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REVIEW

Use of Dapagliflozin in the Management of Type 2 Diabetes Mellitus: A Real-World Evidence Study in Indian Patients (FOREFRONT)

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Abstract

Background: Dapagliflozin is approved in India based on a controlled clinical study. This study included type 2 diabetes mellitus (T2DM) Indian patients to determine effectiveness of dapagliflozin in the real-world setup.
Methods: Data were collected retrospectively and prospectively for 3 months. Primary endpoint was mean change in glycated hemoglobin (HbA1c) from baseline to months 3 and 6. Patients were stratified by baseline HbA1c and body mass index (BMI). Paired *t*-test or Wilcoxon signed-rank test at 5% level of significance with two-sided 95% confidence intervals analyzed endpoints.
Results: Total 98.1% ($n = 1941/1978$) patients completed the study, majority of them were men (57.5%), <60 years (77.8%). Mean (standard deviation [SD]) HbA1c decreased significantly from baseline (9.11% [1.44]) to month 3 (8.11% [1.22]; $\Delta = 1.00\%$ [1.01]) and month 6 (7.62% [1.04]; $\Delta = 1.49\%$ [1.18]), $P < 0.001$. Per baseline HbA1c stratification, the largest mean (SD) decrease in HbA1c was in patients with baseline HbA1c >10% (1.86% [1.32] at month 3; 2.80% [1.22] at month 6). Decrease in mean body weight was significant from baseline (78.15 kg [13.48]) to month 3 (77.01 kg [13.21]; $\Delta = 1.14$ kg [2.21]) and month 6 (76.16 kg [13.09]; $\Delta = 1.86$ kg [3.04]), $P < 0.001$, with maximum weight loss in patients with BMI >30 kg/m^2 (1.60 kg [2.50] and 2.56 kg [3.50] at months 3 and 6, respectively). Systolic/diastolic blood pressure also improved. Of the 58 (2.9%) patients having ≥1 adverse event (AE), 9 (0.5%) had vulvovaginitis and 4 (0.2%) each had fungal infection and urinary tract infection (UTI). One patient had a serious AE (SAE) of UTI. No patients died or discontinued the study because of AEs or SAEs.
Conclusion: Dapagliflozin significantly decreased HbA1c and body weight in Indian T2DM patients. Dapagliflozin was well tolerated and no new safety signals were detected.

Keywords: Dapagliflozin, India, Real-world evidence, T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disorder with a global estimated prevalence of 500 million patients in 2018,[1] of which 72.9 million are in India.[2] By 2045, India is estimated to have the largest population with diabetes in the world (134.3 million).[2] More than half of the patients with T2DM in India fail to achieve the optimal glycemic control (glycated hemoglobin [HbA1c] of <7%) recommended by most guidelines.[3–6] Improved glycemic control reduces the incidence and progression of diabetes-related complications.[7–9]

Dapagliflozin, one of the seven types of SGLT2 inhibitors, is approved worldwide for the treatment of T2DM in patients who have inadequate glycemic control by conventional drugs.[10] Findings from clinical trials have confirmed that patients on dapagliflozin show glycemic control similar to that of metformin and have low risk for hypoglycemia; additional clinical benefits including body weight loss and blood pressure (BP) reduction have also been reported with dapagliflozin use.[11–15] Nevertheless, some safety concerns such as genital mycotic infections and urinary tract infection (UTI) have been reported in studies worldwide with SGLT2 inhibitor therapy (including dapagliflozin).[16]

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Dapagliflozin is currently approved in India on the basis of global studies that included a limited number of Indian patients in whom a significant decrease in the HbA1c values (–0.84% [–1.17, –0.50], $P < 0.0001$) was demonstrated compared with placebo after 6 months of use.[17] However, it is uncertain whether data from real-world studies of dapagliflozin will obtain similar outcomes as seen in clinical trials. To understand dapagliflozin use in routine clinical practice, we conducted this real-world study to determine the effectiveness and safety of dapagliflozin in Indian patients with T2DM.

