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ORIGINAL ARTICLE

Real-world assessment of effectiveness and safety profile of remogliflozin etabonate in management of type 2 diabetes mellitus

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Abstract

Aim To assess the real-world effectiveness and safety of remogliflozin in the management of type 2 diabetes mellitus (T2DM) in a large uncontrolled population.

Methods A retrospective cohort analysis was conducted at 1578 sites across India. Medical records of all patients who had received a remogliflozin-based regimen for a 3-month duration as per routine practice for the management of T2DM were analysed for effectiveness and safety. The efficacy assessments included mean change in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), bodyweight, BMI, and blood pressure from baseline to 3 months. Safety assessments included incidence of adverse events reported.

Results A total of 5452 eligible patients' data were analysed. The mean change of HbA1c level from baseline (8.63%) to 3-month follow-up (7.68%) was − 0.95%. The mean change in FPG and PPG from baseline to the end of follow-up was − 42.4 mg/dL and − 69.1 mg/dL, respectively. A significant reduction in glycemic parameters was observed from baseline to follow-up. The overall incidence of adverse events (AEs) was about 25.9%. Genito-urinary tract infections (12.6%) were more frequently reported AEs, and no severe AEs were reported.

Conclusion Remogliflozin etabonate was effective in improving glycemic parameters. It was well-tolerated in the real-world setting used for glycemic management of T2DM.

Keywords Remogliflozin etabonate · Type 2 diabetes mellitus · HbA1c · Adverse events

Background

Type 2 diabetes mellitus (T2DM) is one of the most important and prevalent chronic non-communicable diseases today, in India, which is anticipated rise to 101 million by 2030 [1]. As improved glycemic control is associated with reduced risk of micro and macrovascular complications, optimal therapy for patients with T2DM requires an appropriate selection of glucose-lowering therapies considering side effects like hypoglycemia and weight gain with some other agents.

However, initial metformin monotherapy, as recommended by clinical guidelines, most often are insufficient to achieve or maintain glycaemic targets. Consequently, treatment with additional glucose-lowering agents to existing anti-diabetic therapy is required [2, 3].

SGLT2i represents a new class of anti-diabetic drugs that recent guidelines have recommended as one of the first-line anti-diabetic agents in the management of T2DM [4]. SGLT2 inhibitors exhibit additional unique benefits of reduction in both body weight and blood pressure (BP) [5].

Remogliflozin, available as prodrug remogliflozin etabonate (RE), is a novel potent selective inhibitor of SGLT2 that has been approved recently in India [6]. Recent phase III pivotal study of RE in Indian subjects demonstrated RE to be an efficacious and tolerable agent in Indian T2DM

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patients and was found to be non-inferior to dapagliflozin in the management of T2DM [7].

The real-world evidence (RWE) is the clinical evidence which demonstrates the usage and potential benefits and/or risks of a medical product derived from analysis of real-world data (RWD). RWD has potential to complement the knowledge available from conventional randomized clinical trials (RCTs), whose design limitations make it difficult to generalize findings to population at large uncontrolled settings. The present study was planned to be as retrospective cohort analysis of RWD of Indian T2DM patients from routine clinical settings to further characterize the clinical effectiveness and safety profile.

Methodology

This multi-centric retrospective cohort analysis was planned with data retrieved from medical records of patients treated in routine practice with remogliflozin regimens at multiple centres across India. The study protocol was approved by the Independent Ethics Committee. The study conduct was in compliance with study protocol, the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines E6 (R2), the Indian Council of Medical Research (ICMR), the National Ethical Guidelines for Biomedical and Health Research Involving Human Participant (2017), and applicable regulations. The data for this study was retrieved from medical records collected from 1578 sites from all over India between October 2019 and March 2020.

At each study centre, the medical records of adult (≥ 18 years) patients of either gender were screened for fresh initiation of remogliflozin for the management of T2DM as per routine practice and had completed 3-month follow-up after initiation of remogliflozin. A maximum of up to first 20 patients at each study centre were considered for analysis.

The day of initiation of remogliflozin was considered to be the index date (day 0, baseline). The assessment day was considered 3 months from the index date (day 90, follow-up). The investigators retrieved the available clinical data from the medical records of eligible patients treated at the respective centres and captured in de-identified manner in the case report forms (CRFs). The following data was planned for retrieval designed on day 0: baseline demographics (age, gender, height, BMI, duration of DM, family history of DM, co-morbid conditions, and concomitant medications). The data planned for retrieval on both day 0 and day 90 included body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), serum creatinine, urine albumin-to-creatinine ratio (UACR), serum uric acid, and serum electrolytes (Na, K, Cl, Ca). The incident adverse events reported in medical records were to be captured for the entire observation period of 3 months from day 0.

The study intended to assess the effectiveness as well as the safety of remogliflozin in the real-world setting. The endpoints considered for assessment of clinical effectiveness included mean change from baseline to 3-month follow-up in HbA1c, FPG, and PPG levels for glycemic parameters. The mean change from baseline at 3 months in total body weight, BMI, SBP, and DBP was assessed in non-glycemic parameters from the available real-world data. Safety assessment included the incidence of adverse events in terms of symptoms and signs as transcribed from medical records. The safety assessment also included assessment of renal function, viz., eGFR, serum creatinine, serum uric acid, UACR, and serum electrolytes as available in the medical records. Further subgroup analyses were planned on the basis of baseline HbA1c and baseline BMI. The endpoints assessed in the subgroups included glycemic parameters (HbA1c, FPG, PPG) and body weight.

Statistical analysis

The CRFs, with data transcribed from medical records as available, from all centres were pooled together. Only CRFs with non-missing essential demographic characteristics (age, gender, weight, height) and availability of baseline and follow-up measurements of any one of 3 glycemic parameters were selected for data analysis. All statistical analyses were done using the software STATA. All characteristics were summarized descriptively. For continuous variables, data were represented using means ± SD. For categorical data, the number and percentage were used in the data summaries. The intragroup change from baseline was tested by paired *t*-test. For intragroup assessment, medical records wherein both the baseline and 3-month measurements for corresponding parameter were available were considered. For subgroup analysis, only patients' records with baseline and follow-up assessment available for all the parameters to be assessed were considered. All *p* values were two-tailed, and the values were considered statistically significant if $p < 0.05$.

