Review Article

A review of clinical efficacy and safety of canagliflozin 300 mg in the management of patients with type 2 diabetes mellitus

K. M. Prasanna Kumar, Sujoy Ghosh[1], William Canovatchel[2], Nishant Garodia[3], Sujith Rajashekar[3]

Bangalore Diabetes Hospital, Bengaluru, Karnataka, [1]Department of Endocrinology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India, [2]Janssen Research and Development, LLC, Raritan, NJ, USA, [3]Janssen Medical Affairs, Mumbai, Maharashtra, India

ABSTRACT

Currently available antihyperglycemic agents, despite being effective, provide inadequate glycemic control and/or are associated with side effects or nonadherence. Canagliflozin, a widely used orally active inhibitor of sodium-glucose cotransporter 2 (SGLT2), is a new addition to the therapeutic armamentarium of glucose-lowering drugs. This review summarizes findings from different clinical and observational studies of canagliflozin 300 mg in patients with type 2 diabetes mellitus (T2DM). By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose, thereby increasing urinary glucose excretion in patients with T2DM. Canagliflozin 300 mg has been shown to be effective in lowering glycated hemoglobin, fasting plasma glucose, and postprandial glucose in patients with T2DM. Canagliflozin 300 mg also demonstrated significant reductions in body weight and blood pressure and has a low risk of causing hypoglycemia, when not used in conjunction with insulin and insulin secretagogues. Canagliflozin 300 mg was generally well tolerated in clinical studies. The most frequently reported adverse events include genital mycotic infections, urinary tract infections, osmotic diuresis, and volume depletion-related events.

Key words: Canagliflozin, glycated hemoglobin, hypoglycemic agents, pleiotropic benefits, sodium-glucose cotransporter 2 inhibitor, type 2 diabetes mellitus

Introduction

The prevalence of diabetes is growing at an alarming rate globally and is reaching epidemic proportions. The current global prevalence of 415 million is projected to increase to 642 million by 2040 if preventive measures are not put in place.[1] Over 60.0% of the world's population with diabetes resides in Asia,[2] of which India and China contribute the largest.[1] The DiabCare study reports that a vast majority (80.3%) of patients with diabetes in India have poor glycemic control and that type 2 diabetes mellitus (T2DM) begins at an early age.[3] Studies from different parts of India have provided evidence of increasing prevalence of overweight and obesity in India.[4-6] According to the recent data published in the Indian Council of Medical Research India Diabetes-3 study, the estimated prevalence of overweight and obesity is projected to increase to 88 million and 395 million, respectively.[7] Increase in obesity increases the risk of diabetes.[6,8]

Corresponding Author: Dr. Nishant Garodia, Janssen Medical Affairs, Johnson and Johnson Pvt. Ltd., 501, Arena Space, Jogeshwari (E), Mumbai, Maharashtra, India. E-mail: ngarodia@ITS.JNJ.com

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An array of glucose-lowering agents targeting different tissues such as liver, skeletal muscles, and adipose tissues is available for the management of T2DM [Figure 1].[9-14] However, they are unable to restore normal levels of glycated hemoglobin (HbA1c) in the long run[15-17] and over half of the patients do not attain the American Diabetes Association-recommended glycemic goal (HbA1c <7.0%).[18-21] In addition, concerns about weight gain, fear and pain with injections, patient adherence, fluid retention, increased risk of hypoglycemia, congestive heart failure, and gastrointestinal disorders hinder their application in clinical practice.[22-26]

The sodium-glucose cotransporter 2 (SGLT2) found in the proximal renal tubule is a low-affinity, high-capacity transporter responsible for the majority (90.0%) of renal glucose reabsorption.[27,28] The SGLT2 inhibitors have a novel mechanism of action as they decrease the amount of glucose reabsorbed. Both national and international guidelines support the use of SGLT2 inhibitors either as monotherapy or as add-on therapy for the management of T2DM.[29-33] Recently, the National Institute for Health and Care Excellence guideline has approved the use of canagliflozin as monotherapy when diet and exercise do not provide adequate glycemic control and metformin was contraindicated or not tolerated or as add-on therapy with antihyperglycemic agents (AHAs), widening the available treatment options for practicing clinicians.[34,35] Among the available SGLT2 inhibitors, canagliflozin is widely used as doses of 100 and 300 mg once daily (OD).[36] Across studies, canagliflozin 300 mg has demonstrated improvement of glycemic and nonglycemic parameters and is generally well tolerated in patients with T2DM.[37-40] Therefore, the present review summarizes knowledge on canagliflozin 300 mg and the possible differences of canagliflozin 300 mg from other AHAs. This review also aims to understand the additional benefits and risks associated with canagliflozin 300 mg to provide better guidance to the practicing clinicians for recommending canagliflozin 300 mg in patients with T2DM.

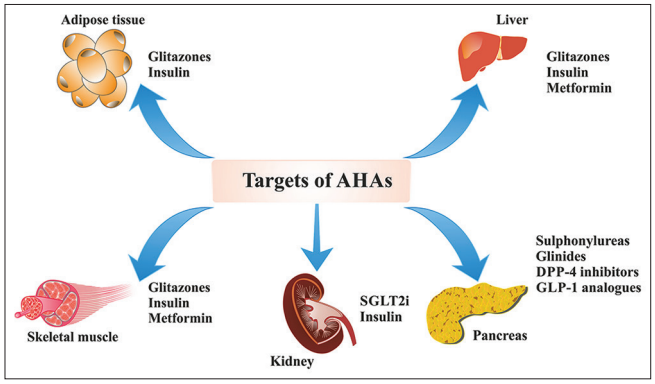

Figure 1: Target organs of antihyperglycemic agents. AHA: Antihyperglycemic agent; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; SGLT2i: Sodium-glucose cotransporter 2 inhibitor

Review Method

The studies were identified by conducting a literature search from electronic database till August 2016, using PubMed, The Cochrane Library, Google, Google Scholar, and ongoing trials registers at Clinical Trials (http://www.clinicaltrials.gov/). Other data sources included conference posters from International Diabetes Federation, International Society for Pharmacoeconomics and Outcomes Research, and European Association for the Study of Diabetes. The search was made using various Medical Subject Headings terminologies for canagliflozin versus placebo and other comparators to assess its efficacy and safety. These articles were screened and publications considered relevant to the topic were included in the study. Review articles, systematic reviews, and meta-analyses were also included in the review.

