DRUG EVALUATION

Diabetes Management

Canagliflozin for the treatment of adults with Type 2 diabetes

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Practice points

- Type 2 diabetes mellitus (T2DM) is a chronic and progressive metabolic disease, with growing prevalence worldwide.
- SGLT2 inhibitors are a new class of oral antihyperglycemic agents with an insulin-independent mechanism of lowering the renal threshold for glucose and increasing urinary glucose excretion, thereby lowering plasma glucose.
- Canagliflozin is an SGLT2 inhibitor approved in the USA, EU and other countries as adjunct to diet and exercise for the treatment of adults with hyperglycemia.
- Canagliflozin has been evaluated in ~10,000 patients with T2DM in placebo- and active-controlled Phase III studies of up to 104 weeks, including special populations (e.g., older patients, patients with moderate renal impairment and patients with elevated cardiovascular risk).
- In placebo-controlled, Phase III studies, canagliflozin improved glycemic control and lowered bodyweight and blood pressure in a broad range of patients with T2DM on a variety of background antihyperglycemic agents, including older patients, patients with moderate renal impairment and patients with elevated cardiovascular risk.
- In active-controlled, Phase III studies, canagliflozin 300 mg demonstrated superiority to glimepiride and sitagliptin 100 mg in HbA1c lowering as add-on to metformin at 52 weeks; canagliflozin 300 mg also demonstrated superiority to sitagliptin 100 mg in HbA1c lowering as add-on to metformin and sulfonylurea over 52 weeks.
- Canagliflozin was generally well tolerated, with increased incidences of adverse effects related to the mechanism of action (e.g., genital mycotic infections, urinary tract infections, osmotic diuresis-related adverse events, volume depletion-related adverse events); the incidence of hypoglycemia was low with canagliflozin in patients not on background sulfonylurea or insulin.
- Canagliflozin is being investigated for other possible therapeutic uses, such as treatment for diabetic nephropathy, obesity and Type 1 diabetes mellitus.

SUMMARY Canagliflozin is an SGLT2 inhibitor approved for the treatment of adults with Type 2 diabetes mellitus (T2DM). A comprehensive Phase III program evaluated canagliflozin in a broad range of patients with T2DM on various background therapies; studies were also conducted in special populations, including older patients and those with moderate renal impairment. Canagliflozin provided clinically meaningful reductions in HbA1c, bodyweight and blood pressure versus placebo and active comparators in studies up to 104 weeks. Canagliflozin was generally well tolerated, with increased incidences of adverse events related to the mechanism of action, including genital mycotic infections and osmotic diuresis-related adverse events. Overall, canagliflozin appears to be a useful treatment option for patients with inadequately controlled T2DM.

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KEYWORDS
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• mechanism of action
• safety • SGLT2 inhibitor • Type 2 diabetes

Introduction

• Unmet therapeutic needs in Type 2 diabetes

Diabetes is a global health concern, affecting more than 382 million individuals worldwide in 2013 [1]. The worldwide prevalence of diabetes is expected to increase by ~55% by 2035 [1]. Recent estimates suggest that ~40% of individuals in the USA will develop diabetes in their lifetime, with Hispanic men and women and non-Hispanic black women at the greatest risk (>50%) [2]. Approximately 90% of individuals with diabetes have Type 2 diabetes mellitus (T2DM), which is characterized by hyperglycemia, insulin resistance and decreased β-cell function [1]. Comorbidities, including obesity and hypertension, together with other risk factors (e.g., age, family history, lifestyle, sleep apnea, smoking, mental illness), may contribute to the anticipated increase in T2DM prevalence [1,3].

As reducing hyperglycemia can lower the risk of microvascular and macrovascular complications, one of the key goals of T2DM management is glycemic control [4]. Additionally, lowering bodyweight and blood pressure (BP) can reduce diabetes-related complications [4–8]. Dietary changes and regular physical activity are often implemented as part of the treatment regimen; however, many patients will require therapeutic intervention to control the disease [4,6–8]. A variety of antihyperglycemic agents (AHAs) are available to lower plasma glucose in patients with T2DM [4]. Metformin is often the first-line therapy recommended to patients who have inadequate glycemic control after implementing lifestyle modifications, but poor gastrointestinal tolerability with immediate-release formulations has been associated with more frequent discontinuations in some patients [9]. When patients are no longer able to maintain glycemic control using metformin monotherapy, combination therapy with other AHAs (e.g., sulfonylureas, GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors [DPP-4], insulin) may be required [4]. Many patients, particularly those with significant hyperglycemia, begin fixed-dose combinations with metformin. With advances in T2DM management strategies in recent years, patient health outcomes appear to be improving [10]; however, achieving diabetes-related treatment goals remains a challenge for many patients [11]. In part, this may be related to the negative side effects of some AHAs, including weight gain (sulfonylureas, insulin), hypoglycemia (sulfonylureas, insulin) and poor gastrointestinal tolerability (metformin, GLP-1 receptor agonists) [4]. Perceived ease of use may also affect some patients' willingness to initiate and adhere to treatments such as insulin or GLP-1 receptor agonists [4,12]. Therefore, there remains an unmet therapeutic need in T2DM management for oral AHAs that are effective at reducing hyperglycemia without increasing the risk of hypoglycemia or promoting weight gain.

• Role of the kidneys in T2DM

Under normoglycemic conditions, the kidneys are responsible for filtering ~180 g of glucose per day, of which nearly all is reabsorbed into the circulation by sodium glucose co-transporters (SGLTs) and glucose transporters (GLUTs) [13,14]. SGLT2, a glucose transporter found in the early proximal tubule of the kidney, is responsible for the majority of renal glucose reabsorption; SGLT1, a glucose transporter found in the distal proximal tubule, also contributes to renal glucose reabsorption [15]. SGLT1 is also expressed in the intestinal mucosa where it is involved in intestinal glucose reabsorption [16].

When the filtered glucose load exceeds the tubular maximal glucose resorptive capacity (T_mG), glucosuria occurs [14,15,17,18]. The plasma glucose concentration at which glucosuria occurs is the renal threshold for glucose (RT_G; ~10–11 mmol/l [180–200 mg/dl] in healthy individuals; **Figure 1**). Patients with T2DM have been reported to have enhanced renal glucose reabsorption capacity [19] and enhanced expression of SGLT2 compared with healthy individuals [20]. While the mechanisms underlying changes in SGLT2 expression in T2DM are not well understood, changes in HNF-1α and HNF-3β activity have been reported to contribute to alterations in SGLT2 expression [21]. Consistent with these reports, patients with T2DM in Phase I studies of canagliflozin had mean pretreatment RT_G values that were typically between 12.4 and 13.5 mmol/l (224–245 mg/dl) [22–24]. The increase in RT_G in T2DM compared with healthy individuals leads to enhanced glucose reabsorption into the bloodstream, and thereby contributes to the sustained hyperglycemia in T2DM.

• SGLT2 inhibition for treatment of T2DM

In patients with T2DM, SGLT2 inhibition lowers RT_G, which increases urinary glucose excretion (UGE) and decreases plasma glucose levels. Increased UGE is also associated with a mild

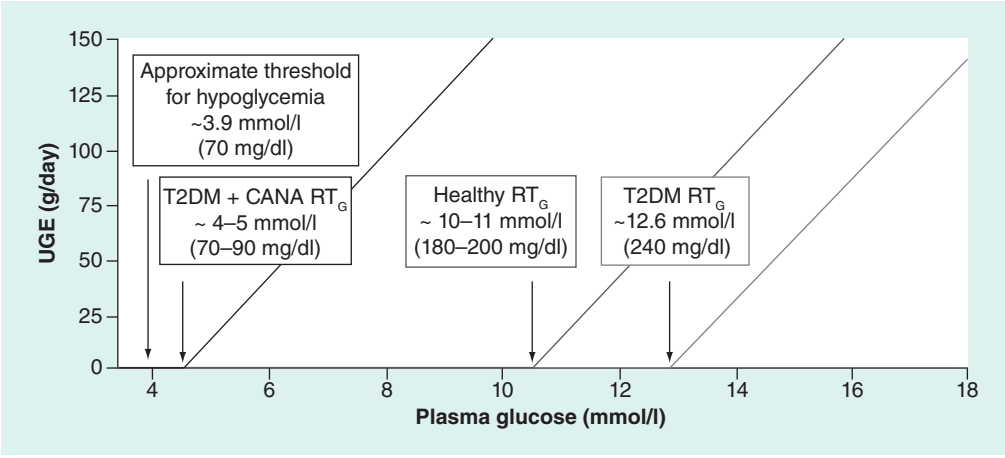

Figure 1. Comparison of RT_G in healthy individuals and in patients with T2DM with and without CANA. Note that the figure depicts idealized threshold relationships between UGE and plasma glucose; the actual relationships include some splay in the regions near RT_G.
CANA: Canagliflozin; RT_G: Renal threshold for glucose; T2DM: Type 2 diabetes mellitus; UGE: Urinary glucose excretion.
Figure adapted from [13,25], with permission from [13] copyright © 2014 Elsevier.

