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ORIGINAL RESEARCH

Efficacy of a Combination of Metformin and Vildagliptin in Comparison to Metformin Alone in Type 2 Diabetes Mellitus: A Multicentre, Retrospective, Real-World Evidence Study

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Background: Early use of combination therapy in diabetes patients may lead to sustained glycemic control and thereby reduce the progression of diabetic complications. Given the limitation of the traditional stepwise intensification strategy, early combination therapy can be an effective approach. Therefore, this study aims to assess the real-world efficacy of a combination of metformin and vildagliptin in comparison to metformin alone in type 2 diabetes mellitus (T2DM) patients in India.

Methods: This was an observational, retrospective, non-interventional study based on electronic medical records (EMRs) of 2740 T2DM patients, retrieved from 2010 onwards from 22 diabetes centres across India. Adult drug naïve patients with a 5-year history of T2DM treated with either metformin or a combination of metformin and vildagliptin for at least 3 months were considered for this study. Efficacy assessment was done to evaluate the post-treatment HbA1c levels and patients requiring additional oral antidiabetic drugs (OADs) at the time of follow-up visit. Patients were also analyzed for the occurrence of adverse events.

Results: Out of the total, 2452 patients were in metformin only arm, and 288 patients were in metformin plus vildagliptin treatment arm. A more significant reduction in HbA1c level was observed in metformin plus vildagliptin arm than metformin only arm (median: −0.5% vs 0%, respectively; $p<0.001$). Patients requiring additional OAD at follow-up were significantly lesser in the metformin plus vildagliptin arm than the metformin only arm (15.6% vs 35.2%, respectively; $p<0.001$). The adverse events were comparable across the two arms, and commonly reported adverse events were giddiness, fatigue and gastric discomfort.

Conclusion: The findings of this EMR-based real-world study emphasizes the need for early initiation of combination therapy (metformin plus vildagliptin) over metformin monotherapy for achieving better glycemic control.

Keywords: metformin, vildagliptin, type-2 diabetes, electronic medical records, real-world study

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Introduction

Type 2 Diabetes mellitus (T2DM) is a chronic non-communicable disease that has become a pandemic today.[1] According to the International Diabetes Federation, the global prevalence of T2DM was 9.3% (463 million) in 2019, which is expected to increase to 10.9% (700 million) by 2045.[2] India was estimated to have

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the second-largest T2DM population in the world at 77 million in 2019; and this is projected to increase to 134 million by 2045.[3]

Although the therapeutic armament for T2DM is growing, lifestyle modification remains the mainstay for its management. Pharmacotherapy initially focused on metformin monotherapy as the starting regimen for T2DM. There was evidence for the efficacy of early combination therapy in patients with higher glycosylated hemoglobin (HbA1c) levels, but this is now also available for patients at lower HbA1c levels.[4,5] Although intensification of metformin monotherapy with higher doses has improved glycemic control, the increased incidence of gastrointestinal adverse events has contributed to reduced patient compliance.[6]

Therefore, the limitations of the stepwise intensified treatment approach warrant new treatment strategies. Before responsiveness to monotherapy begins to decline, early use of more aggressive combination therapy can be an effective approach.[1,7,8] This approach may provide several advantages, including greater glycemic control and the ability to act on different pathological mechanisms involved in glucose dysregulation. Moreover, early interventions are advantageous for slowing the progression of T2DM disease and the associated macrovascular and microvascular complications.[1]

Vildagliptin is a potent and selective dipeptidyl peptidase-4 inhibitor (DPP4i) that increases alpha- and beta-cell responsiveness to glucose without causing weight gain or increasing the hypoglycemia risk.[9,10] The INITIAL study and VERIFY trial based studies demonstrated that early combination therapy (vildagliptin plus metformin) provided better glycemic control than initial metformin monotherapy for T2DM patients.[11–14] However, there exist a lacuna of real-world data based evidence wherein the comparative effectiveness of combination therapy and monotherapy has not been assessed in real-world Indian settings. This evidence will aid the treating clinicians in decision making to provide the individualized and holistic care to the patients for better diabetes management. According to a recent Indian expert's panel opinion,[15] a more proactive, early, and aggressive approach has been recommended to be followed with early introduction of the intervention for diabetes. It was recommended that early combination therapy provides a good legacy effect and therefore, helps in improving glycemic profiles without significantly increasing the incidence of side effects. Hence, this study has been designed to provide real-world evidence to assess the impact of early combination therapy by facilitating evidence-based management.

