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ORIGINAL RESEARCH

Real-World Effectiveness and Safety of Imeglimin in Type 2 Diabetes: Prospective Multi-Center Study in Bangladesh

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Background: This study assessed the real-world effectiveness and safety of imeglimin among Bangladeshi patients with type 2 diabetes mellitus (T2DM).

Methods: This prospective, multi-center observational study was conducted across 15 specialized diabetes care centers in Bangladesh from January 2024 to December 2024. Adults with uncontrolled T2DM (HbA1c >7%) prescribed imeglimin (500–2000 mg daily) either as monotherapy or combination therapy were enrolled. A total of 898 subjects were assessed at baseline, 3 months, and 6 months. Primary outcomes were changes in HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPPG). Secondary outcomes included body mass index (BMI), blood pressure, lipids, and safety parameters.

Results: The mean age was 46.2 ± 13.1 (SD) years, with 67% being female. Baseline HbA1c decreased from 9.2±1.4% to 7.1±1.0% at 6 months (mean change: −2.1%, p<0.001). FPG reduced from 9.37±2.53 to 7.28±4.63 mmol/L (p<0.001) and PPPG from 14.36±3.29 to 8.95±1.76 mmol/L (p<0.001). BMI decreased from 28.1±4.2 to 25.6±3.6 kg/m^2 (p<0.001). Significant improvements occurred in blood pressure, lipids, and renal parameters. Adverse events were mild; 3.6% reported ≥1 event (gastrointestinal 2.4%, dehydration 1.3%). No serious adverse events occurred.

Conclusion: Imeglimin demonstrated substantial glycemic improvements and favorable safety in real-world Bangladeshi patients with poor glycemic control.

Keywords: type 2 diabetes mellitus, imeglimin, glycemic control, real-world effectiveness, Bangladesh

Introduction

T2DM is a chronic metabolic disorder characterized by persistent hyperglycemia due to insulin resistance, impaired insulin secretion or both. It is a leading cause of mortality worldwide, primarily through micro- and macrovascular complications.[1,2] Achieving early optimal glycemic control is essential to prevent complications and reduce morbidity and mortality;[3] hence, current management focuses on individualized lifestyle and pharmacologic strategies for targeted glycemic control.

Imeglimin, an oral anti-hyperglycemic agent, has emerged as a promising treatment option for T2DM because of its novel mechanism of action in targeting mitochondrial bioenergetics.[4] According to the American Diabetes Association (ADA) recommended Standards of Care in Diabetes—2025, diabetes should be managed through a patient-centered approach. Pharmacologic therapy, including glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose cotransporter-2 (SGLT-2) inhibitors, should be individualized on the basis of the presence of comorbidities.[5]

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Metformin remains a widely used first-line pharmacotherapeutic agent because of its efficacy, safety profile, and cost-effectiveness.[6] Other commonly used medications for diabetes management, including dipeptidyl peptidase-4 (DPP-4) inhibitors and secretagogues, usually improve insulin secretory capacity.[7–9] However, these drugs do not directly address the underlying mitochondrial dysfunction, which is a key contributor to the disease and associated complications. In this context, imeglimin offers a novel mechanism of action distinct from that of existing antihyperglycemic drugs.[10]

The underlying mechanism of inadequate glycemic control in T2DM patients involves the progressive failure of pancreatic β-cells to compensate for insulin resistance and increased insulin secretion, along with the lack of treatments that provide sustained effects.[11] Imeglimin targets these pathophysiological processes by reducing reactive oxygen species production, improving mitochondrial function and integrity, enhancing the structure and function of the endoplasmic reticulum, and promoting glucose-stimulated insulin secretion while inhibiting β-aapoptosis, thereby preserving β-cell mass. Additionally, imeglimin inhibits hepatic glucose production and improves insulin sensitivity,[12] thus contributing to improved glycemic control in patients with T2DM.

Several clinical trials aimed at evaluating the role of imeglimin in the management of T2DM have been conducted and reported excellent efficacy and safety.[4,13–19] The TIMES 1 trial, a double-blind, placebo-controlled study over 24 weeks, revealed that, compared with placebo, imeglimin significantly reduced glycosylated hemoglobin (HbA1c) by 0.87%, with a comparable safety profile.[14] The TIMES 2 trial, an open-label study over 52 weeks, reported HbA1c reductions ranging from 0.46% to 0.92%, depending on the treatment combination, with most adverse events being mild or moderate.[15] The TIMES 3 trial, a double-blind study over 52 weeks in patients on insulin therapy, demonstrated a 0.64% reduction in HbA1c with imeglimin, with very few hypoglycemic events in the imeglimin group.[19] A subsequent Phase 4 trial in Japan confirmed imeglimin's glucose-lowering effects along with favorable effects on body weight and serum lipids in a real-world setting.[20]

The therapeutic goal for HbA1c is generally individualized, with most guidelines recommending a target of 6.5–7.0%, depending on factors such as age, comorbidities, and the risk of hypoglycemia.[21] Achieving optimal glycemic control remains a significant challenge, which is even more pronounced in resource-limiting countries such as Bangladesh, where approximately 68% of patients with diabetes have poor glycemic control, with an HbA1c >7%.[22]

The action of each antihyperglycemic drug may vary across different populations due to genetic, environmental, and lifestyle factors.[23] South Asian patients, including Bangladeshis, develop T2DM at younger ages and lower BMI.[24,25] Due to high carbohydrate consumption, these populations exhibit pronounced insulin resistance alongside rapid β-cell failure- phenotypes where imeglimin's dual mitochondrial targeting may yield amplified effects. Additionally, differences in healthcare systems, access to care, polypharmacy practice and adherence to treatment regimens can significantly influence the effectiveness of medications.

Despite data from clinical trials and real-world studies in other countries, there is a real-world evidence gap from the Bangladeshi population. While clinical trials establish efficacy in controlled Japanese settings, these findings may not translate to population of Bangladesh. This study fills this critical gap by evaluating imeglimin effectiveness in routine Bangladeshi clinical practice.

Methods

Study Design and Population

This prospective observational study was conducted across 15 diabetes centers in Bangladesh among the patients with T2DM with the aim of evaluating the effectiveness of imeglimin in a real-world setting. The study period spanned from January 2024 to December 2024.

