ORIGINAL ARTICLE

Imeglimin in Indian Adults with Type 2 Diabetes: A Prospective Multicenter Real-world Cohort Study of Prescription Patterns, Glycemic Change, and Safety

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Abstract

Background: Imeglimin is a novel oral glucose-lowering agent targeting mitochondrial dysfunction. While randomized trials demonstrate its efficacy, real-world data in diverse populations remain limited. We evaluated the effectiveness, safety, and utilization patterns of imeglimin in Indian adults with inadequately controlled type 2 diabetes (T2D).

Materials and methods: This prospective, multicenter, observational cohort study enrolled adults with T2D newly initiated on imeglimin across 11 Indian centers. Participants were followed for 6 months. The primary outcome was the change in HbA1c from baseline. Effectiveness was analyzed in a complete-case cohort using linear mixed-effects models to adjust for covariates, while safety was assessed in all participants with at least one post-baseline evaluation.

Findings: The baseline cohort included 736 participants (mean age 52.4 years, mean baseline HbA1c 9.8%). Imeglimin was predominantly prescribed as an add-on therapy (84.6%), most frequently alongside three or more other agents (57.9%). In the complete-case cohort ($n = 337$; 46% of baseline), adjusted mean HbA1c decreased by 1.28% (95% CI −1.41 to −1.14) at 3 months and 2.27% (−2.41 to −2.13) at 6 months ($p < 0.001$). Greater reductions were significantly associated with higher baseline HbA1c. Adverse events were reported in 9.9% of the safety cohort ($n = 573$), most commonly mild gastrointestinal symptoms (5.2%). Hypoglycemia occurred in 1.2%. Two cases of lactic acidosis were reported, though causality with imeglimin was not established.

Conclusion: In routine clinical practice, the initiation of imeglimin among Indian adults with T2D was associated with clinically meaningful reductions in HbA1c, fasting plasma glucose, and postprandial glucose over a 6-month period, alongside a favorable safety profile. These real-world findings support the clinical utility and tolerability of imeglimin as an effective therapeutic option for glycemic management in this population. Future randomized controlled trials with extended follow-up are warranted to establish definitive causal treatment effects and evaluate long-term clinical outcomes.

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Introduction

Type 2 diabetes (T2D) is a chronic, progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and increased hepatic glucose output. As per the International Diabetes Federation (IDF), diabetes is a major global health challenge, affecting over 589 million adults worldwide and projected to reach 853 million by 2050.[1] India has an estimated 101 million adults with diabetes and 136 million with prediabetes, making it the country with the second-highest burden globally.[2]

Despite the availability of multiple oral glucose-lowering agents (OGLAs), glycemic control remains suboptimal in routine clinical practice. Many people fail to achieve individualized glycemic targets due to progressive β-cell dysfunction, adverse effects, and therapeutic inertia.[3,4] Importantly, currently available therapies predominantly target isolated components of glucose dysregulation and do not adequately address the interconnected defects of insulin resistance, impaired insulin secretion, and underlying cellular energetic dysfunction.

Mitochondrial dysfunction is increasingly recognized as a central determinant in the pathophysiology of T2D, linking impaired β-cell function, heightened oxidative stress, reduced ATP generation, and dysregulated hepatic glucose metabolism.[5–7] Defective mitochondrial quality control leads to the accumulation of dysfunctional mitochondria, contributing to impaired insulin secretion and increased β-cell apoptosis.[7] Targeting this axis offers a mechanistically integrated therapeutic approach. Imeglimin, a first-in-class "glimin," directly modulates mitochondrial bioenergetics, improves mitochondrial integrity, and reduces oxidative stress, thereby restoring glucose-stimulated insulin secretion, enhancing insulin sensitivity, and suppressing β-cell apoptosis.[5,8–10]

This mechanism is particularly relevant to the Asian Indian phenotype, characterized by early β-cell dysfunction, increased visceral adiposity, and heightened cardiometabolic risk despite relatively lower body mass index.[8] These features are closely linked to mitochondrial inefficiency and metabolic inflexibility. Clinical trials, including the TIMES program, have demonstrated that imeglimin improves glycemic control with favorable tolerability both as monotherapy and in combination with other agents.[9,11,12] Early Indian real-world evidence further suggests clinically meaningful reductions in HbA1c and fasting glucose, including in patients intolerant to metformin.[13] Imeglimin received regulatory approval in India in 2022, expanding therapeutic options for patients inadequately controlled on existing therapies. However, large prospective real-world data from diverse Indian populations remain limited. This study, therefore, aims to evaluate the effectiveness and safety of imeglimin over 6 months in routine clinical practice, addressing an important evidence gap.

Materials and Methods

Study Design and Population

This was a prospective, multicenter, observational cohort study conducted at 11 study sites (primary and secondary care settings) across eight cities, covering all zones of India. The data were collected from December 2023 to June 2025. After enrollment, participants were followed up for 6 months.

The study included adult participants (≥18 years) with a clinical diagnosis of T2D who were newly initiated on imeglimin either as monotherapy or in combination with other OGLAs. Participants below 18 years of age and those diagnosed with other forms of diabetes, including type 1 diabetes (T1D), gestational diabetes mellitus (GDM), or maturity-onset diabetes of the young (MODY), were excluded.

Sampling and Sample Size Achieved

All consecutive eligible individuals who met the inclusion criteria and visited the study site for routine care during the recruitment period, and who provided informed consent, were included. The enrollment of consecutive patients was strictly implemented to minimize selection bias and ensure a representative real-world cohort.

Participant flow and attrition were documented using a CONSORT-style flow diagram (Fig. 1).

