Humalog 50/50 (Lilly)	SQ vial/pen	50 units/mL, 3–110 mL (5s)	$34.16–42.43
	Lispro protamine/lispro	Humalog 75/25 (Lilly)	SQ vial/pen	75–25 units/mL, 3–10 mL (5s)	$34.16–42.43
	Regular	Humulin R (Lilly)	SQ vial	100 units/mL, 3–10 mL	$17.84
	Regular	Humulin R U500 (Lilly)	SQ vial/pen	500 units/mL, 3–20 mL (2s)	$89.22–114.84

† Price per unit provided for generic formulation, if available. * Available as generic.
AWP = average wholesale price; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; IR = immediate release; s = syringes; SGLT2 = sodium-glucose cotransporter 2; SQ = subcutaneous; XR = extended release.

table continues

Table 3 Summary of FDA-Approved Medications for Use in Patients With Type-2 Diabetes[31] (continued)

Class	Generic Name	Brand Name (Manufacturer)	Formulation Availability	Unit (Package Size)	AWP/Unit†
Insulin	Isophane/regular	Humulin 70/30 (Lilly)	SQ vial/pen	70-30 units/mL, 3–10 mL (5s)	$17.84–37.70
	Isophane	Humulin NPH (Lilly)	SQ vial/pen	100 units/mL, 3–10 mL (5s)	$17.84–37.70
	Glargine	Lantus (Sanofi-Aventis US)	SQ vial/pen	100 units/mL, 3–10 mL (5s)	$30.72
	Detemir	Levemir (Novo Nordisk)	SQ vial/pen	100 units/mL, 3–10 mL (5s)	$33.57
	Isophane/regular	Novolin 70/30 (Novo Nordisk)	SQ vial	100 units/mL, 10 mL	$16.52
	Isophane	Novolin N (Novo Nordisk)	SQ vial	100 units/mL, 10 mL	$16.52
	Regular	Novolin R (Novo Nordisk)	SQ vial	100 units/mL, 10 mL	$16.52
	Aspart	Novolog (Novo Nordisk)	SQ vial/pen	100 units/mL, 3–10 mL (5s)	$33.07–42.58
	Aspart protamine/ aspart	Novolog 70/30 (Novo Nordisk)	SQ vial/pen	70-30 units/mL, 3–10 mL (5s)	$34.30–42.58
	Glargine	Toujeo (Sanofi-Aventis US)	SQ pen	300 units/mL, 1.5 mL (3s)	$94.29
	Degludec	Tresiba (Novo Nordisk)	SQ pen	100, 200 units/mL, 3 mL (5s)	$36.93–73.86
Combination injectables	Degludec/liraglutide	Xultophy (Novo Nordisk)	SQ pen	100 units, 3.6 mg/mL, 3mL (5s)	$79.30
	Glargine/lixisenatide	Soliqua (Sanofi-Aventis US)	SQ pen	100 units, 33 mcg/mL, 3mL (5s)	$57.75
Alternative agents	Acarbose*	Precose (Bayer Healthcare)	Tablets	25, 50, 100 mg (100)	$0.90–1.17
	Bromocriptine	Cycloset (Veroscience)	Tablets	0.8 mg (200)	$4.75
	Colesevelam	Welchol (Daiichi Sankyo)	Tablets	625 mg (180)	$4.16

† Price per unit provided for generic formulation, if available. * Available as generic.
AWP = average wholesale price; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; IR = immediate release; s = syringes; SGLT2 = sodium-glucose cotransporter 2; SQ = subcutaneous; XR = extended release.

SGLT2 Inhibitors

As the most recent class of novel antidiabetes agents, SGLT2 inhibitors—canagliflozin (Invokana, Janssen), dapagliflozin (Farxiga, AstraZeneca), empagliflozin, and ertugliflozin (Steglatro, Merck)—are available only as brands and cost more than generic oral agents (Table 3).[31] However, adding an SGLT2 inhibitor to existing oral antihyperglycemic agents may potentially result in lower direct and indirect drug costs associated with nonadherence when compared to adding injectable agents such as GLP-1 RAs, particularly in patients with a needle phobia. SGLT2 inhibitors facilitate glucose excretion rather than reabsorption. Because SGLT2 inhibitor transporters are glucose-dependent, these medications lower the renal glucose threshold to promote greater glucose excretion.[47] With an effective HbA_{1c} reduction of approximately 1.1%, SGLT2 inhibitors can also promote weight loss of 2 to 3 pounds.[48] Patients with elevated blood pressure may experience additional benefits from an SGLT2 inhibitor. One meta-analysis determined that systolic blood pressure can be lowered by 2 mm Hg in one year and 7 mm Hg in two years. Diastolic blood pressure can be lowered by two to three points in one to two years, respectively.[48]

CV outcomes studies have been published for agents in this class. Empagliflozin was linked to a reduction in CV mortality, overall mortality, and hospitalization due to HF in patients with pre-existing CVD.[49] Most recently, CV outcomes data for canagliflozin were published from the CANVAS trial, which assessed canagliflozin in more than 10,000 patients with T2DM who had either a prior history of CVD or at least two CV risk factors.[50] The results showed canagliflozin reduced the overall risk of CVD and the risk of HF hospitalization. The trial also demonstrated potential renal protective effects for canagliflozin, but it indicated an increased risk of amputation in patients treated with canagliflozin compared with placebo.