Adult (aged ≥ 18 years) patients with T2DM with inadequate glycemic control (HbA1c >7.0%) despite treatment with diet and exercise alone or in combination with antihyperglycemic agents- including biguanides, DPP-4 inhibitors, glinides, α-glucosidase inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, thiazolidinediones, secretagogues, and insulin—were considered for inclusion in this study. Patients with type 2 diabetes mellitus who were routinely prescribed imeglimin were included in this study.

The exclusion criteria included acute conditions such as acute coronary syndrome, stroke, or transient ischemic attack (TIA) within three weeks prior to inclusion, viral fever, acute diarrhea, and acute or decompensated liver disease. Patients were also excluded for having chronic conditions such as non-T2DM diabetes, an eGFR <15 mL/min,[26] or known contraindications to imeglimin.

A total of 898 patients with T2DM were enrolled in this study.

Participant Enrollment and Consent Obtaining

Before enrollment, written informed consent was obtained from each participant after the study objectives, procedures, potential risks, and benefits were explained. The participants were given the opportunity to ask questions. The participation in this study was voluntary and the participants had right to withdraw themselves from this study anytime without any penalty or any hamper in their current or future treatment.

Study Procedure and Data Collection

Data were collected through face–to-face interviews. Information regarding their sociodemographic profile (age, sex, area of residence, occupation) and clinical information (disease duration, comorbidities, complications, current medications) were collected and recorded in a pretested semi-structured case record form. The body weight and height of each subject were assessed, along with vital signs (blood pressure and pulse). A set of laboratory investigations, including HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), serum creatinine, the serum lipid profile and serum alanine aminotransferase, were performed. FPG was measured after ≥8-hour overnight fast. PPPG was measured 2 hours following standard meal (≥75g carbohydrate equivalent, consistent with ADA diagnostic criteria. Timing was confirmed via patient logbooks. The serum lipid profile included total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels. Serum creatinine was assessed through Enzymatic Coloremetric Method.

All participants received imeglimin as part of their treatment regimen, either as monotherapy (starting from a daily dose of 500 mg to a maximum of 2000 mg) or in combination with other antihyperglycemic agents, including metformin, sulfonyleureas, GLP-1, DPP-4 inhibitors, SGLT-2 inhibitors, or insulin, at the discretion of the treating physician. All participants were advised about diet and lifestyle modifications.

They were instructed to maintain a predesigned supplied logbook to record regular blood glucose profiles; events of hypoglycemia; other adverse effects, such as dizziness, diarrhea, nausea, and heartburn; and the need to change medications.

Follow-up of the Participants

Two comprehensive physical follow-up visits were conducted for each participant at the end of the 3rd and 6th months, which included detailed evaluations of their clinical condition along with assessments of body weight and laboratory investigations.

Additionally, all participants were followed up monthly via telephone communication by an assigned research assistant to monitor glycemic control. If needed, in-person follow-up visits were arranged for dose adjustments or other clinical decisions on the basis of both the physician's and the patient's discretion.

During physical follow-up visits, patients' logbooks and adverse event forms were checked, and the management regimen was adjusted accordingly. Self-monitored blood glucose and other clinical events were assessed from patient-maintained logbooks. Priority was given to telephone communication, and any significant health conditions reported over the phone were documented accordingly (Figure 1).

Adverse Event Monitoring and Treatment Modifications

Adverse events (AEs) were defined as any unintended or unfavorable medical occurrences, whereas adverse drug reactions referred to harmful and unintended responses with a reasonable causal link to the investigational product.[27] Serious adverse events (SAEs) included death, life-threatening conditions, hospitalization, significant disability, congenital anomalies, or any event deemed serious by clinical judgment.

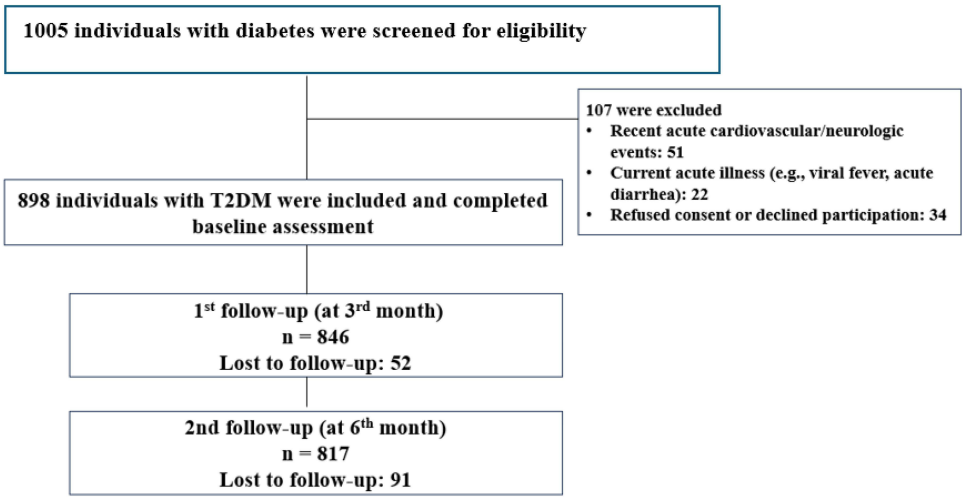

Figure 1 Enrollment and follow-up of study participants. Flowchart showing participant enrollment across 15 diabetes centers in Bangladesh from January 2024 to December 2024, screening criteria, inclusion/exclusion, baseline assessment (n=898), and follow-up at 3 and 6 months with completion rates.

A standardized grading system was used to classify the AEs. The grade 1 events were mild and involved transient symptoms with no need for intervention. The number of Grade 2 events was moderate, causing mild functional limitations and possibly requiring minimal treatment. The Grade 3 events were severe, limiting daily activities and often requiring medical attention. The grade 4 events were life-threatening, necessitating urgent intervention or hospitalization. Fatal outcomes were categorized as Grade 5.

The participants were instructed to report any adverse events (AEs) during visits or scheduled follow-ups. All events were documented with information on onset, duration, severity, resolution, and required interventions. The management strategy was selected according to severity. SAEs were reported within 24 hours, followed by thorough investigation. Hypoglycemic events were addressed according to severity, ranging from oral glucose for mild cases to intravenous glucose for severe cases. Follow-up consultations were conducted to monitor the resolution of AEs, ensuring that they subsided within a reasonable timeframe.

