New Therapeutic Strategies for Type 2 Diabetes CME

Ahmad Yehya, M.D.; *Archana R. Sadhu,* M.D.

HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS

ABSTRACT: Pharmacological options for treatment of type 2 diabetes (T2D) have advanced rapidly during the last 10 years, allowing clinicians to target different pathophysiological defects in this disease. There are currently 12 different classes of drugs available to treat T2D. The most exciting development is the demonstration of cardiovascular (CV) benefits from two of these new classes, the glucagon-like peptide-1 receptor agonists (GLP-1 RA) and selective sodium glucose transporter 2 (SGLT2) inhibitors. These drugs have challenged conventional algorithms in the management of T2D by exceeding expectations in cardiovascular outcome trials and demonstrating an unexpected reduction in CV events. This review focuses on the physiologic actions and the CV outcomes associated with dipeptidyl peptidase-4 (DPP-4) inhibitor, GLP-1 RA, and SGLT2 inhibitor use. Understanding their potential may revolutionize our approach to the management of T2D.

NEW THERAPEUTIC STRATEGIES FOR TYPE-2 DIABETES

Incretins are hormones secreted by the enteroendocrine cells in response to meals. The two most important incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Secreted after eating, these two incretins regulate insulin secretion from the beta cells of the islets of Langerhans in the pancreas through a mechanism dependent on the glucose level; on the other hand, they also prevent alpha cells from secreting glucagon.[1] GLP-1 is secreted in response to elevated glucose levels in the lumen of the gastrointestinal tract and stimulates insulin release while inhibiting glucagon secretion.[2,3] In addition, GLP-1 is associated with weight loss because it delays gastric emptying and suppresses appetite.[4] This makes GLP-1 receptor agonists (GLP-1 RA) an ideal therapeutic class for glucose and weight management.

The half-life of natural GLP-1, however, is only about 2 minutes because it is immediately degraded by the enzyme dipeptidyl peptidase-4 (DPP-4); thus, its therapeutic potential is limited in its natural form. DPP-4 inhibitors suppress the DPP-4 enzyme, thereby decreasing clearance and increasing the concentrations of both GLP-1 and GIP. This results in lower fasting and postprandial glucose concentrations due to improved beta-cell responsiveness to prevailing glucose concentrations and suppression of glucagon secretion. Despite increases in active GLP-1 concentrations, DPP-4 inhibitors do not affect gastric emptying and gastric accommodation.[5]

Another novel strategy for lowering blood glucose uses renal physiology. Sodium-glucose cotransporters (SGLT) in the kidney are responsible for mediating glucose reabsorption in the kidney, gut, and heart. Found mainly in the proximal convoluted tubule, SGLT2 greatly mediates kidney glucose reabsorption. Thus, SGLT2 inhibitors prevent the kidneys' reabsorption of glucose proximally, thereby enhancing glucose excretion in the urine and effectively lowering glucose levels in circulation. Since SGLT2 receptors work in a glucose-dependent fashion, a higher glycemic index increases the effect of SGLT2 inhibitors and potentiates glucose lowering regardless of insulin action; hence, there is no relation between the activity of these medications and pancreas beta-cell function. Furthermore, due to the high sodium gradient across the membrane of the proximal convoluted tubule (resulting in a passive diffusion of sodium), glucose is actively transported with sodium by the SGLT2 receptor into the tubular cells and is later passively reabsorbed.[6-8] Moreover, in addition to being hypoglycemic agents, SGLT2 inhibitors have recently been described as potential weight-loss agents and have also demonstrated blood-pressure–lowering effects through osmotic diuresis.[9] This may be the mechanism by which SGLT2 inhibitors improve cardiovascular (CV) physiology and reduce CV events.

CARDIOVASCULAR OUTCOMES TRIALS

In 2008, the U.S. Food and Drug Administration (FDA) determined that new diabetes medications being tested in clinical trials should not be associated with increased CV events. Specifically, it mandated that novel drugs should initially demonstrate noninferiority versus placebo, and once this criterion is met, superiority trials can then be conducted.[4,10] This resulted in a series of cardiovascular outcome trials (CVOTs) evaluating the effects of potential therapies for T2D.