Given that the pharmacological effect of these agents takes place primarily in the nephron, renal function should be monitored to avoid worsening adverse effects. Thus, SGLT2 inhibitors tend to have stricter renal dosing criteria (avoid initiation with dapagliflozin in patients with an eGFR less than 60 mL/min/1.73 m^2), whereas DPP-4 inhibitors and GLP-1 RAs

allow for renal dose reductions in patients with an eGFR as low as 30 mL/min/1.73 m^2, are preferred for use in patients with renal insufficiency (linagliptin), or can be used in patients with end-stage renal disease (semaglutide).[3,26,38,51] SGLT2 inhibitor use is contraindicated in patients with severe renal impairment. Common adverse effects of SGLT2 inhibitors include development of urinary tract infections (UTI), dehydration, hypotension, or reduced bone density.[47] The FDA has also published safety alerts regarding risk of acute kidney injury, increased rate of amputations, risk of euglycemic diabetic ketoacidosis, and risk of hospitalization from UTIs.[51–54] In May 2017, the FDA added a boxed warning to canagliflozin about the increased risk of leg and foot amputations. A mechanism of action resulting in combined natriuresis and volume contraction in patients on both thiazide diuretics and SGLT2 inhibitors has been theorized.[55] Although it is not an overall class effect, precautions are justified when SGLT2 inhibitors are used in patients with a history of prior amputations, peripheral vascular disease, neuropathy, or diabetic foot ulcers.

Select Insulin Therapy

Insulin therapy should be considered when glycemic control is not otherwise achieved by pharmacotherapy, when HbA_{1c} is greater than 9% according to the AACE consensus statements previously discussed, or when other agents are contraindicated in special populations, such as patients with renal failure, on dialysis, or with critical illnesses. Human insulins range from rapid to intermediate to long-acting in pharmacokinetic duration.[56] However, recent developments in long-acting basal and concentrated insulins have improved safety, addressed highly insulin-resistant patients, and minimized glucose fluctuations. Two brands of insulin glargine are available in the U.S., Basaglar (Eli Lilly) and Lantus (Sanofi-Aventis US). Basaglar was found to be noninferior to comparator insulin glargine 100 units/mL at 24 weeks for mean reduction in HbA_{1c} for both type-1 and type-2 diabetes.[7] Basaglar and Lantus are not interchangeable, however, and their AWPs differ slightly (Table 3).[31,57,58]

A newer molecular agent, insulin degludec (Tresiba, Novo Nordisk), was approved in 2015 as a basal insulin made of multihexamers that provide a half-life of 25 hours and a long duration of action of at least 42 hours after eight once-daily injections. Compared with insulin glargine (U100), insulin degludec (U100 and U200) reduces HbA_{1c} from baseline comparably, with lower rates of nocturnal hypoglycemia.[59] Furthermore, prespecified and adjudicated severe hypoglycemia occurred significantly less in the degludec group compared with the glargine group in one study.[60] Insulin degludec may fill a clinical niche for patients who remain uncontrolled on current basal insulin therapy despite titrations resulting in fluctuating glucose levels (due to unpredictable meal or work schedules) or who experience nocturnal hypoglycemia. Insulin degludec may also provide a more flexible dosing schedule that does not result in insulin stacking.[61] Similarly, concentrated insulin glargine U300 showed comparable HbA_{1c} reductions with consistently less nocturnal hypoglycemia risk compared with insulin glargine U100.[62] In addition, patients using concentrated insulin glargine U300 used less overall basal insulin compared with insulin glargine U100. There are, however, no active-comparator trials between concentrated insulin glargine U300 and insulin degludec U200.

