MARY VOUYIOUKLIS, MD
Department of Endocrinology, Diabetes,
and Metabolism, Cleveland Clinic

Canagliflozin: Improving diabetes by making urine sweet

ABSTRACT

Canagliflozin is the first sodium-glucose cotransport 2 (SGLT2) inhibitor approved in the United States for treating type 2 diabetes mellitus. This drug blocks reabsorption of glucose in the proximal tubule, lowering the renal threshold for glucose and thereby increasing glucose excretion. Its novel mechanism of action is insulin-independent. Trials have demonstrated reductions in fasting glucose and hemoglobin A_{1c} levels, with the added benefit of weight loss. The adverse effects most often reported include genital yeast infections and urinary tract infections. Ongoing trials will further elucidate possible long-term risks of this drug.

KEY POINTS

Type 2 diabetes is ubiquitous and, despite an abundance of agents, often remains uncontrolled.

Canagliflozin and other drugs of its class cause glucose to be spilled in the urine by reducing the amount reabsorbed by the kidney.

In clinical trials, canagliflozin lowered hemoglobin A_{1c} levels by approximately 1 absolute percentage point.

Beyond the adverse effects to be expected from the mechanism of action of the drug (ie, genital yeast infections, urinary tract infections, and hypotension caused by osmotic diuresis), canagliflozin seems to increase plasma levels of low-density lipoprotein cholesterol. This may be worrisome, as diabetic patients are already at increased risk of cardiovascular disease.

GLYCOSURIA USED TO BE a sign of uncontrolled diabetes and was something to be corrected, not a therapeutic mechanism. But now we have a new class of drugs that lower plasma glucose levels by increasing the renal excretion of glucose.

Here, we will review canagliflozin, the first in a new class of drugs for type 2 diabetes: how it works, who is a candidate for it, and what to watch out for.

THE NEED FOR NEW DIABETES DRUGS

Diabetes mellitus affects more than 25.8 million people in the United States—8.3% of the population—and this staggering number is rising.[1] Among US residents age 65 and older, more than 10.9 million (26.9%) have diabetes.[1] People with uncontrolled diabetes are at risk of microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as cardiovascular disease. Diabetes is the leading cause of blindness, chronic kidney disease, and nontraumatic lower-limb amputation in the United States.[1]

Type 2 diabetes accounts for more than 90% of cases of diabetes in the United States, Europe, and Canada.[2] It is characterized by insulin resistance, decreased beta-cell function, and progressive beta-cell decline.[3]

Current American Diabetes Association guidelines for the treatment of diabetes recommend a hemoglobin A_{1c} target of less than 7.0%.[4] Initial management includes lifestyle modifications such as changes in diet and an increase in exercise, as well as consideration of

Drugs mentioned in this article

Canagliflozin (Invokana)	Phenobarbital
Colesevelam (Welchol)	Phenytoin (Dilantin)
Dapagliflozin (Forxiga)	Pioglitazone (Actos)
Digoxin (Lanoxin)	Rifampin (Rifadin)
Glimepiride (Amaryl)	Ritonavir (Norvir)
Metformin (Glucophage, others)	Sitagliptin (Januvia)

metformin treatment at the same time. If glucose levels remain uncontrolled despite these efforts, other drugs should be added.

A number of oral and injectable antihyperglycemic drugs are available to help achieve this goal, though none is without risk of adverse effects. Those available up to now include metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, gliptins, glucagon-like peptide-1 agonists, amylin analogues, colesevelam, dopamine agonists, and insulin.[5] Most of the available antihyperglycemics target the liver, pancreas, gut, and muscle to improve insulin sensitivity, reduce insulin resistance, or stimulate insulin secretion.

Despite the abundance of agents, type 2 diabetes remains uncontrolled in many patients. Only 57.1% of participants with previously diagnosed diabetes in the 2003–2006 National Health and Nutrition Examination Survey were at the hemoglobin A_{1c} goal of less than 7.0%.[6] Possible reasons for failure include adverse effects such as hypoglycemia, weight gain, and gastrointestinal symptoms resulting in discontinued use, nonadherence to the prescribed regimen, and failure to increase the dosage or to add additional agents, including insulin, to optimize glycemic control as beta-cell function declines over time.

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■ HOW THE KIDNEYS HANDLE GLUCOSE

In the kidney, glucose is filtered in the glomerulus and then is reabsorbed in the proximal tubule. Normally, the filtered glucose is all reabsorbed unless the glucose load exceeds the kidney's absorptive capacity. Membrane proteins called sodium-glucose cotransporters reabsorb glucose at the proximal tubule and return it into the peripheral circulation. Glucose enters the tubular epithelial cell with sodium by passive cotransport via the sodium-glucose cotransporters, and then exits on the other side via the glucose transporter GLUT in the basolateral membrane.

