



Original Article

A Study to Evaluate Clinical Effectiveness and Safety of Fixed-Dose Combination of Metformin, Sitagliptin and Dapagliflozin in Indian Type 2 Diabetes Mellitus Patients in Real-World Practice (MESIDA2 Study)

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Received: 12-05-2026

Accepted: 15-06-2026

Available online: 30-06-2026

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major public health challenge in India, with a rapidly growing burden driven by sedentary lifestyles, dietary changes, and genetic predisposition. Triple fixed-dose combination (FDC) pharmacotherapy targeting multiple pathophysiological pathways offers a promising strategy for achieving comprehensive glycaemic control while improving adherence and reducing pill burden. This study evaluates the real-world clinical effectiveness and safety of a triple FDC comprising Metformin, Sitagliptin (DPP-4 inhibitor), and Dapagliflozin (SGLT-2 inhibitor) in Indian patients with T2DM over a three-month treatment period.

Methods: The MESIDA2 (Metformin, Sitagliptin, Dapagliflozin) study was a multicentre, prospective, observational, real-world study conducted across India. Patients with T2DM prescribed the triple FDC (Dapagliflozin + Metformin + Sitagliptin) by their treating physicians were enrolled. Key efficacy endpoints included change in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight at three months from baseline. Safety was assessed through the Clinician's Global Assessment (CGA) and reporting of adverse drug reactions (ADRs). Statistical analysis was performed using paired t-test, with $p < 0.05$ considered statistically significant.

Results: A total of 26,685 patients were enrolled across multiple centres in India. The mean age was 59.1 ± 11.2 years, with 62.5% males. After three months of FDC therapy, significant reductions were observed in all primary efficacy endpoints: HbA1c decreased from $8.33 \pm 1.41\%$ to $7.16 \pm 1.16\%$ (mean reduction: 1.17%; $p < 0.0001$), FPG from 177.0 ± 52.4 to 141.4 ± 45.2 mg/dL (mean reduction: 36.0 mg/dL; $p < 0.0001$), PPG from 248.6 ± 77.7 to 187.5 ± 60.8 mg/dL (mean reduction: 60.7 mg/dL; $p < 0.0001$), and body weight from 75.8 ± 13.2 to 72.7 ± 12.5 kg (mean reduction: 3.06 kg; $p < 0.0001$). The Clinician's Global Assessment rated safety as Excellent/Good in 94.4% and effectiveness as Excellent/Good in 94.3% of patients. Adverse drug reactions were reported in less than 2% of patients, with no serious ADRs attributable to the FDC.

Conclusions: The triple FDC of Metformin, Sitagliptin, and Dapagliflozin demonstrated significant improvements in glycaemic parameters and body weight reduction in real-world Indian T2DM patients, with an excellent safety and tolerability profile. These findings support its use as an effective and well-tolerated therapeutic option for the management of T2DM in Indian clinical practice.

Keywords: Type 2 diabetes mellitus; Triple fixed-dose combination; Metformin; Sitagliptin; Dapagliflozin.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the fastest-growing metabolic diseases globally, with India bearing a particularly high burden [1]. According to the International Diabetes Federation (IDF), India had approximately 101 million people with diabetes in 2023, making it the country with the second highest number of people with diabetes in the world [1]. The complex pathophysiology of T2DM, characterized by progressive insulin resistance, beta-cell dysfunction, and multiple organ involvement, necessitates a multifaceted pharmacological approach that targets several pathophysiological mechanisms simultaneously [3,4].

Current clinical guidelines from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and the Research Society for the Study of Diabetes in India (RSSDI) recommend individualized, patient-centred therapy for T2DM, with emphasis on combination treatments that address diverse mechanisms of hyperglycaemia [2,12,14]. Metformin, the cornerstone of T2DM therapy, reduces hepatic glucose production and improves insulin sensitivity without causing hypoglycaemia or weight gain [8]. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, enhances incretin-mediated insulin secretion and suppresses glucagon, with a low hypoglycaemia risk and weight-neutral profile [7,9].

