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MINI REVIEW

# Canagliflozin in the treatment of diabetes: Perspectives

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## ABSTRACT

The worldwide prevalence of type 2 diabetes mellitus (T2DM) has surpassed more than 380 million people in 2014 and the projections of new T2DM cases for the next years are not encouraging. At present, combination of diet and exercise do not guarantee an adequate control of glucose homeostasis in T2DM patients. Thus, oral agents that act improving peripheral insulin sensitivity and/or pancreatic beta-cell function are additionally used as monotherapy or in combination. However, many patients still experience inadequate control with the pharmacotherapy 'weapons' currently available. Canagliflozin is a novel selective inhibitor of sodium-glucose co-transporter 2 (SGLT2) that lowers blood glucose concentration mainly by augmenting urinary glucose excretion. Besides having an effective action in reducing HbA1c, canagliflozin treatment also may benefit those patients aiming to control body weight, blood pressure and hypoglycemia episodes since this drug positively impact on such parameters. Among the adverse effects, genital infections are the most frequent. Much caution is required for some groups of patients including those elderly and with chronic kidney disease since canagliflozin can worse their quality of life. Given its overall cardiometabolic improvements, canagliflozin seems to be an important ally to the treatment of a selective group of T2DM patients and its efficacy and safety must be kept under monitoring through long-term clinical trials as well as experimental studies to certify whether this class of drug comes to stay among T2DM therapy.

**Keywords:** *Canagliflozin, diabetes, SGLT, hyperglycemia, insulin resistance*

## Introduction

According to the sixth edition of Diabetes Atlas, released by the International Diabetes Federation, the prevalence of diabetes worldwide in 2014 is around 8.3% of the total population, which consists of approximately 387 million people. The IDF Diabetes Atlas also reveals an estimated increment of 205 million new diabetes cases by 2035.[1] This scenery can become more worrying when considering that more than 470 million people will have prediabetes (intermediate hyperglycemia) by 2030; a state of high-risk diabetes development.[2]

Around 90-95% of people diagnosed with diabetes belong to the type 2 diabetes mellitus (T2DM) category, a chronic disease of multifactorial origin that includes genetic susceptibility, lifestyle (increased inactivity together with increased hypercaloric diet) and metabolic programming at prenatal and/or postnatal periods among other factors.[3] In general, the altered glucose homeostasis in T2DM is initially managed with an oral agent, mostly metformin (biguanide class) treatment. However, due to T2DM progressive nature, monotherapy is normally associated with a high failure rate until the fifth year of treatment.[4] Thus, association with a second therapy that includes agents with complementary action mechanisms (e.g., sulfonylureas, thiazolidinediones, incretin mimetic drugs) is required for adequate control of glucose homeostasis and to reduce adverse effects.[5]

The main focus of therapeutic strategies that include the aforementioned drugs has been on agents that act by improving peripheral insulin sensitivity and/or beta-cell function (insulin secretion). However, at present, no monotherapy is efficient to achieve acceptable, long-lasting glycemic control in the majority of patients, which has led to scientific efforts on developing novel drugs with improved efficacy and safety.[6]

## Canagliflozin - sodium-glucose co-transporter 2 (SGLT2) inhibitor

Canagliflozin, a novel selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), appears as an important pharmacotherapy to handle the imbalanced glucose homeostasis in diabetes since it blocks the reabsorption of filtered glucose in the kidneys.[7] As SGLT2 is found exclusively in the kidneys[8], canagliflozin is not expected to impair intestinal glucose absorption since brush border of the small intestine express exclusively SGLT1.[9] Commercialization of canagliflozin, the first SGLT2

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inhibitor drug, (commercially named INVOKANA®) was approved by the United States Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2013. Meta-analysis studies have demonstrated that canagliflozin promotes significant glycosuria favoring not only the improvement of glycemic control but also the weight loss as a result of caloric loss. Additionally, it improves the blood pressure (BP) parameters.[10,11]