Analysis Sets

- *Baseline cohort*: All participants initiated on imeglimin at baseline (n = 736).
  - *3-month case cohort*: Participants with baseline and follow-up HbA1c available at 3 months from baseline (n = 475).
- *Complete-case cohort*: Participants with baseline and follow-up HbA1c available at 3 months and 6 months (n = 337).
- *Safety cohort*: Participants with at least one post-baseline safety assessment (n = 573).

Data Collection Instrument and Variables

A customized electronic case record form (MEDEVA eCRF) was developed specifically for this study to ensure standardized and comprehensive data collection. The eCRF captured key demographic information [age, gender, body mass index (BMI)], relevant comorbidities, detailed medical history, and ongoing pharmacological treatments, including antidiabetic and concomitant medications. It also included fields to record the duration of diabetes, previous antidiabetic therapy patterns, and any changes in lifestyle interventions (e.g., diet and exercise) during the study period. Furthermore, the eCRF documented whether background antidiabetic therapies remained stable or were modified during follow-up, as well as any dose escalation or de-escalation of imeglimin or concomitant medications.

As this was a real-world observational study, laboratory assessments (e.g., HbA1c, FPG, PPG) were performed at local site laboratories according to their standard institutional methods and routine clinical practice, rather than using a centralized laboratory. Data entry was performed in real time during participants' visits, with all information obtained as part of routine clinical care to minimize additional burden. Built-in validation checks in the eCRF reduced data entry errors and ensured completeness for subsequent analysis.

Safety data included all AEs and SAEs reported during the observation period, along with their severity, relationship to imeglimin as assessed by the investigator, and actions taken. Adverse event collection was both spontaneous (as reported by the patient) and actively solicited by the investigator at each follow-up visit. Hypoglycemia was reported by participants and was defined as blood glucose <70 mg/dL or symptomatic events resolving with carbohydrate intake.

Ethics Committee Approval

The study received ethics approval from the Institutional Human Ethics Committee–Udyaan Healthcare (Registration number: ECR/1300/Inst/UP/2019).

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (revised by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and adhered to the International Council for Harmonization Good Clinical Practice (ICH-GCP) guidelines [E6 (R2), Step 6]. All procedures complied with the applicable local regulatory requirements, including the Good Clinical Practices for Clinical Research in India (2004, CDSCO), the New Drugs and Clinical Trials Rules (2019) and their subsequent amendments, as well as the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017).

Informed Consent and Data Privacy

Informed consent was obtained from all study participants prior to their enrollment.

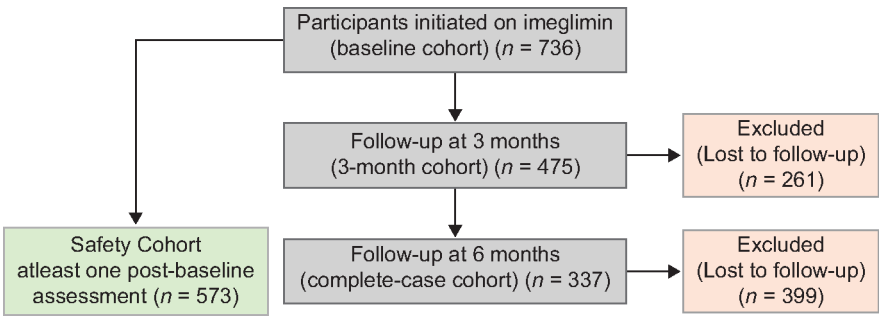

Fig. 1: Flow of participants through the study, including baseline cohort, 3-month cohort, complete-case cohort, and safety analysis set

Participants were fully informed about the nature, purpose, and procedures of the study, including any potential risks or benefits involved. Physicians maintained confidentiality in accordance with their agreement; participants' IDs are not identifiable to external parties. Data usage was restricted solely to this study, with any further use contingent on additional written permission to protect privacy and uphold ethical standards.

Statistical Analysis

The collected data underwent aggregate-level analysis (de-identified with respect to participant or site) using Python software. Categorical data were presented as frequencies and proportions, with statistical significance assessed using the Chi-square test. Continuous variables (e.g., HbA1c, FPG, PPG, weight, BMI) were summarized using means and standard deviations (SD) at each time point.

Primary effectiveness analysis was based on complete-case longitudinal data. Missing outcome data were not imputed. To evaluate changes in continuous clinical and laboratory parameters across all three time points simultaneously (baseline, 3 months, and 6 months), linear mixed-effects models were utilized. This approach ensured that all available repeated measures contributed to the analysis without needing a complete follow-up. Furthermore, a complete-case sensitivity analysis was performed to assess the robustness of the primary findings.

Normality of within-participants differences was assessed using the Shapiro–Wilk test. Although some deviations from normality were observed, the large sample sizes ($N \approx 337$) allowed reliance on the central limit theorem, under which the sampling distribution of the mean difference approximates normality. Accordingly, specific within-patient changes between individual time points (baseline to 3 months, baseline to 6 months, and 3 to 6 months) were evaluated using paired *t*-tests, with results summarized as mean (SD), mean differences with 95% confidence intervals, and two-sided *p*-values.

No formal sample size calculation was mandated; sample size was determined by feasibility and the number of participants enrolled across participating centers. Subgroup analysis was performed by age, gender, duration of diabetes, and baseline HbA1c value. This was exploratory in nature and therefore needs to be interpreted with caution, given the limited power. Visualizations were created using Microsoft Office. Statistical significance was determined using standard hypothesis testing with a threshold of a two-sided *p*-value less than 0.05. All tests adhered to methodological guidelines to ensure the validity and reliability of the study's conclusions.

Results

Patient Profile (Baseline Cohort, *n* = 736)

A total of 736 participants with T2D were included in the baseline analysis. The mean age of the study population was 52.4 ± 11.4 years. Males constituted 56.9% of the cohort, while females accounted for 43.1%. The mean BMI was 26.7 (4.7) kg/m^2. The mean baseline HbA1c was 9.8 ± 2.2% for the enrolled cohort, and the mean systolic and diastolic blood pressures were 131.8 ± 13.9 mm Hg and 81.3 ± 9.1 mm Hg, respectively. The mean duration of T2D was 6.7 ± 4.7 years, and 32.9% of participants reported a family history of T2D.

