

# Short-term outcomes of type 2 diabetes mellitus patients treated with canagliflozin in real-world setting

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### ABSTRACT

**Objective:** This study is aimed to evaluate the characteristics, treatment, and outcomes of patients treated with canagliflozin in the real-world setting within the first 4 months of the product's availability in India. **Patients and Methods:** It is a retrospective study with data collected from Indian clinical database. Patients aged 18 and above who were prescribed canagliflozin were included in this study. All the patients were on other antihyperglycemic agents (AHAs) before the initiation of canagliflozin. **Results:** Overall, nine patients were included in the study, and data for these patients with mean duration of follow-up of 16 weeks was analyzed. Mean age was 47.9 years and mean duration of type 2 diabetes was 6.7 years. Among patients with available laboratory data at baseline and follow-up, mean glycosylated hemoglobin A1c (HbA1c) decreased from 9.0% at baseline to 6.8% at follow-up ( $P < 0.005$ ); mean weight reduced from 69.9 kg at baseline to 67.9 kg at follow-up. When compared to baseline, the usage and or dose of other AHAs were reduced during follow-up. **Conclusion:** Canagliflozin after it became available in India, improved all glycemic parameters and also reduced the weight of the type two diabetic patients who were poorly controlled by multiple AHAs.

**Key words:** Canagliflozin, India, sodium glucose co-transporter 2 inhibitors, type 2 diabetes mellitus

## INTRODUCTION

According to the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, India has about 62.4 million people with diabetes and 77.2 million people with prediabetes.<sup>[1]</sup> Treatment guidelines recommend glycosylated hemoglobin A1c (HbA1c) goal of 7.0% or less for most of the patients along with the management of other factors that contribute to the complications of type 2 diabetes mellitus (T2DM) viz., blood pressure, body weight, and serum lipids.<sup>[2]</sup> However, despite the availability of

multiple classes of antihyperglycemic agents (AHAs), it was found that only 31% of subjects studied in ICMR-INDIAB study had HbA1c of  $<7\%$ , underscoring that management of the diabetes remains challenging.<sup>[3]</sup>

Canagliflozin is a new molecule belonging to sodium glucose co-transporter 2 (SGLT2) inhibitor class of AHA and has been recently approved by DCGI (Drugs Controller General of India) in 2014 for management of T2DM in India.<sup>[4]</sup> SGLT2 inhibitors lower the blood glucose levels by blocking the reabsorption of filtered glucose in the kidneys and thereby increasing urinary glucose excretion. These agents work through a novel insulin-independent mechanism, complementing the other AHAs. Their unique mechanism of action, coupled with pleiotropic benefits on

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weight and blood pressure, make them attractive choices as add-on therapy to manage T2DM not controlled on other medications.<sup>[5]</sup> Canagliflozin in various clinical trials has shown to improve glycemic control, body weight, and blood pressure.<sup>[6-11]</sup>

This brief communication aims to report the clinical outcomes in Indian patients treated with canagliflozin in a real-world setting and the changes in glycemic and other parameters following 3–5 months of therapy. It should be the first report of its kind after canagliflozin was approved for clinical use in India.

## PATIENTS AND METHODS

Data were collected from clinic database and included patients who were taking canagliflozin daily for 3 months since the day of prescription in April 2015 to August 2015. All patients were above 18 years of age and had estimated glomerular filtration rate >45 mL/min/1.73 m<sup>2</sup> with T2DM. Other medicines were altered as and when required depending on the patient's clinical and laboratory parameters.

Comparisons between baseline and follow-up measures in patients receiving canagliflozin 100 mg were made using paired *t*-test. All statistical analyses were conducted using GraphPad Prism version 6.02 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

## RESULTS

Baseline characteristics of the patients are mentioned in Table 1. In total, nine patients were reviewed in this study of which five were male and four were female. These patients had a mean age of 47.9 years and mean duration of T2DM of 6.7 years. Baseline HbA1c results were available for eight patients, and it was 9.0%. Mean baseline fasting blood glucose (FBG) and postprandial blood glucose (PPBG) of all patients were 226.1 mg/dl and 348.3 mg/dl, respectively. Baseline body weight and body mass index (BMI) was available for all patients, and mean values were 69.9 kg and 26.1 kg/m<sup>2</sup> respectively. Two-third of patients were not hypertensives while remaining one-third were hypertensives and treated by some antihypertensive agents at the time of initiating canagliflozin. The mean baseline blood pressure was 130/80 mmHg. All the patients were initiated on canagliflozin 100 mg once daily. Baseline low-density lipoprotein cholesterol (LDL-C) was available for eight patients, and the mean value was 105.5 mg/dl with all patients being on statins.