Clinical Pharmacology of Canagliflozin

Mechanism of action

Primarily, all the SGLT2 inhibitors act by an insulin-independent mechanism, thereby providing a complementary effect when used in combination with other oral AHAs. Canagliflozin is an orally active, reversible, and selective inhibitor with 250-fold selectivity toward SGLT2 over sodium-glucose cotransporter 1 (SGLT1).[27] By blocking SGLT2, canagliflozin decreases reabsorption of filtered glucose and reduces renal threshold for glucose (RT_G), thereby elevating the urinary glucose excretion (UGE) and reducing raised plasma glucose (PG) in patients with T2DM [Figure 2].[41-43] The increased UGE causes caloric loss of approximately 300−400 kcal/day with canagliflozin 300 mg,[44] resulting in weight loss.

In addition, canagliflozin 300 mg transiently inhibits SGLT1, an important intestinal glucose transporter, due to its locally high intestinal concentrations shortly after dosing.[45] However, circulating concentrations of canagliflozin did not meaningfully inhibit SGLT1 (based on the free [unbound] plasma concentrations of canagliflozin and the *in vitro* inhibitory concentration 50.0%) and studies have shown no glucose malabsorption with canagliflozin as virtually all of the ingested glucose was absorbed during the full 6 h period.[41,45,46] In healthy individuals, canagliflozin 300 mg provided greater reductions in postprandial glucose (PPG) and insulin excursions that could be explained by the increase in UGE due to renal SGLT2 inhibition and delayed absorption of ingested glucose due to intestinal SGLT1 inhibition.[45,47]

Pharmacokinetic and pharmacodynamic properties

The pharmacokinetic (PK) properties of canagliflozin are similar in healthy individuals and patients with T2DM and are independent of age, gender, body weight, and ethnicity.[36] Dose-dependent increase in maximum plasma canagliflozin concentration (C_{max}), area under the plasma concentration-time curve (AUC), and UGE and decrease in RT_G were demonstrated in healthy individuals.[48-50] The time to achieve C_{max} (t_{max}) of canagliflozin 300 mg was 1.5 h and elimination half-life ($t_{1/2}$) was 12.6 h in healthy individuals, which supports OD dosing.[50] In patients with T2DM, the mean C_{max} was achieved 1–2 h after administration and steady-state concentration was reached after 4 days administration of canagliflozin 100–300 mg OD. The apparent canagliflozin elimination $t_{1/2}$ and t_{max} were independent of the dose [Table 1].[41] Canagliflozin is rapidly absorbed and its mean absolute oral bioavailability is nearly 65.0% for a single 300 mg dose.[51] The plasma protein binding of canagliflozin is 99.0% and has no clinically relevant drug–drug interactions, which is therapeutically desired.[52,53] Canagliflozin is metabolized into three inactive *O*-glucuronidation metabolites: M7, M5, and M9.[51,52] It is predominantly (~60.0%) excreted via the fecal route, the remainder (33.0%) is excreted in urine, and <1.0% is excreted as unchanged drug in the urine [Table 2].[36,52,54-56]

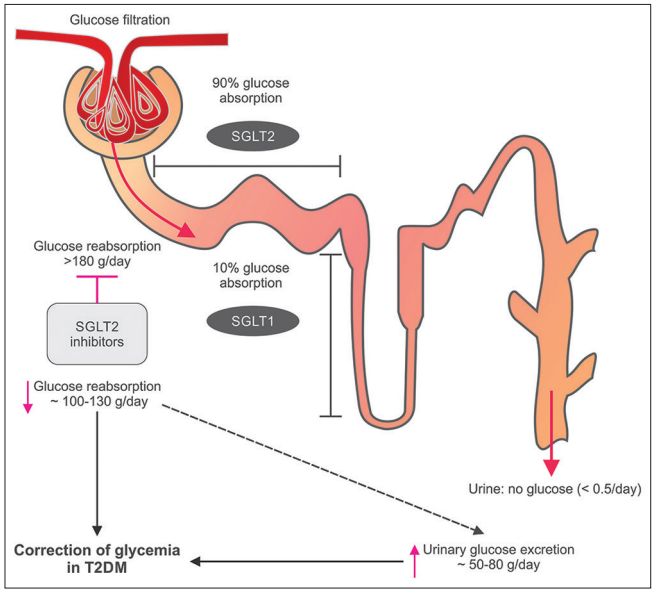

Figure 2: Mechanism of action of sodium-glucose cotransporter 2 inhibitors. T2DM: Type 2 diabetes mellitus; SGLT: Sodium-glucose cotransporter. This figure has been taken from Kalra *et al*.

Following single- and multiple-daily dose administration of canagliflozin in patients with T2DM, dose-dependent reduction in RT_G, with maximal suppression of RT_G from a baseline of ~240 to ~70–90 mg/dL, was observed with canagliflozin 300 mg, suggesting a low risk for treatment-induced hypoglycemia. Canagliflozin was also associated with dose-dependent increase in UGE, mean AUC, and C_{max} and reduction in 24 h mean PG values.[41,51] A PK/pharmacodynamic (PD) model predicting 24 h RT_G profile for canagliflozin 100 and 300 mg demonstrated that 300 mg dose provided near-maximal reduction in RT_G for the full 24 h dosing interval, while a modest suppression of this effect was observed in the overnight period with 100 mg dose.[52] Thus, canagliflozin 300 mg appears to have better PK/PD profiles.

Use in special population

Safety and efficacy of canagliflozin have not been established in children and pregnant women and it is not recommended in nursing women. Canagliflozin is considered safe to be used in patients with mild to moderate hepatic failure patients.[36] It is recommended that the dose of canagliflozin be limited to 100 mg in patients with estimated glomerular filtration rate (eGFR) 45 to <60 mL/min/1.73 m^2 and dose may be increased to 300 mg in patients tolerating 100 mg who have an

Table 1: Summary of mean pharmacokinetic/pharmacodynamic parameters after single- and multiple-dose of canagliflozin in patients with type 2 diabetes mellitus

	Placebo		Canagliflozin 100 mg		Canagliflozin 300 mg	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Pharmacokinetic parameters						
C_{max} (µg/mL)	NR	NR	1.1	1.2	3.5	4.7
t_{max} (h)	NR	NR	1.5	1.5	1.5	1.5
AUC (µg/h/mL)	NR	NR	6.4	8.2	22.6	31.0
$t_{1/2}$ (h)	NR	NR	-	13.7	-	14.9
Pharmacodynamic parameters						
24 h RT_G (mg/dL)	244	235	97.5	76.8	104	85
$UGE_{0-24\ h}$ (g)	12.4	16.2	117.3	119.1	113.1	111.5
$MPG_{0-24\ h}$ (mg/dL)	214	215	169	158	164	151

AUC: Area under the plasma concentration-time curve, C_{max}: Maximum plasma canagliflozin concentration, MPG: Mean plasma glucose, NR: Not reported, RT_G: Renal threshold for glucose, t_{max}: Time to achieve C_{max}, $t_{1/2}$: Elimination half-life, UGE: Urinary glucose excretion

