

## REVIEW ARTICLE

# Effects of canagliflozin on cardiovascular risk factors in patients with type 2 diabetes mellitus

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**Summary**

**Background and aims:** Cardiovascular disease is the most common cause of morbidity and mortality among people with type 2 diabetes mellitus (T2DM). The main contributors to cardiovascular risk in T2DM are chronic hyperglycaemia, reduced insulin sensitivity, hypertension and dyslipidaemia. Other cardiovascular risk factors include obesity and visceral adiposity, increased arterial stiffness and renal dysfunction. Results from clinical trials, including a long-term cardiovascular outcome study, have shown that sodium glucose co-transporter 2 (SGLT2) inhibitors can provide multiple cardiometabolic benefits beyond glycaemic control including inducing mild osmotic diuresis, natriuresis and weight loss. This review article describes the effects of canagliflozin on cardiovascular risk factors based on results from its clinical development programme.

**Methods:** This review is based on structured searches to identify literature related to the effects of canagliflozin on cardiovascular risk factors in patients with T2DM.

**Discussion and conclusions:** Canagliflozin treatment has been shown to provide glycaemic improvements as well as reductions in blood pressure and body weight across a broad range of patients with T2DM, including those with elevated cardiovascular risk. Other observed effects of canagliflozin that may contribute to improved cardiometabolic outcomes include reduction in uric acid levels, decreased albuminuria and increases in serum magnesium. Results of ongoing long-term cardiovascular outcomes studies of canagliflozin are expected to provide additional evidence on the cardiometabolic effects of canagliflozin treatment.

## 1 | INTRODUCTION

Diabetes is a major global health emergency, affecting approximately 415 million adults and contributing to five million deaths each year. It has been estimated that up to 91% of people with diabetes have type 2 diabetes mellitus (T2DM).<sup>1</sup> Cardiovascular disease (CVD) is a serious complication of T2DM, contributing to the majority of morbidity and mortality in this population.<sup>2-4</sup> Chronic hyperglycaemia and reduced insulin sensitivity, along with comorbidities of hypertension and dyslipidaemia, are the main contributors to an increased risk of CVD in people with T2DM. Other contributors to this risk may include

obesity, especially visceral adiposity, increased arterial stiffness and renal dysfunction.<sup>5</sup>

Recent findings from long-term, large-scale, cardiovascular outcome trials of antihyperglycaemic agents (AHAs) have shown that some T2DM treatments can provide cardiometabolic benefits beyond glycaemic control. For example, in the EMPA-REG OUTCOME trial in patients with T2DM and established CVD, the sodium glucose co-transporter 2 (SGLT2) inhibitor empagliflozin was associated with a significant decrease in the risk of major cardiovascular events (three-point MACE; cardiovascular death, non-fatal myocardial infarction [MI] and non-fatal stroke) vs placebo.<sup>6</sup> Reduction in cardiovascular

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death drove the primary finding, as the rates of non-fatal MI and non-fatal stroke were not significantly different for empagliflozin and placebo.<sup>6</sup> In addition, the risk of heart failure hospitalisation and all-cause mortality was significantly reduced with empagliflozin vs placebo,<sup>6</sup> and empagliflozin treatment was associated with slower progression of kidney disease compared with placebo.<sup>7</sup> In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial in patients with T2DM and high cardiovascular risk, treatment with the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide was associated with a significant reduction in the risk of death from cardiovascular causes and a non-significant reduction in the risk of non-fatal MI, non-fatal stroke and hospitalisation for heart failure compared with placebo.<sup>8</sup>

Findings from these and other cardiovascular outcome studies may, in time, lead to greater use of newer agents (such as SGLT2 inhibitors and GLP-1 receptor agonists) in patients at high cardiovascular risk. Recent European Cardiovascular Society guidelines on CVD prevention state that use of an SGLT2 inhibitor should be considered early in the course of diabetes management for patients with existing CVD based on observed reductions in CVD, total mortality and heart failure hospitalisations.<sup>9</sup> Use of SGLT2 inhibitors is also supported by the growing body of evidence on therapies that can provide multifactorial benefits, such as weight loss and reduced blood pressure (BP), in addition to lowering blood glucose.<sup>4,10</sup> SGLT2 inhibitors have been shown to provide clinically important improvements in glycaemic control and to induce mild osmotic diuresis, natriuresis and negative energy balance, which contribute to reductions in BP and body weight across a broad range of patients with T2DM.<sup>11</sup> Recent publications suggest that the cardioprotective effects seen with empagliflozin are likely to be relevant for the SGLT2 inhibitor class as a whole.<sup>12-16</sup>

Although many of the improvements in cardiovascular risk factors have been reported for all SGLT2 inhibitors, this review article focuses on describing the effects of canagliflozin on cardiovascular risk factors based on results from its clinical development programme. Results of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program<sup>17,18</sup> will provide evidence on whether the observed effects on cardiovascular risk factors translate into cardiovascular benefits in patients with T2DM.

