Expert eValuation of Efficacy and Rationality of Vildagliptin "EVER-Vilda": An Indian Perspective

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ABSTRACT: Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor is effective in reducing HbA1c levels in patients with type 2 diabetes (T2DM) when administered as monotherapy, dual or triple combination therapy. In India, Vildagliptin is commonly prescribed in T2DM patients because it reduces mean amplitude of glycemic excursion (MAGE), has lower risk of hypoglycemia and is weight neutral. Early combination therapy with vildagliptin and metformin is effective and well-tolerated in patients with T2DM, regardless of age or ethnicity. In view of already existing data on vildagliptin and the latest emerging clinical evidence, a group of endocrinologists, diabetologists and cardiologists convened for an expert group meeting to discuss the role and various combinations of vildagliptin in T2DM management. This practical document aims to guide Physicians and Specialists regarding the different available strengths and formulations of vildagliptin for the initiation and intensification of T2DM therapy.

KEYWORDS: dpp-4 inhibitors, type 2 diabetes mellitus, vildagliptin, oral hypoglycemic agents, hyperglycemia

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Introduction

Diabetes is a major global health problem, with an estimated 537 million adults in 2021, with a predicted rise to 783 million by 2045.[1] India is commonly referred to as the "Diabetes capital of the world" due to its high prevalence of the disease, with 17% of the total number of diabetes patients worldwide residing in India. At present, India has nearly 80 million people with diabetes, and this figure is anticipated to reach 135 million by 2045.[2]

There are different types of oral antidiabetic agents that are used to manage type 2 diabetes mellitus (T2DM), such as biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP-4i), SGLT-2 inhibitors, alpha-glucosidase inhibitors and oral glucagon-like peptide 1 (GLP-1) receptor agonist (oral Semaglutide). Each class of medication has a unique mechanism of action to help regulate blood sugar levels. These medications are typically used in combination with lifestyle changes, such as a healthy diet and exercise. In the 1990s, it was discovered that DPP-4 can deactivate incretin hormones like GLP-1 and GIP. Clinical studies conducted in the 2000s found that DPP-4 inhibitors can help lower glucose levels in individuals with type 2 diabetes, alone or

in combination with other therapies. They also have a low risk of causing hypoglycemia. From 2006 to 2013, regulatory bodies approved 5 DPP-4 inhibitors, including sitagliptin, vildagliptin, alogliptin, saxagliptin, and linagliptin, for use in the market.[3]

In India, the prescriptions of T2DM are written with particular emphasis on cost considerations leading to the relatively less frequent prescription of DPP-4i as shown in multiple prescription studies.[4] Real-world data (2021) in India showed that DPP-4i (91.23%) was the most prescribed oral antidiabetic agent (OAD) in the elderly population (>60 years), followed by metformin (74.74%). DPP-4i was the second most common OAD after metformin to be prescribed in patients with chronic kidney disease (CKD) or Cardiovascular disease (CVD).[5] Vildagliptin is usually prescribed as a part of a comprehensive treatment plan for type 2 diabetes, which may also include dietary changes, exercise, and other medications. In a drug utilization study in Kerala, metformin, followed by vildagliptin, was the most commonly prescribed OAD.[6]

Development of vildagliptin

The clinical registration for vildagliptin commenced in 2002 and concluded in 2006, with new drug applications submitted to several countries. In a study conducted over 4 weeks, vildagliptin was effective in reducing HbA1c levels in patients who had not previously taken any medication, with the reduction amounting to 0.4% from a baseline of 7.1%-7.2%. The study also revealed decreased glucagon levels during meals in humans, which had not been examined in animals treated with DPP-4i.[7] Further clinical profiling studies conducted over the last 12 years have shown that vildagliptin therapy enhances the sensitivity of pancreatic islet α- and β-cells to glucose. This leads to increased insulin secretion and reduced glucagon secretion, particularly in hyperglycemic states, and reduced insulin secretion and increased glucagon secretion during hypoglycemia.[8]

Vildagliptin: Clinical evidence

In treatment-naive patients with T2DM (n = 632), the largest clinical trial assessed vildagliptin monotherapy at doses of 50 mg once or twice daily and 100 mg once daily. The results showed that the 3 dose levels of vildagliptin resulted in a mean reduction in HbA1c levels of 0.5%, 0.5%, and 0.6%, respectively when compared with placebo (P = .006, .006, and .001, respectively). The reductions in fasting plasma glucose levels from baseline were 18, 14.4, and 14.4 mg/dl for the 3 respective dose levels (P = .021, .093, and .058, respectively, compared with placebo). Only the 50 mg twice-daily dose group showed a significant change in fasting lipid parameters, with a 4.5% reduction in total cholesterol levels (P = .048 compared with placebo).[9]