Table 2: Comparison between sodium-glucose cotransporter 2 inhibitors

Parameters	Canagliflozin	Dapagliflozin	Empagliflozin
Year of launch (global)	2013	2014	2014
Therapeutic indication	Treatment of T2DM as an adjunct to diet and exercise	Treatment of T2DM as an adjunct to diet and exercise	Treatment of T2DM as an adjunct to diet and exercise
Recommended starting doses	100 mg OD, taken before first meal of the day	5 mg OD, taken in the morning with or without food	10 mg OD, taken in the morning with or without food
Dose adjustments	May be increased to 300 mg OD in patients tolerating 100 mg OD who have an eGFR ≥60 mL/min/1.73 m^2 or require additional glycemic control	May be increased to 10 mg OD in patients tolerating 5 mg OD who require additional glycemic control	May be increased to 25 mg OD in patients tolerating 10 mg OD who require additional glycemic control
Selectivity for SGLT2 >SGLT1	250-fold	1200-fold	>2500-fold
Bioavailability (%)	~65.0	78.0	>60.0
Distribution (L)	Vd: 119	Vd: 118	Vd: 73.8
Time to peak (h)	1–2	1–2	1
Metabolism	UGT1A9 and UGT2B4 to two inactive metabolites; minor oxidative metabolism (~7.0%) through CYP3A4	Primarily mediated by UGT1A9 to an inactive metabolite (dapagliflozin 3-*O*-glucuronide, 61%); CYP-mediated metabolism (minor)	Primarily through glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9 to minor metabolites
Excretion			
Feces	41.5% as unchanged drug, 7.0% as hydroxylated metabolite, 3.2% as O-glucuronide metabolite	21.0%; ~15.0% as unchanged drug	41.2%; majority as unchanged drug
Urine	~33.0% (30.5% as *O*-glucuronide metabolites, <1.0% as unchanged drug)	75.0%; <2.0% as unchanged drug	54.4%; 50.0% as unchanged drug
Use in special population			
Elderly patients	Can be used	Can be used	Can be used
Pregnancy	Category C	Category C	Category C
Nursing mother	Not to be administered	Not to be administered	Not to be administered
Pediatric use	Safety and efficacy not established	Safety and efficacy not established	Safety and efficacy not established
Hepatic impairment	No dosage adjustment required in patients with mild or moderate hepatic impairment Not recommended in patients with severe hepatic impairment	No dosage adjustment required in patients with mild or moderate hepatic impairment Not recommended in patients with severe hepatic impairment	May be used in patients with hepatic impairment
Renal impairment	No dose adjustment needed in patients with eGFR ≥60 mL/min/1.74 m^2 Limited to 100 mg in patients with eGFR 45 to <60 mL/min/1.74 m^2 Should not be initiated in patients with eGFR <45 mL/min/1.74 m^2 Contraindicated in patients with severe renal impairment (eGFR ≤30 mL/min/1.74 m^2), ESRD, or dialysis	No dose adjustment needed in patients with eGFR ≥60 mL/min/1.74 m^2 Should not be initiated in patients with <60 mL/min/1.74 m^2 Contraindicated in patients with severe renal impairment (eGFR ≤30 mL/min/1.74 m^2), ESRD, or dialysis	No dose adjustment needed in patients with eGFR ≥45 mL/min/1.74 m^2 Should not be initiated in patients with <45 mL/min/1.74 m^2 Contraindicated in patients with severe renal impairment (eGFR ≤30 mL/min/1.74 m^2), ESRD, or dialysis
Regulatory status			
FDA	Yes	Yes	Yes
EMA	Yes	Yes	Yes
India	Yes	Yes	Yes

CYP: Cytochromes P450, EMA: European Medicines Agency, eGFR: Estimated glomerular filtration rate, ESRD: End-stage renal disease, FDA: Food and Drug Administration, OD: Once daily, SGLT: Sodium-glucose cotransporter, T2DM: Type 2 diabetes mellitus, UGT: UDP-glucuronosyltransferase, Vd: Volume of distribution

eGFR ≥60 mL/min/1.73 m^2 or require additional glycemic control.[36] However, it is contraindicated in patients with eGFR <45 mL/min/1.73 m^2 and in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), patients with end-stage renal disease, or patients on dialysis [Table 2].[36]

Therapeutic Indications and Regulatory Status

The US Food and Drug Administration (US FDA) in 2013 approved the use of canagliflozin as an adjunct to diet and exercise to improve glycemic control in patients

with T2DM.[36] The recommended starting dose of canagliflozin is 100 mg OD, taken before the first meal of the day. In patients tolerating canagliflozin 100 mg OD who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control, the dose can be increased to 300 mg OD.[36] In the same year, the European Medicines Agency approved the use of canagliflozin 100 and 300 mg as monotherapy when diet and exercise do not provide adequate glycemic control and metformin was contraindicated or not tolerated or as add-on therapy with AHAs,[57] while the Central Drugs Standard Control Organization permitted the use of canagliflozin 100 and 300 mg in 2014 in India as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.[58] Other SGLT2 inhibitors such as dapagliflozin, and empagliflozin are also approved for the treatment of T2DM [Table 2].[54-56]

Therapeutic Efficacy of Canagliflozin 300 mg

Monotherapy

The 26-week monotherapy study Canagliflozin Treatment And Trial Analysis-Monotherapy (CANTATA-M) comparing canagliflozin 100 and 300 mg with placebo in patients with T2DM had mean baseline HbA1c levels ranging from 8.0% to 10.6%.[59] In this study, canagliflozin 300 mg demonstrated significant improvements in HbA1c, fasting PG (FPG), and PPG levels from baseline versus placebo (all parameters $P < 0.001$) [Figure 3].[59] Proportion of patients achieving HbA1c <7.0% was higher in the canagliflozin 300 mg than placebo group (62.4% vs. 20.6%) [Table 3].[59] Furthermore, the glucose-lowering effect of canagliflozin 300 mg was maintained over a 52-week extension phase [Figure 3].[60]

Add-on therapy

The effectiveness of combination therapy with canagliflozin and AHAs was examined in several randomized controlled studies [Table 3].[61-70] The studies were of 26−104 weeks duration, with mean baseline HbA1c levels ranging from ≥7.0% to ≤10.5%. Across studies, patients received canagliflozin (100 and 300 mg), sitagliptin (100 mg), glimepiride (6 and 8 mg), metformin (≥1500−≥2000 mg/day), and insulin (≥50 IU/day). In a 52-week dual-therapy study comparing canagliflozin 300 mg against sitagliptin 100 mg; canagliflozin 300 mg was superior to sitagliptin in reducing HbA1c levels (−0.9% vs. −0.7%); difference (95% confidence interval [CI]) versus sitagliptin was −0.15% (−0.27, −0.03) for canagliflozin 300 mg [Figure 4].[63] As an adjunct to metformin