For patients who are highly insulin resistant and require a total daily insulin dose of 200 units or more, the addition of a concentrated U500 regular insulin is available in a safer, convenient pen device using an alternative Kwikpen technology.[63] Historically, administration of U500 regular insulin involved detailed instructions for appropriately calculating, prescribing, and administering the concentrated insulin with tuberculin syringes. Syringes are now available that are specially made for U500. The KwikPen offers a safer alternative for patients to self-administer regular insulin U500 and for providers to prescribe in units rather than converting to milliliters.[64]

ALTERNATIVE AGENTS

Alternative pharmacological classes for glycemic control include TZDs, alpha-glucosidase inhibitors, dopamine agonists, bile acid sequestrants, and amylin analogues. While typically less expensive, they are less effective in lowering HbA_{1c} and are not as well tolerated (Table 3).[31] The AACE consensus statements place alpha-glucosidase inhibitors among second-line options, while bromocriptine (Cycloset, Salix Pharmaceuticals), pramlintide (Symlin, AstraZeneca), and colesevelam (Welchol, Daiichi Sankyo, Inc.) are reserved as last-line options. The ADA does not include these agents in its pharmacological approaches to glycemic treatment as monotherapy, dual therapy, or triple therapy.[3]

TZDs/Glitazones

Oral pioglitazone and rosiglitazone agonize the peroxisome proliferator-activated receptor, which regulates the transcription of insulin-responsive genes, thus enhancing insulin sensitivity in adipose tissue, skeletal muscle, and the liver to help decrease plasma glucose, insulin, and ultimately HbA_{1c} by 1% to 1.25%. Additional effects include decreased hepatic glucose output and improved lipid profiles.[6]

Pioglitazone has not been shown clearly to improve clinically relevant outcomes but may reduce the risk of MI and stroke. TZDs are not generally recommended as a drug of choice due to notable adverse effects, such as peripheral edema, weight gain, bone fracture risk in postmenopausal women and elderly men, and increased risk of HF compared with sulfonylureas.[65,66] With boxed warnings for risk of HF, patients with unstable HF and a history of MI should avoid use, particularly rosiglitazone. Pioglitazone has also been associated, controversially, with increased risk of bladder cancer when used for more than one year. Thus, patients who have ruled out other alternative agents, are younger, or have few or no comorbidities with high insulin resistance may consider TZDs as optional oral agents to help improve insulin sensitivity.[3,8,65–67]

Alpha-Glucosidase Inhibitors

The alpha-glucosidase inhibitors acarbose and miglitol delay glucose absorption in the GI system by inhibiting alpha-glucosidase enzymes that cause carbohydrate breakdown and absorption, resulting in an HbA_{1c} reduction up to 0.5%.[68,69] The challenge of multiple daily administrations of acarbose or miglitol results in potentially lower adherence rates. In addition, the most common adverse effects are GI-related, including diarrhea, abdominal pain, and flatulence, which can be self-limiting. Therefore, it is important to avoid alpha-glucosidase inhibitors in patients with inflammatory bowel diseases and a

history of ulceration or obstruction. These medications also have a risk of hypoglycemia when used as part of dual or triple therapy.[70] Other than the unpleasant side effect profile, alpha-glucosidase inhibitors are most beneficial for patients with prediabetes who require additional postprandial control, with studies showing a reduction in CV risk.[71]

Dopamine Agonist

Bromocriptine, a dopamine agonist available as brand-only for T2DM-approved dosing of 0.8 mg, is typically used at higher doses to treat patients with Parkinson's disease or hyperprolactinemia. In diabetes, it is used to lower glucose by regulating circadian rhythm pathways that facilitate glucose utilization.[72,73] The most common side effects are dizziness, nausea, vomiting, and headache. The doses used for diabetes are lower than those used for Parkinson's disease: 1.6–4.8 mg versus 2.5–100 mg daily. When investigated for use in T2DM patients, bromocriptine demonstrated less CV risk than placebo.[74]

Bile Acid Sequestrant

Colesevelam, a bile acid sequestrant, is typically used to lower cholesterol. In diabetes, it is used to reduce absorption of glucose in the stomach and small intestine, potentially lowering HbA_{1c} by 0.5%. Colesevelam is under patent with no generic formulation available, making it more expensive and less effective compared with other oral agents.[75,76] The most common adverse effects are constipation, nausea, and vomiting. The side effects and lack of efficacy result in colesevelam being reserved for use as a third-line or last-line option. It also increases triglycerides through its activity on cholesterol. It should be avoided in patients with hypertriglyceridemia or familial cholesterol disorders.[77] Colesevelam is helpful for patients with diabetes who are already taking it for hyperlipidemia because of its glucose-lowering activity.

Amylin Analogue

Pramlintide, the first approved hormone analogue to have activity in the GI tract, is a synthetic amylin analogue that reduces gastric emptying, lowers glucose absorption, and decreases glucagon release; it promotes slight weight loss.[77] It is used at mealtimes along with insulin in patients with T1DM or T2DM to reduce postprandial glucose levels and reduce HbA_{1c} by approximately 0.4%.[78] Pramlintide offers an alternative option for patients already on mealtime insulin who do not tolerate GLP-1 RAs and other oral therapies but are at or near HbA_{1c} goals. It is available as brand-only and is formulated in a pen device to allow for easier administration.[79] Along with common adverse effects of hypoglycemia, nausea, and vomiting, pramlintide should not be used in patients with gastroparesis because it further delays gastric emptying.