Study Objectives

1. To understand the effectiveness of the combination of metformin and vildagliptin in comparison to metformin monotherapy in newly diagnosed T2DM patients during a follow-up period of 2 years.
2. To understand patterns of oral antidiabetic therapy during a follow-up period of 2 years.

Materials and Methods

This was an observational, retrospective, non-interventional study based on electronic medical records (EMRs) of patients with T2DM. The EMRs of 2740 patients fulfilling study criteria were retrieved from 2010 onwards from 22 diabetes centres across India. The study was approved by Royal Pune Independent Ethics Committee (RPIEC) located at Pune, India (Ethics Approval Number: THBR20-009).

The sample size for this study was estimated using treatment allocation ratio 8:1, with α probability (~0.05), p=proportion of the population (p = 0.7%), effect size (0.02), power (1-β error probability = ~0.80) and two tailed approach. Hence, the required sample size for the designed study was 2452: 288 enhancing the precision to the treatment arm by reducing the sampling error to 5%.

Adult drug naïve patients with T2DM who were either on metformin or a combination of metformin and vildagliptin for at least 3 months were considered eligible for this study. The minimum requirements were patients having at least a follow-up period of 2 years after the first/index visit, at least two HbA1c values, and at least one detailed prescription during a follow-up period of 2 years. The diagnostic criteria followed for T2DM were based on fasting blood glucose, postprandial blood glucose, and HbA1c levels.

Patients with a duration of T2DM more than 5 years were excluded. Patients with serum creatinine>1.5 mg/dL for males and >1.4 mg/dL for females, positive for hepatitis B & C, AST/ALT >2, total bilirubin> 1.5 mg/dL, and history of myocardial infarction, heart failure or malignancy were also excluded.

Patients were divided into two arms based on treatment details – (a) Patients on monotherapy with metformin (b) Patients on combination therapy with metformin and vildagliptin. The two treatment arms were compared in terms

of age, gender, mean HbA1c and other oral antidiabetic drugs (OADs).

Definitions

Short Duration Patients

These patients were diagnosed with T2DM for less than 5 years.

Drug Naïve

This study considered only those patients where T2DM patients initiated or were on metformin monotherapy or the combination of metformin and vildagliptin for equal or more than 3 months.

Improvement in HbA1c Status

Improvement in HbA1c status is defined by HbA1c level below 7% (at follow-up) as compared to the baseline HbA1c status.

Non-Improvement in HbA1c Status

Non-improvement in HbA1c status is defined by HbA1c level above 7% (at follow-up) as compared to the baseline HbA1c status.

Study Endpoints

Primary Endpoints

The primary endpoints were to estimate the percentage of patients achieving glycemic control of HbA1c <7%. The percentage of patients requiring additional OAD while on metformin monotherapy or combination therapy with metformin plus vildagliptin over a follow-up period of 2 years was also estimated.

Secondary Endpoints

Assessment of time-period for additional drug requirement, percentage of patients on combination therapy at the HbA1c level >7.5% and percentage of patients reported adverse events in both the arms in the defined follow-up period.

Statistical Analysis

Data analysis was done using R Studio-3.6.2. Descriptive statistical analysis was conducted on categorical and continuous variables. Categorical variables were expressed as percentages and compared by using the Chi-square test for proportions. Continuous variables expressed as means were compared using t-statistics, and median values were compared using the Mann Whitney-*U* test. The post-treatment HbA1c levels at the follow-up visit were compared across treatment arms using a similar duration of follow-up as in the metformin and vildagliptin treatment group. Statistical significance was considered at $p<0.05$.

Results

A total of 2740 patients were included and analyzed; of which 2452 patients were in the metformin only treatment arm and 288 patients were included in the metformin plus vildagliptin treatment arm. Baseline characteristics of the study patients are presented in Table 1. Females accounted for 39.1% of the study population. The mean age of patients in metformin only and metformin plus vildagliptin treatment arms were similar (49.2 years vs 48.3 years, respectively; $p=0.1$). The mean duration of diabetes was significantly greater in the metformin only arm than the metformin plus vildagliptin arm of the study (2.9 years vs 1.7 years, $p<0.001$, respectively). A higher proportion of patients had HbA1c >7.5% in metformin plus vildagliptin arm compared to metformin only arm (56.9% vs 22.2%; $p<0.00001$, respectively). The baseline mean HbA1c levels were similar in metformin and metformin plus vildagliptin arm across HbA1c categories ≤7.5% and >9%.