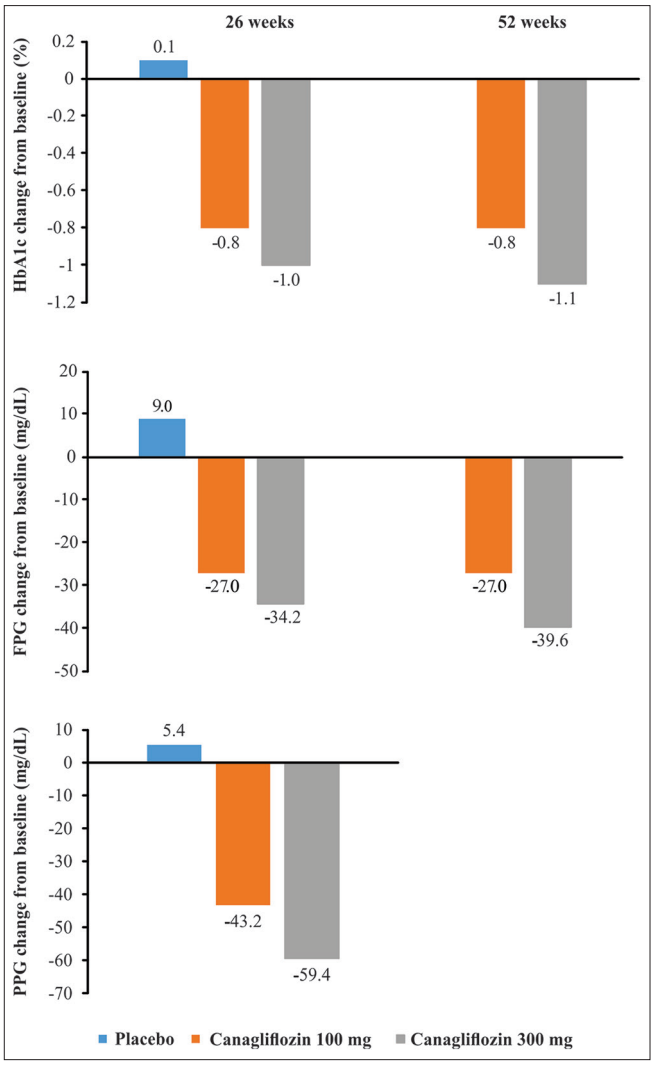

Figure 3: Mean change in glycated hemoglobin, fasting plasma glucose, and postprandial glucose in clinical studies with canagliflozin monotherapy versus placebo. HbA1c: Glycated hemoglobin; FPG: Fasting plasma glucose; PPG: Postprandial glucose

and sitagliptin 100 mg, canagliflozin 300 mg (doses pooled) caused greater reductions in HbA1c than placebo (−0.91% vs. −0.01%; $P < 0.001$).[71] Similar results were demonstrated in another 52-week triple therapy study of canagliflozin 300 mg versus sitagliptin 100 mg, wherein canagliflozin 300 mg was once again superior to sitagliptin in lowering HbA1c (−1.03% vs. −0.66%) and FPG levels (−28.7 vs. −2.2 mg/dL, $P < 0.001$) [Figure 4].[64] Likewise, canagliflozin 300 mg demonstrated a superior HbA1c reduction versus glimepiride (−0·12%; 95% CI: −0·22 to − 0·02) in another 52-week study with add-on metformin therapy [Figure 4].[65] In the follow-up study, HbA1c reduction was maintained over 104 weeks with canagliflozin 300 mg (−0.74%) but increased with glimepiride (−0.55%).[66] In the CANTATA-MSU study, canagliflozin 300 mg led to significant reductions in HbA1c (−1.1% vs. −0.1%, $P < 0.001$), FPG (−30.6 vs.

Table 3: Comparison of canagliflozin as monotherapy, combination therapy and with insulin in different clinical studies

Study	Dose and duration	Number of patients (*n*)	Mean change from baseline in HbA1c (%)	Percentage of patients achieving HbA1c <7.0%	Mean change from baseline in FPG (mg/dL)	Mean change from baseline in PPG (mg/dL)
Monotherapy						
CANTATA-M[59]	CANA 100 mg CANA 300 mg PBO 26-week	584	CANA 100: −0.8 CANA 300: −1.0 PBO: 0.1 *P* < 0.0001 for both	CANA 100: 44.5 CANA 300: 62.4 PBO: 20.6 *P* < 0.001 for both	CANA 100: −27.0 CANA 300: −34.2 PBO: 9.0 *P* < 0.001 for both	CANA 100: −43.2 CANA 300: −59.4 PBO: 5.4 *P* < 0.001 for both
Add-on therapy						
CANTATA-D[63]	CANA 100 mg + MET CANA 300 mg + MET SITA + MET PBO + MET 26-week	1284	CANA 100: −0.8 CANA 300: −0.9 SITA: −0.8 PBO: −0.2 *P* < 0.001 for both CANA doses	CANA 100: 45.5 CANA 300: 57.8 SITA: 54.5 PBO: 29.8	CANA 100: −27.0 CANA 300: −37.8 SITA: −19.8 PBO: 1.8 *P* < 0.001 for both CANA doses	CANA 100: −48.6 CANA 300: −57.6 SITA: −48.6 PBO: −10.8 *P* < 0.001 for both CANA doses
CANTATA-D2[64]	CANA 300 mg + MET + SU SITA 100 mg + MET + SU 52-week	755	CANA 300: −1.0 SITA 100: −0.7	CANA 300: 47.6 SITA 100: 35.3	CANA 300: −28.7 SITA 100: −2.2	CANA 300: −58.5 SITA 100: −39.9
CANTATA-SU[65]	CANA 100 mg + MET CANA 300 mg + MET GLIM + MET 52-week	1450	CANA 100: −0.8 CANA 300: −0.9 GLIM: −0.8	CANA 100: 54 CANA 300: 60 GLIM: 56	CANA 100: −24.3 CANA 300: −27.4 GLIM: −18.4	NR
CANA versus GLIM[66]	CANA 100 mg + MET CANA 300 mg + MET GLIM + MET 104-week	1450	CANA 100: −0.7 CANA 300: −0.7 GLIM: −0.6	CANA 100: 42.5 CANA 300: 50.2 GLIM: 43.9	CANA 100: −19.3 CANA 300: −22.5 GLIM: −10.6	NR
CANTATA-MP[67]	CANA 100 mg + MET + PIO CANA 300 mg + MET + PIO PBO + MET + PIO 26-week	342	CANA 100: −0.9 CANA 300: −1.0 PBO: −0.3 *P* < 0.001 for both CANA doses	CANA 100: 46.9 CANA 300: 64.3# PBO: 32.5	CANA 100: −26.8 CANA 300: −33.2 PBO: 2.5	NR
CANVAS trial collaborative group[70]	CANA 100 mg + INS CANA 300 mg + INS PBO + INS 52-week	2072	CANA 100: −0.6 CANA 300: −0.7 PBO: 0.03 *P* < 0.0001 for both CANA doses	CANA 100: 23.2 CANA 300: 28.6 PBO: 9.9	CANA 100: −19.8 CANA 300: −27.0	NR