Insulin Secretagogues: Sulfonylureas and Meglitinides

Sulfonylureas (glyburide, glipizide, and glimepiride) lower blood glucose by stimulating pancreatic islet cells to secrete insulin. As insulin secretagogues, they have been shown to reduce HbA_{1c} by 1% to 2%. Prolonged administration of sulfonylureas produces extrapancreatic effects that contribute to hypoglycemic activity, inducing reduction of basal hepatic glucose production and enhanced peripheral sensitivity to insulin receptors that can vary with potency among patients with T2DM. Their effect has been found to deteriorate in response to glucose after 12 to 18 months of chronic administration.[80,81] Treatment initiation with a sulfonylurea is associated with an increased risk of CV events (coronary heart disease, HF, unstable angina, ischemic stroke, acute MI, or revascularization procedure) compared with metformin.[82] Sulfonylurea utilization has been trending lower due to declining efficacy in long-term use, unfavorable adverse effects of weight gain and risk of hypoglycemia, and lack of CV benefit compared with other antidiabetes agents.

Similarly, meglitinides (nateglinide and repaglinide) increase insulin secretion while reducing postprandial glucose levels. Meglitinides offer a modest HbA_{1c}-lowering effect, but patient adherence may be challenging due to the frequent dosing schedule. Both meglitinides and sulfonylureas result in a higher incidence of hypoglycemia and weight gain.[3]

Even though insulin secretagogues cost much less than other agents (Table 3), their lack of efficacy and lack of long-term CV outcome improvements have limited their roles. Sulfonylureas in particular have sparked caution in patients with underlying CVD and HF. If they are used, agents with a short duration of action, such as glipizide, are preferred.[3] Furthermore, utilization of these agents should be reserved for patients who can recognize and self-manage hypoglycemic episodes, who have a consistently scheduled diet, and who are not at high fall risk given the possibility of hypoglycemia.[3]

Basal Insulin Combination Agents

A new subclass of agents that combines long-acting insulin with a GLP-1 RA recently received FDA approval. Two are now available on the market: insulin glargine combined with lixisenatide (Soliqua 100/33, Sanofi-Aventis US) and insulin degludec combined with liraglutide (Xultophy 100/3.6, Novo Nordisk), which are indicated as an adjunct to diet and exercise in adults who remain uncontrolled on basal insulin. Criteria for initiation require a maximum total daily dose of basal insulin: no more than 50 units and no more than 60 units for degludec/liraglutide and glargine/lixisenatide, respectively.[83,84] In clinical trials, these agents demonstrated significant HbA_{1c} reductions (1.6% to 1.9% for degludec/liraglutide and 1.1% to 1.6% for glargine/lixisenatide).[85–90] Studies also demonstrated weight reductions of approximately 2 kg.[85–90] The most common adverse effect for both agents is hypoglycemia.[83,84] GLP-1 RAs alone commonly cause nausea, but combining them with long-acting basal insulin decreased the incidence of nausea. This may be due to slower titration of the GLP-1 RA component in combination with the long-acting insulin component.[83–85,89] These agents carry the same warnings as the individual GLP-1 RA components, including risk of thyroid carcinoma (insulin degludec combined with liraglutide), pancreatitis (both agents), and gastroparesis (both agents).[83,84] Clinically speaking, these agents are very easy to start for insulin-naïve patients and a good option for those needing pre- and postprandial coverage without four injections per day. They may prove to be more challenging for patients already established on insulin therapy because of the titration needed when initiating GLP-1 RA therapy due to nausea and other GI side effects. A provider may be able to try one month of a GLP-1 RA separately with appropriate titration for a patient already on insulin prior to switching to the combination.