Diabetes-related complications were present in 24.3% of participants, with neuropathy being the most common (19.0%), followed by nephropathy (4.8%), retinopathy (3.9%), diabetic foot (3.1%), and cardiovascular complications (1.5%). Regarding comorbid conditions, hypertension was the most prevalent (32.3%), followed by dyslipidemia (9.2%) and obesity (5.4%). Other comorbidities, including chronic kidney disease, heart failure, ischemic heart disease, liver disorders, and cerebrovascular accident, were infrequently reported (Table 1).

Prescription Patterns of Imeglimin (Baseline Cohort, *n* = 736)

At baseline, 62% of participants were initiated on imeglimin 1000 mg and 36.8% on imeglimin 500 mg. Regarding treatment patterns, 15.4% received imeglimin as monotherapy, whereas for 84.6%, imeglimin was an add-on therapy to existing OGLAs. In 57.9% participants, imeglimin was added to three or more OGLAs, followed by OGLAs plus insulin (15.8%), two OGLAs (6.7%), and one OGLA (4.2%). Concomitant drug class use showed that metformin (72.6%), sulfonylureas (69.7%), and DPP-4 inhibitors (59.2%) were the most frequently co-prescribed medications, followed by SGLT2 inhibitors (41.6%),

Table 1: Baseline cohort—demographic characteristics

Characteristics	*Base (N = 736)*
Age (years)	
18–30	20 (2.7)
31–40	109 (14.8)
41–50	196 (26.6)
51–60	237 (32.2)
61–70	136 (18.5)
≥70	38 (5.2)
Mean (SD)	52.4 (11.4)
Gender	
Female	317 (43.1)
Male	419 (56.9)
BMI, mean (SD)	26.7 (4.7)
HbA1c (%), mean (SD)	9.8 (2.2)
Blood pressure, systolic/diastolic (mm Hg), mean (SD)	131.8 (13.9)/81.3 (9.1)
Duration of T2D (years), mean (SD)	6.7 (4.7)
Presence of family history of T2D (yes), n (%)	242 (32.9)
Complication due to T2D, *n* (%)	
Neuropathy	140 (19.0)
Nephropathy	35 (4.8)
Retinopathy	29 (3.9)
Diabetic foot	23 (3.1)
Cardiovascular complications	11 (1.5)
None	557 (75.7)
Comorbid conditions, *n* (%)	
Hypertension (HTN)	238 (32.3)
Dyslipidemia (DL)	68 (9.2)
Obesity	40 (5.4)

BMI, body mass index; DL, dyslipidemia; HbA1c, glycated hemoglobin; HTN, hypertension; SD, standard deviation; T2D, type 2 diabetes.

Table 2: Prescription details of imeglimin initiation at baseline (baseline cohort, *n* = 736)

Variables	*Base (N = 736)*
Imeglimin strength at baseline, *n* (%)	
Imeglimin 1000 mg BD	152 (20.7)
Imeglimin 1000 mg OD	304 (41.3)
Imeglimin 500 mg BD	15 (2.0)
Imeglimin 500 mg OD	256 (34.8)
Imeglimin 1000 mg – dosage not specified	3 (0.4)
Imeglimin 500 mg – dosage not specified	6 (0.8)
Imeglimin monotherapy and combination therapy, *n* (%)	
Imeglimin monotherapy	113 (15.4)
Imeglimin + 1 OGLA	31 (4.2)
Imeglimin + 2 OGLAs	49 (6.7)
Imeglimin + 3 OGLAs	146 (19.8)
Imeglimin + >3 OGLAs	281 (38.1)
Imeglimin + OGLA + insulin	116 (15.8)
Class of OGLA in combination with imeglimin, *n* (%)	
Metformin	534 (72.6)
SGLT2i	306 (41.6)
DPP4i	436 (59.2)
SU	513 (69.7)
GLP-1 RA	3 (0.4)
TZD	162 (22.0)
AGI	221 (30.0)

alpha-glucosidase inhibitors (30.0%), and thiazolidinediones (22.0%) (Table 2).

Sensitivity Analysis: Completers (Complete Case Cohort *n* = 337) vs Noncompleters (*n* = 399)

A comparison of baseline characteristics between study completers (*n* = 337) and noncompleters (*n* = 399) revealed no significant differences in gender, BMI, or duration of T2D. However, completers were significantly younger (mean 50.9 vs 53.6 years, $p = 0.001$) and had a higher prevalence of diabetes-related complications (37.1% vs 13.5%, $p < 0.001$). Glycemic control at baseline was significantly worse among completers, who exhibited higher mean HbA1c (10.2% vs 9.4%, $p = 0.001$) and fasting plasma glucose (194.7 vs 171.0 mg/dL, $p < 0.001$). Completers were prescribed more intensive baseline regimens and were less likely to receive imeglimin as monotherapy (6.2% vs 23.1%) and more likely to require combinations with more than three oral antidiabetic drugs (42.4% vs 34.6%, $p < 0.001$) (Table S1).

Effectiveness of Imeglimin (Complete Case Cohort *n* = 337)

Glycemic Parameters–Unadjusted Change in HbA1c Over Time

HbA1c levels showed a statistically significant and sustained reduction from baseline, with a mean change of −1.28% at the 3-month follow-up (95% CI: −1.4% to −1.15%; $p < 0.001$) and −2.27% at the 6-month follow-up (95% CI: −2.45% to −2.09%; $p < 0.001$). A further significant decrease was observed −0.99% decrease between the 3-month and 6-month assessments (95% CI: −1.08% to −0.91%; $p < 0.001$), indicating continued decline in HbA1c over 6 months (Fig. 2 and Table S2).

