

Who is the Ideal Candidate for Canagliflozin?

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Abstract

Canagliflozin is a sodium-glucose linked-cotransport 2 (SGLT2) receptor inhibitor recently approved for the treatment of type 2 diabetes mellitus (T2DM). By inhibiting glucose reabsorption in the kidney, this medication has been shown to be effective in improving glycemic control with an insulin-independent mechanism that avoids the side effects of the latter. Based upon its effectiveness, mechanism of action, and secondary effects of weight loss and decreased blood pressure, patients may be optimally suited for canagliflozin if they are inadequately controlled on metformin with haemoglobin A1c 7-9%, obese, and/or hypertensive. Based on possible adverse effects associated with glycosuria and osmotic diuresis, patients may not be suited for canagliflozin if they are older, use sulfonylurea or insulin medications, or have risk factors for genitourinary infections, renal impairment, postural hypotension, uncontrolled hyperlipidemia, or urinary frequency. Further research is needed to establish long-term safety, such as regarding cardiovascular disease.

Keywords: Canagliflozin; Diabetes mellitus; Secondary endpoints; Adverse effects; Primary care

Background

Canagliflozin (Invokana[®]) is a sodium-glucose linked-transport 2 (SGLT2) receptor inhibitor newly approved for the treatment of type 2 diabetes mellitus (T2DM). Under normal conditions, the SGLT2 receptor in the proximal tubule resorbs filtered glucose until its resorptive capacity is reached, which is a mechanism that accounts for more than 90% of renal glucose reabsorption [1]. Inhibitors of the SGLT2 receptor reduce glucose reabsorption and promote glycosuria and osmotic diuresis. As such, this agent promotes glycemic control and caloric loss with a mechanism independent of insulin. A novel medication introduced in 2013, canagliflozin is effective in improving haemoglobin A1c levels without the adverse effects associated with insulin and insulin-related agents. Given its unique mechanism of action and distinct side effect profile, it is important to consider the optimal clinical situations for its use.

Ideal Candidates for Canagliflozin

Patients uncontrolled on metformin monotherapy with haemoglobin A1c 7-9%

Patients with T2DM inadequately controlled with metformin monotherapy and haemoglobin A1c 7-9% may be ideal candidates for canagliflozin. Metformin is first-line pharmacotherapy for patients with T2DM [2], and efficacy of canagliflozin in addition to metformin has been demonstrated in three main trials. Rosenstock and colleagues produced a double-blind, placebo-controlled, dose-ranging study in patients (n=451) with haemoglobin A1c range 7-10.5% with stable metformin dose of at least 1500 mg/day for >3 months [3]. Canagliflozin 100 mg and 300 mg daily were associated with HbA1c reductions of 0.76% and 0.92% respectively at 12 weeks (p<0.001). The

CANTATA-SU trial, a randomized, double-blind, placebo-controlled trial (n=1452), demonstrated that patients with HbA1c 7-9.5% on stable metformin regimen had improved haemoglobin A1c levels on canagliflozin 300mg daily rather than glimepiride (-0.12% [95% CI -0.22 to -0.02] [4]. The randomized, double-blind, four-arm, parallel-group, Phase 3 trial by Lavelle-Gonzalez and colleagues in patients with T2DM on metformin with A1c 7-10.5 (n=1284) found that canagliflozin 300mg daily was superior to sitagliptin in lowering A1c at 52 weeks (-0.88% vs. -0.73%, respectively) [5]. These data demonstrate canagliflozin is effective as a second agent in the setting of metformin monotherapy when compared to placebo, sulfonylureas, and sitagliptin.

For those uncontrolled on metformin monotherapy, ideal candidates for canagliflozin are those patients with haemoglobin A1c 7-9%. Firstly, the efficacy trials enrolled patients with haemoglobin A1c 6.9-10.5% [3,4,6-13]. Secondly, use of canagliflozin has been associated with decrease in haemoglobin A1c ranging between 0.44-1.11% (300mg daily), with results generally near 1% [3-13]. Given that target haemoglobin A1c is generally 7-8% depending on risks for hypoglycemia, patients with initial haemoglobin A1c values of 7-9% on monotherapy are ideal for this medication because they allow for the addition of canagliflozin to help reach target haemoglobin A1c without use of supplemental insulin. For patients with higher haemoglobin A1c values, initiation and titration of insulin may be preferable to prevent hypoglycemia and side effects associated with polypharmacy.

Patients prone for hypoglycemia

Ideal candidates for canagliflozin may be those patients that are prone to hypoglycemia. Based on its mechanism of action by increasing glycosuria, canagliflozin does not involve increased insulin levels, and as such patients are theoretically at lower risk for hypoglycemia. Indeed, documented hypoglycemia for patients with uncontrolled T2DM was low regardless of dosage [3,7]. Moreover, a

study by Devineni et al. demonstrated that there was no evidence of intestinal glycemic malabsorption with use of canagliflozin [13]. Exceptions, as discussed below, include those patients who are on sulfonylurea medications, elderly, and chronic kidney disease.

