

Canagliflozin: a novel treatment option for type 2 diabetes

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Abstract: Type 2 diabetes continues to be a challenging disease to manage. The addition of new agents with a positive risk–benefit ratio could potentially assist clinicians and patients in achieving adequate diabetes control. Canagliflozin, the first sodium–glucose cotransporter 2 inhibitor presently available on the market, offers a unique mechanism of action: it inhibits renal reabsorption of glucose, thereby increasing urinary glucose excretion. It reduces hemoglobin A_{1c} by approximately 0.37%–1.16%; it also reduces the patient’s weight and systolic blood pressure and has a low risk for hypoglycemia. Adverse effects include an increased risk of urinary tract infections and genital mycotic infections. In this manuscript we review canagliflozin and its potential role in management of type 2 diabetes mellitus.

Keywords: canagliflozin, SGLT2 inhibitor, type 2 diabetes, oral hypoglycemic

Introduction

Diabetes affects 25.8 million people in the US, which accounts for more than 8% of the population; nearly 2 million new cases are diagnosed each year.¹ In the late 1980s, only about 2% of those with diabetes achieved all their therapeutic goals (using American Diabetes Association goals at time of study: hemoglobin A_{1c} [A_{1c}] <7%, blood pressure (BP) <130/80 mmHg, and cholesterol goals (low-density lipoprotein [LDL] <100 mg/dL).² In 2010, the number of persons with diabetes reaching all their therapeutic goals had approached 20%. While that is a significant increase, it is clear that the vast majority of patients with diabetes are not receiving optimal care. When considering therapeutic goals as of 2010, only a little over half (52.5%) of patients with diabetes had achieved their A_{1c} goal, 51.1% had achieved their blood pressure goal; and 56.7% had achieved their LDL cholesterol goal.² Thus, whereas improvements have been seen over the past 2 decades, there is certainly more room for improvement. A number of new pharmacologic agents for type 2 diabetes mellitus (T2DM) have become available in recent years; their use as treatment may increase the number of patients reaching their therapeutic goals.

A number of injectable and oral medications are available for treating T2DM; each carries risks and benefits that must be considered to select the most appropriate therapy for the patient. Some factors to consider include A_{1c} and glucose reduction, dosing complexity, adverse events (AEs), effects on weight and cholesterol, cardiovascular (CV) effects, and cost. Metformin is generally considered the initial drug of choice for T2DM because of its highly favorable risk–benefit ratio.³ It usually produces A_{1c} reductions of 1% or greater, does not cause weight gain or hypoglycemia, does not adversely affect cholesterol, is inexpensive, and is generally well tolerated. Should a

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patient require addition of a second agent, the aforementioned factors must be accounted for when taking a patient-centered approach to diabetes management. Agents with multiple advantages may assist more people to reach their therapeutic goals. Canagliflozin (INVOKANA™; Janssen Pharmaceuticals, Johnson and Johnson, New Brunswick, NJ, USA) the first sodium-glucose cotransporter 2 (SGLT2) inhibitor available on the market, offers a unique mechanism of action: it inhibits renal reabsorption of glucose, thus increasing urinary glucose excretion. It also reduces weight and systolic blood pressure and has a low risk of hypoglycemia. AEs include increased risk of urinary tract infections (UTIs) and genital mycotic infections. In this manuscript, we review the potential role for canagliflozin in management of T2DM.

Pharmacology and pharmacokinetics of canagliflozin

Nearly all plasma glucose (PG) that is filtered at the glomerulus of the kidney is reabsorbed in the proximal tubule, with less than 1% being excreted into the urine. Reabsorption of the filtered glucose is mediated primarily by the glucose transporter protein SGLT2, and to a lesser extent, by the sodium-glucose cotransporter 1 (SGLT1). SGLT1 is located in the kidney, intestine, and heart, whereas SGLT2 is located primarily in the S1 segment of the proximal tubules; SGLT2 is responsible for reabsorbing 90% of the filtered glucose in the kidney⁴ and can reabsorb nearly all glucose filtered by the glomerulus up to a PG concentration of approximately 180 mg/dL, the renal threshold for glucose (RTG).^{5–7} This threshold can be increased up to 240 mg/dL in those with T2DM.⁸ At PG levels exceeding the RTG, SGLT2 becomes saturated and urine glucose concentrations increase proportionately to PG levels. By inhibiting SGLT2, renal glucose reabsorption is reduced, leading to increased urine glucose excretion and a subsequent reduction in PG.⁹ Importantly, SGLT2 inhibition reduces PG in an insulin-independent manner, potentially mitigating the risk for hypoglycemia.

Canagliflozin is a selective inhibitor for SGLT2 that lowers the RTG to approximately 80 mg/dL, increasing the urinary excretion of glucose.⁹ At higher doses (300 mg per day or higher), canagliflozin may also inhibit SGLT1 in the intestine and delay postprandial glucose absorption;¹⁰ doses of 100 mg daily do not appear to have a significant affinity for the SGLT1 receptor.

Canagliflozin reaches peak plasma concentrations within 1 to 2 hours following oral administration, and steady state levels are reached in 4 to 5 days;¹¹ it has a bioavailability of 65% and is highly protein bound (99%), mainly to albumin.

Following single oral doses, the terminal half-life was 10.6 and 13.1 hours for canagliflozin 100 mg and 300 mg, respectively. With continued dosing, canagliflozin reduces the RTG throughout the 24 hour dosing interval, allowing for once daily dosing. Metabolism is mainly via O-glucuronidation via uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) and uridine diphosphate glucuronosyltransferase B4 (UGT2B4) to inactive metabolites, which are renally eliminated. Cytochrome P450 (CYP) metabolism of canagliflozin is minimal, reducing the potential for drug–drug interactions. Approximately 33% of canagliflozin metabolites are renally eliminated and approximately 42% is excreted in the feces.¹¹

Clinical trials

Search criteria

PubMed was searched using the term “canagliflozin” and “SGLT2” from inception to May 2013. The reference lists from identified articles were hand searched for additional relevant information. Only published trials conducted in humans were included; if studies evaluated doses other than 100 mg and 300 mg, only the information for the US Food and Drug Administration (FDA)-approved doses was evaluated in detail and is reported in this review.