Clinical trials have indicated that vildagliptin does not significantly impact weight and does not increase the risk of cardiovascular and cerebrovascular (CCV) events.[10] The J-VICTORIA study observed that patients with T2DM who received vildagliptin had significantly lower mean 24-hour blood glucose levels, Mean amplitude of glycemic excursion (MAGE), the highest blood glucose level after supper, and hyperglycemia after breakfast compared to those taking sitagliptin (Table 1). However, there were no notable differences in plasma levels of glycosylated hemoglobin (HbA1c), glycoalbumin (GA), C-peptide immunoreactivity (CPR), and B-type natriuretic peptide (BNP), or plasminogen activator inhibitor-1 (PAI-1) between patients treated with vildagliptin and those treated with sitagliptin.[11]

Vildagliptin is available in 2 forms: immediate release (IR) tablets which are taken at a dose of 50 mg twice daily (BID), and a modified release (MR) formulation, which was developed for once daily (QD) dosing at a dose of 100 mg. Vildagliptin is also produced as a fixed-dose combination with sodium-Glucose Co-Transporter Inhibitor (SGLT2i) or metformin to determine the pharmacokinetics and safety of both formulations; a study was conducted on healthy adult subjects using an open-label, randomized, 2-period, single- and multiple-dose, 2-way crossover, steady state design. The study found that the 100 mg MR QD formulation of vildagliptin could be a valuable alternative to the 50 mg IR BID formulation to improve treatment adherence and patient compliance.[12]

Once daily vildagliptin. A phase-4 study conducted in India found that the once-daily dose of Vildagliptin 100 mg SR is as effective and safe as the twice-daily dose of 50 mg in reducing HbA1C, FPG, and PPPG when taken in conjunction with metformin 1000 mg. The study suggests that the once-daily Vildagliptin SR 100 mg formulation is bioequivalent to the twice-daily vildagliptin IR 50 mg formulation. Additionally, the once-daily formulation can provide more than 80% DPP-4 inhibition coverage over 24 hours, which may result in a clinically meaningful glucose-lowering effect and reduced pill burden for patients with diabetes.[13]

Vildagliptin versus other OADs. In a real-world study, vildagliptin and empagliflozin showed similar reductions in HbA1c (−0.97% ± 0.68 for empagliflozin and −0.82% ± 1.57 for vildagliptin, P = .980), fasting blood glucose, systolic blood pressure, and weight of participants. Also, the safety of both drugs was comparable.[14] Additionally, vildagliptin (50 mg BD) was found to be non-inferior to pioglitazone(30 mg OD) in lowering HbA1c, and more patients with vildagliptin reached their target HbA_{1c} compared to patients on vildagliptin and glimepiride without causing hypoglycemia.[10]

Vildagliptin and its combination with metformin. The VERIFY study showed that early combination therapy of antidiabetic medications significantly reduced the relative risk for time to initial treatment failure (HbA1c ⩾ 7.0%) by 49% (HR 51, P < .0001) compared to initial metformin monotherapy. After 5 years, the number of patients with reasonable glycemic control for an extended period was more than twice as high in the early

Table 1. Clinical study details of J-VICTORIA study.[11]

STUDY DESIGN	N	TREATMENT	RESULTS			*P* VALUE
			PARAMETER	VILDAGLIPTIN	SITAGLIPTIN	
Observational, randomized study	20	Vildagliptin 100 mg daily (50 mg BID) Or sitagliptin 50 mg daily (OD)	Mean 24-h blood glucose (mg/dL)	142.1 ± 35.5	153.2 ± 37.0	.012
			MAGE (mg/dL)	110.5 ± 33.5	129.4 ± 45.1	.040
			Highest blood glucose level after supper	206.1 ± 40.2	223.2 ± 43.5	.015
			AUC (⩾180 mg/dL) within 3 hours (mg/min/dL)	484.3	897.9	.025
			Urinary CPR level (μg/day)	97.0 ± 41.6	85.2 ± 39.9	.008

Abbreviations: AUC, area under curve; BID, twice daily; CPR, C-peptide immunoreactivity; OD, once daily.

combination therapy group compared to those who received initial metformin monotherapy. Additionally, the median time to loss of glycemic control was almost doubled in the early combination group (61.9 months) compared to the initial metformin monotherapy group (36.1 months), extending the need for treatment intensification by more than 2 years.[15]

Legacy effect of vildagliptin. Apart from delaying the time to primary treatment failure, early combination therapy also reduced the risk of time to secondary treatment failure by 26% (HR = 0.74, $P < .0001$) in VERIFY. This suggests a "legacy effect" by which only the early normalization of blood glucose can help to attenuate diabetes progression.[15]

Putting an early combination of vildagliptin therapy into action. The VERIFY study recommends early combination therapy for the treatment of diabetes, which requires changes in all aspects of diabetes management, including early diagnosis, treatment initiation, intensification, and follow-up.[15]

A randomized trial showed that a combination of vildagliptin and Metformin resulted in higher HbA1c reduction with a similar safety profile to monotherapy. Combining vildagliptin with low-dose metformin (−1.6%) may provide equivalent or superior HbA1c lowering without GI tolerability issues associated with higher doses of metformin (−1.8%).[16] A meta-analysis revealed that exenatide + metformin and vildagliptin + metformin had better efficacy in improving insulin sensitivity in T2DM patients.[17] The OMEGA study showed that vildagliptin with or without metformin as an add-on to insulin effectively achieved reasonable glycemic control without hypoglycemic events[18] (Table 2).

