EXPERT OPINION

Canagliflozin, an inhibitor of sodium–glucose cotransporter 2, for the treatment of type 2 diabetes mellitus

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Introduction: Canagliflozin is an orally administered sodium glucose cotransporter 2 inhibitor proposed for the treatment of type 2 diabetes. Canagliflozin improves glycemic control in an insulin-independent fashion through inhibition of glucose reuptake in the kidney.

Areas covered: This article reviews the available data on the pharmacodynamics, the pharmacokinetics and metabolism, and the efficacy and safety of canagliflozin. Relevant articles were identified via PubMed using the search term canagliflozin with no date restriction. The authors also discuss the abstracts from canagliflozin studies presented at large diabetes conferences.

Expert opinion: Canagliflozin offers a relatively modest reduction in HbA1c, FPG, and PPG. It has a low incidence of hypoglycemia and a reduction in body weight. Dose adjustment may be recommended in the elderly, those on loop diuretics, and those with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 if there are concerns or symptoms of volume-related side effects. Issues remain with observed increases in low-density lipoprotein cholesterol (LDL-C) and the odds of heart attack and stroke. Canagliflozin offers a novel mechanism of action, a modest glycemic control, and a favorable side-effect profile. It was approved by the US Food and Drug Administration in April 2013 and is undergoing evaluation by the European Medicines Agency.

Keywords: canagliflozin, diabetes mellitus, SGLT2 inhibitor, sodium glucose cotransporter

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive, multifactorial disease that affects over 340 million people worldwide with other hundreds of millions at risk for diabetes [1]. T2DM is associated with significant morbidity, ranking as the leading cause of renal failure, new-onset blindness, and limb amputations [2]. Heart disease and stroke are 2 – 4 times more common in patients with diabetes, and these cardiovascular complications remain a leading cause of mortality. T2DM, conservatively, is the seventh leading cause of death worldwide.

The United Kingdom Prospective Diabetes Study [3] demonstrated that within 6 years of diagnosis, one-fifth of subjects reported at least one diabetes-related micro- or macrovascular complication. Multiple recent studies including ACCORD, ADVANCE, VADT, and ORIGIN showed that intensive glucose control had no benefit on macrovascular disease [4-7]. However, hyperglycemia appears to be the main mediator of microvascular complications [8]. Achieving a glycosylated hemoglobin A1c (HbA1c) < 7% reduces the microvascular complication rate by 25%, and for every 1% decrease in HbA1c, there is a 35% reduction

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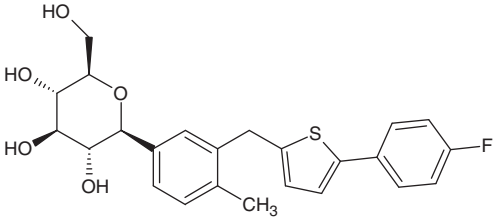
Box 1. Drug summary.

Drug name	Canagliflozin
Phase	FDA approved
Indication	Insulin-independent AHA in type 2 diabetes mellitus
Pharmacology description	Sodium–glucose cotransporter-2 inhibitor
Root of administration	Oral
Chemical structure	
Pivotal trials	[34,42]

in the risk of microvascular complications, a 25% reduction in diabetes-related deaths, and a 7% reduction in all-cause mortality.

Therefore, achieving and maintaining goal glycemic control is pivotal to the treatment of T2DM. Using available lifestyle and therapeutic interventions to accomplish this goal is the primary role of the diabetologist.

2. Overview of the market

Recommendations from the American Diabetes Association and the European Association for the Study of Diabetes strongly endorse lifestyle modification for all patients with T2DM. Therapeutic treatment algorithms are based on severity of disease, tolerability, and therapeutic efficacy [9,10]. Classes of medications, such as biguanides, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and α-glucosidase inhibitors, are tier one and two oral options. Metformin is the drug of choice for initial therapy, unless contraindicated or not tolerated. Addition of second-line therapy can be tailored to patient comorbidities (i.e., age, risk of hypoglycemia, weight gain, and renal function). However, patients unable to achieve glycemic goal (HbA1c < 7%) may benefit from addition of glucagon-like polypeptide-1 (GLP-1) agonists and/or insulin therapy, both injectable. With the high prevalence of diabetes, new pharmacologic targets represent opportunities to complement current therapy.

Multiple new antidiabetic therapies are being investigated, including dual peroxisome proliferator-activated receptor (PPAR) modulators (in Phase III trials), 11β-hydroxysteroid dehydrogenase type 1 inhibitors, glucokinase activators, and glycogen phosphorylase activators. However, sodium–glucose cotransporter 2 (SGLT2) inhibitors have garnered the most excitement and are furthest in development. This article will review the available data on the pharmacodynamics, pharmacokinetics and metabolism, and efficacy and safety of canagliflozin, an SGLT2 inhibitor.

3. Introduction to the compound

T2DM is characterized by i) an early relative insulin deficiency (which over time can result in near total insulin deficiency) and ii) insulin resistance. These pathologic defects give rise to hyperglycemia. Multiple antidiabetic agents target these mechanisms (i.e., sulfonylureas, insulin, TZDs, and metformin). Canagliflozin improves glycemic control in an insulin-independent fashion through inhibition of SGLT2 within the kidney (**Box 1**).

The glomerulus filters circulating plasma glucose within the kidney. Once filtered, glucose is reabsorbed in the proximal tubule [10-12]. Glucose transport across the apical or luminal membranes of the epithelial cells of the proximal tubules is coupled with sodium transport via SGLTs. SGLT2 is the predominant cell membrane carrier protein within the kidney, accounting for nearly 90% of renally reabsorbed glucose. Located within the S1 segment of the early proximal convoluted tubule (PCT), it has a low affinity for glucose (K_m = 2 mM) with a high capacity of glucose transport [10]. SGLT1 mediates a smaller percentage of glucose reabsorption (~ 10%) within the S2/3 segment of the late PCT and has a low capacity for glucose transport. The main role of SGLT1 is glucose absorption within the gastrointestinal tract.

The nephron reabsorbs all of the filtered plasma glucose, up to about 144 g/24 h [11]. The PCT sodium gradient between the luminal and intracellular space drives the secondary active transport of glucose within the epithelial cell (**Figure 1**) [10-12]. Then, glucose is passively reabsorbed into the blood via glucose transporter 2 (GLUT2). Once the absorptive capacity of the PCT is exceeded and SGLTs are saturated, glycosuria occurs. By inhibiting SGLTs, urinary glucose excretion (UGE) increases by lowering the renal glucose excretion threshold (RT_g) [13-17]. This ultimately results in lower plasma glucose levels.