Monotherapy

The CANTATA-M (Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise) trial investigated the safety and efficacy of canagliflozin monotherapy in addition to diet and exercise in patients with T2DM (Table 1).¹² Eligible patients were aged 18–80 years and met one of the following criteria: 1) not receiving an oral antidiabetic agent (ADA) with an A_{1c} >7% but <10% at screening (main study); or 2) on monotherapy (except thiazolidinedione) or combination therapy with metformin plus a sulfonylurea (at <50% maximum doses) with an A_{1c} of 6.5–9.5% at screening; a fasting blood glucose (FBG) <270 mg/dL, and an A_{1c} of >7% but <10% after a 2 week washout period. Patients with a baseline A_{1c} >10% but <12% and an FBG of <350 mg/dL 1 week before randomization were eligible for enrollment into the “high glycemic” cohort. Patients were excluded if they had an estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m² at screening or CV disease, or if they were receiving any other ADA other than metformin and/or a sulfonylurea.¹²

The primary outcome was the change in A_{1c} from baseline to week 26 for canagliflozin versus placebo in the

Table 1 Efficacy of canagliflozin in clinical trials

Study	Design and intervention	Primary outcome	Secondary outcomes
Stenlöf et al ¹²	<ul style="list-style-type: none"> – 26 week R, DB, PC, PG – Main study: can 100 mg (n=195), can 300 mg (n=197), or pcb (n=192) added to diet and exercise – High glyceimic: can 100 mg (n=47) or can 300 mg (n=44) added to diet and exercise 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Main study (LS mean difference compared to pcb): can 100 mg: –0.91%; can 300 mg: –1.16% – High glyceimic: can 100 mg: –2.13%; can 300 mg: –2.56% 	<ul style="list-style-type: none"> – FBG: reduced by 27 mg/dL with can 100 mg and 34 mg/dL with can 300 mg – BVW: –1.9 kg with can 100 mg and –2.9 kg with can 300 mg (LS mean difference versus pcb)
Rosenstock et al ¹³	<ul style="list-style-type: none"> – 26 week R, DB, PC, PG, DR study – Can 100 mg (n=64), can 300 mg (n=64), sita 100 mg (n=65), or pcb (n=65) added to baseline metformin therapy 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Can 100 mg: –0.76%; can 300 mg: –0.92%; sita 100 mg: –0.74%; pcb: –0.22% 	<ul style="list-style-type: none"> – FBG: can 100 mg: –25.2 mg/dL; can 300 mg: –25.2 mg/dL; sita 100 mg: –12.6 mg/dL; pcb: 3.6 mg/dL – BVW: can 100 mg: –2.6 kg; can 300 mg: –3.4 kg; sita 100 mg: –0.4 kg; pcb: –0.8 kg
Schernthaner et al ¹⁴	<ul style="list-style-type: none"> – 52 week R, DB, AC, NI – Can 300 mg (n=378), Sita 100 mg (n=378) with metformin plus sulfonylurea 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Can 300 mg: –1.03%; Sita 100 mg: –0.66% 	<ul style="list-style-type: none"> – FBG: can 300 mg: –28.7 mg/dL; Sita 100 mg: –2.2 mg/dL – BVW: can 300 mg: –2.6 kg; sita 100 mg: –0.1 kg
Devineni et al ¹⁵	<ul style="list-style-type: none"> – 28 day R, DB, PC – Can 100 mg (n=10), can 600 mg (n=10), or pcb (n=9) with insulin therapy 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Can 100 mg: –0.37%;[^] can 600 mg: –0.55%[^] 	<ul style="list-style-type: none"> – FBG: can 100 mg: –2.37 mmol/L;[^] can 600 mg: –2.48 mmol/L[^] – BVW: can 100 mg: –0.68 kg;[^] can 600 mg: –1.24 kg[^]
Yale et al ¹⁶	<ul style="list-style-type: none"> – 26 week R, DB, PC study in patients with stage 3 CKD – Can 100 mg (n=90), can 300 mg (n=89), or pcb (n=90) in addition to background therapy 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Can 100: –0.37%; can 300 mg: –0.44%; pcb: –0.03% 	<ul style="list-style-type: none"> – FBG: not statistically different between groups – BVW: can 100: –1.4 kg; can 300 mg: –1.6 kg; pcb: 0.2 kg
Bode et al ¹⁷	<ul style="list-style-type: none"> – 26 week R, DB, PC study in patients aged 55–80 years – Can 100 mg, can 300 mg, or pcb in addition to background therapy 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Can 100: –0.60%; can 300 mg: –0.73%; pcb: –0.03% 	<ul style="list-style-type: none"> – FBG: can 100 mg: –25.5 mg/dL; can 300 mg: 27.7 mg/dL – BVW: can 100 mg: –2.1 kg; can 300 mg: –2.7 kg

Note: [^]Compared to placebo.