osmotic diuresis and net caloric loss, which can lead to reductions in BP and bodyweight [26]. Because the rate of UGE depends on the glomerular filtration rate (GFR) and plasma glucose concentration [27,28], the effect of SGLT2 inhibition on increasing UGE is expected to be attenuated in patients with impaired renal function (lower estimated GFR [eGFR]). Canagliflozin (INVOKANA®, Janssen Pharmaceuticals, Inc., NJ, USA; Janssen-Cilag International NV, Beerse, Belgium) is an SGLT2 inhibitor developed for the treatment of hyperglycemia in adults with T2DM [29–42]. It is currently approved in the USA, EU and numerous other countries for once-daily administration [43,44]. A fixed-dose combination of canagliflozin and metformin (INVOKAMET®, Janssen Pharmaceuticals, Inc, NJ, USA; VOKANAMET®, Janssen-Cilag International NV, Beerse, Belgium) for twice-daily administration is also approved in the USA and EU [45,46]. In clinical studies, canagliflozin improved glycemic control, reduced bodyweight and BP, and was generally well tolerated in a broad range of patients with T2DM on a variety of background AHAs [29–42].

• Pharmacokinetics & pharmacodynamics of canagliflozin

Canagliflozin 100 and 300 mg administered once daily are rapidly absorbed, with peak plasma canagliflozin concentrations achieved 1–2 h after dosing and half-lives of 10.6 and 13.1 h, respectively; steady state is achieved after 4–5 days [43,44]. The main metabolic elimination pathway is *O*-glucuronidation by UGT1A9 and UGT2B4 to the inactive metabolites M5 and M7; oxidative metabolism is minimal in humans [43]. Canagliflozin is extensively (99%) bound to plasma proteins [47]. In healthy individuals, ~33% of an orally administered dose is excreted in the urine and ~60% is excreted in the feces [47]. The pharmacokinetic profile of canagliflozin is similar in healthy individuals and patients with T2DM, and supports once-daily dosing [22–24,27,48–50]. No clinically meaningful interactions were observed between canagliflozin and glyburide, metformin, simvastatin, probenecid, cyclosporine A, oral contraceptives and warfarin in healthy individuals [51–53]. There was an increase in the area under the curve (AUC) and mean peak drug concentration (C_{max}) of digoxin (20 and 36%, respectively) when co-administered with canagliflozin 300 mg; therefore, patients taking canagliflozin with concomitant digoxin should be monitored appropriately [43]. In addition, canagliflozin concentrations were modestly lower with co-administration of rifampin, which may necessitate additional monitoring of plasma glucose levels [53].

In patients with T2DM, canagliflozin lowers mean RT_G from ~12.6 mmol/l (240 mg/dl) to ~4–5 mmol/l (70–90 mg/dl) over 24 h, resulting in increased UGE (~80–120 g/day; **Figure 1**) [22–24,49],

with an associated caloric loss of 320–480 kcal/day. The increase in UGE leads to reductions in both fasting and postprandial plasma glucose in patients with T2DM [22,24,54,55]. Canagliflozin 300 mg maintains near-maximal suppression of RT_G over 24 h, whereas canagliflozin 100 mg provides near-maximal RT_G suppression for ~13 h, with a modest attenuation of the effect in the overnight period [22,55]. In a Phase I study, canagliflozin was associated with an initial reduction in plasma volume that attenuated over 12 weeks [56]. Canagliflozin treatment led to small increases in 24-h urine volume that were also attenuated with sustained treatment; these were not associated with meaningful increases in excretion of sodium or potassium compared with placebo.

Although canagliflozin is a selective SGLT2 inhibitor, it is also a low-potency SGLT1 inhibitor (IC_{50} is ~160-fold higher for SGLT1 vs SGLT2) [28,57]. Single doses of canagliflozin >200 mg reduced postprandial glucose (PPG) and insulin excursions for the first meal following dosing to a greater extent than could be explained by UGE [22]. A subsequent dual-tracer study confirmed that canagliflozin 300 mg given before a mixed meal delayed, but did not prevent, intestinal glucose absorption in healthy individuals, leading to reduced PPG and insulin concentrations [58]; no effects on intestinal glucose absorption were observed with empagliflozin, another SGLT2 inhibitor, in patients with T2DM [59]. Similarly, in a crossover study, canagliflozin 300 mg reduced PPG excursion at the meal following dosing, whereas a similar effect was not observed with dapagliflozin 10 mg [60]. These effects with canagliflozin are believed to result from local and transient intestinal SGLT1 inhibition, as the free plasma drug concentrations are not high enough to provide meaningful renal SGLT1 inhibition. Consistent with the Phase I study showing intestinal glucose absorption is delayed but not prevented, no increase in symptoms of carbohydrate malabsorption were reported in canagliflozin-treated patients in the Phase III program. Because of the reduced PPG and delayed intestinal glucose absorption with canagliflozin 300 mg, it is recommended that, for once-daily treatment, canagliflozin be administered prior to the first meal of the day [43].

Overview of the canagliflozin clinical program

The efficacy and safety of canagliflozin have been evaluated in ~10,000 patients with T2DM enrolled in placebo- and active-controlled Phase III studies of up to 104 weeks in duration **(Figure 2)**. Approximately 36% of patients were recruited from North America, 26% from Europe, 8% from South and Central America, and 30% from the rest of the world [61]. Baseline characteristics of participants are shown in **Table 1**. Of note, most black/African–American participants were from the USA, with the proportion of these participants in the canagliflozin program consistent with the prevalence of T2DM in this patient population in the USA. The clinical program included placebo-controlled studies of canagliflozin as monotherapy and in combination with other AHAs (e.g., dual therapy with metformin or sulfonylurea, triple therapy with metformin and sulfonylurea or metformin and pioglitazone, combination with insulin [alone or with other AHAs]). Active-controlled studies of canagliflozin 100 and 300 mg versus sitagliptin or glimepiride added to background metformin, and canagliflozin 300 mg versus sitagliptin added to background metformin and sulfonylurea, were also conducted. Additionally, placebo-controlled studies were conducted to determine the efficacy and safety of canagliflozin 100 and 300 mg in special populations of patients with T2DM on various background therapies, including studies in older patients (aged 55–80 years), patients with moderate renal impairment (eGFR ≥30 and <50 ml/min/1.73 m^2) and patients with elevated cardiovascular risk (CANVAS study).

Efficacy of canagliflozin in clinical studies

• Glycemic efficacy

Change from baseline in HbA1c with canagliflozin was the primary efficacy end point in each study and substudy across the clinical program; other glycemic efficacy end points included the proportion of patients who achieved HbA1c <7.0% and change from baseline in fasting plasma glucose. In a broad range of patients, canagliflozin 100 and 300 mg provided dose-dependent reductions from baseline in HbA1c as monotherapy and combination therapy for up to 104 weeks [29–42]. The incremental contribution of the 300 mg dose versus the 100 mg dose to glycemic efficacy was consistent across studies. In general, a higher proportion of patients achieved HbA1c <7.0% with canagliflozin 100 and 300 mg versus placebo during treatment [29–34,37–40,42]. Larger reductions in HbA1c and better HbA1c goal attainment with canagliflozin 300 mg versus sitagliptin and glimepiride

