ROSALIND FRANKLIN UNIVERSITY OF MEDICINE & SCIENCE COLLEGE OF PHARMACY STUDENT WRITING CLUB:

Novel Antihyperglycemics and their Uses in Type 2 Diabetes Mellitus and Beyond

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Abstract

While United States guidelines for the treatment of type 2 diabetes mellitus (T2DM) have not undergone a major change in the most recent update, the number of treatments and the amount of research into novel approaches are in constant flux. Currently, there are 11 antihyperglycemic classes used in the treatment of T2DM. The newer SGLT-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), adjunct to lifestyle modifications, help reduce hemoglobin A1c and maintain glycemic control; however, recent investigations for their use beyond T2DM have earned them a place in the treatment of heart failure, chronic kidney disease, and obesity management.

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder associated with a wide range of long-term complications. The primary pathophysiology responsible for a T2DM diagnosis is insulin resistance, although its manifestation can vary from one person to another, with potential implications for damaging many organs, including the eyes, heart, vasculature, and kidneys.[1] Macrovascular complications from untreated or subtherapeutic treatment can include atherosclerotic cardiovascular diseases (ASCVD) such as stroke or myocardial infarction.[2] Potential microvascular complications include retinopathy, neuropathy, and nephropathy.[2,3] Resulting chronic kidney disease (CKD) and heart failure from these complications can be seen in patients with T2DM. Comorbid conditions in T2DM, such as dyslipidemia, hypertension, and obesity, further aggravate these complications.[4] In turn, the treatment protocol for each patient with T2DM must include the mitigation and close monitoring of these potential complications.

Certain antihyperglycemic agents have shown efficacy in lowering the risk of some of these diabetes-related complications in addition to improving glycemic control. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are two such antihyperglycemic classes. When compared to placebo, GLP-1 RAs provide A1c reduction ranging from 0.78 to 1.9% while SGLT2is provide A1c reduction ranging from 0.4 to 1.1%. [5-7] In addition to glycemic control, SGLT2is in general have shown a significant reduction in major cardiovascular (CV) events including CV deaths; worsening heart failure and heart failure-related hospitalizations; and worsening of kidney disease or progression to end-stage renal disease (ESRD).[8] Additionally, GLP-1 RAs have shown reductions in major CV events, including CV deaths and worsening of kidney disease. Specific GLP-1 RAs, such as semaglutide and liraglutide, both at higher doses, are also approved for the chronic management of obesity. Table 1 summarizes these agents and their additional indications; however, the rest of the article elaborates on the evidence supporting these additional indications.

Sodium-Glucose Cotransporter-2 Inhibitors

Currently, in the United States, there are four SGLT2is approved for use by the Food and Drug Administration (FDA). The generic and brand names of the agents in this drug class are canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro®). These agents inhibit the reabsorption of sodium and glucose from the renal tubule, resulting in increased arteriole dilation and decreased glomerular pressure.[9] They decrease the glucose excretion threshold in the kidneys, allowing increased elimination of glucose in the urine. The natriuresis process aids in the decrease of systolic blood pressure, thereby improving a significant risk factor for CV events. They are generally taken as a once-daily regimen and require renal dose adjustments based on patients' estimated glomerular filtration rates (eGFR) values. The most common adverse events reported with this class are diuresis, urinary tract infection including mycologic infections, and hyperkalemia.[10,11] The rare but serious adverse events reported with this class are hypoglycemia, lower limb amputation and bone fractures, and necrotizing fasciitis.[12-14]

Canagliflozin (Invokana®) gained its first FDA approval in 2013 for the treatment of T2DM, but in recent years, with new research, new indications have been added, which include risk reduction of major adverse CV events (MACE) in adults with T2DM and established ASCVD; and risk reduction of ESRD, increase of serum creatinine, CV death, and hospitalization from of heart failure in adults with T2DM and diabetic nephropathy with microalbuminuria.[15] When used as an add-on therapy, canagliflozin has been shown to result in fewer hypoglycemic incidents, reduced postprandial glucose levels, statistically significant weight reduction, and reduction in systolic blood pressure.[16] The CREDENCE trial has shown that a dose