Abbreviations: AC, active control; A_{1c} , hemoglobin A_{1c} ; BW, body weight; Can/can, canagliflozin; CKD, chronic kidney disease; DB, double-blind; DR, dose ranging; FBG, fasting blood glucose; LS, least squares; NI, noninferiority; PC, placebo-controlled; pcb, placebo; PG, parallel group; R, randomized; Sita/sita, sitagliptin.

modified intent-to-treat (mITT) population, which included all patients who received at least one dose of study medication. Secondary outcomes included the proportion of patients achieving an A_{1c} <7% and changes from baseline in FBG, BP, high-density lipoprotein (HDL), triglycerides (TG), and body weight. Comparisons between treatment regimens were performed using the least squares (LS) mean method. To have 90% power to detect a between-group difference of 0.5%, at least 85 patients per group were needed. However, for AE tracking purposes, 150 patients per group were targeted for enrollment.¹²

Those patients not receiving an ADA at screening underwent a 2 week placebo run-in period followed by randomization, whereas those receiving an ADA at screening underwent an 8 week washout and placebo run-in period. Patients in the main study were randomized in a double-blind fashion at a 1:1:1 ratio to receive canagliflozin 100 mg daily (n=195), canagliflozin 300 mg daily (n=197), or placebo (n=192) for 26 weeks. The high glyceimic cohort consisted of 47 patients randomized to receive canagliflozin 100 mg daily and 44 patients randomized to canagliflozin 300 mg daily,

both for 26 weeks; there was no placebo group. Metformin was used as a glyceimic rescue for elevated FBG values in both cohorts.

At randomization, the mean age in the main study was 55.4 years; 44% of patients were male, 67.6% were White, and 7% were Black. The mean A_{1c} was 8%, the mean FBG was 171 mg/dL, and the mean body weight and body mass index (BMI) were 86.8 kg and 30.4 kg/m², respectively. The high glyceimic cohort had a mean age of 49.3 years; 54% of patients were male, 60.4% were White, and 4.4% were Black. The mean A_{1c} and FBG were 10.6% and 241 mg/dL, respectively, and patients weighed an average of 82.5 kg and had a BMI of 30.5 kg/m². In the main study, 48% of patients were receiving an ADA at screening, whereas 23% of the subjects in the high glyceimic cohort were receiving an ADA.

In all, 584 patients in the main study were included for analysis (mITT population). After 26 weeks of treatment, canagliflozin 100 mg and 300 mg reduced the baseline A_{1c} by 0.77% and 1.03%, respectively, which led to an LS mean difference of –0.91% and –1.16% compared with

placebo ($P < 0.001$ for both doses) (Table 1). In the high glycemic cohort, the baseline A_{1c} was reduced by 2.13% with canagliflozin 100 mg and 2.56% with canagliflozin 300 mg in the 91 subjects who were included in the analysis. In both cohorts, similar reductions in A_{1c} were seen regardless of current use or history of treatment with an ADA at baseline.

Secondary outcomes were also improved with canagliflozin compared with placebo, including a higher proportion of patients reaching an $A_{1c} < 7\%$, larger reductions in FBG (mean decrease of 27 mg/dL with canagliflozin 100 mg and 34 mg/dL with canagliflozin 300 mg), and a LS mean difference in body weight of -1.9 kg and -2.9 kg for canagliflozin 100 mg and 300 mg, respectively. Systolic BP and HDL were also improved with canagliflozin, whereas TG and diastolic BP were not statistically different compared to placebo. LDL was marginally increased by 2% and 6.1% in those receiving canagliflozin 100 mg and 300 mg, respectively, compared to placebo. Fewer patients receiving canagliflozin required rescue therapy with metformin (2.6% and 2.0% with canagliflozin 100 mg and 300 mg, respectively) compared with those randomized to receive placebo (22.7%).

AEs considered to be related to study medication occurred in 9.4% of patients receiving placebo; 17.4% of those receiving canagliflozin 100 mg daily; and in 25.4% in those receiving canagliflozin 300 mg daily. Only ten patients receiving canagliflozin (2.6%) discontinued the study due to AEs compared to two patients receiving placebo (1%). Importantly, genital mycotic infections were seen in a higher percent of both males (4.1%) and females (8.1%) receiving canagliflozin compared with those receiving placebo (no cases in males, but in 3.9% of females). However, most infections were mild to moderate in severity and were effectively treated with traditional oral or topical treatments; a mild increase in the risk for urinary tract infections was also noted. No cases of severe hypoglycemia were noted; only 3.6%, 3%, and 2.6% of patients receiving canagliflozin 100 mg, 300 mg, or placebo, respectively, experienced mild hypoglycemia. Increases in blood urea nitrogen (BUN) and serum creatinine (SCr) were also noted in those receiving canagliflozin.

Combination therapy: canagliflozin versus sitagliptin

A 12 week randomized, double-blind, placebo-controlled, parallel group dose-ranging study evaluated the safety and efficacy of canagliflozin in patients with T2DM who were receiving stable doses of metformin.¹³ Eligible patients

included those receiving stable metformin monotherapy for >3 months at a dose of $>1,500$ mg/day who had a baseline A_{1c} of $>7\%$ but $<10.5\%$; serum creatinine was also required to be <1.4 mg/dL for females and <1.5 mg/dL for males. No specific exclusion criteria were provided.¹³

The mean age of the study patients was 52.9 years and 52% were male; no information regarding race or ethnicity was provided. The baseline A_{1c} ranged from 7.6%–8% across the treatment groups, and the average FBG was 162 mg/dL; the mean bodyweight and BMI were 87.1 kg and 31.5 kg/m², respectively. The average metformin dose was 1,890 mg/day, and the mean duration of diabetes was 6 years.