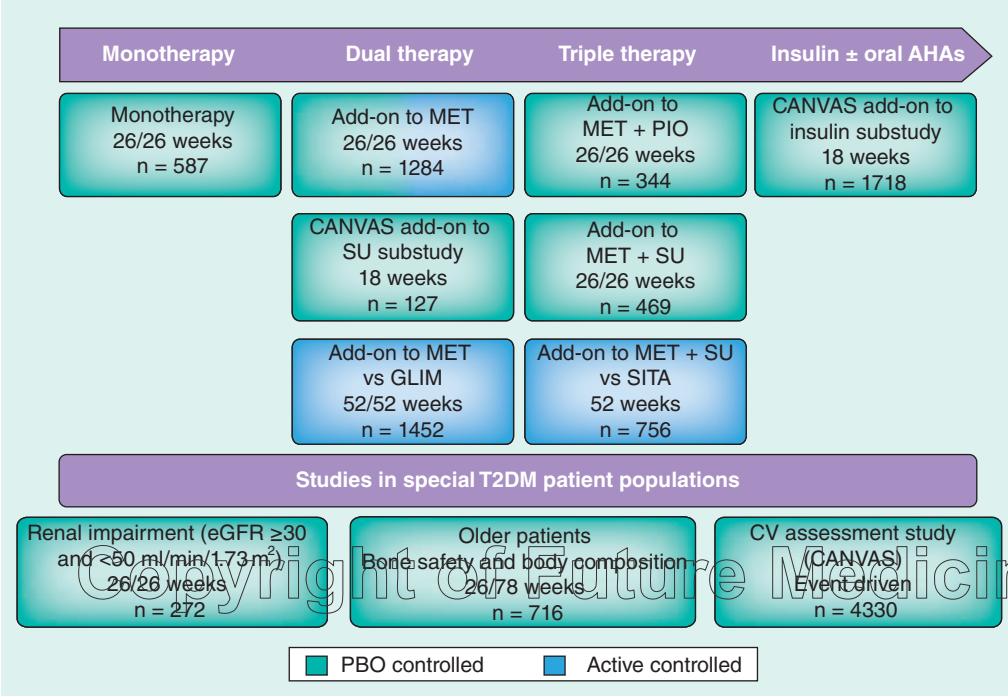

Figure 2. Overview of the CANA clinical program.
AHA: Antihyperglycemic agent; CANA: Canagliflozin; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; GLIM: Glimepiride; MET: Metformin; PBO: Placebo; PIO: Pioglitazone; SITA: Sitagliptin; SU: Sulfonylurea; T2DM: Type 2 diabetes mellitus.

were also seen for up to 52 or 104 weeks, respectively [35,36,41]. Canagliflozin also provided dose-dependent reductions from baseline in fasting plasma glucose compared with placebo and active comparators [29–42].

In the placebo-controlled studies of canagliflozin as monotherapy, add-on to metformin, add-on to metformin plus sulfonylurea, and add-on to metformin plus pioglitazone, statistically significant reductions from baseline in HbA1c were seen with canagliflozin 100 and 300 mg compared with placebo during the 26-week core treatment period **(Figure 3A)** [29–32]; these HbA1c reductions were sustained over 52 weeks [30–32,40]. Glycemic improvements were also seen with canagliflozin versus placebo in the substudies of CANVAS, which were used to generalize the broad use of combination therapy with insulin or sulfonylurea **(Figure 3A)** [33,34]. Canagliflozin provided improvements in HbA1c compared with placebo at 18 weeks in patients on background insulin ≥20 IU/day or ≥30 IU/day (i.e., add-on to insulin substudy) that were sustained over 52 weeks [33]. Significant reductions in HbA1c were also seen in patients on background sulfonylurea (i.e., add-on to sulfonylurea substudy) at 18 weeks [34].

Pooled data from the four 26-week, placebo-controlled studies were used to evaluate the efficacy of canagliflozin in subgroups based on baseline HbA1c, known duration of T2DM, renal function status and age. Consistent with other AHAs [63], HbA1c reductions with canagliflozin were larger in subgroups of patients with higher baseline HbA1c [64]. Among patients in the high glycemic cohort of the monotherapy study (baseline HbA1c >10.0 and ≤12.0%), which was not placebo-controlled, canagliflozin 100 and 300 mg also provided substantial reductions in HbA1c (–2.13 and –2.56%, respectively; **Figure 3B**) [29]. Furthermore, given that the mechanism of action of canagliflozin requires the filtration of glucose at the glomerulus, patients with greater degrees of renal impairment had smaller reductions in HbA1c with canagliflozin, as described below. Duration of T2DM did not notably impact the efficacy of canagliflozin [64].

Glycemic efficacy was also evaluated in a pooled population of patients with stage 3 chronic kidney disease (CKD; eGFR ≥30 and <60 ml/min/1.73 m²) and in subgroups of patients with stage 3A CKD (eGFR ≥45 and <60 ml/min/1.73 m²) and stage 3B CKD (eGFR ≥30 and <45 ml/min/1.73 m²) [62]. Because the

Table 1. Baseline characteristics of patients enrolled in the canagliflozin clinical program.

Characteristic	Worldwide (n = 10,301)	USA (n = 2634)
Mean (SD) age, years	59.5 (9.5)	58.8 (9.9)
Sex, n (%):		
– Male	5965 (58)	1523 (58)
– Female	4336 (42)	1111 (42)
Race, n (%)†:		
– White	7411 (72)	2158 (82)
– Black or African–American	452 (4)	359 (14)
– Asian	1643 (16)	50 (2)
– Other‡	795 (8)	67 (3)
Ethnicity, n (%)†:		
– Hispanic or Latino	1699 (16)	444 (17)
– Not Hispanic or Latino	8563 (83)	2177 (83)
– Not provided	39 (<1)	13 (<1)

†Percentages may not total 100% due to rounding.
‡Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple and other.
SD: Standard deviation.
Data taken from [61].

glycemic efficacy of canagliflozin depends on renal function, HbA1c reductions observed with canagliflozin in patients with stage 3 CKD were smaller compared with those with normal or mildly impaired renal function [62]. Canagliflozin is not indicated for patients with stage 3B CKD; therefore, efficacy results presented here focus on patients with stage 3A CKD. Canagliflozin 100 and 300 mg provided reductions from baseline in HbA1c compared with placebo in the overall stage 3 CKD population (-0.52, -0.62 and -0.14%, respectively; mean baseline HbA1c was 8.1% and eGFR was 48.2 ml/min/1.73 m^2). Reductions in HbA1c in the stage 3A CKD subgroup were similar to the overall stage 3 CKD population **(Figure 3C)**. As expected, HbA1c reductions were smaller with canagliflozin 100 and 300 mg and placebo in patients with stage 3B CKD (-0.18, -0.34 and 0.05%, respectively). In a dedicated study of patients with moderate renal impairment (eGFR ≥30 and <50 ml/min/1.73 m^2), canagliflozin 100 and 300 mg provided reductions in HbA1c compared with placebo over 52 weeks [38,39].

HbA1c reductions were slightly greater in patients aged <65 versus ≥65 years, which is likely related to reduced renal function in older patients **(Table 2)** [65]. When adjusting for differences in baseline eGFR, changes in HbA1c were similar in younger versus older patients [66].

In head-to-head, active-controlled studies, canagliflozin 100 mg demonstrated noninferiority and canagliflozin 300 mg demonstrated superiority to sitagliptin 100 mg [31] and glimepiride (mean dose of 5.6 mg; **Figure 3D**) [35] as add-on to metformin over 52 weeks. Glycemic improvements with canagliflozin 100 and 300 mg versus glimepiride were durable over 104 weeks (-0.65, -0.74 and -0.55%, respectively) [41]. Canagliflozin 300 mg also demonstrated superiority to sitagliptin as add-on to metformin plus sulfonylurea over 52 weeks **(Figure 3E)** [36].

Overall, the insulin-independent mechanism of canagliflozin provides consistent glycemic efficacy in a broad range of patients with varying disease severity and baseline characteristics versus placebo and active comparators.

• Reductions in bodyweight

Across studies, canagliflozin 100 and 300 mg provided consistent, dose-dependent reductions in bodyweight compared with placebo and active comparators (~2–5%). Body composition analyses demonstrated that approximately two-thirds of the weight loss associated with canagliflozin is attributable to loss of fat mass and one-third is attributable to loss of lean mass [35,67], consistent with the pattern seen with weight loss associated with diet and exercise [68]. In the placebo-controlled studies, canagliflozin 100 and 300 mg provided significant reductions from baseline in bodyweight compared with placebo during the core 18- or 26-week treatment periods **(Figure 4A)** [29–31,33,34,40]; weight loss was generally sustained over 52 weeks [30–33,40].

Weight changes with canagliflozin 100 and 300 mg and placebo in the stage 3A CKD subgroup **(Figure 4B)** were similar to those seen in the

overall stage 3 CKD population (-2.0, -2.4 and -0.5%, respectively) [62]. In the pooled, placebo-controlled population, bodyweight reductions were seen with both canagliflozin doses compared with placebo in patients aged <65 and ≥65 years **(Table 2)** [65].

Canagliflozin 100 and 300 mg provided significant reductions in bodyweight compared with sitagliptin [31] and glimepiride **(Figure 4C)** [35] as add-on to metformin over 52 weeks. Weight loss with canagliflozin 100 and 300 mg versus glimepiride was sustained over 104 weeks (-4.1, -4.2 and 0.9%, respectively) [41]. Canagliflozin 300 mg significantly lowered bodyweight compared with sitagliptin, which was weight neutral, as add-on to metformin plus sulfonylurea over 52 weeks **(Figure 4D)** [36].

