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Patient Profiling and Outcome Assessment of Vildagliptin and Dapagliflozin FDC in Persons with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2D) is a condition characterized by rapid progression, and in certain instances, managing glucose levels may not be adequately achieved with a single pill. Vildagliptin and dapagliflozin in a Fixed-Dose Combination (FDC) complement each other's actions, aiding in the control of glycemia. The primary goal of this retrospective investigation was to gain insight into the patient characteristics, safety profile, and efficacy of the FDC in reducing weight and glycated hemoglobin levels.

Methods: Retrospective data from T2D patients who were prescribed the FDC and had two follow-up visits between May 1, 2022, and January 31, 2023, were enrolled in the study.

Results: The average age of the study sample was 55.8 years, with nearly two-thirds being male (65.5%). At 6 months after FDC medication, glycated hemoglobin (HbA1c) significantly decreased by 1.2% (Baseline: 8.4%, Follow-up: 7.2%, p-value <0.001), indicating improved glycemic control. An average weight decrease of 4.3 kg (Baseline: 76.9Kg, Follow-up: 72.5Kg, p-value <0.001), was noted in patients receiving the FDC. Weight loss was higher in males (4.5 kg) than in females (4.0 kg). Safety analysis was carried out for all randomized patients and no major AEs were noted. No patients were withdrawn from the study due to safety concerns. No episode of hypoglycemia occurred during the study time. There were no statistical differences in the hepatic enzymes at the end of six months in the study groups.

Conclusion: The Fixed Dose Combination of Vildagliptin and Dapagliflozin effectively enhances glycemic control by demonstrating a significant reduction in mean HbA1c levels after six months compared to baseline. However, further multicenter studies are necessary to substantiate these findings.

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Introduction

Diabetes poses a rapidly growing health challenge and a potential epidemic in both low- and middle-income areas, encompassing both urban and rural regions of India, as highlighted by the ICMR-INDIAB study. The Noncommunicable Disease (NCD) Monitoring Framework, aligned with indicators set by the Ministry of Health and Family Welfare, Government of India, adapted from the Global NCD framework established by the World Health Organization (WHO), underscores the imperative to curtail the escalation of diabetes and reduce premature deaths from NCDs by 25% by the year 2025. The proportion of deaths caused by NCDs in India has risen from 37.9% in 1990 to 66% in 2019 [1-4].

Type 2 diabetes mellitus (T2D) is a progressive condition, often necessitating the use of multiple medications as beta cell function diminishes with time. Oral antidiabetic agents (OADs) come with their own set of side effects, and using metformin alone as a monotherapy is often insufficient to effectively manage hyperglycemia in the majority of patients. Consequently, an unmet need persists, calling for newer drugs that effectively lower glycated hemoglobin (HbA1c) levels while being either weight-neutral or, ideally, promoting weight loss, without exacerbating the risk of hypoglycemia. In pursuit of enhanced glycemic control, healthcare professionals have conventionally employed a combination of therapeutic agents targeting insulin resistance and defects in insulin secretion. Combining various drugs aims to achieve synergy, augmentation, and improved tolerability by mitigating or counteracting the adverse effects of individual components while also addressing different pathological processes. From the patient's perspective, combination therapy offers the convenience of taking a single medication, potentially resulting in better adherence to the treatment regimen [5-8].

The past decade witnessed the emergence of several new classes of AHAs that effectively reduce HbA1c levels without inducing

hypoglycemia. These include glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), and sodium-glucose co-transporter-2 inhibitors (SGLT-2i). SGLT-2i, lower plasma glucose levels by inhibiting the renal reabsorption of glucose by the kidneys, irrespective of β-cell function or mass. This action induces glucosuria and leads to an increase in glucagon levels. On the other hand, DPP-4i inhibits the enzyme responsible for degrading incretin hormones, promoting insulin secretion, and reducing glucagon secretion. The rationale behind combining a DPP-4i and an SGLT-2i is not only due to their complementary actions but also because they target at least six of the eight components within the "ominous octet [9-11].