DPP-4 Inhibitor Trials

The first of these CVOTs studied the DPP-4 inhibitors, known as the "gliptin" drugs. The Trial Evaluating Cardiovascular

Outcomes with Sitagliptin (TECOS) concluded that sitagliptin was not associated with an increased incidence of adverse CV outcomes or heart failure admissions when taken by T2D patients with an existing diagnosis of CV disease.[11,12] On the other hand, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction study (SAVOR-TIMI) deduced that saxagliptin, another DPP-4 inhibitor, did not affect the rate of ischemic events, although the rate of hospitalization for heart failure increased by 27%.[13]

In addition, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study showed that, compared to placebo, alogliptin did not increase the rates of major adverse CV incidents in T2D patients who recently had an acute coronary syndrome.[14] Another DPP-4 inhibitor, linagliptin, is being evaluated in the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in patients with Type 2 Diabetes (CAROLINA), with results expected in 2019 (Table 1).[15] There is currently an FDA warning of increased risk of heart failure for medications containing saxagliptin and alogliptin.

GLP-1 RA Trials

The first in a series of CVOTs with GLP-1 RA (i.e., the "glutide" drugs) was the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA). This study showed that adding lixisenatide to the standard of care was not associated with significant CV or other serious adverse incidents in T2D patients with recent acute coronary syndrome.[16] However, the next two CVOTs involving this drug class showed much more groundbreaking results. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, a large multicenter double-blind trial, confirmed that liraglutide not only did not increase heart failure admissions but also reduced CV events by 13%, all-cause mortality by 15%, and CV death by 22%. Therefore, liraglutide was the first to reveal both a CV and mortality benefit.[17] Furthermore, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) demonstrated that diabetic patients at high risk of CV disease experienced a 26% reduction in CV death, nonfatal myocardial infarction, or nonfatal stroke after receiving semaglutide versus placebo.[18] On the other hand, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) showed that exenatide use did not lead to significant differences in the rates of serious CV incidents in T2D patients, regardless of previous CV disease (Table 1).[19]

GLP-1 analogs are well known for their gastrointestinal side effects, such as nausea, vomiting, constipation, diarrhea, and abdominal pain, all of which can be epigastric or diffuse and can be associated with increased lipase; such symptoms have been reported to be the main reason for medication cessation in clinical trials. Less common side effects are neurological events such as headache, fatigue, and dizziness. On rare occasions, these agents have been described to cause hypoglycemia.[4] In addition, GLP-1 analogs can be used in patients with stage 3 chronic kidney disease (CKD), which is described as an estimated glomerular filtration rate (eGFR) of 30 to 59 mL/min/1.73 m^2; however, these medications should not be started if the eGFR is below this level.[4,20] GLP-1 analogs are contraindicated in patients with a history of acute pancreatitis or acute gallbladder disease and can have an additive effect to insulin that increases the risk for hypoglycemia. Rare instances of hypersensitivity reactions and suicidal behavior have also been described.[4,21,22] Moreover, such medications have resulted in medullary thyroid cancer (MTC) in rats and mice experiments; therefore, they are absolutely contraindicated in individuals with a history of MTC or multiple endocrine neoplasia type 2 even though there have been no reports of MTC observed in humans to date. It is worth mentioning that GLP-1 agonists have demonstrated a statistically significant increase in heart rate; however, the clinical significance of such an increase has been minuscule with regard to CV events, even at the high dose of 1.8 mg.[21,22]

SGLT2 Inhibitor Trials

SGLT2 inhibitors, the "gliflozin" drugs, are the second class of drugs with two consistently positive CVOTs. In fact, the first diabetes medication to show CV benefit since the FDA mandate was revealed in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes study (EMPA-REG OUTCOME). Patients with T2D at high risk for CV events who received empagliflozin had a 14% lower rate of the primary composite CV outcome (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) and of death from any cause compared to patients receiving a placebo. In addition, the empagliflozin group had a 38% reduction in CV deaths, a 35% reduction in hospitalization for heart failure, and a 32% reduction in death from any cause (Table 1).[23]

Subsequently, the Canagliflozin Cardiovascular Assessment Study (CANVAS) explored the risks of canagliflozin on the rates of CV events in T2D patients who already had a high risk of CV disease.[9,24] In two trials involving this patient population, those treated with canagliflozin had a 14% lower risk of CV events, 13% lower risk of CV death, and 33% lower risk of hospitalization for heart failure versus those receiving a placebo. However, there was a greater risk of amputation, primarily at

the level of the toe or metatarsal, in the canagliflozin group (Table 1).[24]