Nonselective SGLT inhibitors, such as phlorizin, had poor absorption and significant gastrointestinal side effects [18,19] but led to the development of compounds more specific for SGLT2. Empagliflozin and canagliflozin are in Phase III

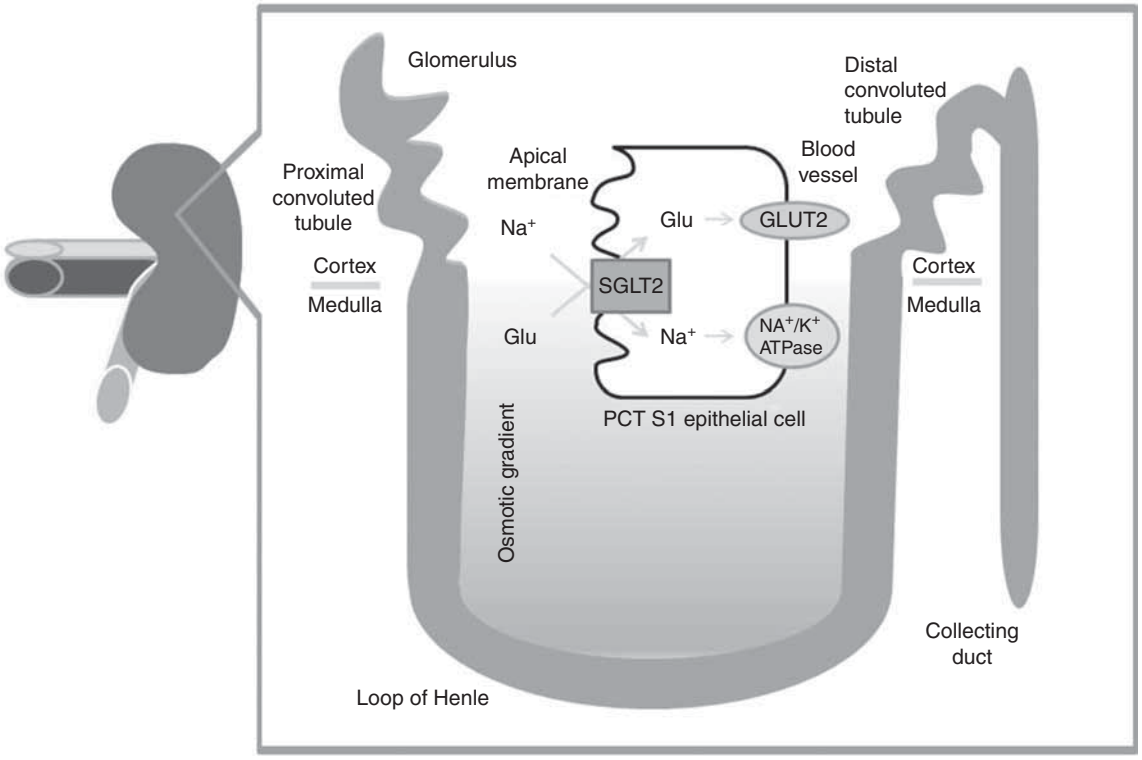


Figure 1. Mechanisum of SGLT2 within the PCTs.
ATP: Adenosine triphosphare; Glu: Glucose; GLUT2, Glucose transporter 2; K: Potassium; Na: Sodium; PTC: Proximal convoluted tubule.

development (remogliflozin and sergliflozin never made it to Phase III development). Currently, canagliflozin is the only SGLT2 inhibitor approved by the US Food and Drug Administration (FDA). Dapagliflozin is the only SGLT2 inhibitor approved by the European Medicines Agency.

4. Chemistry

Canagliflozin, (2*S*,3*R*,4*R*,5*S*,6*R*)-2-{3-[5-(4-fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol, is an orally administered SGLT2 inhibitor in tablet formulation [20,21].

5. Pharmacodynamics

Canagliflozin is 250 times more potent for SGLT2 compared to SGLT1 when tested *in vitro* [22]. From *in vitro* studies, the 50% inhibitory concentrations for SGLT2 and SGLT1 were reported as 2.2 – 4.4 nmol/l and 684 – 910 nmol/l, respectively [16,17]. Estimated systemic inhibition of SGLT1 *in vivo* suggested only modest inhibition of systemic SGLT1-mediated glucose uptake (21% inhibition predicted at C_{max} for 300 mg dose) [20]. There was no evidence of glucose malabsorption when tested clinically with 100 mg daily and 300 mg twice daily dosing [23].

Following oral administration of 300 mg canagliflozin in healthy subjects, the plasma appearance of orally ingested glucose was delayed compared to placebo and area under the curve (AUC) for the rate of appearance was reduced at both 1 h (31%) and 2 h (20%) but similar to placebo over 2 – 6 h [24]. Reduced glucose-dependent insulinotropic peptide (GIP) and increased peptide YY and GLP-1 suggested reduced glucose absorption from the upper intestine and increased absorption from the lower intestine. These findings are consistent with transient inhibition of SGLT1 in the gastrointestinal tract. Using delayed plasma acetaminophen concentrations as a surrogate for gastric emptying, canagliflozin appears to delay gastric emptying.

Canagliflozin pharmacodynamics has been studied in healthy and obese subjects as well as subjects with type 2 diabetes. In a Phase I study, single escalating oral doses of canagliflozin (10, 30, 100, 200, 400, 600, or 800 mg per day or 400 mg twice daily) or placebo were investigated in healthy men [25]. Canagliflozin was dosed pre-breakfast (fasting). For the twice daily dosing, the second dose was administered in the evening. UGE increased in a dose-dependent manner. At doses > 200 mg, the maximum 24-h UGE, 70 g of glucose, was achieved. The RT_g decreased in a dose-dependent fashion. The maximal renal threshold was 3.4 mmol/l. Doses of 400 mg twice daily and 800 mg daily had similar effects on both 24-h UGE and the RT_g. Near maximal RT_g, suppression was

observed during the first 13 h with 100 – 200 mg doses. Doses > 200 mg achieved maximal suppression of RT_g over 24 h. Postprandial glucose (PPG) and serum insulin after breakfast were reduced with doses > 200 mg, with significantly different incremental AUC for both when compared to placebo ($p < 0.05$). PPG levels after lunch and dinner were unaffected.