The various treatment-related attributes at follow-up visit are depicted in Table 2. Significantly greater reduction in HbA1c level was observed in metformin plus vildagliptin arm in comparison to metformin only arm (median: −0.5% vs 0%, respectively; $p<0.001$). Reduction in HbA1c level was slightly higher in males as compared to females in the combination group (males vs females: −0.6% vs −0.5%; $p<0.001$) and the reduction was similar in metformin only group across both the genders (males vs females: 0% vs 0%; $p<0.001$). Only 45 (15.6%) patients in the metformin plus vildagliptin arm required an add-on therapy versus 863 (35.2%) in the metformin only arm ($p<0.001$). The average time taken for the first add on drug requirement was longer in the metformin only arm than the combination arm (14.3 vs 10.4 months, respectively; $p<0.05$). 49% percentage of patients achieved glycemic control of HbA1c <7% in combination arm versus 48% reduction in metformin only arm over similar duration of follow-up (49.0% vs 48.3%; $p=0.829$).

Across each baseline HbA1c category, different groups of HbA1c levels were assessed at the follow-up visit (Table 3). In ≤7.5% baseline HbA1c category, a higher proportion of patients were found to be in the follow-up HbA1c ≤7.5% subgroup of combination arm as compared

Table 1 Baseline Characteristics of Treatment Arms

Baseline Variables		Metformin (N= 2452)	Metformin + Vildagliptin (N= 288)	*p*
Gender Female, N (%) Male, N (%)		 978 (39.9%) 1474 (60.1%)	 92 (31.9%) 196 (68.1%)	 0.009
Age (years), Mean (SD)		49.2 (9.4)	48.3 (10.5)	0.119
BMI (kg/m^2), Mean (SD)		28.2 (4.2)	28.5 (4.5)	0.291
SBP (mmHg), Mean (SD)		127.9 (15.8)	128.8 (17.5)	0.346
DBP (mmHg), Mean (SD)		81.5 (8.6)	82.1 (9.5)	0.225
Weight (in kg), Mean (SD)		74.5 (12.8)	77.5 (14.0)	<0.001
Triglyceride levels, Mean (SD)		162.9 (102.6)	158.8 (98.9)	0.541
Age at onset of T2DM (years), Mean (SD)		46.3 (9.3)	46.3 (10.2)	0.968
Duration of T2DM (years), Mean (SD)		2.9 (1.2)	1.7 (1.7)	<0.001
Baseline HbA1c levels (%), Mean (SD)		7.1 (0.9)	8.1 (1.6)	<0.001
HbA1c <7%	N (%) Mean (SD)	1268 (51.7%) 6.4 (0.4)	71 (76.3%) 6.4 (0.3)	<0.001 0.781
HbA1c ≤7.5%	N (%) Mean (SD)	1907 (77.8%) 6.7 (0.5)	124 (43.1%) 6.8 (0.5)	<0.001 0.062
HbA1c >7.5%	N (%) Mean (SD)	545 (22.2%) 8.4 (1.0)	164 (56.9%) 9.1 (1.4)	<0.00001 <0.00001
HbA1c >9%	N (%) Mean (SD)	92 (3.8%) 10.1 (1.2)	67 (23.3%) 10.5 (1.2)	<0.001 0.07

Note: Level of significance was considered to be $p<0.05$.
Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin.

to metformin only arm (85.5% vs 80.4%, respectively). The mean treatment duration at follow-up visit was lower for the combination arm than metformin arm in follow-up HbA1c categories ≤7.5% (8.1 vs 9.6 months, respectively) and >7.5% - ≤9% (9.3 vs 15.5 months, respectively).

In >9% baseline HbA1c category, combination therapy arm was having a higher proportion of patients in follow-up HbA1c subgroup ≤7.5% indicating that improvement was observed more in combination therapy arm than metformin only arm (55.2% vs 28.3%, respectively). The mean treatment duration at follow-up visit was lower for the combination arm than the metformin arm in follow-up HbA1c categories ≤7.5% (6.6 vs 7.4 months, respectively).