Results

A total of 5452 eligible patient's data were analysed in this study. The mean age at diagnosis was 54.9 ± 10.27 years, with male predominance (61.4%). At the time of presentation, 61.5% of patients had positive family history of diabetes (FHD), and the average duration of diabetes was found to be 6.2 ± 4.29 years. Out of total 5452 patients, approximately 64.5% of patients were presented with co-morbid conditions at diagnosis. Hypertension (54.9%) and dyslipidemia (46.2%)

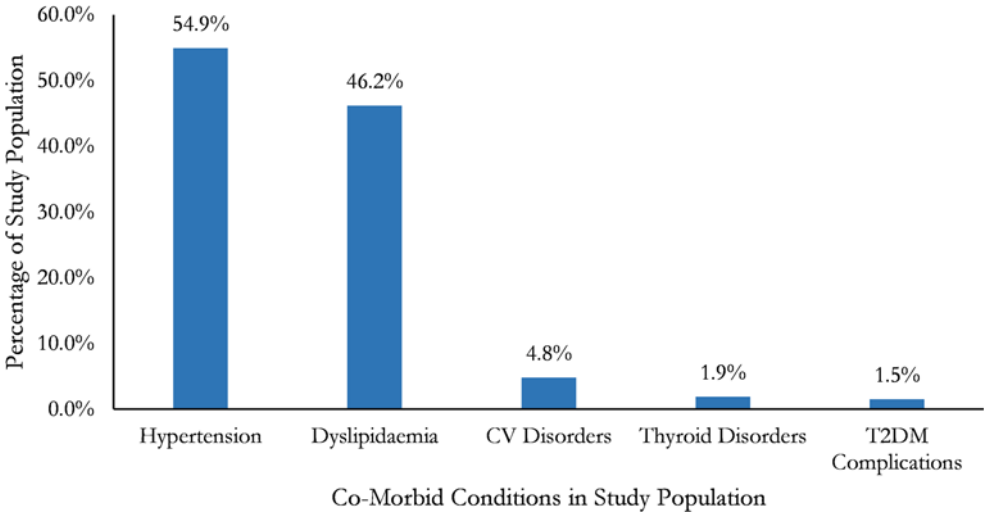

Fig. 1 Prevalence of comorbid conditions in total population. **Legend:** N=5452; CV=Cardiovascular; T2DM=Type 2 diabetes mellitus

were the most frequently observed co-morbid diseases among all patients (Fig. 1).

In the present study, more than half of the patients (55%) were on two concomitant oral anti-diabetic drugs (OADs), followed by 27.4% and 16.7% of patients on one and > 2 concomitant OADs, respectively, along with remogliflozin treatment. The most common concomitant regimen was metformin plus sulfonyl urea combination (33.8%). Figure 2 presents the summary statistics of concomitant OADs along with remogliflozin treatment. Approximately 55% of patients were on concomitant medication other than anti-diabetic drugs (ADDs), which are most common as being anti-hypertensive (59%) agents.

The mean baseline characteristics of the patients in terms of HbA1c levels, FPG, and PPG presentation were found to be 8.6 ± 1.04%, 181.4 ± 36.29 mg/dL, and 257.7 ± 59.56 mg/dL, respectively. The average body weight and BMI were noticed to be 74.6 kg and 28.3 kg/m^2 at diagnosis. Table 1 describes the baseline characteristics of the study participants.

Effect of remogliflozin on glycemic parameters

The mean change from baseline in HbA1c levels at 3 months was − 0.95% (Fig. 3) which was found to be statistically significant ($p < 0.05$). The mean reduction in FPG level from baseline level of 181.4 mg/dL was − 42.4 mg/dL, while the mean reduction in PPG from baseline of 257.7 mg/dL was − 69.1 mg/dL at the 3-month follow-up ($p < 0.05$ for both) (Fig. 4). The changes in glycemic parameters from baseline to follow-up are shown in Table 2.

The mean body weight reduced by 2.6 kg from 74.4 to 71.8 kg in 3 months, with a mean change of – 1 kg/m^2 in BMI. As > 50% of patients were on concomitant anti-hypertensive medications, the change in blood pressure was assessed only in the patients who had normal BP at baseline and were not receiving any BP-altering medications. The reduction in systolic and diastolic BP from baseline to 3-month follow-up was − 3.3 mmHg and − 2.3 mmHg.

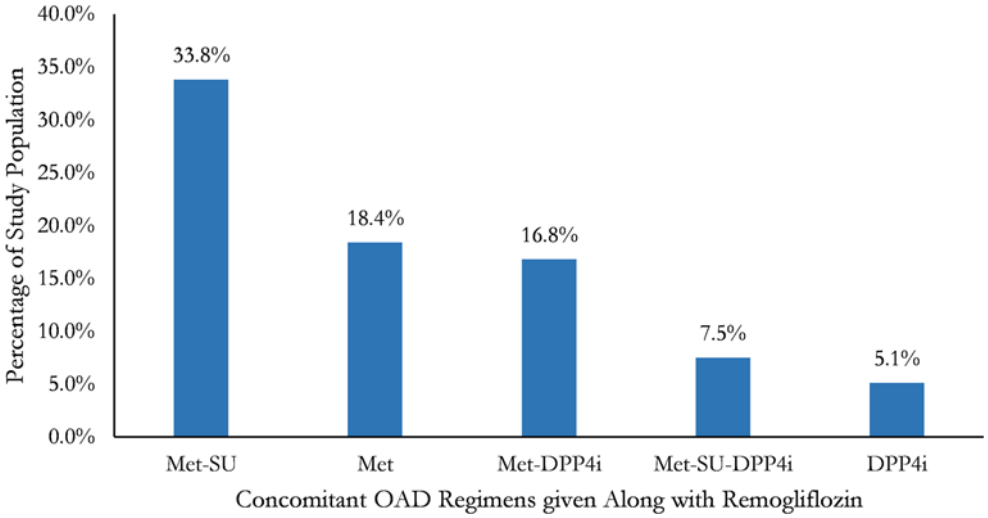

Fig. 2 Proportion of OAD regimens concomitantly administered with remogliflozin. **Legend:** DPP4i - Dipeptidyl Peptidase-4 inhibitor; Met – Metformin; SU – Sulfonyl Urea

Table 1 Baseline characteristics of the study population

Baseline characteristics		*N* = 5452
Age (years)		54.9 ± 10.27
Gender (*n*, %)	Males	3350 (61.4%)
	Females	2102 (38.6%)
Duration of T2DM (years)[1]		6.2 ± 4.29
Family history of T2DM[2] (*n*, %)		2913 (61.5%)
Height (cms)		162.7 ± 9.54
Weight (kg)		74.6 ± 9.77
BMI (kg/m^2)		28.3 ± 4.67
HbA1c (%)[3]		8.6 ± 1.04
FPG (mg/dL)[4]		181.4 ± 36.29
PPG (mg/dL)[5]		257.7 ± 59.56
Co-morbid conditions (> 2%) (n, %)		***3518 (64.5%), N (%)***
Hypertension^		2993 (54.9)
Dyslipidaemia^		2520 (46.2)
Cardiovascular disorders^		265 (4.8)
Concomitant medications (n, %)		
One concomitant OAD		1495 (27.4)
*Metformin^*		*1007(67.4)*
*DPP4i^*		*276 (18.5)*
Two concomitant OADs		3000 (55.0)
*Met+SU^*		*1846 (61.5)*
*Met+DPP4i^*		*915 (30.5)*
More than 2 concomitant OADs		914 (16.7)
*Met+SU+DPP4i^*		*409 (44.7)*
*Met+SU+AGI^*		*269 (29.4)*