Dapagliflozin has shown its effectiveness in managing blood glucose levels, reducing blood pressure, and aiding in weight loss in many patients. Additionally, it provides benefits to individuals with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for cardiovascular disease (CVD).Vildagliptin is a potent anti-diabetic medication thanks to its efficacy profile, minimal risk of hypoglycemia, and absence of weight gain. These benefits have been harnessed by integrating vildagliptin and dapagliflozin into a single tablet. Nonetheless, there is a dearth of data regarding its utilization among Indian patients. Therefore, this study assessed and compared the effects of the fixed-dose combination (FDC) of Vildagliptin + Dapagliflozin, including its safety profile and efficacy in reducing weight and HbA1c levels [12,13].

Materials and Methods

This study had a retrospective design involving data collection from individuals diagnosed with T2D who were prescribed Vildagliptin 100mg SR + Dapagliflozin 10mg FDC and had attended two follow-up visits between May 1, 2022, and January 31, 2023. The study received approval from an independent ethics committee, Udyaan Healthcare, on February 12, 2023 (Registration No. ECR/1300/Inst/UP/2019). A total of 1,727 clinical records from 72 centers across the country were initially included in the study based on the defined inclusion criteria. After excluding records with missing information, the analysis focused on 1,587 records (Figure 1). This study's eligible participants were adults diagnosed with T2D who were prescribed an FDC of vildagliptin and dapagliflozin.

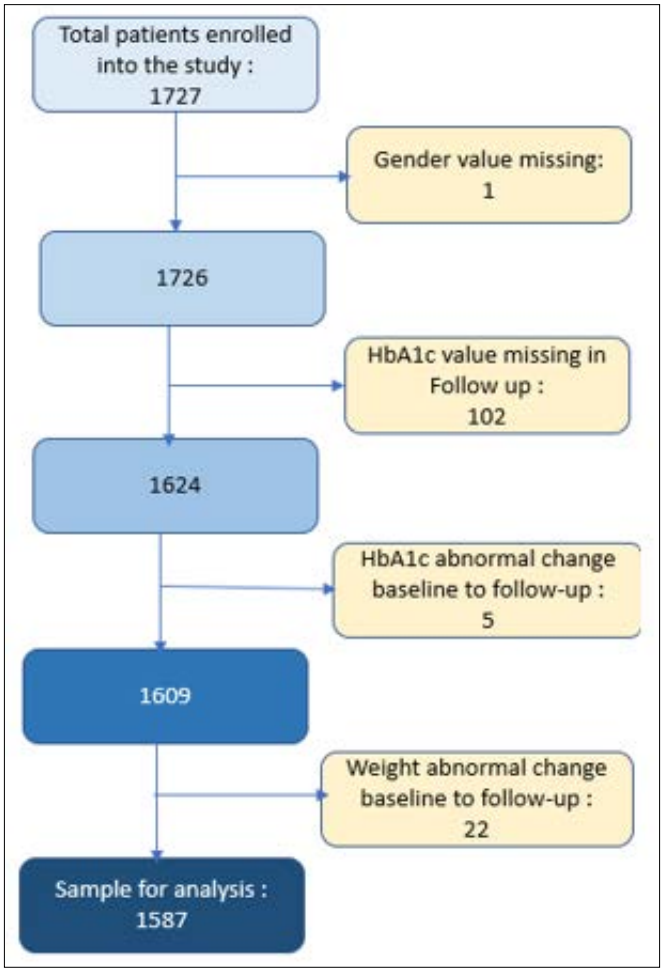

Figure 1: Sample Achieved

An Electronic Case Report Form (eCRF) was employed to gather data related to medical history, comorbidities, diabetes complications, medications, and laboratory values. Any documented adverse clinical events were duly recorded. Additionally, the study included an assessment of hypoglycemic incidents and an evaluation of medication adherence. The study outcome included changes in the HbA1c levels and weight at 6 months. The secondary outcome included major adverse outcomes like fatal, nonfatal, or hospitalization over the course of six months. During the baseline and subsequent follow-up visits, blood glucose levels, HbA1c levels, and weight were measured using standard hospital protocols as part of routine care. In accordance with the study protocol, only patients with baseline

and 6-month outcome measurements were included in the data analysis for assessing outcomes.