Methods

This was a multicenter prospective noninterventional observational study (clinicaltrials.gov identifier: NCT03071016) conducted at 46 sites across India between March 2017 and March 2018 (Fig. 1). After obtaining approval from the Institutional Review Board of each participating center, the study was conducted in compliance with the protocol and all relevant regulatory guidelines. Patients were eligible if they had received dapagliflozin treatment as part of routine medical care according to the local prescribing information.

Male and female patients aged ≥18 years with inadequately controlled T2DM (HbA1c >7%) with existing antidiabetic therapy and who were initiated on dapagliflozin treatment at least 3 months before study enrolment and had available clinicodemographic data were included in the study. Patients with type 1 diabetes, prior medical condition that would interfere with the safe completion of the study,

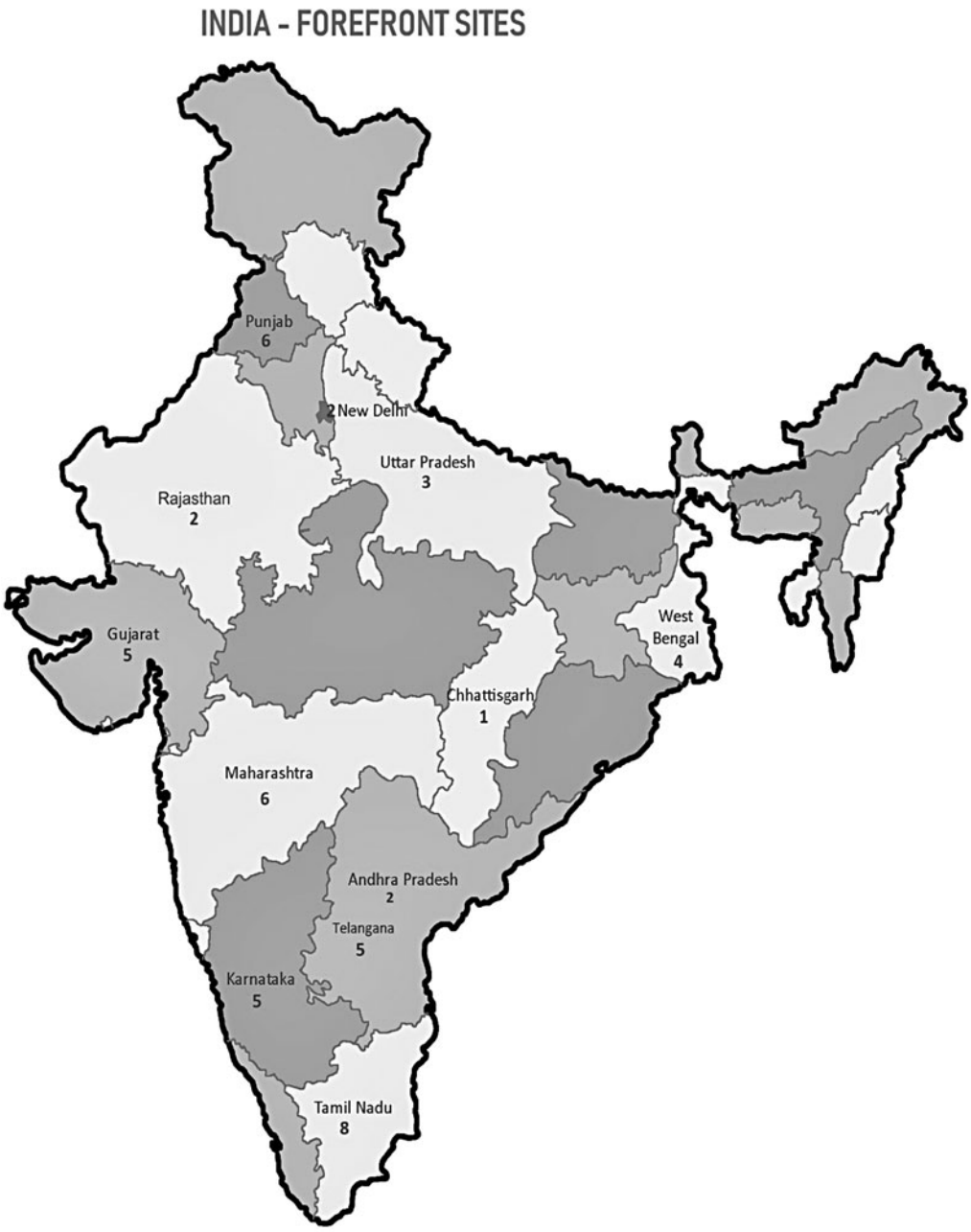

FIG. 1. Study sites across India

pregnant or lactating women, and individuals requiring hospitalization for any cause were excluded.