Patients from both arms were switched to various combinations such as metformin and other OADs (except vildagliptin); metformin, vildagliptin, and other OADs; vildagliptin and other OADs (except metformin); or only metformin, vildagliptin and other OADs. Overall, 59.2% of the patients in the metformin only arm and 47.2% of the patients in the combination arm remained unchanged in their drug regimen. Furthermore, 13.2% of patients in metformin and vildagliptin arm were down titrated to metformin and 1% to vildagliptin in the follow-up visit on achieving HbA1c target of <7%.

The association between the drug switching pattern and the HbA1c levels at which drug switching happened were assessed. In the metformin only arm, an increase in HbA1c level was seen at the time of switching or in the immediate follow up HbA1c values. In the metformin only arm, the patients were continued on metformin only or switched to vildagliptin only when HbA1c level of <7% was noted during the immediate follow-up. However, the patients were switched to metformin and others (except vildagliptin), metformin and vildagliptin, metformin plus vildagliptin and others, and other OADs (except metformin), when HbA1c level of >7% was observed during the immediate follow-up.

Table 2 Treatment Details and HbA1c Levels at Follow Up Visit

Categories	Metformin (N= 2452)	Metformin + Vildagliptin (N= 288)	*p*
Post-treatment HbA1c levels over similar duration of follow-up (%)			
HbA1c <7%, N (%)	1184 (48.3%)	141 (49.0%)	0.829
HbA1c ≤7.5%, N (%)	1623 (66.2%)	195 (67.7%)	0.606
HbA1c >7.5%, N (%)	522 (21.3%)	93 (32.3%)	<0.0001
HbA1c level at the follow-up visit (%)			
Mean (SD)	7.2 (1.3)	7.4 (1.5)	0.014
Change in HbA1c level from baseline to follow-up (%)			
Overall Median (Range)	0 (17.6)	−0.5 (13.2)	<0.001
Gender wise change in HbA1c level from baseline to follow-up (%)			
Male Median (Range)	0 (14.9)	−0.6 (13.2)	<0.001
Female Median (Range)	0 (12.1)	−0.5 (10.6)	<0.001
Patients requiring add-on drug			
N (%)	863 (35.2%)	45 (15.6%)	<0.001
Duration for add-on drug requirement (Months)			
Mean (SD)	14.3 (9.2)	10.4 (8.1)	0.005

Note: Level of significance was considered to be $p<0.05$.
Abbreviations: HbA1c, glycosylated hemoglobin; SD, standard deviation.

In the metformin and vildagliptin arm, the patients were switched to metformin only, vildagliptin only or continued metformin and vildagliptin when HbA1c level <7% was noted during the immediate follow-up. However, the patients were switched to metformin and others (apart from vildagliptin), metformin plus vildagliptin and others, when HbA1c level >7% was observed during the immediate follow-up.

Table 3 Change in HbA1c Levels by Different Baseline and Follow-Up HbA1c Level Categories

Baseline HbA1c Levels (%)	Follow-up HbA1c Levels (%)	Metformin	Metformin + Vildagliptin	*p*
		Patient Count N (%)	Patient Count N (%)	
≤7.5%	≤7.5% >7.5%–≤9% >9%	1534 (80.4%) 263 (13.8%) 110 (5.7%)	106 (85.5%) 11 (8.8%) 7 (5.6%)	0.292
>9%	≤7.5% >7.5%–≤9% >9%	26 (28.3%) 34 (36.9%) 32 (34.8%)	37 (55.2%) 14 (20.9%) 16 (23.9%)	0.002

Note: Level of significance was considered to be $p<0.05$.
Abbreviation: HbA1c, glycosylated hemoglobin.

The immediate-release formulation of metformin was prescribed to a significantly greater proportion of patients in the combination arm than those in the metformin only arm (77.4% vs 41.6%, respectively; $p<0.0001$). The extended-release formulation of metformin was prescribed significantly greater proportion in the metformin only arm than those in the combination arm (58.4% vs 22.6%, respectively; $p<0.0001$). In both the treatment arms, 39% of patients were on other antidiabetic medications (other than metformin alone, vildagliptin alone and metformin plus vildagliptin combination).

Patients were analyzed for the occurrence of adverse events (Table 4). Patients belonging to the metformin only arm experienced giddiness (18.5%), fatigue (13.6%), gastric discomfort (4.1%), constipation (2.2%), bloating (0.6%) and hypoglycemia (0.2%). Common adverse events reported in the metformin plus vildagliptin arm were fatigue (15.5%), giddiness (13.3%) and gastric discomfort (4.1%). None of the patients reported constipation, bloating and hypoglycemia in the combination group during their treatment period. The difference in the adverse events was not statistically significant between the treatment arms.