Table 4 Summary of Effects for Select Type-2 Diabetes Medications

Generic Name (Brand Name, Manufacturer)	% A1c Reduction[12]	Postprandial/ Fasting Effects[4]	Notes	Precautions/ Contraindications
Dipeptidyl Peptidase-4 Inhibitors[37–40]				
Alogliptin (Nesina, Takeda)	0.5–1%	Postprandial	• Daily dosing • Weight neutral • Alogliptin available as generic • Saxagliptin may worsen heart failure • Linagliptin requires no renal dose reduction	• Pancreatitis • Type-1 diabetes • Diabetic ketoacidosis
Linagliptin (Tradjenta, Boehringer Ingelheim)				
Saxagliptin (Onglyza, AstraZeneca)				
Sitagliptin (Januvia, Merck)				
Sodium-Glucose Cotransporter 2 Inhibitors[31,51,53,54]				
Canagliflozin (Invokana, Janssen)	0.8–1.2%	Mixed	• Daily dosing • Weight loss • Empagliflozin has new cardiovascular data	• Hypersensitivity • Type-1 diabetes • Diabetic ketoacidosis • Canagliflozin: leg and foot amputations • Bone mineral density loss • Dapagliflozin: risk of bladder cancer
Dapagliflozin (Farxiga, AstraZeneca)				
Empagliflozin (Jardiance, Boehringer Ingelheim)				
Ertugliflozin (Steglatro, Merck)				
Glucagon-Like Peptide-1 Receptor Agonists[21–26,36,96]				
Exenatide (Byetta, AstraZeneca)	0.6–1.2%	Mixed (Byetta is primarily postprandial)	• Daily (Byetta, Victoza, Adlyxin) or weekly (Bydureon, Tanzeum, Trulicity, Ozempic) dosing • Weight loss	• Gastroparesis • Pancreatitis • History of medullary thyroid carcinoma
Exenatide XR (Bydureon, AstraZeneca)				
Liraglutide (Victoza, Novo Nordisk)				
Albiglutide (Tanzeum, GlaxoSmithKline)				
Dulaglutide (Trulicity, Eli Lilly and Co.)				
Lixisenatide (Adlyxin, Sanofi-Aventis US)				
Semaglutide (Ozempic, Novo Nordisk)				
Combination Glucagon-Like Peptide-1 Receptor Agonists and Insulin[83,84]				
Liraglutide/Insulin degludec (Xultophy, Novo Nordisk)	0.6–2.1%	Mixed	• Daily dosing • Weight neutral	• Hypoglycemia • Hypersensitivity • Hypokalemia • Fluid retention
Lixisenatide/Insulin glargine (Soliqua, Sanofi-Aventis US)				

Perhaps the best use of these agents is to target patients who are not controlled on a GLP-1 RA and/or basal insulin (at less than 50 or 60 units per day depending on the agent, as noted above) and who are reluctant to start additional injections. If a patient is already taking one of the two components of these agents and needs additional therapy, the combinations can offer cost-savings of approximately 20% compared to use of each agent separately.

A summary of select oral and combination agents and their pharmacological effects can be found in Table 4.

CARDIOVASCULAR OUTCOMES

The pathophysiology of T2DM is complex and associated with an increased risk of CVD. Because of this, with so many agents that can be utilized to manage T2DM, it is important to consider which agents will contribute to increased risk or potentially improve the CV risk associated with T2DM. MI and stroke account for 80% of deaths associated with T2DM. Previous studies have reported that metformin improves CV outcomes compared with sulfonylureas; however, evidence is limited to subgroup analyses and observational trials. Proposed

mechanisms for the potential protective effect of metformin include improved glucose control, reduction in methylglyoxal levels, decrease in very-low-density lipoprotein secretion and plasma triglyceride levels, and reduced postprandial lipemia.[90]

While most studies show an increased risk of CVD with TZDs, rosiglitazone and pioglitazone have been shown to improve diastolic dysfunction, to enhance myocardial insulin sensitivity, and to be neutral to left ventricular (LV) function.[91] A systematic review of the literature suggests that pioglitazone may slow the progression of atherogenesis and reduce CV events.[90] Retrospective studies of DPP-4 inhibitors suggest a reduction in CV events. Both SAVOR-TIMI (saxagliptin) and EXAMINE (alogliptin) were prospective studies that did not show this; however, both had very short treatment periods (1.5–2.1 years).[42,92] The TECOS study (duration, three years) showed that sitagliptin, among patients with T2DM and established CVD, did not appear to increase the risk of major adverse CV events, hospitalization for HF, or other adverse events. This prospective study also did not show a reduction in CV events.[93] The linagliptin (CAROLINA) study is still ongoing to assess its impact on CV outcomes.[94]

GLP-1 RAs and SGLT2 inhibitors have shown promising roles in diabetes and CV risk reduction. These benefits have earned them classification as second- and third-line agents, according to the AACE algorithm.[8] In preclinical studies, GLP-1 RAs were shown to improve glucose utilization and increase LV contractility, stroke volume, and cardiac output. Other preclinical and clinical studies have shown various outcomes, such as decreases in infarct size and myocardial wall thickening, and improved LV output, LV ejection fraction, maximal ventilation oxygen consumption, and six-minute walking distances. GLP-1 RAs have also been shown to decrease inflammatory markers.[90] Among the clinical CV outcomes trials of GLP-1 RAs, LEADER (liraglutide), SUSTAIN-6 (semaglutide), ELIXA (lixisenatide), and EXSCEL (exenatide) have been reported.[95–98] The trial populations, follow-up, outcomes, and number needed to treat can be found in Table 5. The REWIND (dulaglutide) and LYDIA (liraglutide) trials are ongoing.[99–101]