• Reductions in BP

Canagliflozin 100 and 300 mg provided clinically meaningful reductions in systolic BP (SBP) versus placebo and active comparators in the core treatment periods across studies [29–33,35–38,40–42]. In the placebo-controlled studies, SBP reductions observed at week 26 were generally sustained at week 52 **(Figure 5A)** [30,32,40]. Both canagliflozin doses lowered SBP in the add-on to insulin substudy at 18 weeks, while only canagliflozin 300 mg provided a notable reduction in SBP compared with placebo at 18 weeks in the add-on to sulfonylurea substudy **(Figure 5A)** [33,34]. In general, no notable changes in pulse rate were seen with canagliflozin across studies [29–42].

Change in SBP was also assessed in subgroups based on baseline SBP and baseline use of antihypertensive agents; larger reductions from baseline in SBP were observed in patients with elevated baseline SBP (≥140 mmHg), and use of antihypertensive agents did not notably affect BP lowering with canagliflozin [69]. SBP reductions in the stage 3A CKD **(Figure 5B)** subgroup were similar to those seen in the overall stage 3 CKD population (-4.4, -6.0 and -1.6 mmHg with canagliflozin 100 and 300 mg and placebo, respectively) [62]. Both canagliflozin doses provided larger reductions from baseline in SBP compared with placebo in patients aged ≥65 years versus <65 years **(Table 2)** [65].

Canagliflozin 100 and 300 mg were associated with statistically significant reductions in SBP compared with sitagliptin as add-on to metformin over 52 weeks [31], and canagliflozin 300 mg significantly lowered SBP compared with sitagliptin as add-on to metformin plus sulfonylurea over 52 weeks **(Figure 5C)** [36]. Reductions in SBP were seen with canagliflozin 100 and 300 mg compared with glimepiride as add-on to metformin at week 52 **(Figure 5C)** and week 104 (-2.0, -3.1 and 1.7 mmHg, respectively) [35,41].

• Effects on β-cell function

Canagliflozin improved indices of β-cell function over 26–52 weeks in the three clinical studies in which these measures were assessed [29,30,36,70]. Canagliflozin improved measures of β-cell function based on fasting blood samples (i.e., homeostatic model assessment of β-cell function [HOMA2-%B], proinsulin/C-peptide ratio) [29,30,36]. In patients who underwent a mixed-meal tolerance test, increases in the C-peptide AUC (AUC_C) to glucose AUC (AUC_G) were seen with canagliflozin compared with placebo or sitagliptin [29,30,36]; canagliflozin treatment also generally improved model-based indices of β-cell function, including β-cell glucose sensitivity and the insulin secretion rate at specified plasma glucose concentrations [70]. These improvements may be related to the reversal of glucotoxicity leading to improved β-cell function and insulin release or an "unloading" of β-cells due to reduced demand [71,72]. Of note, canagliflozin, which does not directly target β-cells, was associated with similar improvements in measures of β-cell function compared with sitagliptin, which increases the active levels of incretin hormones that act directly on β-cells [36,70]. In addition to the likely indirect effects of SGLT2 inhibition on β-cell function, recent data suggest that SGLT2 inhibition leads to modest increases in plasma glucagon concentrations [54,59,73], and that increases in glucagon may be due, at least in part, to direct effects of SGLT2 inhibitors on α-cells [74].

Safety of canagliflozin in clinical studies

• Overall safety and tolerability

Safety and tolerability of canagliflozin were assessed in each study and have been reported previously [29–42,75]. Safety data presented below were pooled from Phase III studies. Across the clinical program, canagliflozin 100 and 300 mg were generally well tolerated, with similar overall incidence of adverse events (AEs) compared with placebo and active comparators and a low incidence of serious AEs across groups [29–42,75]. A slightly higher incidence of AEs led to discontinuation with canagliflozin compared with placebo or active comparators. Canagliflozin was associated with a higher incidence of AEs associated with its

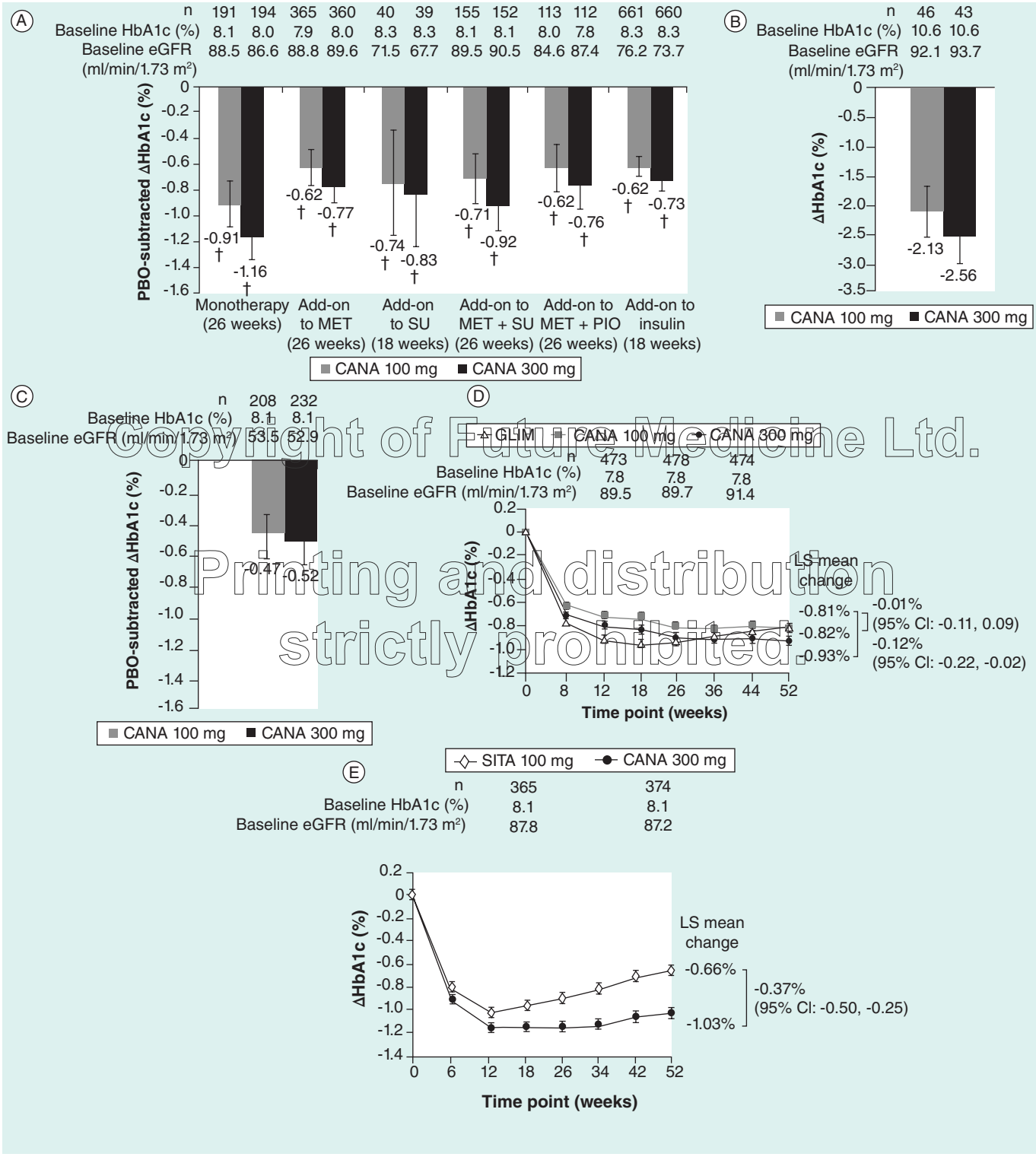

Figure 3. Changes in HbA1c in: (A) the PBO-controlled studies at week 18 or 26 [29–34]; (B) high glycemic subset of the monotherapy study at week 26 [29]; (C) stage 3A CKD subgroup at week 26 [62]; (D) add-on to MET versus GLIM study over 52 weeks [35]; and (E) add-on to MET + SU versus SITA study over 52 weeks [31]. Data in **(A)** and **(C)** are PBO-subtracted LS mean change (95% CI) from baseline; data in **(B)** are LS mean change (95% CI) from baseline; and data in **(D)** and **(E)** are LS mean change (±SE) from baseline.
†$p < 0.001$ vs PBO.

