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Canagliflozin: A Review in Type 2 Diabetes

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Abstract Canagliflozin (Invokana®) is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated in various countries worldwide for the once-daily oral treatment of type 2 diabetes (T2D). Canagliflozin lowers blood glucose levels independently of insulin, with the inhibition of SGLT2 reducing renal reabsorption of glucose and increasing excretion of glucose in the urine. In well-designed clinical trials, canagliflozin (as first-line monotherapy or add-on therapy to other antihyperglycaemic agents) improved glycaemic control in adults with T2D, including those of older age and/or at high cardiovascular (CV) risk, and also had beneficial effects on their bodyweight and blood pressure (BP). CV risk reduction, as well as possible renal benefits, were also seen with canagliflozin in T2D patients at high CV risk in the CANVAS Program, an integrated analysis of two large CV outcomes studies. Canagliflozin was generally well tolerated, had a low risk of hypoglycaemia and was most commonly associated with adverse events such as genital and urinary tract infections and increased urination, consistent with its mechanism of action. Although the amputation and fracture risk observed among recipients of the drug require further investigation, canagliflozin is an important option for T2D management in adults.

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Canagliflozin: clinical considerations in type 2 diabetes

Lowers blood glucose levels by increasing urinary glucose excretion, an effect independent of insulin
Provides effective glycaemic control as first-line monotherapy or as add-on therapy
Reduces bodyweight, BP and overall CV risk
Generally well tolerated with a low risk of hypoglycaemia

1 Introduction

Type 2 diabetes (T2D) is a progressive metabolic disease characterized by hyperglycaemia, due to insulin resistance/insufficient insulin production [1]. Patients are often obese, have lipid disturbances and elevated blood pressure (BP),

and are at an increased risk of microvascular and macrovascular complications [1]. Achieving good glycaemic control (e.g. HbA_{1C} level <7%) is a key management goal, for which numerous antihyperglycaemic agents (AHAs) with varying mechanisms of action are now available [2]. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively recent AHA class with a good benefit/risk balance [3]. By inhibiting SGLT2 (a key protein in glucose resorption in the kidney), these drugs increase urinary glucose excretion (UGE), causing blood glucose levels to decline independently of insulin [4]. One of the most widely available SGLT2 inhibitors is canagliflozin (Invokana®), which is approved for the treatment of T2D in various countries worldwide, including the USA and EU. This article reviews data relevant to the use of canagliflozin in T2D in the EU; fixed-dose canagliflozin/metformin tablets are also now available, but are beyond the scope of this article.

2 Pharmacodynamic Properties

Canagliflozin is a competitive inhibitor of SGLT2 [5, 6], and thus reduces both renal glucose reabsorption and the renal threshold for glucose (RT_G), with subsequent increases in UGE [7–9]. These increases in UGE reduce plasma glucose levels [7–9], provide calorie and thus bodyweight loss (Sect. 4.2) and have an osmotic diuretic effect (that may help reduce BP; Sect. 4.3) [9]. Maximal RT_G suppression in T2D patients was seen with canagliflozin 300 mg/day in phase 1 trials, with 24-h mean RT_G values reduced from ≈13 to 4–5 mmol/L (i.e. values greater than plasma glucose levels usually associated with hypoglycaemia symptoms, indicating a low hypoglycaemia risk; Sect. 5.3) [9].

Canagliflozin is highly selective for SGLT2 in vitro [5, 6, 10] (with one study, for instance, demonstrating ≈160-fold greater selectivity for SGLT2 than SGLT1 [10]), although the drug can inhibit SGLT1, albeit with lower potency. As SGLT1 is key in gastrointestinal glucose absorption, canagliflozin in the small intestines after oral administration may transiently inhibit intestinal SGLT1, and thus glucose absorption [11]. Indeed, in small placebo-controlled crossover studies in T2D patients [12] or healthy volunteers [13], canagliflozin reduced postprandial glucose (PPG) excursions by both non-renal (possibly via intestinal SGLT1 inhibition) and renal (via SGLT2 inhibition) mechanisms. Notably, canagliflozin 300 mg/day was associated with less extensive PPG excursions, lower 24-h mean RT_G and greater 24-h UGE than dapagliflozin 10 mg/day in healthy volunteers [14]. Various measures of β-cell function improved with canagliflozin regimens in T2D trials [9, 15–19], likely as an indirect consequence of reduced glucotoxicity [20].

Canagliflozin (100 or 300 mg/day) was generally associated with small changes in serum electrolytes (including sodium, calcium, bicarbonate, phosphate, potassium and magnesium) [21], normalization of serum magnesium levels in hypomagnesaemia [22], and reductions in serum uric acid levels (possibly via increased urinary uric acid excretion) [23] in pooled (post hoc [22, 23]) analyses of T2D phase 3 trials. Of the serum electrolyte abnormalities studied, potassium above the upper limit of normal plus >15% increase from baseline was the most common with canagliflozin 100 and 300 mg/day, both in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 (5 and 7 vs. 5% of placebo recipients) and in those with an eGFR ≥45 to <60 mL/min/1.73 m^2 (5 and 9 vs. 6%) [21].

Elderly patients with T2D who added canagliflozin to their current AHA regimen in a phase 3 study (Sect. 4.5) had significant small reductions in bone mineral density at the total hip (but no other skeletal sites), as measured by DXA, over 104 weeks of therapy compared with adding placebo [24]. Increases in biomarkers of bone turnover were also seen over 52 weeks in the canagliflozin versus placebo groups; these changes were partly due to bodyweight loss, and bone strength was not impacted [24].

Consistent with its CV profile (Sect. 4.4), canagliflozin significantly ($p < 0.05$ vs. placebo) attenuated increases in CV stress biomarkers (NT-proBNP and high sensitivity troponin I) in a post hoc analysis [25] of the aforementioned elderly patient trial. Moreover, when data from another phase 3 study were assessed post hoc [26], serum levels of certain adipokines were reduced (leptin and IL-6) or increased (adiponectin) with canagliflozin versus glimepiride, when each was added to metformin therapy over 52 weeks, indicating potential improvements in adipose tissue function and overall cardiometabolic health with canagliflozin therapy.

3 Pharmacokinetic Properties

Canagliflozin is rapidly absorbed after oral administration, reaching maximum plasma concentrations 1–2 h post-dose in T2D patients [7] and healthy volunteers [9]. The drug has a mean absolute oral bioavailability of ≈65% [27] and reaches steady-state in 4–5 days [7, 9]. Exposure increases in proportion to dose and there is up to 36% accumulation of the drug in plasma at the recommended dosages (100 or 300 mg/day) [7, 9]. Food does not impact canagliflozin pharmacokinetics [28], enabling it to be taken with or without food [9]; however, as canagliflozin may help reduce PPG excursions by delaying glucose absorption in the intestine (Sect. 2), administration before the first meal of the day is advised [9].

Canagliflozin is extensively (99%) plasma protein bound, and has a mean volume of distribution at steady state of 83.5 L after intravenous infusion [9]. Metabolism of canagliflozin occurs primarily via *O*-glucuronidation [by uridine 5′-diphospho-glucuronosyltransferase (UGT) 1A9 and 2B4], producing two main inactive metabolites [29]; metabolism via CYP3A4 is minimal (≈7%) [9]. Canagliflozin is eliminated via the faeces (41.5% as parent drug; 10.2% as metabolites) and urine (33%, mainly *O*-glucuronide metabolites), and recommended doses have renal clearance rates of 1.30–1.55 mL/min [9]. The mean elimination half-life of canagliflozin 100 or 300 mg/day in T2D patients was 13.7 and 14.9 h [7].

Mild or moderate hepatic impairment does not alter canagliflozin pharmacokinetics to a clinically relevant extent [30] and does not necessitate dosage adjustment [9]; the drug has not been assessed, and is thus not recommended, in severe hepatic impairment [9]. Renal impairment increases canagliflozin exposure and reduces pharmacodynamic response to the drug [30]. The canagliflozin dosage does not require adjustment in patients with an eGFR of 60 to <90 mL/min/1.73 m^2; however, if eGFR persistently declines below 60 or 45 mL/min/1.73 m^2, dosage adjustment/consideration or discontinuation is necessary [9]. Canagliflozin should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 or used in patients with end-stage renal disease/on dialysis. Renal function monitoring is advised [9].