Two sodium-glucose transporters that act in the proximal tubule of the kidney have been identified: SGLT1 and SGLT2. SGLT2 reabsorbs most of the glucose in the early segment of the proximal tubule, while SLGT1 reabsorbs the remaining glucose at the distal end.[7] SGLT2 is responsible for more than 90% of renal tubular reabsorption of glucose and is found only in the proximal tubule, whereas SGLT1 is found mainly in the gastrointestinal tract.[8]

Patients with type 2 diabetes have a higher capacity for glucose reabsorption in the proximal tubule as a result of the up-regulation of SGLT2.[9]

■ SGLT2 INHIBITORS AND TYPE 2 DIABETES

Drugs that inhibit SGLT2 block reabsorption of glucose in the proximal tubule, lowering the renal threshold for glucose and thereby increasing urinary glucose excretion and lowering the serum glucose level in patients with hyperglycemia. This mechanism of action is insulin-independent.

On March 29, 2013, canagliflozin became the first SGLT2 inhibitor to be approved in the United States for the treatment of type 2 diabetes.[10] However, it is not the first of its class to be introduced.

Dapagliflozin was the first SGLT2 inhibitor approved in Europe and has been available there since November 2012. However, the US Food and Drug Administration withheld its approval in the United States in January 2012 because of concerns of a possible association with cancer, specifically breast and bladder cancers, as well as possible liver injury.[10] Canagliflozin does not appear to share this risk.

Several other SGLT2 inhibitors may soon be available. Empagliflozin is in phase III trials, and the manufacturer has filed for approval in the United States. Ipragliflozin is awaiting approval in Japan.

■ CANAGLIFLOZIN: PHARMACOKINETICS AND THERAPEUTIC EFFICACY

Canagliflozin reaches its peak plasma concentration within 1 to 2 hours of oral administration.[11] Its half-life is 10.6 hours with a 100-mg dose and 13.1 hours with a 300-mg dose. A steady state is typically achieved in 4 to 5 days.[11]

Canagliflozin lowers fasting plasma glucose and hemoglobin A_{1c} levels in a dose-dependent manner.[10,11] These effects are independent of age, sex, body mass index, and race.[12] Postprandial glucose levels are also lowered.

Other potential benefits of canagliflozin include lowering of the systolic blood pressure and, especially important in obese people with type 2 diabetes, weight loss.[12] Aside from metformin, which occasionally results in modest weight loss, other oral drugs used in treating type 2 diabetes are weight-neutral or can cause weight gain.

Trials of canagliflozin

Nine phase III trials of canagliflozin have enrolled 10,285 patients, in one of the largest clinical trial programs in type 2 diabetes to date.[10] Several of these trials evaluated canagliflozin as monotherapy, whereas others assessed its effect as an add-on therapy in combination with another antihyperglycemic agent such as a sulfonylurea, metformin, pioglitazone, or insulin. There has not yet been a trial directly comparing canagliflozin with metformin.

Four of the placebo-controlled trials evaluated canagliflozin as monotherapy, canagliflozin added to metformin alone, canagliflozin added to metformin plus glimepiride, and canagliflozin added to metformin plus pioglitazone.

When canagliflozin was used as monotherapy, hemoglobin A_{1c} levels at 26 weeks were an absolute 0.91% lower in the canagliflozin 100 mg/day group than in the placebo group, and an absolute 1.16% lower in the canagliflozin 300 mg/day group than in the placebo group ($P < .001$ for both).[12] Patients lost 2.8% of their body weight with canagliflozin 100 mg and 3.3% with canagliflozin 300 mg, compared with 0.6% with placebo.

Systolic blood pressure fell by a mean of 3.7 mm Hg with the 100-mg dose and by a mean of 5.4 mm Hg with the 300-mg dose compared with placebo ($P < .001$ for both dose groups).[12]

When canagliflozin was added to metformin, with glimepiride as the comparator drug, there was a 5.2% weight reduction with the 100-mg dose, a 5.7% reduction with 300 mg, and a 1% gain with glimepiride. Hemoglobin A_{1c} fell about equally in the three groups.[11]

When canagliflozin was added to metformin and a sulfonylurea, with sitagliptin as the comparator third drug, the 300-mg canagliflozin dosage group had a 2.8% weight reduction.[11]

■ WHAT ARE THE ADVERSE EFFECTS?

Overall, canagliflozin seems to be well tolerated. The most common adverse effects reported in the clinical trials were genital yeast infections, urinary tract infections, and increased urination.