Real-world data from India also suggests that combining metformin with vildagliptin significantly reduced HbA1c compared to metformin alone (median: −0.5%%vs 0%, respectively; $P < .001$).[19]

Early combination therapy with vildagliptin and metformin is effective and well-tolerated in patients with type 2 diabetes, regardless of age or ethnicity. Early combination therapy can lead to better glycemic control and delay the need for treatment escalation compared to initial metformin monotherapy. Vildagliptin and metformin combination therapy have a lower risk of hypoglycemia and better tolerability than higher doses of metformin alone. The findings of the Indian real-world study concluded the need for early initiation of combination therapy (metformin and vildagliptin combination) over metformin monotherapy for better glycemic control.[19]

The RWE study suggests that vildagliptin, both as monotherapy and in combination with metformin, is an effective and well-tolerated therapy for reducing HbA1c and achieving target glycemic control in patients with T2DM. [21] The studies conducted in Indian and Japanese patient populations showed that long-term vildagliptin combination therapy was safe and effective in real-world settings.[22] The INITIAL study conducted in an Asian population of drug naïve T2DM patients with high baseline HbA1c levels and often associated with cardiovascular risk factors demonstrated that vildagliptin/metformin combination therapy was associated with a significant and clinically relevant reduction in HbA1c from baseline. The Effect was seen as early as week 12 and was maintained over 24 weeks, with good tolerability reported.[23]

Safety of DPP-4 inhibitors

Cardiovascular outcome trials thus far have proven cardiovascular safety for ischemic events in patients treated with vildagliptin, sitagliptin, saxagliptin, alogliptin and linagliptin. Data showing an increased hospitalization rate in the case of saxagliptin (SAVOR-TIMI 53 trial) did not seem to be a class effect.[24,25]

Renal safety. Considering the prevalence of chronic kidney disease as a late-stage complication of progressive T2DM, the renal safety of an anti-diabetes medication is an essential factor to consider. Vildagliptin, mainly excreted via the kidneys, may not be suitable for patients with renal insufficiency. However, patients with mild renal impairment can take vildagliptin without requiring a dose adjustment, while those with moderate or

Table 2. Clinical trial for the combination of vildagliptin and metformin.

STUDY	STUDY DESIGN	PATIENT CHARACTERISTICS	N	TREATMENT AND DURATION	RESULTS			REF
					PARAMETER	GROUP 1	GROUP 2	
The OMEGA study	Prospective, observational study	T2DM uncontrolled on insulin	88	Vildagliptin/metformin combination or vildagliptin or 12 weeks		VM	V	El Ebrashy et al[18]
					HbA1c reduction	−1.3 ± 0.9%#	−1.1 ± 0.9%#	
					Reduction in body weight	−2.5 ± 7.3 kg*		
					Reduction in insulin dose	−24.11 ± 22.3 IU#		
					AE	8 (8.9%)	11 (1.2%)	
EMR study, India	Observational, retrospective, non-interventional study	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	2740	Metformin (M) Or VM combination	Median HbA1c reduction	M group 0%	VM group −0.5%**	Mohan et al[19]
					Additional OAD at follow-up	35.2%	15.6%**	
					Adverse events	comparable		
VIRTUE study	Multicenter, prospective, observational cohort study	Patients with type 2 diabetes who fast during Ramadan.	573	Vildagliptin + metformin Or SU+ metformin 6 weeks	hypoglycemia	3.7%**	25.5%	Hassoun et al[20]
					Difference in HbA1c reduction	−0.18%** favoring V+M		
					Difference in body weight reduction	−0.68 kg** favoring V+M		

Abbreviations: EMR, electronic medical records; OMEGA, observational cohort study to assess the effectiveness, safety and tolerability of vildagliptin and MEtformin plus vildaGliptin in reducing the HbA1c in type 2 diabetic patients uncontrolled on insulin therapy in a real-world setting in Egypt; SU, sulfonylurea; VIRTUE, VildagliptIn expeRience compared wiTh sulfonylUreas obsErved during Ramadan; VM, Vildagliptin and metformin.
#$P < .0001$. **$P < .001$. *$P < .01$.

severe renal impairment should take a reduced dose of 50 mg once daily. Clinical trials lasting 24 and 52 weeks, respectively, involving patients with T2DM and moderate or severe renal insufficiency who were already receiving stable antidiabetic therapy, showed that vildagliptin (50 mg po, q.d.) had a similar safety profile to placebo. Moreover, a recently published clinical trial demonstrated that vildagliptin has the potential to be a safe and effective treatment for patients with new-onset diabetes following kidney transplantation, highlighting its utility for treating other kidney disorders.[26]