After a 3–4 week pretreatment screening phase, patients were randomized to receive canagliflozin once daily at a dose of 50 mg ($n=64$), 100 mg ($n=64$), 200 mg ($n=65$), or 300 mg ($n=64$), canagliflozin 300 mg twice daily (BID) ($n=64$), sitagliptin 100 mg daily ($n=65$), or placebo ($n=65$) for 12 weeks, in addition to baseline metformin therapy. The Sitagliptin arm was included to provide a benchmark for clinical efficacy and was not compared statistically to placebo or any dose of canagliflozin. The primary outcome was the change in A_{1c} from baseline after 12 weeks of treatment; secondary outcomes included changes in weight and FBG, urinary glucose-to-creatinine ratio, and assessment of beta-cell function. Outcomes were analyzed in the ITT population, which included 451 patients. Results for the 100 mg and 300 mg once daily canagliflozin doses will be emphasized hereinafter as they represent the currently approved doses.

After 12 weeks of treatment, canagliflozin 100 mg and 300 mg significantly reduced the baseline A_{1c} by 0.76% and 0.92%, respectively, compared with a 0.2% reduction with placebo ($P < 0.001$ for both doses compared to placebo) (Table 1). Sitagliptin 100 mg daily produced a 0.74% reduction in the A_{1c} , whereas canagliflozin 100 mg and 300 mg reduced the baseline body weight by 2.6 kg and 3.4 kg, respectively, and both doses reduced FBG by 25.2 mg/dL. The weight loss produced by canagliflozin was progressive throughout the study and did not appear to plateau by study end. Urinary glucose excretion was increased with canagliflozin 100 mg and 300 mg to 51.5 mg/dL and 49.4 mg/dL, respectively; and the RTG decreased to 80 mg/dL with canagliflozin 300 mg daily. Treatment with canagliflozin also improved HDL and TG but caused a minor increase in LDL in only those receiving BID canagliflozin (specific increase not reported). Beta-cell function was also improved in both canagliflozin and sitagliptin compared with placebo.

The incidence of AEs was similar across treatment groups, and only eleven patients discontinued the study early due to

an AE; nine of these subjects were randomized to receive canagliflozin (2.8%). Events that occurred in more than ten patients included urinary tract infections (UTIs), headache, vulvovaginal mycotic infections, nausea, nasopharyngitis, diarrhea, and pollakiuria. The risk for UTI was not increased with canagliflozin treatment, although the risk for genital mycotic infections in females was increased, most commonly vulvovaginal candidiasis. Only one event was observed in females receiving placebo (3%) compared with 28 events (18%) in females receiving canagliflozin. However, these infections were generally mild in severity and responded to topical and/or oral treatments. Importantly, there were no cases of severe hypoglycemia and only eleven cases of symptomatic hypoglycemia, seven of which occurred in those receiving canagliflozin (2.2%). Important limitations to consider include the short study duration (12 weeks) and small sample size, as only 128 patients received a currently approved dose of canagliflozin.

It is not uncommon for T2DM in many patients to progress to the point of needing multiple medications to reach therapeutic goals. Schernthaner et al¹⁴ studied canagliflozin in a 52 week, randomized, noninferiority, double-blind Phase III study to determine the efficacy of using canagliflozin in patients taking metformin and a sulfonylurea compared to sitagliptin in uncontrolled patients.

To be eligible, participants must have been taking >1,500 mg of metformin daily and a sulfonylurea dose of at least half the maximum labeled dose. Participants were also required to have an A_{1c} between 7.0% and 10.5%. Subjects were excluded if they presented with any of the following: type 1 diabetes; CV disease or uncontrolled hypertension; receiving insulin or any other oral hypoglycemic therapy other than metformin or a sulfonylurea; $eGFR < 55 \text{ mL/min/1.73 m}^2$ (60 mL/min/1.73 m² based on restriction of metformin use), serum creatinine of $\geq 1.5 \text{ mg/dL}$ (men) or $\geq 1.4 \text{ mg/dL}$ (women); or repeated FBG values $> 300 \text{ mg/dL}$.

The study included 755 participants who were randomized to receive either canagliflozin 300 mg daily (n=378) or sitagliptin 100 mg daily (n=378) in addition to their baseline therapy. Subjects first underwent a 2 week single blinded placebo run-in period, followed by 52 weeks of treatment with study medication and a 4 week follow-up period. Once enrolled in the study, participants presenting with an FBG of at least 270 mg/dL between day 1 and week 6, 240 mg/dL between week 6 and week 12, or 200 mg/dL between week 12 and week 26 were removed from the study. Patients with an $A_{1c} \geq 8.0\%$ after week 26 were also removed from the study,

as were those who met the initial exclusion criteria regarding serum creatinine or eGFR or developed a contraindication to metformin.

After 52 weeks of treatment, 210 subjects in the canagliflozin 300 mg daily group and 254 subjects in the sitagliptin 100 mg daily group completed the study; however, all patients were included in the ITT analysis. Participants in each arm had similar baseline characteristics, with an average age of 56.7 years, average A_{1c} of 8.1%, and a duration of diabetes of > 9 years. A majority of the participants, 64.2%, were White; only 11.7% of the participants identifying themselves as Black or African American.

The primary endpoint, change in A_{1c} from baseline at week 52, was found to be -1.03% and -0.66% in the canagliflozin 300 mg daily and sitagliptin 100 mg daily groups, respectively, with a difference of -0.37% (95% confidence interval [CI], -0.50 to -0.25) (Table 1). The authors noted that this result not only met the criteria for noninferiority but also indicated that canagliflozin 300 mg daily may actually be superior to sitagliptin 100 mg daily in their study subjects. Canagliflozin and sitagliptin reduced FBG by 28.7 mg/dL and 2.2 mg/dL, respectively, and 47.6% of the canagliflozin 300 mg daily group versus 35.3% of the participants in the sitagliptin 100 mg daily group reached an A_{1c} level of $< 7\%$. A higher rate of discontinuation was seen in the sitagliptin group (22.5%) compared with the canagliflozin group (10.6%) when those receiving sitagliptin met withdrawal criteria due to poor glycemic control. This further indicates that participants appeared to be better controlled with canagliflozin 300 mg daily than with sitagliptin 100 mg daily.