TABLE 1. Therapeutic Agents for T2DM with Additional FDA Indications

	SGLT2i			GLP-1 RA		
	CANAGLIFLOZIN	DAPAGLIFLOZIN	EMPAGLIFLOZIN	LIRAGLUTIDE	SEMAGLUTIDE	DULAGLUTIDE
BRAND NAME	Invokana®	Farxiga®	Jardiance®	Victoza® Saxenda®	Ozempic® Rybelsus® Wegovy®	Trulicity®
FDA INDICATIONS*	Cardiovascular (CV) disorders prophylaxis	Risk of CKD progression, CV disorders, Heart Failure (HFrEF)	CV disorders prophylaxis, HFrEF	CV disorders prophylaxis, chronic weight management	CV disorders prophylaxis, chronic weight management	CV disorders prophylaxis
HF BENEFITS	✗	✓	✓	✗	✗	✗
RENAL BENEFITS	✗	✓	✓	✓	✓	✗
ASCVD BENEFITS	✓	✓	✓	✓	✓	✓

*INDICATED FOR TYPE 2 DIABETES MELLITUS

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; FDA = US Food and Drug Administration; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HFrEF = heart failure with reduced ejection fraction; SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2DM = type 2 diabetes mellitus

of canagliflozin 100 mg daily reduces the risk of ESRD and death from CV disease compared to a placebo (HR 0.70; 95% CI [0.59-0.82]).[8]

Dapagliflozin (Farxiga®) was FDA approved for improving glycemic control in adults with T2DM in 2014. Its positive impact on renal and CV outcomes includes lowering the risk of kidney failure and major CV events in patients with T2DM with concurrent renal and CV diseases.[17] In particular, renal outcomes show improvements in eGFR, and CV outcomes include decreased CV death in patients with heart failure and reduced ejection fraction (HFrEF) or hypertensive heart failure.[18] These outcomes have been consistently achieved in patients with T2DM, both with and without comorbidities impacting renal or cardiac function.[19,20] While diminishing renal function is a common complication of T2DM, delaying its progression in patients with or without diabetes has been assisted by dapagliflozin in patients with eGFR ranging from 25 to 75 mL/min/1.73 m^2.[21] In the DAPA-CKD trial, the composite risk of a sustained decline in eGFR of 50%, onset of ESRD, and death from renal or CV causes was found to be significantly lower with the use of dapagliflozin compared to placebo (HR 0.61; 95% CI [0.51 - 0.72]). These findings were consistent among patients both with and without diabetes mellitus present, showing a potential for the use of SGLT2is outside of glycemic control. Despite these findings, dapagliflozin is not recommended for patients with T2DM when eGFR is below 45 mL/min/1.73 m^2. Additionally, the analysis following the DAPA-CKD trial concluded that not only did dapagliflozin reduce the risk for major adverse kidney events including eGFR decline, but dapagliflozin also reduced the risk of major adverse CV events and death.

Dapagliflozin has been shown to mitigate risk factors for major adverse CV events in patients with T2DM and ASCVD risk factors. In the DECLARE-TIMI trial, 17,160 patients with T2DM were double blinded to either 10 mg of dapagliflozin once daily or placebo to analyze the drug's CV safety and efficacy.[23] Patients had either established ASCVD or risk factors for ASCVD. The primary safety outcomes in the trial included 3 point MACE: time to first event of CV death, myocardial infarction, or ischemic stroke. Participants were followed for a median of 4.2 years. The trial found that dapagliflozin did not result in a lower rate of MACE (HR 0.93; 95% CI [0.84 - 1.03]), but did allow for a lower rate of CV death or hospitalization for heart failure (HR 0.83; 95% CI [0.73 - 0.95]), which also reflected a lower rate of hospitalization for heart failure (HR 0.73; 95% CI [0.61- 0.88]). In the DAPA-HF study, dapagliflozin was found to be most effective to prolong life and minimize hospitalizations in patients with HFrEF (HR 0.70; 95% CI[0.59 to 0.83]).[24] Patients included in the study had heart failure in New York Heart Association functional class II or greater, a left ventricular ejection fraction ≤ 40%, and an elevated N-terminal pro-B-type natriuretic peptide concentration, while receiving standard heart failure treatment.[25] A total of 4,744 patients were randomized;