The triple combination of these three agents provides complementary and synergistic mechanisms of action: suppression of hepatic glucose output, enhancement of insulin secretion and glucagon inhibition, and renal glucose excretion [11]. Despite the pharmacological rationale and growing global evidence, real-world data on this triple FDC in the Indian population remain limited. The MESIDA2 study was therefore designed to evaluate the clinical effectiveness and safety of this triple FDC in a large, real-world cohort of Indian T2DM patients. Fixed-dose combinations (FDCs) offer several practical advantages: they reduce pill burden, improve medication adherence, decrease the risk of prescribing errors, and can achieve more rapid glycaemic targets by simultaneously targeting multiple pathways [13].

Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, exerts its glucose-lowering effect through an insulin-independent mechanism — increasing urinary glucose excretion — and additionally confers cardiovascular and renal protective benefits, as demonstrated in landmark trials such as DECLARE-TIMI 58 and DAPA-CKD [5,15].

METHODS

2.1 Study Design and Setting

The MESIDA2 study was a multicentre, prospective, observational, real-world study conducted across multiple hospitals and outpatient diabetes clinics in India. The study was designed to capture real-world clinical practice and patient outcomes under routine care conditions. Physicians who prescribed the triple FDC (Dapagliflozin + Metformin + Sitagliptin) to their patients with T2DM were eligible to enrol patients. Data were collected at two time points: baseline (at initiation of FDC therapy) and at 3 months (12 ± 2 weeks post-initiation).

2.2 Eligibility Criteria

Inclusion and Exclusion Criteria

Eligible participants were adults aged 18 years or older with a confirmed diagnosis of type 2 diabetes mellitus (T2DM). Patients were required to have been prescribed the fixed-dose combination (FDC) of dapagliflozin, metformin, and sitagliptin by the treating physician, based on clinical judgment. Only those with complete baseline and 3-month follow-up laboratory and clinical data, and who provided written informed consent, were included.

Patients were excluded if medical records were missing or incomplete, or if they had type 1 diabetes mellitus or other specific forms of diabetes. Pregnant women or those planning pregnancy during the study period were not eligible. Individuals with severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², or end-stage renal disease were excluded. Additional exclusion criteria included a history of hypersensitivity to any component of the FDC and concurrent participation in another interventional clinical trial.

2.3 Study Drug

The study drug consisted of a triple FDC tablet containing Dapagliflozin (5 mg or 10 mg) + Metformin (500 mg) + Sitagliptin (50 mg or 100 mg). The dose selected was at the physician's discretion based on the patient's clinical profile, renal function, and prior glycaemic control.

2.4 Outcome Measures

The primary efficacy endpoint was change in HbA1c from baseline to 3 months. Secondary efficacy endpoints included changes in: (1) Fasting Plasma Glucose (FPG), (2) Postprandial Plasma Glucose (PPG), and (3) Body weight. Safety was assessed through the Clinician's Global Assessment of Safety (CGA-S) and Effectiveness (CGA-E), rated on a four-point scale (Excellent, Good, Fair, Poor), and by reporting of adverse drug reactions (ADRs).

2.5 Statistical Analysis

Descriptive statistics including mean $\pm$ standard deviation (SD), frequency (n), and percentage (%) were used for continuous and categorical variables respectively. Paired samples t-test was used to assess within-group changes from baseline to 3 months for continuous outcomes. Statistical significance was set at $p < 0.05$. All analyses were performed using Python. Outlier values outside physiologically plausible ranges were excluded from continuous variable analyses.

RESULTS

3.1 Baseline Demographic and Clinical Characteristics

A total of 26,685 patients with T2DM were enrolled in the study. The mean age of enrolled patients was 59.1 ± 11.2 years (median: 58 years; range: 18–100 years), reflecting a predominantly middle-aged to older cohort. Male patients constituted 62.5% (n=16,676) and female patients 37.5% (n=10,009) of the study population. Mean height was 162.5 ± 10.8 cm and mean baseline body weight was 75.9 ± 14.1 kg. Baseline systolic blood pressure was 140.7 ± 22.6 mmHg and diastolic blood pressure was 95.8 ± 19.3 mmHg. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics (N=26,685)