[1] *n* = 5069; [2] *n* = 4734; [3] *n* = 5358; [4] *n* = 4785; [5] *n* = 4962

All values are mean ± SD unless specified otherwise

^The proportion on subitems derived considering the total n from the parent list item

AGI, α-glucosidase inhibitor; *BMI*, body mass index; *DPP4i*, dipeptidyl peptidase-4 inhibitor; *FPG*, fasting plasma glucose; *HbA1c*, glycated haemoglobin; *Met*, metformin; *SU*, sulfonyl urea; *TZD*, thiazolidinedione; *T2DM*, type 2 diabetes mellitus; *PPG*, postprandial plasma glucose; *OAD*, oral anti-diabetic drug

Assessment of non-glycemic parameters

The change in all non-glycemic parameters was statistically significant. Non-glycemic parameters have been exploratorily analysed as they are available pre- and postdata assessment. The changes in non-glycemic parameters from baseline to follow-up are shown in Table 2 and Figs. 5, 6, and 7.

Subgroup analysis

The subgroup analysis was conducted on the basis of baseline levels of HbA1c and BMI, as per availability of parameter at baseline and follow-up. Accordingly, 4445 patients were divided into 3 subgroups of < 8.5%, 8.5–10%, and > 10% as per baseline HbA1c, and 4145 patients were divided into 3 subgroups of < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2 as per baseline BMI.

Subgroup analysis as per baseline HbA1c

To evaluate the effects of remogliflozin treatment, patients were classified into 3 subgroups on baseline HbA1c levels. At baseline, 2162 patients had HbA1c < 8.5%, 1957 patients had HbA1c 8.5–10%, and 326 patients had HbA1c > 10%. Baseline demographic characteristics of the patients at baseline HbA1c are given in Table 3. With remogliflozin treatment, patients across the 3 baseline subgroups had significant reduction in HbA1c, FPG, PPG, and body weight from baseline to follow-up. The change in HbA1c showed proportional reduction as per baseline HbA1c. The same trend was observed with FPG, PPG, and weight loss. Larger HbA1c reductions (− 1.76%) were seen among patients with higher baseline HbA1c (> 10%) (Figs. 8, 9, and 10).

Subgroup analysis as per baseline BMI

In the overall sample, at baseline, 945 patients had BMI < 25 kg/m^2, 1961 had BMI 25–30 kg/m^2, and 1239 patients had BMI > 30 kg/m^2. Demographic characteristics of the patients at baseline BMI are described in Table 4. With the use of remogliflozin, the subgroups of BMI at baseline had significant reduction in HbA1c, FPG, PPG levels, and body weight from baseline to 3-month follow-up. The greater reduction in body weight was observed in patients with higher baseline BMI. The reduction of 2.0 kg and 3.3 kg in body weight was seen in subgroup of BMI 25–30 kg/m^2 and BMI > 30, respectively (Figs. 11, 12, and 13).

Non-glycemic parameters have been observed in low set of study population where data was available. Hence, this data is not representative of study to be considered.

Safety assessment of remogliflozin treatment

The reporting in safety section of the CRFs was observed to be low (437 CRFs), and hence, only these were considered for safety analysis. Of the 437 records, 25.9% (113) patients reported total of 136 events. Table 5 shows the incidences of adverse events with remogliflozin-based regimens. Genitourinary tract infections (GTIs) (12.5%) were most frequent AE associate with the use of remogliflozin.

The mean eGFR of 83.8 mL/min at baseline decreased by − 1.8 mL/min at 3 months, while serum creatinine decreased by − 0.07 mg/dL ($p > 0.05$ for both; Table 6). The serum uric acid and UACR showed statistically significant change from baseline of − 0.35 mg/dL and − 6.1 mg/g, respectively, at 3 months. The changes in serum sodium, potassium, chloride,

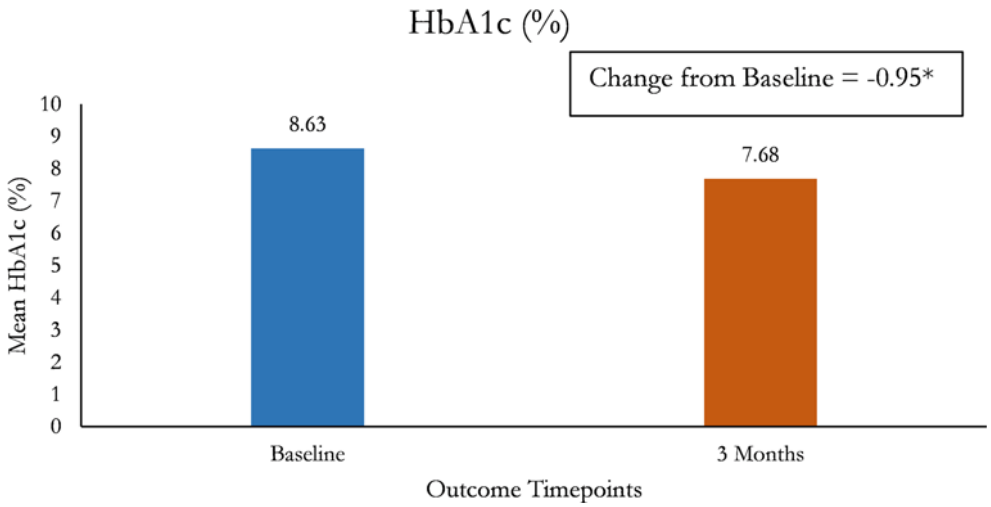

Fig. 3 Change in glycemic parameters (HbA1c). **Legend:** N=5358; HbA1c = glycosylated haemoglobin; * = P<0.05, statistically significant