Data collection

After obtaining voluntary written informed consent, the baseline data were collected retrospectively from past medical records. The baseline was considered 3 months before the first visit. Baseline data included demographics, significant medical and surgical history, vital signs, HbA1c values, antidiabetic therapy, and other concomitant medication use. The current visit data were considered for assessing change at 3 months from baseline (retrospective); similarly data collected 3 months after this visit were used for assessing the effectiveness and safety of dapagliflozin at 6 months from baseline (retrospective). Total study duration for an individual patient was 6 months (3 months retrospective and 3 months prospective) (Fig. 2).

The primary outcome measure was mean change in HbA1c from baseline at months 3 and 6. Secondary outcome measures included mean changes from baseline at months 3 and 6 stratified by baseline HbA1c levels (<8%, 8% to 10%, and >10%), body weight, body weight stratified by baseline body mass indices (BMI, <25, 25–30, >30 kg/m^2), and BP. Safety assessments included monitoring and recording of incidence of all adverse events (AEs), adverse drug reactions, and serious adverse events (SAEs).

Statistical analyses

Assuming that treatment with dapagliflozin will decrease HbA1c by 0.68% (0.99), a sample size of 85 was considered adequate to detect this mean (standard deviation [SD]) decrease with 100% power and a level of significance of 0.05. However, we planned to enroll a much larger sample size of 2000, which can detect a mean reduction in HbA1c of 0.1% with a power >98%; this also ensured a pan-India real-world representative sample of patients on dapagliflozin therapy. The target population analyzed included all enrolled patients who took dapagliflozin and who had at least one HbA1c reading available from postbaseline visits.

Summary statistics for quantitative variables included the number of observations (n), arithmetic mean, SD, minimum, maximum, and median. Qualitative variables were presented as absolute and relative frequencies. Primary and secondary quantitative variables for changes across time (baseline to follow-up) were analyzed using paired t-test or Wilcoxon signed-rank test at 5% level of significance with two-sided 95% confidence intervals; $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SAS 9.4).

Results

Of the 1978 patients enrolled, 1941 (98.1%) completed the 6-month follow-up; remaining 37 (1.9%) patients were lost to follow-up. Table 1 summarizes the demographic and clinical characteristics of patients.

The mean (SD) age of patients was 52.31 (10.43) years; most patients (77.8%) were <60 years of age with male predominance (57.5%). Majority ($n = 1114/1978$, 56.3%) of the patients had HbA1c between 8% and 10%; equal proportions had values <8% (22.0%) and >10% (21.6%). More than two-thirds of patients had BMI >25 kg/m^2 (25–30 kg/m^2: 38.1% and >30 kg/m^2: 39.2%). The most prevalent medical condition was hypertension ($n = 939$, 47.5%), followed by dyslipidemia ($n = 739$, 37.4%), hypothyroidism ($n = 196$, 9.9%), hyperlipidemia ($n = 47$, 2.4%), coronary artery disease ($n = 14$, 0.7%), and retinopathy ($n = 13$, 0.7%).