Glycemic parameters–Change in HbA1c (Adjusted Analysis: Linear Mixed-effects Regression Model)

To examine HbA1c change while accounting for individual patient heterogeneity and adjusting for demographic, anthropometric, and clinical covariates, a linear mixed-effects regression model was fitted with a random intercept at the patient level.

A linear mixed-effects model demonstrated a significant reduction in HbA1c over time. Compared to baseline, HbA1c decreased by −1.28% at 3 months (95% CI: −1.41 to −1.14; $p < 0.001$) and −2.27% at 6 months (95% CI: −2.41 to −2.13; $p < 0.001$), indicating a progressive and sustained improvement in glycemic control.

Baseline HbA1c showed a strong association with treatment response, with patients in higher baseline HbA1c categories experiencing significantly greater reductions. Compared to patients with HbA1c <7%, those with baseline HbA1c of 8–8.99%, 9–9.99%, and ≥10% demonstrated additional reductions of −0.66%, −0.87%, and −1.51%, respectively (all 0.001), indicating a clear dose-response relationship.

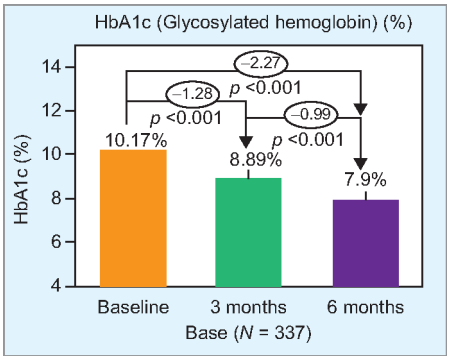

Fig. 2: HbA1c values at baseline and follow-up

No statistically significant associations were observed for BMI, duration of diabetes, insulin use, or number of backgrounds OGLAs, suggesting that the reduction in HbA1c was consistent across these patient subgroups. A low-to-moderate patient-level random effect variance (0.238) has been observed (Table 3).

Other Glycemic Parameters–FPG and PPG

Mean FPG reduced by −48.22 mg/dL at the 3-month follow-up (*n* = 295, 95% CI: −53.56 mg/dL to −42.89 mg/dL; $p < 0.001$) and by −75.19 mg/dL at the 6-month follow-up (95% CI: −81.72 mg/dL to −68.65 mg/dL; $p < 0.001$). PPG showed a change of −76.59 mg/dL (*n* = 295, 95% CI: −85.1 mg/dL to −68.08 mg/dL; $p < 0.001$) and −112.97 mg/dL at the respective follow-ups (*n* = 295, 95% CI: −122.63 mg/dL to −103.3 mg/dL; $p < 0.001$) (Table 4).

Weight and BMI Changes

Body weight and BMI remained stable over 6 months of follow-up, with no statistically significant changes observed between baseline and 3 months, baseline and 6 months, or 3 and 6 months (all $p > 0.05$) (Table 5).

Safety and Tolerability of Imeglimin

The imeglimin regimen was generally well tolerated, with an acceptable safety profile over the treatment period. No SAEs were reported during the follow-up period, and no study participants discontinued the study drug because of AEs or intolerability. The majority of participants reported no complaints (90.1%). Nausea or vomiting was the most frequently observed, affecting 5.2% of patients. Gastrointestinal problems and urinary tract infections were each reported by 1.4%. Hypoglycemia was reported in 1.2% of participants (Table 6).

In two cases of lactic acidosis, a serious adverse event (SAE) was reported; additional

information was sought from the site investigators.

Case 1: A 46-year-old female, on glimepiride, metformin, and imeglimin, presented with 1-day vomiting post-travel. She was dehydrated; labs showed glucose 322 mg/dL, urine 1+ ketones, and mildly elevated lactate (3.2 mmol/L). Lactic acidosis attributed to dehydration with metformin contribution, not imeglimin. IV fluids resolved symptoms; antidiabetics were held temporarily and restarted.

Case 2: A 58-year-old female, on imeglimin 1000 mg twice a day, Dapagliflozin 10 mg, and Humalog mix 50 100 IU/ML injection for management of T2D, presented with severe UTI infection, acidosis diagnosed as DKA, and dehydration post-travel. The patient was admitted to the hospital, and an insulin infusion was initiated as rescue therapy. Patient stabilized and switched completely to insulin therapy. Imeglimin was stopped. Lactic acidosis attributed to severe infection and DKA, possibly due to poor adherence during travel and SGLT2i.

The site principal investigator reported both cases, given the participant's enrollment in the study. However, causality with imeglimin use was definitively excluded in both instances.

Table 3: Prescription details of imeglimin initiation at baseline (complete case cohort, *n* = 337)

Variable	*Estimate (β)*	*95% CI*	*p-value*
Time			
3 months vs baseline	−1.28	(−1.41, −1.14)	<0.001
6 months vs baseline	−2.27	(−2.41, −2.13)	<0.001
Age group (years)			
50–59 vs <50	0.14	(−0.05, 0.33)	0.141
≥60 vs <50	0.35	(0.13, 0.57)	0.002
Gender			
Male vs female	0.05	(−0.11, 0.21)	0.518
BMI group			
Healthy vs underweight	0	(−0.53, 0.52)	0.988
Overweight vs underweight	0.05	(−0.47, 0.57)	0.857
Obesity I vs underweight	0.14	(−0.36, 0.64)	0.575
Obesity II vs underweight	0.17	(−0.37, 0.71)	0.527
Diabetes duration			
6–10 years vs >10 years	0.23	(−0.04, 0.49)	0.095
≤5 years vs >10 years	0.07	(−0.21, 0.35)	0.626
HbA1c groups at baseline			
7–7.99% vs <7%	0.01	(−0.39, 0.41)	0.954
8–8.99% vs <7%	−0.66	(−1.04, −0.28)	0.001
9–9.99% vs <7%	−0.87	(−1.26, −0.49)	0.001
≥10% vs <7%	−1.51	(−1.86, −1.16)	0.001
Insulin use			
Yes vs No	−0.04	(−0.28, 0.20)	0.753
Number of OGLAs			
Mono vs dual	0.10	(−0.34, 0.53)	0.668
Triple vs dual	0.15	(−0.27, 0.58)	0.480
Quadruple vs dual	0.07	(−0.31, 0.44)	0.722
Five vs dual	0.20	(−0.18, 0.59)	0.293
Six vs dual	0.11	(−0.29, 0.51)	0.577
Seven vs dual	0.19	(−0.70, 1.09)	0.671
Random effect (patient)	Variance = 0.238		