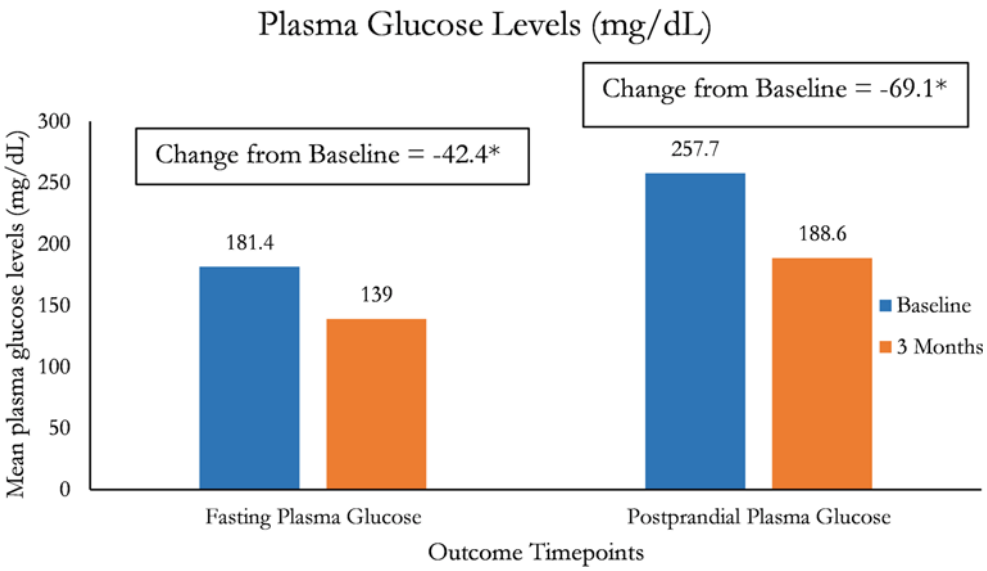

Fig. 4 Change in glycemic parameters (FPG and PPG). **Legend:** Change from baseline in Mean FPG levels, (N=4785); PPG (N=4962), FPG =Fasting Plasma Glucose; PPG=Postprandial Plasma Glucose; * = P<0.05, statistically significant

Table 2 Change in glycemic parameters and non-glycemic parameters

Parameters	*N*	Baseline	Follow-up (3 months)	Mean change from baseline
Glycemic parameters				
HbA1C (%)	5358	8.6 ± 1.04	7.68 ± 0.84	− 0.95*
FPG (mg/dL)	4785	181.4 ± 36.29	139 ± 27.15	− 42.4*
PPG (mg/dL)	4962	257.7 ± 59.56	188.6 ± 42.03	− 69.1*
Non-glycemic parameters				
Body weight (kg)	5241	74.6 ± 9.77	71.8 ± 9.51	− 2.6*
BMI (kg/m^2)	5241	28.3 ± 4.67	27.3 ± 4.53	− 1.0*
SBP (mmHg)	1886	126.9 ± 6.92	123.6 ± 7.54	− 3.3*
DBP (mmHg)	1886	82.4 ± 7.10	80.1 ± 7.29	− 2.3*

All values are mean ± SD unless specified otherwise; *statistically significant, $p < 0.05$; *BMI*, body mass index; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *HbA1c*, glycated haemoglobin; *PPG*, postprandial plasma glucose; *SBP*, systolic blood pressure

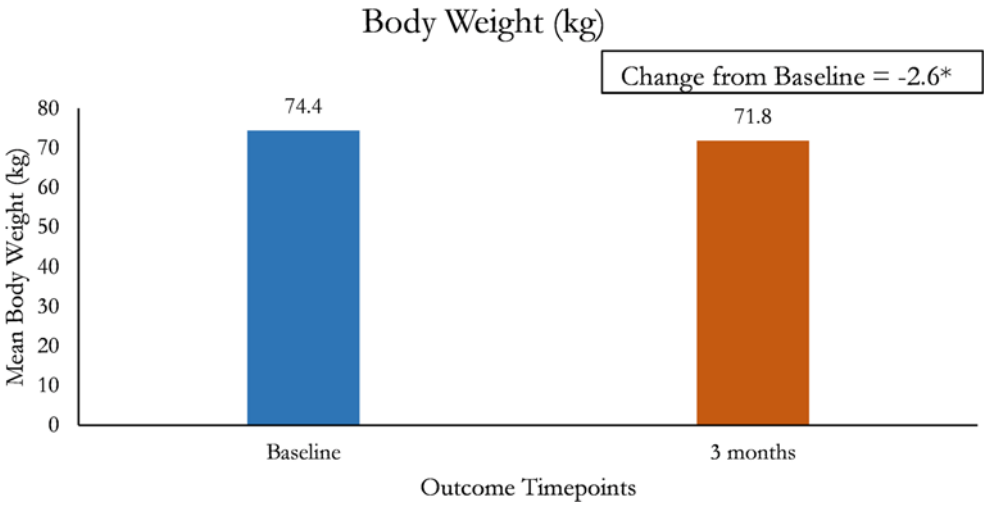

Fig. 5 Change in non-glycemic parameters (body weight). Legend: change from baseline in mean body weight values ($N = 5241$); *$p < 0.05$, statistically significant

and calcium from baseline to 3 months were − 1.7 mEq/L, − 0.1 mEq/L, 1 mEq/L, and − 0.1 md/L, respectively.

Discussion

The intensification of treatment of T2DM patients with addition of one or more ADDs for adequate glycemic control in routine practice is a well-established fact. This current analysis planned to assess the real-world effectiveness and safety of remogliflozin demonstrated significant reduction in glycemic (HbA1c, FPG, PPG) parameters after 3 months of treatment but also good safety and tolerability profile with remogliflozin-based anti-diabetic regimens.

The baseline demographics, comorbidities, and anti-diabetic therapy observed in the study population were comparable to epidemiology of T2DM patients and prescriptions practices in India. The age, BMI, and gender distribution in study population were similar to that reported by Singla et al. [8]. Though occurrence of comorbidities observed in study population was similar as reported by Iglay et al. [9], the incidence rate was lower. This could plausibly be due to reporting bias in retrospective data collection. It could also be due to use in low co-morbid patients on account of its recent launch and no experience with remogliflozin in treating physicians. The popular choice of metformin and sulfonylureas utilization as evident in Indian practice [8, 10] was also observed in the current study.

A significant decrease in HbA1c (− 0.95%, $p < 0.001$) was noticed after 3 months of treatment with remogliflozin added to ongoing background anti-diabetic therapy in uncontrolled settings of routine clinical practice. A real-world assessment in an uncontrolled clinical setting, resembling the current study, was conducted by Viswanathan et al. [11], Chakravorty et al. [12], and Munk et al. [13] to investigate the effectiveness of dapagliflozin, canagliflozin, and empagliflozin, respectively. The FOREFRONT study [11] by Viswanathan et al. reported a significant reduction of − 1% in HbA1c after 3 months of treatment with add-on Dapagliflozin to ongoing therapy. Similarly, Chakravorty et al. [12] have reported reduction of − 0.9% in HbA1c with