A recent publication described a large retrospective cohort (N = 105,862) from a large health system. A time-dependent Cox multiple regression analysis was used to assess the association between GLP-1 RA exposure and risk of acute MI, stroke/cerebrovascular accident (CVA), and overall mortality, as well as the composite of all three outcomes. There were significantly lower rates of acute MI (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.65–0.99; $P = 0.045$), CVA (HR, 0.82; 95% CI, 0.74–0.91; $P < 0.001$), overall mortality (HR, 0.48; 95% CI, 0.41–0.57; $P < 0.001$), and the composite outcome (HR, 0.82; 95% CI, 0.74–0.91; $P < 0.002$) during the consolidated time that patients were exposed to GLP-1 RAs compared with corresponding rates during intervals without GLP-1 RA exposure. GLP-1 RAs were associated with a significant decrease in CVA, mortality, and the composite outcome in patients with and without established CVD, not significantly affecting acute MI in these subgroups, after adjusting for potential confounders.[102]

Recently, much excitement and discussion have surrounded CV risk reduction with SGLT2 inhibitors. It is well described that these agents address other CV risk factors such as blood pressure (reductions in systolic blood pressure of up to 6 mm Hg), weight, and glucose control. Along with blocking glucose reabsorption, SGLT2 inhibitors reduce protein and sodium reabsorption in the nephron that results in osmotic diuresis, milder than specific diuretic agents. This loss of fluid volume activates the renin–angiotensin–aldosterone system and starts a counter-regulatory response to maintain homeostasis. SGLT2 inhibitors have documented benefits for reducing preload and afterload work on the heart.[103]

Despite the potential for SGLT2 inhibitors to cause a small, dose-related increase in LDL-C, sometimes accompanied by an increase in HDL-C, there are no CV outcomes trials at this time demonstrating that LDL-C increases by these agents translate into an increase in real-life CV events. SGLT2 inhibitors have been shown in multiple trials to have a positive benefit on CVD while helping to lower blood pressure.[49] The exact mechanism by which this occurs is not fully described. It is hypothesized that the SGLT2 inhibitor mechanism of action in relation to CVD also involves a reduction in glucose variability, uric acid levels, and urinary albumin excretion. Recent studies suggest SGLT2 inhibitors can reduce the rate of GFR decline in patients with diabetic nephropathy, and more will be learned as renal outcomes are published from ongoing trials.[104,105] Although pleiotropic effects have been inferred, improved glycemic control, lowering of blood pressure, decreases in intraglomerular pressure, reductions in albuminuria, and amelioration of volume overload are all plausible renoprotective mechanisms.[50]

EMPA-REG (empagliflozin) was the first CV outcomes trial published with an SGLT2 inhibitor and was recently followed by the CANVAS (canagliflozin) trial.[49,50] One major difference in CANVAS was the inclusion criteria. CANVAS enrolled patients without existing CVD but at risk for CVD, who accounted for 34.4% of patients—thus forming a primary prevention and secondary prevention population. This broader population likely influenced the higher number needed to treat. The main results are shown in Table 6. In CANVAS, adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 versus 3.4 participants per 1,000 patient-years; HR, 1.97; 95% CI, 1.41–2.75); amputations were primarily at the level of the toe or metatarsal.

DISCUSSION

Outside of the limitless HbA_{1c} reductions with insulin due to the ability to titrate to needed effect, the greatest HbA_{1c}-lowering effects are seen with metformin and secretagogues. These agents are inexpensive compared with other antihyperglycemic options. Metformin is considered first-line for management of T2DM based on durability, minimal risk for hypoglycemia, potential for weight loss, potential benefit on macrovascular events, and expanded use in patients with renal dysfunction.[3,8] However, secretagogues have fallen out of favor as part of dual- and triple-therapy regimens due to their limited durability, risk of hypoglycemia, potential for weight gain, and uncertainty for CV harm.[8]

As described earlier, the AACE consensus statements and ADA guidelines consider a variety of characteristics when deciding in what order to consider antihyperglycemic agents if metformin cannot be used as monotherapy or added to another regimen.[4,9] After metformin, the AACE consensus statements