Discussion

This prospective, multicenter real-world study demonstrates that imeglimin produces substantial glycemic improvements in Indian adults with inadequately controlled T2D, achieving adjusted HbA1c reductions of 1.28% at 3 months and 2.27% at 6 months. The drug was well-tolerated with low adverse event rates (9.9%) and minimal hypoglycemia (1.2%). These results exceed typical randomized trial efficacy; however, the observational design, 54% attrition, and high baseline HbA1c necessitate cautious interpretation. The study reveals that imeglimin is currently reserved for late-stage use despite a mechanistic rationale for earlier positioning in the Asian Indian phenotype.

Mechanistic Rationale: Two Concerns and a Single Solution

The substantial glycemic improvements observed in this cohort can be contextualized through imeglimin's unique mechanism of action, which addresses the core pathophysiological defects of T2D. As highlighted in a recent narrative review by Samajdar et al., the pathogenesis of T2D is fundamentally driven by two interconnected concerns: insulin resistance and progressive β-cell dysfunction, both of which are deeply rooted in mitochondrial dysfunction. Imeglimin, as the first-in-class "glimin," offers a "single

Table 4: Glycemic parameters – FPG and PPG

Parameters	*Sample size*	*Baseline mean (SD)*	*Follow-up 1 (3 months) mean (SD)*	*Follow-up 2 (6 months) mean (SD)*	*Mean change (baseline–FU2)*	*95% CI (lower, upper)*	*p-value (paired t-test)*
PPG (postprandial plasma glucose) (mg/dL)	295	289.93 (102.09)	213.34 (63.45)	176.97 (43.25)	−112.97	(−122.63, −103.30)	<0.001
FPG (fasting plasma glucose) (mg/dL)	295	194.71 (66.05)	146.48 (38.63)	119.52 (26.80)	−75.19	(−81.72, −68.65)	<0.001

Table 5: Weight and BMI

Parameters	*Sample size*	*Baseline mean (SD)*	*Follow-up 1 (3 months) mean (SD)*	*Follow-up 2 (6 months) mean (SD)*	*Mean change (baseline–FU2), 95% CI*	*p-value (RM-ANOVA test)*
Weight (kg)	260	69.88 (14.0)	69.50 (12.50)	69.49 (12.29)	−0.39 (−1.35, 0.57)	0.393
BMI	258	25.96 (4.37)	25.97 (4.19)	25.97 (4.11)	0.01 (−0.10, 0.12)	0.975

Table 6: Safety profile–incidence of adverse events (safety analysis set, *n* = 573)

Adverse event	*n (%)*
Nausea or vomiting	30 (5.2)
Gastrointestinal problems	8 (1.4)
Urinary tract infection	8 (1.4)
Hypoglycemia	7 (1.2)
Headache	6 (1.0)
Genital infection	3 (0.5)
Lactic acidosis	2 (0.3)
At least one complaint	57 (9.9)
None reported	516 (90.1)

solution" to these dual concerns by directly modulating mitochondrial bioenergetics.[14]

By improving mitochondrial function, imeglimin reduces oxidative stress and enhances ATP generation, which restores glucose-stimulated insulin secretion and attenuates β-cell apoptosis.[14] Concurrently, it reduces hepatic gluconeogenesis and augments glucose uptake in skeletal muscle, thereby ameliorating insulin resistance.[14] This multimodal mechanism is particularly relevant for the Asian Indian phenotype, which is characterized by early β-cell dysfunction, high visceral adiposity, and mitochondrial stress despite relatively modest BMI. By simultaneously targeting these foundational defects, imeglimin provides a comprehensive therapeutic approach that delivers additive glycemic benefits, especially in patients inadequately controlled by conventional therapies that target isolated components of glucose dysregulation.[15–17].

Effectiveness in Context: Comparative and Real-world Evidence

Imeglimin demonstrated substantial effectiveness in this prospective Indian real-world cohort, with adjusted mean HbA1c reductions of 1.28% at 3 months and 2.27% at 6 months, indicating progressive and clinically meaningful glycemic improvement over time. The nonsignificance of BMI and OGLA count is a substantive finding that indicates these variables do not significantly modify the primary treatment effect, reduction in HbA1c.