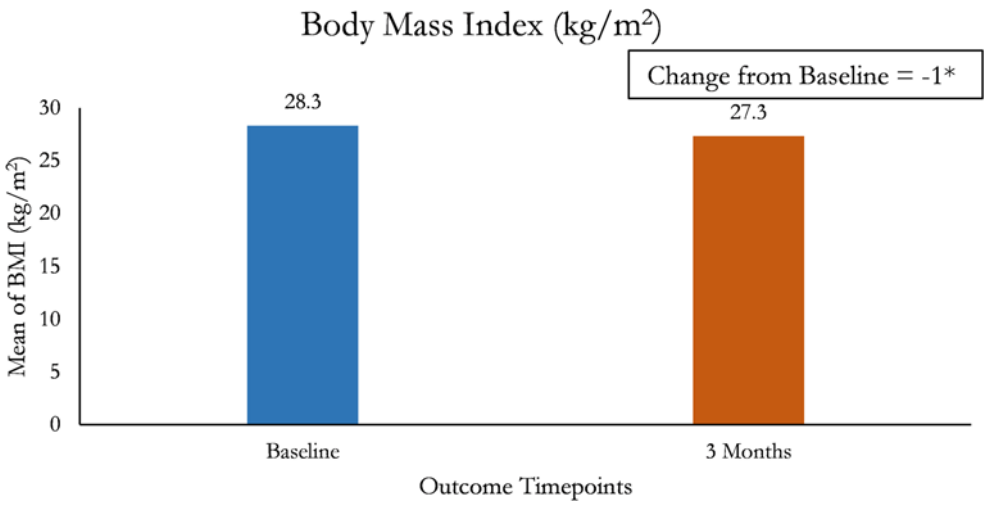

Fig. 6 Change in non-glycemic parameters (BMI). Legend: change from baseline in mean body mass index ($N = 5241$); *$p < 0.05$, statistically significant

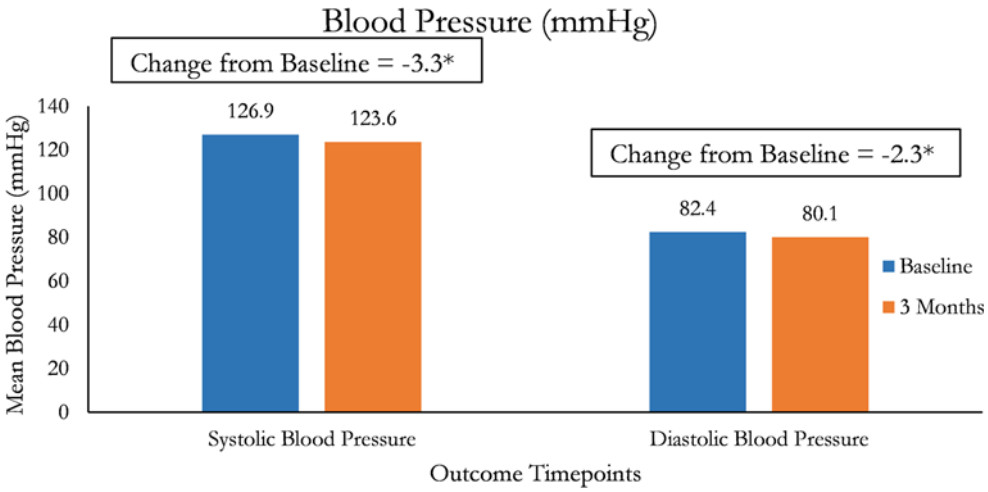

Fig. 7 Change in non-glycemic parameters (blood pressure). Legend: change from baseline in mean SBP and DBP ($N = 1886$). SBP, systolic blood pressure; DBP, diastolic blood pressure; *$p < 0.05$, statistically significant

Table 3 Baseline glycemic and metabolic characteristics of the patients in subgroups as baseline HbA1c

HbA1c subgroups	< 8.5%	8.5–10%	> 10%
N	2162	1957	326
HbA1c (%)	7.86 ± 0.39	9.11 ± 0.47	10.9 ± 0.74
Weight (kg)	73.6 ± 9.49	74.9 ± 9.48	77.5 ± 10.53
BMI (kg/m^2)	27.9 ± 4.33	28.4 ± 4.55	29.8 ± 5.18
FPG (mg/dL)	168.5 ± 29.28	186.7 ± 33.81	213.3 ± 39.87
PPG (mg/dL)	239.7 ± 54.31	272.8 ± 53.49	314.9 ± 50.40

All values are mean ± SD unless specified otherwise; *BMI*, body mass index; *FPG*, fasting plasma glucose; *HbA1c*, glycated haemoglobin; *PPG*, postprandial plasma glucose

canagliflozin, and Munk et al. [13] have reported reduction of − 0.91% in HbA1c with empagliflozin after 3 months of treatment when added on to existing therapy of patients. A real-world assessment of SGLT2i as add-on therapy that included both empagliflozin and dapagliflozin by Hong et al. [14] also reported − 0.94% reduction in HbA1c at 12 weeks. The results in the current study are in good agreement with these reports on other SGLT2i suggestive of similar glycemic reduction with remogliflozin as compared to other SGLT2i in routine practice. The phase III study of RE observed − 0.49% and − 0.72% reduction in HbA1c at 12 and 24 weeks in patients uncontrolled on metformin monotherapy [7], whereas the phase II study of RE observed change from baseline of − 0.96% in HbA1c at 12 weeks in drug naïve T2DM patients [15].

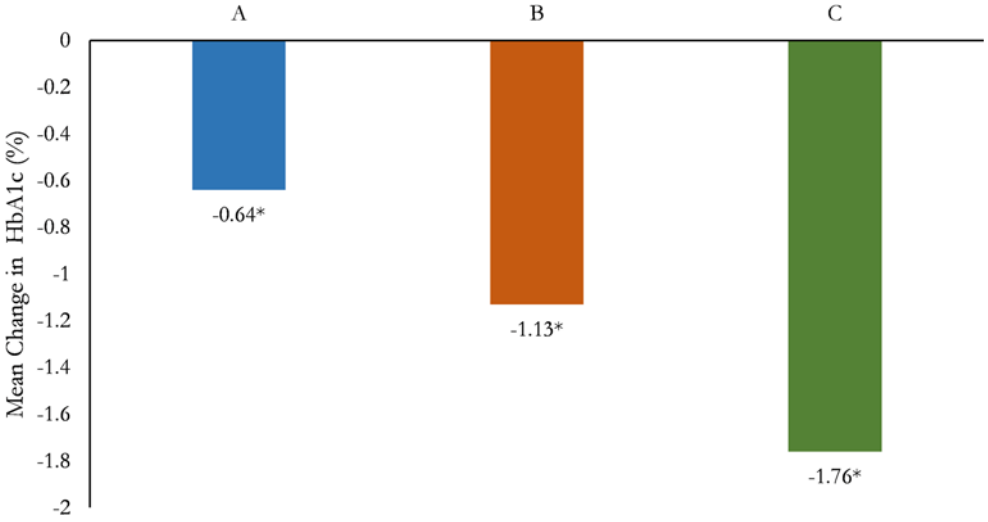

Fig. 8 Change in mean HbA1c levels in subgroups based on baseline HbA1c levels. Legend: Change from baseline in Mean HbA1c levels. ***A***= Subgroup with baseline HbA1c <8.5%, (N=2162); ***B***= Subgroup with baseline HbA1c 8.5-10%, (N = 1957); ***C***= Subgroup with baseline HbA1c >10%, (N = 326); HbA1c = Glycosylated Haemoglobin; * = P<0.05, statistically significant