Parameter	Value
Total Patients Enrolled (N)	26,685
Age (years), mean $\pm$ SD	59.1 ± 11.2
Median Age (years)	58
Male, n (%)	16,676 (62.5%)
Female, n (%)	10,009 (37.5%)
Height (cm), mean $\pm$ SD	162.5 ± 10.8
Body Weight (kg), mean $\pm$ SD	75.9 ± 14.1
Systolic BP (mmHg), mean $\pm$ SD	140.7 ± 22.6
Diastolic BP (mmHg), mean $\pm$ SD	95.8 ± 19.3

3.2 BMI Distribution

A significant proportion of the study population was overweight or obese by Asian-specific BMI cut-offs. The largest group was overweight (23.0–24.9 kg/m²) at 36.9% (n=9,843), followed by normal BMI (18.5–22.9 kg/m²) at 35.0% (n=9,333), obese (≥ 25 kg/m²) at 16.5% (n=4,409), and underweight (< 18.5 kg/m²) at 11.6% (n=3,100). The BMI distribution is detailed in Table 2 and Figure 1.

Table 2: BMI Distribution of Study Population

BMI Category	n	%
Normal BMI (18.5–22.9 kg/m ²)	9,333	35.0%
Overweight (23.0–24.9 kg/m ²)	9,843	36.9%
Obese (≥ 25 kg/m ²)	4,409	16.5%
Underweight (< 18.5 kg/m ²)	3,100	11.6%

Figure 1: BMI Distribution of Study Population

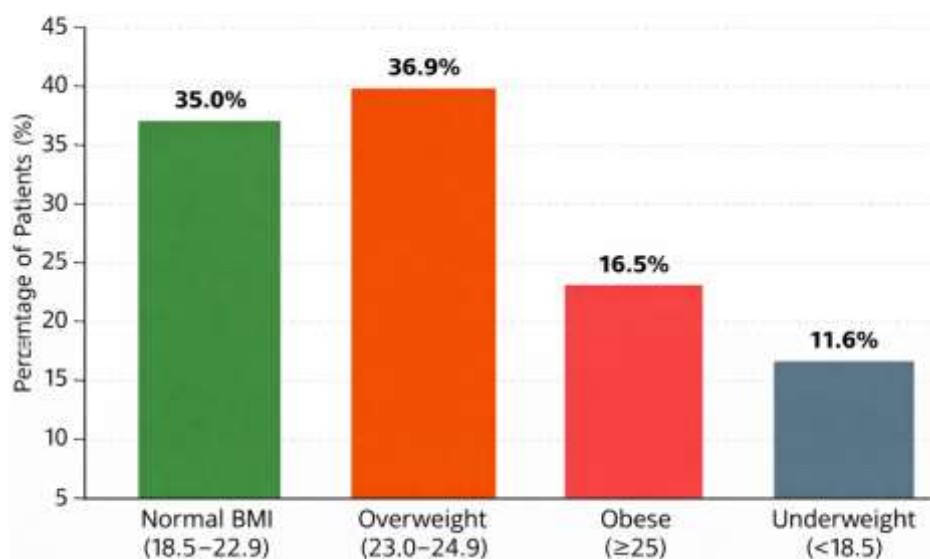


Figure 1: BMI Distribution of Study Population

3.3 Risk Factors and Complications at Diagnosis

The most prevalent modifiable risk factor was a family history of diabetes (34.2%, n=9,116), followed by physical inactivity (21.9%, n=5,841), alcohol intake (15.0%, n=4,005), active smoking (14.6%, n=3,888), and tobacco use (11.2%, n=2,983). The most common complications present at the time of diagnosis were diabetic neuropathy (59.2%, n=15,806), nephropathy (40.1%, n=10,708), coronary artery disease (CAD, 30.3%, n=8,083), stroke (28.2%, n=7,529), and retinopathy (15.6%, n=4,170). Figure 2 illustrates the burden of diabetic complications at diagnosis.