Obese patients

Ideal candidates for canagliflozin may be those patients such as the obese that would benefit from losing weight. By inhibiting the SGLT2 receptor, canagliflozin increases glycosuria, and its use is associated with loss of 400 kcal/day due to urinary caloric losses [3]. Indeed, in many of the available efficacy studies, canagliflozin was associated with a 2.3-4.2% body weight reduction depending on dose [3,5,6,8,10,12]. This is a particularly helpful secondary endpoint given that several diabetes regimens are associated with weight gain, and weight reduction in patients with T2DM and metabolism syndrome is beneficial.

Hypertensive patients

Ideal candidates for canagliflozin may be those with hypertension who may benefit from some additional blood pressure reduction. Within the CANTATA-M study of those uncontrolled with diet and exercise (n=451), patients were seen to have a decreased blood pressure (-3.7 mmHg and -5.4 mmHg for 100 mg and 300 mg dosages, both $p < 0.001$) at one year [12], which are results that have been reproduced [7,9]. The reduction in blood pressure is most likely attributed to osmotic diuresis, but mild weight loss may be a contributing factor [10]. While the drug is associated with risks for postural hypotension as discussed below, this effect may be helpful for some patients who may need additional blood pressure reduction to reach the target blood pressure in type 2 diabetes of <140/90. Osmotic diuresis may virtually activate the renin-angiotensin-aldosterone system. The clinical consequences of this activation, if any, need to be investigated.

Suboptimal Candidates for Canagliflozin

Patients at risk for urinary tract infection (UTI)

Patients may not be ideal for canagliflozin if they have a history of urinary tract infections, pyelonephritis, or other associated risk factors (e.g. indwelling foley). By inhibiting the SGLT2 receptor, canagliflozin increases urinary glucose excretion (UGE) and can thereby facilitate pathogenesis. In their early study of this issue, Nicolle et al conducted a randomized, double-blind, placebo-controlled, dose-ranging phase two trial that showed rates of bacteriuria and UTI were not increased compared to sitagliptin [14]. However, four major efficacy studies have shown increased rates of urinary tract infections [4,9,11,12]. While these adverse effects were treated and did not require drug discontinuation, patients treated with canagliflozin certainly need education about this possible effect and treatment when indicated.

Patients at risk for genital yeast infection

Patients may be suboptimal candidates for canagliflozin if they have a history of genital yeast infections such as vaginal candidiasis or balanitis. By inhibiting the SGLT2 receptor, canagliflozin increases UGE and thereby can mediate mycotic infections. For instance, in patients on metformin monotherapy, canagliflozin use at the highest tested dose was associated with 5% of vulvovaginal mycotic infection compared to 0% in placebo [3]. In the randomized, double-blind,

Phase 3 CANTATA-M study, canagliflozin was associated with higher rates of genital mycotic infections compared to placebo and sitagliptin [7]. While these adverse effects were generally mild and treated with few discontinuations, patients again require education and treatment about this possible effect.

Patients with renal impairment

Patients are not ideal for canagliflozin if they have renal impairment, such as chronic kidney disease (CKD) stage III. Canagliflozin relies on effective renal filtration as part of its mechanism. Indeed, use of this medication is contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m², and requires dose reduction with eGFR of 45-59 ml/min/1.73 m² [15]. In their randomized, double-blind, placebo-controlled, phase 3 trial, Yale and colleagues found that patients with T2DM and CKD stage III treated with canagliflozin 100 and 300 mg reduced HbA1c from baseline [11]. However, at 26 weeks, Canagliflozin 100 mg was associated with 0.30% reduction in HbA1c compared to placebo ($p < 0.05$) while Canagliflozin 300mg was associated with 0.44% drop in HbA1c compared to placebo ($p < 0.001$). Though there are improvements in glycemic control for patients with CKD stage III, benefits are more limited than in the broader population where HbA1c reductions can be twice as much. Moreover, there is exacerbation of renal function, which trends towards baseline but does not return to it. In the study conducted by Yale and colleagues, eGFR was decreased by 3.9 ml/min/1.73 m² with canagliflozin 300 mg compared to decrease of 1.4 ml/min/1.73 m² with placebo [11]. Also, a known adverse effect of canagliflozin is hyperkalemia [15]. Patients started on canagliflozin need close monitoring of eGFR and potassium levels within weeks of initiation, especially when other medications alter the renin-angiotensin-aldosterone system.