Eighty obese [body mass index (BMI) > 30 kg/m^2] subjects were randomized for 14 days to ascending doses of canagliflozin (30, 100, 300, or 600 mg daily or 300 mg twice daily) or placebo [26]. Canagliflozin, in a dose-dependent manner, significantly increased UGE at doses 100 mg daily or greater ($p < 0.0001$) and decreased maximal RT_g to 3.6 mmol/l. Over the study period, body weight decreased from baseline between 2.1 and 3.5 kg in the treatment groups.

After a 2-week washout of antihyperglycemic agents (AHAs), 116 subjects with T2DM (mean HbA1c 8%) were randomized to canagliflozin (30, 100, 200, or 400 mg daily or 300 mg twice daily) or placebo for 16 days [27]. A trend in a dose-dependent increase in UGE and decrease in RT_g was demonstrated. A maximal mean reduction in 24-h RT_g at day 16 of 5.0 mmol/l was observed with 400 mg daily and 300 mg twice daily. Mean fasting plasma glucose (FPG) and 24-h plasma glucose significantly declined from baseline compared to placebo ($p < 0.01$). Subjects treated with canagliflozin showed a 1 – 1.5 kg greater weight loss than placebo.

In a 28-day randomized, double-blind, placebo-controlled trial, patients with T2DM not optimally controlled on insulin therapy alone or in combination with metformin, sitagliptin, and/or a TZD were randomized to receive 100 mg daily or 300 mg twice daily of canagliflozin or placebo [23]. The least-square-mean (LSM) difference from baseline of $UGE_{24\ h}$ between canagliflozin 100 mg daily and placebo was 67 g ($p < 0.05$) and 154 g between 300 mg twice daily and placebo ($p < 0.05$). At baseline, RT_g was approximately 12.4 – 12.7 mmol/l, which is higher than what has been reported previously in healthy subjects (10.0 – 11.1 mmol/l) but similar to what has been observed in diabetic patients [20,28,29]. The LSM difference from baseline of RT_g was reduced by 6.6 and 8.9 mmol/l with 100 mg daily and 300 mg twice daily, respectively, versus placebo ($p < 0.05$, both groups). In the 100-mg daily and 300-mg twice daily groups, respectively, HbA1c was reduced by 0.54 and 0.73%, FPG was reduced by 2.6 and 2.8 mmol/l, and body weight was reduced by 0.7 and 1.2 kg, relative to placebo.

RT_g was calculated in these studies using a new formula that takes into account plasma and urinary glucose measurements after an oral glucose load [20]. This method was validated by the company sponsor by comparing the measured RT_g with the RT_g measured with "gold standard" method of a stepped glycemic clamp. Across published and unpublished data (but supplied in a briefing document provided to the FDA advisory committee by the drug sponsor), mean 24-h RT_g was reduced to 2.8 – 3.3 mmol/l in healthy, nondiabetic subjects and to approximately 3.9 – 5.0 mmol/l in subjects with T2DM [20].

Using plasma glucose and C-peptide concentrations from two short studies of canagliflozin (16 days and 12 weeks), significant improvements in beta-cell function, as assessed by insulin secretion rate and homeostatic assessment model (HOMA2-β), were seen in subjects with T2DM treated with at least 100 mg of canagliflozin ($p < 0.05$ vs. placebo) [30].

6. Pharmacokinetics and metabolism

Based on the data supplied to the FDA advisory committee, the mean absolute oral bioavailability of 300 mg canagliflozin was 65% [20]. Food did not affect absorption, but in large Phase III studies, the drug was administered prior to meals in order to take advantage of the observed PPG lowering effect.

Following single-dose and multiple-dose administration of 100 and 300 mg of canagliflozin in healthy subjects, T_{max} was between 1 and 2 h postdose [20]. C_{max} was 1059 – 3148 ng/ml and increased in a dose-proportional manner up to a dose of 1200 mg. AUC_∞ for single-dose administration and $AUC_{24\ h}$ for multiple-dose administration also increased in a dose-proportional manner. Steady state was achieved after 4 – 5 days. After intravenous administration, the mean apparent volume of distribution for canagliflozin at steady state was 119 l.

In T2DM patients, not optimally controlled on insulin therapy alone or in combination with metformin, sitagliptin, and/or a TZD, T_{max} of canagliflozin was achieved between 2.75 and 4 h of dosing [23]. There was a dose-dependent increase in C_{max}, 773 ng/ml with 100 mg daily and 3556 ng/ml with 300 mg twice daily. The elimination half-life of 100 mg daily or 300 mg twice daily of canagliflozin ranged from 12 to 15 h. This supports the sponsor's recommendation for once-daily dosing of canagliflozin [20].

Canagliflozin undergoes O-glucuronidation [20]. There are two major human metabolites, ether (*O*)-glucuronides M5 and M7. Both are chemically nonreactive and pharmacologically inactive with respect to SGLT2 and SGLT1 inhibition *in vitro*. Canagliflozin is extensively protein bound (> 99%). Excretion of canagliflozin and its metabolites occurs primarily in the feces (60%) and urine (32.5%).

6.1 Drug–drug interactions

In clinical efficacy and safety studies, no adverse drug–drug interactions were reported. In *in vitro* and/or *in vivo* studies, canagliflozin has not been found to have a clinically relevant effect on the AUC or C_{max} of coadministered drugs, including ethinyl estradiol and levonorgestrel, glyburide, warfarin, simvastatin, digoxin, metformin, hydrochlorothiazide (HCTZ), and acetaminophen [20,31-33]. Coadministration of rifampin substantially reduced AUC and C_{max} of canagliflozin 300 mg daily. Otherwise, canagliflozin pharmacokinetics were not altered by drugs that affect enzymes or drug transporters involved in canagliflozin metabolism. Canagliflozin is not expected to be affected by displacement protein-binding interactions, as it is

highly bound to albumin and α-acid glycoprotein and has a low extraction ratio [20].

7. Clinical efficacy

The clinical efficacy of canagliflozin in T2DM has been assessed according to its introduction as monotherapy and as add-on therapy to metformin, metformin plus sulfonylurea, metformin + TZD, and insulin with or without other AHA. While three clinical efficacy studies have been published as full articles (one Phase II and two phase III studies), a majority of results from large phase III studies have only been published in abstract form thus far. For details and results of each study described below, see **Tables 1** and **2**. The mean baseline HbA1c ranged from 7.7 to 8.3% across studies.