Cardiac safety. A meta-analysis of 40 phase III and IV trials involving over 17 000 patients confirmed the cardiovascular safety of vildagliptin. The meta-analysis, which included patients with advanced disease, elderly patients, patients with renal impairment, and patients with congestive heart failure, used prospectively adjudicated CV events to determine that the incidence of major adverse cardiovascular events (MACE) was not significantly higher with vildagliptin compared to the comparator drug, with a risk ratio of 0.82 (95% CI 0.61-1.11). The risk ratios for the individual MACE endpoints, such as myocardial infarction, stroke, and CV death, were also similar to the comparator. Thus, an additional outcome trial was deemed unnecessary.[26]

The incidence of heart failure events was also not higher with vildagliptin compared to the comparator, as shown by a risk ratio of 1.08 (95% CI 0.68-1.70). The Vildagliptin In Ventricular Dysfunction Diabetes (VIVIDD) trial, which was a 52-week, double-blind, randomized study, evaluated the safety of vildagliptin in patients with congestive heart failure (CHF) of New York Heart Association (NYHA) class I-III. The study showed that vildagliptin did not cause a change in left ventricular function or worsen pre-existing CHF. Additionally, an analytical, non-interventional, multi-database study also provided evidence on the safety of vildagliptin in CHF patients under real-life conditions. The study showed that the adjusted incidence risk ratios (IRRs) for CHF were similar for vildagliptin and other non-insulin antidiabetic medications, with IRRs ranging from 0.49 to 1.03. This indicates that vildagliptin is safe for use in CHF patients.[27]

Pancreatic safety. Several meta-analyses have shown that DPP-4 inhibitors are not associated with an increased risk of pancreatitis or pancreatic cancer, with no significant differences across individual molecules of the class.[28,29] DPP-4 inhibitors are less likely to cause drug-induced pancreatitis than sulfonylureas.[30]

A meta-analysis of 55 RCTs concluded that the use of DPP-4i does not raise the risk of pancreatitis.[31] Another study involving 69 RCTs discovered that vildagliptin does not increase the risk of pancreatitis compared to a placebo.[32] However, other meta-analyses that analyzed 3 large phase III RCTs (namely, the SAVOR-TIMI 53, EXAMINE, and TECOS trials) concluded that DPP-4i resulted in a higher risk of acute pancreatitis when compared to a placebo.[33,34] Focusing solely on these 3 RCTs resulted in a higher HR (1.78, 95% CI: 1.13-2.81) for the risk of pancreatitis.[35]

Dementia. Patients with diabetes have a 73% higher risk of dementia than those without diabetes. Type 2 diabetes shares several pathophysiological components with dementia, such as glucotoxicity, insulin resistance, inflammation, and oxidative stress. These similarities suggest that antidiabetic medications may be effective against dementia. DPP-4i use decreases the risk of dementia compared to SU use in elderly patients with type 2 diabetes in a real-world clinical setting.[36] A study in Taiwan concluded the neutral Effect of vildagliptin on dementia risk.[37]

Diabetic retinopathy. In preclinical studies, Vildagliptin inhibited inflammatory and thrombogenic reactions in the retinas of obese T2DM rats, suggesting that it may play a protective role against diabetic retinopathy.[38]

Position in the treatment algorithm of T2DM (DPP4i perspective)

International guideline recommendation for Dpp4 inhibitor in type 2 diabetes mellitus is elaborated in Table 3.

The South Asian Health Foundation 2020 consensus recommends DPP-4 inhibitors as a preferable class for South Asian people with type 2 diabetes to sulfonylureas due to the lower BMI cut-off for obesity and their good hypoglycemia risk profile during fasting. Early and aggressive management strategies should be employed in South Asian people with type 2 diabetes, with a clear objective to reduce the risk of microvascular and macrovascular complications.[47]

Vildagliptin in special population

DPP-4 inhibitors in the elderly. Several studies have shown that vildagliptin and linagliptin are effective and well-tolerated in elderly patients with type 2 diabetes mellitus (T2DM). In a pooled analysis of 10 studies with vildagliptin in 301 patients aged ⩾ 75 years, the drug was found to be effective and well-tolerated. In a 24-week randomized placebo-controlled study of linagliptin in 241 patients aged ⩾ 70 years, the drug was found to significantly reduce HbA1c and fasting blood glucose levels, with the target treatment outcome of HbA1c < 7.0% achieved more often in patients on linagliptin treatment than in those on placebo. Hypoglycemia was the most common adverse event in both groups but did not differ between groups.[48]

Similar favorable results were obtained in a 24-week randomized placebo-controlled study of combined treatment of vildagliptin and insulin. In a pre-planned subgroup analysis of elderly patients aged 65 years or older, vildagliptin significantly

Table 3. Guideline recommendations for DPP-4 inhibitor in the treatment of T2DM.