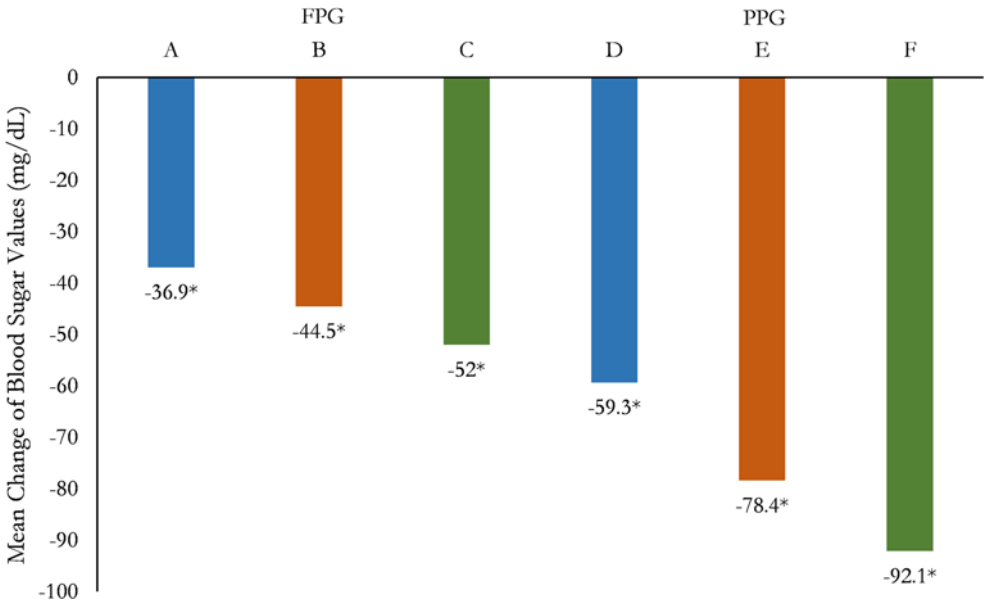

Fig. 9 Change in mean plasma glucose levels in subgroups based on baseline HbA1c levels. **Legend**: Change from baseline in FPG & PPG levels. ***A,D***= Subgroup with baseline HbA1c <8.5%, (N= 2162); ***B,E***=Subgroup with baseline HbA1c 8.5-10%, (N = 1957); ***C,F***=Subgroup with baseline HbA1c >10%, (N = 326); FPG = Fasting Plasma Glucose; PPG = Postprandial Plasma Glucose; HbA1C = Glycosylated Haemoglobin; * = P<0.05, statistically significant.

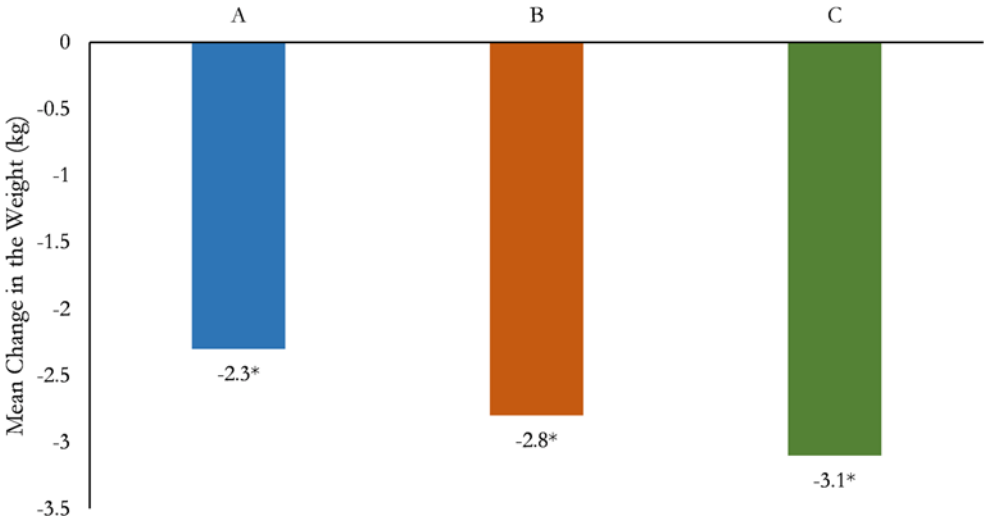

Fig. 10 Change in mean body weight in subgroups based on baseline HbA1c levels. **Legend:** Change from baseline in Mean Body weight values. ***A***= Subgroup with baseline HbA1c <8.5%, (N=2162); ***B***= Subgroup with baseline HbA1c 8.5-10%, (N = 1957); ***C***= Subgroup with baseline HbA1c >10%, (N = 326); HbA1c = Glycosylated Haemoglobin;* = P<0.05, statistically significant

The mean change in FPG and PPG levels was − 42.4 mg/dL and − 69.1 mg/dL, respectively, at 3-month postbaseline. A real-world assessment of SGLT2i (including empagliflozin and dapagliflozin) by Hong et al. [14] observed − 30.3 mg/dL reduction in FPG at 3 months. A retrospective analysis of canagliflozin add-on to teneligliptin reported FPG reduction of − 27.3 mg/dL at 3 months [16]. Though reports of PPG reduction with SGLT2i in the real-world setting are

Table 4 Baseline glycemic and metabolic characteristics of the patients in subgroups as baseline BMI

BMI subgroups	< 25 kg/m^2	25–30 kg/m^2	> 30 kg/m^2
N	945	1961	1239
BMI (kg/m^2)	22.9 ± 1.54	27.5 ± 1.39	33.5 ± 3.67
Weight (kg)	65.4 ± 5.77	73.7 ± 7.36	82.2 ± 8.72
HbA1c (%)	8.4 ± 0.91	8.6 ± 0.98	8.8 ± 1.01
FPG (mg/dL)	174.8 ± 31.44	181.1 ± 34.96	182.0 ± 35.89
PPG (mg/dL)	255.2 ± 54.35	259.2 ± 56.94	262.1 ± 61.30

All values are mean ± SD unless specified otherwise; *BMI*, body mass index; *FPG*, fasting plasma glucose; *HbA1c*, glycated haemoglobin; *PPG*, postprandial plasma glucose