Operational Definition

Diabetes Mellitus

"Following ADA recommended "Standards of Care in Diabetes—2023", the diagnosis of diabetes is done on the basis of specific criteria related to blood glucose levels and HbA1c testing. The condition can be diagnosed if the fasting plasma glucose (FPG) level is ≥126 mg/dl (7.0 mmol/l) after at least 8 hours of caloric intake. Alternatively, a diagnosis can be made if a 2-hour plasma glucose level during an oral glucose tolerance test (OGTT) is ≥200 mg/dl (11.1 mmol/l), using a glucose load containing 75 g of anhydrous glucose dissolved in water. An HbA1c level of ≥6.5% (48 mmol/mol), tested with a laboratory method that is NGSP-certified and standardized to the DCCT assay, also meets the diagnostic criteria. Additionally, if a patient presents with classic symptoms of hyperglycemia or a hyperglycemic crisis, a random plasma glucose level of ≥200 mg/dl (11.1 mmol/l) is sufficient for diagnosis. In cases where unequivocal hyperglycemia is not present, the diagnosis requires two abnormal test results either from the same or separate test samples.[28]"

Body Mass Index (BMI)

"BMI of the participants was determined via the following formula:

Weight in kilograms ÷ the square of height in meters.

The Asia–Pacific classification, which was defined by the Western Pacific Regional Office of the WHO, was used to categorize BMI according to the following categories: underweight (<18.50 kg/m^2), normal (18.50–22.99 kg/m^2), overweight (23.00–24.99 kg/m^2), and obese (≥25 kg/m^2).[29]"

Hypoglycemia

"Hypoglycemic episodes were categorized as either symptomatic or biochemically confirmed. Symptomatic hypoglycemia was defined by the presence of clinical signs such as dizziness, blurred vision, palpitations, nausea, sweating, confusion, tremors, or intense hunger, irrespective of biochemical confirmation. Biochemically confirmed hypoglycemia was characterized by a self-monitored plasma glucose level of <3.9 mmol/L (as measured by a glucometer), with or without accompanying symptoms, and was relieved by glucose intake. Severe hypoglycemia was defined as an episode requiring external assistance or associated with seizures or loss of consciousness.[30]"

Estimated Glomerular Filtration Rate (eGFR)

"eGFR was determined via the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, which incorporates serum creatinine, age and sex.

The formula used is as follows:

$eGFR=141\times\min(Scr/\kappa,1)^{\alpha}\times\max(Scr/\kappa,1)^{-1.209}\times0.993^{age}\times$ (1.018 if female, else 1).

Here,

Scr: Serum creatinine (measured in mg/dL.

κ: 0.7 for females and 0.9 for males.

α: −0.329 for females and −0.411 for males.

Age: Patient age in years.[31]"

Statistical Analysis

Data analysis was conducted with the statistical software SPSS (IBM Corp., NY, USA) version 25.0. Descriptive statistics were used to summarize the baseline characteristics of the participants. Continuous data were expressed with mean and standard deviation. Categorical data were presented count, frequency and percentages. The association between categorical data was assessed using the chi-square test whereas differences in continuous variables across follow-up visits were assessed by repeated measure ANOVA. Other tests were used whenever necessary. A p-value of <0.05 was considered statistically significant.

Ethical Consideration

This study was conducted in accordance with the "Declaration of Helsinki" and approved by the Bangladesh Medical University Institutional Review Board. All participants provided written informed consent.

Results

Baseline Characteristics

The age of the study participants was 46.2±13.1 (SD) years, with the highest proportion belonging to the 41–50 years age group (27.1%). A female predominance was observed (66.9% female vs 33.1% male), and most of the female participants were housewives (62.5% of the total study participants). Most participants resided in urban areas (51.2%). The mean BMI was 28.1 ±4.2 kg/m^2, 75.3% of the participants were obese, and 16% were overweight. The average duration of diabetes was 7.4±5.4 (SD) years. A significant proportion of the participants had comorbidities, with dyslipidemia (76.5%) and hypertension (67.5%) being the most common. Concomitant AHAs were - metformin 68.3%, sulfonylureas 36.2%, insulin 16.8%, SGLT2 inhibitors 9.6% and DPP4 inhibitors 7% (Table 1).

Changes in Glycemic Status and Other Associated Parameters

The HbA1c levels decreased notably from 9.2% to 7.1% (p<0.001), with a mean change of 2.1%. FPG (9.4±2.5 vs 7.3 ±4.6 mmol/l) and PPPG (14.4±3.3 vs 8.9±1.8 mmol/l) also markedly decreased ($p < 0.001$ for both). BMI decreased from 28.1 kg/m^2 to 25.6 kg/m^2 (p<0.001). The reductions in systolic and diastolic blood pressure, lipid parameters, ALT, serum creatinine, and eGFR were improved also significant ($p < 0.001$ for all) (Table 2).

Table 1 Baseline Characteristics of the Study Participants (n=898)

	n (%)
Age group (years) (n=876)	
18-30	107 (12.2)
31-40	212 (24.2)
41-50	237 (27.1)
51-60	196 (22.4)
61-70	97 (11.1)
>70	27 (3.1)
Mean±SD (years)	46.2±13.1
Gender (n=897)	
Male	297 (33.1)
Female	600 (66.9)
Area of residence (n=859)	
Urban	460 (51.2)
Semi-urban	206 (22.9)
Rural	193 (21.5)
Occupation (n=865)	
Service holder	162 (18.7)
Businessman	121 (14)
Housewife	542 (62.5)
Unemployed	24 (2.8)
Farmer	2 (0.2)
Student	9 (1)
Others	5 (0.6)
BMI category (kg/m^2) (n=818)	
Underweight	2 (0.2)
Normal BMI	69 (7.7)
Overweight	131 (16)
Obese	616 (75.3)
Mean±SD	28.1±4.2
Duration from diagnosis of T2DM (years) (n=857)	
≤ 5	407 (47.5)
6-10	269 (31.4)
>10	181 (21.1)
Mean±SD	7.4±5.4
Comorbidities and complications*	
Dyslipidemia	687 (76.5)
Hypertension	606 (67.5)
Neuropathy	181 (20.2)
Fatty liver disease	161 (17.9)
Bronchial asthma	94 (10.5)
CKD	80 (8.9)
COPD	55 (6.1)
Coronary artery disease	44 (4.9)
Hyperthyroidism	43 (4.8)
Hypothyroidism	19 (2.1)
IHD	11 (1.2)
Stroke	9 (1)
PCOS	6 (0.7)
PAD	6 (0.7)
Heart failure	4 (0.4)