The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) is a 6-year trial exploring the potential benefits of dapagliflozin on CV outcome in T2D patients.[9,25] This trial aims at confirming the CV benefits of SGLT2 inhibitors while exploring the potential side effects. The estimated study completion date is April 2019.[25]

With regard to the adverse events observed with the gliflozins, euglycemic ketoacidosis may be the most worrisome. In addition, SGLT2 inhibitors increase glucosuria, making the urinary tract more favorable for bacterial and fungal growth and, in turn, increasing the incidence of both urinary tract and vaginal yeast infections. Hypoglycemia is a less common side effect with these drugs.[8] Drug-drug interactions are rare with SGLT2 inhibitors, and the doses of such medications need not be altered when used with other hypoglycemic agents.[8,26] A recent meta-analysis looking at potential interference of SGLT2 inhibitors with calcium and phosphate concentrations concluded that they did not increase the risk of bone fracture in patients with T2D.[27]

THE FUTURE OF NOVEL AGENTS

With all of the treatment options that now exist for T2D, clinicians may need guidance to determine the most effective pharmacotherapy for their patients. Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have developed guidelines that clinicians can reference for a treatment algorithm. The ADA continues to recommend metformin, if not contraindicated, as the first-line agent for monotherapy. However, for patients with atherosclerotic CV disease whose A1c target is not achieved after 3 months on monotherapy, the ADA also recommends that a second agent with evidence of CV risk reduction be considered.[28] Moreover, there is now much discussion about selecting a drug based on the patient's specific risk/benefit profile to achieve optimal outcomes. Using this strategy, the AACE guidelines include several options for first-line monotherapy, including SGLT2 inhibitors, GLP-1 RA, and DPP-4 inhibitors.[29] Some international societies, such as the Korean Diabetes Association, also recognize that GLP-1 RA may be the best option if weight loss, avoidance of hypoglycemia, and reduction in CV disease are a priority.[30]

There is increasing sentiment that GLP-1 RA and SGLT2 inhibitors should surpass traditional drugs (i.e., metformin) in the treatment algorithm for patients with T2D and CV disease. This personalized treatment is part of a larger concept of patient-centered care, which evaluates the patient's risk/benefit profile when considering adverse drug effects, disease duration, life expectancy, established vascular complications and/or other comorbidities, individual patient perceptions, and the patient's resources and support system.[31] It must also be recognized that, for most Americans, the most dominating factor when choosing a treatment is cost (Table 2).[32] Until there is uniformity in the clinical guidelines and mitigation of drug costs, it will be challenging for patients to gain access to these new classes of drugs.

CONCLUSION

Management of T2D has never before had so many options supported by clinical trials. The reduction in CVD morbidity and mortality must be considered when choosing a treatment for each patient in order to deliver the most optimal patient outcomes. However, more understanding of the mechanism of action in newer therapies is still needed. Ongoing trials evaluating the application of some of these drugs, particularly SGLT2 inhibitors, in nondiabetic patients with CV disease and heart failure will be revealing. At this time, clinical education on the benefits and risks of these drugs and providing access to patients is a priority.

KEY POINTS

- In clinical trials, glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose transporter 2 (SGLT2) inhibitors have consistently demonstrated cardiovascular (CV) benefits in patients with type 2 diabetes (T2D).
- These drugs have challenged the conventional algorithms in the management of T2D by exceeding expectations in CV outcomes trials and demonstrating an unexpected reduction in CV events.
- Such trials have placed a new toolkit in the hands of prescribers who manage patients with T2D.
- The costs of such medications can prohibit their use in some circumstances, especially in the setting of variable financial coverage for patients.

Conflict of Interest Disclosure:
Dr. Sadhu is a consultant for Novo Nordisk.