GUIDELINES	RECOMMENDATION
ADA, 2023[39]	Early combination therapy with metformin and vildagliptin (DPP-4 inhibitor) increases glycemic durability compared to a stepwise approach to treatment.
RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus, 2020[40]	DPP-4 inhibitors, sulfonylurea (or glinides), SGLT2 inhibitors, or AGIs can be used initially for cases where metformin is contraindicated or not tolerated
ICMR guideline T2DM, 2018[41]	Sulfonylureas, DPP-4 inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are second-line oral agents preferred.
IDF guideline, 2012[42]	Second line: Add a sulfonylurea (with a low risk of hypoglycemia) to metformin if glycemic targets are not achieved. Alternatively, add a DPP-4 inhibitor.
NICE guidelines, 2022[43]	• If metformin is contraindicated or not tolerated, consider initial drug treatment with a DPP-4 inhibitor, pioglitazone, or sulfonylurea. • If initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification/if metformin is contraindicated or not tolerated, consider dual therapy with metformin and a DPP-4 inhibitor or metformin and pioglitazone or metformin and a sulfonylurea. • if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either triple therapy with etformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone, and a sulfonylurea. • DPP-4 inhibitor therapy should only be continued if the person has a reduction of at least 5.5 mmol/mol [0.5%] in HbA1c in 6 months
SEMDSA, 2017[44]	• Consider a DPP-4 inhibitor as an add-on to metformin or other initial drug therapy in selected patients not achieving or maintaining their glycemic targets. • Consider a DPP-4 inhibitor as the third glucose-lowering drug in selected patients not achieving or maintaining their glycemic targets on an existing oral two-drug regimen
The Canadian Diabetes Association, 2020[45]	• In newly diagnosed T2DM patients - If A1C values are ⩾1.5% above the target, initiating metformin in combination with a second antihyperglycemic agent (SGLT2 inhibitor or DPP-4 inhibitor) should be considered to increase the likelihood of reaching the target. • In patients with existing T2DM—If reducing the risk of hypoglycemia is a priority: Incretin agents (DPP-4 inhibitor or GLP1-RA), SGLT2i, acarbose and/or pioglitazone should be considered as add-on medication to improve glycemic control with a lower risk of hypoglycemia than other agents. • In T2DM patients on insulin—A DPP-4 inhibitor may be considered as an add-on therapy to improve glycemic control with potential benefits of less weight gain and lower hypoglycemia risk compared to additional insulin
World Health Organization—HEART-D, 2020[46]	Intensification of treatment when metformin and sulfonylurea fail to control glycemia: • Refer for insulin treatment or add human insulin to oral medication. • If insulin is unsuitable, a DPP-4 inhibitor, SGLT-2 inhibitor or thiazolidinedione (TZD) may be added.

Abbreviations: ADA, American diabetes association; ICMR, Indian Council of Medical Research; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence; RSSDI-ESI, Research Society for the Study of Diabetes in India- Endocrine Society of India; SEMDSA, Society for Endocrinology, Metabolism and Diabetes of South Africa; T2DM, type 2 diabetes mellitus.

reduced HbA1c levels compared to placebo, with confirmed hypoglycemia somewhat lower in the vildagliptin group. Elderly patients with T2DM can have greater postprandial glucagon and glucose levels than younger individuals, and suppression of inappropriate glucagon secretion mediated by vildagliptin may explain the higher efficacy observed in this population.[49]

DPP-4 inhibitors during fasting. During Ramadan fasting in patients with type 2 diabetes, DPP-4 inhibitors are considered the safest class of oral glucose-lowering drugs, as they significantly reduce the risk of hypoglycemia compared to sulfonylureas (OR = 0.38, $P < .00001$).[50]

Research trials have reported highly variable rates of hypoglycemia (3%-40%) with SUs/OADs during Ramadan fasting, but vildagliptin has been shown to significantly reduce this risk in cohorts of Indo-Pakistani and UK South Asian Muslim patients in the VECTOR study. Another study found a higher incidence of hypoglycemia during Ramadan fasting in the group treated with SU and metformin than vildagliptin plus metformin. Recent clinical trials have shown that vildagliptin is effective, well-tolerated, and associated with a low incidence of hypoglycemia, particularly in high-risk populations such as the elderly, those with renal impairment, and those requiring insulin-based therapy with metformin and DPP-4 inhibitors[51] (Table 4).

Table 4. Patient profile of vildagliptin combined with other oral hypoglycemic agents.

PATIENT PROFILES
Glycemic characteristics • Newly diagnosed HbA1c 6.5%-7% • Elderly person with moderate HbA1c • Intolerance to metformin IR Co-morbid conditions • Obese person/ need to avoid weight gain • Cardiac or renal risk factors • High risk of hypoglycemia • Gastrointestinal complaints • Moderate CKD • Patients with CVD Lifestyle • Person who operate machinery • Fasting periods like Ramadan or Navratri or Ekadashi • Inability/unwillingness to perform frequent monitoring

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GI, gastrointestinal; HbA1c, plasma glycosylated hemoglobin levels; IR, immediate release.

Need for Consensus

In view of already existing data on vildagliptin and the latest emerging clinical evidence, we need a clinical consensus on the role of vildagliptin in the initiation and intensification of combination therapy. This clinical consensus is a practical document for the guidance of HCPs regarding the different available strengths and formulations of vildagliptin (once daily, sustained release [SR] and fixed dose combination [FDC]).