42% had known diabetes and 3% had undiagnosed diabetes. Among those without T2DM, 67% had pre-diabetes and 33% had a normal A1c. Dapagliflozin increased glycemic control with a low intrinsic propensity for causing hypoglycemia, glucosuria induced body weight reduction, and reduced levels of serum uric acid, lipids, and blood pressure.[26]

Empagliflozin (Jardiance®) was approved in 2014 by the FDA for the improvement of glycemic control in adults with T2DM. As further data became available, the indications for reducing CV death risk, established ASCVD, and reducing heart failure-related hospitalizations were added. Dosing for each indication is slightly different: 10 mg daily for heart failure while 10 mg daily as a starting dose with the potential to increase to 25 mg daily for T2DM treatment.[27] Renal dose adjustment is required for patients with T2DM or HFrEF that fall below a specific eGFR level.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) randomized 3,730 patients with HFrEF class II-IV to receive empagliflozin 10 mg once daily or placebo in addition to recommended therapy to test the primary outcome of CV death or hospitalization for worsening heart failure.[28] The study found that the primary outcome occurred significantly less in the treatment group compared to the placebo group regardless of the presence or absence of diabetes (HR 0.75; 95% CI [0.65- 0.86]). This study showed that the decrease in annual rate in eGFR was slower in the treatment group versus the placebo group (–0.55 vs. –2.28 mL/min/1.73 m^2 per year, P<0.001).[29]

Moreover, a meta-analysis of the DAPA-HF trial and EMPEROR-Reduced trial showed an improvement in combined clinical outcomes for CV death or first hospitalization for heart failure, composite of heart failure recurrent hospitalizations or CV death, and risk for the first hospitalization for heart failure in patients with HFrEF with or without T2DM.[30] Also, it showed that there were no significant differences in clinical outcomes between these two trials.

The most recent trial, completed in October 2021, was the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), which showed significant clinical outcomes for patients with heart failure with a preserved ejection fraction (HFpEF).[31] It randomized 5,988 patients with class II-IV heart failure and an ejection fraction of more than 40% to receive empagliflozin 10 mg once daily or placebo in addition to usual therapy to test the primary outcome of a composite of CV death or hospitalization for heart failure. The study found that the primary outcome occurred significantly less in the treatment group compared to the placebo group regardless of the presence or absence of diabetes (HR 0.79; 95% CI [0.69 - 0.90]). Also, the study found that the total number of hospitalizations for heart failure was lower in the treatment group compared to the placebo group (HR 0.73; 95% CI [0.61-0.88]). The study found that empagliflozin compared to the placebo showed a slower progression in the rate of decline in eGFR.

Ertugliflozin (Steglatro®) is an SGLT2i approved for T2DM management. The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) randomized 8,246 patients with T2DM who were 40 years old or older and had established ASCVD to test the primary outcome of composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.[32] The trial showed that the deaths from CV causes or heart failure hospitalizations did not differ significantly in the ertugliflozin group compared to the placebo group (HR 0.88; 95% CI [0.75-1.03], P=0.11 for superiority). One of the secondary outcomes tested the renal composite outcomes of

ertugliflozin, which included death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. That outcome showed no significant benefit (HR 0.81; 95% CI [0.63-1.04]).

Glucagon-like Peptide-1 Receptor Agonists

The GLP-1 RAs are increasingly being used for other indications besides T2DM management, such as obesity, renal, and CV risk reduction, by improving cardiometabolic parameters. Most of these agents are available in the injection form with the exception of semaglutide, for which an oral tablet formulation is available. Depending on the agent, the dosing frequency varies; however, most follow a gradual titration to help tolerate gastrointestinal (GI) side effects.[33-35] They exert their main effects by increasing glucose-dependent insulin secretion, slowing gastric emptying, and acting in some areas of the brain that are involved in regulation of appetite. Some common adverse events are GI-related, such as nausea, diarrhea, and vomiting, but these have been shown to subside after the first few weeks of treatment. The rare but severe adverse effects include acute pancreatitis, pancreatic cancer, and malignant thyroid C cell tumor. Overall, GLP-1 RAs are still a favorable option for treatment of T2DM because they are effective at lowering A1c while presenting a low risk of hypoglycemia and offering the aforementioned additional benefits.