Higher than therapeutic concentrations of canagliflozin did not inhibit or induce key CYP isoenzymes in vitro, and there was no clinically relevant impact of canagliflozin on CYP3A4 in vivo [9]. However, as canagliflozin is metabolized by UGT1A9 and UGT2B4, and transported by p-glycoprotein (p-gp) and breast cancer resistance protein (BCRP), drugs that induce these enzymes may reduce canagliflozin exposure; thus, if coadministered, canagliflozin dosage adjustment (and, in some instances, additional AHAs) may be necessary [9]. There is also potential for canagliflozin exposure to be reduced by cholestyramine, necessitating staggered administration [9]. Canagliflozin weakly inhibits p-gp and may thus increase plasma concentrations of p-gp substrates; monitoring is advised [7, 9]. Intestinal BCRP inhibition by canagliflozin cannot be ruled out and may increase exposure to drugs transported by BCRP [9]. Canagliflozin may augment the effects of diuretics, increasing dehydration and hypotension (Sect. 5.2) risks [9]. There is also an increased risk of hypoglycaemia if canagliflozin is used in combination with an insulin secretagogue or insulin (Sect. 5.3); reduction of the insulin or insulin secretagogue dosage may be required [9].

4 Therapeutic Efficacy

The clinical efficacy of oral canagliflozin, as monotherapy or add-on therapy, in adults with inadequately-controlled T2D, has been evaluated in numerous placebo- and/or active comparator-controlled trials of randomized, double-blind (or open-label [31]) design, some of which had double-blind extensions. Unless otherwise specified, trials were phase 3 and used the change from baseline in HbA_{1C} (usually at 26 or 52 weeks; range 16–52 weeks) as the primary endpoint. Real-world data are also now available. Discussion focuses on recommended canagliflozin dosages (i.e. 100 or 300 mg/day); some data are from abstracts [32–38].

4.1 Glycaemic Parameters

In patients with T2D inadequately controlled by diet and exercise, monotherapy with canagliflozin 100 or 300 mg/day improved glycaemic control over 26 weeks, with each dosage significantly reducing HbA_{1C} and fasting plasma glucose (FPG) levels relative to placebo; the proportion of patients achieving an HbA_{1C} target of <7% also significantly favoured the canagliflozin groups (Table 1) [15]. Improvements in glycaemic control were sustained over 52 weeks in canagliflozin recipients who continued to receive the drug in the extension of this trial (Table 1) [39]. Moreover, a secondary analysis of another study in this setting found canagliflozin 100 or 300 mg/day to be non-inferior to metformin extended-release (XR) in improving HbA_{1C} over 26 weeks (Table 1) [40].

Canagliflozin was also an effective add-on therapy in patients with T2D inadequately controlled by their current AHA regimen. Indeed, as an add-on to metformin, canagliflozin 100 or 300 mg/day significantly improved HbA_{1C} and other glycaemic parameters over 26 weeks relative to placebo (Table 2) [41]. Moreover, compared with adding sitagliptin [41] or glimepiride [42] in this setting, adding canagliflozin 100 mg/day was noninferior and adding canagliflozin 300 mg/day was superior in lowering HbA_{1C} levels over 52 weeks (Table 2). A target HbA_{1C} of <7.0% was reached by 41–60% of patients at 52 weeks in these trials (Table 2) [41, 42], with the odds of achieving this target without concomitant hypoglycaemia being 2.1- and 2.9-fold greater with canagliflozin 100 and 300 mg/day than with glimepiride (post hoc analysis) [32]. Reductions in FPG were also significantly [41] or numerically [42] greater in the canagliflozin than in the active comparator groups at 52 weeks in these studies (Table 2). Longer term, the relative glycaemic benefits of the canagliflozin and glimepiride regimens were generally sustained over up to 104 weeks' therapy (Table 2) [43].

Table 1 Efficacy of oral canagliflozin as first-line monotherapy in adults with inadequately-controlled T2D in double-blind phase 3 trials

Study (acronym)	Regimen (mg od) [no. of pts]	Week of eval	Change from BL [BL]		% pts with HbA_{1C} <7%	Change from BL [BL] Bodyweight (kg)
			HbA_{1C}[a] (%)	FPG (mmol/L)		
Stenlöf et al. [15]	CAN 100 [195]	26	−0.77* [8.1]	−1.5* [9.6]	44.5*	−2.5* [85.9]
(CANTATA-M)	CAN 300 [197]		−1.03* [8.0]	−1.9* [9.6]	62.4*	−3.4* [86.9]
	PL [192]		+0.14 [8.0]	+0.5 [9.2]	20.6	−0.5 [87.5]
Stenlöf et al. [39]	CAN 100 [166]	52	−0.81 [8.0]	−1.5 [9.5]	52.4	−2.8 [86.4]
(CANTATA-M ext)[b]	CAN 300 [166]		−1.11 [8.0]	−2.2 [9.4]	64.5	−3.9 [87.2]
Rosenstock et al. [40]	CAN 100 [237]	26	−1.37[c] [8.8]	−2.1 [10.9]	38.8	−2.8† [90.3]
	CAN 300 [238]		−1.42[c] [8.8]	−2.5 [10.7]	42.8	−3.7† [93.0]
	MET-XR [237]		−1.30 [8.8]	−1.9 [10.6]	43.0	−1.9 [92.1]

Changes from BL are least squares means and BL values are means

BL baseline, *CAN* canagliflozin, *ext* extension, *eval* evaluation, *FPG* fasting plasma glucose, *HbA_{1C}* glycosylated haemoglobin, *MET-XR* metformin-extended release, *od* once daily, *PL* placebo, *pts* patients

* $p < 0.001$ vs. PL; † $p < 0.05$ vs. MET-XR

[a] Primary endpoint at week 26

[b] Pts ($n = 155$) originally randomized to PL in CANTATA-M were switched to sitagliptin 100 mg od for this ext; efficacy data were not reported

[c] Noninferiority of CAN 100 or 300 mg od vs. MET-XR was established [key secondary analysis; primary analysis compared CAN/MET-XR combination arms (not reported here) vs. MET-XR]

Similarly, in patients with T2D inadequately controlled by metformin plus either a sulfonylurea [16], pioglitazone [18] or sitagliptin (phase 4 trial) [44], adding canagliflozin (100 or 300 mg/day) significantly lowered both HbA_{1C} and FPG levels and significantly increased the proportion of patients achieving HbA_{1C} levels <7% versus placebo over 26 weeks, with these benefits sustained up to 52 weeks [16, 18] (Table 2). Another trial in a similar patient population found adding canagliflozin 300 mg/day to metformin plus a sulfonylurea to be more effective in lowering HbA_{1C} and FPG levels over 52 weeks than adding sitagliptin, and numerically more canagliflozin than sitagliptin recipients achieved HbA_{1C} <7% (Table 2) [17].

4.2 Bodyweight

Canagliflozin (100 or 300 mg/day) significantly reduced bodyweight relative to placebo over 26 weeks, both when used as monotherapy in patients with T2D inadequately controlled by diet and exercise (Table 1) [15] and when used as add-on therapy in patients whose T2D was inadequately controlled by metformin, either alone [41] or in combination with another oral AHA [16, 18, 44] (Table 2). In all settings, weight loss was sustained with canagliflozin up to 52 weeks (Tables 1 and 2) [16, 18, 39, 41].

In active comparator-controlled trials, canagliflozin (100 or 300 mg/day) as monotherapy [40] or added to ongoing metformin monotherapy [41, 42] or metformin plus a sulfonylurea [17] significantly reduced bodyweight over 26 weeks versus metformin-XR monotherapy [40] and over 52 weeks versus adding sitagliptin [17, 41] or glimepiride [42], with the benefit of canagliflozin versus glimepiride being maintained over 104 weeks' treatment [43] (Table 2). Notably, in a post hoc analysis [45] of one of these studies [42, 43], more overweight/obese patients (BMI ≥25 kg/m^2) lost ≥4.5 kg in bodyweight with canagliflozin than with glimepiride over 52 and 104 weeks.

