Diabetes mellitus (DM) is a metabolic disorder affecting about 5% to 13% of the population in the US. Since 1552, the earliest record of a person with DM, many treatment advances have been made. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are one of the newest antidiabetic pharmaceuticals on the market. The SGLT2 inhibitor drugs include canagliflozin, dapagliflozin, empagliflozin, iragliflozin, and tofogliflozin; however, only canagliflozin, dapagliflozin, and empagliflozin have been approved by the US Food and Drug Administration (FDA). These pharmaceuticals promote glycosuria via the kidneys and enhance sugar excretion from the body. Along with lifestyle changes and self-care measures, such as healthful eating and increased physical activity, SGLT2 inhibitor pharmaceuticals provide antidiabetic efficacy by facilitating normoglycemia and minimizing vascular pathology.

Although SGLT2 inhibitor pharmaceuticals are newly introduced into the market, their discovery dates to 1835. Phlorizin, a nonselective SGLT inhibitor, was first isolated by French chemists from the bark of an apple tree. Phlorizin inhibits SGLT1 mostly in small intestinal cells, and SGLT2 similarly affects the kidney. Renal SGLT2 is the primary therapeutic target. Canagliflozin was the first pharmaceutical SGLT2 inhibitor approved by the FDA in 2013. Dapagliflozin’s FDA approval followed in 2013 and empagliflozin in 2014.

MECHANISM OF ACTION
In healthy individuals, tubular glucose is absorbed, resulting in no urinary glucose excretion. Sodium-glucose cotransporters 1 and 2 contribute to the renal absorption of glucose. A SGLT2 is responsible for 90% of the glucose reuptake in the segment 1 of the proximal tubule, while SGLT 1 is accountable for the remaining 10%. Unlike other antidiabetic medications, which act by increasing insulin secretion or improving insulin sensitivity for the receptors, SGLT2 inhibitor drugs prevent the reuptake of glucose into the bloodstream. This selective action spares the inhibition of SGLT1 present in other tissues, avoiding gastrointestinal effects.

BENEFITS
The SGLT2 inhibitor action is focused on renal excretion of glucose and is independent of insulin action. This action reduces hypoglycemia, weight gain, and liver disease adverse effects (AEs) of older drugs. Moreover, this newer class of antihyperglycemic medications have documented beneficial effects, though there are some risks as well (Table).

Hemoglobin A1c Levels
Canagliflozin, dapagliflozin, and empagliflozin reduce hemoglobin A1c (HbA1c) levels. Inagaki and colleagues found significant reductions in HbA1c and weight gain with > 100 mg canagliflozin compared with that of placebo when used for 12 weeks. In a study where 2.5-mg, 5-mg, and 10-mg dapagliflozin was compared with placebo, the mean HbA1c change from the baseline was -0.23% with placebo; -0.58% at 2.5 mg; -0.77% at 5 mg; and -0.89% at 10 mg. Empagliflozin was more effective in reducing HbA1c levels than was sitagliptin. When patients were treated with 10-mg empagliflozin, 25-mg empagliflozin, and sitagliptin, HbA1c
levels dropped -1.44%, -1.43%, and -1.04%, respectively.9

**Cholesterol**

Sodium-glucose cotransporter 2 inhibitors have the beneficial effect of reducing vascular disease risk factors.10,11 A study by Hayashi and colleagues found that dapagliflozin decreases harmful atherogenic small, low-density lipoprotein-cholesterol (LDL-C), increases less atherogenic large, buoyant LDL-C, and increases high-density, lipoprotein-2 cholesterol (HDL-2C).10 Empagliflozin, however, can cause a small dose-dependent increase in HDL-C and LDL-C.11 Although there is an increase in serum LDL-C concentrations, empagliflozin can induce a decrease in intestinal absorption of cholesterol, thus promoting fecal excretion of LDL-C and macrophage-derived cholesterol.11

**Weight Loss**

A study by Weber and colleagues found that the SGLT2 inhibitor dapagliflozin lead to a reduction in body weight from -1.0 kg to -0.3 kg compared with placebo.12 Cefalu and colleagues found that daily prescribing of 100 mg or/and 300 mg of canagliflozin evidenced dose-dependent loss of weight.13 Neeland and colleagues found that empagliflozin utilization resulted in less adiposity indices in 3,300 subjects.14