## 2 | EFFECTS OF CANAGLIFLOZIN TREATMENT ON CARDIOVASCULAR RISK FACTORS

Canagliflozin acts by inhibiting SGLT2, which is the primary mediator of renal glucose reabsorption. Such inhibition lowers the renal threshold for glucose excretion ( $RT_G$ ), which increases urinary glucose excretion (UGE) and reduces plasma glucose levels in an insulin-independent manner.<sup>19</sup> Canagliflozin is indicated as an adjunct to diet and exercise for the treatment of adults with T2DM.<sup>11</sup> A summary of the impact of canagliflozin on cardiovascular risk factors is provided in Table 1, along with an overview of the mechanisms that may contribute to these effects.

### Review criteria

Structured searches were performed to identify published literature related to the effects of the SGLT2 inhibitor canagliflozin on cardiovascular risk factors in patients with T2DM. Articles and congress abstracts identified in these searches were evaluated for clinical data on the effects of canagliflozin on cardiometabolic outcomes and for information about potential mechanisms associated with these effects.

### Message for the clinic

To reduce the risk of cardiovascular disease in patients with T2DM, treatment should focus on multifactorial risk reduction. Published results suggest canagliflozin may contribute to improved cardiometabolic outcomes by lowering HbA1c, body weight and blood pressure; reducing hyperinsulinaemia and uric acid levels; and increasing serum magnesium levels. Additional evidence on the cardiovascular and renal effects of canagliflozin will be available upon completion of large-scale outcomes trials.

## 2.1 | Glycaemic effects

Chronic hyperglycaemia has been suggested to be a contributor to the increased risk of CVD in people with T2DM,<sup>5</sup> and glucose control is often considered to be a cornerstone of comprehensive cardiovascular risk reduction strategies.<sup>20</sup> However, based on findings from studies assessing cardiovascular risk in T2DM, such as ACCORD, ADVANCE and VADT, there is not universal agreement that lowering plasma glucose levels is a driver for improvements in cardiovascular outcomes. These studies evaluated intensive glucose-lowering strategies with established therapies and reported negative or neutral effects on cardiovascular outcomes.<sup>21-23</sup> Thus, the American Diabetes Association and the European Association for the Study of Diabetes recommend treatment strategies that provide glycaemic control within a multifactorial cardiovascular risk reduction framework.<sup>20</sup>

In a clinical trials programme that enrolled ~10 000 patients with T2DM, including older patients, patients with moderate renal impairment, and patients with elevated cardiovascular risk, treatment with canagliflozin 100 and 300 mg was associated with clinically significant, dose-dependent reductions in HbA1c, both as monotherapy and as part of combination therapy with metformin ± a sulphonylurea for up to 104 weeks.<sup>11</sup> In active-controlled Phase 3 studies, canagliflozin 300 mg provided greater reductions in HbA1c compared with both glimepiride and sitagliptin.<sup>11</sup>

In addition to reducing HbA1c levels, the increase in UGE that occurs with canagliflozin treatment is associated with reductions in postprandial glucose and insulin excursions.<sup>11,19,24-27</sup> Further reductions in postprandial glucose also occur through a non-renal mechanism. While data indicate that canagliflozin does not have systemic effects