Table 4 Adverse Events by Treatment Group

Adverse Events	Metformin (N=810) n (%)	Metformin + Vildagliptin (N=97) n (%)	*p*
Giddiness	150 (18.5%)	13 (13.3%)	0.215
Fatigue	110 (13.6%)	15 (15.5%)	0.611
Gastric discomfort	33 (4.1%)	4 (4.1%)	0.47
Constipation	18 (2.2%)	0 (0%)	–
Bloating	5 (0.6%)	0 (0%)	–
Hypoglycemia	2 (0.2%)	0 (0%)	–

Note: Level of significance was considered to be $p<0.05$.

The gastrointestinal adverse events with the immediate and extended-release formulation of metformin were compared for the metformin only arm. It was found that immediate-release formulation demonstrated higher number of adverse events as compared to extended-release formulation such as gastric discomfort (4.4% vs 3.8%; $p= 0.690$), constipation (2.3% vs 2.1%; $p=0.838$) and bloating (1.2% vs 0.2%; $p=0.085$). Similarly, in the metformin plus vildagliptin arm, immediate-release metformin was associated with higher adverse events such as acidity (2.6%), gastric discomfort (3.8%), nausea (3.8%) and indigestion (2.6%). However, with extended-release metformin formulation, only one patient reported gastric side effect (gastric discomfort).

Discussion

The efficacy and safety of vildagliptin alone or metformin have been well established in various randomized controlled trials predominately among Caucasian populations.[16,17] Our study confirms similar findings for Indian T2DM patients in real-world settings. This study demonstrates better glycemic control with metformin plus vildagliptin dual therapy than metformin monotherapy since the observed reduction in HbA1c levels was higher in the combination arm than metformin only arm. Furthermore, the proportion of patients requiring additional OAD at follow-up were significantly lesser within the combination arm than the metformin only arm.

The "pathophysiologic approach" using initial combination therapy with antidiabetic agents that correct well-established pathophysiologic defects of T2DM has been associated with better outcomes than the traditional "treat to failure" approach. In addition to insulin resistance in muscle/ liver and failure of beta cells (the "triumvirate"), there are five other pathophysiological abnormalities that are associated with the development of T2DM, which are collectively referred to as "ominous octet". A paradigm shift has been observed wherein the initial combination therapy correcting the majority of the known pathogenic abnormalities in T2DM is now preferred. The use of DPP4i in combination with metformin has gained the spotlight due to its weight neutrality, modest efficacy, and safety. Furthermore, a combination of metformin/DPP4i therapy may lead to an increase in glucagon-like peptide-1 (GLP-1) levels and thereby produces additional glucose-lowering effects.[18]

In our study, the mean duration for add-on therapy at follow-up was significantly less in the metformin plus vildagliptin arm than the metformin only arm. The time to add-on-therapy was lesser with the combination arm since other OADs were added earlier to achieve the target HbA1c levels. This result is congruent with an EMR data-based study which reported that the addition of DPP4i to metformin is associated with an earlier requirement for a third line glucose-lowering agent.[19] The 2021 American Diabetes Association (ADA) guidelines also recommend that the choice of add-on OAD should be based on target HbA1c, avoidance of side effects, cost, and patient preferences.[20]

In the present study, the baseline HbA1c levels were higher in combination arm as compared to the metformin only arm (8.1% vs 7.1%). According to ADA (Standards of Medical Care in Diabetes), when HbA1c is ≥1.5% above the glycemic target, then patient requires dual combination therapy to achieve their target HbA1c level.[20] Our study showed congruence with ADA 2021 guidelines wherein patients presenting with higher HbA1c were prescribed with combination therapy.