The weight loss associated with canagliflozin seems mainly due to fat mass reduction [42] and, in a pooled analysis of four phase 3 placebo-controlled studies ($n = 2250$) [46], contributed to some of the HbA_{1C}- (Sect. 4.1) and systolic BP (SBP)- (Sect. 4.3) lowering effects of the drug (≈15 and ≈42%, respectively).

4.3 Other Parameters

In general, BP was modestly lowered with canagliflozin (as monotherapy or add-on therapy) in the trials discussed so far. For instance, in placebo-controlled studies [15, 16, 18, 41, 44], mean changes from baseline (126–131 mmHg) in SBP over 26 weeks ranged from −5.8 to −3.3 mmHg with canagliflozin (100 or 300 mg/day) versus −2.7 to +1.5 mmHg with placebo, with the between-group difference being statistically significant ($p < 0.025$) in all but one trial [16]. Mean changes from baseline (76–79 mmHg) in diastolic BP (DBP) in the respective groups ranged from −3.5 to −1.7 mmHg and from −1.7 to +0.3 mmHg ($p = 0.002$ for canagliflozin vs. placebo, where reported/assessed [44]). Moreover, when

Table 2 Efficacy of oral canagliflozin as add-on therapy to metformin, with or without other oral antihyperglycaemic agents, in adults with inadequately-controlled T2D in double-blind trials; all trials were phase 3, except one [44] which was phase 4

Study (acronym)	Regimen (mg od) [no. of pts]	Week of eval	Change from BL [BL]		% of pts with HbA_{1C} <7%	Change from BL [BL]
			HbA_{1C}[a] (%)	FPG (mmol/L)		Bodyweight (kg)
Add-on to MET						
Lavalle-González et al. [41]	CAN 100 + MET [368]	26	−0.79** [7.9]	−1.5** [9.4]	46**	−3.3** [88.7]
(CANTATA-D)	CAN 300 + MET [367]		−0.94** [8.0]	−2.1** [9.6]	58**	−3.6** [85.4]
	SIT 100 + MET [366]		−0.82[b] [7.9]	−1.1[b] [9.4]	55[b]	−1.1[b] [87.6]
	PL + MET [183]		−0.17 [8.0]	+0.1 [9.1]	30	−1.1 [86.7]
	CAN 100 + MET [368]	52	−0.73[c] [7.9]	−1.5[†] [9.4]	41[d]	−3.3[†] [88.7]
	CAN 300 + MET [367]		−0.88[c] [8.0]	−2.0[†] [9.6]	55[d]	−3.7[†] [85.4]
	SIT 100 + MET [366]		−0.73 [7.9]	−1.0 [9.4]	51	−1.2 [87.6]
Cefalu et al. [42]	CAN 100 + MET [483]	52	−0.82[c] [7.8]	−1.35[b] [9.2]	54[b]	−3.7[††,e] [86.8]
(CANTATA-SU)	CAN 300 + MET [485]		−0.93[c] [7.8]	−1.52[b] [9.1]	60[b]	−4.0[††,e] [86.6]
	GLIM + MET [482]		−0.81 [7.8]	−1.02 [9.2]	56	+0.7 [86.6]
Leiter et al. [43]	CAN 100 + MET [483]	104	−0.65 [7.8]	−1.1[f] [9.2]	43[b]	−3.6[f] [86.8]
(CANTATA-SU ext)	CAN 300 + MET [485]		−0.74[f] [7.8]	−1.3[f] [9.1]	50[b]	−3.6[f] [86.6]
	GLIM + MET [482]		−0.55 [7.8]	−0.6 [9.2]	44	+0.8 [86.6]
Add-on to MET + Other Oral Antihyperglycaemic Agent						
Wilding et al. [16]	CAN 100 + MET + SU [157]	26	−0.85** [8.1]	−1.0** [9.6]	43**	−1.9**[e] [93.5]
(CANTATA-MSU)	CAN 300 + MET + SU [156]		−1.06** [8.1]	−1.7** [9.3]	57**	−2.5**[e] [93.5]
	PL + MET + SU [156]		−0.13 [8.1]	+0.2 [9.4]	18	−0.8 [90.8]
	CAN 100 + MET + SU [157]	52[b]	−0.74 [8.1]	−1.1 [9.6]	39	−2.0 [93.5]
	CAN 300 + MET + SU [156]		−0.96 [8.1]	−1.5 [9.3]	53	−3.1 [93.5]
	PL + MET + SU [156]		+0.01 [8.1]	+0.6 [9.4]	19	−1.0 [90.8]
Schernthaner et al. [17]	CAN 300 + MET + SU [377]	52	−1.03[c] [8.1]	−1.7** [9.4]	48[b]	−2.3** [87.6]
(CANTATA-D2)	SIT 100 + MET + SU [378]		−0.66 [8.1]	−0.3 [9.1]	35	+0.1 [89.6]
Forst et al. [18]	CAN 100 + MET + PIO [113]	26	−0.89** [8.0]	−1.5** [9.4]	47*	−2.6** [94.2]
	CAN 300 + MET + PIO [114]		−1.03** [7.8]	−1.8** [9.1]	64**	−3.7** [94.4]
	PL + MET + PIO[g] [115]		−0.26 [8.0]	+0.1 [9.1]	33	−0.2 [94.0]
	CAN 100 + MET + PIO [113]	52	−0.92 [8.0]	−1.5 [9.4]	52	−2.5 [94.2]
	CAN 300 + MET + PIO [114]		−1.03 [7.8]	−1.8 [9.1]	66	−3.6 [94.4]
Rodbard et al. [44]	CAN[h] + MET + SIT [107]	26	−0.91** [8.5]	−1.7** [10.3]	32**	−3.1**[e] [93.8]
	PL + MET + SIT [106]		−0.01 [8.4]	−0.1 [10.0]	12	−1.6 [89.9]

Changes from BL are least squares means and BL values are means

BL baseline, *CAN* canagliflozin, *ext* extension, *eval* evaluation, *FPG* fasting plasma glucose, *GLIM* glimepiride (uptitrated to 6 or 8 mg od), HbA_{1C} glycosylated haemoglobin, *MET* metformin (generally ≥2000 mg/day; ≥1500 mg/day if higher dosages not tolerated), *od* once daily, *PIO* pioglitazone (30 or 45 mg/day), *PL* placebo, *pts* patients, *SIT* sitagliptin, *SU* sulfonylurea (≥50% maximal dosage)

* $p < 0.01$, ** $p \leq 0.001$ vs. PL; † $p < 0.001$, †† $p < 0.0001$ vs. active comparator group

[a] Primary endpoint at week 26 [16, 18, 41, 44] or 52 [17, 42]

[b] No formal statistics performed/reported for CAN vs. PL [16], GLIM [42, 43] or SIT [17], or SIT vs. PL [41], for these endpoints/timepoints

[c] Based on prespecified criteria, CAN 100 was noninferior to, and CAN 300 more effective than, SIT [17, 41] and GLIM [42]

[d] The 95% CI for the odds ratio excluded 1 for CAN 100 vs. SIT, but not CAN 300 vs. SIT

[e] P-values are for percentage changes in bodyweight, and are assumed to also apply to kg changes

[f] The 95% CI for the CAN vs. GLIM comparison excluded 0

[g] Ninety pts in this group entered the 26-week ext, during which they received SIT + MET + PIO to maintain blinding

[h] Pts received CAN 100 mg od, with titration to CAN 300 mg od permitted at week 6 in eligible pts; pooled data are presented

four 26-week phase 3 placebo-controlled trials were pooled ($n = 2313$), the SBP- and DBP-lowering effects of canagliflozin were seen regardless of whether antihypertensives were, or were not, taken concomitantly [47], and improvements in arterial stiffness markers were also seen with the drug [48].