(*Continued*)

Table 1 (Continued).

	n (%)
Concomitant AHA*	
Metformin	613 (68.3)
Sulphonyleureas	325 (36.2)
Insulin	151 (16.8)
SGLT2 inhibitors	86 (9.6)
DPP4 inhibitors	63 (7)
Alpha-glucosidase inhibitor	5 (0.6)
GLP1RA	5 (0.6)

Notes: Percentages represent valid responses and are calculated after excluding missing data. *Multiple response considered.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; IHD, Ischemic Heart Disease; PCOS, Polycystic Ovary Syndrome PAD, Peripheral Artery Disease; IHD, Ischemic Heart Disease; AHA, Anti-hyperglycemic agents; SGLT2, Sodium-glucose cotransporter 2; DPP4, Dipeptidyl Peptidase 4; GLP1RA, Glucagon-like Peptide-1 Receptor Agonist.

Table 2 Changes in Parameters from Baseline to 3- and 6-month Follow-up (n=898)

	Baseline mean±SD	3-Month mean±SD	6-Month mean±SD	*p*
HbA1c (%)	9.2±1.4	8.1±1.1†	7.1±1‡,¶	<0.001
FPG (mmol/l)	9.4±2.5	7.9±1.4†	7.3±4.6¶	0.001
PPPG (mmol/l)	14.4±3.9	10.8±2.1†	8.9±1.8‡,¶	<0.001
Body weight (kg)	66±9.3	63.1±8.2†	60.5±8.3‡,¶	<0.001
BMI (kg/m^2)	28.1±4.2	26.8±3.7†	25.6±3.6‡,¶	<0.001
SBP (mmHg)	132.2±16.4	129.1±13.2†	124.7±12.4‡,¶	<0.001
DBP (mmHg)	80.2±9.2	78.9±7.3†	77.4±7.9‡,¶	<0.001
Creatinine (mg/dl)	0.94±.21	0.83±.14†	0.69±.2‡,¶	<0.001
eGFR (mL/min/1.73m^2)	67.7±20.7	82.8±18.8†	87.2±19.9‡,¶	<0.001
ALT (U/L)	46.9±16.6	40.9±13.6†	33.1±9.4‡,¶	<0.001
Total cholesterol (mg/dl)	218.6±57.1	181.8±48.8†	154.73±39.9‡,¶	<0.001
Triglyceride (mg/dl)	251.7±110.4	203.9±99.6†	160.7±62.1‡,¶	<0.001
LDL (mg/dl)	68.2±49.5	58.6±41.8†	61.8±36.7‡,¶	<0.001
HDL (mg/dl)	39.5±14	44.9±18.4†	48.3±21.9‡,¶	<0.001

Notes: The p-value was determined using repeated measure ANOVA to assess the changes in metabolic parameters from baseline to 3-month and 6-month follow-up. Post-hoc pairwise comparisons were conducted to evaluate the differences between the time points. "†" indicates statistically significant difference between baseline and 3-month follow-up. "‡" indicates statistically significant difference between baseline and 6-month follow-up. "¶" indicates statistically significant difference between 3-month follow-up and 6-month follow-up.

Abbreviations: BMI, Body Mass Index; eGFR, Estimated Glomerular Filtration Rate; ALT, Alanine Aminotransferase; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein.

Adverse Events

During this 6-month treatment period, at least one adverse event was experienced by 3.6% (n=32) of the patients. All of the reported events were mild in severity. Among the reported adverse events, gastrointestinal symptoms were the most common (2.4%), followed by dehydration (1.3%). Hypoglycemia and syncope were reported in 0.1% of the subjects. None of them experienced serious adverse events (Table 3).

Changes in Glycemic Parameters Among Participants with and without Obesity

HbA1c levels significantly decreased in both obese and non-obese groups ($p<0.001$ for both), with similar proportional reductions (obese −21.8% vs non-obese −22.9%, $p=0.244$). FPG and PPPG also significantly decreased in non-obese

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Table 3 Frequency of Adverse Events Among the Study Participants (n=898)

Adverse Events	Grade	N	%
Any TAEs		32	3.6
Gastrointestinal symptoms		22	2.4
Nausea	Grade 1	12	1.3
Vomiting	Grade 1	12	1.3
Abdominal pain	Grade 1	7	0.8
Heart burn	Grade 1	7	0.8
Dehydration	Grade 1	12	1.3
Hypotension	Grade 1	2	0.2
Hypoglycemia	Grade 1	1	0.1
Syncope	Grade 1	1	0.1

(p<0.001 for both) and obese individuals (p=0.02 for FPG and p<0.001 for PPPG). FPG showed similar percent changes (obese −27.3% vs non-obese −26.8%, p=0.661), while PPPG showed greater percent reduction in obese individuals (obese −37.3% vs non-obese −29.3%, p=0.008) (Table 4).

Changes in Glycemic Parameters According to Duration of Diabetes

HbA1c, FPG, and PPPG levels significantly decreased in both groups (p<0.001 for all). HbA1c showed similar percent changes (≤10 years −21.4% vs >10 years −23.3%, p=0.058), but FPG and PPPG showed significantly greater reductions in individuals with longer T2DM duration (>10 years: FPG −31.8% vs ≤10 years −25.8%, p<0.001; PPPG −37.4% vs −32.3%, p=0.008) (Table 5).

Participants with T2DM duration of ≤2 years and >2 years both showed significant reductions in HbA1c, FPG, and PPPG (p<0.001 for all). The differences in percentage reductions of HbA1c and PPPG between groups were not statistically significant (HbA1c: p=0.118; PPPG: p=0.631), whereas FPG reduction was significantly greater in individuals with >2 years disease duration (p=0.023) (Supplementary Table 1).