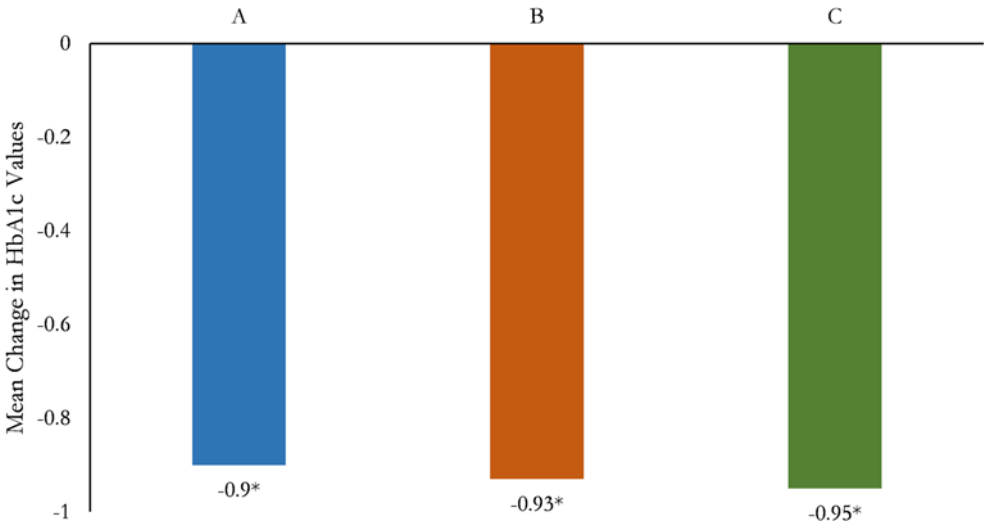

Fig. 11 Change in mean of HbA1c in subgroups based on baseline BMI values. **Legend:** Change from baseline in Mean HbA1c levels. ***A***= Subgroup with baseline BMI < 25, (N=945); ***B***= Subgroup with baseline BMI 25-30, (N = 1961); ***C***= Subgroup with baseline BMI >30, (N = 1239); * = P<0.05, statistically significant

limited, Chakravorty et al. [12] have observed − 53.6 mg/dL reduction in PPG after 3 months of add-on therapy with canagliflozin. The results are in good agreement with study results, and the marginal variance can be attributed to labile nature of plasma glucose levels.

The body weight and BMI reduction observed after 3-month follow-up was − 2.6 kg and – 1 kg/m^2, respectively. The weight reduction observed at 3 months of add-on SGLT2i therapy ranged from 1.4 to 2.2 kg [12, 17]. However, a study performed by Sykes et al. [15] demonstrated reduction in bodyweight, ranging from 1.36 to 3.51 kg at week 12 in patients receiving RE. A meta-analysis of 34 randomized clinical trials with 9154 patients showed that SGLT2i including canagliflozin, dapagliflozin, and empagliflozin were associated with a loss of body weight within a range of − 2.0 to − .2.3 kg [18]. Similarly, the BMI reduction at 3 months after initiation of SGLT2i ranged from 0.5 to 2.7 kg/m^2 in real-world studies [12, 19]. The results observed in study are comparable to reported reductions with other SGLT2i.

The reduction in systolic and diastolic BP from baseline to 3-month follow-up was − 3.3 mmHg and − 2.3 mmHg, respectively. Limited studies [14, 17, 19] have evaluated effect of SGLT2i on blood pressure in the real-world setting; these reported SBP reduction ranging from − 2.2 to − 4.7 mmHg, while DBP reduction ranges from − 1.3 to − 1.5 mmHg after 3-month therapy. A systemic review effect of SGLT2i on BP by Storgaard et al. [18] has estimated SBP and DBP reduction of − 3.9 mmHg and − 2.0 mmHg. The BP reduction observed in the current study is similar to BP reduction observed in phase III study of remogliflozin [7] in line with reductions observed with the use of SGLT2i.

A systematic review which included data from sixty-eight randomized controlled trials showed that addition of SGLT2i to other OADs resulted a significant impact on the reduction

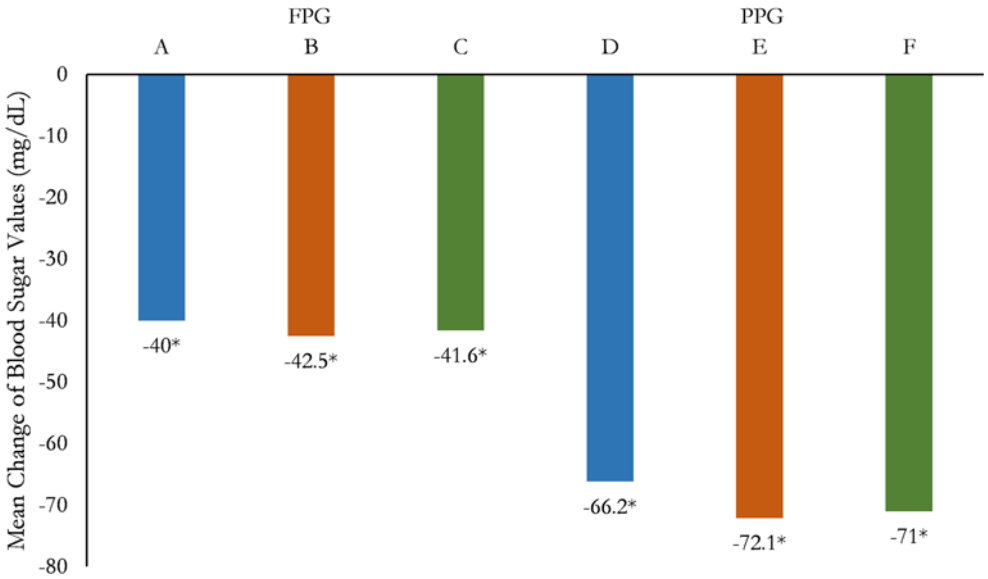

Fig. 12 Change in Mean of FPG and PPG in subgroups based on baseline BMI values. **Legend:** Change from baseline in Mean FPG and PPG levels. ***A,D***= Subgroup with baseline BMI < 25, (N=945); ***B,E***= Subgroup with baseline BMI 25-30, (N = 1961); ***C,F*** = Subgroup with baseline BMI >30, (N = 1239); FPG = Fasting Plasma Glucose; PPG = Postprandial Plasma Glucose; * = P<0.05, statistically significant