Figure 2: Complications at the Time of Diagnosis

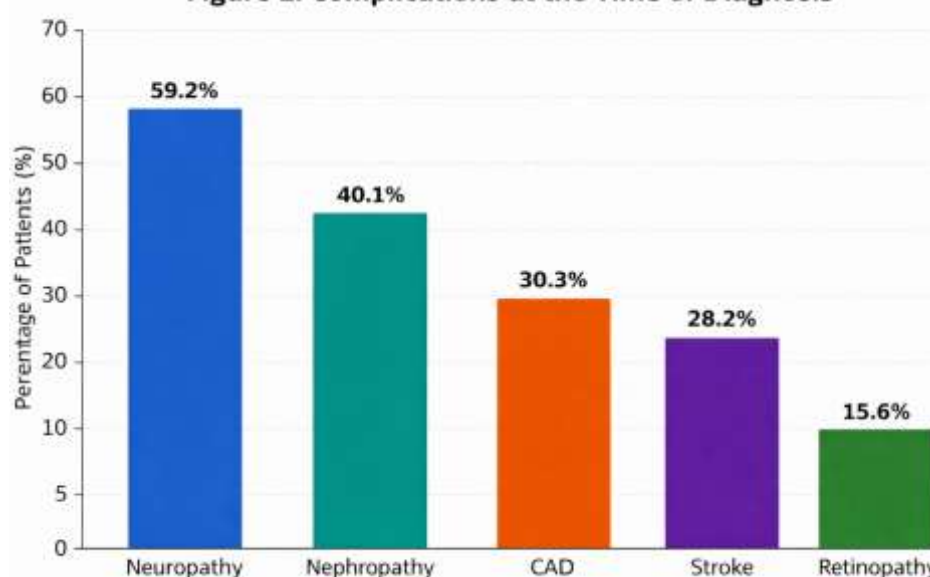


Figure 2: Complications at the Time of Diagnosis

3.4 Previous Anti-Diabetic Drug History

The majority of patients had prior exposure to anti-diabetic medications before initiation of the triple FDC. Metformin was the most commonly used prior agent (74.6%, n=19,910), followed by sulfonylureas (SU, 42.1%), DPP-4 inhibitors (DPP4i, 34.8%), SGLT-2 inhibitors (SGLT-2i, 29.5%), pioglitazone (14.8%), alpha-glucosidase inhibitors (AGI, 9.2%), insulin/insulin analogues (2.7%), and GLP-1 receptor agonists (0.8%), as shown in Figure 3.