Changes in Glycemic Parameters Among Participants Receiving Imeglimin Monotherapy or Imeglimin in Combination with Other HAAs

HbA1c significantly decreased with imeglimin monotherapy and combination therapy (p<0.001 for both), with comparable proportional reductions (monotherapy −20.8% vs combination −21.9%, p=0.397). FPG showed significantly greater reduction with combination therapy (combination −27.2% vs monotherapy −23.9%, p=0.049), while PPPG improvements were similar between groups (monotherapy −33.2% vs combination −34.2%, p=0.631) (Table 6).

Table 4 Percentage Changes (%Δ) in Glycemic Status From Baseline to 6-month Follow-up Stratified by Obesity (n=818)

	Obese n=616			(%Δ)	Non-Obese n=202			(%Δ)	*p*¶
	Baseline mean±SD	6- Month mean±SD	*p*†		Baseline mean±SD	6- Month mean±SD	*p*‡		
HbA1C (%)	9.1±1.6	7.5±1.0	<0.001	−21.8±10.8	9.1±1.3	7.1±1	<0.001	−22.88±10.7	0.244
FPG (mmol/l)	9.3±2.4	6.5±1.2	<0.001	−27.3±13.4	9.3±2.4	6.6±1.1	<0.001	−26.8±14.1	0.661
PPPG (mmol/l)	13.1±3.2	10.23±1.6	0.02	−37.3±15.1	14.5±3.3	8.8±1.7	<0.001	−29.3±20.6	0.008

Notes: "†" indicates difference between baseline and 6-month follow-up in obese group. "‡" indicates difference between baseline and 6-month follow-up in non-obese group. "¶" indicates difference in changes from baseline to 6 months between the obese and non-obese groups. p value was determined by paired *t* test†‡ and independent student *t* test.

Abbreviations: FPG, Fasting plasma glucose; PPPG, Post prandial plasma glucose.

Table 5 Percentage Changes (%Δ) in Glycemic Status from Baseline to 6-month Follow-up Stratified by Duration of T2DM (n=857)

	Duration of T2DM ≤ 10 Years n=676			(%Δ)	Duration of T2DM >10 Years n=181			(%Δ)	$p^{¶}$
	Baseline mean±SD	6- Month mean±SD	$p^{†}$		Baseline mean±SD	6- Month mean±SD	$p^{‡}$		
HbA1C (%)	9.1±1.4	7.1±1.0	<0.001	−21.4±10.5	9.6±1.6	7.3±1.4	<0.001	−23.26±11.7	0.058
FPG (mmol/l)	9±2.3	6.5±1.1	<0.001	−25.8±13.4	11.1±2.8	7.3±1.5	<0.001	−31.8±15.9	<0.001
PPPG (mmol/l)	13.8±3.3	8.9±1.7	<0.001	−32.3±16.8	14.9±3.3	9±1.8	<0.001	−37.3±16.9	0.008

Notes: "†" indicates difference between baseline and 6-month follow-up in participants with duration of T2DM ≤ 10 years. "‡" indicates difference between baseline and 6-month follow-up in participants with duration of T2DM > 10 years. "¶" indicates difference in changes from baseline to 6 months between the participants with duration of T2DM ≤ 10 years and >10 years. p value was determined by paired *t* test†,‡ and independent student *t* test.
Abbreviations: FPG, Fasting plasma glucose; PPPG, Post prandial plasma glucose.

Table 6 Percentage Changes (%Δ) in Glycemic Parameters Among Participants Receiving Imeglimin Monotherapy and Imeglimin in Combination with Other AHAs

	Imeglimin Monotherapy n=108			(%Δ)	Imeglimin in Combination with Other AHAs n=790			(%Δ)	$p^{¶}$
	Baseline mean±SD	6- Month mean±SD	$p^{†}$		Baseline mean±SD	6- Month mean±SD	$p^{‡}$		
HbA1C (%)	8.9±1.3	7±1	<0.001	−20.8±10.8	9.2±1.4	7.4±1.1	<0.001	−21.9±10.8	0.397
FPG (mmol/l)	8.9±2.4	6.5±1.1	<0.001	−23.8±14.9	9.4±2.5	6.9±1.3	<0.001	−27.2±14.1	0.049
PPPG (mmol/l)	13.1±3.3	8.4±1.3	<0.001	−33.21±14.9	14.4±3.3	9±1.8	<0.001	−34.2±17.2	0.631

Notes: "†" indicates difference between baseline and 6-month follow-up in participants receiving imeglimin monotherapy. "‡" indicates difference between baseline and 6-month follow-up in participants receiving imeglimin with combination of other AHAs. "¶" indicates difference in changes from baseline to 6 months between these groups. p value was determined by paired *t* test†,‡ and independent student *t* test.
Abbreviations: FPG, Fasting plasma glucose; PPPG, Post prandial plasma glucose.

HbA1c, FPG, and PPPG all decreased significantly in both participants receiving and not receiving metformin (p<0.001 for all). The percentage of reductions did not differ significantly between metformin users and nonusers (HbA1c: p=0.137; FPG: p=0.827; PPPG: p=0.580) (Table 7).

Significant improvements in HbA1c, FPG, and PPPG was observed over six months with imeglimin treatment. HbA1c reduction was greatest in the group receiving imeglimin combined with metformin and other AHAs (−2.2 ± 1.3%), compared to imeglimin with metformin (−1.9 ± 1.1%) and imeglimin monotherapy (−1.8 ± 1.1%) ($p = 0.021$). Reductions in FPG and PPPG did not differ significantly among the three groups (p = 0.419 and 0.267, respectively) (Figure 2).

Changes in Glycemic Parameters Among Participants with or without Insulin

Both insulin users and nonusers experienced significant HbA1c, FPG, and PPPG reductions (p<0.001 for all). Insulin users demonstrated significantly greater proportional reductions in HbA1c and FPG (HbA1c: insulin −24.24% vs no insulin −21.24%, p=0.005; FPG: insulin −32.9% vs no insulin −25.8%, p<0.001), while PPPG improvements were identical between groups (insulin −34.36% vs no insulin −34.36%, p=0.989) (Supplementary Table 2).

HbA1c levels progressively declined in participants receiving imeglimin monotherapy or in combination with metformin or insulin. Fasting plasma glucose steadily decreased, with a greater reduction observed in those receiving imeglimin plus insulin. Postprandial plasma glucose showed the most pronounced decrease across all treatment groups (Supplementary Figure 1).