In trials that compared active agents as monotherapy [40] or as add-on therapy to metformin-based regimens

[17, 41, 42], canagliflozin (100 or 300 mg/day) reduced SBP over 26 weeks versus metformin-XR (no between-group statistics reported) [40] and over 52 weeks versus sitagliptin ($p < 0.001$) [17, 41] or glimepiride (no p-value; comparison not prespecified) [42]; DBP-lowering effects were also evident in the canagliflozin versus the comparator groups. The SBP- and DBP-lowering effects of canagliflozin were durable, being sustained over 104 weeks of treatment [43].

In terms of lipids, canagliflozin (as monotherapy or add-on therapy) was generally associated with modest increases in HDL-C (3–8%) and LDL-C (1–12%) levels (LDL-C:HDL-C ratio changes ranged from −4 to +5%) and modest reductions in triglyceride levels (2–10%) relative to placebo over 26 weeks in key clinical trials [15, 16, 41, 44]; similar findings were generally seen at 52 weeks [16, 18, 39]. In active comparator-controlled trials, canagliflozin as monotherapy for 26 weeks [40] or added to metformin-based therapy for 52 weeks [17, 41, 42] increased HDL-C levels [17, 40–42] and (in some studies [17, 40, 42]) LDL-C levels, versus metformin-XR monotherapy [40] or adding sitagliptin [17, 41] or glimepiride [42] to metformin-based therapy. Canagliflozin also reduced triglyceride levels relative to metformin-XR [40] and glimepiride [42], but did not differ from sitagliptin in terms of triglyceride changes [17, 41]. Longer-term data from the glimepiride-controlled trial at 104 weeks were generally consistent with these findings [43].

In a post hoc analysis [49] of the glimepiride-controlled trial [43], canagliflozin also appeared to preserve renal function relative to glimepiride over 104 weeks. The annual slope of eGFR decline was significantly ($p < 0.01$) smaller with canagliflozin 100 or 300 mg/day than with glimepiride (0.5 and 0.9 vs. 3.3 mL/min/1.73 m^2), with canagliflozin 300 mg/day (but not 100 mg/day) also significantly ($p < 0.01$ vs. glimepiride) reducing the urinary albumin: creatinine ratio, independent of HbA_{1C} changes [49].

4.4 High CVD Risk Patients

Efficacy data for canagliflozin in patients with inadequately-controlled T2D and an elevated risk of cardiovascular disease (CVD) are available from prespecified [50, 51] and post hoc [52] subgroup analyses of CANVAS, a trial designed primarily to assess the impact of canagliflozin on CVD risk [53]. In these patients, adding canagliflozin 100 or 300 mg/day to insulin (with or without other AHAs) significantly improved HbA_{1C} and FPG measures over 18 weeks relative to adding placebo, and these benefits were sustained to week 52 (Table 3) [50]. Similarly, adding canagliflozin 100 or 300 mg/day to ongoing sulfonylurea monotherapy [51] or a dipeptidyl peptidase 4 (DPP4) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist (RA), with or without other AHAs [52], improved glycaemic measures over 18 weeks versus adding placebo, although some subgroups were small (Table 3). Over 18–52 weeks, canagliflozin, compared with placebo, reduced bodyweight by up to 3.5 kg across subgroups (Table 3) [50–52] and, in the largest substudy (i.e. patients on background insulin) [50], reduced SBP and DBP and had minimal impact on the LDL-C:HDL-C ratio.

These findings are generally supported by an integrated analysis of CANVAS and a similarly designed phase 4 trial of canagliflozin (CANVAS-R) in T2D patients at high CV risk (i.e. the CANVAS Program, $n = 10{,}142$; mean follow-up 188.2 weeks) [54], as well as by a post hoc pooled analysis of four 26-week placebo-controlled phase 3 trials ($n = 2313$) in which canagliflozin (100 or 300 mg/day) regimens improved glycaemic control, bodyweight and SBP relative to placebo regardless of patient CVD history/risk factors [55].

However, the main aim of the CANVAS Program was to assess CV outcomes with canagliflozin (100 or 300 mg/day; pooled) in T2D patients at high CV risk (66% had a history of CVD) [54]. In this analysis, canagliflozin significantly reduced the risk of the primary composite endpoint of CV death, nonfatal myocardial infarction or nonfatal stroke by 14% relative to placebo (Fig. 1), with a consistent effect observed across the majority of subgroups evaluated (most of which were prespecified). The individual components of the primary endpoint did not significantly differ between the two treatment groups, although numerically favoured canagliflozin (Fig. 1). Benefit was observed with canagliflozin versus placebo for some other CV outcomes, including hospitalization for heart failure [hazard ratio (HR) 0.67; 95% CI 0.52–0.87] and the composite of CV death or hospitalization for heart failure (HR 0.78; 95% CI 0.67–0.91). Canagliflozin was also associated with renal benefits versus placebo, reducing the risk of albuminuria progression (HR 0.73; 95% CI 0.67–0.79) and the composite of a 40% eGFR reduction, need for renal-replacement therapy or renal death (HR 0.60; 95% CI 0.47–0.77) [54].

4.5 Older Patients

In older patients ($n = 714$) aged 55–80 years with T2D inadequately controlled by oral/injectable AHA regimens, adding canagliflozin 100 or 300 mg/day significantly ($p < 0.001$) improved glycaemic control over 26 weeks versus adding placebo, as measured by mean changes from baseline in HbA_{1C} (−0.60 and −0.73 vs. −0.03%; overall baseline value 7.7% across groups) and FPG (−1.0 and −

Table 3 Efficacy of oral canagliflozin as add-on therapy to insulin- or incretin mimetic-based therapy or sulfonylurea monotherapy in pre-specified [50, 51] or post hoc [52] subgroup analyses of the phase 3 CANVAS trial

Regimen (mg od) [no. of pts]	Week of eval	HbA_{1C} (%)		FPG (mmol/L)		% of pts with HbA_{1C} <7%	Bodyweight (kg)	
		Change from BL [BL]	Diff vs. PL	Change from BL	Diff vs. PL		Change from BL	Diff vs. PL
Add-on to INS therapy [50]								
CAN 100 + INS ± OAA [661]	18	−0.63[a] [8.3]	−0.62**	NR [9.2]	−1.2**	19.8**	NR [94.4]	−1.9**[b]
CAN 300 + INS ± OAA [660]		−0.75[a] [8.3]	−0.73**	NR [9.2]	−1.6**	25.8**	NR [94.8]	−2.4**[b]
PL + INS ± OAA [636]		−0.01[a] [8.3]		NR [9.2]		8.3	NR [94.8]	
CAN 100 + INS ± OAA [664]	52	−0.55 [8.3]	−0.58[c]	NR [9.2]	−1.1[c]	23.2	NR [94.4]	−2.8[b,c]
CAN 300 + INS ± OAA [664]		−0.69 [8.3]	−0.73[c]	NR [9.2]	−1.5[c]	28.6	NR [94.8]	−3.5[b,c]
PL + INS ± OAA [639]		+0.03 [8.3]		NR [9.2]		9.9	NR [94.8]	
Add-on to SU [51]								
CAN 100 + SU [42]	18	−0.70 [8.3]	−0.74**	−1.4 [10.3]	−2.1[d]	25	−1.2 [85.1]	−0.2
CAN 300 + SU [40]		−0.79 [8.3]	−0.83**	−2.0 [9.8]	−2.7**	33	−2.4 [80.4]	−1.4*
PL + SU [45]		+0.04 [8.5]		+0.7 [10.3]		5	−1.0 [85.5]	
Add-on to incretin-mimetic therapy [52]								
CAN 100 + DPP4i ± OAA [103]	18	−0.46 [8.1]	−0.56[c]	NR	−1.1[c]	22	−2.7 [91.5]	−2.0[c]
CAN 300 + DPP4i ± OAA [111]		−0.64 [8.0]	−0.75[c]	NR	−1.5[c]	34[c]	−3.5 [92.4]	−2.7[c]
PL + DPP4i ± OAA [102]		+0.1 [8.1]		NR		15	−0.8 [88.6]	
CAN 100 + GLP-1ra ± OAA [35]	18	−0.83 [8.2]	−1.00[c]	NR	−1.8[c]	29[c]	−3.3 [109.2]	−2.7[c]
CAN 300 + GLP-1ra ± OAA [30]		−0.89 [8.3]	−1.06[c]	NR	−2.5[c]	35[c]	−3.9 [111.2]	−3.3[c]
PL + GLP-1ra ± OAA [30]		+0.17 [7.9]		NR		7	−0.6 [105.6]	