There have been multiple trials that showcase the benefit of adding a GLP-1 RA to a patient's regimen to reduce the risk of having a CV event. In the LEADER trial, researchers evaluated liraglutide (Victoza®) and its long-term effects on CV outcomes.[36] They randomized 9,430 patients to either receive liraglutide or placebo to test the primary outcome of first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke in a time to event analysis. The study found that the number of primary events occurred in significantly fewer participants that received liraglutide compared to placebo (HR 0.87; 95% CI [0.78 - 0.97]; P<0.001 for noninferiority; P=0.01 for superiority). Significantly fewer patients also died from CV causes in the liraglutide group compared to placebo (HR 0.78; 95% CI [0.66 - 0.93]).

Semaglutide subcutaneous injection (Ozempic®) is FDA approved for risk reduction of major CV events in those with established T2DM and CV disease.[34] Semaglutide shows benefit in glucose, weight, and blood pressure lowering similarly to liraglutide; however, it is only dosed once weekly compared to daily injections for liraglutide. The SUSTAIN-6 study randomized about 3,000 participants to either subcutaneous semaglutide or placebo to assess the primary outcome of first occurrence of CV death, nonfatal stroke or myocardial infarction.[37] In the study, they found that the rate of the primary outcome was significantly lower in the semaglutide group compared to the placebo (HR 0.74; 95% CI [0.58 - 0.95]; P=0.02.

Dulaglutide (Trulicity®) is a once-weekly injectable GLP-1 RA that is FDA approved for reducing major adverse CV events for those with T2DM with ASCVD or major ASCVD risk factors.[35] The REWIND trial evaluated CV benefits of dulaglutide.[38] In this study, the authors assessed the effect of dulaglutide for the primary endpoint which was the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes including unknown causes. In 9,900 participants who underwent randomization, they found that those in the dulaglutide group experienced significantly lower rates of first occurrence compared to the placebo group (HR 0.88; 95% CI [0.79–0.99]). The study establishes the use of dulaglutide to reduce the risk of CV events for those not only with CV disease but those who have risk factors for developing CV disease as well.

In addition to ASCVD risk reduction, the secondary outcomes of the cardiovascular outcomes trials (CVOT) evaluated the effects of GLP-1 RA on renal outcomes.[36,37] Within the LEADER and SUSTAIN-6 trials, the authors evaluated that liraglutide and semaglutide both reduced the risk of new or worsening nephropathy. Although these trials did not select the patient population to specifically reflect those with CKD, a large number of the population included people with stage 3a kidney disease. The proof of benefit with renal outcomes with semaglutide is ongoing and will be evaluated in the FLOW trial; however, these findings of potential benefit are still reflected in the guidelines and GLP-1 RAs are recommended after a failed use of a SGLT2is in patients with established CKD.[8]

It has been shown that obesity management has a strong correlation with delaying the progression of prediabetes and treatment of diabetes.[39] Weight loss is known to improve glycemic control and ultimately reduce A1c. Although diet and physical activity will remain as a first-line recommendation for weight loss, GLP-1 RAs can be incorporated into an individual's therapy for additional weight loss. Based on study findings discussed later, subcutaneous higher dose semaglutide (Wegovy®) and higher dose liraglutide (Saxenda®) are also FDA-approved for the chronic management of obesity in people without T2DM.