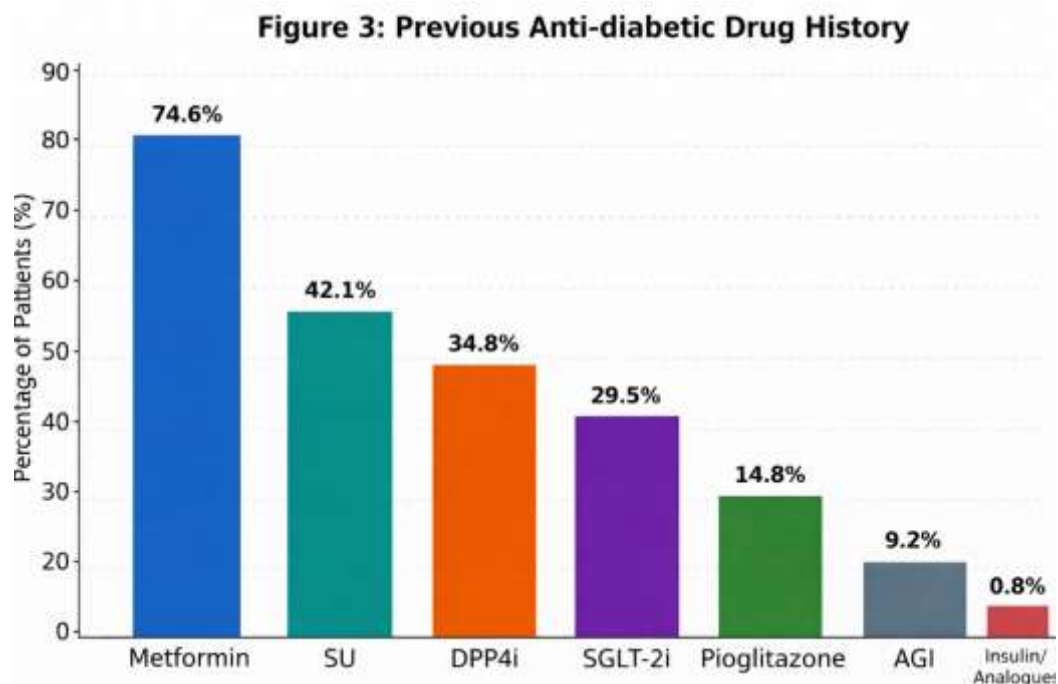


Figure 3: Previous Anti-Diabetic Drug History

3.5 Reasons for Prescribing the Triple FDC

High baseline HbA1c was the most frequently cited reason for prescribing the triple FDC (66.3% of prescriptions), followed by excellent efficacy (55.6%), cardiovascular benefit (52.9%), good safety profile (48.5%), less weight gain (27.5%), and insulin resistance improvement (19.2%). The distribution of reasons reflects the multifactorial benefit profile that clinicians attributed to the triple FDC. These are illustrated in Figure 4.

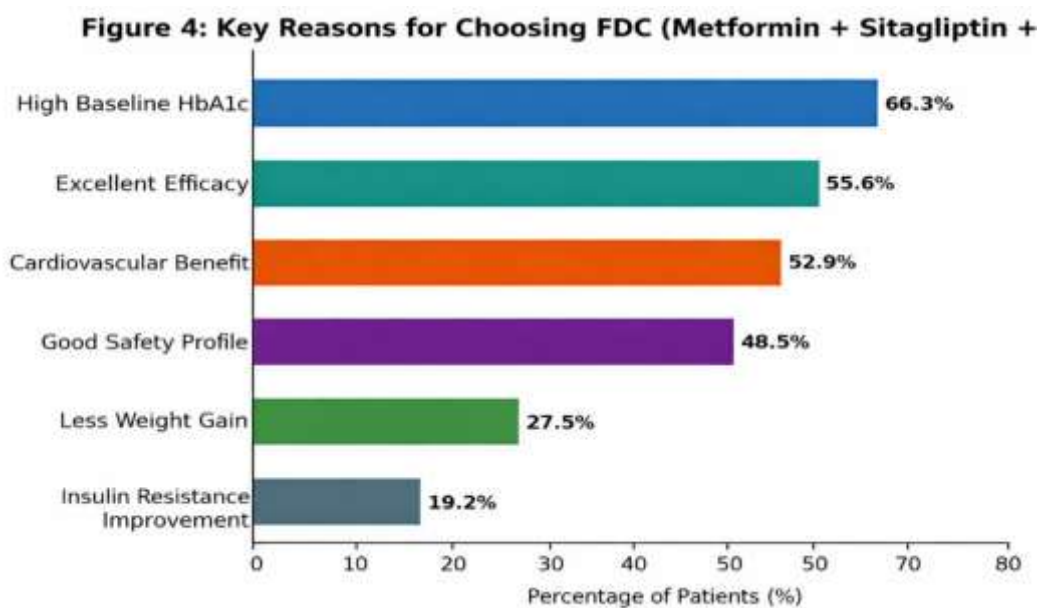


Figure 4: Key Reasons for Choosing FDC (Metformin + Sitagliptin + Dapagliflozin)

3.6 Efficacy Outcomes at 3 Months

All primary and secondary efficacy parameters showed statistically significant improvements at 3 months compared to baseline (all $p < 0.0001$). Detailed efficacy outcomes are presented in Table 3 and Figure 5.

Table 3: Clinical Efficacy Outcomes at 3 Months

Parameter	Baseline Mean $\pm$ SD	Post-3 Months Mean $\pm$ SD	Mean Change (Δ)	p-value
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HbA1c (%)	8.33 ± 1.41	7.16 ± 1.16	-1.17 ± 1.19	<0.0001
FPG (mg/dL)	177.0 ± 52.4	141.4 ± 45.2	-36.0 ± 39.6	<0.0001
PPG (mg/dL)	248.6 ± 77.7	187.5 ± 60.8	-60.7 ± 69.8	<0.0001
Body Weight (kg)	75.8 ± 13.2	72.7 ± 12.5	-3.06 ± 6.13	<0.0001