To further understand the participant demographics, we classified the duration of diabetes into three categories: less than 5 years, 5 to 10 years, and over 10 years. Additionally, we categorized the baseline HbA1c levels into four groups: HbA1c < 7%, HbA1c ≥ 7% and < 8%, HbA1c ≥ 8% and < 9%, and HbA1c ≥ 9%. Categorical data is presented as n (%) and compared accordingly. Continuous data is compared and presented as either mean with standard deviation (SD) or median with interquartile range. The study examined changes in continuous data within each group and compared the mean changes between groups. The t-test and ANOVA are used to test for significant differences between groups, and the paired t-test is used to test for significance in the difference between baseline and follow-up measurements.

Results

A total of 1587 records were analyzed in the study. The average age of the participants was 55.8 years. Of these patients, 1040 (65.5%) were male and 547 (34.5%) were female. Hypertension emerged as the most prevalent condition. CVD and dyslipidemia were the second most common conditions observed following hypertension. 22.1% of the participants were on fixed-dose therapy of vildagliptin + dapagliflozin, 76.2% were on this FDC alongside other OADs, and 1.7% were on insulin therapy. Among those on other OADs alongside the FDC of vildagliptin + dapagliflozin, 90.5% were on biguanides, 54.4% on sulfonylureas, 11.9% on alpha-glucosidase inhibitors, and 6.1% on thiazolidinediones.

Please refer to Table 1 below for a comprehensive representation of patient demographic details, baseline HbA1c levels, and co-morbidity patterns.

Table 1: Patient Demographic Details

	n =	Overall 1587
Age, n (%)	< 50 yrs	457 (28.8%)
	50 to 59 yrs	585 (36.9%)
	>=60 yrs	545 (34.39%)
	Mean (SD)	55.8 (10.4)
Gender, n (%)	Male	1040 (65.5%)
	Female	547 (34.5%)
Duration of Diabetes, n(%)	<=5 yrs	688 (43.4%)
	>5 yrs	899 (56.6%)
	Mean (SD)	6.3 (3.8)
Baseline HbA1c, n (%)	<7%	97 (6.1%)
	7% to 7.99%	437 (27.59%)
	8% to 8.99%	616 (38.8%)
	>=9%	437 (27.5%)
	Mean (SD)	8.4 (1.1)
Complications & Comorbidities, n (%)	Hypertension	825 (52%)
	CVD	236 (14.99%)
	Dyslipedemia	232 (14.69%)
	Neuropathy	224 (14.19%)
	Nephropathy	159 (10%)
	Retinopathy	141 (8.9%)
	Diabetic Foot	113 (7.1%)
	Diabetic ketoacidosis	35 (2.2%)
	Peripheral Artery Disease	27 (1.7%)
	Cerebrovascular Disease	17 (1.1%)
Medications, n (%)	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC only	351 (22.19%)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Other OADs	1209 (76.2%)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Insulin	14 (0.9%)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Other OADs + Insulin	13 (0.89%)

Concomitant medications, n (%)		n=1222
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Biguanides	1106 (90.5%)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Sulfonylureas	665 (54.4%)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Thiazolidinediones	74 (6.196)
	Vildagliptin 100mg SR + Dapagliflozin 10mg FDC + Alpha glucosidase inhibitors	146 (11.9%)