## Canagliflozin – the evidence and perils

In a phase I placebo-controlled study with healthy men receiving a single dose of canagliflozin (varying from 30 to 800 mg), it was demonstrated that canagliflozin decreased the calculated 24-h mean renal threshold for glucose (RTG), achieving a maximal reduction to approximately 60 mg/dL and augmented 24-h mean urinary glucose excretion (UGE). Individuals subjected to canagliflozin treatment at doses over 200 mg before breakfast had attenuated plasma glucose and insulin increment during that meal.[12] Transient postural dizziness and headache were the most frequent (8%) adverse effects.[12] Phase Ib placebo-controlled study confirmed the canagliflozin potential to reduce RTG and to increase UGE after 28 days of treatment in T2DM patients suboptimally controlled on insulin and receiving one oral antihyperglycemic agent.[13] These patients also had reduced fasting plasma glucose (FPG) and HbA1c values, and presented body weight loss mainly at 300 mg dosage regimen with similar adverse effects among groups. A dose-ranging, placebo-controlled, multicenter, 12-week study with T2DM patients inadequately controlled with metformin monotherapy demonstrated that canagliflozin added onto metformin significantly improved glycemic control compared to placebo and sitagliptin groups.[14] This was paralleled with a significant weight loss and low incidence of hypoglycemia. The safety and tolerability of canagliflozin treatment in these patients were favorable except for increased frequency of genital infection in females.[14] The weight loss caused by canagliflozin treatment were also investigated in a phase 2b, 12-wk study with overweight/obese patients without T2DM showing that canagliflozin administration resulted in reduction of body weight around 2.5% compared to 1.3% in placebo. This was also paralleled with increased urinary adverse effects in women.[15] By these first clinical studies, it was reasonably acceptable that canagliflozin treatment could render significant improvements in the glycemic control that might be tested in more prolonged studies.

The long-term safety and efficacy profile of canagliflozin treatment were investigated along phase III studies conducted from 26 to 52 weeks in T2DM patients as add-on therapy to diet and exercise[16], metformin monotherapy[17], metformin plus sulfonylurea[18,19], metformin plus pioglitazone[20], and to insulin-treated patients.[21] In general, canagliflozin treatment at 100 and 300 mg produced significant improvement in glycemic control, although it was mostly accompanied by increased genital infections in females. Canagliflozin treatment at 100 and 300 mg improved glycemic parameters and reduced body weight after 26-week treatment in T2DM patients inadequately controlled with diet and exercise.[16] In patients being treated with metformin plus sulfonylurea, canagliflozin treatment at doses of 100 and 300 mg ameliorated the HbA1c and FPG after 52-weeks of therapy compared to placebo- or sitagliptin-treated patients.[18,19] In another phase III study with T2DM patients managed with metformin plus pioglitazone, canagliflozin treatment at 100 and 300 mg improved the glycemic and blood pressure (BP) parameters after a 52-week period.[20] When added to insulinotherapy, canagliflozin treatment reduced HbA1c and FPG values, decreased body weight and BP at both 18- and 52-wk periods.[21] Canagliflozin treatment also demonstrated a better effect upon glycemic control compared to glimepiride after 52-week treatment in T2DM patients with metformin monotherapy.[22] Considering the beneficial effect of canagliflozin therapy with patients subjected to insulinization, it could also be of interest for the management of T1DM. The effects of canagliflozin treatment upon attenuation of blood glucose after meal tolerance tests seem to also involve a non-renal mechanisms, possibly through inhibition of intestinal SGLT1[23,24] and augmented beta-cell function.[25]

Since canagliflozin act on reducing RTG and increasing UGE, there is a parallel diuretic osmosis that favors the reduction of BP as can be observed by several phase III studies.[12,20,21,26] This positive effect of canagliflozin treatment in the BP parameters is accompanied by increased incidence of osmotic diuresis-related adverse effects (e.g., pollakiuria [increased urine volume] and polyuria [increased urine frequency] and with low incidence of intravascular volume reduction-related adverse effects (e.g., orthostatic hypotension and postural dizziness).[26] Despite canagliflozin seeming to have a positive impact on BP control, caution is recommended in patients where low blood pressure may be a concern.[27] Some phase III studies conducted with T2DM patients with chronic kidney disease (CKD) at stage 3a, where the estimated glomerular filtration rate

(eGFR) was >45 and <60 ml/min/1.73 m$^2$, and at stage 3b, where the eGFR was >30 and <45 ml/min/1.73 m$^2$, canagliflozin treatment provided clinically important improvements in glycemic control and sustained reductions in body weight and BP over 52 weeks, and was generally well tolerated in patients with T2DM and only within a subset of stage 3 CKD.[28,29]

## Concluding remarks

Based on considerable low rates of glycemic control in diabetic population and the exclusive mechanism of action and acceptable efficacy of SGLT2 inhibitors, this drug has a potential add-on therapy in T2DM patients whose blood glucose levels are inadequately controlled with other antidiabetic agents. Not only diabetic, but also subgroups with HbA1c levels in the range of 7-8%, overweight/obese patients or those with uncontrolled hypertension could benefit from canagliflozin therapy.[30] Canagliflozin treatment should not be recommended in expansion need CKD patients as well as in elderly people and must be accompanied with caution in patients with established cardiovascular disease and high LDL-C levels until new clinical trials become available. A recent published review is recommended for a panoramic view of positive and negative impact of canagliflozin treatment.[30]

Results from ongoing studies that include large randomized trials as well as experimental studies will help in understanding the long-term effects, safety and efficacy of canagliflozin and other SGLT2 inhibitors (under evaluation) with respect to cardiometabolic aspects.