Figure 3. Changes in HbA1c (cont.).
CANA: Canagliflozin; CI: Confidence interval; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; GLIM: Glimepiride; LS: Least squares; MET: Metformin; PBO: Placebo; PIO: Pioglitazone; SE: Standard error; SITA: Sitagliptin; SU: Sulfonylurea.
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mechanism of action (e.g., genital mycotic infections, urinary tract infections [UTIs], osmotic diuresis-related AEs, volume depletion-related AEs), consistent with findings from other SGLT2 inhibitors [43,76,77]; most were mild or moderate in intensity and few led to discontinuations.

Genital mycotic infections were more common with canagliflozin compared with placebo or active comparators [29–42,75,78]. In the pooled, placebo-controlled population, the incidence of genital mycotic infections was higher with canagliflozin 100 and 300 mg compared with placebo in women (10.4, 11.4 and 3.2%, respectively) and men (4.2, 3.7 and 0.6%, respectively), with no dose relationship observed [75,78]. Most events were mild or moderate in intensity and generally did not lead to study discontinuation. Patients with a history of genital mycotic infection and uncircumcised males were more likely to experience an infection [78]. Infections were generally well managed with standard antifungal and/or antibacterial treatments, and few patients experienced a recurrence (females, 2.3%; males, 0.9%).

A modest increase in the incidence of UTIs was seen with canagliflozin 100 and 300 mg compared with placebo (5.9, 4.3 and 4.0%, respectively, in the pooled, placebo-controlled population) [75,79]. The incidence of UTIs was similar with canagliflozin 100 and 300 mg and sitagliptin over 52 weeks as add-on to metformin and add-on to metformin plus sulfonylurea [31,36]. Similarly, there was no notable difference in UTIs with canagliflozin compared with glimepiride [35,41]. UTIs were generally mild or moderate in intensity and few were serious or led to study discontinuation. No meaningful increases in upper UTIs were observed with canagliflozin treatment versus control.

Osmotic diuresis-related AEs (e.g., polakiuria [increased urine frequency], polyuria [increased urine volume]) were more common with canagliflozin 100 and 300 mg compared with placebo (6.7, 5.6 and 1.8%, respectively, in the pooled, placebo-controlled population) [75]; the incidence of osmotic diuresis-related AEs was generally higher with canagliflozin versus sitagliptin and glimepiride [31,35,36,41]. The incidence of volume depletion-related AEs (e.g., orthostatic hypotension, postural dizziness, dehydration) was generally low (1.2, 1.3 and 1.1% with canagliflozin 100 and 300 mg and placebo, respectively, in the pooled, placebo-controlled population) and few led to study discontinuation [75]. Based on findings from a broad population including pooled data from all placebo- and active-controlled studies up to 52 weeks, patients aged ≥75 years, patients with renal impairment, or patients taking loop diuretics were at increased risk of volume depletion-related AEs with canagliflozin [43].

• Hypoglycemia

Across studies, documented hypoglycemia included biochemically confirmed episodes

Table 2. Efficacy of canagliflozin in patients aged <65 and ≥65 years.

Parameter	Patients <65 years			Patients ≥65 years		
	PBO (n = 509)	*CANA 100 mg (n = 674)*	*CANA 300 mg n = 685)*	*PBO (n = 137)*	*CANA 100 mg (n = 159)*	*CANA 300 mg (n = 149)*
Baseline eGFR (ml/min/1.73 m²)	90.0	90.9	91.3	75.9	77.3	77.4
Baseline HbA1c (%):	8.1	8.0	8.0	7.8	7.9	7.9
– LS mean change	-0.2	-0.9	-1.1	-0.1	-0.7	-0.9
Baseline bodyweight (kg):	90.0	90.9	89.4	86.3	84.6	84.4
– LS mean change	-0.6	-2.5	-3.1	-0.5	-2.4	-3.2
– LS mean change (%)	-0.6	-2.8	-3.4	-0.6	-2.9	-3.8
Baseline SBP (mmHg):	127.3	126.9	127.6	132.7	132.5	134.2
– LS mean change	-0.3	-4.2	-4.8	-0.8	-4.6	-5.9

CANA: Canagliflozin; eGFR: Estimated glomerular filtration rate; LS: Least squares; PBO: Placebo; SBP: Systolic blood pressure.
Data taken from [65].

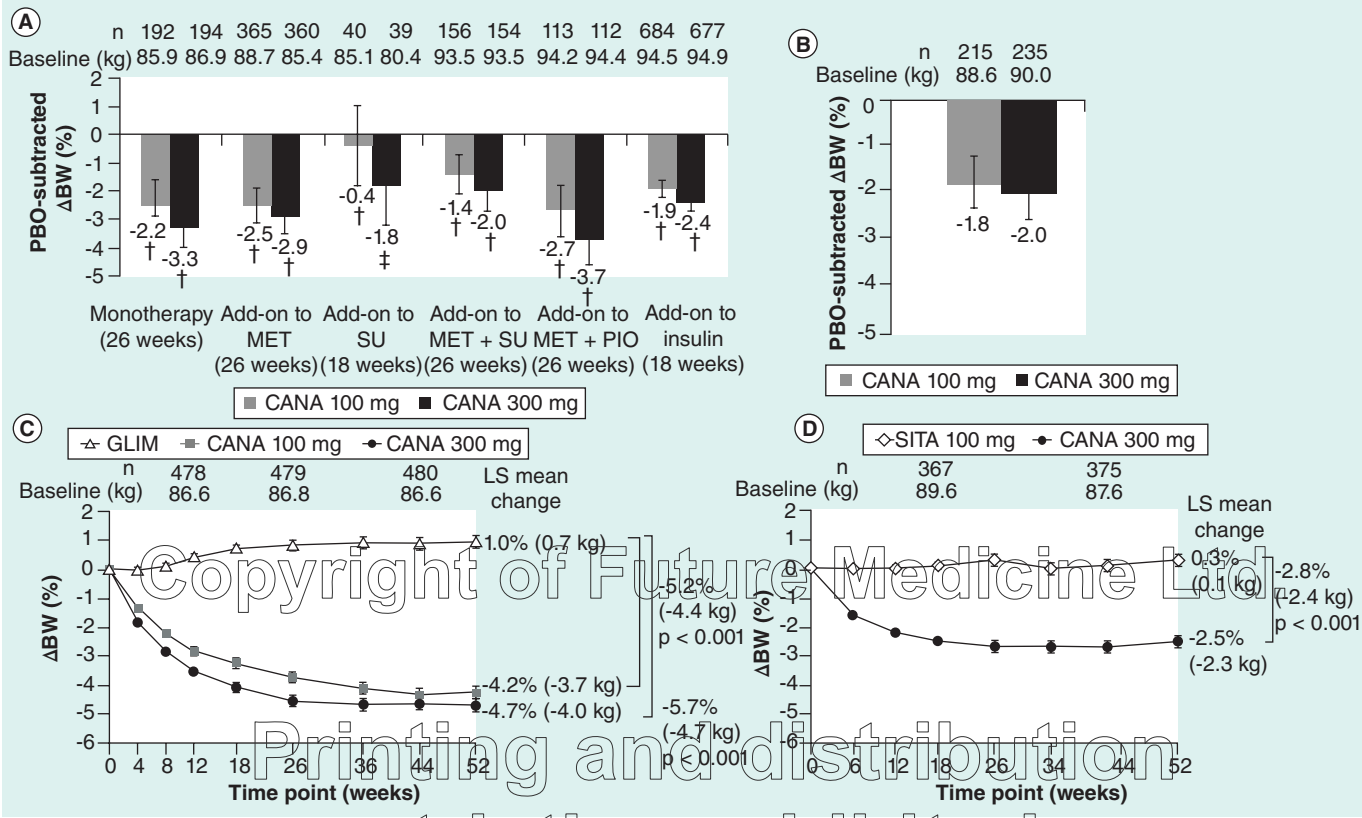

Figure 4. Percentage changes in bodyweight in: (A) the PBO-controlled studies at week 18 or 26 [29–34]; **(B)** stage 3A CKD subgroup at week 26 [62]; **(C)** add-on to MET versus GLIM study over 52 weeks [35]; and **(D)** add-on to MET + SU versus SITA study over 52 weeks [31]. Data in **(A)** and **(B)** are PBO-subtracted LS mean change (95% CI) from baseline, and data in **(C)** and **(D)** are LS mean change (±SE) from baseline.

†p < 0.001 vs PBO.

‡p < 0.025 vs PBO.