Table 2: Impact on HbA1c

Gender						
	Overall	Male	Female	P-Value	Test	
n=	1587	1040	547			
HbA1c (Glycosylated Hemoglobin): (%), mean (SD)						
Baseline	8.4 (1.1)	8.4 (1.1)	8.4 (1.2)	0.463	Two Sample T-test	
Follow up	7.2 (0.8)	7.2 (0.8)	7.1 (0.8)	0.153	Two Sample T-test	
Difference	1.2 (0.9)	1.2 (0.8)	1.3 (0.9)	0.712	Two Sample T-test	
P-Value (for Difference)	<0.001	<0.001	<0.001		Paired Sample T-test	
Age						
	< 50 yrs	50 to 59 yrs	>= 60 yrs	P-Value	Test	
n=	457	585	545			
HbA1c (Glycosylated Hemoglobin): (%), mean (SD)						
Baseline	8.2 (1.0)	8.5 (1.1)	8.5 (1.2)	<0.001	One-way ANOVA	
Follow up	7.1 (0.8)	7.2 (0.8)	7.3 (0.9)	<0.001	One-way ANOVA	
Difference	1.1 (0.7)	1.4 (1.0)	1.2 (0.9)	<0.001	One-way ANOVA	
P-Value (for Difference)	<0.001	<0.001	<0.001		Paired Sample T-test	
HbA1c (Glycosylated Hemoglobin)						
	<7%	>=7% & <8%	>=8% & <9%	>=9%	P-Value	Test
n=	97	437	616			
HbA1c (Glycosylated Hemoglobin): (%), mean (SD)						
Baseline	6.7 (0.3)	7.5 (0.3)	8.4 (0.3)	9.8 (0.9)	<0.001	One-way ANOVA
Follow up	6.0 (0.5)	6.7 (0.4)	7.2 (0.5)	7.8 (0.9)	<0.001	One-way ANOVA
Difference	0.7 (0.4)	0.8 (0.4)	1.1 (0.5)	2.0 (1.1)	<0.001	One-way ANOVA
P-Value (for Difference)	<0.001	<0.001	<0.001	<0.001		Paired Sample T-test
Duration of T2DM						
		<= 5 yrs	>5 yrs	P-Value	Test	
n=		688	899			
HbA1c (Glycosylated Hemoglobin): (%), mean (SD)						
Baseline		8.2 (0.9)	8.6 (1.2)	<0.001	Two Sample T-test	
Follow up		7.1 (0.7)	7.3 (0.8)	<0.001	Two Sample T-test	
Difference		1.2 (0.7)	1.3 (0.9)	<0.001	Two Sample T-test	

P-Value (for Difference)		<0.001	<0.001		Paired Sample T-test

Table 3: Impact on Weight

Gender						
	Overall	Male	Female	P-Value	Test	
n=	1587	1040	547			
Weight: (Kg), mean (SD)						
Baseline	76.9 (12.3)	79.4 (12.0)	72.0 (11.2)	<0.001	Two Sample T-test	
Follow up	72.5 (11.6)	75.0 (11.3)	67.9 (10.6)	<0.001	Two Sample T-test	
Difference	4.3 (3.3)	4.5 (3.3)	4.0 (3.3)	0.011	Two Sample T-test	
P-Value (for Difference)	<0.001	<0.001	<0.001		Paired Sample T-test	
Age						
n=	< 50 yrs	50 to 59 yrs	>= 60 yrs	P-Value	Test	
	457	585	545			
Weight: (Kg), mean (SD)						
Baseline	77.6 (14.1)	76.5 (12.4)	76.6 (10.3)	0.291	One-way ANOVA	
Follow up	73.5 (13.2)	72.2 (11.7)	72.1 (9.8)	0.1	One-way ANOVA	
Difference	4.1 (3.0)	4.3 (3.1)	4.5 (3.7)	0.129	One-way ANOVA	
P-Value (for Difference)	<0.001	<0.001	<0.001		Paired Sample T-test	
HbA1c (Glycosylated Hemoglobin)						
	<7%	>=7% & <8%	>=8% & <9%	>=9%	P-Value	Test
n=	97	437	616	437		
Weight: (Kg), mean (SD)						
Baseline	74.1 (14.9)	75.2 (12.5)	77.5 (11.9)	78.3 (11.7)	<0.001	One-way ANOVA
Follow up	69.6 (14.7)	71.0 (11.8)	73.5 (11.2)	73.5 (11.2)	<0.001	One-way ANOVA
Difference	4.4 (4.4)	4.1 (2.9)	4.0 (2.8)	4.9 (3.9)	<0.001	One-way ANOVA
P-Value (for Difference)	<0.001	<0.001	<0.001	<0.001		Paired Sample T-test
Duration of T2DM						
			<= 5 yrs	>5 yrs	P-Value	Test
n=			688	899		
Weight: (Kg), mean (SD)						
Baseline			75.5 (12.1)	77.9 (12.3)	<0.001	Two Sample T-test
Follow up			71.4 (11.5)	73.4 (11.5)	<0.001	Two Sample T-test
Difference			4.2 (2.9)	4.4 (3.6)	0.077	Two Sample T-test
P-Value (for Difference)			<0.001	<0.001		Paired Sample T-test