#*P*<0.001 versus placebo. Glucose levels presented in mmol/L has been converted to mg/dL by multiplying the values by 18. CANA: Canagliflozin, CANTATA: Canagliflozin Treatment And Trial Analysis, CANVAS: CANagliflozin cardioVascular Assessment Study, D: DPP-4 inhibitor, FPG: Fasting plasma glucose, GLIM: Glimepiride, HbA1c: Glycated hemoglobin, INS: insulin, M: Monotherapy, MET: Metformin, MP: Metformin and Pioglitazone, NR: Not reported, PPG: Postprandial glucose, PBO: Placebo, PIO: Pioglitazone, SU: Sulfonylurea, SITA: Sitagliptin

3.6 mg/dL, $P < 0.001$), and PPG (−55.8 vs. −19.8, P = not reported) versus placebo in patients with T2DM uncontrolled with background metformin + sulfonylurea (SU).[68] Proportion of patients achieving HbA1c <7.0% was higher in the canagliflozin 300 mg than placebo group (56.6% vs. 18.0%)[68] [Figure 5][59,63-65,70] and was maintained over the 52-week treatment period.[68] The efficacy of canagliflozin 300 mg in HbA1c level reduction was also confirmed in the CANTATA-MP.[66] These findings suggest that canagliflozin 300 mg is a novel option as an add-on therapy to metformin and/or SU in controlling HbA1c levels in patients with T2DM.[66]

Canagliflozin 300 mg added-on to dipeptidyl peptidase-4 inhibitors (DPP-4is) or glucagon-like peptide-1 (GLP-1) receptor agonists improved HbA1c control better than DPP-4is (−0.75%, 95% CI: −0.95, −0.54) or GLP-1 receptor agonists (−1.06%, 95% CI: −1.43, −0.69).[72] As an adjunct to insulin ± oral hypoglycemic agents (OHAs) [Figure 4],[69,70] canagliflozin 300 mg caused greater reductions in HbA1c (−0.9% vs. −0.2%) and FPG (−42.3 vs. 8.6 mg/dL) than placebo.[69] Similar improvements in glycemic parameters were observed with canagliflozin 300 mg in patients with T2DM from India[73,74] and Japan.[75]

In elderly patients with T2DM uncontrolled on stable regimen of OHAs, administration of canagliflozin 300 mg showed significantly improved HbA1c (−0.7% vs. −0.03%, $P < 0.001$) and FPG (−20.3 vs. 7.4 mg/dL, $P < 0.001$) levels than placebo.[76] Significant efficacy was sustained over 104 weeks, suggesting effectiveness of canagliflozin 300 mg in this age group.[77] Because canagliflozin acts independently of insulin secretion and action, it can be used at any stage of the disease regardless of baseline HbA1c or the duration of diabetes.[78]

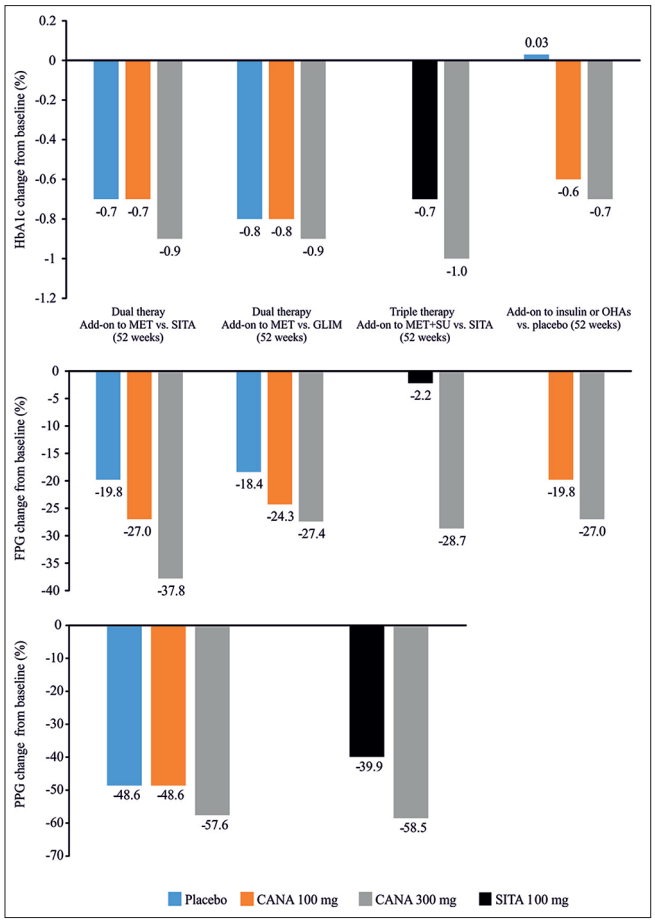

Figure 4: Mean change in glycated hemoglobin, fasting plasma glucose, and postprandial glucose in clinical studies with canagliflozin as add-on therapy versus placebo/active comparators, sitagliptin, glimepiride, and insulin. HbA1c: Glycated hemoglobin; CANA: Canagliflozin; FPG: Fasting plasma glucose; GLIM: Glimepiride; MET: Metformin; OHAs: Oral hypoglycemic agents; PPG: Postprandial glucose; SITA: Sitagliptin; SU: Sulfonylurea

Indirect comparison of canagliflozin 300 mg with other antihyperglycemic agents

In the absence of head-to-head study data, indirect comparisons based on Bayesian network meta-analysis had been used to compare glycemic benefits of canagliflozin with other AHAs. Across studies, patients received canagliflozin (100 and 300 mg), dapagliflozin (10 mg), empagliflozin (10 and 25 mg), exenatide (5, 10, and 20 μg), liraglutide (1.2 and 1.8 mg), and pioglitazone 30 mg. Canagliflozin 300 mg as add-on therapy achieved more effective glycemic control versus DPP-4is,[79-81] exenatide (5 and 10 μg),[80] and liraglutide (1.2 mg)[82] and was similar to liraglutide (1.8 mg) and exenatide (20 μg).[80,81,83]

Pleotropic Effects of Canagliflozin 300 mg

Besides glucose control, canagliflozin 300 mg directly or indirectly exhibits additional benefits on nonglycemic parameters.