During treatment, in addition to dapagliflozin, the most frequently used antidiabetic medication was metformin ($n = 1821$, 92.3%), followed by glimepiride ($n = 1185$, 59.9%) and teneligliptin ($n = 498$, 25.2%). About one-fifth of our study population ($n = 359$, 18.1%) was receiving insulin. Telmisartan ($n = 575$, 29.1%) and amlodipine ($n = 210$,

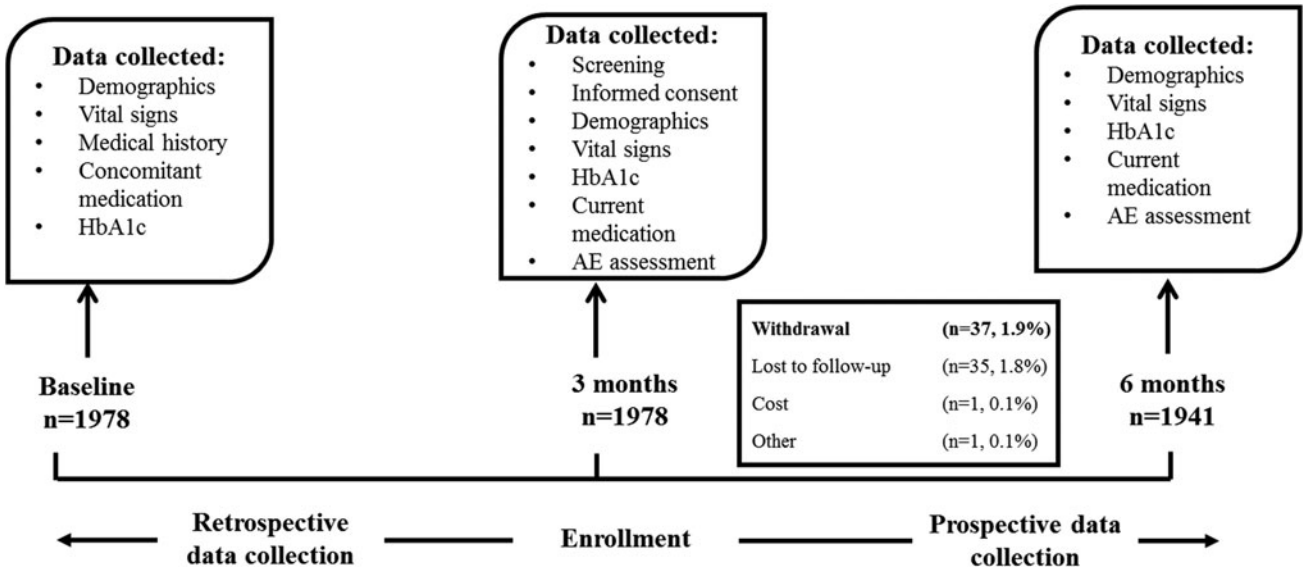

FIG. 2. Study design and patient disposition. Baseline was considered 3 months before the enrollment and baseline data were collected retrospectively. AE, adverse event; HbA1c, glycated hemoglobin.

Table 1. Demographics and Baseline Characteristics

	Dapagliflozin (N = 1978)
Age, mean (SD), years	52.31 (10.43)
Men, *n* (%)	1138 (57.5)
Weight (kg), mean (SD)	78.15 (13.48)
BMI (kg/m^2), mean (SD), *n* = 1918	29.30 (5.28)
Weight (kg) by BMI stratification	
BMI <25 kg/m^2, *n* = 388	64.45 (6.46)
BMI = 25–30 kg/m^2, *n* = 754	74.78 (8.24)
BMI >30 kg/m^2, *n* = 776	88.30 (12.58)
HbA1c (%), mean (SD)	9.11 (1.44)
HbA1c (%) by HbA1c stratification, mean (SD)	
<8%, *n* = 436	7.60 (0.26)
8%–10%, *n* = 1114	8.84 (0.60)
>10%, *n* = 428	11.32 (1.09)
Medical history, *n* (%)	
Hypertension	939 (47.5)
Dyslipidemia	739 (37.4)
Hypothyroidism	196 (9.9)
Concomitant medications (in ≥10% patients), *n* (%)	
Antidiabetic (in addition to dapagliflozin)	
Metformin	1821 (92.3)
Glimepiride	1185 (59.9)
Teneligliptin	498 (25.2)
Gliclazide	275 (13.9)
Vildagliptin	268 (13.5)
Voglibose	259 (13.1)
Sitagliptin	225 (11.4)
Pioglitazone	209 (10.6)
Insulin	359 (18.1)
Antihypertensive	
Telmisartan	575 (29.1)
Amlodipine	210 (10.6)
Antihyperlipidemic	
Rosuvastatin	533 (26.9)
Atorvastatin	404 (20.4)

BMI, body mass index; HbA1c, glycated hemoglobin; SD, standard deviation.