Figure 5. Change in Key Clinical Parameters After 3 Months of FDC Therapy

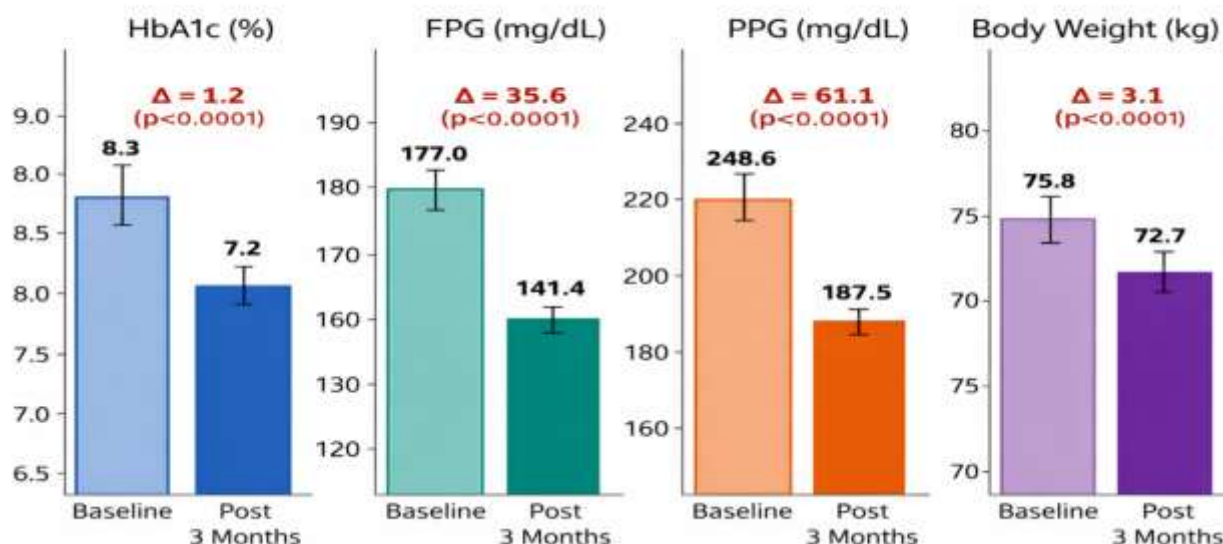


Figure 5: Change in Key Clinical Parameters After 3 Months of FDC Therapy

HbA1c: Mean HbA1c reduced from $8.33 \pm 1.41\%$ at baseline to $7.16 \pm 1.16\%$ at 3 months, representing a mean reduction of $1.17 \pm 1.19\%$ ($p<0.0001$). This magnitude of HbA1c reduction is clinically meaningful and consistent with the known combined efficacy of DPP-4 inhibitor and SGLT-2 inhibitor added to Metformin backbone therapy.

FPG: Fasting plasma glucose decreased from a mean of 177.0 ± 52.4 mg/dL at baseline to 141.4 ± 45.2 mg/dL at 3 months, a reduction of 36.0 ± 39.6 mg/dL ($p<0.0001$). This reflects the hepatic glucose output suppression mediated by Metformin and the additive renal glycosuria effect of Dapagliflozin.

PPG: Postprandial plasma glucose was markedly reduced from 248.6 ± 77.7 mg/dL at baseline to 187.5 ± 60.8 mg/dL at 3 months (mean reduction: 60.7 ± 69.8 mg/dL; $p<0.0001$). This pronounced effect on postprandial glucose reflects the incretin-mediated enhancement of glucose-dependent insulin secretion by Sitagliptin.

Body Weight: Statistically significant body weight reduction was observed, with mean weight decreasing from 75.8 ± 13.2 kg at baseline to 72.7 ± 12.5 kg at 3 months, representing a mean reduction of 3.06 ± 6.13 kg ($p<0.0001$). Weight loss is an important cardiometabolic benefit particularly attributable to the caloric loss from urinary glucose excretion with Dapagliflozin.