**TABLE 1** Effects of canagliflozin on factors associated with cardiometabolic benefits and risks

Parameter	Effect of canagliflozin <sup>a</sup>	Potential SGLT2i-associated mechanisms or effects of SGLT2i on factors	Predicted effect on CV outcomes
Hyperglycaemia	↓	Urinary glucose excretion Potential secondary effects based on improvements in insulin sensitivity and/or beta-cell function	Reduction in chronic hyperglycaemia and glucose variability may improve CV outcomes
Plasma insulin	↓	Decreases in plasma glucose reduce glucose stimulation of beta cells Increased insulin clearance	Reduced hyperinsulinaemia may lower CV risk
Body weight and visceral adiposity	↓	Net caloric loss as a result of urinary glucose excretion	Modest weight loss may reduce CVD risk in patients with T2DM Loss of visceral fat can lower CVD risk by reducing inflammation and the potential for atherogenesis
Blood pressure	↓	Osmotic diuresis, natriuresis, reduced intravascular volume, weight loss	Reductions in blood pressure can significantly reduce risk of CHD and mortality
Albuminuria	↓	Decreased urinary albumin excretion via reduction in GFR through reduction in glucose and sodium reabsorption in the proximal tubule	Reduced albuminuria is associated with reduced risk of CV and renal disease and associated mortality May slow progression of diabetic nephropathy
Kidney function	↑	Reduced GFR through reduction in glucose and sodium reabsorption in the proximal tubule	May provide renoprotective benefits and slow progression of diabetic nephropathy
LDL-C	↑	Possible metabolic effects of urinary glucose excretion and haemoconcentration	Abnormalities in lipoprotein metabolism increase CV risk in T2DM Increasing LDL-C may promote atherogenesis and increase risk for development of CVD
HDL-C	↑	Possible metabolic effects of urinary glucose excretion and haemoconcentration Associated with improvements in glycaemic control and reduced body weight	Increased catabolism of HDL-C in T2DM reduces cardioprotective effects SGLT2i may modulate the impact of T2DM on HDL-C levels
Triglycerides	↓	Associated with improvements in glycaemic control and reduced body weight	Increased triglyceride level is a primary lipid abnormality in T2DM Decreases in triglycerides with SGLT2i may reduce risk for development of CVD
Uric acid	↓	Increased delivery of glucose to transporters that exchange glucose for uric acid	May reduce risk for nephropathy, CHD, and mortality
Serum magnesium	↑	Consequence of mild osmotic diuresis and possibly alterations in renal handling of magnesium	May reverse magnesium deficiencies that are associated with cardiac hypertrophy, aortic stiffening, arrhythmias, and rapid declines in renal function
Haemoglobin/haematocrit	↑	Plasma volume contraction due to osmotic diuresis; increased haematopoiesis; increases in erythropoietin levels	Results are mixed on CV effects of increased haemoglobin/haematocrit Increases in the EMPA-REG OUTCOME study were associated with improvements in HF and mortality risk, but may increase risk of thrombotic events
Ketones	↑	Shift in substrate delivery to the heart and changes in cardiac insulin sensitivity	Improvements in myocardial and renal fuel metabolism may reduce CV risk, but there is also speculation about increased risk of thrombotic events

CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; SGLT2i, sodium glucose co-transporter 2 inhibitors; T2DM, type 2 diabetes mellitus. <sup>a</sup>Arrows indicate the direction of statistically significant changes associated with canagliflozin treatment.

on SGLT1 (eg, in the kidney, heart or skeletal muscle),<sup>28,29</sup> the 300-mg dose may provide transient, local inhibition of SGLT1 in the intestine. This intestinal SGLT1 inhibition may slow glucose absorption from the morning meal and delay the appearance of glucose in plasma.<sup>24</sup> It has been hypothesised that such reductions in postprandial hyperglycaemia and insulin variability may have a greater impact on reducing cardiovascular risk than simply reducing average blood glucose levels

(ie, HbA1c) because processes that trigger oxidative stress and endothelial dysfunction are often upregulated when glucose levels peak or fluctuate widely between high and low levels.<sup>30</sup>

The glycaemic efficacy of canagliflozin is largely independent of beta-cell function and insulin sensitivity.<sup>31</sup> Thus, it is not surprising that canagliflozin has been shown to significantly improve glycaemic control in patients with T2DM across a range of ages, weight/

body mass index categories, baseline HbA1c levels and disease durations.<sup>32,33</sup> The risk of hypoglycaemia is generally low with canagliflozin when it is used alone or in combination with other AHAs that have a low intrinsic risk of causing hypoglycaemia.<sup>11</sup> A post hoc analysis of data from a Phase 3 study in patients with T2DM inadequately controlled on metformin showed that a higher proportion of patients achieved their glycaemic goals (ie, HbA1c <7% or <6.5%) without hypoglycaemia after 52 weeks of treatment with canagliflozin vs the sulphonylurea glimepiride.<sup>34</sup> Notably, hypoglycaemia may be associated with an increased risk of cardiovascular events. The Outcomes Reduction with an Initial Glargine Intervention (ORIGIN) trial compared an insulin strategy with standard care using oral AHAs in patients with early T2DM who were at a high risk for cardiovascular outcomes. It was observed that patients who experienced severe hypoglycaemia (ie, requiring assistance or glucose  $\leq 2.0$  mmol/L [ $\leq 36$  mg/dL]) had significantly increased risks for the composite of cardiovascular death, non-fatal MI or stroke, as well as all-cause mortality, cardiovascular death and arrhythmic death.<sup>35</sup> It remains to be seen if the low risk of hypoglycaemia that is associated with canagliflozin treatment will also be associated with improved cardiovascular outcomes.