Along with the reduction in glucose, a significant reduction in body weight, systolic BP, and diastolic BP was seen with canagliflozin relative to sitagliptin at -2.6 kg versus -0.1 kg ($P < 0.001$), -5.1 mmHg versus 0.9 mmHg ($P < 0.001$), and -3.0 mmHg versus -0.3 mmHg (difference of -2.7 mmHg , 95% CI, -3.8 to -1.7). Also, both HDL and LDL were increased in the canagliflozin group compared with the sitagliptin group, by 7.6% versus 0.6% (difference of 7%, 95% CI 4.6–9.3) and 11.7% versus 5.2% (difference of 6.4%, 95% CI 1.7–11.2).

Overall study discontinuations in the canagliflozin and sitagliptin groups were reported as 168 and 123, respectively. The incidence of any AE appeared to be fairly similar between the two groups, with 293 and 289 patients reporting an AE in the canagliflozin and sitagliptin group, respectively; however, canagliflozin was associated with a higher incidence of genital mycotic infections compared with sitagliptin (45 versus eight cases). There was only one reported discontinuation

resulting from mycotic infection in the canagliflozin group. The incidence of UTIs was similar in each group, as were increases in urinary frequency. Any other AE reported by less than 2% of the participants was considered to be negligible by the authors.

The authors concluded that the addition of canagliflozin 300 mg daily can significantly improve glycemic control, reduce weight, and reduce systolic BP when added to oral therapy with metformin and a sulfonylurea. Important limitations were the short study duration and the unknown efficacy of canagliflozin if it is added to other oral ADAs besides metformin and a sulfonylurea.

Canagliflozin combined with insulin

Because of its unique mechanism of action, the use of canagliflozin may provide additional benefit when used in combination with insulin. In a small, randomized, double-blind, placebo-controlled study, Devineni et al¹⁵ enrolled 29 patients with T2DM currently not controlled on insulin and one or no ADA. Subjects were randomized to either canagliflozin 100 mg daily (n=10) or placebo (n=5) in cohort 1 or canagliflozin 300 mg BID (n=10) or placebo (n=4) in cohort 2. Subjects were followed weekly while participating in this study.

Study subjects were between the ages of 18 and 65 years, diagnosed with T2DM for ≥ 6 months, were on stable insulin therapy for ≥ 2 weeks, and had a BMI of 25–35 kg/m², an FBG 59–270 mg/dL, an A_{1c} 7%–5%, and a serum creatinine of <1.5 mg/dL for men and <4 mg/dL for women. Potential subjects were excluded if they had history of CV, hematologic, respiratory, renal, or gastrointestinal disease. Also excluded were those with type 1 diabetes, those who had received an insulin infusion within the past 3 months, those who had a history of diabetic ketoacidosis, and women at risk of becoming pregnant.

The authors reported that the baseline characteristics were similar between groups; however, statistical analysis was not conducted and/or not reported. Key characteristics for placebo, canagliflozin 100 mg, and canagliflozin 300 mg BID groups, respectively, are as follows; average age 52.8, 50.5, and 47.2 years; average weight of 95.1, 107.8, and 94.1 kg; average A_{1c} of 8.3%, 8.45%, and 8.4%; average total daily insulin use of 38.4, 114.6, and 51.4 units.

At the end of the 28 days, a significant decrease in A_{1c} of 0.37% was observed in the canagliflozin 100 mg group ($P < 0.05$) and 0.55% in the canagliflozin 300 mg BID group ($P < 0.05$) compared with placebo (Table 1). This correlated to a reduction in FBG of 42.7 mg/dL and 44.6 mg/dL in the

canagliflozin 100 mg daily and 300 mg BID groups, respectively, compared with placebo ($P < 0.05$ for both groups). A reduction in 24 hour PG levels along with an increase in urinary glucose excretion (67.20 g/day and 153.60 g/day) was also seen in the canagliflozin 100 mg and 300 mg BID groups, respectively, compared with placebo ($P < 0.05$). Body weight decreased by 0.68 kg in the canagliflozin 100 mg group and by 1.24 kg in the canagliflozin 300 mg BID group compared with placebo; only the decrease in body weight for the 300 mg BID group reached statistical significance.

All groups had a similar overall rate of AEs reported. The canagliflozin 300 mg BID group did report a higher incidence of headaches (n=6) when compared with both canagliflozin 100 mg daily (n=3) and placebo (n=2). Patients taking canagliflozin did see a clinically insignificant increase in serum creatinine compared with placebo, which returned to baseline once canagliflozin was discontinued. All other laboratory markers reported in the study appeared to show no clinically significant change in any group other than changes in urinary urate excretion, which was reduced with canagliflozin.

Based on this study, it appears that canagliflozin may be beneficial in patients with T2DM who are uncontrolled with insulin therapy. Because of the size of this study and the short follow-up time, more data will be needed to fully assess the potential benefits and risk with the combination of canagliflozin and insulin.

Safety in specific populations

Yale et al¹⁶ conducted a study with the objective of determining the safety and efficacy of canagliflozin in subjects diagnosed with stage 3 chronic kidney disease (CKD) (Table 2). This randomized double-blind, placebo-controlled Phase III study included 269 subjects randomized to receive canagliflozin 100 mg daily, canagliflozin 300 mg daily, or placebo for 26 weeks. Results of a 26 week double-blind extension period were planned to be reported separately. Patients may have also been initiated on glycemic rescue therapy either by an up-titration of current medications or with the addition of other oral medications if FBG became >270 mg/dL during week 1 to 6, >240 mg/dL during week 6 to week 12, or >200 mg/dL during week 12 to week 26.