3.7 Safety and Tolerability

The Clinician's Global Assessment of Safety (CGA-S) and Effectiveness (CGA-E) provided an overall clinical impression of the FDC therapy. Safety was rated as Excellent in 60.5% and Good in 33.9%, giving a combined Excellent/Good rating of 94.4% of patients. Only 2.67% received a Poor rating. Effectiveness was rated Excellent in 58.8% and Good in 35.5%, with a combined Excellent/Good rating of 94.3%, as shown in Table 4 and Figure 6.

Table 4: Clinician's Global Assessment of Safety and Effectiveness

Assessment	Safety: n (%)		Effectiveness: n (%)	
	n	%	N	%
Excellent	16,136	60.5%	15,686	58.8%

Good	9,041	33.9%	9,475	35.5%
Fair	796	2.98%	794	2.98%
Poor	712	2.67%	730	2.74%

Figure 6. Clinician's Global Assessment of Safety and Effectiveness

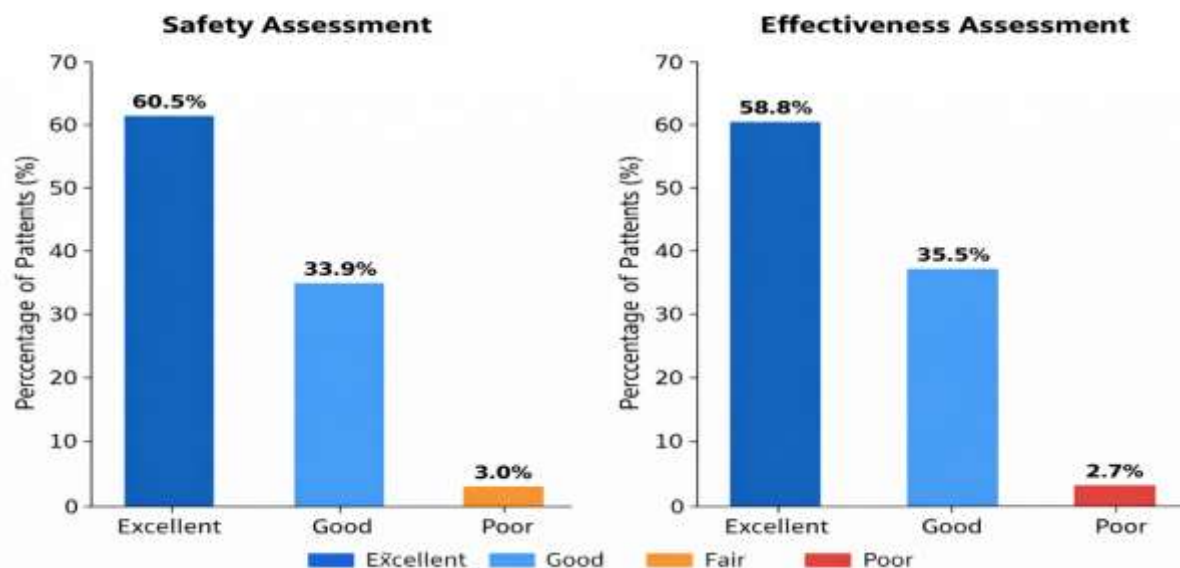


Figure 6: Clinician's Global Assessment of Safety and Effectiveness

Adverse drug reactions (ADRs) were uncommon: 98.4% of patients (n=26,256) reported no ADRs. The most commonly reported adverse effects among those who experienced ADRs were consistent with the known class-effect profiles of SGLT-2 inhibitors (urinary tract and genital infections) and were generally mild and self-limiting. No serious ADRs requiring discontinuation of therapy were reported at a population-wide level, confirming the excellent tolerability of the triple FDC.

DISCUSSION

The mean reduction in HbA1c of 1.17% achieved in 3 months is substantial, given that each additional percentage point reduction in HbA1c is associated with significant reductions in microvascular (25–30%) and macrovascular complications [3,4]. This result is consistent with the meta-analytic data showing approximately 0.5–0.8% reduction with DPP-4 inhibitors and 0.5–0.7% with SGLT-2 inhibitors, with the additive effects of both agents combined with Metformin exceeding the sum of individual contributions [7,11].

The mean baseline HbA1c of 8.33% indicates that the enrolled population had suboptimal glycaemic control prior to initiation of the FDC, consistent with the real-world scenario in India where many patients present with poorly controlled diabetes [12].