10.6%) were antihypertensive drugs used. The most often used antihyperlipidemic was rosuvastatin (*n* = 533, 26.9%), followed by atorvastatin (*n* = 409, 20.4%) (Table 1).

Effectiveness outcomes

Glycemic control. The mean (SD) HbA1c values at baseline were 9.11% (1.44). Treatment with dapagliflozin showed a clinically significant mean decrease in HbA1c value from baseline at 3 months (1.00% [1.01%]) and also at 6 months (1.49% [1.18%]), $P < 0.001$ (Fig. 3A). The mean (SD) HbA1c reduced from 9.11% (1.44%) at baseline (retrospective) to 8.11% (1.22%) at 3 months and to 7.62% (1.04%) at 6 months.

Dapagliflozin demonstrated a statistically significant reduction in HbA1c levels from baseline to 3 and 6 months ($P < 0.001$) in all the HbA1c stratification categories (<8%, 8–10%, >10%). In patients with HbA1c <8% at baseline, the mean decrease was statistically significant at 3 (0.45% [0.59%]) and 6 months (0.62% [0.71%]), $P < 0.001$ for both. A similar statistically significant decrease was also reported in patients with HbA1c 8% to 10% (0.88% [0.77%] at 3 months and 1.33% [0.85%] at 6 months) and in patients with HbA1c >10% (1.86 [1.32] at 3 months and 2.80 [1.22] at 6 months), $P < 0.001$ for all comparisons (Fig. 3).

Weight change. The mean (SD) weight at baseline, 3 months, and 6 months was 78.15 kg (13.48), 77.01 kg (13.21), and 76.16 kg (13.09), respectively. Treatment with dapagliflozin demonstrated a statistically significant reduction in body weight from baseline to 3 and 6 months, with a mean (SD) change of 1.14 (2.21) and 1.86 (3.04) kg, respectively. Similar reductions in weight were observed after stratification by baseline BMI (<25, 25–30, >30 kg/m^2) from baseline to 3 and 6 months ($P < 0.001$). The maximum decrease was reported in patients with baseline BMI >30 kg/m^2 (1.60 [2.50] kg at 3 months and 2.56 [3.50] kg at 6 months) (Table 2 and Fig. 3B).

Effect on vital signs. With dapagliflozin treatment, the mean (SD) decrease in systolic blood pressure/diastolic blood pressure (SBP/DBP) from baseline at 3 and 6 months was 3.24 (11.44)/1.13 (7.67) and 3.77 (12.22)/1.46 (8.30) mmHg, respectively. The mean (SD) reduction in heart rate was 0.51 (6.22) and 0.94 (7.34) beats/min, respectively; however, these results were not statistically significant.

Safety and tolerability

Of 1978 enrolled patients, 58 (2.9%) patients experienced at least one AE. Of the total 76 AEs, 24 were related to infections and infestations; the most common was vulvovaginitis (*n* = 9, 0.5%), followed by fungal infection and UTI in 4 patients each (0.2%). Only three patients reported hypoglycemia (0.2%). Most of the AEs were mild in severity and recovered without sequelae. One patient with a SAE of UTI was hospitalized; however, the patient completed the study. Hb1Ac values for this patient decreased from 12.6% at baseline to 9.2% at month 3 and 11.1% at month 6. There were no other reported hospitalizations or deaths during the study period (Table 3).

Discussion

This pan-India observational study has generated the first nationwide real-world evidence for dapagliflozin in Indian patients with T2DM. The large diverse population in our study included patients from different regions (both urban and rural), types of health centers (tertiary care and primary care, government hospitals, and private clinics), and clinical practice settings (endocrinologists, diabetologists, and general physicians) in India. The findings from our study demonstrate that 3-month dapagliflozin treatment reduced HbA1c significantly by 1%, which further reduced by ~1.5% at the end of 6 months. In addition, there was a significant decrease in body weight with no adverse safety findings. Patients' vital parameters such as BP improved; however, the changes were not statistically significant.