Changes from BL are least squares means, BL values are means. INS dosage was ≥20 IU/day; SU, DPP4i and GLP-1ra dosages were stable

BL baseline, *CAN* canagliflozin, *diff* difference, *DPP4i* dipeptidyl peptidase 4 inhibitor, *eval* evaluation, *FPG* fasting plasma glucose, GLP-1ra glucagon-like peptide-1 receptor agonist, *HbA_{1C}* glycosylated haemoglobin, *INS* insulin, *NR* not reported, *OAA* other antihyperglycaemic agent, *od* once daily, *PL* placebo, *pts* patients, *SU* sulfonylurea

* $p < 0.02$, ** $p < 0.001$ vs. PL

[a] Estimated from a graph

[b] Values are diff vs. PL in percent bodyweight change (corresponding *p*-values are for percentage, not kg, diffs)

[c] 95% CI for between-group difference excluded 0 (p-values not available, as outcome [50] or statistical testing [52] was not prespecified)

[d] Based on hypothesis testing sequence, the diff vs. PL was not considered statistically significant (nominal $p < 0.001$)

1.1 vs. +0.4 mmol/L; overall baseline value 8.7 mmol/L) levels [56]. Significant ($p < 0.001$) bodyweight loss also occurred with canagliflozin versus placebo during this period (mean changes from baseline −2.2 and −2.8 vs. −0.1 kg; overall baseline value 90 kg) [56]. Longer term, canagliflozin 100 or 300 mg/day largely maintained improvements versus placebo in HbA_{1C} levels (mean changes from baseline: −0.32 and −0.43 vs. +0.17%), as well as FPG levels and bodyweight, over 104 weeks in a 78-week extension ($n = 624$) [57].

Notably, canagliflozin (as monotherapy or add-on therapy) improved glycaemic control versus placebo regardless of whether patients were aged ≥65 or <65 years ($n = 445$ and 1868 [58]; $n = 1147$ and 2906 [59]) or ≥75 or <75 years ($n = 183$ and 3975) [60] in pooled analyses of four [58] or six [59, 60] phase 3 trials of 18–26 weeks' duration (some analyses [59, 60] also included the two prespecified CANVAS substudies). However, glycaemic improvements were slightly more pronounced in the younger age groups, possibly because they had better renal function [58–60] and/or slightly higher baseline HbA_{1C} [58].

4.6 Other Patients

In Asian patients with T2D, canagliflozin 100 or 300 mg/day, as first-line monotherapy [31, 61] or added to oral AHA [31, 62] or insulin [38, 63] regimens, significantly ($p < 0.05$) improved HbA_{1C} and bodyweight versus corresponding placebo regimens in phase 3 (or phase 4 [63]) trials of 16–24 weeks' duration (total $n = 146$–676), with improvements in these parameters sustained over 52 weeks in an extension [38] and a noncomparative trial (total $n = 1299$; primary endpoint not specified) [31].

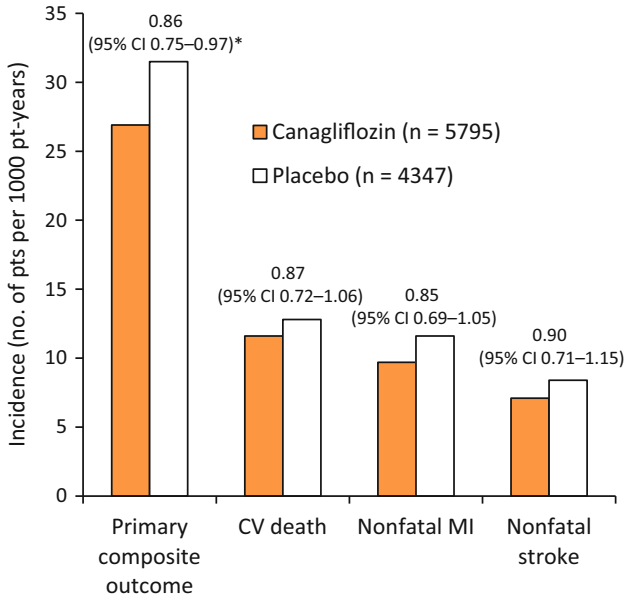

Fig. 1 Primary composite cardiovascular outcome and its individual components in adults with T2D at high cardiovascular risk in the integrated CANVAS Program (canagliflozin 100 or 300 mg/day; pooled data) [54]. *$p = 0.02$ for superiority (subsequent to demonstrating noninferiority; primary hypothesis). *CV* cardiovascular, *HR* hazard ratio, *MI* myocardial infarction, *pt(s)* patient(s)

Indeed, in post hoc analyses, race, ethnicity and geographical region did not impact the glycaemic or bodyweight benefits of canagliflozin regimens in placebo-controlled trials (pooled; $n = 124$–3108 per group) [64–68] or in one ($n = 1450$) [65] or three ($n = 551$; pooled) [68] active comparator-controlled studies.

Reductions in HbA_{1C} and bodyweight (of $\approx$0.5 and $\approx$2%, respectively) were also seen with canagliflozin (100 or 300 mg/day) versus placebo in T2D patients with renal impairment (eGFR 45 to <60 mL/min/1.73 m^2) in a pooled analysis ($n = 721$) of phase 3 trials; most (94%) patients were receiving an AHA regimen at baseline [69]. Moreover, in a post hoc pooled analysis of six 18- to 26-week, placebo-controlled, phase 3 studies ($n = 4053$) [59], canagliflozin (100 or 300 mg/day), as monotherapy or add-on therapy, lowered HbA_{1C} levels in T2D patients regardless of their renal function, although efficacy declined with increasing renal impairment.

In patients with T2D who met metabolic syndrome criteria in two phase 3 trials ($n = 1169$ or 586; post hoc analysis), adding canagliflozin 100 or 300 mg/day to ongoing metformin-based therapy generally improved glycaemic (HbA_{1C}, FPG) as well as non-glycaemic (e.g. bodyweight, BMI, waist circumference, BP, HDL-C and, in some instances, triglycerides) metabolic parameters over 52 weeks relative to adding glimepiride or sitagliptin, although LDL-C levels generally increased [70].

4.7 Additional Analyses

Canagliflozin (100 or 300 mg/day), as monotherapy or add-on therapy, was effective in lowering HbA_{1C} levels in T2D patients, regardless of baseline patient/disease characteristics such as BMI [59], HbA_{1C} level [71] or T2D duration [71] in post hoc pooled analyses of placebo-controlled phase 3 trials of 18–26 weeks' duration ($n = 2313$ [71]; $n = 4053$ [59]). Moreover, post hoc analyses of composite endpoints have confirmed the concomitant benefit of canagliflozin on glycaemic and other metabolic parameters (e.g. bodyweight, BP and lipids) in T2D patients [33, 72–75]. Combined reductions in bodyweight and HbA_{1C} with canagliflozin may lead to improvements in liver enzyme levels in T2D patients, according to additional pooled phase 3 study data [76].

4.8 Real-World Studies

The efficacy of canagliflozin in the real-world setting has been shown in various analyses of US healthcare claims databases and/or healthcare datasets. Among the largest of those fully published ($n = 1044$–2261 evaluable), canagliflozin regimens reduced ($p < 0.001$, where specified [77]) HbA_{1C} levels from baseline by a mean of 0.7–0.97% over 3, 6 [78] or 12 [79] months or a mean of 185 days [77]. Limited data available from other large analyses ($n = 1227$–$16{,}163$) [34–37] were generally consistent with these findings, and HbA_{1C} reductions were greater ($p < 0.05$) with canagliflozin regimens than with DPP4 inhibitor regimens over $\approx$183 days' mean follow-up [36] and GLP-1 RA regimens after 30 months' treatment (although were not significantly different over initial 12 months) [37]. In another of these analyses (designed primarily to assess bodyweight), canagliflozin regimens were associated with mean reductions ($p < 0.0001$) from baseline in bodyweight, ranging from −1.8 kg at 3 months to −2.6 kg at 12 months in the overall population [35].

