

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 worsen 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup>

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.<sup>6</sup>

## 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.<sup>7</sup> As SGLT2 is found exclusively in the kidneys<sup>8</sup>, canagliflozin is not expected to impair intestinal glucose absorption since brush border of the small intestine express exclusively SGLT1.<sup>9</sup> 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.<sup>10,11</sup>

### 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.<sup>12</sup> Transient postural dizziness and headache were the most frequent (8%) adverse effects.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>14</sup> 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.<sup>15</sup> 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<sup>16</sup>, metformin monotherapy<sup>17</sup>, metformin plus sulfonylurea<sup>18,19</sup>, metformin plus pioglitazone<sup>20</sup>, and to insulin-treated patients.<sup>21</sup> 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.<sup>16</sup> 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.<sup>18,19</sup> 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.<sup>20</sup> When added to insulinotherapy, canagliflozin treatment reduced HbA1c and FPG values, decreased body weight and BP at both 18- and 52-wk periods.<sup>21</sup> Canagliflozin treatment also demonstrated a better effect upon glycemic control compared to glimepiride after 52-week treatment in T2DM patients with metformin monotherapy.<sup>22</sup> 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<sup>23,24</sup> and augmented beta-cell function.<sup>25</sup>

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.<sup>12,20,21,26</sup> 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).<sup>26</sup> Despite canagliflozin seeming to have a positive impact on BP control, caution is recommended in patients where low blood pressure may be a concern.<sup>27</sup> 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<sup>2</sup>, and at stage 3b, where the eGFR was >30 and <45 ml/min/1.73 m<sup>2</sup>, 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.<sup>28,29</sup>

### 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.<sup>30</sup> 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.<sup>30</sup>

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 *Diabetesity*.

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