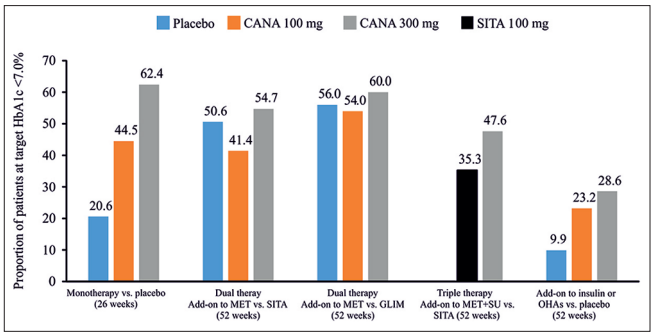

Figure 5: Proportion of patients achieving glycated hemoglobin <7.0% in clinical studies with canagliflozin as add-on therapy versus placebo/active comparators, sitagliptin, glimepiride and insulin. HbA1c: Glycated hemoglobin; CANA: Canagliflozin; GLIM: Glimepiride; MET: Metformin; OHAs: Oral hypoglycemic agents; SITA: Sitagliptin; SU: Sulfonylurea

Body weight

In the clinical development program of canagliflozin (CANTATA), canagliflozin 100 and 300 mg doses were evaluated for body weight reduction. Unlike some AHAs, canagliflozin 300 mg is not associated with weight gain but rather demonstrates a weight loss effect that can be attributed to caloric loss amounting to 300–400 kcal/day.[44] Change in body weight from baseline to study end ranged from −2.5 to −4.7 kg with canagliflozin 300 mg [Figure 6].[59,60,63-65,68,70] Across all phase 3 studies, canagliflozin consistently reduced body weight when used as mono- or dual- or triple-therapy; canagliflozin 300 mg caused numerically greater reductions in body weight than canagliflozin 100 mg.[59] Dual-energy X-ray absorptiometry analysis revealed that this reduction in body weight was majorly due to loss of body fat mass, rather than a loss of fluid or lean mass.[65] The weight-reducing effect of canagliflozin is an important therapeutic consideration for patients with T2DM who are overweight or obese. Interestingly, in a 12-week, randomized, double-blinded study of 376 obese and overweight patients without diabetes, canagliflozin 300 mg significantly reduced body weight versus placebo ($P < 0.05$).[84]

Blood pressure and cardiovascular safety

Canagliflozin caused clinically meaningful reduction in blood pressure (BP) than placebo/active comparators [Figure 7].[59,63-65,70] When assessed in a pooled placebo-controlled population, average systolic BP (SBP) and diastolic BP (DBP) reductions were −4.7 and −1.9 mmHg, respectively, with canagliflozin 300 mg versus placebo.[85] This effect might be ascribed to increased osmotic diuresis and sodium excretion and weight loss.[86,87] However, the BP reduction with canagliflozin 300 mg did not result in increased heart rate.[88] Thus, the pleiotropic benefits of canagliflozin in terms of weight loss and BP reductions can be optimally utilized in countries such as

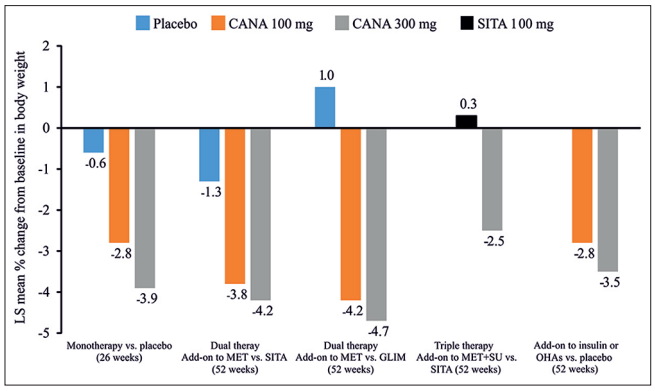

Figure 6: Percent change in body weight in clinical studies with canagliflozin as monotherapy or add-on therapy versus placebo/active comparators, sitagliptin, glimepiride and insulin. CANA: Canagliflozin; GLIM: Glimepiride; LS: Least squares; MET: Metformin; OHAs: Oral hypoglycemic agents; SITA: Sitagliptin; SU: Sulfonylurea

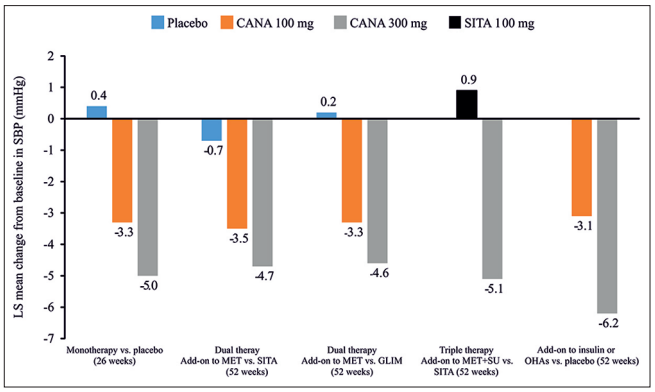

Figure 7: Change in systolic blood pressure in clinical studies with canagliflozin as monotherapy or add-on therapy versus placebo/active comparators, sitagliptin, glimepiride and insulin. CANA: Canagliflozin; GLIM: Glimepiride; LS: Least squares; MET: Metformin; OHAs: Oral hypoglycemic agents; SITA: Sitagliptin; SU: Sulfonylurea; SBP: Systolic blood pressure

India where T2DM with its associated comorbidities such as hypertension and obesity is increasing at an alarming pace.

Although canagliflozin 300 mg appears to have a beneficial effect on cardiovascular (CV) risk factors such as HbA1c, body weight, and BP, there is paucity of data on clinical outcomes such as stroke, myocardial infarction, and CV death. In a pooled meta-analysis of phase 2 and 3 studies, composite primary end-point (nonfatal stroke, nonfatal myocardial infarction, time to event of CV death, and unstable angina requiring hospitalization) showed that canagliflozin does not increase the CV risk relative to comparators.[89] An evaluation of long-term effects of canagliflozin on CV outcomes is underway in the large-scale, double-blind, placebo-controlled Canagliflozin Cardiovascular Assessment Study (CANVAS)[90] and a pooled analysis with another CV outcome study of similar design and in a similar population, CANVAS-R,[91] will be completed and submitted to the Health Authorities in 2017.