Impact on HbA1c

The study recorded the HbA1c levels of patients both before and after the administration of the FDC therapy. Following a 6-month period of FDC medication, an average reduction of 1.28% in HbA1c levels was observed, signifying a substantial enhancement in glucose control. Among participants who initially exhibited elevated HbA1c levels (>7%), 67.2% achieved glycemic control (HbA1c < 7%) within the 6-month timeframe. Furthermore, findings revealed a correlation ($p<0.001$) between the baseline HbA1c values and the magnitude of the subsequent reduction. Specifically, individuals with higher baseline HbA1c values experienced a more pronounced drop. The group with a baseline HbA1c of ≥9% exhibited the most reduction, with a drop of 2.0%. In contrast, the 7-8.9% group and the 8-8.9% group had reductions of 0.8% and 1.1% respectively, while the <7% group experienced a reduction of 0.7%. Additionally, we observed that the duration of diabetes was a contributing factor, with a greater reduction in HbA1c levels

among participants with longer diabetes duration. Specifically, those with a diabetes duration exceeding 5 years experienced a reduction of 1.3%, compared to a 1.2% reduction in those with a duration of less than or equal to 5 years. The most substantial reductions in HbA1c levels were observed in cases where both the baseline HbA1c levels were high, and the duration of diabetes was prolonged.

For a comprehensive visualization of the percentage reduction in HbA1c, change in HbA1c by age groups, gender, baseline HbA1c groups, and duration of T2D groups, please refer to Table 2 provided below.

Impact of FDC on Weight

The effect of FDC therapy on weight was also analyzed. Throughout the 6-month study period, we observed an average weight reduction of 4.3 kgs among the participants. Male patients experienced a slightly greater decrease in weight, with a mean reduction of 4.5 kgs, compared to female patients, who exhibited a mean decrease of 4.0 kgs. When examining the relationship between age and weight reduction, we found that participants under the age of 50 years demonstrated an average weight loss of 4.1 kg. In the age group of 50 years to <60 years, the weight reduction averaged 4.3 kgs, while participants aged 60 years and above experienced the highest weight drop, with an average of 4.5 kgs. Furthermore, our analysis revealed a correlation ($p<0.001$) between baseline HbA1c levels and weight loss. Patients with a baseline HbA1c level ≥9% exhibited the most significant weight reduction, with an average drop of 4.9 kgs, compared to other groups. Additionally, patients with a T2D duration exceeding 5 years exhibited a higher weight reduction, with an average decrease of 4.4 kgs, compared to those with a T2D duration of less than or equal to 5 years, who experienced an average weight loss of 4.2 kgs.

For reference, Table 3 illustrates the effect of FDC therapy on weight changes concerning gender, age, baseline HbA1c, and duration of T2D groups.

Safety Profile

Safety analysis was carried out for all randomized patients and no major AEs were noted. No patients were withdrawn from the study due to safety concerns. No episode of hypoglycemia occurred during the study time.