The mean (SD) HbA1c level achieved after 6 months of dapagliflozin treatment was 7.62% (1.04%) in our patient population; this is close to the target HbA1c level (<7.0%) recommended by the American Diabetes Association.[10,18] The reduction in HbA1c value from baseline to 6 months was much higher (1.49%) than the results from a phase 3 approval

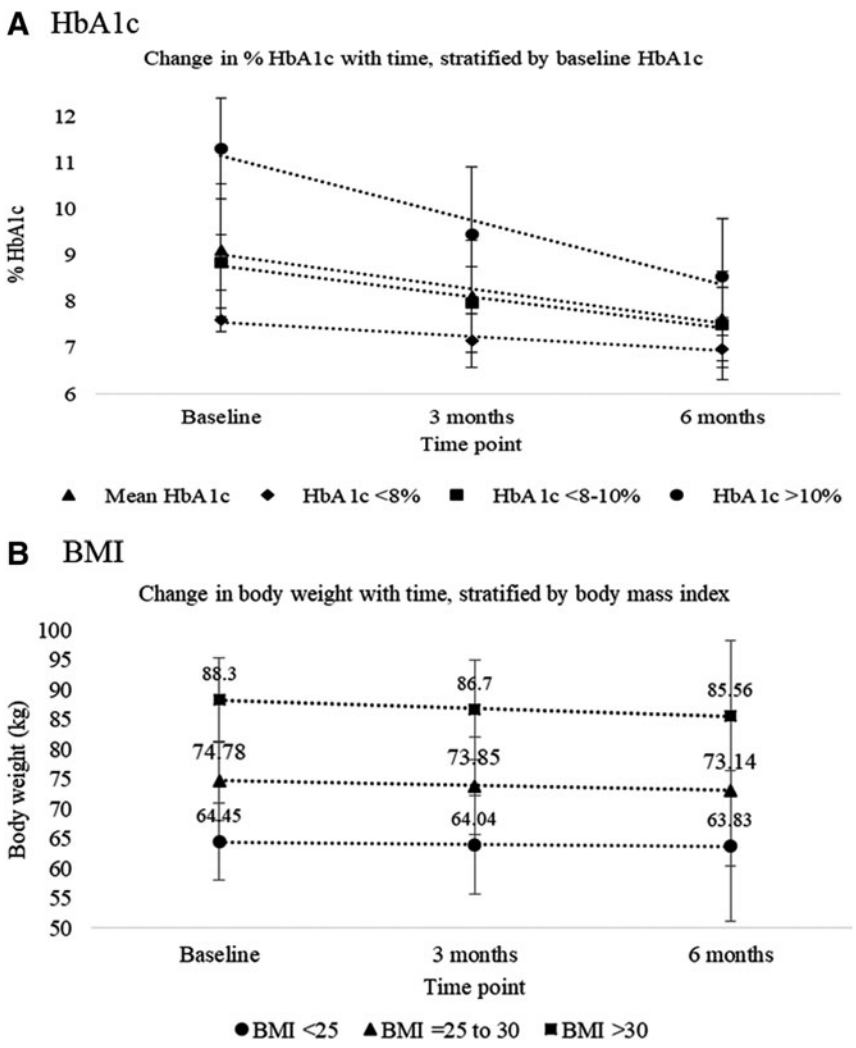

FIG. 3. Mean (SD) change from baseline to 3 and 6 months in HbA1c and body weight stratified by (A) Baseline HbA1c and (B) Body mass index. BMI, body mass index; SD, standard deviation.