5 Tolerability

Oral canagliflozin, as monotherapy or add-on therapy, was generally well tolerated for up to 104 weeks in patients with T2D, including those of older age and/or at high CV risk, in the key phase 3 or 4 trials discussed in Sect. 4. In the pooled analysis of four placebo-controlled phase 3 trials ($n = 2313$) [80], treatment-related adverse events (AEs) occurred in up to 1.7-fold more canagliflozin 100 or 300 mg/day than placebo recipients over 26 weeks (20.5 and 22.9 vs. 13.2%) and, consistent with canagliflozin's mechanism of action (Sect. 2), the most common AEs

associated with the drug were female genital mycotic infection (GMI; 10.4 and 11.4 vs. 3.2%), urinary tract infection (UTI; 5.9 and 4.3 vs. 4.0%), increased urination (5.3 and 4.6 vs. 0.8%) and male GMI (4.2 and 3.7 vs. 0.6%). AEs were generally mild or moderate and few patients experienced serious AEs (≈3% in each group) or death (<0.3% in each group) [80]. The tolerability profiles of the two canagliflozin dosages were generally similar over 12–104 weeks in a meta-analysis of ten randomized trials ($n = 5394$) [81].

In active comparator-controlled studies, canagliflozin regimens were generally similar to sitagliptin or glimepiride regimens in terms of the incidence of treatment-related AEs (20–34 vs. 20–28%) and discontinuations because of AEs (3–7 vs. 3–6%) over 52 weeks [17, 41, 42], with 104-week data from the glimepiride-controlled trial being consistent with these findings [43]. The tolerability profile of canagliflozin was further supported by a post hoc pooled analysis (of seven placebo- or active comparator-controlled T2D trials) that compared the tolerability of canagliflozin therapy with that of non-canagliflozin therapy (i.e. placebo, sitagliptin or glimepiride; pooled) over 52–104 weeks ($n = 5598$) [82].

5.1 Genitourinary Infections

Canagliflozin increases UGE (Sect. 2), which may contribute to GMIs [9]. Canagliflozin 300 mg/day significantly ($p < 0.00001$; 3.76-fold) increased the risk of GMIs versus placebo over 12–26 weeks in a meta-analysis of eight placebo-controlled trials ($n = 1338$) [83]. The most common GMIs with canagliflozin (100 or 300 mg/day) over 26 weeks included vulvovaginal mycotic infection in women (5.9 and 5.3 vs. 1.3% with placebo) and balantitis in men (2.2 and 1.7 vs. 0%) in the pooled analysis of four placebo-controlled studies [80]. GMIs in this analysis were never serious, rarely (<1% of patients) led to therapy discontinuation and responded to standard antifungal treatment [80], lasting a median of 7 and 18 days in treated female and male canagliflozin recipients [84].

The likelihood of GMIs with canagliflozin 300 mg/day was significantly greater ($p < 0.00001$; 4.95-fold) than with sitagliptin or glimepiride over 12–52 weeks in a meta-analysis of four active comparator-controlled trials ($n = 2510$) [83]. Similarly, in individual studies, the GMI incidence was numerically greater with canagliflozin (100 or 300 mg/day) than with sitagliptin or glimepiride regimens over 52 weeks, both in men (2–9 vs. 0.5–1%) and women (10–15 vs. 2–4%) [17, 41, 42], although did not further increase versus glimepiride over 104 weeks [43].

Despite being a common AE with canagliflozin, UTIs did not significantly differ in incidence between canagliflozin 300 mg/day and placebo over 12–26 weeks in the meta-analysis of eight trials [83]. UTIs with canagliflozin (100 or 300 mg/day), although often symptomatic, were rarely serious (≤0.2% of patients) [85] and responded to standard therapy without canagliflozin discontinuation [9] when four placebo-controlled studies were pooled. Compared with other active agents, the UTI incidence with canagliflozin did not significantly differ from that with sitagliptin or glimepiride in the meta-analysis of four 12- to 52-week trials [83], with data from individual sitagliptin- or glimepiride-controlled studies of ≤ 104 weeks' duration generally supporting these findings [17, 41–43].

5.2 Osmotic Diuresis and Volume Depletion

By increasing UGE, canagliflozin can trigger osmotic diuresis. Treatment-related AEs related to osmotic diuresis (e.g. increased urine volume/frequency) occurred in 6.1-fold more canagliflozin (100 or 300 mg/day) than placebo recipients (4.9 and 4.9 vs. 0.8%) in the pooled analysis of four 26-week trials [47]; these AEs typically occurred during the first 6 weeks of therapy and none were serious [80]. Consistent with these findings, over 12–52 weeks, canagliflozin significantly ($p < 0.01$) increased the risk of osmotic diuresis-related AEs compared with placebo and active comparators (sitagliptin or glimepiride) in meta-analyses ($n = 3853$ and 5057) [83].

AEs related to volume depletion (e.g. postural dizziness, orthostatic hypotension) were rare (≈1% incidence) with canagliflozin in the pooled analysis of four placebo-controlled trials [47] and occurred predominantly in patients on antihypertensives [80]. Moreover, these AEs did not significantly differ in incidence between canagliflozin and placebo or active comparators (sitagliptin or glimepiride) in meta-analyses ($n = 3334$ and 4910) [83]. When risk factors for volume depletion-related AEs were assessed in a pooled analysis of eight phase 3 trials ($n = 9439$), the incidence was generally numerically greater with canagliflozin 100 or 300 mg/day than with comparators in patients who were receiving loop diuretics (3.2 and 8.8 vs. 4.7%), had a baseline eGFR of 30 to <60 mL/min/1.73 m^2 (4.8 and 8.1 vs. 2.6%) or were aged ≥75 years (4.9 and 8.7 vs. 2.6%) [9]. Similarly, in the individual CANVAS trial (in which patients generally had more T2D complications), the incidence of volume depletion-related AEs was 2.8 and 4.6% with canagliflozin 100 or 300 mg/day versus 1.9% with placebo [9]. However, canagliflozin did not increase the incidence of volume depletion-related AEs that were serious or that led to discontinuation in these studies [9].

Volume depletion with canagliflozin may reduce eGFR, although the reductions are usually small, occur in the first few weeks of therapy [9, 80] and stabilize/attenuate thereafter [80, 86]. However, large (>30%), albeit

transient, eGFR reductions have occurred with canagliflozin in patients more susceptible to volume depletion (such as the high-risk patients discussed in the preceding paragraph), although did not usually require treatment interruption [9]. Renal-related AEs (e.g. reduced GFR, increased blood creatinine) occurred with an incidence of <3% and were rarely serious (≤0.2% of patients) with canagliflozin or comparators over 26 [80] or up to 104 [87] weeks' therapy in pooled analyses of placebo- and/or active comparator-controlled trials [80, 87]. Nevertheless, a possible signal for acute renal injury was detected with canagliflozin, as well as other SGLT2 inhibitors, when postmarketing data from the US FDA AE Reporting System were assessed [87].

5.3 Hypoglycaemia

Hypoglycaemia was relatively uncommon when canagliflozin (100 or 300 mg/day) was used as monotherapy [15, 39] or added to metformin (alone [41] or in combination with sitagliptin [44] or pioglitazone [18]) over 26 weeks (3–4 vs. 2–3% with placebo) or 52 weeks (4–7%) in clinical trials [15, 41, 44] and their extensions [18, 39]. In patients receiving metformin, the incidence of hypoglycaemia with add-on canagliflozin 100 or 300 mg/day was not markedly different from that with add-on sitagliptin (7 and 7 vs. 4%) [41] but was significantly ($p < 0.0001$) lower than with add-on glimepiride (6 and 5 vs. 34%) [42] over 52 weeks, with the benefit over glimepiride maintained at week 104 [43]. Severe hypoglycaemia was rare (<1%) with canagliflozin in these trials, where specified [15, 18, 41–44].