There were no statistical differences in the hepatic at the end of six months in the study groups. This confirms that the FDC therapy is safe in terms of changes to liver enzyme parameters (Table 4).

Table 4: Change in ALT/ AST

Effect of Dapagliflozin (10mg) + Vildagliptin (100mg)			
Parameter	**Baseline**	**Follow up**	**P-value**
AST/SGOT (U/L)	35.1 ± 16.0	34.7 ± 14.1	0.087
ALT/SGPT (U/L)	37.2 ± 16.2	36.6 ± 13.5	0.076

Discussion

Utilizing a combination of SGLT-2i and DPP-4i is a logical strategy supported by physiological and pharmacological reasoning. Dapagliflozin induces glucosuria, which leads to an increase in endogenous glucose production that counteracts its glucose-lowering effect. On the other hand, vildagliptin inhibits glucagon secretion and reduces endogenous glucose production. Based on these discoveries, combining an SGLT-2i with a DPP-4i may enhance the potential of individuals with T2D to attain their glycemic target and synergistically lower HbA1c levels. Additionally, pharmacokinetic-pharmacodynamic studies have indicated the absence of drug-drug interactions between SGLT-2i and DPP-4i, rendering them a suitable pharmacological combination., conducted systematic reviews and meta-analyses, which corroborated our current study's findings, showing that the combination therapy of SGLT-2i and DPP-4i led to significant improvements in HbA1c levels, reductions in fasting plasma glucose, and weight with low risk of hypoglycemia [14-18]. Based on an expert opinion-based consensus involving over 200 healthcare practitioners (HCP) in India, there is unanimous agreement that the vildagliptin–dapagliflozin FDC presents an appealing treatment option for individuals with T2D. This combination is regarded as a first-line therapy for obese T2D patients and those with T2D accompanied by hypertension. Furthermore, it serves as a second-line therapy for obese T2D patients who do not achieve adequate control with metformin alone, for T2D patients with hypertension who remain uncontrolled on metformin, as well as in patients taking two OADs and have HbA1c levels above 8%. Additionally, it is deemed suitable for a wide spectrum of T2D patients, including those who are obese, elderly, have a history of ASCVD, or are dealing with heart failure [19].

In the present study, the average weight drop over 6 months is 4.3 kg. Vildagliptin helps maintain weight neutrality, whereas dapagliflozin leads to weight loss by reducing body fat, possibly due to caloric restriction and fluid loss caused by osmotic diuresis. FDCs showed reduced rates of adverse effects when compared to their respective monotherapies. The reduction in gastrointestinal side effects can be attributed to interactions between DPP-4 and SGLT-2 proteins at the renal tubular cell-membrane level or the inhibition of the DPP-4 enzyme found in specific pathogenic microorganisms, potentially rendering them inactive. A bioequivalence study on a fixed-dose combination of dapagliflozin/ vildagliptin reported that they were well-tolerated, as evidenced by no discontinuation of therapy due to adverse events and no alterations in vital parameters. In the present study, only 3.7% of the patients reported adverse events that could have been easily managed. Several independent studies have demonstrated the benefits of dapagliflozin and vildagliptin in reducing liver enzyme levels. As the combination of dapagliflozin and vildagliptin is a relatively recent drug, it is imperative to conduct assessments of its long-term efficacy, safety, and cost-effectiveness [20-26].

Conclusion

The present study underscores that Vildagliptin 100mg SR + Dapagliflozin 10mg FDC holds promise as a therapeutic choice for patients with T2D. It emerges as a suitable option for T2D patients, given its synergistic capacity to facilitate the attainment of glycemic targets, along with several additional glycemic benefits such as weight reduction and improvement in liver enzymes. Nonetheless, the need for multicentric studies is evident to validate both the advantages and potential drawbacks of the vildagliptin-dapagliflozin FDC.

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Conflict of interest
Dr Abhijit Pednekar, Dr Amit Gupta and Dr Sona Warrier are employees of USV Pvt Ltd. All other authors have no conflicts of interest to declare.

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