7.1 Glycemic control

As monotherapy, canagliflozin was shown to reduce HbA1c by 0.91 and 1.16% with 26 weeks of treatment with 100 and 300 mg per day, respectively (placebo-corrected; $p < 0.001$ vs. placebo) [34]. It was noted that a majority of the improvements in HbA1c occurred by week 12. In the 100- and 300-mg daily groups, respectively, 44.5 and 62.4% of subjects achieved an HbA1c value of < 7.0% by week 26, which was significantly greater than the proportion of placebo-treated subjects who reached the same goal (20.6%; $p < 0.001$ vs. placebo). Additionally, placebo-corrected FPG was significantly reduced by 2.0 and 2.4 mmol/l, compared to placebo ($p < 0.001$).

As add-on to a stable background of metformin, canagliflozin doses ranging from 50 mg daily to 300 mg twice daily reduced HbA1c from 0.70 to 0.95% at 12 weeks, with all doses having a significantly greater effect than placebo (– 0.22%; $p < 0.001$) [35]. Similarly, in a 52-week study of canagliflozin 100 or 300 mg daily, HbA1c declined by 0.82 and 0.93%, respectively (compared to a reduction of 0.81% in glimepiride 6 – 8 mg daily; both canagliflozin doses were non-inferior to glimepiride, and canagliflozin 300 mg daily was superior to glimepiride) [36]. In the former study, 53 – 72% of subjects receiving canagliflozin doses of ≥ 100 mg daily achieved an HbA1c of < 7%, compared to 34% of subjects receiving placebo ($p < 0.05$ by logistic regression) [35]. Reductions in FPG in the 12-week study ranged from 16.2 to 27.0 mg/dl ($p < 0.001$ vs. placebo).

Canagliflozin therapy on a background of metformin and pioglitazone for 26 weeks induced reductions in HbA1c of 0.89 and 1.03% in canagliflozin 100- and 300-mg daily groups, compared to a decline of 0.26% in the placebo group ($p < 0.001$ vs. placebo) [37]. The proportion of participants in each group that achieved an HbA1c of < 7.0% was 46.9, 64.3, and 32.5%, respectively ($p < 0.001$ vs. placebo).

In a 26-week study of subjects on stable metformin plus sulfonylurea therapy, canagliflozin 100 mg and 300 mg daily reduced HbA1c 0.71 and 0.92% and reduced FPG 1.2 and 1.9 mmol/l, respectively, relative to placebo ($p < 0.001$ vs. placebo, both parameters) [38]. In a 52-week study of a similar population, canagliflozin 300 mg daily reduced HbA1c 1.03%, compared to a 0.66% reduction with sitagliptin 100 mg daily (canagliflozin was both non-inferior and superior to sitagliptin in HbA1c reduction). FPG was reduced by 1.7 and 0.3 mmol/l in the canagliflozin and sitagliptin groups, respectively ($p < 0.001$ canagliflozin vs. sitagliptin) [39].

In subjects treated with insulin with or without AHA, canagliflozin 100 and 300 mg daily for 18 weeks resulted in HbA1c reductions of 0.65 and 0.73%, relative to placebo ($p < 0.001$ vs. placebo) [40]. FPG was reduced by 1.25 and 1.61 mmol/l, compared to placebo ($p < 0.001$ vs. placebo). Also relative to placebo, 12.1 and 17% of subjects in the 100- and 300-mg daily groups, respectively, attained an HbA1c of < 7% by the end of the study period ($p < 0.001$ by logistic regression vs. placebo).

7.2 Body weight

After 26 weeks of monotherapy with canagliflozin 100 or 300 mg daily, body weight reduced by 2.2% (1.9 kg) and 3.3% (2.9 kg), respectively, relative to placebo ($p < 0.001$ vs. placebo) [34]. As an add-on to metformin, canagliflozin ranging from 50 mg daily to 300 mg twice daily resulted in 2.3 – 3.4% reductions in body weight from baseline after 12 weeks, compared to a 1.1% decrease in the placebo group ($p < 0.001$ vs. placebo) [35]. After 52 weeks of treatment on a background of metformin therapy, body weight decreased by 4.2 and 4.7% in 100- and 300-mg daily canagliflozin groups, respectively, compared to a 1.0% increase in body weight with glimepiride therapy (both canagliflozin groups vs. glimepiride, $p < 0.001$) [36]. When added to stable metformin plus sulfonylurea therapy for 26 weeks, canagliflozin 100 and 300 mg daily resulted in placebo-corrected body weight reductions of 1.4 and 2.0%, respectively ($p < 0.001$ vs. placebo) [38]. After 52 weeks, canagliflozin 300 mg daily lowered body weight by 2.5% from baseline (compared to an increase of 0.3% in sitagliptin 100-mg daily treatment group, $p < 0.001$) [39]. In patients on background insulin therapy with or without AHAs, 18 weeks of canagliflozin 100 or 300 mg daily reduced body weight by 1.9 and 2.4%, respectively, relative to placebo ($p < 0.001$ vs. placebo) [40].

7.3 Blood pressure

With canagliflozin 100- or 300-mg daily monotherapy, systolic blood pressure (SBP) was reduced to 3.7 and 5.4 mmHg after 26 weeks (placebo-corrected, $p < 0.001$ vs. placebo) [34]. In patients treated with metformin and sulfonylurea, SBP decreased by 2.2 and 1.6 mmHg after 26 weeks, in 100- and 300-mg daily treatment groups, respectively, relative to placebo, but changes were not statistically significant compared to placebo [38]. In a similar group of patients treated with canagliflozin for 52 weeks, SBP decreased from baseline by 5.1 mmHg (compared to 0.9 mmHg in sitagliptin 100-mg daily treatment group, $p < 0.001$) [39]. After 18 weeks of treatment in patients concurrently treated with insulin with or without AHA, SBP

Table 1. Summary of changes in clinical parameters with canagliflozin treatment*.