Eligible patients had to have stage 3 CKD (eGFR ≥ 30 and <50 mL/min/1.73 m²) and T2DM that was inadequately controlled (A_{1c} $\geq 7.0\%$ and $\leq 10.5\%$), and either be receiving a stable oral hypoglycemic regimen (monotherapy or combination therapy) or no treatment at all. Potential participants were excluded if they had recurrent FBG >270 mg/dL during the pretreatment phase, were receiving immunosuppressant

Table 2 Safety in specific populations

Study	Design and intervention	Primary outcome	Adverse drug events
Yale et al ¹⁶	<ul style="list-style-type: none"> – 26 week R, DB, PC – stage 3 chronic kidney disease (CKD) (eGFR ≥ 30 and < 50 mL/min/1.73 m²) – can 100 mg (n=90), can 300 mg (n=89), or pcb (n=90) 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – LS mean difference compared to pcb: can 100 mg: 0.3% ($P < 0.05$); can 300 mg: 0.4% ($P < 0.001$) 	<ul style="list-style-type: none"> – Mycotic infections: can 100 mg (n=2); can 300 mg (n=2); pcb (n=0) – Change in eGFR: can 100 mg: -9.1%; can 300 mg: -10.1%; pcb: -4.5% – Change in BUN: can 100 mg: +12.1%; can 300 mg: +12.5%; pcb: +4.9%
Bode et al ¹⁷	<ul style="list-style-type: none"> – 26 week R, DB, PC – Average age of 63.6 years – Can 100 mg (n=241), can 300 mg (n=236), or pcb (n=237) 	<ul style="list-style-type: none"> – Reduction in A_{1c} from baseline – Compared to pcb: Can 100 mg: -0.57%; can 300 mg: -0.7% 	<ul style="list-style-type: none"> – Mycotic infections: can 100 mg (n=22); can 300 mg (n=20); pcb (n=2) – Pollakiuria: can 100 mg (n=6); can 300 mg (n=12); pcb (n=5) – Polyuria: can 100 mg (n=4); can 300 mg (n=4); pcb (n=0) – Hypoglycemia mono-therapy: can 100 mg (n=4); can 300 mg (n=3); pcb (n=2) – Hypoglycemia combination therapy: can 100 mg (n=78); can 300 mg (n=82); pcb (n=66)

Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled; eGFR, estimated glomerular filtration rate; can, canagliflozin; pcb, placebo; A_{1c}, hemoglobin A_{1c}; LS, least squares; BUN, blood urea nitrogen.

medications, had a history of previous transplant, currently on dialysis, previous or current CV issues, or had a cerebrovascular incident within 3 months of screening.

Initially, 269 patients were randomized and 234 subjects completed the study with 77, 75, and 82 patients in the placebo, canagliflozin 100 mg daily, and canagliflozin 300 mg daily groups, respectively. Baseline characteristics of these subjects included an average age of 68.5 ± 8.3 years, and average A_{1c} of $8.0\% \pm 0.9\%$, an average FBG of 164.0 ± 49.6 mg/dL, an average body weight of 91.2 ± 18.0 kg, and an average eGFR of 39.4 ± 6.9 mL/min. The authors did not report any significant differences in these baseline characteristics between treatment groups.

After 26 weeks of treatment, canagliflozin 100 mg and 300 mg led to an LS mean difference in the A_{1c} of 0.3% ($P < 0.05$) and 0.4% ($P < 0.001$), respectively, compared to placebo (Table 1). A higher percentage of subjects reached an A_{1c} $< 7\%$ in the canagliflozin 300 mg group (32.6%) and canagliflozin 100 mg group (27.3%) compared with the placebo group (17.2%). This correlated with a slight reduction in FBG values in all groups, but the difference was not statistically significant.

Treatment with canagliflozin also resulted in a significant reduction in body weight when compared with placebo, reducing body weight by 1.2% and 1.5% in the canagliflozin 100 mg and 300 mg groups, respectively, whereas body weight increased by 0.3% in the placebo group. Systolic BP was the only other endpoint found to be significantly reduced compared with placebo, reduced by 5.7 mmHg and 6.1 mmHg in the canagliflozin 100 mg and 300 mg

groups, respectively. The authors did not find any significant difference in diastolic BP, TG, LDL, or HDL cholesterol between groups.

The total number of AEs reported was not significantly different between groups. A higher incidence of genital mycotic infections was seen in the canagliflozin 100 mg and 300 mg groups compared with placebo (2, 2, and 0 cases, respectively). There was a decrease in eGFR seen in all groups but was slightly higher in the canagliflozin 100 mg and 300 mg groups compared with placebo (-9.1%, -10.1%, and -4.5%, respectively). An increase in blood urea nitrogen was also seen in all groups: 12.1%, 12.5%, and 4.9% in the canagliflozin 100 mg, 300 mg, and placebo groups, respectively.

It appears that canagliflozin can still be an effective treatment option in a population with an eGFR of 30–50 mL/min. However, the A_{1c} lowering effects may be diminished in this population and should be taken into consideration when its use is considered in the stage 3 CKD patient population.

Bode et al¹⁷ looked at the use of canagliflozin in an elderly population (ages 55–80 years) with T2DM uncontrolled by their current glucose-lowering regimen. This regimen could include any oral hypoglycemic agent or injectable treatment (including insulin). This randomized double-blind Phase III trial was completed over 26 weeks and is currently being followed with a 78 week extension period. Patients were randomized to receive canagliflozin 100 mg daily, 300 mg daily, or placebo.