BW: Bodyweight; CANA: Canagliflozin; CKD: Chronic kidney disease; GLIM: Glimepiride; LS: Least squares; MET: Metformin; PBO: Placebo; PIO: Pioglitazone; SE: Standard error; SITA: Sitagliptin; SU: Sulfonylurea.

(concurrent fingerstick or plasma glucose ≤3.9 mmol/l [70 mg/dl], with or without symptoms) and severe episodes (i.e., those requiring the assistance of another individual or resulting in seizure or loss of consciousness); the incidence of hypoglycemia in the canagliflozin clinical program is summarized in **Table 3**. Among patients in the pooled, placebo-controlled population who were not on background AHAs associated with hypoglycemia (i.e., sulfonylurea), the incidence of documented hypoglycemia over 26 weeks was low across groups, but slightly higher with canagliflozin 100 and 300 mg compared with placebo (3.8, 4.3 and 2.2%, respectively) [75]; the incidence of biochemically documented hypoglycemia with glucose levels <3.1 mmol/l (56 mg/dl) was low and similar across groups (0.7, 0.6 and 0.4%, respectively) [64]. Consistent with other AHAs with a low intrinsic risk of hypoglycemia, patients who were on background AHAs associated with hypoglycemia reported more documented hypoglycemia episodes across groups, with a moderate, dose-dependent increase observed with canagliflozin 100 and 300 mg compared with placebo (27.4, 30.1 and 15.4%, respectively) [75]. Severe hypoglycemia episodes were reported infrequently (≤1 [0.6%] per group) regardless of background AHAs [75].

The incidence of documented hypoglycemia was low and similar with canagliflozin and sitagliptin as add-on to metformin [31]. As add-on to metformin plus sulfonylurea, the incidence of hypoglycemia with canagliflozin 300 mg was similar to sitagliptin (43.2 and 40.7%, respectively),

despite a nearly 0.4% larger reduction in HbA1c with canagliflozin [36]. The incidence of hypoglycemia was significantly lower with canagliflozin 100 and 300 mg relative to glimepiride as add-on to metformin over 52 weeks (5.6, 4.9 and 34.2%, respectively) [35]; over 104 weeks, hypoglycemia episodes were reported in 6.8, 8.2 and 40.9% of patients, respectively [41].

• Fasting plasma lipids

Changes in fasting plasma lipids with canagliflozin were assessed across studies [29–42,75]. In general, canagliflozin was associated with mean percentage decreases in triglycerides and increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) versus comparators. The

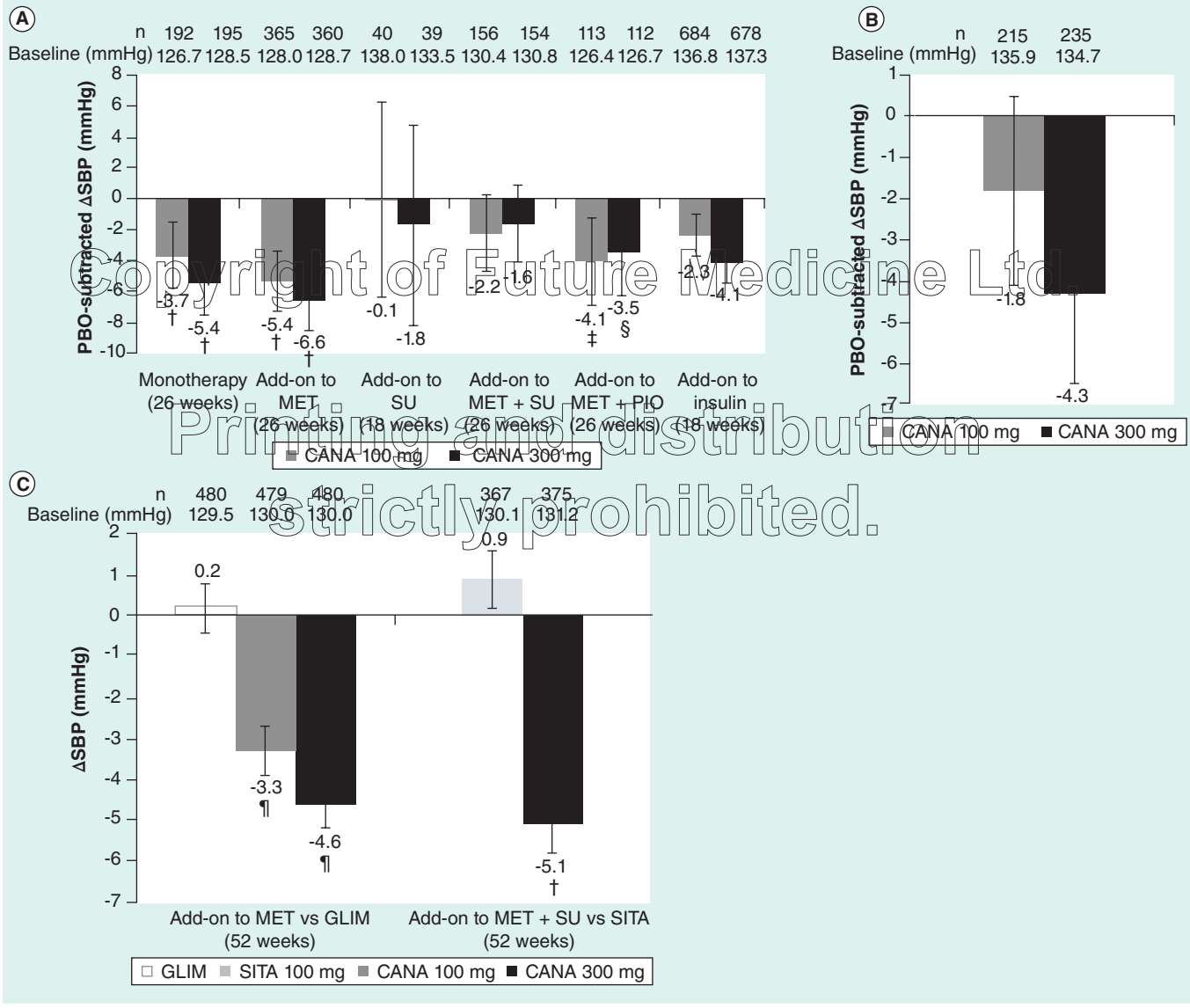

Figure 5. Changes in SBP in: (A) the PBO-controlled studies at week 18 or 26 [29–34]; **(B)** stage 3A CKD subgroup at week 26 [62]; and **(C)** add-on to MET versus GLIM [35] and add-on to MET + SU versus SITA studies over 52 weeks [31]. Data in **(A)** and **(B)** are PBO-subtracted LS mean change (95% CI) from baseline, and data in **(C)** and **(D)** are LS mean change (±SE) from baseline.

†$p < 0.001$ vs PBO or SITA.

‡$p < 0.01$ vs PBO.

§$p < 0.025$ vs PBO.

¶Statistical comparison vs GLIM not performed (not prespecified).

CANA: Canagliflozin; CI: Confidence interval; CKD: Chronic kidney disease; GLIM: Glimepiride; LS: Least squares; MET: Metformin; PBO: Placebo; PIO: Pioglitazone; SBP: Systolic blood pressure; SE: Standard error; SITA: Sitagliptin; SU: Sulfonylurea.

Table 3. Summary of documented hypoglycemia episodes.