Therapy	Author	Duration (weeks)	Subjects (n)	Treatment groups	Mean baseline HbA1c (%)	ΔHbA1c (%)	ΔFPG (mmol/l)	ΔBody weight (%)
Monotherapy	Stenlöf *et al.* (full article)	26	584	Placebo	8.0			
				100 mg canagliflozin daily		– 0.91‡	– 2.0‡	– 2.2‡
				300 mg canagliflozin daily		– 1.16‡	– 2.4‡	– 3.3‡
Add-on to metformin	Rosenstock *et al.* (full article)	12	451	Placebo	7.8	– 0.22	+ 0.2	– 1.1
				50 mg canagliflozin daily		– 0.79‡	– 0.9‡	– 2.3‡
				100 mg canagliflozin daily		– 0.76‡	– 1.4‡	– 2.6‡
				200 mg canagliflozin daily		– 0.70‡	– 1.5‡	– 2.7‡
				300 mg canagliflozin daily		– 0.92‡	– 1.4‡	– 3.4‡
				300 mg canagliflozin twice daily		– 0.95‡	– 1.3‡	– 3.4‡
				100 mg sitagliptin daily		– 0.74‡	– 0.7‡	– 0.6
	Cefalu *et al.* (abstract only)	52	1450	6 – 8 mg glimepiride daily	7.8	– 0.81	na	+ 1.0
				100 mg canagliflozin daily		– 0.82		– 4.2§
				300 mg canagliflozin daily		– 0.93		– 4.7§
Add-on to metformin + pioglitazone	Forst *et al.* (abstract only)	26	342	Placebo	7.9	– 0.26	na¶	na¶
				100 mg canagliflozin daily		– 0.89‡		
				300 mg canagliflozin daily		– 1.03‡		
Add-on to metformin + sulfonylurea	Wilding *et al.* (abstract only)	26	469	Placebo	8.1			
				100 mg canagliflozin daily		– 0.71‡	– 1.2‡	– 1.4‡
				300 mg canagliflozin daily		– 0.92‡	– 1.9‡	– 2.0‡
	Gross *et al.* (abstract only)	52	755	100 mg sitagliptin daily	8.1	– 0.66	– 0.3	+ 0.3
				300 mg canagliflozin daily		– 1.03	– 1.7#	– 2.5#
Add-on to insulin ± one or more AHAs	Matthews *et al.* (abstract only)	18	1718 (elevated cardiovascular risk)	Placebo	8.3			
				100 mg canagliflozin daily		– 0.65‡	– 1.25‡	– 1.9‡
				300 mg canagliflozin daily		– 0.73‡	– 1.61‡	– 2.4‡
Add-on to one or more AHAs	Bode *et al.* (abstract only)	26	714 (55 – 80 years old)	Placebo	7.7			
				100 mg canagliflozin daily		– 0.57‡	– 1.4‡	– 2.3‡
				300 mg canagliflozin daily		– 0.70‡	– 1.5‡	– 3.0‡
Monotherapy or add-on to one or more AHAs	Yale *et al.* (full article)	26	269 (stage 3 chronic kidney disease)	Placebo	8.0	– 0.03	+ 0.03**	– 0.3**
				100 mg canagliflozin daily		– 0.33‡‡	– 0.83	– 1.2
				300 mg canagliflozin daily		– 0.44‡	– 0.65	– 1.5
Mean change ± SD§§						– 0.8 ± 0.2	– 1.4 ± 0.4	– 2.6 ± 0.9

*Values are placebo-subtracted least-squares mean changes from baseline, except where placebo or active comparator values are listed.

‡$p < 0.001$ vs. placebo.

§$p < 0.001$ vs. glimepiride.

¶ΔFPG and body weight were reported as significantly different between canagliflozin groups and placebo, but values were not provided.

#$p < 0.001$ vs. sitagliptin.

**Statistical analysis not performed.

‡‡$p < 0.05$ vs. placebo.

§§Mean change ± SD was calculated based on all canagliflozin treatment groups.

Table 2. Summary of changes in cardiovascular-related parameters with canagliflozin treatment*.

Therapy	Author	Duration (weeks)	Subjects (n)	Treatment groups	ΔSBP (mmHg)	ΔDBP (mmHg)‡	ΔHDL (%)	ΔTG (%)	ΔLDL (%)‡
Monotherapy	Stenlöf *et al.* (full article)	26	584	Placebo					
				100 mg canagliflozin daily	– 3.7§	– 1.6	+ 6.8¶	– 5.4	+ 2.0
				300 mg canagliflozin daily	– 5.4§	– 2.0	+ 6.1¶	– 10.2	+ 6.1
Add-on to metformin	Rosenstock *et al.* (full article)	12	451	Placebo	na	na			
				50 mg canagliflozin daily			+ 3.4	– 11.0	– 0.5
				100 mg canagliflozin daily			+ 0.2	– 10.9	– 4.4
				200 mg canagliflozin daily			+ 4.8	– 9.3	+ 3.0
				300 mg canagliflozin daily			+ 4.1	– 16.0#	– 1.0
				300 mg canagliflozin twice daily			+ 9.0¶	– 18.1¶	+ 7.2
				100 mg sitagliptin daily			– 1.8	– 6.1	– 7.7
	Cefalu *et al.* (abstract only)	52	1450	6 – 8 mg glimepiride daily	na	na	na	na	na
				100 mg canagliflozin daily					
				300 mg canagliflozin daily					
Add-on to metformin + pioglitazone	Forst *et al.* (abstract only)	26	342	Placebo	na§§	na	Na	Na	na
				100 mg canagliflozin daily					
				300 mg canagliflozin daily					
Add-on to metformin + sulfonylurea	Wilding *et al.* (abstract only)	26	469	Placebo					
				100 mg canagliflozin daily	– 2.2	– 1.1	+ 2.6	– 6.2	+ 0.5
				300 mg canagliflozin daily	– 1.6	– 0.5	+ 3.5	– 3.1	+ 4.6
	Gross *et al.* (abstract only)	52	755	100 mg sitagliptin daily	+ 0.9	– 0.3	+ 0.6	+ 11.9	+ 5.2
				300 mg canagliflozin daily	– 5.1**	– 3.0	+ 7.6	+ 9.6	+ 11.7
Add-on to insulin ± one or more AHAs	Matthews *et al.* (abstract only)	18	1718 (elevated cardiovascular risk)	Placebo					
				100 mg canagliflozin daily	– 2.6§	– 1.0	+ 0.8	+ 0.2	– 6.3
				300 mg canagliflozin daily	– 4.4§	– 1.8	+ 4.7§	– 2.0	– 6.6
Add-on to one or more AHAs	Bode *et al.* (abstract only)	26	714 (55 – 80 years old)	Placebo					
				100 mg canagliflozin daily	– 4.6§	– 1.6	+ 5.3§	– 4.8	+ 7.5
				300 mg canagliflozin daily	– 7.9§	– 3.2	+ 4.7§	+ 0.7	+ 7.8
Monotherapy or add-on to one or more AHAs	Yale *et al.* (full article)	26	269 (stage 3 chronic kidney disease)	Placebo	– 0.3‡	– 1.4	+ 1.5‡	+ 7.9‡	+ 6.3
				100 mg canagliflozin daily	– 6.1	– 2.6	+ 4.0	+ 6.2	+ 6.4
				300 mg canagliflozin daily	– 6.4	– 3.5	+ 3.0	+ 11.9	– 1.0
Mean change ± SD‡‡					– 4.5 ± 1.9	– 2.0 ± 1.0	4.4 ± 2.3	– 4.3 ± 8.6	2.3 ± 5.4