Table 5 Glucagon-Like Peptide-1 Receptor Agonist Trials: Cardiovascular Outcomes

Patients Included	Median Follow-Up	Primary Results	Secondary Results	NNT (Primary Outcome)
LEADER (liraglutide)[95]				
T2DM patients with established CV disease or CV risk factors	3.8 years	Primary composite outcome in time-to-event analysis—first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke— occurred in significantly fewer liraglutide patients (608/4,668 [13.0%]) than placebo patients (694/4,672 [14.9%]) (HR, 0.87; 95% CI, 0.78–0.97; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority).	Fewer patients died from CV causes in liraglutide group (219 [4.7%]) than placebo group (278 [6.0%]) (HR, 0.78; 95% CI, 0.66–0.93; $P = 0.007$). Rate of death from any cause was lower with liraglutide (381 [8.2%]) than placebo (447 [9.6%]) (HR, 0.85; 95% CI, 0.74–0.97; $P = 0.02$). Rates of nonfatal MI, nonfatal stroke, and HF hospitalization were nonsignificantly lower with liraglutide than placebo.	652
SUSTAIN-6 (semaglutide)[96]				
At baseline, 83.0% had established CV disease, CKD, or both	2.1 years	Primary outcome (three-point MACE: CV death, nonfatal MI, nonfatal stroke) occurred in 108/1,648 patients (6.6%) in semaglutide group and 146/1,649 patients (8.9%) in placebo group (HR, 0.74; 95% CI, 0.58–0.95; $P < 0.001$ for noninferiority). Nonfatal MI occurred in 2.9% of semaglutide patients and 3.9% of placebo patients (HR, 0.74; 95% CI, 0.51–1.08; $P = 0.12$); nonfatal stroke occurred in 1.6% and 2.7%, respectively (HR, 0.61; 95% CI, 0.38–0.99; $P = 0.04$).	Rates of death from CV causes were similar in each group. Rates of new or worsening nephropathy were lower in semaglutide group, but rates of retinopathy complications were significantly higher (HR, 1.76; 95% CI, 1.11–2.78; $P = 0.02$).	43
ELIXA (lixisenatide)[97]				
T2DM with MI or hospitalization for unstable angina in ≤ 180 days	25 months	An event in the primary composite end-point—CV death, MI, stroke, or hospitalization for unstable angina—occurred in 406 patients (13.4%) in lixisenatide group and 399 (13.2%) in placebo group (HR, 1.02; 95% CI, 0.89–1.17). This showed noninferiority of lixisenatide to placebo ($P < 0.001$) but not superiority ($P = 0.81$).	No significant between-group differences in rate of hospitalization for HF (HR, lixisenatide, 0.96; 95% CI, 0.75–1.23) or rate of death (HR, 0.94; 95% CI, 0.78–1.13).	N/A
EXSCEL (exenatide ER)[98]				
T2DM patients with broad range of CV risk	5 years	The primary composite outcome event (three-point MACE: CV death, nonfatal MI, nonfatal stroke) occurred in 839/7,356 patients (11.4%) in exenatide group and 905/7,396 patients (12.2%) in placebo group (HR, 0.91; 95% CI, 0.83–1.00). No difference between groups.	No differences in death from any cause, death from CV causes, fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for HF, or hospitalization for acute coronary syndrome.	N/A

CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; NNT = number needed to treat; T2DM = type-2 diabetes mellitus.

give preference to GLP-1 RAs over all other antihyperglycemic agents due to their ability to lower HbA_{1c}, minimal risk for hypoglycemia, likelihood to result in weight loss, and potential for daily or weekly dosing.[8] In addition, liraglutide has shown potential benefit in patients with established CVD or risk factors, and the ADA has recommended liraglutide should be given preference in patients with "established atherosclerotic cardiovascular disease."[8] According to available cost data and potential CV benefits, liraglutide's once-daily dosing may be preferred among GLP-1 RAs.

The AACE consensus statements list SGLT2 inhibitors as a second option.[8] Although SGLT2 inhibitor lowering of HbA_{1c} may not be as significant as GLP-1 RAs (approximately 1% versus 1.5%), their potential to decrease weight and systolic

Table 6 Sodium-Glucose Cotransporter 2 Inhibitor Trials: Cardiovascular Outcomes

Methodology and Patients	Primary Results	Secondary Results	NNT (Primary Outcome)
EMPA-REG (empagliflozin)[49]			
Multicenter, randomized, double-blind, placebo-controlled, open-label trial in patients with T2DM, high risk for CV events, BMI ≤ 45	The primary outcome (three-point MACE: CV death, nonfatal MI, nonfatal stroke) occurred in 490/4,687 patients (10.5%) in pooled empagliflozin group and 282/2,333 (12.1%) in placebo group (HR, empagliflozin, 0.86; 95% CI, 0.74–0.99; $P = 0.04$ for superiority).	No significant between-group differences in MI or stroke rates, but empagliflozin group had significantly lower rates of death from CV causes (3.7%, vs. 5.9% for placebo; 38% RR reduction), hospitalization for HF (2.7% vs. 4.1%, respectively; 35% RR reduction), and death from any cause (5.7% vs. 8.3%, respectively; 32% RR reduction). Incident or worsening nephropathy occurred in 12.7% of empagliflozin patients and 18.8% of placebo patients (HR, empagliflozin, 0.61; 95% CI, 0.53–0.70; $P < 0.001$). Serum creatinine level doubled in 1.5% of empagliflozin patients and 2.6% of placebo patients (significant RR reduction, 44%).	63
CANVAS (canagliflozin)[50]			
Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with T2DM and history or high risk of CV disease	The rate of the primary outcome (three-point MACE: CV death, nonfatal stroke, and nonfatal MI) was lower with canagliflozin than placebo (26.9 vs. 31.5 participants per 1,000 patient-years; HR, 0.86; 95% CI, 0.75–0.97; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority).	While not statistically significant, results showed a possible benefit of canagliflozin with respect to progression of albuminuria (HR, 0.73; 95% CI, 0.67–0.79) and composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, need for renal-replacement therapy, or death from renal causes (HR, 0.60; 95% CI, 0.47–0.77).	224