Methodology

A group of 25 experts consisting of endocrinologists, diabetologists and cardiologists from India, convened for 2 advisory board meetings in November 2022 and January 2023 to discuss the various role and combinations of vildagliptin in management of T2DM. All meetings were conducted physically. The experienced endocrinologists were selected based on their seniority (over at least 10 years of experience in diabetes management). Experts framed statements based on available scientific evidence, experience, and collective clinical judgment from practical experience with vildagliptin. Objectives and specific topics relating to vildagliptin 50 mg BD and vildagliptin combination therapy were discussed, and each expert shared their views, which led to group discussions. The consensus was formed if the agreement to the statement was more than 80% within the group.

Expert Opinion

DPP-4 inhibitors

The pathophysiology of type 2 diabetes mellitus (T2DM) involves the gradual loss of β cell mass and function, in conjunction with insulin resistance, which often begins in the prediabetic stage. The subsequent decline in the incretin effect, likely due to irregularities in the secretion and function of GLP-1, follows these defects. Despite the literature indicating a modest HbA1c reduction of 0.5%-0.9% with DPP-4 inhibitors, clinical practice suggests a more significant reduction, particularly among Indians who have demonstrated an excellent response to these inhibitors.[49,52]

The expert further discussed the history of DPP-4 inhibitors and vildagliptin. The first DPP-4 inhibitor that entered the market was sitagliptin, followed by vildagliptin and saxagliptin, alogliptin, and linagliptin. All the experts agreed that DPP-4 inhibitors have a good safety profile and tolerance and do not cause any immune-related adverse effects. DPP-4 inhibitors have demonstrated the ability to enhance metabolic control in T2DM patients, with minimal risk of adverse effects, including hypoglycemia, which is particularly important in treating the elderly and a large subset of diabetic patients.

All the experts agreed that although various DPP-4 inhibitors have different pharmacokinetic and pharmacodynamic profiles, they are remarkably similar with regard to their antihyperglycemic properties with a very safe profile (neutral concerning weight, without causing hypoglycemia)

Early combination therapy in T2DM

All the experts agreed that DPP-4 inhibitors are helpful in the early stages of diabetes when the patient still retains a β cell population capable of responding to GLP-1 stimulation. The UK Prospective Diabetes Study (UKPDS) was discussed, which showed that monotherapy does not provide long-term stable glycemic control, requiring the addition and combination of glucose-lowering agents.[53] The experts agreed that initiating combination therapy early with agents with complementary modes of action could potentially change the course of the disease. This approach could lead to more extended periods of stable HbA1c levels, delay therapy intensification, and reduce the risk of chronic complications associated with T2DM.

Vildagliptin

Experts discussed vildagliptin for the management of T2DM. Vildagliptin is a highly selective, reversible inhibitor of the enzyme DPP-4 approved by the EU in 2007 for treating T2DM, with a recommended dose of 50 mg twice daily. Vildagliptin treatment results in a rapid inhibition of DPP-4 (around 95% of maximal inhibition).

Vildagliptin is the first gliptin to show suppression of glucagon. Vildagliptin enhances endogenous glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) levels by blocking the incretin-degrading enzyme DPP-4. It may restore the deranged islet-cell balance in T2DM by stimulating meal-related insulin secretion and by decreasing postprandial glucagon levels. Vildagliptin inhibits glucagon secretion in hyperglycemia but appears to enhance glucagon counter-regulation during hypoglycemia in type 2 diabetes.

DPP-4 inhibitor like vildagliptin has better durability and lower risk of hypoglycemia compared to SU.[54]

VERIFY trial: Early treatment initiation versus stepwise approach

The multinational VERIFY study included patients with an Hba1c of 6.5% to 7.5%. The study presented evidence over 5 years, demonstrating the potential benefits of initiating early combination therapy. The time to loss of glycemic control was nearly doubled, and more than twice the number of patients were able to maintain extended glycemic control when treated with vildagliptin-metformin combination therapy, as compared to metformin alone. Additionally, the study indicated a delay in secondary treatment failure among patients receiving combination therapy. These findings suggest that early combination therapy may provide a smoother and more effective treatment trajectory than the conventional stepwise approach.[15]

Importance of maintaining glycemic control

Early glycemic control can lower the risk of disease progression and reduce the likelihood of cardiovascular and other complications associated with diabetes. However, it is essential to maintain the achieved glycemic control to reap the benefits. Physicians must avoid the urge to de-escalate treatment or initiate drug holidays after observing decreased HbA1c levels to pre-diabetic or normoglycemic levels. Improved glycemic control through combination therapy may help reduce long-term costs associated with disease complications and offset the higher initial treatment costs.