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Table 7 Percentage Changes (%Δ) Glycemic Status from Baseline to 6-month Follow-up Stratified by Use of Metformin (n=898)

	Metformin								$p^{¶}$
	Yes n=613			(%Δ)	No n=285			(%Δ)	
	Baseline mean±SD	6- Month mean±SD	$p^{†}$		Baseline mean±SD	6- Month mean±SD	$p^{‡}$		
HbA1C (%)	9.1±1.4	7±.91	<0.001	−22.17±10.8	9.3±1.6	7.4±1.1	<0.001	−20.9±10.8	0.137
FPG (mmol/l)	9.2±2.3	6.5±1.2	<0.001	−26.85±13.6	9.9±2.9	6.9±1.3	<0.001	−27.1±15.6	0.827
PPPG (mmol/l)	14.3±3.3	9±1.8	<0.001	−34.7±17.2	14.1±3.4	8.9±1.6	<0.001	−33.7±16.5	0.580

Notes: "†" indicates difference between baseline and 6-month follow-up in participants receiving metformin. "‡" indicates difference between baseline and 6-month follow-up in participants who did not receive metformin. "¶" indicates difference in changes from baseline to 6 months between these groups. p value was determined by paired *t* test[†,‡] and independent student *t* test.
Abbreviations: FPG, Fasting plasma glucose; PPPG, Post prandial plasma glucose.

In participants with very poor baseline glycemic control (HbA1c >9%), HbA1c, FPG, and PPPG levels decreased significantly more than in the poorly controlled group (HbA1c p<0.001; FPG p<0.001; PPPG p=0.061), with notably greater percentage reductions (HbA1c: −27.2% vs −16.6%; FPG: −29.1% vs −24.8%) (Table 8).

After 6 months, both groups experienced significant reductions in BMI ($p < 0.001$ for both groups). Obese participants demonstrated significantly greater proportional BMI reduction (obese −9.4% vs non-obese −5.7%, p<0.001) (Supplementary Table 3).

Patients with very poor glycemic control demonstrated pronounced reductions in all three glycemic indices, including HbA1c, FPG), and PPPG, compared with those with poor glycemic control (Supplementary Figure 2).

Discussion

The glycemic outcome of any antihyperglycemic agent may differ across different populations due to a combination of genetic, environmental, and lifestyle factors, as well as differences in healthcare systems, access to medical care, and adherence to treatment regimens. Imeglimin has demonstrated significant efficacy in diabetes management in previous trials and offers a novel approach distinct from existing antihyperglycemic medications.[4,13–19] Imeglimin has been commercially available in Bangladesh since August 2023 and has been increasingly used in routine clinical practice. The present study assessed the real-world effectiveness and safety of imeglimin among patients with T2DM in Bangladesh and reported significant improvements in glycemia and other parameters in the context of T2DM, with minimal adverse events.

Most of the participants came from the 4th decade of life, with an average age of 46 years. Previous studies on patients with T2DM in Bangladesh reported a slightly greater mean age of approximately 50 years, which is greater than that reported in the present study.[22,32,33] Recently, an insight has been developed indicating a younger age of diabetes onset in South Asian populations than in Western countries,[34,35] which aligns with the findings of the present study. A notable predominance of female subjects was observed, with two-thirds of the total subjects being female, which is consistent with previous studies in Bangladesh.[36,37] However, studies have been conducted in Bangladesh, where a male predominance has been reported,[32,38] and the global pattern also reveals a male predominance in T2DM patients.[35] This gender disparity may be attributed to cultural factors affecting healthcare-seeking behavior and participation in clinical studies. Additionally, other studies conducted in Bangladesh reported that more females with diabetes consulted with diabetic centers.[39] Approximately half of the subjects resided in urban areas, and the other half resided in rural areas, reflecting the fact that T2DM is no longer confined to urban areas. The majority of participants were housewives, which correlates with the gender distribution and cultural norms in Bangladesh, where women predominantly engage in household activities.