The mean duration of follow-up was 16 weeks (standard deviation [SD] = 3.5). Of the patients with follow-up HbA1c

results (*n* = 9), the mean HbA1c was 7.0% (SD = 1.3). Among patients with both baseline and follow-up HbA1c results (*n* = 8), the mean decreased from 9.0% (SD = 1.9) to 6.8% (SD = 1.3), difference of means being -2.2% (95% confidence interval [CI] = -3.2 to -1.2) (*P* < 0.005) [Table 2]. During the baseline period, most patients had HbA1c levels >7.0% (75% of patients). After canagliflozin therapy as add-on to ongoing regimens, the distribution shifted with proportion of patients with HbA1c >7.0% decreasing significantly to 33.3%. After 16 weeks of mean canagliflozin treatment, 66.7% of patients achieved a HbA1c level of ≤7.0% as compared to 25% of patients at baseline [Figure 1].

Efficacy of canagliflozin was further assessed by changes in the FBG, PPBG, BMI, and weight. After 16 weeks of treatment duration, mean decrease in FBG from baseline was 90.3 mg/dl (95% CI = -142.3 to -38.3) (*P* < 0.005) and mean decrease in PPBG from baseline was 137.6 mg/dl (95% CI = -218.6 to -56.55) (*P* < 0.005). Body weight and BMI decreased significantly by -2.06 kg (95% CI = -3.790 to -0.3213) (*P* < 0.05) and -0.78 kg/m<sup>2</sup> (95% CI = -1.440 to -0.1219) (*P* < 0.05), respectively [Table 2].

**Table 1: Baseline characteristics of T2DM patients treated with canagliflozin**

Parameters	Baseline values (mean, (SD))
Age (years)	47.9 (8.5)
Duration of T2DM (years)	6.7 (3.5)
Count of AHAs	2.4 (0.5)
HbA1c (%)	9.0 (1.9)
FBG (mg/dL)	226.1 (46.0)
PPBG (mg/dL)	348.3 (50.1)
Weight (kg)	69.9 (6.9)
BMI (kg/m <sup>2</sup> )	26.1 (2.6)
SBP (mmHg)	122.9 (9.8)
DBP (mmHg)	80 (7.1)
LDL-C (mg/dL)	105.5 (21.8)

T2DM: Type 2 diabetes mellitus, AHAs: Antihyperglycemic agents, HbA1c: Glycosylated hemoglobin, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL-C: Low density lipoprotein cholesterol, SD: Standard deviation

**Table 2: Follow-up data of T2DM patients treated with canagliflozin**

Parameters ( <i>n</i> )	Follow-up values (mean, (SD))	Change of means (95% CI)	<i>P</i>
HbA1c (%) (8)	6.8 (1.3)	-2.2 (-3.2 to -1.2)	<0.005
FBG (mg/dL) (9)	135.8 (36.3)	-90.3 (-142.3 to -38.4)	<0.005
PPBG (mg/dL) (9)	210.8 (94.7)	-137.6 (-218.6 to -56.6)	<0.005
Weight (kg) (9)	67.9 (6.7)	-2.1 (-3.8 to -0.32)	<0.05
BMI (kg/m <sup>2</sup> ) (9)	25.3 (2.5)	-0.78 (-1.44 to -0.12)	<0.05
SBP (mmHg) (9)	122.2 (10.9)	-0.7 (-6.3 to 4.9)	NS
DBP (mmHg) (9)	79.3 (3.7)	-0.7 (-6.3 to 4.9)	NS
LDL-C (mg/dL) (8)	91.4 (50.6)	-14.1 (-56.9 to 28.7)	NS

T2DM: Type 2 diabetes mellitus, HbA1c: Glycosylated hemoglobin, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL-C: Low density lipoprotein cholesterol, SD: Standard deviation, CI: Confidence interval, NS: Not significant

At baseline, the mean number of AHAs used by the patients were 2.4 (SD = 0.53). The most common medications used were metformin (100% of patients) followed by sulfonylureas (SUs) (77.8%), thiazolidinedione (TZD) (33.3%), insulin (22.2%), and alpha-glucosidase inhibitors (AGIs) (11.1%). Five out of nine patients were on two AHAs at baseline while remaining four patients on three AHAs. At baseline, two out of nine patients were on combination of insulin with an oral AHA.