Parameter	Patients, n (%)		
	Comparator	*CANA 100 mg*	*CANA 300 mg*
Pooled, PBO-controlled studies (week 26)			
Patients not on background SU (n)[†]:	490	676	678
– Any documented hypoglycemia	11 (2.2)	26 (3.8)	29 (4.3)
– Severe hypoglycemia	0	1 (0.1)	1 (0.1)
Patients on background SU (n):	156	157	156
– Any documented hypoglycemia	24 (15.4)	43 (27.4)	47 (30.1)
– Severe hypoglycemia	1 (0.6)	1 (0.6)	0
Active-controlled studies (week 52)			
Patients not on background SU:			
– Add-on to MET vs GLIM (n)	482	483	485
• Any documented hypoglycemia	165 (34.2)	27 (5.6)	24 (4.9)
• Severe hypoglycemia	15 (3.1)	2 (0.4)	3 (0.6)
Patients on background SU:			
– Add-on to MET + SU vs SITA (n)	378	–	377
• Any documented hypoglycemia	154 (40.7)	–	163 (43.2)
• Severe hypoglycemia	13 (3.4)	–	15 (4.0)

This table is a summary of documented hypoglycemia episodes including biochemically documented episodes (fingerstick or plasma glucose ≤3.9 mmol/l [70 mg/dl]) with or without symptoms and severe episodes (i.e., those requiring the assistance of another individual or resulting in seizure or loss of consciousness). All events are reported for prior to initiation of rescue medication.
[†]Excluding the add-on to MET + SU study.
CANA: Canagliflozin; GLIM: Glimepiride; MET: Metformin; PBO: Placebo; SITA: Sitagliptin; SU: Sulfonylurea.
Data taken from [35,36,43,75].

mechanism of LDL-C increases is not known, but may be related to metabolic changes associated with increased UGE and intravascular volume reduction with canagliflozin [80]. LDL-C increases have also been reported with other SGLT2 inhibitors [43,76,77]. In patients with eGFR ≥30 and <50 ml/min/1.73 m^2 who have decreased UGE, LDL-C was decreased with canagliflozin 300 mg (-1.0%) compared with increases with canagliflozin 100 mg (6.4%) and placebo (6.3%) [38]. Minimal changes in the LDL-C/HDL-C ratio and small dose-dependent increases in non–HDL-C that were smaller than increases in LDL-C were observed with canagliflozin across studies. Relative to placebo, small, dose-related increases in total cholesterol were seen with canagliflozin 100 and 300 mg in the pooled, placebo-controlled population [75]. Lipid changes in the pooled, placebo-controlled population are summarized in **Figure 6**.

• Cardiovascular safety

The cardiovascular safety of canagliflozin is being evaluated in ~10,000 patients in the ongoing CANVAS and CANVAS-R (renal end points) studies. An interim meta-analysis of data from Phase II/III studies in a broad patient population to support health authority filings suggests that canagliflozin treatment is not associated with an increased risk of cardiovascular harm. The hazard ratio (95% CI) for risk of major adverse cardiovascular events was 0.91 (0.68, 1.22) [47].

• Renal safety

Across studies, treatment with canagliflozin was associated with reductions in eGFR (approximately -1 to -6%) and commensurate increases in serum creatinine (~2–8%) that generally occurred early after initiation of treatment (up to week 6) and stabilized or attenuated over the study duration [29–32,35–41,75]. This trend was also observed in patients with stage 3 CKD [39,62] and in older patients [42]. **Figure 7** shows representative data for mean eGFR over time from the 104-week study of canagliflozin versus glimepiride as add-on to metformin [41]. The incidence of renal-related AEs (e.g., renal impairment, blood creatinine increased) was 0.6, 1.7 and 0.6% with canagliflozin 100 and 300 mg and placebo, respectively, among patients with normal renal function in the pooled, placebo-controlled population over 26 weeks [75]. The incidence of renal-related AEs was higher with canagliflozin 100 and 300 mg compared with placebo in the stage 3 CKD population (8.9, 9.3 and 3.7%, respectively) [62].

In patients with moderate renal impairment (eGFR ≥30 and <50 ml/min/1.73 m^2), canagliflozin 100 and 300 mg provided reductions in the median urine albumin/creatinine ratio compared with placebo (-16.4, -28.0 and 19.7%, respectively) over 52 weeks [39]. In addition, both canagliflozin doses reduced albuminuria over 52 weeks, with fewer patients progressing and more patients regressing in stages of albuminuria versus placebo.

• Electrolytes

Canagliflozin was associated with small changes in serum electrolytes (e.g., sodium, potassium, bicarbonate, calcium, magnesium, phosphate) across studies [29–32,35–41,75,81]. In the pooled, placebo-controlled population, the incidence of AEs related to changes in electrolytes was low with canagliflozin 100 and 300 mg and placebo, and transient elevations in potassium were seen with canagliflozin; mean percent increases in potassium were 0.6, 1.0 and 0.5%, respectively, in patients with eGFR ≥60 ml/min/1.73 m^2 at week 26 [81]. Potassium elevations meeting outlier criteria (i.e., >5.4 mmol/l and >15% increase from baseline) at any time postbaseline were more frequent with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo in patients with eGFR ≥60 ml/min/1.73 m^2 (6.8, 4.5 and 4.7%, respectively). In patients with eGFR ≥45 and <60 ml/min/1.73 m^2, the incidence of potassium elevations was 9.1, 5.2 and 5.5%, respectively; potassium elevations were similar for placebo and canagliflozin 100 mg, the indicated dose in this population. Potassium elevations were typically <6.5 mmol/l; elevations ≥6.5 mmol/l were rare, but more frequent in patients taking antihypertensive agents that affect potassium excretion.

• Bone mineral density & fractures

Over 104 weeks, canagliflozin did not adversely affect bone mineral density [44]. In the general population of patients with T2DM who were not enrolled in CANVAS, no difference in the incidence of fractures was seen with canagliflozin compared with control; in the pooled, placebo-controlled population, the incidence of

	Triglycerides			LDL-C			HDL-C			LDL-C/HDL-C			Non-HDL-C			Total cholesterol		
n	564	753	741	562	746	730	564	750	735	562	746	730	563	747	729	564	753	741
Baseline (mmol/l)†	2.1	2.1	2.0	2.8	2.8	2.7	1.2	1.2	1.2	2.5	2.5	2.4	3.8	3.7	3.6	5.0	4.9	4.8
LS mean change (mmol/l)†	0.00	-0.11	-0.22	-0.06	0.06	0.15	0.03	0.09	0.11	-0.12	-0.13	-0.07	-0.06	0.00	0.07	-0.02	0.10	0.18

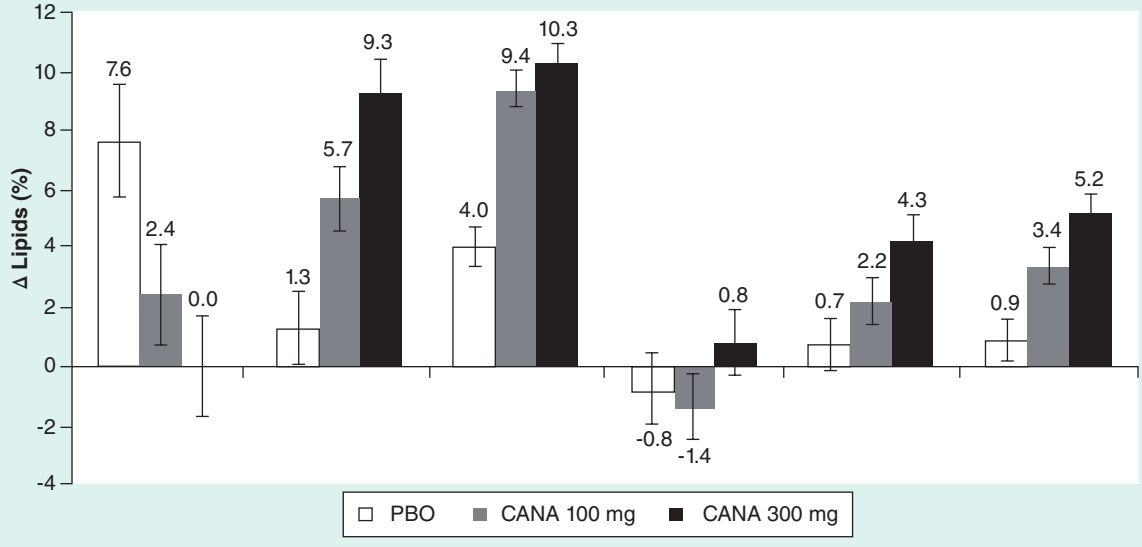

Figure 6. Changes in fasting plasma lipids over 26 weeks (pooled, PBO-controlled population) [75]**.** Data are LS mean percent change (±SE) from baseline.

†Units of mol/mol for LDL-C/HDL-C. To convert from mmol/l to mg/dl, multiply by 88.5 for triglycerides and 38.6 for LDL-C, HDL-C and total cholesterol.

CANA: Canagliflozin; HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LS: Least squares; PBO: Placebo; SE: Standard error.