*Values are placebo-subtracted least-squares mean changes from baseline, except where placebo or active comparator values are listed.
‡Statistical analysis not performed.
§$p < 0.001$ vs. placebo.
¶$p < 0.01$ vs. placebo.
#$p < 0.05$ vs. placebo.
**$p < 0.001$ vs. sitagliptin.
‡‡Mean change ± SD was calculated based on all canagliflozin treatment groups.
§§ΔSBP was reported as significantly different between both canagliflozin groups and placebo, but values were not provided.

dropped 2.6 and 4.4 mmHg in 100- and 300-mg daily treatment groups, respectively, relative to placebo ($p < 0.001$ vs. placebo) [40]. Across studies, reductions in diastolic blood pressure ranged from 1.0 to 2.0 mmHg (placebo-corrected) and 3.0 mmHg (not placebo-corrected) [34,38-40].

7.4 Lipids

High-density lipoprotein cholesterol (HDL-C) increased across studies. With canagliflozin monotherapy, HDL-C was increased 6.8 and 6.1%, compared to placebo, in 100- and 300-mg daily treatment groups, respectively ($p < 0.001$ and $p < 0.01$, respectively, vs. placebo) [33]. With concurrent metformin therapy in the Phase II dose-ranging study, canagliflozin treatment was only significantly associated with an increase in HDL-C at the 300-mg twice daily treatment level (4.0 mg/dl, placebo-corrected, $p < 0.01$ vs. placebo) [35]. HDL-C increased nonsignificantly compared to placebo in canagliflozin 100- and 300-mg daily treated patients on background metformin plus sulfonylurea therapy (2.6 and 3.5%, respectively, placebo-corrected) [38]. HDL-C was also increased nonsignificantly in subjects on metformin and sulfonylurea treated with canagliflozin 300 mg daily compared to sitagliptin 100 mg daily (7.6 vs. 0.6%, respectively) [39]. In patients on stable insulin therapy with or without AHA, canagliflozin 300 mg daily significantly increased HDL-C by 4.7% but 100 mg daily did not (0.8%) (placebo-corrected, $p < 0.001$ and $p = 0.46$, respectively) [40].

Triglycerides did not tend to change significantly with canagliflozin therapy. Only in one 12-week study of patients on background metformin therapy, there was a significant reduction of triglycerides from baseline of 28.5 and 35.3 mg/dl in the 300-mg daily and 300-mg twice daily groups ($p < 0.05$ and $p < 0.01$, respectively, vs. placebo) [35].

Low-density lipoprotein cholesterol (LDL-C) numerically increased across canagliflozin treatment studies, but statistical analyses were not performed. Increases ranged from 0.5 to 11.7% (placebo-corrected) [34,38-40]. Due to the variance in increases of HDL-C and LDL-C, the change in the ratio of LDL-C to HDL-C also varied, ranging from – 4.0 to 6.1% (placebo-corrected), but again, statistical analyses were not performed for this parameter [34,38-40].

Changes in non-HDL-C and apolipoprotein B (ApoB) were reported only in the monotherapy study [34]. Non-HDL-C increased by 0.7, 2.7, and 0.7% in the canagliflozin 100- and 300-mg daily groups and placebo group, respectively (statistical analysis not performed). ApoB (measured and analyzed in about 60% of the participant population) increased by 1.2, 3.5, and 0.9% in the canagliflozin 100- and 300-mg daily groups and placebo group, respectively (significance not reported).

7.5 Special populations

7.5.1 Older subjects

Clinical efficacy of canagliflozin appears to be similar in older people (age range 55 – 80 years, mean age 63.6 years) concurrently treated with one or more AHA [41]. Placebo-corrected declines in HbA1c (0.57 and 0.70%) and FPG (1.4 and 1.5 mmol/l) in canagliflozin 100- and 300-mg daily treatment groups, respectively, were significantly greater than placebo ($p < 0.001$). Body weight was reduced by 2.3 and 3.0%, and SBP was reduced by 4.6 and 7.9 mmHg (placebo-corrected, $p < 0.001$ vs. placebo for both parameters). HDL-C was significantly increased by 5.3 and 4.7% in both groups, respectively, relative to placebo ($p < 0.001$).

7.5.2 Subjects with chronic kidney disease

The clinical efficacy of canagliflozin was also tested in patients with chronic kidney disease [estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m^2; mean baseline eGFR 39.4 ml/min/1.73 m^2] [42]. Placebo-subtracted changes in HbA1c were – 0.30 and – 0.40% for canagliflozin 100 and 300 mg daily, respectively ($p < 0.05$ and $p < 0.001$, respectively, vs. placebo). For other clinical parameters, canagliflozin treatment resulted in numerically greater improvements than placebo, but statistical analyses were not performed (see **Tables 1** and **2** for results).

8. Safety and tolerability

Safety and tolerability data reviewed below were derived from Phase II and III clinical efficacy and safety studies as well as a pooled analysis of data derived from eight Phase III studies (non-canagliflozin, n = 3262; canagliflozin 100 mg, n = 3092; canagliflozin 300 mg, n = 3085; total, n = 9439) that was included in the aforementioned briefing document provided to an FDA advisory panel [20].

8.1 Serious adverse events

Across studies, the rates of serious adverse events (AEs) and AE-related discontinuations were generally low and similar among canagliflozin, active-comparator, and placebo groups [34-42]. Results of a meta-analysis of cardiovascular events were reported in the pooled analysis [20]. For a composite end point that included cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina, hazards ratios (HRs) were 0.91 [95% confidence interval (CI), 0.65, 1.28] and 0.92 (95% CI, 0.65, 1.28) for the canagliflozin 100- and 300-mg daily treated subjects, respectively, versus non-canagliflozin-treated subjects. The HR was < 1 for each individual type of event included in the composite end point except combined fatal and nonfatal stroke, for which the HR was 1.47 (95% CI, 0.83, 2.59) for canagliflozin versus non-canagliflozin treatment. In a follow-up analysis that included results from two additional studies, the HR was 1.29 (95% CI, 0.80, 2.09). Upon examination of the trial that recruited subjects with an elevated cardiovascular risk, more subjects randomized to canagliflozin experienced a cardiovascular event in the first 30 days of treatment compared to placebo-treated subjects [20]. However, from 31 – 90 days of treatment, there were more cardiovascular events in the placebo groups

compared to the canagliflozin groups. As the pattern of events could not be temporally associated with AEs related to reduced intravascular volume, it was concluded by the authors of the briefing document supplied to the FDA advisory panel that the increase in cardiovascular events in canagliflozin group in the first 30 days was likely a chance finding.