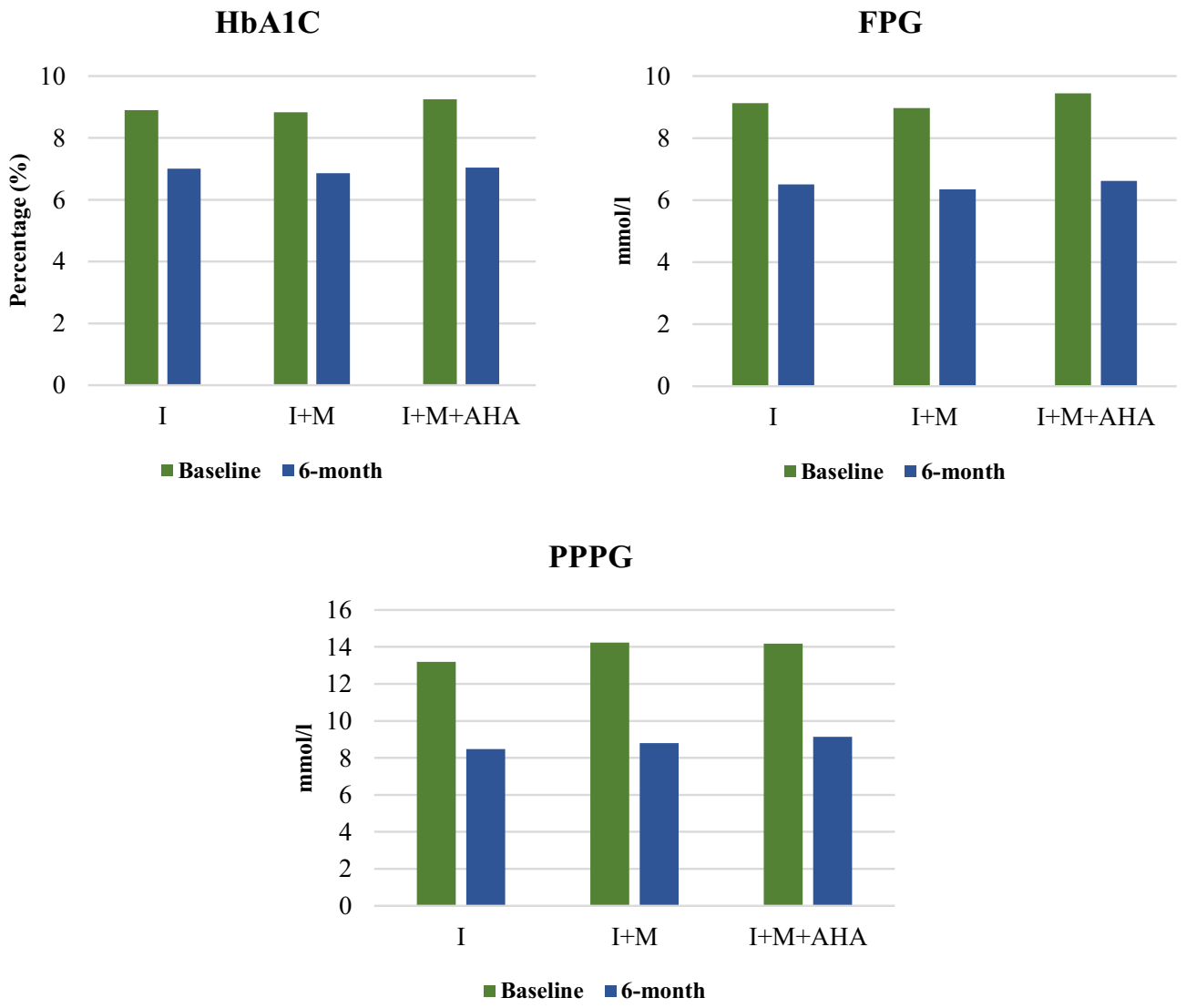

Figure 2 Changes in glycemic parameters over six months in participants receiving imeglimin monotherapy, imeglimin and metformin without any other AHA, imeglimin and metformin with other AHA. Line graphs demonstrating mean changes in HbA1c, across three treatment groups: imeglimin monotherapy (I), imeglimin with metformin (I+M), and imeglimin with metformin plus other antihyperglycemic agents (I+M+AHA).
Abbreviations: FPG, Fasting Plasma Glucose; PPPG, Postprandial Plasma Glucose.

More than three-fourths of the participants in this study were overweight or obese, which is in line with the recognized association between obesity and T2DM.[40] Internationally, the IDF estimates that up to 90% of individuals with T2DM are obese or overweight,[41] further supporting the high prevalence of obesity among individuals with diabetes observed in this study. In Bangladesh, adult obesity is increasing, especially in urban areas- underscoring the growing risk for diabetes even as obesity rates are lower than the global average.[42] The study also reported a significant number of subjects with hypertension and dyslipidemia, which aligns with the established understanding that T2DM often clusters with other cardiometabolic conditions.[43,44] The average duration of T2DM was seven years, with one-fourth of them suffering from the disease for more than ten years.

During enrollment, the mean HbA1c of the study patients was 9.15%. Following six months of imeglimin therapy, a significant reduction in HbA1c was observed, with a mean of 7.11% (mean change in HbA1c was 2.1%). FPG and PPPG were also significantly reduced. Previous trials reported similar findings[4,13–19] However, the changes observed in this study, especially in HbA1c, surpassed the findings from previous studies. The TIMES 1 trial reported a 0.87% reduction in HbA1c in patients with T2DM after 6 months of imeglimin monotherapy.[14] Moreover, the TIMES 2 and

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Table 8 Percentage Changes (%Δ) in Glycemic Status from Baseline to 6-month Follow-up Stratified by Glycemic Control Status (n=898)

	Poor Control (HbA1c 7–9%) n= 457			**(%Δ)**	**Very Poor Control (HbA1c >9%) n= 441**			**(%Δ)**	***p*¶**
	Baseline mean±SD	**6- Month mean±SD**	***p*†**		**Baseline mean±SD**	**6- Month mean±SD**	***p*‡**		
HbA1C (%)	8.7±.5	6.7±.7	<0.001	−16.5±9.5	10.2±1.2	7.4±1.1	<0.001	−27.2±9.2	<0.001
FPG (mmol/l)	8.7±1.7	6.4±1	<0.001	−24.8±14.3	10.1±3.1	6.7±1.3	<0.001	−29.1±13.1	<0.001
PPPG (mmol/l)	13.3±3	8.6±1.7	<0.001	−32.9±17.6	15.4±3.3	9.4±1.7	<0.001	−36.2±15.9	0.061

Notes: "†" indicates difference between baseline and 6-month follow-up in participants with poor glycemic control. "‡" indicates difference between baseline and 6-month follow-up in participants with very poor glycemic control. "¶" indicates difference in changes from baseline to 6 months between these groups. p value was determined by paired *t* test[†,‡] and independent student *t* test.
Abbreviations: FPG, Fasting plasma glucose; PPPG, Post prandial plasma glucose.

TIMES 3 trials reported an HbA1c reduction ranging from 0.56% to 0.92% after 52 weeks of combination therapy with imeglimin and other OADs.[15,19] The relatively pronounced change in glycemic control in this study might be due to several factors specific to the study subjects as well as the Bangladeshi population. Compared with Japanese participants, study participants had higher baseline HbA1c levels, which might have resulted in greater absolute reductions. In this study, participants with baseline HbA1c >9% showed significantly greater improvements in HbA1c, FPG and PPPG than did participants with HbA1c 7%-9%. This finding is consistent with previous studies showing that patients with higher baseline HbA1c often experience more pronounced glycemic control following intervention.[45] Alongside the pharmacological effects, monthly follow-up may have induced a Hawthorne effect, improving adherence and lifestyle compliance, while regression-to-the-mean is expected given the markedly high baseline HbA1c, representing a poorly controlled patient. In addition, all participants received concurrent care escalation- including structured diet and exercise counseling and physician-directed dose adjustments. Collectively, these contextual factors might be account for a substantial proportion of the observed glycemic improvement.

However, many participants were on combination therapy involving other OADs and insulin, which may have enhanced the effects of imeglimin through complementary mechanisms. While HbA1c reductions were similar between imeglimin monotherapy and combination therapy, FPG showed significantly greater reduction with combination therapy. Notably, imeglimin monotherapy achieved clinically meaningful glycemic control independently, supporting its potential use as standalone therapy in selected patients with inadequate response to other agents or as an alternative to polypharmacy. Subgroup comparisons among imeglimin monotherapy, imeglimin with metformin (without additional AHAs), and imeglimin with metformin along with other AHAs revealed a significant reduction in HbA1c across all groups, with the greatest reduction noted among those receiving imeglimin, metformin, and other AHAs. Similarly, participants receiving insulin demonstrated significantly greater proportional reductions in HbA1c and FPG compared to non-insulin users, while PPPG improvements were identical. This pattern reflects markedly higher baseline disease severity and insulin resistance in insulin-requiring patients, suggesting imeglimin's enhanced efficacy in advanced T2DM with greater metabolic dysfunction.