These reductions are numerically greater than those reported in randomized trial-based meta-analyses, where imeglimin monotherapy or add-on therapy typically achieves HbA1c decrements in the range of 0.5–0.9%. Hagi et al. pooled nine placebo-controlled trials (n ≈ 1,655) and reported HbA1c reductions of approximately 0.45–0.71% with imeglimin 1,000–1,500 mg twice daily, both as monotherapy and adjunctive therapy,[18] while Singh et al. found mean falls of about 0.9% in monotherapy trials with smaller, though still significant, effects when used as an add-on;[19] Abdelhaleem et al. similarly concluded that imeglimin provides modest but clinically relevant HbA1c lowering when added to standard regimens, highlighting that the magnitude of benefit varies with baseline glycemia and background treatment.[20] Comparisons with key clinical trials further support the robustness of the observed effect. In the Japanese TIMES program, TIMES 1 showed that imeglimin monotherapy 1,000 mg twice daily reduced HbA1c by about 0.9% versus placebo over 24 weeks, while TIMES 2 demonstrated sustained HbA1c reductions of roughly 0.8–1.0% over 52 weeks in monotherapy or combination settings, and TIMES 3 reported additional HbA1c decreases of around 0.6–0.7% when imeglimin was added to insulin.[21]

However, this large magnitude of HbA1c decline must be interpreted cautiously within the context of a single-arm, real-world observational design. The pronounced reduction likely reflects several factors beyond the pharmacological effect of imeglimin alone, including the high baseline HbA1c (9.8%), concurrent optimization of background multidrug regimens, and the coadministration of insulin. Most critically, the primary effectiveness analysis was based on a complete-case cohort, with approximately 54% of the initial cohort lost to follow-up at 6 months. As detailed in our sensitivity analysis, noncompleters differed significantly from completers, presenting with higher baseline HbA1c levels and a greater prevalence of diabetes-related complications. Because missing data were not imputed, the reported 2.27% reduction is subject to severe attrition and survivor bias. Furthermore, the observed decline may partly reflect regression to the mean, improved patient adherence following a new prescription, more frequent clinical follow-up, and clinician selection of patients deemed likely to respond. Therefore, these findings represent an association rather than a definitive causal treatment effect.

Real-world evidence, such as the INDI-TIMES study, which documented HbA1c reductions of approximately 1.1–1.3% over 3–6 months in more than 8,000 Indian participants, and other observational series, including other single-center practice studies showing improvements of around 0.8–1.2%, closely align with or modestly trail the present results while confirming effectiveness across diverse demographic and treatment strata.[22] Earlier add-on trials by Fouqueray et al., with metformin or DPP-4 inhibitors, which demonstrated incremental HbA1c reductions of about 0.4–0.6%, further corroborate imeglimin's role as a useful adjunct in inadequately controlled T2D.[23]

To better contextualize these findings, it is instructive to consider recent comparative evidence. A record-based retrospective study by Samajdar et al. evaluated the effectiveness of imeglimin vs vildagliptin as add-on therapies in Indian patients with T2D inadequately controlled on metformin and sulfonylureas.[24] In that study, patients had a lower baseline HbA1c (approximately 8.3%) and a shorter duration of diabetes compared to the present cohort. Despite these differences in baseline profiles, the comparative study demonstrated that imeglimin achieved a significantly greater HbA1c reduction (−0.98%) compared to vildagliptin (−0.59%) over 3 months.[24] While our present study is prospective and multicenter, offering robust longitudinal data, the record-based comparative study by Samajdar et al. provides crucial contextual evidence supporting the efficacy of imeglimin as an add-on therapy relative to an established dipeptidyl peptidase-4 (DPP-4) inhibitor.[24]

Together, these complementary study designs reinforce the clinical utility of imeglimin in diverse real-world settings, without necessarily confirming superiority in the absence of head-to-head randomized trials.

Safety, Tolerability, and Metabolic Neutrality

Imeglimin demonstrated a favorable safety and tolerability profile over the 6-month follow-up, with a low overall incidence of reported adverse events (9.9%). The most frequently reported events were mild gastrointestinal symptoms, such as nausea or vomiting (5.2%), which aligns with the known safety profile of the drug. Importantly, the incidence of hypoglycemia was notably low (1.2%). Two investigator-reported events of lactic acidosis were recorded, and further investigation into both these cases revealed no causality of the event with imeglimin use. Given the observational nature of the study, the presence of multiple concomitant antidiabetic therapies, and limited biochemical adjudication, a causal relationship with imeglimin could not be established.

This favorable tolerability is consistent with the findings from the comparative study by Samajdar et al., which reported comparable and low adverse drug reaction rates for both imeglimin (5.71%) and vildagliptin (4.58%), with no severe hypoglycemic events.[24] In TIMES-2, around 70–75% of individuals experienced at least one treatment-emergent adverse event over 52 weeks, with nasopharyngitis and gastrointestinal symptoms (including nausea) occurring in ≥5% and hypoglycemia

in about 3–4%, mostly mild and rarely leading to discontinuation.[21]

The overall incidence of reported adverse events in this study (9.9%) is lower than that observed in randomized clinical trials of imeglimin, where treatment-emergent adverse events have been reported in approximately 60–75% of individuals over longer follow-up periods. This difference is likely attributable to the real-world observational design, shorter duration of follow-up, less intensive and protocol-driven safety monitoring, and reliance on spontaneous reporting in routine clinical practice, which may result in under-ascertainment of mild or transient events, particularly gastrointestinal symptoms.

INDI-TIMES study has also reported very low rates or absence of recorded adverse events with Imeglimin, reinforcing its favorable tolerability but similarly raising the possibility that minor gastrointestinal symptoms are underreported outside trial settings.[22] Notably, emerging data in special populations, including individuals with metformin intolerance, advanced chronic kidney disease, and those on dialysis, suggest that imeglimin can be used safely with appropriate monitoring, expanding its potential utility in complex, high-risk individuals commonly seen in Indian practice.[13] Taken together, the predominance of mild gastrointestinal events, rare hypoglycemia, and lack of a clear signal for serious toxicity in this and other studies support a generally favorable tolerability profile for Imeglimin, while underscoring the need for more systematic, prospective safety capture to better quantify event rates in everyday practice.