Additionally, the comparable mean HbA1c levels (7.2% metformin only arm and 7.4% combination therapy arm) were observed at the time of follow up in both arms. In addition, patients with HbA1c >7.5% at the follow-up visit was higher in the combination arm than the metformin only arm. This could be explained by the fact those with higher baseline HbA1c are given combination therapy. Hence, given the higher baseline HbA1c levels in the combination therapy arm, more reduction was seen in it than in the metformin arm. This finding is consistent with a randomized controlled trial (RCT), which showed that vildagliptin plus high dose or low dose metformin combination therapy led to the higher reduction of HbA1c levels (up to 1.8% and 1.6%, respectively) as compared to metformin monotherapy (1.4%).[21] Reduction in HbA1c level was slightly higher in males as compared to females in the combination group. However, in metformin only group, the reduction was similar across both the genders. The

results from the present study pertaining to combination therapy concurred with the previous finding that there exists the gender-related distinction in efficacy/treatment response in T2DM.[22]

Furthermore, 13.2% of patients in the combination group were down titrated from metformin and vildagliptin combination to metformin. This could be due to the achievement of glycemic targets (HbA1c <7%) due to the use of combination therapy.[4] However, when HbA1c was >7%, there was a drug switching pattern observed in our study. The patients had to switch over from the monotherapy or combination therapy to other monotherapy or combination therapy with other drug classes over the treatment period. Similar patterns were reported by a population-based retrospective cohort study wherein drug classes switching was observed across monotherapies and combination therapies.[23] According to the prior research, HbA1c level ≥7% signifies imperfect glycemic control which demonstrates that there might be a need of treatment initiation or modification.[24] Based on HbA1c above 7%, patients might require a treatment revision by drug addition or switch in real-world practice.[25]

The current study showed that adverse events such as giddiness, fatigue and gastric discomfort were similar for the metformin only arm and the metformin plus vildagliptin arm. This finding is congruent with the VERIFY trial, which showed that the adverse events were comparable in metformin alone and metformin plus vildagliptin combination therapy.[12]

Additionally, our study showed that immediate-release metformin had greater gastrointestinal adverse events than the extended-release formulation of metformin in both the treatment arms. A randomized clinical trial conducted on Caucasian T2DM patients also reported that gastrointestinal adverse events were more common with the immediate-release formulation of metformin when compared to extended-release metformin.[26]

The study has significant limitations with respect to the imbalance in baseline HbA1c levels across the treatment arms, which could be addressed by including patients with longer duration of T2DM in future studies. This retrospective EMR-based study was associated with inherent challenges such as unavailability of significant information such as dietary record of the patients, plasma and urine glucose, ketone body measurements, abnormalities of lipid and protein metabolites, lifestyle and occupation details of the patients, dose and frequency of medication and weight loss, loss of follow-up, under-reporting of adverse events or complications, and lack of appropriate documentation.

Conclusion

The findings of our EMR-based study emphasize the need for early initiation of combination therapy with metformin plus vildagliptin over metformin monotherapy for achieving better glycemic control. This is the first study in real-world settings within India to show that the combination therapy of metformin and vildagliptin was efficacious and safe in the management of T2DM. Our study has generated real-world evidence regarding the clinical benefits of initial combination therapy over metformin alone. It has highlighted the advantages of the early initiation of combination therapy in patients presenting even with lower HbA1c levels. As compared to the data derived from RCTs, data routinely obtained from the EMRs better reflects the actual practice in clinical settings. Early use of combination therapy can help to reduce clinical inertia, which is a major contribution to diabetes-related complications.

Abbreviations

DPP4i, dipeptidyl peptidase-4 inhibitor; EMRs, electronic medical records; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; OADs, oral antidiabetic drugs; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

Data Sharing Statement

Data will be available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study was approved by Royal Pune Independent Ethics Committee (RPIEC) located at Pune, India (Ethics Approval Number: THBR20-009). The study involves retrospective analysis of available data, documents like informed consent form (ICF), patient diary, etc. were not applicable:

1. The research involves no more than minimal risk to subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.

Therefore, as per the "Declaration of Helsinki", the study does not necessitate the obligation to obtain informed consent as well as patient data confidentiality and compliance

were maintained throughout the study. Accordingly, permission for ICF waiver was obtained from IEC before the initiation of the data collection process for this study.

Consent for Publication

All authors provided written consent to publish this study.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors, V Mohan, Abdul Zargar, Manoj Chawla, Ameya Joshi, Usha Ayyagari, Bipin Sethi, declare that they serve as CME speakers and/or advisory board members for Dr. Reddy's Laboratories Ltd, India. The authors, Kumar Gaurav, Seema Vikas Bhagat, Amey Ishwara Mane, declare that they work in Medical Affairs Department in Dr. Reddy's Laboratories Ltd, India. Usha Rani H Patted has been an ex-employee at Dr.Reddy's Laboratories Ltd, and reports being employed at Dr Reddy's Laboratories Ltd, during the conduct of the study. The authors reported no other conflicts of interest for this work.

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