Patients at risk for postural hypotension

Patients are not optimal for canagliflozin if they have low normal blood pressures or are at risk for postural hypotension. By inhibiting the SGLT2 receptor, canagliflozin increases glycosuria and functions as an osmotic diuretic. As discussed, the blood pressure effect appears to be 3 to 5 mmHg, depending on the dose [12]. In patients on metformin monotherapy, canagliflozin use was associated with hypovolemia related adverse effects in 0-6% of the patients across treatment groups (2% in placebo, 2% in sitagliptin group) [3]. Those with hypertension may benefit from this effect, while those normotensive or sensitive to volume status, such as the elderly, may have increased risk for falls. Thus, patients who are elderly or are prescribed multiple anti-hypertensive agents may not be ideal for canagliflozin. Those given this medication should be counselled to avoid dehydration.

Patients with history of urinary frequency and polyuria

Canagliflozin is not ideal for those patients with a history of urinary frequency or polyuria, whether secondary to diabetes itself or otherwise. By inhibiting the SGLT2 receptor, canagliflozin increases glycosuria, which some patients may experience as frequency and polyuria. For instance, in patients uncontrolled with diet and exercise, canagliflozin was associated with urinary frequency (2.6% 100 mg, 3.0% 300 mg, 0.5% placebo) as well as polyuria (3.0% 300 mg, 0% placebo) [12]. For those with urinary frequency or polyuria at baseline, this effect of canagliflozin may be frustrating or even embarrassing.

Patients should be counselled about this effect and techniques to ameliorate night time symptoms.

Patients with uncontrolled hyperlipidemia and coronary artery disease

Canagliflozin may not be ideal for patients who are not at goal regarding plasma levels of low-density lipoprotein-cholesterol (LDL-C). Two studies have shown that this drug medication was associated with increased high-density lipoprotein-cholesterol levels (HDL-C) but also increased plasma concentrations of LDL-C [7,9]. The mechanism for this lipid effect is unknown, but could be related in part to reduction in intravascular volume. The potential negative impact of increasing LDL-C levels by canagliflozin on cardiovascular events is still unclear. The Canagliflozin Cardiovascular Assessment Study (CANVAS) is an on-going large randomized trial that specifically examines the effect of canagliflozin on cardiovascular morbidity and mortality in patients with type-2 diabetes and high cardiac risk at baseline [16]. Until results of the CANVAS trial become available, it may be wise to avoid using canagliflozin in patients with uncontrolled hyperlipidemia or history of cardiovascular events. Nevertheless, regardless of baseline cholesterol levels, all patients started on this medication would benefit from regular lipid panel monitoring.

Patients on sulfonylurea and insulin medications

Patients with uncontrolled T2DM on sulfonylurea and insulin medications may not be suitable candidates for canagliflozin due to increased incidence of hypoglycemia. Wilding et al conducted a randomized, placebo controlled, double-blind phase 3 trial evaluating canagliflozin in addition to metformin and sulfonylureas, and they found increased incidence of documented, though not severe, hypoglycemia compared to placebo [6]. 33.8% of patients on canagliflozin 100 mg experienced hypoglycemia compared to 36.5% of those on 300 mg daily and only 17.9% for placebo. While these events were not significant enough for drug discontinuation and were not necessarily symptomatic, patients on sulfonylurea and insulin medications are not ideal candidates for canagliflozin, especially given the fact that rates of hypoglycemia are higher in this population than those patients receiving canagliflozin on metformin monotherapy.

Older patients

Older patients with uncontrolled diabetes may not be ideal candidates for canagliflozin. In a study of older patients aged 55-80 years (n=716), Bode et al showed that efficacy of canagliflozin was attenuated. Thus, the HbA1c reduction in patients randomized to 100 mg and 300 mg dosages were -0.60% and -0.73%, respectively [9]. Moreover, this study revealed higher documented rates of hypoglycemia for both doses compared to placebo. Given that older individuals are also at higher risk for many of the adverse events listed above such as genitourinary infections, falls related to postural hypotension, and renal impairment, this medication should be used cautiously in the elderly, especially given its decreased efficacy and increased frequency of hypoglycemia in this population [9].

Conclusion

A novel medication in the treatment of T2DM, canagliflozin inhibits the SGLT2 receptor and increases glycosuria, thereby improving glycemic control and increasing caloric loss with an

insulin-independent mechanism. Given its efficacy, mechanism, and secondary effects of weight loss and decreased blood pressure, diabetic patients may be optimally suited for this medication if they are inadequately controlled on metformin with haemoglobin A1c 7-9%, obese, and/or hypertensive. Based on its possible adverse effects, patients may not be suited for canagliflozin if they are older, use sulfonylurea or insulin medications, or have risk factors for genitourinary infections, renal impairment, postural hypotension, uncontrolled hyperlipidemia, or urinary frequency. Further research is needed to establish long-term safety, especially with regards to cardiovascular disease. Patients should be counselled about the advantages of canagliflozin as well as its side effects.

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