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## Conflict of interest

Dr. Rafacho is an editorial advisory board member of Diabesity.

## References

1. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas.
2. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012; 379:2279-90. PubMed Full Text
3. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab.* 2011; 96:1654-63. PubMed Full Text
4. Riddle M. Combining sulfonylureas and other oral agents. *Am J Med.* 2000; 108 (Suppl 6a):15S-22S. PubMed Full Text
5. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract.* 2009; 15:540-59. PubMed Full Text
6. Gershell L. Type 2 diabetes market. *Nat Rev Drug Discov.* 2005; 4:367-8. PubMed Full Text
7. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, et al. Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *J Med Chem*. 2010; 53:6355-60. PubMed Full Text
8. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Kidney Int.* 2009; 75:1272-7. PubMed Full Text
9. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. *Drugs.* 2010; 70:377-85. PubMed Full Text
10. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2014; 70:1149-58. PubMed Full Text
11. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J Am Soc Hypertens.* 2014; 8:262-75.e9. PubMed Full Text
12. Sha S, Devineni D, Ghosh A, Polidori D, Chien S, Wexler D et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. *Diabetes Obes Metab*. 2011; 13:669-72. PubMed Full Text
13. Devineni D, Morrow L, Hompesch M, Skee D, Vandebosch A, Murphy J, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab*. 2012; 14:539-45. PubMed Full Text
14. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. Canagliflozin DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012; 35:1232-8. PubMed Full Text
15. Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects

without diabetes mellitus. *Obesity (Silver Spring)* 2014; 22:1042-9. PubMed Full Text

16. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, 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; 15:372-82. PubMed Full Text
17. Lavalle-González FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013; 56:2582-92. PubMed Full Text
18. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 2013; 36:2508-15. PubMed Full Text
19. Wilding JP, Charpentier G, Hollander P, González-Gálvez G, Mathieu C, Vercruysse F, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract.* 2013; 67:1267-82. PubMed Full Text
20. Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G, Stein P. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab.* 2014; 16:467-77. PubMed Full Text
21. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, et al. On behalf of the CANVAS Trial Collaborative Group. Efficacy and Safety of Canagliflozin, an Inhibitor of Sodium Glucose Cotransporter 2, When Used in Conjunction With Insulin Therapy in Patients With Type 2 Diabetes. *Diabetes Care* 2014. PubMed Full Text
22. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013; 382:941-50. PubMed Full Text
23. Polidori D, Sha S, Mudaliar S, Ciaraldi TP, Ghosh A, Vaccaro N, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. *Diabetes Care* 2013; 36:2154-61. PubMed Full Text
24. Stein P, Berg JK, Morrow L, Polidori D, Artis E, Rusch S, Vaccaro N, Devineni D. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces post-meal glucose excursion in patients with type 2 diabetes by a non-renal mechanism: results of a randomized trial. *Metabolism* 2014; 63:1296-303. PubMed Full Text
25. Polidori D, Mari A, Ferrannini E. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. *Diabetologia* 2014; 57:891-901. PubMed Full Text
26. Weir MR, Januszewicz A, Gilbert RE, Vijapurkar U, Kline I, Fung A, et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. *J Clin Hypertens* (Greenwich). 2014; 16:875-82. PubMed Full Text
27. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. *J Am Soc Hypertens.* 2014; 8:330-9. PubMed Full Text
28. Yamout H, Perkovic V, Davies M, Woo V, de Zeeuw D, Mayer C, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. *Am J Nephrol.* 2014; 40:64-74. PubMed Full Text
29. Yale JF, Bakris G, Cariou B, Nieto J, David-Neto E, Yue D, et al. DIA3004 Study Group. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus andchronic kidney disease. *Diabetes Obes Metab.* 2014; 16:1016-27. PubMed Full Text
30. Mikhail N. Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes. *World J Diabetes*. 2014; 5:854-9. PubMed Full Text