Prescription Patterns and Therapeutic Inertia

This prospective, multicenter, real-world study provides valuable insights into the utilization, effectiveness, and safety of imeglimin among Indian adults with T2D. A key contribution of this study is the detailing of current prescription patterns in routine clinical practice. Imeglimin was predominantly utilized as an add-on therapy, with over 80% of patients receiving it in combination with multiple OGLAs, and nearly 16% receiving it alongside insulin. Monotherapy accounted for only 15.4% of prescriptions. Notably, the majority of patients were initiated on imeglimin only after the failure of three or more OGLAs, yet it produced significant HbA1c reductions. This pattern suggests that the drug retains glycemic efficacy even in metabolically complex, treatment-experienced individuals, and that the magnitude of benefit is closely linked to baseline HbA1c rather than to its position in the therapeutic sequence.[22]

This prescription pattern highlights a significant degree of therapeutic inertia in the management of T2D. The late adoption of imeglimin in the treatment sequence reflects a tendency to reserve newer agents for metabolically complex, treatment-experienced individuals with high baseline HbA1c (mean 9.8%), rather than in early sequencing.

While the data demonstrate that imeglimin retains substantial glycemic efficacy even in advanced disease stages, this pattern suggests that its current clinical positioning is driven more by prescribing customs and recent market entry than by pharmacological limitations.[12,21]

From a pathophysiological standpoint, the typical Asian Indian phenotype represented in this cohort, characterized by early β-cell dysfunction, high visceral adiposity and mitochondrial stress at relatively modest BMI-provides a strong rationale for considering imeglimin before overt failure of other oral agents.[8] By simultaneously enhancing glucose-stimulated insulin secretion, improving mitochondrial bioenergetics and attenuating hepatic gluconeogenesis, imeglimin targets core defects that emerge early in the natural history of T2D, and there is no mechanistic reason to reserve these actions only for individuals already on multiple therapies.[5,15] Indeed, introducing imeglimin earlier, for example, as part of an initial combination strategy with metformin or DPP-4 inhibition in individuals with high baseline HbA1c or rapid glycemic deterioration, may help to achieve durable control while limiting the need for early insulin initiation or further escalation of secretagogue doses.[12,23]

These observations have important implications for therapeutic inertia, which remains a major barrier to timely intensification in T2D and is associated with prolonged exposure to suboptimal glycemia and increased risk of complications.[17] Instead of waiting for unequivocal failure of existing oral regimens, clinicians managing individuals with the high-risk Indian phenotype should actively consider imeglimin when HbA1c remains above individualized targets despite one or two agents, particularly in those with evidence of early β-cell decline, fluctuating post-prandial excursions, or intolerance to further dose escalation of current therapy.[8] In this context, the favorable tolerability profile observed in this and other real-world series—marked by weight neutrality, low hypoglycemia risk, and absence of major organ-specific toxicity—even in elderly individuals, those with renal impairment or metformin intolerance, supports its use as a pragmatic, earlier add-on option in routine practice. Collectively, the patient profile and response pattern in this cohort reinforce the view that imeglimin should be viewed not merely as a late-stage rescue therapy, but as a versatile component of earlier multidrug regimens for Asian Indian individuals with T2D who are at high lifetime risk of complications.

Strengths and Limitations

The strengths of this study include its prospective, multicenter design and the large sample size, which capture the realities of imeglimin utilization in routine Indian clinical practice. The documentation of complex polypharmacy and the inclusion of patients with high baseline HbA1c provide a pragmatic view of treatment dynamics that are often excluded from tightly controlled RCTs.

This study has several limitations that should be acknowledged. Its observational, single-arm design without a comparator group precludes causal inference and makes it difficult to separate the effect of imeglimin from concurrent lifestyle modifications or adjustments to background therapies. Accordingly, the observed reductions in glycemic parameters in this study should be interpreted as associative rather than causal. Selection bias is possible because only participants who returned for all follow-up visits and had complete HbA1c data were included in the effectiveness analysis (337/736, ~46%), potentially over-representing adherent or motivated individuals; baseline characteristics of noncompleters were compared and found to be significantly different on key parameters (younger, higher HbA1c, more complications at baseline) (Table S1). The follow-up duration of 6 months is relatively short, limiting conclusions about long-term glycemic durability, impact on diabetes complications, micro-/macrovascular events, or very rare adverse events. Treatment decisions—including dose, timing of imeglimin initiation, and combination regimens—were heterogeneous, and the study sites were predominantly urban primary and secondary care centers. Consequently, the external validity and generalizability of these findings to rural Indian populations, public hospital settings, and economically constrained demographic groups may be limited. Finally, the reliance on spontaneous adverse event reporting in routine care may have led to an under-ascertainment of mild or transient side effects compared to protocol-driven surveillance in clinical trials.

Future Research Directions

The findings from this real-world cohort highlight the need for further research to optimize the clinical positioning of imeglimin.

Given its unique mechanism targeting mitochondrial dysfunction, future prospective, randomized, active-comparator trials are warranted to evaluate the efficacy of imeglimin when introduced earlier in the disease trajectory, compared to its current use as a late-stage rescue therapy. Additionally, long-term studies are needed to assess the durability of glycemic control, the potential for β-cell preservation, and the impact on cardiovascular and renal outcomes in diverse populations, including rural and resource-limited settings.

Conclusion

In routine clinical practice, the initiation of imeglimin among Indian adults with type 2 diabetes was associated with clinically meaningful reductions in HbA1c, fasting plasma glucose, and postprandial glucose over a 6-month period, alongside a favorable safety profile. These real-world findings support the clinical utility and tolerability of imeglimin as an effective therapeutic option for glycemic management in this population. Future randomized controlled trials with extended follow-up are warranted to establish definitive causal treatment effects and evaluate long-term clinical outcomes.