Genital yeast infections were more common in women than in men, occurring in 10.4% of women who received canagliflozin 100 mg and in 11.4% of women who received 300 mg, compared with only 3.2% in the placebo group.[11]

Urinary tract infections occurred in 5.9% of the 100-mg group and in 4.3% of the 300-mg group, compared with 4.0% of the placebo group.[11]

Postural hypotension. Lowering of blood pressure and symptoms of postural hypotension were also reported, and these may be attributed to the drug's mild osmotic diuretic effect. The risk of adverse effects of volume depletion was dose-dependent; in patients over age 75, they occurred in 4.9% of those taking 100 mg and in 8.7% of those taking 300 mg, compared with 2.6% of those in the placebo or active-comparator groups.[11] Therefore, one should exercise particular caution when starting this drug in the elderly or in patients taking diuretics or multiple antihypertensive drugs.

Hypoglycemia. When canagliflozin was used as monotherapy, the incidence of hypoglycemia over 26 weeks was similar to that with placebo, occurring in 3.6% of the 100-mg group, 3.0% of the 300-mg group, and 2.6%

Patients lost 2.8% of their body weight with canagliflozin 100 mg and 3.3% with 300 mg, vs 0.6% with placebo

of the placebo group.[12] Canagliflozin was associated with fewer episodes of hypoglycemia than were sulfonylureas, and the number of episodes was similar to that in patients taking gliptins. There was a higher overall incidence of hypoglycemia when canagliflozin was used in combination with a sulfonylurea or with insulin than when it was used as monotherapy.[11]

Hyperkalemia. Patients with moderate renal impairment or who are on potassium-sparing drugs or drugs that interfere with the renin-angiotensin-aldosterone system may be at higher risk of hyperkalemia, so close monitoring of potassium is recommended. There was also a dose-dependent increase in serum phosphate and magnesium levels, more notably in patients with moderate renal impairment within the first 3 weeks of starting the drug.[11]

Patients on canagliflozin who are also taking digoxin, ritonavir, phenytoin, phenobarbital, or rifampin should be closely monitored because of the risk of drug-drug interactions.[11] Specifically, there was an increase in mean peak digoxin concentrations when used with canagliflozin 300 mg, and the use of phenytoin, phenobarbital, and ritonavir decreased the efficacy of canagliflozin.

■ WHAT ARE THE CARDIOVASCULAR RISKS OR LONG-TERM CONCERNS?

Dose-dependent increases in low-density lipoprotein cholesterol (LDL-C) may be seen with canagliflozin. Mean changes from baseline compared with placebo were 4.4 mg/dL (4.5%) with canagliflozin 100 mg and 8.3 mg/dL (8%) with canagliflozin 300 mg.[11]

There was also an increase in non-high-density lipoprotein cholesterol (non-HDL-C).[12] Compared with placebo, mean non-HDL-C levels rose by 2.1 mg/dL (1.5%) with canagliflozin 100 mg and 5.1 mg/dL (3.6%) with 300 mg.[11]

In the 26-week canagliflozin monotherapy trial, archived blood samples in a small subgroup of patients (n = 349) were measured for apolipoprotein-B, which was found to increase by 1.2% with canagliflozin 100 mg and 3.5% with canagliflozin 300 mg, compared with 0.9% in the placebo group.[12]

Although small, the increase in LDL-C

seen with this drug could be a concern, as diabetic patients are already at higher risk of cardiovascular events. The mechanism of this increase is not yet known, though it may be related to metabolic changes from urinary glucose excretion.[12]

The Canagliflozin Cardiovascular Assessment Study (CANVAS) is a randomized placebo-controlled trial in more than 4,000 patients with type 2 diabetes who have a history of or are at high risk of cardiovascular events. Currently under way, it is evaluating the occurrence of major adverse cardiovascular events (the primary end point) in patients randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, or placebo once daily for up to 4 years. Secondary end points will be the drug's effects on fasting plasma insulin and glucose, progression of albuminuria, body weight, blood pressure, HDL-C, LDL-C, bone mineral density, markers of bone turnover, and body composition.[10] This trial will run for 9 years, to be completed in 2018.[13]

The CANVAS investigators have already reported that within the first month of treatment, 13 patients taking canagliflozin suffered a major cardiovascular event, including stroke (one of which was fatal) compared with just one patient taking placebo. These events were not seen after the first month. The hazard ratio for major adverse cardiovascular events within the first 30 days was 6.49, but this dropped to 0.89 after the first 30 days.[10]

Additional issues that should be addressed in long-term postmarketing studies include possible relationships with cancers and pancreatitis and the safety of the drug in pregnancy and in children with diabetes.[10]

■ WHO IS A CANDIDATE FOR THIS DRUG?

Canagliflozin is approved for use as monotherapy in addition to lifestyle modifications. It is also approved for use with other antihyperglycemic drugs, including metformin.