Early intensification in patients on metformin and high HbA1c

In the VERIFY trial, patients on vildagliptin/metformin had reasonable glycemic control, no weight gain, and remission for half a decade. For patients diagnosed with HbA1c levels above 8.0%-8.5%, metformin monotherapy may not be sufficient to achieve target levels of HbA1c. Additionally, many patients with diabetes may encounter multiple treatment failures after diagnosis, often attributed to delayed intervention. Due to various reasons, it becomes difficult for treating physicians to intensify therapy within 6 months of failure of metformin monotherapy.[15]

DPP-4 inhibitors in later stages of T2DM

All the experts agreed that DPP-4 inhibitors could also be used in the later stages of the disease, combined with other oral antidiabetic agents, in poorly controlled patients, as is the current clinical indication. All experts prescribe DPP-4 inhibitors in conjunction with insulin in uncontrolled T2DM.

How do physicians choose a combination of OADs?

(a) Baseline Hba1c
(b) Synergistic mode of action.
(c) Minimal risk of hypoglycemic
(d) Lowest risk of weight gain.
(e) Time frame for achieving target HbA1c (preferably 3 months)

Proposed indications for combination therapy are discussed in Table 5.

Switching between DPP4 inhibitors

Most experts agreed that all gliptins are the same in terms of anti-glycemic Effect and safety. In India, the DPP4-inhibitors are usually differentiated based on cost.

If patient requests for an OAD at night, switch from vildagliptin 50 mg BD to once daily DPP-4 inhibitor If patients are not achieving their desired glycemic control while taking Teneligliptin or Evogliptin, they can be switch to vildagliptin, sitagliptin, or linagliptin. In cases where quality is a concern. For an example, use of generics without quality assurance, a shift to quality assured vildagliptin can be considered.

Switching to DPP-4 inhibitor in case of OAD failure

Similar to resistant hypertension, there is a concept called oral antidiabetic (OAD) failure. It is defined as a clinical situation where HbA1c remains above goal, despite concurrent use of optimum dose of 3 oral glucose lowering drugs of different classes, one of which should be metformin and the second, preferably a sulfonylurea, provided adequate diet and exercise have been followed, and co-morbid conditions causing hyperglycemia ruled out.[55]

- There are patients with T2DM having uncontrolled Hba1c after having been on SU for 5 to 7 years (OAD failure). Such treatment may be intensified with vildagliptin/metformin FDC.
- Patients on metformin and maximal dose of SU can be switched to DPP4 inhibitors like vildagliptin with or without a concomitant reduction in SU dose.
- Patients on alpha-glucosidase inhibitors or SU who are not able to target glycemic control can be interchanged to vildagliptin.

Vildagliptin for patients with heart disease

Cardiologists usually see different types of patients—ambulatory HF, post-MI with/without LV dysfunction, post-PCI, and post-CABG, HTN, DM, dyslipidemia, and middle-aged

Table 5. Proposed indications for vildagliptin and metformin combination.

PATIENT PROFILE	EXPERT OPINION
HbA1c < 7.5%	If patient does not respond/ tolerate metformin
Hba1c >7.5%, and the patient has not tried lifestyle changes (diet and exercise)	The patient can be prescribed metformin and vildagliptin combination. If a patient shows good clinical response, then down titrate to metformin monotherapy
Hba1c >7.5% and the patient does not follow lifestyle changes	Patient can be prescribed metformin and vildagliptin combination
Hba1c 7.5%-8%	Initiation in treatment naïve patient or as intensification in patients who do not respond sufficiently to metformin.
Hba1c > 8.5	Initiation with/without a third glucose lowering drug, in treatment naïve patients; or as intensification in person not responding adequately to existing therapy.
Metformin intolerance	Vildagliptin twice daily or Vildagliptin SR once daily or Vildagliptin + SGLT2i (eg, Dapagliflozin)
For intensification of therapy in T2DM	• Metformin + vildagliptin • Vildagliptin SGLT2i • Vildagliptin + SU • Vildagliptin, along with insulin
Hba1c is 6.5%-7.5%, and the patient does not respond to metformin monotherapy	Add vildagliptin as an add-on to metformin
Elderly patients with Hba1c > 7.5%	Vildagliptin/metformin FDC

Abbreviations: FDC, fixed dose combination; HbA1c, plasma levels of glycosylated hemoglobin; SGLT2i, sodium/glucose cotransporter-2 inhibitors; SU, sulfonylurea; SR, sustained release; T2DM, type 2 diabetes mellitus.

people going for a cardiologist's opinion. Cardiologists do not prefer monotherapy for the management of T2DM in a patient with a risk of CVD or existing cardiac comorbidities. Metformin, DPP4i, and SGLT2i are the most prescribed OADs. Experts discussed regarding the Taiwan National registry, the short-term use of vildagliptin in patients with type 2 diabetes mellitus at very high CV risk was not associated with increased risks of CV death, non-fatal MI, non-fatal stroke, all-cause mortality or hospitalization for HF.[56] The results of the CARMELINA study showed that Linagliptin had a neutral effect on non-fatal stroke. Among adults with type 2 diabetes and high CV and renal risk, DPP4i added to usual care compared with placebo added to standard care resulted in a non-inferior risk of a composite CV outcome over a median of 2.2 years.[57]