**Albuminuria**

Sodium-glucose cotransporter 2 inhibitors have a renoprotective role in patients with type 2 DM (T2DM). In those receiving renin-angiotensin blockers with T2DM and hypertension, dapagliflozin decreased their albuminuria.15 Canagliflozin has a similar potential.16 Empagliflozin reduced the urine albumin-creatinine ratio in patients with macro- or micro-albuminuria, supporting a direct renal effect by SGLT2 inhibitors.17

**Systolic Blood Pressure**

Sodium-glucose cotransporter 2 inhibitors can have beneficial effects on physiologic vascular outcomes. In patients with T2DM and hypertension, dapagliflozin reduced mean systolic blood pressure (SBP) compared with placebo: -7.3 mm Hg vs -10.4 mm Hg, respectively.12 Prescribing canagliflozin treatment at 100 mg or 300 mg reduced SBP (-4.3 mm Hg and -5.0 mm Hg, respectively, vs placebo at -0.3 mm Hg).18 Subjects taking empagliflozin 10 mg or 25 mg exhibited an adjusted mean BP change from baseline of -4.60 mm Hg and -5.47 mm Hg, respectively, whereas placebo induced a -0.67 mm Hg decline.19

**RISKS**

Nausea, fatigue, polyuria, polydipsia, and xerostomia are common SGLT2 AEs. Use of SGLT2 inhibitors can induce certain other more serious AEs as well.

**Increased Risk for Amputations**

The Canagliflozin Cardiovascular Assessment Study (CANVAS) and the Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R) documented that canagliflozin doubled the incidence of leg and foot amputations in research participants compared with placebo (6.3 vs 3.4 per 1,000 patient-years).16 Therefore, canagliflozin should be prescribed with caution in persons with a prior history of foot ulceration, neuropathy, and/or vascular diseases.20

**Acute Renal Injury**

The mechanism of kidney damage by SGLT2 inhibitor drugs is not completely understood. About 100 patients experienced renal failure after the intake of SGLT2 inhibitor drugs.21 Among them, more than half reported symptom onset within a month of starting the medication, and their symptoms improved after discontinuing the SGLT2 medication. As a result, the FDA issued a warning to monitor renal function before initiating and during such pharmacotherapy.22

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**TABLE Benefits and Risks of SGLT2 Inhibitors**

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Abbreviations: HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose cotransporter 2.
Ketoacidosis
Sodium-glucose cotransporter 2 inhibitors might lead to elevated ketone body levels and euglycemic ketoacidosis; however, this risk reportedly is negligible. Use of SGLT2 inhibitors is not recommended for patients evidencing the presence of precipitating factors like acute gastroenteritis or insulin pump failure.

Genitourinary Infections
About 10% to 15% of women taking SGLT2 inhibitor medications developed urinary tract infections and vulvovaginitis. This could be because of a glycosuria effect caused by SGLT2 inhibitors.

Hypotension
Sodium-glucose cotransporter 2 inhibitors cause contraction of intravascular volume. Therefore, patients taking SGLT2 inhibitors are at risk for hypotension, leading to dizziness and potentially dangerous falls. Patients already taking volume-depleting medications, such as diuretics, should be advised to use this group of medications with caution and report these AEs.

Bone Fractures
A clinical trial revealed that SGLT2 inhibitors, such as canagliflozin, decrease bone mineral density possibly leading to bone fractures. Bone fractures occurred in about 1.5% of cases of patients taking 100 mg and 300 mg of canagliflozin compared with a 1.1% fracture rate among the placebo group.

CONCLUSION
Since the FDA approval of SGLT2 inhibitor medications, their usage has increased. The American Diabetes Association first recommends nonpharmacologic approaches, such as diet modification, exercise, and weight loss for patients diagnosed with DM, followed by a medicinal intervention with metformin if required. Sodium-glucose cotransporter 2 inhibitors are suggested as an additional medication in dual or triple pharmacotherapies when metformin alone fails to achieve normoglycemia.

Prior to starting a patient on SGLT2 inhibitor medication, clinicians should monitor hydration adequacy, check bone density, review the patient’s cardiac profile, and assess hepatic and renal function. Prescribing SGLT2 inhibitors should be restricted if the patient has a history of type 1 DM, ketosis-prone T2DM, and in those with a glomerular filtration rate of < 60 mL/min. Considering the preexisting medical conditions of the patient and monitoring the blood glucose levels, renal function, and volume status at every visit should minimize risks and enhance the benefits of prescribing this new medication class.

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