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Conflict of Interest

None.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Table S1: Sensitivity analysis: completers (complete case cohort, *n* = 337) vs noncompleters (*n* = 399)

Parameters	*Completers*	*Noncompleters*	*p-value*	*Test*
Sample size (N)	337	399		
Gender, *n* (%)				
Female	142 (42.1)	175 (43.9)	0.692	Chi-squared
Male	195 (57.9)	224 (56.1)		
Age (years), mean (SD)	50.9 (11.4)	53.6 (11.2)	0.001	Two-sample *t*-test
BMI baseline, mean (SD)	28.0 (31.1)	27.2 (4.9)	0.671	Two-sample *t*-test
Duration of type 2 diabetes, mean (SD)	6.7 (4.2)	6.7 (5.2)	0.979	Two-sample *t*-test
Complication due to diabetes – at least one complication, *n* (%)				
No	212 (62.9)	345 (86.5)	<0.001	Chi-squared
Yes	125 (37.1)	54 (13.5)		
Class combinations at baseline, *n* (%)				
Only imeglimin	21 (6.2)	92 (23.1)		
Imeglimin + 1 OAD	14 (4.2)	17 (4.3)	<0.001	Chi-squared
Imeglimin + 2 OADs	28 (8.3)	21 (5.3)		
Imeglimin + 3 OADs	85 (25.2)	61 (15.3)		
Imeglimin + >3 OADs	143 (42.4)	138 (34.6)		
Imeglimin + OAD(s) + insulin	46 (13.6)	70 (17.5)		
Antidiabetic class–insulin, *n* (%)				
No	291 (86.4)	329 (82.5)	0.179	Chi-squared
Yes	46 (13.6)	70 (17.5)		
HbA1c (%) grouping, *n* (%)				
<7%	20 (5.9)	50 (12.5)	<0.001	Chi-squared
7–7.99%	35 (10.4)	66 (16.5)		
8–8.99%	56 (16.6)	68 (17.0)		
9–9.99%	48 (14.2)	59 (14.8)		
≥10%	178 (52.8)	156 (39.1)		
HbA1c (%), mean (SD)	10.2 (2.1)	9.4 (2.2)	<0.001	Two-sample *t*-test
PPG (postprandial glucose) (mg/dL) grouping, *n* (%)				
Low (<100)	0 (0.0)	1 (0.4)		
Normal (100–140)	18 (6.1)	11 (4.6)	0.407	Chi-squared
High (>140)	278 (93.9)	228 (95.0)		
PPG (postprandial glucose) (mg/dL), mean (SD)	289.7 (102.0)	250.5 (86.5)	<0.001	Two-sample *t*-test
Fasting plasma glucose (FPG) (mg/dL) grouping, *n* (%)				
Normal (<100)	20 (6.8)	18 (7.3)	0.479	Chi-squared
Prediabetes (100–125)	31 (10.5)	34 (13.8)		
Diabetic (>125)	244 (82.7)	195 (78.9)		
Fasting plasma glucose (FPG) (mg/dL), mean (SD)	194.7 (66.0)	171.0 (61.6)	<0.001	Two-sample *t*-test

Table S2: Glycemic parameter—HbA1c (unadjusted values)

Parameters (N = 337)	*Sample size*	*HbA1c at baseline mean (SD)*	*HbA1c at 6 months mean (SD)*	*Mean difference in HbA1c (baseline–6 months) (%)*	*95% CI (baseline–FU2) (%)*	*p-value (paired t-test)*
OHA combinations						
Only imeglimin	21	9.10 (2.57)	7.44 (1.12)	−1.65	(−2.51, −0.79)	<0.001
Imeglimin + 1 OHA	14	9.55 (1.89)	7.40 (1.18)	−2.16	(−3.16, −1.15)	<0.001
Imeglimin + 2 OHAs	28	9.68 (1.57)	7.43 (1.22)	−2.24	(−2.76, −1.72)	<0.001
Imeglimin + 3 OHAs	85	9.63 (1.98)	7.60 (1.22)	−2.03	(−2.37, −1.68)	<0.001
Imeglimin + >3 OHAs	143	10.52 (2.14)	8.21 (1.74)	−2.31	(−2.61, −2.01)	<0.001
Imeglimin + OHA(s) + insulin	46	11.04 (1.81)	8.12 (1.19)	−2.92	(−3.36, −2.49)	<0.001
Gender						
Male	195	10.18 (2.18)	7.96 (1.54)	−2.23	(−2.48, −1.98)	<0.001
Female	142	10.15 (2.01)	7.82 (1.40)	−2.33	(−2.60, −2.06)	<0.001
Age groups						
18–50 years	151	10.17 (2.02)	7.59 (1.27)	−2.58	(−2.85, −2.31)	<0.001
50–59 years	110	10.45 (2.12)	8.07 (1.51)	−2.38	(−2.70, −2.07)	<0.001
≥60 years	76	9.77 (2.21)	8.27 (1.71)	−1.50	(−1.86, −1.13)	<0.001
Baseline HbA1c						
<7%	20	6.25 (0.59)	6.11 (0.58)	−0.15	(−0.35, 0.06)	0.154
7–7.99%	35	7.53 (0.31)	7.31 (1.36)	−0.22	(−0.69, 0.25)	0.349
8–8.99%	56	8.63 (0.24)	7.16 (0.73)	−1.48	(−1.68, −1.27)	<0.001
9–9.99%	48	9.48 (0.30)	7.48 (1.07)	−1.99	(−2.32, −1.67)	<0.001
≥10%	178	11.80 (1.29)	8.56 (1.48)	−3.24	(−3.45, −3.02)	<0.001
Duration of T2D						
≤5 years	117	9.94 (1.92)	7.43 (0.99)	−2.52	(−2.84, −2.20)	<0.001
6–10 years	137	9.96 (2.17)	7.79 (1.45)	−2.17	(−2.48, −1.87)	<0.001
>10 years	40	11.11 (2.26)	8.38 (1.11)	−2.74	(−3.26, −2.22)	<0.001