## 2.2 | Effects on insulin secretion/resistance

In patients with T2DM, insulin resistance has been shown to develop in target tissues, including liver, adipose, muscle and myocardium. Insulin resistance is a major driver of adverse cardiovascular outcomes that acts synergistically with hyperglycaemia to promote atherosclerosis.<sup>36</sup> Specifically, reduced insulin signalling in endothelial tissue is associated with increased vascular dysfunction, inflammation, oxidative stress and the development of atherosclerotic lesions.<sup>36</sup>

Analysis of data from three Phase 3 studies of canagliflozin as monotherapy and as add-on to metformin plus sulphonylurea showed that 6-12 months of canagliflozin treatment improves both fasting and postprandial measures of beta-cell function and insulin secretion.<sup>37</sup> Insulin secretion rate was significantly increased with canagliflozin compared with baseline at all plasma glucose concentrations (7-16 mmol/L); these increases were of similar magnitude with canagliflozin vs sitagliptin.<sup>37</sup> Insulin sensitivity, measured using the oral glucose insulin sensitivity index corrected for UGE, also improved by approximately 15% with canagliflozin treatment.<sup>37</sup> It has been hypothesised that such improvements in insulin sensitivity are a result of weight loss and the reversal of glucotoxicity. Improvement in hyperinsulinaemia may reduce the risk of atherosclerosis beyond that of glucose lowering alone.<sup>5,38</sup> In a rodent model, Watanabe and colleagues showed that the combination of canagliflozin with pioglitazone reduced hyperinsulinaemia and improved whole-body insulin sensitivity compared with pioglitazone monotherapy.<sup>39</sup> Further studies are needed to confirm whether indirect improvement in insulin sensitivity of the magnitude observed in studies of canagliflozin has a significant effect on atherosclerosis risk in people with T2DM.<sup>5</sup>

## 2.3 | Effects on body weight and adiposity

Modest weight loss of between 5% and 10% can contribute to improvements in glycaemic control and may reduce CVD risk factors in overweight and obese patients with T2DM.<sup>40</sup> While overall results from the Look AHEAD study in overweight or obese patients with T2DM did not find an association between intensive lifestyle intervention promoting weight loss and a reduced rate of adverse cardiovascular events,<sup>41</sup> a recent post hoc analysis of risk based on magnitude of weight loss showed that patients who lost more than 10% of their body weight had a 20% reduction in risk of the composite of cardiovascular death, non-fatal acute MI, non-fatal stroke or hospitalisation for angina<sup>42</sup>; prospective studies are needed to further examine the effects of weight loss on cardiovascular outcomes.

Across Phase 3 studies, canagliflozin 100 and 300 mg have been associated with dose-dependent reductions in body weight.<sup>11</sup> Generally, average body weight reductions observed with canagliflozin treatment were between 2% and 5%,<sup>11</sup> and more patients achieved a weight loss of at least 5% or 10% with canagliflozin than with placebo or active comparators.<sup>43,44</sup> This weight loss was sustained over 104 weeks of treatment in clinical trials.<sup>44-46</sup>

Weight loss associated with canagliflozin and other SGLT2 inhibitors is a result of reductions in both visceral and subcutaneous adipose tissue.<sup>47-50</sup> Body composition measurements from a Phase 3 study of canagliflozin in patients with T2DM inadequately controlled on metformin showed a mean change in visceral adipose tissue of -7.3% with canagliflozin 100 mg, -8.1% with canagliflozin 300 mg, and 0.1% with glimepiride at 52 weeks; change in subcutaneous adipose tissue was -5.4% with canagliflozin 100 mg, -5.6% with canagliflozin 300 mg and 1.8% with glimepiride.<sup>50</sup> The loss of visceral fat with canagliflozin treatment is noteworthy because visceral fat mass has been shown to increase cardiometabolic risk in patients with T2DM by promoting atherogenic, thrombotic and inflammatory abnormalities.<sup>47</sup> In addition, visceral adiposity has been associated with concentric left ventricle remodelling, reduced cardiac output and increased systemic vascular resistance.<sup>51</sup> Thus, the weight-related benefits associated with canagliflozin treatment are enhanced by reductions in visceral adiposity that may reduce cardiovascular complications and mortality.<sup>5</sup>