8.2 Hypoglycemia

In studies of canagliflozin as monotherapy or as an add-on to a diabetes treatment not associated with hypoglycemia (i.e., metformin), the rates of hypoglycemia ranged from 2 to 7% compared to 2 to 3% in placebo groups [34,35,41]. Results from the pooled analysis were similar with 2.2, 3.8, and 4.3% of subjects reporting hypoglycemia events for placebo and canagliflozin 100- and 300-mg daily groups, respectively (not considered to be dose-related) [20]. The event rate per subject-year exposure was 0.10, 0.22 and 0.18 for the three groups, respectively. In trials involving canagliflozin as an add-on to a diabetes treatment associated with hypoglycemia (i.e., sulfonylurea or insulin), hypoglycemia occurred in 26 – 53% of canagliflozin-treated subjects, compared to 15 – 38% of subjects in placebo groups [38,40-42]. As noted by the authors of the pooled analysis, when canagliflozin 300 mg daily was compared to sitagliptin 100 mg daily (an AHA not associated with increased risk of hypoglycemia) in patients on background metformin plus sulfonylurea therapy, the rates of hypoglycemia were similar in the two treatment groups (43.2 vs. 40.7%, respectively; event rate per subject-year exposure, 3.81 vs. 4.14) [20,39].

8.3 Urinary tract infections/genital mycotic infections

The rates of urinary tract infections were low throughout trials, ranging from 4 – 8% in canagliflozin treatment groups and 2 – 6% in placebo and active-comparator groups [34,36-42]. Results from the pooled data analysis were similar, with 8.2 and 6.7% rates of urinary tract infection AEs in canagliflozin and non-canagliflozin groups, respectively [20].

Consistent with the increase in UGE, genital mycotic infections, identified by subject-reported symptoms, occurred more frequently in canagliflozin-treated subjects than in placebo or active-comparator-treated subjects. The rates of infection in males and females treated with canagliflozin were 2 – 9 and 8 – 24%, respectively. In placebo and active-comparator groups, the rates of infection in males and females were 0 – 1 and 0 – 5%, respectively [34,36-42]. From the pooled analysis, the rate of vulvovaginitis was 14.3% in canagliflozin-treated patients versus 3.1% in non-canagliflozin-treated patients [20]. Male genital infections occurred at a rate of 8.3 and 1.6% in the two groups, respectively. In a 12-week, Phase II, dose-ranging study of canagliflozin, self-administered vaginal swabs for Candida culture were collected from 198 females at baseline and end of study [35,43]. In an analysis published separately from the original study, it was reported that 31 and 14% of canagliflozin- and placebo/sitagliptin-treated subjects, respectively, converted from negative cultures at baseline to positive cultures at week 12 (odds ratio, 2.8; 95% CI, 1.0 – 7.3 for canagliflozin vs. placebo/sitagliptin) [43]. Subjects with a positive culture at baseline (23/198, 12%) were at increased risk of experiencing a symptomatic vulvovaginal AE (odds ratio, 9.1; 95% CI, 2.4 – 34.0). Across studies, patients were treated with oral and/or topical antifungal therapies, usually without discontinuation of study treatment [34,36,38-42].

8.4 Osmotic diuresis- and volume-related AEs

Subjects were monitored for osmotic diuresis-related AEs (i.e., pollakiuria, polyuria, thirst). Symptoms occurred at a similar rate among treatment groups, with < 3 – 6% of subjects reporting symptoms for each specific AE within this category [34,36,38-42]. Results from the pooled analysis showed that 2.4, 7.3, and 7.9% of subjects in the non-canagliflozin and canagliflozin 100- and 300-mg groups, respectively, experienced an osmotic diuresis-related AE, with 0.1, 0.3, and 0.3% experiencing events requiring discontinuation [20]. Events were considered non-dose-related and generally occurred within the first 6 weeks of treatment.

Volume-related AEs (i.e., postural dizziness, orthostatic hypotension) were only reported in two studies (monotherapy and canagliflozin add-on to insulin), with symptom rates of 0 – 3% in canagliflozin groups and 0% in placebo groups [34,40]. In the pooled analysis, the volume-related AEs were increased dose-dependently with canagliflozin 100 and 300 mg daily, compared to non-canagliflozin treatment, at rates of 3.2, 4.6, and 2.4%, respectively [20]. The rates of serious AEs in this category were similar across groups. In the 300-mg group, events occurred earlier, within 12 weeks. Further analysis revealed an increased risk of reduced intravascular volume AEs with age ≥ 75 years, use of loop diuretics, or eGFR < 60 ml/min/1.73 m^2. The rates of AEs in these subgroups were > 8 and 3 – 5% in the canagliflozin 300- and 100-mg groups, respectively. In response to volume-related AEs, dosing of blood pressure medications, including diuretics, was often modified.

8.5 Other AEs

From the pooled data analysis, constipation occurred in 3.13.0, and 2.4% of subjects in canagliflozin 100- and 300-mg and non-canagliflozin groups, respectively [20]. Rash and urticaria, respectively, were reported in 1.6 versus 1.3% and 0.4 versus 0.3% of subjects randomized to canagliflozin and non-canagliflozin treatment. After 52 weeks of canagliflozin treatment in older subjects, small reductions in bone density occurred, as assessed in the total hip and lumbar spine, but were postulated to arise from small reductions in body weight [20]. There were a numerically larger number of low-trauma upper limb fractures early in canagliflozin treatment compared to placebo. It was concluded that canagliflozin treatment would not increase low-trauma fracture risk via reduced bone density; however, a relationship between this risk and reduced intravascular volume AEs has not been

completely ruled out. The rates of breast, bladder, and renal cancers were low, and there was no meaningful imbalance of events among treatment groups [20].