Safety and Tolerability of Canagliflozin 300 mg

Hypoglycemia

Hypoglycemia is a potential side effect of some OHAs and insulin therapy. However, canagliflozin when used as monotherapy or combination therapy does not stimulate insulin release and event rate range does not contribute to the risk of hypoglycemia. This is because the observed RT_G values with canagliflozin treatment are above the usual threshold for hypoglycemia (≤70.0 mg/dL), a level that is above the PG concentration at which hypoglycemic symptoms occur.[36] Proportion of hypoglycemia episodes (mild to moderate) with canagliflozin 300 mg was lower than glimepiride (5% vs. 34%)[65] and comparable with sitagliptin (6.8% vs. 4.1%).[63] There were no episodes of severe hypoglycemia reported in most of the studies.[60,63,65] Hypoglycemia rates may be increased when canagliflozin 300 mg was used in combination with insulin or insulin secretagogues and the doses of which may need to be suitably reduced to avoid the risk of hypoglycemia.[36]

Other adverse events

The overall incidence of adverse events (AEs) was similar with canagliflozin 100 and 300 mg [Table 4].[92] Canagliflozin 300 mg was well tolerated in the treatment of patients with T2DM. The most frequently reported AEs with canagliflozin 300 mg were genital mycotic infections (GMIs), urinary tract infections (UTIs), osmotic diuresis (thirst or frequent urination), and volume depletion-related events (hypotension, postural dizziness, and orthostatic hypotension).[92] A pooled analysis of four phase 3 studies showed that canagliflozin 300 mg dose was associated with more frequent occurrences of GMIs versus placebo in women (11.4% vs. 3.2%) and men (3.7% vs. 0.6%).[92] The GMIs mostly occurred during the first 3 months of canagliflozin treatment initiation and declined over time in both men and women with T2DM.[93,94] There was no difference in the incidence of GMI in patients ≥65 years versus <65 years of age.[95] Most GMIs were generally mild to moderate in severity and could be managed with topical or oral antifungal drugs.[95]

The incidence of UTIs was higher in the canagliflozin treatment groups, albeit minimal increases than control, nondose-dependent, similar in severity, and no difference of upper UTI.[96] The UTIs occurred more frequently in female patients, and most diagnosed infections were generally considered to be mild to moderate in nature and responded to standard antimicrobial treatment.[92] Incidence

Table 4: Summary of overall safety and selected adverse events in the overall population

Patients	Placebo (*N*=646)	CANA 100 mg (*N*=833)	CANA 300 mg (*N*=834)
Any AE	348 (59.4)	501 (60.1)	494 (59.2)
Serious AEs	22 (3.4)	28 (3.4)	22 (2.6)
Genital mycotic infection			
Men*	2 (0.6)	17 (4.2)	15 (3.7)
Women**	10 (3.2)	44 (10.4)	49 (11.4)
UTI	26 (4.0)	49 (5.9)	36 (4.3)
Osmotic diuresis -related AEs†	5 (0.8)	56 (6.7)	47 (5.6)
Volume depletion -related AEs‡	7 (1.1)	10 (1.2)	11 (1.3)

All values are in *n* (%) unless otherwise stated. *N*: Total number of patients; *n*: Number of patients assessed. *Including balanitis, balanitis candida, balanoposthitis and genital infection fungal, **Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis, †Including dry mouth, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased, ‡Including dehydration, dizziness postural, hypotension, orthostatic hypotension and syncope. AE: Adverse event, CANA: Canagliflozin, UTI: Urinary tract infection

of UTIs was higher with canagliflozin 100 mg versus canagliflozin 300 mg and placebo in patients <65 years and comparable across patients ≥65 years, indicating no dose relationship to the AE.[95] One serious UTI was reported in patients <65 years but not in >65 years patients; none led to study discontinuation in both age-group categories.[95] Mild to moderate UTIs with canagliflozin 300 mg were comparable with sitagliptin 100 mg[63,64] and were only slightly higher compared with glimepiride.[66,67] In postmarketing surveillance by the US FDA, serious events of UTIs including pyelonephritis, requiring hospitalization, have been reported in patients receiving canagliflozin.[36] Hence, it is recommended that patients treated with canagliflozin should be evaluated for signs and symptoms of UTIs, and if confirmed, appropriate medical attention should be sought immediately.

The osmotic diuresis-related AEs occurred more frequently with canagliflozin 300 mg than placebo (5.6% vs. 0.8%)[92] and were greater compared with glimepiride (6.6% vs. 2.1%)[66] and sitagliptin 100 mg (3.0% vs. 0.5%).[63] The AEs related to volume depletion increased in a dose-dependent manner with canagliflozin doses and were greater than with placebo/active comparators, in individuals ≥75 years of age,[95] in patients with an eGFR of <60 mL/min/1.73 m^2, and in patients using loop diuretics.[36] These AEs predominantly occurred in the first 3 months of canagliflozin treatment and declined subsequently.[95] Because of osmotic diuretic effect of canagliflozin, mild and transient changes in eGFR, albumin-creatinine ratio, and blood urea nitrogen were noted with canagliflozin 300 mg. However, these parameters trended toward baseline levels at the 26-week treatment period. In post-marketing surveillance by the US FDA, serious events of acute kidney injury (AKI), requiring hospitalization and dialysis, were reported in patients receiving canagliflozin.[36] Patients treated with canagliflozin should be evaluated for factors that may predispose them to AKI (such as hypovolemia and chronic renal insufficiency). If AKI is confirmed, canagliflozin should be discontinued immediately and appropriate remedial treatment initiated.[36] Long-term outcomes of canagliflozin treatment on renal function are being evaluated in the ongoing Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation study (CREDENCE).[97]

Recently, the US FDA issued a drug safety communication indicating that in patients with T2DM, SGLT2 inhibitors may be associated with diabetic ketoacidosis (DKA) perhaps as a consequence of their noninsulin-dependent glucose clearance, negative fluid and sodium balance, hypoinsulinemia, hyperglucagonemia, glucosuria, decrease in sodium reabsorption, and alteration in insulin-glucagon ratio.[98,99] Mildly elevated blood glucose (<200 mg%), high anion gap metabolic acidosis, ketonuria/ketonemia, reduced carbohydrate intake, infection, acute illness, and alcohol use can also predispose a patient to DKA.[99] The US FDA AE Reporting System database identified 20 cases of DKA in patients with T2DM treated with SGLT2 inhibitors from March 2013 to June 6, 2014.[100] In a pooled analysis of 17,596 patients with T2DM in clinical studies on canagliflozin, the overall incidence of DKA and related events was low with canagliflozin 300 mg (0.1%) and similar across canagliflozin and noncanagliflozin treatment groups.[101] Future long-term studies are required to clarify the potential association of SGLT2 inhibitor with DKA in patients with T2DM, but clinicians need to consider the potential risk when prescribing these drug in patients with T2DM. Patients treated with canagliflozin presenting with symptoms of severe metabolic acidosis should be evaluated for ketoacidosis, irrespective of presenting blood glucose levels (<250 mg/dL). If ketoacidosis is confirmed, canagliflozin should be discontinued immediately and appropriate remedial measures should be undertaken.[36,102] Patients receiving canagliflozin should avoid alcohol consumption and low carbohydrate diets, and should be counseled for self-management of diabetes.[99]