## 2.4 | Effects on blood pressure, pulse pressure and arterial stiffness

BP control is critical in patients with T2DM. The combination of T2DM and hypertension increases the risk of coronary heart disease and associated mortality dramatically (up to six-fold) compared with either disease alone.<sup>52</sup> Elevated pulse pressure (ie, the difference between systolic and diastolic BP) and mean arterial pressure (ie, the average pressure during a single cardiac cycle [ $2/3$  diastolic BP +  $1/3$  systolic BP]) also significantly increase CVD risk in patients with T2DM.<sup>53</sup> In a meta-analysis of CVD risk related to pulse pressure and mean arterial pressure, each 10-mmHg incremental increase in pressure was associated with about a 10% increase in risk for CVD.<sup>53</sup>

Across clinical studies, canagliflozin treatment has been shown to provide significant reductions in BP. Pooled data from four placebo-controlled studies showed mean systolic BP reductions of  $-4.3$  and  $-5.0$  mmHg with canagliflozin 100 and 300 mg, respectively, vs  $-0.3$  mmHg with placebo.<sup>54</sup> In these studies, greater proportions of patients achieved systolic BP targets of  $<140$  and  $<130$  mm Hg with canagliflozin vs placebo.<sup>54</sup> The BP-lowering effects of canagliflozin are not significantly altered when patients are taking antihypertensive medications or other AHAs, and BP reduction with canagliflozin is not associated with meaningful changes in heart rate.<sup>54</sup> In addition, BP reductions with canagliflozin in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR]  $\geq 30$  and  $<50$  mL/min/1.73 m<sup>2</sup>) are comparable to those in patients with normal renal function, despite differences in UGE and HbA1c efficacy observed with canagliflozin in these patient populations.<sup>55,56</sup>

Pooled data from four placebo-controlled studies showed that canagliflozin treatment was associated with reductions in pulse pressure, mean arterial pressure and double product (ie, heart rate  $\times$  systolic BP) compared with placebo.<sup>57</sup> Similar results were observed in a 6-week ambulatory BP monitoring study in patients with T2DM and hypertension; BP reductions with canagliflozin occurred quickly, as early as 2 days after initiation of therapy.<sup>58</sup> These rapid effects on BP are likely due to osmotic diuresis, natriuresis and reduced intravascular volume.<sup>57,58</sup> Long-term reductions in BP are likely a result of weight loss and changes in the renin-angiotensin system.<sup>58</sup> Empagliflozin has been shown to reduce arterial stiffness in patients with type 1 diabetes mellitus, and it has been speculated that SGLT2 inhibitors may improve endothelial function or the elastic properties of various components of connective tissue.<sup>5</sup> SGLT2 inhibitors may also reduce intracardiac filling pressure, which may reduce myocardial stretch and reduce the risk of ventricular arrhythmia.<sup>59</sup>

## 2.5 | Renal effects

Albuminuria is a well-established marker for CVD and renal disease in patients with T2DM, significantly increasing risk of cardiovascular death.<sup>60,61</sup> SGLT2 inhibition has been shown to decrease urinary albumin excretion by reducing glomerular filtration rate (GFR) through reduction in glucose and sodium reabsorption in the proximal tubule, which increases sodium delivery to the macula densa in the distal tubule and suppresses activation of tubuloglomerular feedback.<sup>62-64</sup> As an added benefit, reductions in GFR during sympathetic nervous system activation that result from reduced glycaemia and increased hepatic gluconeogenesis may act to stabilise glucose perturbations.<sup>5</sup>

Across Phase 3 studies of canagliflozin, early transient reductions in eGFR were observed regardless of baseline renal function.<sup>65</sup> Changes in eGFR generally attenuated to near baseline levels and stabilised over time for all patients, including those with chronic kidney disease (CKD).<sup>56,66</sup> In studies of patients with CKD, decreases in median albumin-to-creatinine ratio (ACR) were also observed, which were likely a result of volume contraction.<sup>56,66</sup> A post hoc analysis of results from a Phase 3 study in patients with T2DM inadequately controlled on metformin showed that canagliflozin treatment slowed

the progressive decline in eGFR and lowered the ACR compared with glimepiride.<sup>67</sup> The ongoing CANagliflozin cardioVascular Assessment Study–Renal (CANVAS-R; NCT01989754) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; NCT02065791) studies will provide additional data on the effects of canagliflozin on renal-related outcomes.<sup>18,68</sup>

## 2.6 | Effects on lipids

Dyslipidaemia plays a critical role in the development of CVD, especially in patients with T2DM,<sup>9</sup> and lipid profile management has become an important component of multifactorial T2DM management.<sup>5</sup> Canagliflozin has been shown to have beneficial effects on high-density lipoprotein cholesterol (HDL-C) and triglyceride levels, likely as a result of improvements in glycaemic control and reductions in body weight.<sup>69</sup> In pooled placebo-controlled studies, mean placebo-subtracted increases in HDL-C were 5.4% and 6.3%, respectively, with canagliflozin 100 and 300 mg at Week 26, and mean placebo-subtracted reductions in triglyceride levels were  $-5.2\%$  and  $-7.6\%$ , respectively.<sup>69</sup>