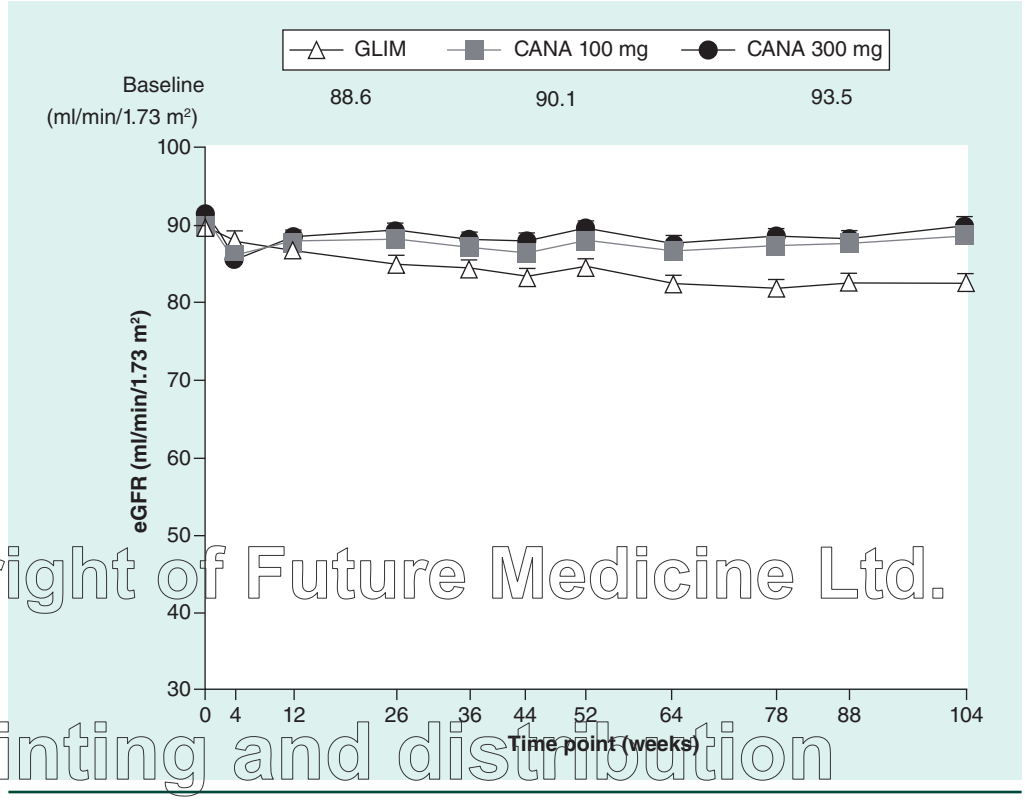

Figure 7. Change in estimated glomerular filtration rate over time in the add-on to metformin versus glimepiride study over 104 weeks [41]. Data are mean (±SE).
CANA: Canagliflozin; eGFR: Estimated glomerular filtration rate; GLIM: Glimepiride; MET: Metformin; SE: Standard error.

fractures was 0.7, 0.6 and 0.3% with canagliflozin 100 and 300 mg and placebo, respectively, over 26 weeks [44]. The incidence rates of bone fractures were 1.6, 1.6 and 1.1 per 100 patient-years of exposure with canagliflozin 100 and 300 mg and placebo, respectively, in patients enrolled in CANVAS (i.e., high cardiovascular risk), with most fractures occurring within the first 26 weeks of treatment [44].

Clinical applications of canagliflozin

Canagliflozin provided consistent improvements in glycemic control, bodyweight and BP, and was generally well tolerated, with a low risk of hypoglycemia, as monotherapy and in combination with other AHAs across Phase III studies [29–42]. Because of its insulin-independent mechanism, canagliflozin is complementary to other AHAs, including insulin. The 2015 update to the American Diabetes Association recommendations for T2DM management included SGLT2 inhibitors, such as canagliflozin, for use in dual therapy with metformin or triple therapy with metformin and sulfonylureas, thiazolidinediones, DPP-4 inhibitors, or insulin, given their similar efficacy to other oral AHAs and potential advantages including weight loss and BP lowering with a low risk of hypoglycemia [4]. Canagliflozin 100 mg is approved for initiation in patients with T2DM and eGFR ≥45 ml/min/1.73 m^2 in the USA and in patients with eGFR ≥60 ml/min/1.73 m^2 in the EU (patients in the EU can remain on canagliflozin 100 mg unless eGFR falls persistently below 45 ml/min/1.73 m^2) [43,44]; patients with eGFR ≥60 ml/min/1.73 m^2 who require additional glycemic control can increase the dosage to 300 mg. Canagliflozin is not indicated for use in patients with eGFR <45 ml/min/1.73 m^2.

While canagliflozin is well tolerated in most patients, patients and their health care providers should be familiar with the symptoms

of AEs related to the mechanism of action of SGLT2 inhibition (e.g., genital mycotic infections, hypotension and dehydration). Some patients may be at increased risk for specific AEs depending on their medical history. For example, patients with a history of genital mycotic infection or uncircumcised males are at greater risk of experiencing a genital mycotic infection with canagliflozin [78]. In addition, patients who are aged ≥75 years, who have moderate renal impairment, and who are taking loop diuretics may be at increased risk of volume depletion-related AEs [43]. Clinicians should monitor LDL-C and treat per standard of care [43].

Conclusion

Canagliflozin was among the first SGLT2 inhibitors approved for the treatment of adult patients with T2DM. Canagliflozin lowers plasma glucose through a novel, insulin-independent mechanism of lowering RT_G, thereby increasing UGE and leading to a mild osmotic diuresis and net caloric loss. Canagliflozin improved glycemic control and reduced bodyweight and BP across Phase III studies in a broad range of patients with T2DM. The safety and tolerability profile of canagliflozin was generally favorable, with increased incidences of AEs related to the mechanism of action of SGLT2 inhibition (i.e., genital mycotic infections, UTIs, osmotic diuresis-related AEs, volume depletion-related AEs), consistent with other agents in this class. As expected, canagliflozin was associated with a low risk of hypoglycemia when used in combination with AHAs not associated with hypoglycemia. Early eGFR reductions were seen with canagliflozin treatment that generally stabilized or attenuated over time. Overall, canagliflozin may be an attractive therapeutic option for patients who require improved glycemic control and would benefit from reductions in bodyweight and BP, along with a low risk of hypoglycemia.

Clinical studies have demonstrated multiple benefits of canagliflozin, which may be viewed favorably by patients and health care providers; furthermore, these studies have provided evidence that canagliflozin may have applications in related therapeutic areas.

Future perspective

Diabetic nephropathy is a microvascular complication affecting ~20–40% of patients with diabetes [82], who are also at an increased risk of macrovascular disease [83]. Hyperglycemia and hyperfiltration at the level of the glomerulus have been proposed to contribute to the onset and progression of diabetic nephropathy in patients with T2DM, resulting in persistent albuminuria and progressive declines in renal function [84]. Preclinical models of diabetes and clinical studies have shown that SGLT2 inhibitors decrease hyperfiltration by directly acting on the kidney to increase tubuloglomerular feedback via increased sodium delivery to the distal tubule that results from inhibition of SGLT2-dependent glucose reabsorption [85]. Because SGLT2 inhibitors have been shown to reduce albuminuria and hyperfiltration, it is possible that canagliflozin may provide renoprotection in patients with T2DM [86]. Canagliflozin is not currently indicated for the treatment of diabetic nephropathy; the CREDENCE trial was designed to determine if canagliflozin has a renoprotective effect in patients with T2DM, stage 2 or 3 CKD, and macroalbuminuria who are receiving standard care, including treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (NCT02065791 [87]). This study will evaluate a composite end point of end-stage renal disease, doubling of serum creatinine, and renal or cardiovascular death in ~3700 patients.

Many patients with T2DM are overweight or obese, and weight loss can lead to improvements in glycemic control, as well as lower risk of diabetes-related complications [4–5,8]. Meaningful weight loss was seen with canagliflozin 100 and 300 mg across Phase III studies in patients with T2DM [29–32,35–41]; in a Phase II study, canagliflozin provided modest weight loss in overweight and obese patients without T2DM over 12 weeks [88]. However, weight loss with canagliflozin is less than would be predicted based on UGE alone; recent studies suggest that this may be attributable to a compensatory increase in food intake [59,89,90]. Canagliflozin is not currently indicated for the treatment of obesity; a clinical study is ongoing to evaluate canagliflozin in combination with phentermine, an appetite suppressant, for weight management in individuals who are overweight and obese (NCT02243202 [87]).

Canagliflozin treatment may also be beneficial in Type 1 diabetes mellitus (T1DM). Patients with T1DM are unable to produce insulin, so T1DM management requires frequent blood glucose monitoring and insulin replacement therapy [91]. Canagliflozin may be attractive for patients with T1DM because it may provide

insulin-independent glycemic control with a low risk of hypoglycemia. Some patients with T1DM may also benefit from the weight loss associated with canagliflozin to offset the weight gain associated with insulin. While canagliflozin is not currently indicated for the treatment of T1DM, a clinical trial is ongoing to evaluate the efficacy and safety of canagliflozin in patients with T1DM who are taking insulin (NCT02139943 [87]).

Financial & competing interests disclosure

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