By contrast, hypoglycaemia tended to be relatively common when canagliflozin was added to an AHA regimen that included a sulfonylurea [16, 17, 51] or insulin [50] in phase 3 trials. For instance, in patients receiving metformin plus a sulfonylurea, the incidence of hypoglycaemia over 52 weeks was approximately twofold greater with add-on canagliflozin 100 or 300 mg/day than with add-on placebo (34 and 37 vs. 18%) [16], but did not markedly differ between add-on canagliflozin 300 mg/day and sitagliptin (43 vs. 41%) [17]; severe hypoglycaemia was not common (≤4% incidence) in any treatment group of either trial. Added to insulin therapy, canagliflozin 100 or 300 mg/day did not significantly differ from placebo in terms of hypoglycaemia (59 and 57 vs. 48%) or severe hypoglycaemia (5 and 6 vs. 4%) incidence over 52 weeks in the prespecified CANVAS insulin substudy [50].

5.4 Other Events

Lower limb amputations (mainly of the toes) appeared to increase in incidence with canagliflozin in T2D patients with, or at high risk of, CVD in long-term trials [9]. For instance, in an interim safety analysis of CANVAS (mean follow-up 4.5 years), the incidence of lower limb amputation was 7 and 5 per 1000 patient-years (PY) with canagliflozin 100 or 300 mg/day versus 3 per 1000 PY with placebo [88]. The integrated CANVAS Program reported similar findings, with significantly more canagliflozin than placebo recipients having toe, foot or leg amputations over a mean 188.2 weeks of follow-up (6.3 vs. 3.4 per 1000 PY; $p < 0.001$); the toe or metatarsal was the highest level of amputation for most patients (71%) [54]. The mechanism underlying this risk has not yet been determined; patients at higher risk of amputation should be monitored and counselled appropriately, and canagliflozin may need to be discontinued if events such as skin ulcer, infection, osteomyelitis or gangrene develop in the lower extremities [9].

Bone fractures may also occur with canagliflozin [54, 89]. Over 188.2 weeks' mean follow-up in the integrated CANVAS Program ($n = 10{,}142$), recipients of canagliflozin (100 or 300 mg/day, pooled) had a significantly greater incidence of all fractures than placebo recipients (15.4 vs. 11.9 per 1000 PY; $p = 0.02$) and the incidence of low-trauma fractures in the respective groups was 11.6 versus 9.2 per 1000 PY (HR 1.23; 95% CI, 0.99–1.52) [54]. Notably, significant heterogeneity for these outcomes was evident between the two trials in the Program [54]. In an interim analysis of the individual CANVAS study ($n = 4327$), the incidence of all fractures over 104 weeks was significantly greater with canagliflozin than with placebo (4.0 vs. 2.6%; HR 1.51; 95% CI 1.04–2.19) [89]. However, pooled data from non-CANVAS studies found no significant fracture risk with these canagliflozin dosages over 52 ($n = 5867$) or 104 ($n = 2164$) weeks versus placebo/active agents (pooled) [89]. The reason for the increased fracture risk with canagliflozin in CANVAS but not non-CANVAS studies is unknown, although differences in factors such as patient age (mean 62 vs. 58 years), loop diuretic use (12 vs. 4% of patients) and eGFR (mean 77 vs. 85 mL/min) have been suggested [89]. When data from CANVAS and non-CANVAS studies were pooled, no significant risk of fracture was evident with canagliflozin versus the comparators [89], with this finding supported by a recent meta-analysis of eight canagliflozin studies, including CANVAS (relative risk of fracture vs. placebo was 0.66; 95% CI 0.37–1.19) [90].

SGLT2 inhibitors, including canagliflozin, require caution in patients at particular risk of diabetic ketoacidosis (DKA), including those with low β-cell function [9]. DKA rarely occurs with canagliflozin, although can be life-threatening or fatal [9]. In an analysis of clinical trial data ($n = 17{,}596$), the incidence of serious DKA and related AEs in patients with T2D was 0.07 and 0.11% with

canagliflozin 100 or 300 mg/day versus 0.03% with comparators [91]. However, no significant difference in DKA incidence was evident between canagliflozin and placebo in the integrated CANVAS Program (0.6 vs. 0.3 per 1000 PY) [54]. The latter analysis also found no significant difference between canagliflozin and placebo in the incidence of bladder, breast or renal cell cancer (0.6–3.1 vs. 0.2–2.6 per 1000 PY) [54].

6 Dosage and Administration

In the EU, canagliflozin is approved for use as monotherapy (as an adjunct to diet and exercise, when metformin is considered inappropriate) and as an add-on therapy (to other AHAs, including insulin) to improve glycaemic control in adults with T2D [9]. Canagliflozin tablets should be taken orally, preferably prior to the first food of the day. The initial dosage is 100 mg once daily; if tolerated (and eGFR is $\geq$60 mL/min/1.73 m^2), this can be increased to 300 mg once daily, if necessary. Care is advised if increasing the dosage in patients for whom the initial diuresis associated with the drug may pose a risk (e.g. those aged $\geq$75 years or with known CVD) [9]. Canagliflozin is not recommended for patients with type 1 diabetes. Local prescribing information should be consulted for further details, including drug interactions, use in special patient populations, contraindications and other warnings and precautions.

7 Place of Canagliflozin in T2D Management

Managing T2D requires an individualized stepwise approach [1, 2], taking into consideration common patient comorbidities (e.g. heart failure, coronary artery disease) and the likelihood that AHA-associated hypoglycaemia (thought to contribute to CV dysfunction and, in high-risk patients, CV events) may have untoward outcomes [2]. Among the numerous AHAs now available, metformin monotherapy remains the standard first-line option for most patients [1, 2], although sequential addition of drugs from other classes is often required to attain/maintain good glycaemic control.

Although most AHAs lower blood glucose levels by increasing insulin secretion and/or sensitivity, SGLT2 inhibitors (e.g. canagliflozin, dapagliflozin and empagliflozin [92]) act independently of insulin (and may even positively influence β-cell function indirectly [20]), enabling them to complement a wide variety of AHAs as part of combination regimens [93]. In treatment guidelines, SGLT2 inhibitors (as well as sulfonylureas, thiazolidinediones, DPP4 inhibitors, GLP-1 RAs and insulin) are generally recommended as second- and/or subsequent-line options for use in combination regimens, although can be used first line if metformin is contraindicated/not tolerated [1, 2] (provided a sulfonylurea or pioglitazone is inappropriate and a DPP4 inhibitor would otherwise be used [1]).

Canagliflozin is one of the most widely available SGLT2 inhibitors [92]. Its approval as a first-line monotherapy or as an add-on to other AHAs, including insulin, in adults with T2D (Sect. 6) was based on numerous well-designed clinical trials in these settings, in which the drug (at 100 or 300 mg/day) provided improved and sustainable glycaemic control over up to 104 weeks' therapy (Sect. 4). The glycaemic efficacy of canagliflozin 100 mg/day was noninferior to that of metformin as first-line monotherapy and to that of sitagliptin or glimepiride as an add-on therapy, whereas canagliflozin 300 mg/day was more effective than sitagliptin or glimepiride in the add-on setting (Sect. 4.1). Real-world data are also now available and support the use of canagliflozin in T2D management (Sect. 4.8).