TABLE 2. CHANGE FROM BASELINE IN PRIMARY AND SECONDARY EFFICACY ENDPOINTS AT 3 AND 6 MONTHS

	Dapagliflozin (N = *1978*)		
Parameters, mean (SD)	*Baseline*	*3 months*	*6 months*
HbA1c (%)	9.11 (1.44)	8.11 (1.22)	7.62 (1.04)[a]
Stratification by HbA1c			
<8%	7.60 (0.26)[b]	7.15 (0.58)[b]	6.98 (0.67)[c]
<8%–10%	8.84 (0.60)[d]	7.96 (0.80)[d]	7.51 (0.79)[e]
>10%	11.32 (1.09)[f]	9.46 (1.45)[f]	8.53 (1.27)[g]
Body weight (kg)	78.15 (13.48)	77.01 (13.21)	76.16 (13.09)[a]
Body weight stratification by BMI (kg)			
BMI <25	64.45 (6.46)[h]	64.04 (6.64)[h]	63.83 (7.06)[i]
BMI = 25–30	74.78 (8.24)	73.85 (8.19)[j]	73.14 (8.35)[k]
BMI >30	88.30 (12.58)	86.70 (12.61)[l]	85.56 (12.70)[m]
SBP (mmHg)	130.33 (14.43)	127.09 (12.32)	126.60 (10.70)[n]
Change from baseline	—	−3.24 (11.44)	−3.77 (12.22)[n]
DBP (mmHg)	80.04 (7.84)	78.91 (6.80)[n]	78.59 (6.34)
Change from baseline	—	−1.13 (7.67)[n]	−1.46 (8.30)
Heart rate (bpm)	80.08 (8.09)[o]	79.57 (8.02)	79.13 (7.64)[n]
Change from baseline	—	−0.51 (6.22)[o]	−0.94 (7.34)[p]

For mean (SD) change from baseline to 3 and 6 months for all the endpoints except BP and heart rate, $P < 0.001$ (paired *t*-test).
[a]$n = 1941$, [b]$n = 436$, [c]$n = 430$, [d]$n = 1114$, [e]$n = 1090$, [f]$n = 428$, [g]$n = 421$, [h]$n = 388$, [i]$n = 383$, [j]$n = 754$, [k]$n = 742$, [l]$n = 776$, [m]$n = 756$, [n]$n = 1941$, [o]$n = 1977$, [p]$n = 1940$.
BP, blood pressure; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3. Summary of Safety Events

	Dapagliflozin (N = *1978*) n *(%)*
Patients with ≥1 adverse event	58 (2.9)
Patients with ≥1 serious adverse event	1
Adverse events reported in >2 patients	
Vulvovaginitis	8 (0.4)
Fungal infection	4 (0.2)
Urinary tract infection	4 (0.2)
Headache	4 (0.2)
Constipation	3 (0.2)
Pyrexia	3 (0.2)
Hypoglycemia	3 (0.2)

trial involving patients (0.82%) and other meta-analyses (0.52%) carried out for dapagliflozin.[15,17,19,20] This greater decrease reported in our study was most probably due to higher baseline HbA1c values.[21,22] Previous studies have shown a positive correlation between baseline HbA1c and subsequent changes in HbA1c levels.[23]

Other global studies with dapagliflozin (as monotherapy or as an add-on therapy) versus placebo have also demonstrated smaller reductions in HbA1c after 24 weeks (0.89% vs. 0.23%, $P<0.0001$; 0.84% vs. 0.30%, $P<0.0001$).[24,25] However, Ji et al. reported similar reductions, as obtained in our study, in Chinese patients receiving dapagliflozin (0.29% for the placebo group vs. 1.04% and 1.11% for the 5- and 10-mg dapagliflozin groups, respectively; $P<0.0001$ for both doses).[26] According to a recent meta-analysis of treatment with SGLT2 inhibitors in Asian and non-Asian patients, reduction in HbA1c levels was more in Asians than in non-Asians, with the difference of 0.05% between groups was not significant ($P>0.05$).[27] In this study, reduction in HbA1c levels was more pronounced when analyzed per baseline HbA1c stratification. Patients with higher baseline HbA1c levels had greater HbA1c reductions than those with lower baseline levels at both 3 months (baseline <8% [HbA1c reduced by 0.45%], baseline <8% to 10% [0.88%], baseline >10% [1.86%]) and 6 months (0.62%, 1.33%, 2.80%, respectively). Patients with higher baseline HbA1c generally have longer known duration of T2DM, and hence, earlier treatment intensification with SGLT2 inhibitors will help them attain target HbA1c levels faster.[28,29]