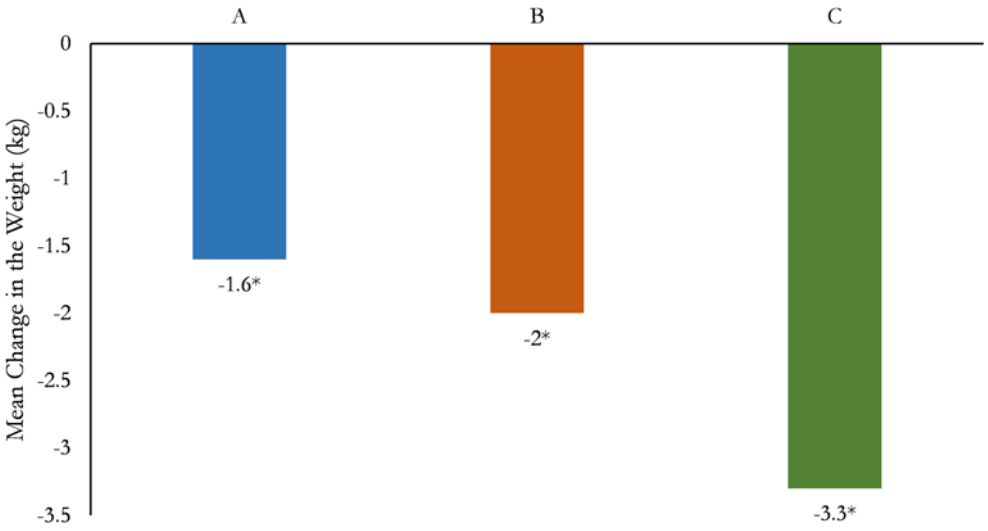

Fig. 13 Change in mean of weight from in subgroups based on baseline BMI values. **Legend:** Change from baseline in Mean Body Weight values. ***A***= Subgroup with baseline BMI < 25, (N=945); ***B***= Subgroup with baseline BMI 25-30, (N = 1961); ***C***= Subgroup with baseline BMI >30, (N = 1239); * = P<0.05, statistically significant

of HbA1c levels, weight loss, and blood pressure [20]. In the subgroup analysis, which was based on baseline HbA1c and BMI, patients treated with RE demonstrated to have clinically relevant and statistically significant reductions in HbA1c, body weight, FPG, PPG, and systolic and diastolic BP regardless of baseline HbA1c and BMI. Larger HbA1c reductions were seen among patients with higher baseline HbA1c. These findings were consistent with observations from various clinical trials of other SGLTs inhibitors [21–23]. Similarly, the reduction in body weight was greater in patients with higher baseline BMI which too has been observed in various trials with SGLT2i [24]

Administration of remogliflozin as add-on therapy was well-tolerated in patients with T2DM. Though present study had a limitation of low safety reporting, the observed incidence rate of treatment emergent adverse event (TEAE) of 25.9% was in agreement with TEAE of 32.6% observed in phase III study with remogliflozin 100 mg BID [7]. The most common AE was genito-urinary tract infections (12.6%) which is cumulative incidence of UTI and GTIs. These have been cumulatively reported due to inability of specific classification on account of non-standardized reporting. The pattern and incidence of adverse events observed in the study are in accordance to known safety profile of SGLT2 inhibitors [25, 26].

The reduction of − 1.8 mL/min in eGFR and − 0.07 mg/dL in serum creatinine was found to be statistically significant in the current study. The reduction in eGFR after initiation of SGLT2i is a known phenomenon, with a biphasic pattern of initial and transient dip over the first 2 weeks followed by recovery to baseline and stabilization during the subsequent months [27]. Hong et al. observed similar reduction of − 1.9 mL/min at 12 weeks in the real-world assessment of SGLT2i therapy [14]. Hence, reduction observed in the current study probably coincides with recovery phase of eGFR as was also observed in phase III study of RE [7]. This could plausibly explain low serum creatinine whose quantum of change can be reasonably considered to be clinically insignificant.

Table 5 Reported incidences of adverse events (> 1%)

Adverse event	*N* = 437	Percentage
Genito-urinary tract infections*	55	12.6%
Acidity	13	2.6%
Body pain/cramps	11	2.5%
Bowel disturbances	9	2.0%
Vomiting	7	1.6%
Giddiness/fatigue	5	1.1%
Others	36	5.4%

*Includes cumulative incidence of GTI and UTI

Conclusion

Remogliflozin etabonate in the real-world setting was found to be an effective agent for improvement of glycemic parameters when used as add-on therapy in the management of Indian T2DM patients, without any new safety concerns. The effectiveness and safety profile are similar to profile observed with other SGLT2i. The results were in accordance to earlier conducted developmental studies with RE.

Limitations of the study

Our findings of the study need to be interpreted within the limitations of this study. The study did not control for modification in background therapy; thereby, the reduction observed needs to be attributed to collective efficacy of

Table 6 Change in renal laboratory parameters and serum electrolyte

Parameters	*N*	Baseline	Follow-up (3 months)	Mean change from baseline
Renal parameters				
eGFR (mL/min)	533	83.8 ± 21.05	82 ± 19.07	− 1.8*
Sr creatinine	627	1.03 ± 0.26	0.96 ± 0.23	− 0.07*
Sr uric acid	698	5.55 ± 1.47	5.2 ± 1.24	− 0.35
UACR	209	19.8 ± 68.12	13.7 ± 34.22	− 6.1
Sr electrolyte concentrations				
Sr sodium	505	139.5 ± 4.36	137.8 ± 3.97	− 1.7
Sr potassium	492	4.1 ± 0.43	4 ± 0.41	− 0.1
Sr calcium	324	9.2 ± 0.51	9.1 ± 0.53	− 0.1
Sr chloride	302	100.9 ± 3.59	101.9 ± 4.18	1

All values are mean ± SD unless specified otherwise; *statistically significant, $p < 0.05$; *eGFR*, estimated glomerular filtration rate; *Sr*, serum; *UACR*, urine albumin to creatinine ratio

remogliflozin and concomitant changes in therapy, if any. The reporting and diagnoses of comorbidities were not validated; therefore, prevalence may have been underestimated. The laboratory data was limited only to patients in whom they were performed and reported, in CRFs, with the possibility of reporting biases. Other limitations include lack of electronic medical records and limited inclusion criteria. Our study results are real-world observations with no parameter being attributed to study drug, and the requirement of well-controlled clinical studies for confirmation of observed trends is necessary.

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Code availability Not applicable

Author contribution All authors contributed to the study conception and design. Dr Sagar Katare, Dr Sachin Suryawanshi, and Dr Hanmant Barkat were involved in study conduct, analysis, study report preparation, manuscript preparation, and review. Dr Bipin Sethi, Dr Subhankar Chowdhury, and Dr Supratik Bhattacharya were involved in study report review and manuscript review. All authors read and approved the final manuscript.

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Data availability Confidentiality of the patient's data was maintained during data handling.

Declarations

Ethics approval This is an observational study. The study conduct was approved by an Independent Ethics Committee.

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