8.6 Renal effects

From the pooled analysis, renal-related AEs occurred at a rate of 2.5, 3.1, and 3.6% in non-canagliflozin and canagliflozin 100- and 300-mg daily groups, respectively [20]. Incidence of renal-related AEs in those with reduced renal function (eGFR < 60 ml/min/1.73 m^2) was 3.7, 8.9, and 9.3%. Most events occurred early, as with volume-related AEs. A greater proportion of subjects in the canagliflozin 300-mg daily group discontinued as a result of an AE related to reduced renal function compared to canagliflozin 100-mg group or placebo in both the overall and renal pooled analyses (1.1 and 1.6%, respectively, vs. 0.5 and 1.2% in canagliflozin 100-mg groups and 0.5 and 1.0% in non-canagliflozin groups).

With canagliflozin treatment, eGFR tends to first decrease and then stabilize or trend back toward baseline [20,42]. This change is most likely the result of pre-renal hemodynamics. In the pooled analysis, using a last observation carried forward analysis, 6.2, 6.4, and 9.7% of subjects on non-canagliflozin and canagliflozin 100 and 300 mg daily, respectively, had a decrease in eGFR > 30 ml/min/1.73 m^2 between baseline and any point during treatment, mostly occurring by week 6 [20]. In subjects with impaired renal function (eGFR < 60 ml/min/1.73 m^2), decreases in eGFR of > 30 ml/min/1.73 m^2 occurred at a rate of 4.9, 9.3, and 12.2% in the three groups [20]. With discontinuation, eGFR tended to increase to at or just below baseline eGFR values. In the 26-week Phase III study of canagliflozin treatment in patients with chronic kidney disease (mean baseline eGFR 39.4 ml/min/1.73 m^2), mean changes in eGFR were – 9.1 and – 10.1% in the canagliflozin 100- and 300-mg daily groups, compared to – 4.5% in the placebo group, with largest reductions observed at week 3 [42].

9. Regulatory affairs

Canagliflozin (trade name INVOKANA®) was approved by the FDA in April 2013 for treatment of adults with T2DM [44,45].

10. Conclusion

In summary, at doses proposed for approval by the FDA (100 and 300 mg daily), canagliflozin treatment induced significant reductions in HbA1c (0.6 – 1.1%), body weight (1.4 – 3.3%), and SBP (2.6-7.9 mmHg), and a significant increase in HDL-C (4.7 – 6.8%) across a range of background T2DM therapies (placebo-corrected). There was a low risk of hypoglycemia in relation to canagliflozin treatment. The main side effects included an increased risk of genital mycotic infections and osmotic diuresis- and reduced intravascular volume-related events. Concerns about increases in LDL-C, as well as an increased HR of fatal and nonfatal stroke and a transient increase in cardiovascular events in the first 30 days of treatment, will need to be addressed in longer term safety monitoring.

11. Expert opinion

Effective treatment of T2DM requires a multifactorial approach, including lifestyle counseling and pharmacologic management. Given the significant number of diagnosed diabetic, prediabetic, and undiagnosed diabetic patients, there are a relatively small number of AHAs at our disposal. Progressive deterioration of beta-cell function, weight gain, and hypoglycemia still remain the major hurdles in treating type 2 diabetes and remain difficult to overcome with the currently available therapies. The mainstay treatments such as metformin, sulfonylurea, and insulin have been nicely complemented by the addition of GLP-1 agonists and DPP-4 inhibitors. Less effective agents such as colesevelam and bromocriptine were not developed for diabetes treatment, but found to have relatively minor antihyperglycemic properties. In the case of SGLT2 inhibitors, the renal filtration of circulating glucose offers a novel, non-insulin-mediated, physiologic mechanism to exploit.

Canagliflozin's relatively modest improvement on HbA1c, FPG, PPG, and weight appear to be similar to dapagliflozin, which is currently approved in Europe [46]. Like dapagliflozin, canagliflozin has been tested and has modest efficacy as add-on therapy to metformin, poiglitazone, sitagliptin, and insulin, but the latter is currently only being considered as adjunct to diet and lifestyle modification. The greatest HbA1c effects are seen in a subset of patients with worse glycemic control (HbA1c > 10%) [34,] and when used as monotherapy, however, canagliflozin was able to complement existing therapy to achieve HbA1c < 7% in a greater proportion of patients compared to placebo in studies of patients with moderate glycemic control (HbA1c 7 – 8%). Dapagliflozin is not recommended with moderate to severe renal dysfunction (eGFR < 60 ml/min/1.73 m^2). Canagliflozin was studied and found to be safe in patients with moderate renal impairment (eGFR < 60 ml/min/1.73 m^2) but may cause a reduction in eGFR, and thus, dose reduction may be necessary in this population [20]. Additionally, dose reduction is suggested for patients > 75 years of age and on concurrent loop diuretics to reduce the risk of renal impairment and volume-related AEs. Of note, there is evidence that canagliflozin exhibited a lesser magnitude of HbA1c reduction and body weight in subjects with an eGFR < 45 ml/min/1.73 m^2 [47].

Based on efficacy, canagliflozin will likely be a second- or third-line treatment, behind metformin, sulfonylurea, insulin, and incretin therapy. However, its side-effect profile, such as low risk of hypoglycemia, weight loss, and safety in the elderly and with renal dysfunction, offers potential therapeutic use in specific populations. In fact, it is these same properties that have garnered such enthusiasm for DPP-4 inhibitors and

GLP-1 agonists. In addition, it offers another option to those patients resistant to injection therapy (insulin and GLP-1 agonists).

The unexplained increase in fatal and nonfatal stroke, as well as the transient increase in cardiovascular events in the first 30 days of treatment, continues to be evaluated. Additionally, the longer term impact of increased LDL-C remains to be determined. Often diabetic patients have comorbid cardiovascular issues including hyperlipidemia. Unfortunately, aggressive monitoring and treatment of LDL-C may be even more necessary. Longer term adherence and tolerability of frequent mycotic infections, especially in female patients, is of interest. The relationship of low-trauma fractures to canagliflozin therapy is not clear. There is an unclear association of breast and bladder cancer observed with dapagliflozin that has not been detected with canagliflozin.

Canagliflozin offers a new tool in the vast array of therapeutic options available to treat T2DM. Its favorable side-effect profile, such as low incidence of hypoglycemia and weight loss, may balance its relatively modest reduction in HbA1c, FPG, and PPG, and mild elevation in LDL-C. Concerns about cardiovascular risks will need to be weighed against the potential benefits, both for FDA approval and in clinical use. More information, including peer-reviewed published data, will be useful to interpret and decide where canagliflozin should fall within the diabetic treatment algorithm.

Declaration of interest

The authors declare that they have no conflict of interest and have received no payment in the preparation of their manuscript.

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