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DRUG (YEAR)	TRIAL	STUDY DESIGN	RESULTS
Alogliptin (2013)	EXAMINE	N = 5380 Randomized, double-blind study in patients with T2D and either an acute MI/USA requiring hospitalization within the previous 15-90 days Groups: alogliptin vs placebo in addition to existing antihyperglycemic and CV drug therapy; primary end point of composite of death from CV causes, nonfatal MI, or nonfatal stroke; 40-mo follow-up	Primary end point: 11.3% with alogliptin vs 11.8% with placebo HR 0.96; [upper bound of the one-sided repeated CI, 1.16]; *P* < .001 for noninferiority
Saxagliptin (2013)	SAVOR-TIMI	N = 16492 Randomized double-blind study in patients with T2D with history of, or at risk for, CV events Groups: saxagliptin vs placebo; primary end point of composite of CV death, MI, or ischemic stroke; secondary end point of composite of CV death, MI, stroke, hospitalization for USA, coronary revascularization, or heart failure; median 2.1-yr follow-up	Primary end point: 7.3% with saxagliptin vs 7/2% with placebo HR 1.00; 95% CI 0.89-1.12; *P* = .99 for superiority; *P* < .001 for noninferiority Secondary end point: 12.8% with saxagliptin vs 12.4% with placebo HR 1.02; 95% CI 0.94-1.11; *P* = .66 Hospitalization for heart failure: 3.5% saxagliptin vs 2.8% placebo; HR: 1.27; 95% CI 1.07-1.51; *P* = .007
Sitagliptin (2015)	TECOS	N = 14671 Randomized, double-blind study of patients with T2D and CV disease Groups: sitagliptin vs placebo plus existing therapy; primary outcome is composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for USA; median 3-yr follow-up	Primary outcome: 839 patients on sitagliptin (11.4%) vs 851 patients on placebo (11.6%) HR: 0.98; 95% CI: 0.88-1.09; *P* < .001 Hospitalization for heart failure: HR: 1.00; 95% CI 0.83-1.20; *P* = .98
Lixisenatide (2015)	ELIXA	N = 6068 Randomized, double-blind study in patients with T2D with MI or USA within the previous 180 days Groups: lixisenatide vs placebo; primary composite end point of CV death, MI, stroke, or hospitalization for USA; median 25-mo follow-up	Primary end point: 13.4% with lixisenatide vs 13.2% with placebo HR: 1.02; 95% CI: 0.89-1.17 Inferiority: *P* < .001; superiority: *P* = .81 Rate of hospitalization for heart failure: HR: 0.96; 95% CI 0.75-1.23 Rate of death: HR: 0.94; 95% CI 0.78-1.13
Empagliflozin (2015)	EMPA-REG	N = 7020 Randomized, double-blind study of patients with T2D at high CV risk Groups: 10 mg or 25 mg of empagliflozin vs placebo; primary composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke; secondary composite outcome of primary outcome plus hospitalization for USA; median 3.1-yr follow-up	Primary outcome: 10.5% with empagliflozin vs 12.1% with placebo HR: 0.86; 95.02% CI 0.74-0.99; *P* = .04 for superiority Rates of death from CV causes: 3.7% empagliflozin vs 5.9% placebo; 38% RRR Hospitalization for heart failure: 2.7% empagliflozin vs 4.1% placebo; 35% RRR Death from any cause: 5.7% empagliflozin vs 8.3% placebo; 32% RRR

Table 1.
Cardiovascular outcome trials. CV: cardiovascular; MI: myocardial infarction; USA: unstable angina; ACS: acute coronary syndrome; T2D: type 2 diabetes; HR: hazard ratio; CI: confidence interval; RRR: relative risk reduction