In our study, a significant reduction in mean (SD) body weight of 1.86 kg (3.04) was observed within 6 months of dapagliflozin treatment. Patients with higher baseline BMI showed greater body weight reductions at both 3 and 6 months than patients who had lower baseline BMI. Dapagliflozin has shown to produce ~200–300 calorie loss per day.[26,27] In global studies, dapagliflozin, when used as monotherapy or as an add-on to metformin in T2DM patients, resulted in a mean decrease in body weight that was greater than with placebo (2.8 to 3.3 kg vs. 2.2 kg; 1.96 to 2.92 kg vs. 0.4 kg, respectively) at 24 weeks.[24,25,28]

Our study findings demonstrate a reduction in BP (SBP: −3.77 mmHg, DBP: −1.46 mmHg) within 6 months of treatment; however, the change was not statistically significant. A randomized, double-blind trial of dapagliflozin conducted to evaluate cardiovascular risk factors demonstrated statistically significant mean placebo-subtracted reduction in SBP at week 8 (1.97 mmHg); reductions were maintained at week 24 (1.95 mmHg) and week 52 (3.58 mmHg).[17] Systematic review and meta-analyses suggest that in addition to improving the glycemic parameters, dapagliflozin also has a positive effect on cardiovascular parameters such as BP and body weight.[30–32] SGLT2 inhibitors are often associated with a risk of genital mycotic and lower UTI due to urinary excretion of glucose; these side effects are observed more often in women than in men.[33] The most common AEs with dapagliflozin are reported to be vulvovaginitis, balanitis, and related genital infection (4%–18%) and lower UTI (4%–12%).[24,25,34] However, we observed a very low incidence of AEs, including genitourinary AEs (vulvovaginitis: 8/1978 [0.4%] and UTI: 4/1978 [0.2%]); majority of the AEs were mild or moderate in severity. The reported incidence of hypoglycemia in our study population was also low ($n=3$, 0.2%); events were mild in severity and affected patients recovered without sequelae. Only one patient experienced a SAE of UTI during the study period. These findings suggest that dapagliflozin was well tolerated in Indian patients.

The limitations of our study include absence of an active comparator arm, which did not allow comparison with other oral antidiabetics namely glucose-dependent insulinotropic peptide-1 (GLP-1) or dipeptidyl peptidase 4 inhibitors (DPP4i). However, the large patient population ensured the generation of reliable data to accurately assess the mean change from baseline in the efficacy parameters. Still, the sample size was not large enough to describe rare AEs.

Another drawback of the study design was that it did not allow assessment of causality due to retrospective data collection for the first 3-month period. Diabetes is often associated with disturbances in the lipid profile of patients.[35,36] However, assessment of dyslipidemia was not carried out in this study. A subgroup analysis in patients receiving insulin would have been helpful to analyze the scenario in the real world. This study is also limited by issues that are inherent to the real-world evidence studies, such as presence of confounders, data quality, and bias.[37,38] These factors may particularly be compounded when data are retrospectively collected. In contrast, in prospective data collection, channeling bias may occur, where physicians tend to select only patients nonresponsive to earlier treatment.[39] Furthermore, acceptance of effectiveness data from authorities is limited due to concerns of study integrity, and randomized clinical trials remain the gold standard.[40]

Conclusion

In this first nationwide real-world clinical study in Indian patients with T2DM, dapagliflozin was well tolerated and significantly reduced HbA1c levels and body weight at 6 months from baseline. No new safety findings were reported in the study, suggesting a reasonable tolerability profile of dapaglifozin. This study thus provides a strong real-world evidence for early use of dapagliflozin to achieve better glycemic control with additional benefits such as weight loss in Indian patients with T2DM in routine clinical practice.

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Author Disclosure Statement

No competing financial interests exist.

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