Canagliflozin has also been shown to increase low-density lipoprotein cholesterol (LDL-C) and total cholesterol relative to placebo.<sup>69</sup> Across four pooled placebo-controlled studies, mean placebo-subtracted increases in LDL-C were 4.5% and 8.0%, respectively, with canagliflozin 100 and 300 mg at Week 26.<sup>69</sup> In a pooled analysis of two active-controlled studies, the percentage of patients with LDL-C levels  $\geq 100$  mg/dL was not increased from baseline to Week 52 with canagliflozin treatment and was not different at Week 52 with canagliflozin vs sitagliptin.<sup>70</sup> In contrast to results in patients with T2DM who have normal or mild renal impairment, reductions in LDL-C have been seen with canagliflozin in patients with moderate renal impairment over 52 weeks (placebo-subtracted differences of  $-3.0\%$  and  $-6.9\%$  with canagliflozin 100 and 300 mg, respectively).<sup>56</sup> The mechanism for the observed changes in LDL-C with SGLT2 inhibition is not fully understood, but it has been hypothesised that these changes are related to downstream metabolic effects of UGE and haemoconcentration.<sup>71</sup>

## 2.7 | Effects on uric acid

Hyperuricaemia in patients with T2DM is associated with an increased risk of gout, nephropathy, coronary heart disease and mortality.<sup>72,73</sup> In a meta-analysis of studies that included more than 20 000 patients with T2DM, Xu and colleagues found that for each 100  $\mu\text{mol/L}$  increase in serum uric acid, patients with T2DM experienced a 28% increase in the risk of vascular complications (eg, stroke, coronary heart disease, peripheral vascular disease and nephropathy) and a 9% increase in risk of mortality.<sup>73</sup>

Several studies have examined the effects of SGLT2 inhibitors on uric acid levels in patients with T2DM.<sup>62,74-76</sup> In Phase 1 studies evaluating the pharmacodynamic effects of canagliflozin in patients with T2DM, fractional urinary excretion of uric acid was increased during the first weeks of treatment with canagliflozin, resulting in a small decrease ( $\sim 0.1$  pH units) in mean urine pH and up to a 20% reduction in serum



uric acid levels from baseline to Week 16.<sup>27,77</sup> These findings were confirmed based on pooled data from four placebo-controlled studies, which showed that patients treated with canagliflozin for 26 weeks had a mean reduction in serum uric acid of ~13% (~0.7 mg/dL) compared with placebo.<sup>74</sup> In the subset of patients with hyperuricaemia at baseline, higher percentages of patients achieved normal uric acid levels (<360 µmol/L [~6 mg/dL]) with canagliflozin 100 mg (23.5%) and canagliflozin 300 mg (32.4%) than with placebo (3.1%).<sup>74</sup> The mechanism by which canagliflozin promotes excretion of uric acid is not well understood, but it has been speculated that SGLT2 inhibition modulates the actions of solute carrier family 2, facilitated glucose transporter member 9 (SLC2A9; also called GLUT9), which exchanges glucose for uric acid.<sup>78,79</sup>

## 2.8 | Effects on magnesium

Hypomagnesaemia (serum magnesium <0.74 mmol/L [1.8 mg/dL]) is associated with rapid progression of T2DM and may increase risks for cardiometabolic complications.<sup>80-84</sup> Specifically, magnesium deficiencies have been linked with cardiac hypertrophy, aortic stiffening, arrhythmias (especially atrial fibrillation and ventricular tachycardia) and rapid declines in renal function in patients with T2DM. Magnesium is necessary for regulation of ion channels in pancreatic beta cells and for autophosphorylation of insulin receptors. As such, magnesium deficiency is strongly associated with declines in beta-cell function and the development of insulin resistance.<sup>80-84</sup>

In a meta-analysis of randomised controlled trials of SGLT2 inhibitors in patients with T2DM, Tang and colleagues found that all evaluated drugs (canagliflozin, dapagliflozin, empagliflozin and ipragliflozin) were associated with modest increases in serum magnesium levels ranging from 0.05 to 0.10 mmol/L.<sup>85</sup> Changes in magnesium levels were similar in patients with normal renal function and with CKD.<sup>85</sup>