Compared to the use of AHAs during the baseline period, there was a downward trend in the use of metformin, TZD, & AGI, and SUs during the follow-up period [Figure 2]. There was also a downward trend in the dosage requirement of on-going medications. In one patient metformin and AGI had to be discontinued due to gastro-intestinal side effects. The two patients on insulin had decreased dose requirement by 12% and 25% respectively, as compared to the baseline dose at the end of follow-up period after addition of canagliflozin 100 mg.

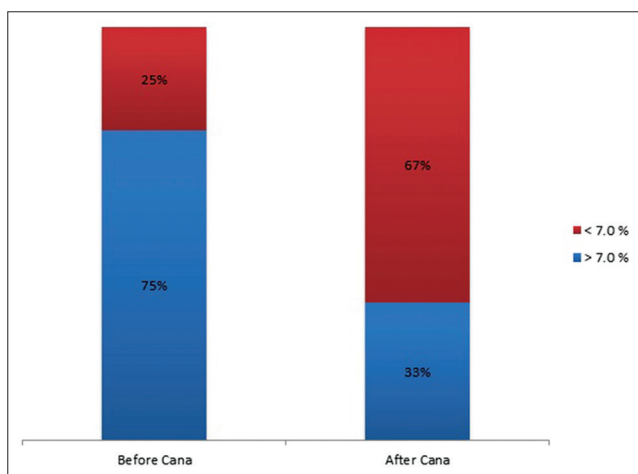
Three out of nine patients were on anti-hypertensive medications, angiotensin receptor blockers (ARBs) being most common. Both systolic and diastolic blood pressures were within normal limits at the baseline; however, there was a marginal decrease in the blood pressure after addition of canagliflozin [Table 2]. In one patient, with combination of ARB and a diuretic, the dose of ARB was reduced to half the dose at baseline and the diuretic was discontinued. There were no changes in dose of antihypertensive agent of other two patients.

Of the patients with follow-up LDL-C results ( $n = 9$ ), the mean LDL-C was 88.8 mg% (SD = 47.9). Among

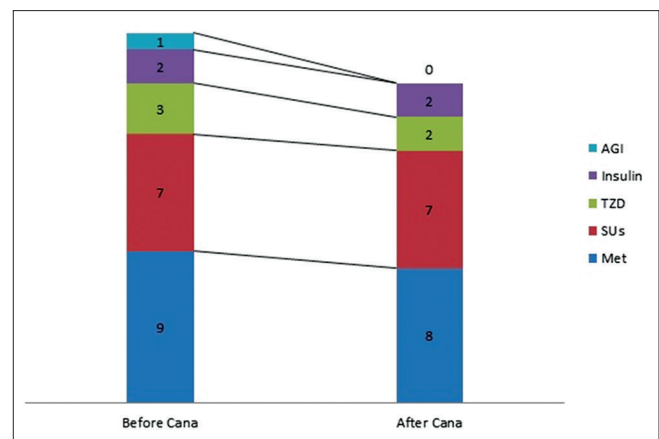
patients with both baseline and follow-up LDL-C results ( $n = 8$ ), the mean decreased from 105.5 mg/dL (SD = 21.8) to 91.4 mg/dL (SD = 50.6), difference of means being - 14.13 mg/dL (95% CI = -56.9 to -28.7) ( $P = ns$ ) [Table 2]. Three patients out of eight with baseline results for LDL-C had increase in LDL-C values while remaining five patients had decrease in the LDL-C levels. All these patients were on statins.