DRUG (YEAR)	TRIAL	STUDY DESIGN	RESULTS
Liraglutide (2016)	LEADER	N = 9340 Randomized, double-blind study of patients with T2D and high CV risk Groups: liraglutide 1.8 mg daily vs placebo; primary composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke; 3.8-yr follow-up	Primary outcome: 13.0% with liraglutide vs 14.9% with placebo HR: 0.87; 95% CI 0.78-0.97; *P* < .001 for noninferiority; *P* = .01 for superiority Deaths overall: HR 0.85; 95% CI 0.74-0.97 CV deaths: HR 0.78; 95% CI 0.66-0.93
Semaglutide (2016)	SUSTAIN 6	N = 3297 patients Randomized, double-blind study in patients with T2D on a standard-care regimen Groups: once-weekly semaglutide (0.5 mg or 1.0 mg) vs placebo; primary composite outcome of CV death, nonfatal MI, or nonfatal stroke; 104-wk follow-up	Primary outcome: 6.6% with semaglutide vs 8.9% with placebo HR: 0.74; 95% CI 0.58-0.95; *P* < .001 for noninferiority Nonfatal MI: 2.9% semaglutide vs 3.9% placebo; HR: 0.74; 95% CI 0.51-1.08; *P* = .12 Nonfatal stroke: 1.6% semaglutide vs 2.7% placebo; HR: 0.61; 95% CI 0.38-0.99; *P* = .04 Rates of death from CV causes were similar in the two groups
Canagliflozin (2017)	CANVAS	N = 10142 Randomized, double-blind study in patients with T2D and high CV risk Groups: canagliflozin vs placebo; primary outcome of composite of death from CV causes, nonfatal MI, or nonfatal stroke; mean 188.2-wk follow-up	Primary outcome: 26.9 canagliflozin vs 31.5 placebo per 1000 patient-years HR: 0.86; 95% CI 0.75- 0.97; *P* < .001 for noninferiority; *P* = .02 for superiority Progression of albuminuria: HR: 0.73; 95% CI 0.67-0.79 Composite outcome of a sustained 40% reduction in estimated glomerular filtration rate, need for renal-replacement therapy, or death from renal causes: HR: 0.60; 95% CI 0.47-0.77 Risk of amputation: 6.3 canagliflozin vs 3.4 placebo participants per 1000 patient-years HR: 1.97; 95% CI 1.41-2.75
Exenatide (2017)	EXSCEL	N = 14752 Randomized, double-blind study in patients with T2D, with or without previous CV disease Groups: extended-release exenatide at dose of 2 mg vs matching placebo once weekly; primary composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke; median 3.2-yr follow-up	Primary composite outcome: 11.4% with exenatide vs 12.2% with placebo HR: 0.91; 95% CI 0.83-1.00; P < .001 for noninferiority; *P* = .06 for superiority Rates of death from CV causes, fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for ACS did not differ significantly between the two groups.
Dapagliflozin (2019)	DECLARE-TIMI 58	PENDING	Estimated April 2019
Ertugliflozin (2019)	VERTIS	PENDING	Estimated October 2019

Table 1.
Continued

BRAND	GENERIC	MANUFACTURER	ROUTE	FORM	DOSAGE^	30-DAY COST*
DPP-4						
Januvia	Sitagliptin phosphate	Merck	oral	tablet	25 mg	$295
			oral	tablet	50 mg	$295
			oral	tablet	100 mg	$295
Onglyza	Saxagliptin	Bristol-Myers Squibb	oral	tablet	2.5 mg	$295
			oral	tablet	5 mg	$295
Tradjenta	Linagliptin	Eli Lilly	oral	tablet	5 mg	$290
Janumet	Sitagliptin phosphate + metformin hydrochloride	Merck Sharp & Dohme Corp.	oral	tablet	50/500 mg	$295
			oral	tablet	50/1000 mg	$295
Nesina	Alogliptin	Takeda	oral	tablet	6.25 mg	$374
			oral	tablet	12.5 mg	$374
			oral	tablet	25 mg	$374
GLP-1						
Victoza	Liraglutide	Novo Nordisk	Subcutaneous	Injection	3 pens of 18 mg/3 mL, 1 carton	$831
Trulicity	Dulaglutide	Eli Lilly	Subcutaneous	Injection	4 pens of 1.5 mg/0.5 mL, 1 carton	$733
Bydureon	Exenatide	AstraZeneca	Subcutaneous	Injection	4 pens of 2 mg/pen, 1 kit	$682
Byetta	Exenatide	AstraZeneca	Subcutaneous	Injection	10 mcg, 1 pen	$731
Saxenda	Liraglutide	Novo Nordisk	Subcutaneous	Injection	Five 3-mL pens of 3 mg/0.5 mL, 1 carton	$1233
Ozempic	Semaglutide	Novo Nordisk	Subcutaneous	Injection	1 pen of 0.25 mg/0.5 mg, 1 carton	$698
Adlyxin	Lixisenatide	Sanofi	Subcutaneous	Injection	Two 3-mL pens of 20 mcg, 1 carton	$610
SGLT-2						
Invokana	Canagliflozin	Janssen	Oral	Tablet	300 mg	$482
Jardiance	Empagliflozin	Eli Lilly	Oral	Tablet	25 mg	$449
Farxiga	Dapagliflozin	AstraZeneca	Oral	Tablet	10 mg	$482
Steglatro	Ertugliflozin	Merck	Oral	Tablet	5 mg	$282

Table 2.
List of DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors approved by the U.S. Food and Drug Administration and related costs (grouped by drug class).
DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide-1; SGLT-2: sodium glucose cotransporter 2

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