In a pooled analysis of data from four placebo-controlled studies, canagliflozin was associated with increased serum magnesium levels compared with placebo after 26 weeks of treatment (mean percent changes of 8.1%, 9.3% and -0.6% with canagliflozin 100 and 300 mg and placebo, respectively).<sup>69</sup> Patients with hypomagnesaemia (serum magnesium <0.74 mmol/L) at baseline were more likely to achieve serum magnesium ≥0.74 mmol/L (ie, normal levels) at Week 26 with canagliflozin than placebo.<sup>86</sup> The mechanism for increased serum magnesium with canagliflozin has not been established, but may be related to improvements in insulin sensitivity<sup>37</sup> or changes in the distal convoluted tubule that alter magnesium reabsorption and/or urinary magnesium excretion.<sup>87,88</sup> It remains to be shown whether normalisation of serum magnesium with SGLT2 inhibitors in patients with T2DM will affect disease progression or cardiometabolic outcomes.

## 2.9 | Effects on haemoglobin/haematocrit

The relationship between increases in haemoglobin/haematocrit and the risk of CVD is not well defined, with some studies showing variations in risk based on age, gender and type of cardiovascular event.<sup>89</sup> Recent data from the Framingham Heart Study showed that higher

haematocrit levels were associated with an increased risk of development of heart failure, even when levels were within normal ranges.<sup>90</sup>

In a pooled analysis of data from four placebo-controlled studies, both doses of canagliflozin were associated with increases in haemoglobin compared with placebo.<sup>69</sup> At Week 26, the proportion of patients with increases in haemoglobin of ≥20 g/L from baseline was 6.0% with canagliflozin 100 mg, 5.5% with canagliflozin 300 mg and 1.0% with placebo. Increases in haematocrit from baseline to Week 26 were 5.8% and 6.3% with canagliflozin 100 and 300 mg, respectively, compared with 0.2% in the placebo group.<sup>69</sup> In the EMPA-REG OUTCOME study, the observed modest increases in haematocrit and haemoglobin levels were strongly associated with improvements in heart failure and mortality risk, suggesting that SGLT2 inhibition may affect mechanisms other than (or in addition to) plasma volume contraction to increase haemoglobin levels and thereby oxygen delivery to ischaemic tissues.<sup>59</sup>

## 2.10 | Effects on ketone bodies

The heart readily consumes ketone bodies and, by some measures, these are a preferred cardiac substrate.<sup>91,92</sup> Together with changes in other substrate delivery to the heart and potential changes in cardiac insulin sensitivity, increased levels of circulating ketone bodies seen with SGLT2 inhibition might lead to improvements in cardiac metabolism. Elevations in ketone bodies seen with SGLT2 inhibitors have been highly variable, with most of the data obtained from small, short-term studies. Results from several Phase 3 studies in Japanese patients with T2DM have shown that, on average, canagliflozin treatment is associated with a roughly two-fold elevation in plasma ketone bodies.<sup>93-96</sup>

## 2.11 | Safety considerations

Overall, canagliflozin has been shown to be generally well tolerated as monotherapy and as part of combination therapy for T2DM.<sup>69</sup> Across four 26-week, placebo-controlled studies, the total incidence of adverse events (AEs) was similar with canagliflozin 100 and 300 mg and placebo.<sup>69</sup> Subsequent analysis of data from seven placebo- and active-controlled studies confirmed the favourable safety profile of canagliflozin for up to 104 weeks.<sup>97</sup> Throughout the clinical development programme, AEs that occurred at a higher rate with canagliflozin vs placebo and other AHA comparators included genital mycotic infections and osmotic diuresis-related AEs, which are related to the mechanism of SGLT2 inhibition.<sup>11</sup> A modest increase in urinary tract infections (UTIs) was seen with canagliflozin 100 and 300 mg vs placebo in the pooled placebo-controlled dataset, but there was no increase in the incidence of serious UTIs with canagliflozin.<sup>69,98</sup>

Due to the reduced efficacy of canagliflozin in patients with renal impairment and the need for more safety data in this population, canagliflozin is not recommended in patients with an eGFR below 45 mL/min/1.73 m<sup>2</sup>.<sup>19,65</sup> As noted for some antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), and for AHAs including some dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists, there have

been postmarketing reports of acute kidney injury with SGLT2 inhibitors.<sup>99-102</sup> However, it is important to note that renal impairment is very common in patients with T2DM and that T2DM is the most common cause of kidney failure in most developed countries.<sup>103,104</sup> Other risk factors for acute kidney injury include hypovolaemia, chronic renal insufficiency, congestive heart failure, and concomitant use of ACE inhibitors, ARBs or nonsteroidal anti-inflammatory drugs.<sup>99</sup>