Obese patients with type 2 diabetes and normal kidney function may have the greatest benefit. Because of canagliflozin's insulin-independent mechanism of action, patients with both early and late type 2 diabetes may benefit from its ability to lower hemoglobin A_{1c} and blood glucose.[14]

Use caution when starting this drug in the elderly or in patients on diuretics or multiple antihypertensive drugs

Although it can be used in patients with moderate (but not severe) kidney disease, canagliflozin does not appear to be as effective in these patients, who had higher rates of adverse effects.[11] It is not indicated for patients with type 1 diabetes, type 2 diabetes with ketonuria, or end-stage renal disease (estimated glomerular filtration rate < 45 mL/min or receiving dialysis).[11] It also is not yet recommended for use in pregnant women or patients under age 18.

The recommended starting dose of canagliflozin is 100 mg once daily, taken with breakfast. This can be increased to 300 mg once daily if tolerated. However, patients with an estimated glomerular filtration rate of 45 to 60 mL/min should not exceed the 100-mg dose. No dose adjustment is required in patients with mild to moderate hepatic impairment. It is not recommended, however, in patients with severe hepatic impairment.[11]

Comment. Although canagliflozin is approved as monotherapy, metformin remains my choice for first-line oral therapy. Because canagliflozin is more expensive and its long-term affects are still relatively unknown, I prefer to use it as an adjunct, and believe it will be a useful addition, especially in obese patients who are seeking to lose weight.

■ WHAT IS THE COST OF THIS DRUG?

The suggested price is $10.53 per tablet (AmerisourceBergen), which is comparable to that of other newer drugs for type 2 diabetes.

■ THE BOTTOM LINE

The availability of canagliflozin as an additional oral antihyperglycemic option may prove helpful in managing patients with type 2 diabetes who experience adverse effects with other antihyperglycemic drugs.

As with any new drug, questions remain about the long-term risks of canagliflozin. However, it seems to be well tolerated, especially in patients with normal kidney function, and poses a low risk of hypoglycemia. The slight increase in LDL-C may prompt more aggressive lipid management. Whether blood pressure-lowering and weight loss will offset this increase in LDL-C is yet to be determined. Ongoing studies will help to further elucidate whether there is an increased risk of cardiovascular events.

Finally, canagliflozin distinguishes itself from other oral diabetes drugs by its added benefit of weight loss, an appealing side effect, especially in the growing population of obese individuals with type 2 diabetes mellitus. ■

Carefully monitor LDL-C, as there may be a slight increase in patients receiving canagliflozin

■ REFERENCES

1. **Centers for Disease Control and Prevention (CDC)**. Diabetes data and trends. www.cdc.gov/diabetes/statistics/. Accessed September 6, 2013.
2. **National Diabetes Information Clearinghouse (NDIC), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**. National diabetes statistics, 2011. www.diabetes.niddk.nih.gov/dm/pubs/statistics/. Accessed September 6, 2013.
3. **Campbell RK**. Fate of the beta-cell in the pathophysiology of type 2 diabetes. J Am Pharm Assoc (2003). 2009; 49(suppl 1):S10–S15.
4. **American Diabetes Association**. Executive summary: standards of medical care in diabetes—2012. Diabetes Care 2012; 35(suppl 1):S4–S10.
5. **Blonde L**. Current antihyperglycemic treatment strategies for patients with type 2 diabetes mellitus. Cleve Clin J Med 2009; 76(suppl 5):S4–S11.
6. **Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS**. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. Am J Med 2009; 122:443–453.
7. **Vallon V**. The proximal tubule in the pathophysiology of the diabetic kidney. Am J Physiol Regul Integr Comp Physiol 2011; 300:R1009–R1022.
8. **DeFronzo RA, Davidson JA, Del Prato S**. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012; 14:5–14.
9. **Pfister M, Whaley JM, Zhang L, List JF**. Inhibition of SGLT2: a novel strategy for treatment of type 2 diabetes mellitus. Clin Pharmacol Ther 2011; 89:621–625.
10. **Food and Drug Administration (FDA)**. FDA Briefing Document. NDA 204042. Invokana (canagliflozin) Tablets. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf. Accessed September 6, 2013.
11. **INVOKANA (canagliflozin) tablets, for oral use**. Prescribing Information. Janssen Pharmaceuticals, Inc. www.janssenpharmaceuticalsinc.com/assets/invokana_prescribing_info.pdf. Accessed September 6, 2013.
12. **Stenlöf K, Cefalu WT, Kim KA, et al**. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013; 15:372–382.
13. **US National Institutes of Health**. ClinicalTrials.gov. CANVAS—CANagliflozin cardioVascular Assessment Study. http://clinicaltrials.gov/show/NCT01032629. Accessed September 6, 2013.
14. **Devineni D, Morrow L, Hompesch M, et al**. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab 2012; 14:539–545.

ADDRESS: Mary Vouyiouklis, MD, Department of Endocrinology, Diabetes, and Metabolism, X20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail vouyiom@ccf.org