The STEP 1 trial examined the use of semaglutide 2.4 mg once weekly subcutaneous injection in adults with obesity, with or without diabetes.[40] The study demonstrated that semaglutide 2.4 mg once weekly resulted in sustained and clinically relevant weight reduction in individuals with overweight or obesity compared to placebo (P<0.001). In the SCALE trial, the authors examined the use of liraglutide 3.0 mg once daily in patients with established obesity (BMI ≥30) or those with a BMI of 27 with dyslipidemia or hypertension for weight management.[41] They found that liraglutide had a mean loss of 8.4±7.3 kg compared to 2.8±6.5 kg difference in placebo (P<0.001) and that 63.2% of patients had lost 5% of their total body weight. This trial concluded that liraglutide provided weight loss benefits along with improved metabolic control.

In the AWARD-11 trial, the safety and efficacy of dulaglutide at higher doses (3.0 mg or 4.5 mg) in patients with T2DM and a BMI of 25 or greater were compared to normal doses (1.5 mg).[42] The authors found that an escalation of dose to 3.0 mg or 4.5 mg resulted in further reductions in weight and A1c (P <0.001). It should also be noted that at all treatment doses, dulaglutide was able to lower A1c by –1.54% for 1.5 mg, –1.64% for 3.0 mg, and –1.77% for 4.5 mg. This study included patients with T2DM; currently, dulaglutide does not have an FDA approval for the management of chronic obesity in patients without diabetes.

Guideline Recommendations

The American Diabetes Association has updated its current recommendations for first-line treatment.[8] This allows healthcare providers to take an individualized approach and initiate an SGLT2i or a GLP-1 RA based on the patient's specific factors, such as obesity, CKD, and CV disease. Metformin has been the first-line treatment for an extended period, and with this change, providers are able to make appropriate changes earlier on and initiate a treatment that has proven benefit in those specific comorbidities. The American Heart Association (AHA) and Kidney Disease: Improving Global Outcomes (KDIGO) organizations have also updated their guidelines based on the findings mentioned. It is now recommended that patients with T2DM and either established ASCVD or at high ASCVD risk should use an SGLT2i to prevent hospitalizations for HF. In the AHA guidelines, SGLT2is and GLP-1 RAs are also strongly recommended for patients with T2DM and established ASCVD or high risk for ASCVD.[43] The KDIGO guidelines recommend early initiation of an SGLT2i in a patient with T2DM and CKD across all albuminuria levels and eGFR stages to maximize potential renal benefits.[44]

Future Developments

The SGLT2is inhibit the reabsorption of sodium and glucose from the renal tubule, resulting in increased arteriole dilation and decreased glomerular pressure.[45] With this discovery of the SGLT2i mechanism of action, there has been a foray into research concerning additional disease state benefits with canagliflozin. It reduces renal oxygen consumption, leading to the hypothesis that canagliflozin can effectively increase erythropoietin production. This oxygen consumption hypothesis was applied further to begin research on how canagliflozin could be used in cancer treatment. In a 2016 study to determine what this mechanism could be, canagliflozin was shown to activate adenosine monophosphate activated protein kinase (AMPK) by reducing mitochondrial respiration in human kidney cells and mice liver cells.[46,47] Canagliflozin inhibited the proliferation and survival of cell clones from prostate, breast, and lung cancer cells as both monotherapy and an add-on to radiation therapy. There are currently two National Cancer Institute-supported clinical trials in progress regarding canagliflozin use in preventing hyperglycemia in patients with metastatic breast cancer; and canagliflozin use with the solid tumor cancer drug, serabelisib.[48] According to the United States National Library of Medicine, there are a total of 23 clinical trials in the United States that are ongoing to learn more about the use and mechanisms of benefit from canagliflozin.[49] These disease states of interest include polycystic ovary syndrome, T2DM in patients with Human Immunodeficiency Virus (HIV), decreased left ventricular function in patients without T2DM, and use in acute COVID-19 treatment.

Conclusion

Given the presence of microvascular and macrovascular complications during the course of T2DM, it is important to address them while achieving glycemic control. The SGLT2is and GLP-1 RAs offer such benefits. They can provide varying levels of cardioprotective benefits, delayed kidney damage progression, and positive metabolic effects. With further research and clinical trials, there are more insights gained into how their pharmacology is applicable beyond T2DM.

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