Possible adverse effects of SGLT2 inhibitors on bone health have been reported. Across Phase 3 studies, canagliflozin was associated with an increased incidence of fractures that generally occurred early after treatment initiation.<sup>105</sup> Most of the observed fractures were located in distal parts of the upper and lower extremities and not in typical osteoporotic regions, such as the hips and spine.<sup>105</sup> Thus, these excess fractures may be due, at least in part, to falls induced by early fluid shifts (ie, transient hypovolaemia) and not a direct effect on bone density. The observed increase in fractures with canagliflozin was driven by interim results from CANVAS, in which patients were older, had a history/high risk of CVD, had a lower baseline eGFR, and reported higher use of loop diuretics. Similar types of fracture (ie, upper extremity) observations have been made in studies with empagliflozin<sup>106</sup> and dapagliflozin<sup>101</sup> in high-risk individuals with T2DM, suggesting that an increased risk of fractures may be a class effect for all SGLT2 inhibitors.

It has been suggested that the observed mild hyperketonaemia and haemoconcentration associated with SGLT2 inhibition may increase the risk for thrombotic events.<sup>12</sup> This may explain the numerically higher incidence of stroke seen with empagliflozin vs placebo (3.5% vs 3.0%; hazard ratio [95% confidence interval], 1.18 [0.98-1.56]) in the EMPA-REG OUTCOME study.<sup>6</sup> Another thrombotic safety signal was raised that is related to peripheral limb ischaemia based on interim results from CANVAS, which showed higher rates of amputations (mostly toes) with canagliflozin 100 mg (seven of every 1000 patients) and canagliflozin 300 mg (five of every 1000 patients) vs placebo (three of every 1000 patients).<sup>107</sup> However, it should be noted that the patient inclusion and exclusion criteria for CANVAS allowed for enrolment of patients with peripheral arterial disease, which may have affected levels of baseline risk for peripheral limb ischaemia. Furthermore, a higher incidence of amputation was not observed across the 12 other completed Phase 3 and Phase 4 clinical trials, which had a mean follow-up time of 0.9 years (0.6 amputations per 1000 patient-years with canagliflozin vs two amputations per 1000 patient-years with placebo/comparator).<sup>97</sup> Upon completion of the trials in the CANVAS Program (ie, CANVAS<sup>17</sup> and CANVAS-R<sup>18</sup>), more comprehensive, long-term safety assessments will be possible using the final study results.

Concerns about an increased risk of diabetic ketoacidosis have been reported with all marketed SGLT2 inhibitors. The overall incidence of serious AEs of diabetic ketoacidosis was generally low across randomised controlled trials of canagliflozin (4/5337 [0.07%] with canagliflozin 100 mg, 6/5350 [0.11%] with canagliflozin 300 mg, and 2/6909 [0.03%] with comparators) and consistent with the observed rate of diabetic ketoacidosis in the general population of patients with T2DM and in patients treated with other SGLT2 inhibitors.<sup>108,109</sup>

### 3 | CONCLUSIONS

Cardiovascular complications are the cause of many adverse outcomes associated with T2DM. Given the high burden of CVD in T2DM, multifactorial risk reduction is an important goal, with treatment strategies focusing on improving glycaemic control, as well as weight loss, BP reduction and improvements in dyslipidaemia.

The EMPA-REG OUTCOME study showed that empagliflozin may provide cardiometabolic benefits that can lead to a reduction in cardiovascular and all-cause mortality in patients with T2DM and established CVD. Of note, the US Food and Drug Administration recently approved a new indication for empagliflozin to reduce the risk of cardiovascular death in adult patients with T2DM and CVD based on results from the EMPA-REG OUTCOME trial.<sup>102</sup> Given the similarities in clinical effects of SGLT2 inhibitors on cardiovascular risk factors,<sup>110</sup> it is possible that these benefits will extend to other drugs in this class.<sup>111</sup> Results from the canagliflozin clinical development programme support that canagliflozin treatment may improve cardiometabolic outcomes in a broad range of patients with diverse clinical characteristics. The potential benefit of this class of agents on persons at risk for congestive heart failure may be particularly important, given the benefits seen in the EMPA-REG OUTCOME trial<sup>112</sup> and the observed effects of SGLT2 inhibitors on BP, volume status and intracardiac filling pressures.<sup>54,113</sup> Additional data on the cardiovascular and renal effects of canagliflozin in patients with a history or high risk of cardiovascular events will be available upon completion of the large-scale CANVAS Program in 2017.<sup>17,18,114</sup>

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### AUTHOR CONTRIBUTIONS

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