Subjects included had an A_{1c} 7%–10% at baseline, were receiving a stable T2DM treatment regimen or receiving

no treatment, had a BMI 20–40 kg/m², and had an FBG 110–270 mg/dL. Subjects were excluded if they had a history of cardiovascular disease, uncontrolled hypertension, an eGFR <50 mL/min, or had any renal condition that established a contraindication to metformin. This study also allowed for an up-titration or addition of medications if further glucose control was needed after initiation of study therapy.

Baseline characteristics were similar between study groups, which consisted of an average age of 63.6 years, with 38.2% of the subjects over 65 years and 6.4% of the patients over 75 years. The average baseline A_{1c} was 7.7%; the average duration of T2DM was 11.7 years; and the average eGFR was 77.5 mL/min.

After 26 weeks of treatment, canagliflozin 100 mg and 300 mg reduced the A_{1c} by 0.57% and 0.7%, respectively, compared with placebo ($P < 0.001$ for both doses) (Table 2). The percent of subjects reaching A_{1c} of <7.0% was 47.7%, 58.8%, and 28.0% in the canagliflozin 100 mg, 300 mg, and placebo groups, respectively. FBG also was reduced by 25.5 mg/dL in the canagliflozin 100 mg and 27.7 mg/dL in the 300 mg group compared with placebo ($P < 0.001$). It was noted that those with a higher baseline A_{1c} had a larger reduction in A_{1c} at the end of the study in both of the canagliflozin groups.

Canagliflozin also led to a significant reduction in body weight (2.1 kg and 2.7 kg decrease in the canagliflozin 100 mg and 300 mg groups, respectively) when compared with placebo ($P < 0.001$). As seen in previous studies, a reduction in both systolic and diastolic BP was noted in those receiving canagliflozin compared of placebo. Modest improvements in the lipid panel were also noted.

Rates of any AE were similar between the canagliflozin 100 mg group and placebo at 174 incidents each, but were slightly higher in the canagliflozin 300 mg group, with 184 incidents reported. A higher rate of mycotic infections was seen in the canagliflozin 100 mg and 300 mg groups compared to placebo with 22, 20, and 2 events, respectively, being reported. Pollakiuria was reported in five, six, and 12 cases and polyuria was observed in zero, four, and four subjects in the placebo, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Discontinuation due to any AE occurred in ten patients receiving placebo, five receiving canagliflozin 100 mg daily, and in 17 receiving canagliflozin 300 mg daily. As expected, hypoglycemia was seen more often in participants on multiple ADAs, including a slightly higher incidence in the canagliflozin 100 mg and 300 mg compared with placebo at 66, 76, and 82 events, respectively. There were no clinically significant changes in laboratory markers between study groups.

Based on this trial, canagliflozin may be a reasonable option for elderly patients without cardiovascular disease. Canagliflozin was shown to be efficacious and was fairly well tolerated in this population. Further studies will be needed to assess the use of canagliflozin in this population with known cardiovascular disease.

Canagliflozin AEs

Despite canagliflozin's efficacy in lowering A_{1c}, it is associated with a low incidence of hypoglycemia; no cases of severe hypoglycemia were reported in the clinical trials. This low risk for hypoglycemia is likely related to the ability of canagliflozin to lower the RTG to approximately 80 mg/dL, which is higher than the cutoff of 70 mg/dL that is associated with hypoglycemia. If the PG falls below 80 mg/dL, then renal reabsorption of glucose mediated by SGLT2 can occur to attenuate further decreases in PG. Accordingly, rates of hypoglycemia were generally similar for both the canagliflozin and placebo groups in clinical trials.¹¹

Canagliflozin most notably increases risk for genital mycotic infections in both males and females (Table 3). The manufacturer notes a rate of occurrence in females of 11.4% with canagliflozin 300 mg and 10.4% with canagliflozin 100 mg compared to only 3.2% with placebo in pooled analysis of four placebo-controlled trials. The risk for a mycotic infection is also increased in males (0.6% with placebo compared to 3.7%–4.2% incidence with canagliflozin), especially in those who are uncircumcised. Canagliflozin was associated with a similar risk for UTIs as placebo.¹¹

As canagliflozin leads to osmotic diuresis, patients may experience orthostatic hypotension, dizziness, hypotension, or syncope. The rate of these reactions is <5%, but the risk is increased in those receiving a loop diuretic, those older than 75 years of age, and in those with moderate renal impairment (eGFR 30–60 mL/min). Canagliflozin can also modestly increase serum uric acid, blood urea nitrogen, and LDL cholesterol while decreasing eGFR. Elevations in potassium have also been noted in those receiving canagliflozin, with a higher risk in those receiving potassium sparing diuretics and those with reduced renal function. Other reactions occurring at a rate >2% include increased thirst, increased urination, nausea, and constipation.¹¹

Dosing and administration

Canagliflozin has been approved by the FDA in two available strengths: a 100 mg oral tablet and a 300 mg oral tablet. It is recommended that canagliflozin be initiated at a dose of 100 mg daily, which can then be titrated to a maximum dose