Safety of canagliflozin was assessed by regular follow-up with patients for signs and symptoms of expected adverse events (AEs) as per the prescribing information of canagliflozin.<sup>[12]</sup> All patients were monitored at least once weekly telephonically by a trained diabetic counselor. Patients had also come to the clinic once in 12 weeks for physical check-up and follow-up. No patient complained of hypoglycemia. However, in patients with downward trends of glycemic parameters, down-titration of active AHAs such as SUs and insulin were done as required in order to avoid hypoglycemia.

All the patients were counseled at the start of therapy as per standard recommendations.<sup>[13]</sup> There were two reports (22% of total patients) of genital mycotic infection (GMI) following canagliflozin. Both the patients were continued on the drug and prescribed local and oral anti-fungal medicines. No incidence of urinary tract infection (UTI) was reported. One patient complained of polyuria while none had any symptoms of volume loss or osmotic changes. No patient had complaints of hypotension, dehydration or hematuria, thromboembolism, coronary event, or stroke during follow-up. Urine ketone was negative for all the patients during follow-up.



**Figure 1:** Distribution of baseline and follow-up glycosylated hemoglobin (HbA1c) levels. Cana: Canagliflozin



**Figure 2:** Antihyperglycemic agents as received at the baseline and follow-up periods. There was a downward trend in the dosage requirement of on-going medications. In one patient both metformin and AGI had to be discontinued due to gastro intestinal side effects. AGI: Alpha glucosidase inhibitors; TZD: Thiazolidinedione; Met: Metformin; SU: Sulfonylurea; Cana: Canagliflozin

## DISCUSSION

In this brief communication, we characterize and examine short-term outcomes in patients who received canagliflozin in a real-world setting soon after it became available in India. All patients with canagliflozin were already on more than one class of AHAs at the baseline, and the majority had baseline HbA1c levels of 7.5% or higher. This indicates that prior to treatment with canagliflozin, patients with T2DM were inadequately managed and did not meet the recommended HbA1c levels, despite prior use of multiple AHAs. Significant reductions in HbA1c levels along with other glycemic parameters such as FBG and PPBG were observed in these patients, after canagliflozin treatment. This was similar to the results obtained in canagliflozin clinical trials.<sup>[6-11]</sup> Decrease in the requirement or dose of other AHAs and insulin can add to cost reduction of management of T2DM in long-term; however, this will depend on the durability of canagliflozin. The 104 weeks long study of canagliflozin compared against glimepiride had shown that canagliflozin to be efficacious in reducing HbA1c all through the trial in a sustained manner.<sup>[14]</sup>

The pleiotropic benefits of canagliflozin in terms of weight loss and blood pressure reduction were seen in these patients. This can be a big advantage in a country like India, where diabetes and obesity are increasing rapidly. As per the recent data published in ICMR-INDIAB-3 study on prevalence of overweight and obesity in India, the projected figures are alarmingly high with nearly 88 million overweight and 395 million with some obesity.<sup>[15]</sup> The mean weight reduction of more than 2 kg from baseline with canagliflozin can reduce some of the burden of obesity and overweight in the patients with T2DM.

Low incidence of AEs in this study assures the safety of canagliflozin in management of T2DM. Though two reports of GMI were reported in follow-up period, both the patients were well managed with local and oral anti-fungal medicines. One of the two patients had a prior history of balanitis. The recent warning of diabetic ketoacidosis with SGLT2 inhibitors was kept in mind during prescription of canagliflozin, and urinary ketone was assessed in all patients at follow-up.<sup>[16]</sup> None of the patients had developed ketone in urine after 16 weeks of therapy.

Although this study had assessed use of canagliflozin in real-world setting, the follow-up period was limited to short timeframe of 16 weeks, and the number of patients were very few. While this dataset is not mature enough to thoroughly investigate persistence, 100% of patients in this study were

continued on canagliflozin till the next follow-up. The patients in this study might not be a representative of larger T2DM population, but baseline characteristics and disease profile were similar to most T2DM patients.

## CONCLUSION

This review provides insights into the real-world prescriptions and short-term outcomes of patients treated with canagliflozin 100 mg daily during the early days after DCGI approval. Further research should investigate both short-term and long-term follow-up in larger patient population, and whether canagliflozin use has significant impact on T2DM patients from India in real-world setting.

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## Conflicts of interest

Dr. Manash P. Baruah has received honorarium from Jenssen Metabolics, Johnsons and Johnsons Pvt. Ltd.

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