In addition to hyperglycaemia, the common comorbidities of T2D, such as obesity, hypertension and dyslipidaemia, should also be addressed to minimize the overall CV risk of T2D [94]. Canagliflozin (like other SGLT2 inhibitors) induces moderate bodyweight loss (Sect. 4.2) through urinary loss of glucose (and thus calories) (Sect. 2) [2, 93]. The ability to reduce bodyweight is shared by few other AHAs (including GLP-1 RAs), with most increasing bodyweight (e.g. sulfonylureas, meglitinides, thiazolidinediones and insulin) or being bodyweight neutral (e.g. DPP4 inhibitors, metformin, α-glucosidase inhibitors) [2, 95]; as such, canagliflozin has a bodyweight profile more favourable than that of glimepiride or sitagliptin as an add-on therapy (Sect. 4.2). Bodyweight losses occur with canagliflozin even in combination with AHAs typically associated with bodyweight gain, and appear primarily due to reductions in fat (Sect. 4.2), which could (through improved insulin sensitivity) contribute to the glycaemic benefits of the drug.

Canagliflozin also appears to modulate various other CVD risk factors, consistent with the SGLT2 inhibitor class [2]. For instance, the drug generally improved serum uric acid levels (Sect. 2), BP (Sect. 4.3) and markers of arterial stiffness (Sect. 4.3), with the latter (along with natriuresis, osmotic diuresis and/or weight loss) likely mediating the drug's BP lowering effects [96, 97]. It also modestly impacted serum lipid levels (generally increasing HDL-C and LDL-C and reducing triglycerides; Sect. 4.3). Studies specifically designed to evaluate the effect of canagliflozin on parameters such as BP and bodyweight would be beneficial.

Consistent with its favourable impact on CV risk factors, canagliflozin reduced the risk of major adverse cardiac

events (MACE) in T2D patients at high CV risk in an integrated analysis of two large CV outcome trials (CANVAS and CANVAS-R); the analysis included patients with and without prior CVD (Sect. 4.4), indicating possible primary and secondary MACE prevention. To date, few other AHAs have demonstrated CV risk reduction in clinical trials, namely empagliflozin and some GLP-1 RAs (e.g. liraglutide) [98, 99]. However, real-world CV benefit was recently demonstrated with the SGLT2 inhibitor class in a pooled analysis of clinical practice data from six countries [100]. In this study (CVD-REAL; $n > 300{,}000$ patients), SGLT2 inhibitors (of which canagliflozin and dapagliflozin accounted for the majority of exposure) were associated with a 39% lower risk of hospitalization for heart failure and a 51% lower risk of all-cause death versus other AHAs in T2D patients, the majority of whom did not have established CVD. Thus, the CV benefit of SGLT2 inhibitors may apply not only to T2D patients at high CV risk (the focus of randomized trials) but also to those at lower risk.

Another real-world CV assessment (of matched patient cohorts; $n = 34{,}708$–$41{,}708$) [101] found no significant difference between canagliflozin and non-gliflozin AHAs (DPP4 inhibitors, GLP-1 RAs or sulfonylureas) in the risk of most CV outcomes over 7 months' mean follow-up, although the risk of hospitalization for heart failure was significantly lower (by 30–49%) with canagliflozin. Of note, the efficacy of canagliflozin for patients with CV risk has not been endorsed by a Health Authority.

Canagliflozin is generally well tolerated and, consistent with its mechanism of action, the most common AEs are genitourinary infections and increased urination (Sect. 5). As with other SGLT2 inhibitors and most other AHAs [2], hypoglycaemia is uncommon with canagliflozin, unless used in combination with drugs that increase the risk of the event (Sect. 5.3), among which are sulfonylureas, insulins and meglitinides [2].

Reductions in eGFR initially occur with canagliflozin due to volume depletion and may explain the signal of acute kidney injury identified with the drug (and other SGLT2 inhibitors) postmarketing (Sect. 5.2). However, current data, including renal outcome results from the CANVAS Program, indicate that long-term canagliflozin therapy may help preserve kidney function (Sects. 4.3 and 4.4), an effect also seen with empagliflozin, possibly due to the impact of SGLT2 inhibition on intrarenal haemodynamics [87]. Indeed, SGLT2 inhibition increases delivery of sodium to the macula densa, leading to increased constriction of afferent arterioles and reduced intraglomerular pressure, which may slow renal function decline [96]. The effects of canagliflozin on renal and CV outcomes in T2D patients with diabetic nephropathy are currently being evaluated (CREDENCE; NCT02065791), as are its effects in T2D patients with congestive heart failure (CANDLE; UMIN000017669).

Other AEs related to volume depletion (such as dizziness and orthostatic hypotension) are generally uncommon with canagliflozin, but may limit its use in patients particularly susceptible to volume depletion, such as the elderly or those on antihypertensives or with CVD (Sect. 5.2). Thus, canagliflozin should not be used in patients taking loop diuretics or who are already volume depleted (any volume depletion should be corrected before initiating canagliflozin), and increasing the canagliflozin dosage requires care in at-risk patients [9]. Further longer-term studies evaluating the benefits versus potential risks of canagliflozin and other SGLT2 inhibitors would be beneficial, including the potential for bone fractures and lower-limb amputations (Sect. 5.4). Notably, a recent analysis of amputations in the FDA AE Reporting System suggested an increased amputation risk with canagliflozin, but not with empagliflozin or dapagliflozin [102]. However, the limitations of such an analysis (e.g. potentially incomplete records; reporting possibly being stimulated by FDA warnings; causal link between AE and drug exposure not definitive) should be taken into consideration when interpreting these findings. Whether these amputations could be associated with decreases in blood volume (as seen with thiazide diuretics [103]) warrants investigation.

Also of interest are robust trials directly comparing canagliflozin with AHAs such as other SGLT2 inhibitors or GLP-1 RAs. Currently, such comparisons are limited to network meta-analyses, across which canagliflozin was at least as effective in improving glycaemic control over 26 (or 26–104 [104]) weeks as empagliflozin [104–106], dapagliflozin [104–106], sitagliptin, pioglitazone or a sulfonylurea [106], when used as monotherapy [106] or as part of a dual [104] or triple [105] AHA regimen. Similar comparisons (including those vs. GLP-1 RAs) had more mixed findings, depending on the canagliflozin/comparator dosage and the timepoint and/or treatment setting assessed [107, 108]. Due to their indirect nature, such analyses (which are available as abstracts) should be interpreted with caution.

Like most AHAs, canagliflozin and other SGLT2 inhibitors have the convenience of oral administration (unlike GLP-1 RAs and insulins, which are injectable), although the cost of SGLT2 inhibitors and other relatively recent AHAs (e.g. DPP4 inhibitors, GLP-1 RAs) is higher than that of older AHAs, such as metformin and sulfonylureas [2]. Various canagliflozin cost-utility analyses conducted from the NHS perspective of the UK [109, 110] or Spain [111, 112] are available (as abstracts). They suggest that, in the monotherapy setting, canagliflozin 100 and 300 mg may dominate (i.e. be less costly with greater quality-

adjusted life-year gains) empagliflozin 10 mg and dapagliflozin 10 mg and dominate (300 mg) or be cost-effective (100 mg) versus empagliflozin 25 mg [110]. As an add-on to metformin, canagliflozin may also dominate (100 mg) or be cost effective (300 mg) versus sitagliptin 100 mg [112] and both canagliflozin dosages may dominate dapagliflozin 10 mg [111] and be cost effective versus a sulfonylurea [109]. Moreover, sitagliptin 100 mg may be dominated by canagliflozin (100 or 300 mg) as an add-on to metformin plus a sulfonylurea [112].

Additional cost analyses conducted in the UK (abstract data) [113] and from an Italian NHS perspective [114] generally support these findings, with canagliflozin estimated to be cost saving versus other SGLT2 inhibitors [113], as well as sitagliptin and glimepiride [114], as add-on therapy. Further cost-utility analyses would be beneficial.

In conclusion, once-daily oral canagliflozin, used as monotherapy or add-on therapy, is an important option for the management of T2D in adults. It improves glycaemic control, as well as bodyweight and BP, and is one of only a few AHAs found to reduce overall CV risk. Canagliflozin is generally well tolerated, although the amputations and fractures associated with the drug require further investigation.

Data selection sources: Database(s): EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data [searches last updated 4 August 2017]. Records were limited to those in English language.
Search terms: Canagliflozin, Canaglu, Invokana, JNJ-28431754, TA-7284, type 2, type II, T2DM, T2D.

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Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/2D48F06076B1EACC.

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