The MESIDA2 study is one of the largest real-world observational studies evaluating the triple FDC of Metformin, Sitagliptin, and Dapagliflozin in Indian T2DM patients, enrolling 26,685 participants across multiple centres in India [13]. The study demonstrates that this triple FDC achieves clinically meaningful and statistically significant improvements in all major glycaemic and anthropometric parameters within a short 3-month period, with a highly favourable safety and tolerability profile.

The significant PPG reduction of 60.7 mg/dL is particularly noteworthy in the Indian context, as Indian patients are known to have a greater postprandial glycaemic excursion relative to their Western counterparts. Sitagliptin's mechanism of potentiating glucose-dependent insulin secretion is ideally suited to attenuating postprandial glucose spikes. Concurrently, the FPG reduction of 36.0 mg/dL reflects both Metformin's suppression of hepatic glucose output and Dapagliflozin's sustained insulin-independent renal glucose excretion throughout a 24-hour period.

The body weight reduction of 3.06 kg at 3 months is an important finding, given the high prevalence of central obesity in Indian T2DM patients and its association with cardiometabolic risk. Dapagliflozin induces caloric loss equivalent to approximately 60–80 g of glucose excreted daily in the urine, contributing to this weight benefit. Weight reduction of this

magnitude is not typically achievable with older agents such as sulfonylureas or insulin, which are often associated with weight gain.

High baseline HbA1c (66.3%) and perceived excellent efficacy (55.6%) were the two most common reasons clinicians cited for choosing this FDC, highlighting the need for effective triple therapy when dual agents are insufficient. The cardiovascular benefit (52.9%) was another major reason, reflecting growing awareness of SGLT-2 inhibitors' cardio-renal benefits in T2DM. These perceptions are supported by landmark cardiovascular outcomes trials including DECLARE-TIMI 58 and EMPA-REG OUTCOME.

The safety profile observed in MESIDA2 is reassuring. With over 94% of patients receiving an Excellent or Good clinician assessment of safety, and less than 2% reporting any adverse drug reaction, the triple FDC demonstrates a favourable benefit-risk ratio in real-world practice. The absence of serious ADRs is consistent with the established safety profiles of each individual component and supports the premise that combining these agents does not result in additive adverse effects. The MESIDA2 study has important implications for clinical practice in India. The prevalence of diabetic complications at baseline — particularly neuropathy (59.2%) and nephropathy (40.1%) — underscores the advanced stage of disease in many Indian patients at the time of presentation, emphasizing the need for early and aggressive glycaemic management [12]. The strong representation of patients with cardiovascular comorbidities (CAD: 30.3%, stroke: 28.2%) further supports the use of a FDC incorporating a cardio-renally protective SGLT-2 inhibitor [5,10,15].

CONCLUSIONS

The MESIDA2 study provides robust real-world evidence from a large cohort of Indian T2DM patients demonstrating that the triple FDC of Metformin, Sitagliptin, and Dapagliflozin is highly effective and well-tolerated. Significant and clinically meaningful reductions in HbA1c (−1.17%), FPG (−36.0 mg/dL), PPG (−60.7 mg/dL), and body weight (−3.06 kg) were achieved within 3 months of therapy initiation. The clinician-assessed safety and effectiveness were rated as Excellent or Good in over 94% of patients, with less than 2% reporting any adverse drug reactions.

These findings support the use of this triple FDC as an effective, adherence-friendly, and safe therapeutic option for managing T2DM in Indian clinical practice, particularly in patients with suboptimal glycaemic control, high cardiovascular risk, or concurrent cardiometabolic comorbidities. Larger randomized controlled trials and longer-duration real-world studies are warranted to further characterize the long-term benefit-risk profile of this triple FDC in the Indian population.

DECLARATIONS

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional ethics committee approval was obtained prior to study initiation. Patient data were anonymized and de-identified prior to analysis. The requirement for written informed consent was waived given the retrospective nature of the study.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This study was supported by Alkem Laboratories Limited. All authors have declared that no additional financial support was received from any other organization for the submitted work.

Data Availability

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

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