Bangladeshi people are typically high-carbohydrate consumers, which can have an impact on glycemic status and may influence the pattern of glycemic change after imeglimin. Hence, the marked improvement in all glycemic parameters is consistent with the mechanism of action of imeglimin, which targets multiple pathways involved in glucose homeostasis, including reduced hepatic glucose production, increased glucose uptake in skeletal muscle, and increased glucose-stimulated insulin secretion.

An overall reduction in body weight was observed among the study participants from baseline to the 6-month follow-up. Similar findings were reported in a real-world study conducted in Japan.[20] The observed weight loss might result from a combination of lifestyle modifications and medications. Weight reduction was more pronounced in obese participants, with a percentage decrease of −9.42% compared to non-obese participants. This differential weight benefit

in obese individuals likely reflects both greater baseline excess weight and potential metabolic advantages of improved insulin sensitivity via imeglimin's mechanism of action. The lipid profile showed favorable changes, with reductions in total cholesterol, triglycerides, and low-density lipoprotein, alongside an increase in high-density lipoprotein, which was corroborated by a previous study.[20] The study also revealed changes in blood pressure and significant improvements in both diastolic and systolic blood pressure, which may be related to improved insulin sensitivity, mild natriuretic effects, or reduced sympathetic nervous system activity. Similar improvements in blood pressure have been reported with other antihyperglycemic agents that increase insulin sensitivity, suggesting that insulin resistance contributes to the management of hypertension in T2DM patients.[46]

Renal function changes are very important in patients with long-term diabetes. Interestingly, this study revealed significant reductions in the serum creatinine level and eGFR, which are unusual for a 6-month observational period. These findings suggest a potential renoprotective effect of imeglimin. While imeglimin's mitochondrial mechanisms including reduced oxidative stress, improved renal cell bioenergetics offer biological plausibility for renoprotection.[46,47] But these findings are observational and potentially confounded by- substantial glycemic improvement, concomitant renoprotective agents, better hydration status, dietary changes, etc. Thus, these hypothesis-generating observations require confirmation in controlled clinical trials.

The safety profile of imeglimin in our study was favorable, with a low frequency of adverse events. The most common adverse events reported were gastrointestinal symptoms and dehydration. Only 3.6% of the subjects experienced at least one adverse event, while all events were mild. One patient reported hypoglycemia, and one patient reported syncope, which was immediately addressed with the highest priority, but both recovered after home remedy. Serious adverse events were not observed in this study. These findings are consistent with previous clinical trials reporting mild gastrointestinal effects as the predominant side effect of imeglimin.[13–16]

Although both obese and non-obese subjects demonstrated significant HbA1c improvements, the percentage reductions were comparable between groups. PPPG reduction was significantly greater in obese individuals, suggesting differential glycemic benefits across parameters by obesity status. Conversely, subjects with longer T2DM duration (>10 years) demonstrated significantly greater improvements in FPG and PPPG compared to those with shorter disease duration. This paradoxical finding suggests enhanced drug responsiveness in established diabetes despite longer disease exposure, potentially reflecting greater insulin resistance that responds favorably to imeglimin's mitochondrial mechanisms.

This observational study has several important limitations that must be explicitly considered when interpreting results. While the observed improvements are substantial, the absence of a control group means we cannot definitively quantify the proportion of the effect attributable solely to Imeglimin. Comparisons between monotherapy and combination therapy are further limited by confounding by indication, as patients receiving combination therapy reflects worse baseline glycemic control, reflecting systematic physician allocation toward higher-risk individuals. This selection bias also limits the generalizability. Study patients were enrolled from tertiary diabetes centers, with over half of participants residing in urban areas, over-represents patients with comparatively better healthcare access. Physician-selected eligibility may have further excluded individuals with extreme comorbidity or poor follow-up potential.

Statistical precision varied across the analysis. While the overall study patients provided narrow confidence intervals around the primary outcome, subgroup analyses were underpowered to detect mild to modest differences, increasing the risk of type II error.

Regarding adverse events, the patients were followed-up to 6-months, so long term effects could not be captured. Moreover, this study relied on patient logbooks and monthly telephone contact for adverse events reporting- which may have limited the reporting to some extents.

These limitations emphasize a possibility that the observed effectiveness likely reflects a combination of imeglimin's pharmacological effects and real-world intensification. So, further clinical trials should be designed and executed involving a more generalized study participants to disentangle drug-specific benefits from contextual factors and establish the true efficacy of imeglimin.

Conclusion

In this real-world study, imeglimin demonstrated significant improvements in glycemic control, body mass index, lipid profiles, and blood pressure over 6 months among Bangladeshi patients with poorly controlled T2DM. Long-term studies are required to establish long-term glycemic benefits and investigate potential cardiorenal effects in diverse real-world populations.

Generative AI Disclosure

No content was generated using ChatGPT or any other AI tool. However, ChatGPT 4.0 was used solely for language polishing and correction of grammatical errors.

Abbreviations

ADA, American Diabetes Association; AEs, Adverse Events; BMI, Body Mass Index; DPP-4, Dipeptidyl Peptidase-4; FPG, Fasting Plasma Glucose; GLP-1, Glucagon-Like Peptide-1; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; OGTT, Oral Glucose Tolerance Test; PMDA, Pharmaceuticals and Medical Devices Agency; PPPG, Postprandial Plasma Glucose; SAEs, Serious Adverse Events; SGLT-2, Sodium-Glucose Cotransporter-2; TIA, Transient Ischemic Attack.

Data Sharing Statement

Patient-level data will be available upon request from the corresponding author.

Ethics Statement

The study protocol was reviewed and approved by the institutional review board (IRB) of Bangladesh Medical University (formerly Bangabandhu Sheikh Mujib Medical University) **(NO. BSMMU/2024/4772-)**.

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All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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