Table 3 Adverse reactions

Study	Female mycotic infection, n (%)	Male mycotic infection, n (%)	Urinary tract infection, n (%)	Pollakuria, n (%)	Polyuria, n (%)	Hypoglycemia, n (%)
Stenlöf et al ¹² (2013)	Pcb: 4 (3.8)	Pcb: 0	Pcb: 8 (4.2)	Pcb: 1 (0.5)	Pcb: 0	Pcb: 5 (2.6)
	C100: 10 (8.8)	C100: 2 (2.5)	C100: 14 (7.2)	C100: 5 (2.6)	C100: 0	C100: 7 (3.6)
	C300: 8 (7.4)	C300: 5 (5.6)	C300: 10 (5.1)	C300: 6 (3)	C300: 6 (3)	C300: 6 (3)
Rosenstock et al ¹³ (2012)	Pcb: 0	Pcb: NR	Pcb: 4 (6)	Pcb: < 2%	NR	Pcb: 1 (2)
	C100: 2 (3)	C100: NR	C100: 2 (3)	C100: < 5%		C100: 1 (2)
	C300: 1 (2)	C300: NR	C300: 2 (3)	C300: < 5%		C300: 0
Schernthaler et al ¹⁴ (2013)	Sit100: 7 (4.3)	Sit100: 1 (0.5)	Sit100: 21 (5.6)	Sit100: 5 (1.3)	Sit100: 0	Sit100: 40.7%
	C300: 26 (15.3)	C300: 19 (9.2)	C300: 15 (4.0)	C300: 6 (1.6)	C300: 3 (0.8)	C300: 43.2%
Devineni et al ¹⁵ (2012)	NR	NR	NR	NR	NR	Pcb: 3 (33)
						C100: 6 (60)
						C300: 3 (30)
Yale et al ¹⁶ (2013)	Pcb: 0	Pcb: 0	Pcb: 5 (5.6)	Pcb: 1 (1.1)	Pcb: 0	Pcb: 36.4% [^]
	C100: 1 (3.1)	C100: 1 (1.7)	C100: 5 (5.6)	C100: 2 (2.2)	C100: 0	C100: 52.9% [^]
	C300: 1 (2.4)	C300: 1 (2.1)	C300: 7 (7.9)	C300: 4 (4.5)	C300: 0	C300: 51.2% [^]
Bode et al ¹⁷ (2013)	Pcb: 2 (2.1)	Pcb: 0	Pcb: 12 (5.1)	Pcb: 5 (2.1)	Pcb: 0	Pcb: 33.7% [^]
	C100: 18 (15.4)	C100: 4 (3.2)	C100: 14 (5.8)	C100: 6 (2.5)	C100: 4 (1.7)	C100: 43.1% [^]
	C300: 12 (11.2)	C300: 8 (6.2)	C300: 19 (8.1)	C300: 12 (5.1)	C300: 4 (1.7)	C300: 47.4% [^]

Note: [^]Those treated with other hypoglycemic therapy.

Abbreviations: Pcb, placebo; C100, canagliflozin 100 mg; C300, canagliflozin 300 mg; NR, not reported; Sit100, sitagliptin 100 mg.

of 300 mg daily based on response to and tolerability for the medication. It is also advised that canagliflozin be taken prior to the first meal of the day.¹¹

The dose of canagliflozin requires adjustment based on renal function. A maximum dose of 100 mg daily should be used in those with an eGFR between 45 mL/min and 60 mL/min. If the eGFR falls below 45 mL/min, canagliflozin should not be used. Canagliflozin is in a pregnancy risk C category; women who are nursing should avoid the use of canagliflozin. Increases in AEs in the geriatric population is noted in the labeling of canagliflozin; however, there are no dose adjustments recommended specifically for these patients. Therefore, close monitoring for safety and efficacy should be utilized when using canagliflozin in this population.

Cost

The cash price for a 1 month supply of canagliflozin is about \$280–\$290, regardless of dose.¹⁸ This is comparable to other newer medications such as sitagliptin and saxagliptin but about \$100 less than exenatide. These options are considerably more expensive than agents like metformin and the sulfonylureas, which cost \$10 or less per month. Insurance coverage will vary, so clinicians will need to consult their local third party formularies and discuss the cost of canagliflozin treatment with their patients.

Unanswered questions

The effect of canagliflozin, if any, on CV outcomes is of great importance, as it is with any antihyperglycemic

agent. This was initially being studied in the Canagliflozin Cardiovascular Assessment Study (CANVAS). CANVAS is a double-blind, placebo-controlled trial that enrolled over 4,000 subjects in the first phase of the study.¹⁹ Subjects were randomized to placebo or canagliflozin 100 or 300 mg daily. A second, larger phase was originally planned but the researchers had to unblind the Phase I results during the regulatory approval process, and could not proceed to the second phase.¹⁹ Thus, larger trials of longer duration are still needed with canagliflozin to assess macrovascular outcomes that will significantly assist in ultimately defining its role in management of type 2 diabetes. Another issue that may evolve is whether or not there is any benefit to inhibiting SGLT1 in addition to SGLT2. While SGLT1 only plays a minimal role in glucose reabsorption, there is some evidence that inhibiting both SGLT1 and SGLT2 provides additional glucose lowering,²⁰ as inhibition of SGLT1 by canagliflozin doses of 300 mg/day or greater may delay glucose absorption from the gastrointestinal tract and reduce postprandial glucose elevations.¹⁰

Summary

Canagliflozin is a novel treatment option for patients with T2DM. By inhibiting the renal reabsorption of glucose canagliflozin reduces the A_{1c} by approximately 0.37%–1.16%; body weight and FBG are also reduced with canagliflozin therapy. Canagliflozin is dosed at a starting dose of 100 mg daily that can be increased to 300 mg daily if needed. Canagliflozin carries a very low risk for hypoglycemia but

appears to increase the risk for genital mycotic infections in both men and women; other potential AEs include increased urination, increased blood urea nitrogen, and serum creatinine, diarrhea, and fatigue. Canagliflozin is unlikely to have drug interactions but does require dose adjustment in patients with a creatinine clearance between 45 and 60 mL/min; it should not be used in patients with eGFR <45 mL/min. Given the favorable efficacy and safety profile of canagliflozin, combined with its novel mechanism of action, canagliflozin represents a welcome addition to the treatment armamentarium for T2DM.

Disclosure

James R Taylor is on the speakers' bureau for Janssen Pharmaceuticals, Inc. Eric Dietrich and Jason Powell report no conflicts of interest in this work.

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