BMI = body mass index; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; NNT = number needed to treat; RR = relative risk; T2DM = type-2 diabetes mellitus.

blood pressure as well as inducing minimal hypoglycemia make an SGLT2 inhibitor a preferred choice.[8] In addition, empagliflozin has received an FDA indication for reducing CV death, and the ADA encourages its use in patients with "established atherosclerotic cardiovascular disease."[3,49] Empagliflozin's daily dosing, similar efficacy, and comparable cost to other SGLT2 inhibitors, along with the ability to use it until eGFR falls below 45 mL/min/1.73m^2, make it an option for many patients.

The GLP-1 RAs and SGLT2 inhibitors have specific considerations that restrict their use, but these are established and providers can monitor patients for potential adverse effects. It is important to carefully evaluate the efficacy data associated with these glucose-dependent agents. HbA_{1c} reductions may be higher with real-world utilization given that baseline HbA_{1c} characteristics in most phase 2 and phase 3 clinical trials average approximately 8.5%; this means a maximum reduction difference of approximately 1% to 2% from the mean baseline may be reported. When studies have looked at higher baseline HbA_{1c} levels, there are greater reductions with glucose-dependent agents. For example, in a study comparing canagliflozin to sitagliptin, the higher the patient's HbA_{1c} level in the subgroup, the greater the potential reduction.[106]

DPP-4 inhibitors are another reasonable option to add as second- or third-line therapy.[3,8] Although their effects on HbA_{1c} lowering are approximately 1%, they are weight neutral, cause minimal hypoglycemia, and are generally well tolerated.[3,8] Their once-daily dosing and cost make them a reasonable choice for adjunct therapy, especially in patients who want to avoid an injectable agent.

TZDs are the last class of antihyperglycemic agents with an HbA_{1c} lowering of approximately 1% and a low risk of hypoglycemia.[3,8] Although TZDs are listed as an option for second- or third-line therapy and are available as generics, they are not an ideal addition due to the potential for weight gain and risk for worsening HF, although there is some evidence they may reduce the risk of stroke.[3,8]

Several other antihyperglycemic agents addressed in the 2018 guidelines are not given preferred status and are rarely used even though some cost less than newer agents.[3,8] The other agents have not shown durability in managing diabetes, do not lower HbA_{1c} to the same extent (less than 1%), may have more complicated dosing regimens, and may have less tolerable adverse effects. Unfortunately, these attributes have not been balanced by CV benefits.

Many of the agents discussed are still considered new and cost-efficacy data are lacking, especially in the United States. However, the hope is that decreasing major adverse cardiac events (MACE) will offset the cost of higher-priced newer agents that are not yet available generically. A summary of GLP-1 RA and SGLT2 inhibitor CV data can be found in Tables 5 and 6. Some of these data continue to emerge, including one study from the United Kingdom that investigated MACE

rates when sulfonylureas were added to metformin versus DPP-4 inhibitors added to metformin. MACE events were 39% lower in the DPP-4 inhibitor group, with costs approximating $24,000 per quality-adjusted life-year gained compared with the sulfonylurea group.[107–109]

CONCLUSION

Over the last 10 years, options for blood-glucose management of diabetes, especially for patients with T2DM, have greatly increased. The various agents provide options for dual and triple therapy in combination with metformin and lifestyle changes. With each agent, it is important to consider the potential efficacy (HbA_{1c} lowering) balanced with the risk for hypoglycemia, the potential effects on weight, adverse effects, and cost. More recently, data from CV outcome trials have provided an additional consideration: whether the agents can reduce CV death in patients with T2DM and CVD. Dual therapy with the addition of a GLP-1 RA or an SGLT2 inhibitor as preferred by AACE consensus statements is likely to achieve the desired weight reduction and have potentially greater cardiac risk reduction than other available agents. As additional data are published, the recommendations for preferred agents will continue to adapt.

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