Evidence of an increased frequency of bone fractures was reported in patients treated with canagliflozin. In the CANVAS study, a nondose-dependent increase in fractures was reported with canagliflozin versus placebo (doses pooled 4.0% vs. 2.6%).[103] Fractures were reported 12 weeks after treatment initiation and were more likely to be from low trauma and affect the upper extremities (e.g. hand and wrist).[36] The increase in fractures may be mediated by falls or other extrinsic factors in the high-risk population, but the

causes of bone fractures in patients exposed to canagliflozin are unknown. No distinct changes in bone mineral density were observed with canagliflozin over 104 weeks.[77]

Foot complications, including leg and toes amputations, are the common complications in patients with T2DM. An interim analysis of the ongoing CANVAS study (median exposure 4.5 years) conducted by the Independent Data Monitoring Committee demonstrated higher incidence of lower limb amputation, primarily of the toe, with canagliflozin treatment versus placebo (100 mg: 7/1000, 300 mg: 5/1000 vs. placebo: 3/1000 patient-year).[104] However, the same risk was not observed across 12 other completed phase 3 or 4 studies in the development program (>8000 patients) or in post-marketing safety surveillance.[104] Although the underlying mechanism linking canagliflozin treatment and an increased risk of amputation is currently unknown, as a precautionary measure, healthcare professionals (HCPs) should also counsel patients about the importance of routine preventive foot care, to notify their HCPs if ulceration, discoloration, new lower extremity pain, tenderness, or gangrene develops and encourage them to remain well hydrated.[104,105]

Treatment Adherence and Persistence of Canagliflozin 300 mg

In addition to the beneficial effects of canagliflozin 300 mg, adherence data play an important role in validating the acceptability of long-term use since better treatment adherence can lead to better glycemic control and clinical outcomes in patients with T2DM.[106] In a 12-month follow-up study of treatment adherence, proportion of days covered (PDC) was 71.0% and medication possession ratio (MPR) was 76.0% in patients with T2DM (N = 881) receiving canagliflozin. The corresponding median PDC was 83.0% and MPR value was 88.0%, indicating good treatment adherence with canagliflozin 300 mg.[107] Furthermore, persistence with AHAs is an important predictor of outcomes in these patients. Low medication persistence has been reported with metformin, SUs, or metformin + SU combination therapy in patients with T2DM.[108,109] Proportion of patients with medication persistency was noted to be higher with canagliflozin 300 mg (65.0%) versus DPP-4is (sitagliptin: 51.0%, linagliptin: 30.2%) and GLP-1 agonists (exenatide: 24.3%, liraglutide: 40.3%, $P < 0.0001$ for all comparisons).[110] In another analysis of treatment persistence in patients (N = 38,083) with T2DM, greater proportion of patients remained persistent on canagliflozin 300 mg (67.0%) versus DPP-4is (47.0% to 53.0%) and GLP-1 receptor agonists (26.0% to 50.0%), indicating more likely consistent use of canagliflozin 300 mg than other AHAs.[111] Gastrointestinal-related side effects of GLP-1 agonists and weight-neutral effects of DPP-4i treatment were cited as the reasons for low persistence with these drugs.[112-114] In addition, DPP-4i and GLP-1 agonists may lose their efficacy over time as insulin resistance worsens and β-cell function deteriorates.[115]

Real-world Experience of Canagliflozin 300 mg

Several real-world studies have explored the efficacy of canagliflozin in patients with T2DM with inadequate glycemic control at baseline. In a retrospective study of this patient population, canagliflozin (doses pooled) treatment significantly reduced mean HbA1c levels from 8.54% at baseline to 7.76% at follow-up ($P < 0.001$).[116] Proportion of patients achieving HbA1c <7.0% was higher in canagliflozin 300 mg (35.3%), and the patients used fewer AHAs (including insulin) during the 3-month follow-up period.[116] In other retrospective, observational studies in similar patient populations (baseline HbA1c ≥7.0%), glycemic goals improved remarkably following canagliflozin (doses pooled) treatment and proportion of patients with HbA1c ≥9.0% at baseline (33.0% was reduced to almost half (16.0%).[117-119] This indicates that prior to canagliflozin treatment initiation, the target HbA1c goal was not achieved despite treatment with multiple AHAs in patients with T2DM. In comparison with DPP-4i, canagliflozin 300 mg was associated with significant reductions in HbA1c (between-treatment difference: −0.37%, P = 0.002). Higher proportion of patients achieved HbA1c goals (<7.0% or <8.0%) with canagliflozin 300 mg versus DPP-4i (HbA1c <7.0% OR: 1.48 vs. HbA1c <8.0% OR: 1.49, both P = 0.003).[120] These findings corroborate those of the phase 3 clinical studies.[66,67] A beneficial effect of canagliflozin was noted in patients with SBP/DBP of ≥140/90 mmHg at baseline; >50.0% patients achieved BP goals after 3 months.[118]

Cost-Effectiveness of Canagliflozin 300 mg

To date, there is a paucity of data regarding the cost-effectiveness of canagliflozin 300 mg in the management of T2DM in India. However, in specific payer settings, canagliflozin 300 mg has shown to be cost-effective versus liraglutide (1.2 and 1.8 mg) and sitagliptin (100 mg).[121-123]

Summary

Canagliflozin 300 mg is efficacious and improved HbA1c, FPG, and PPG levels when administered as monotherapy

and in combination with other AHAs as dual or triple therapy in patients with T2DM. Canagliflozin 300 mg showed superiority to sitagliptin and glimepiride and caused greater HbA1c reductions compared with DPP-4i and was comparable with GLP-1 agonists. Improvements in glycemic control with canagliflozin 300 mg were also observed in elderly patients with T2DM. Canagliflozin 300 mg decreases BP levels and shows a significant weight losing effect with low risk of hypoglycemia. Canagliflozin 300 mg was generally well tolerated in patients with T2DM. Thus, canagliflozin 300 mg could be a viable treatment option for a range of patients with T2DM.

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Conflicts of interest

Dr. K. M. Prasanna Kumar and Dr. Sujoy Ghosh have received honoraria from Johnson and Johnson Pvt. Ltd., India. Dr. William Canovatchel is an employee of Janssen Research and Development, LLC. Dr. Nishant Garodia and Dr. Sujith Rajashekar are employees of Johnson and Johnson Pvt. Ltd, India. We have no other relevant affiliations or financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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