Although when prescribing glucose lowering therapy, one must be aware of the potential effects of some drug on conduction and rhythm. Vildagliptin has been proven not to have any deleterious impact on QTC interval or pro-arrhythmogenic effect (Table 6).[58]

Final Consensus Statements

Place in therapy

1. Vildagliptin can be used as monotherapy in person who have contraindication or are intolerant to metformin.
2. Vildagliptin can be used as initial therapy along with metformin in person with a baseline HbA1c > 7.5%.
3. Vildagliptin can be used to intensify therapy in person with inadequate control on metformin with/without other glucose lowering drugs, provided no GLP-1RA or other DPP4i used concurrently.
4. Vildagliptin can be used as part of dual combination or triple combination therapy, as loose or as fixed dose combination.
5. Vildagliptin can be used in combination with insulin in T2DM patients who are inadequately controlled, have unacceptably high glycemic variability, or need high doses of insulin for control.

Safety

6. In T2DM patients with cardiovascular disease, vildagliptin decreases the risk of adverse CV events.
7. Vildagliptin can be used in T2DM patients who are overweight/obese since it is weight neutral.
8. Vildagliptin can be used in T2DM patients who want to avoid weight gain.
9. Vildagliptin does not prolong QT interval or affect cardiac conduction even at the highest daily therapeutic dose.
10. Vildagliptin is well tolerated with a low incidence of AEs, and it does not increase the risk of cardiovascular/cerebrovascular (CCV) events.

Table 6. Summary of vildagliptin monotherapy and combined with other OADs.

	INITIATION	INTENSIFICATION	INTERCHANGE
Vildagliptin 50 mg Once Daily* Vildagliptin 50 mg Twice Daily/ vildagliptin 100 mg SR OD	1. Renal impairment (50 mg OD)* 2. High PPG (50 mg OD)	1. Uncontrolled on mono/ dual therapy 2. Add on to insulin	Intolerable to metformin
Vildagliptin 50 mg/ metformin 500 mg/850 mg/1000 mg	HbA1c >1.5% higher than target	Uncontrolled on mono/dual therapy	-
Vildagliptin 100 mg SR/ dapagliflozin 10 mg Vildagliptin 50 mg/dapagliflozin 5 mg*/10 mg	1. ASCVD 2. CKD 3. High-risk diabetes 4. Renal impairment*	1. For increased glucose lowering efficacy 2. To reduce cardiac and renal risk	Metformin intolerance
Vildagliptin 100 mg SR + dapagliflozin 10 mg + metformin 500 mg/1000 mg	1. High HbA1c (>8.5%) +High risk of ASCVD/ established ASCVD. 2. High HbA1c (>8.5%) +CKD*	1. Uncontrolled on dual therapy 2. Need for additional CV/ renal benefits	(Safety and Tolerability issues)
Vildagliptin 50 mg/100 mg SR + pioglitazone 15 mg	1. Previous history of stroke/ TIA 2. NAFLD	Uncontrolled on metformin/ other drugs	Intolerance to metformin/ other drugs

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease; OD, once daily; PPG, post prandial glucose; SR, sustained release; TIA, transient ischemic attack.
*Renal Impairment: CKD (3-4 stage), eGFR:<60mL/min/1.73m2

Dosage

11. Vildagliptin 100 mg SR OD is a practical therapeutic alternative to 50 mg IR BID formulation to improve adherence and persistence.
12. Vildagliptin 100 mg SR OD dose is equally effective as 50 mg twice daily vildagliptin in terms of HBA1c, fasting and postprandial blood glucose levels.

Special situations

13. Vildagliptin should be considered one of the safer options while managing diabetes during fasting periods like Ramadan and Navratri
14. Treatment of inpatient hyperglycemia with basal insulin plus DPP4-i is an effective and safe regimen in elderly patients with T2DM.

Declarations

Ethics approval and consent to participate

This article does not contain any new studies with human participants or animals performed by any of the authors.

Consent for publication

N/A.

Author contributions

Sanjay Kalra: Conceptualization. AH Zargar: Conceptualization. GR Sridhar: Writing—original draft. Ashok Kumar Das: Writing—original draft. Jamal Ahmed: Writing—review & editing. Jagdish Chander Mohan: Writing—review & editing. G Vijayakumar: Writing—review & editing. Ajay Kumar: Writing—review & editing. Rakesh Kumar Sahay: Writing—review & editing. Vageesh Ayer: Visualization. Kaushik Pandit: Visualization. Ganapathi Bantwal: Visualization. Arun Srinivas: Visualization. A G Unnikrishnan: Visualization. Sushil Jindal: Visualization. Saumitra Ray: Visualization. Manash P Baruah: Visualization. Kajal Ganguly: Visualization. Sachin Mittal: Visualization. Ameya Joshi: Visualization. Joe George: Visualization. Ganesh HK: Visualization. Nitin Kapoor: Visualization. Santosh Ramakrishnan: Visualization. Chetan Shah: Visualization. Atul Dhingra: Visualization. Balram Sharma: Visualization.

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Availability of data and materials

Data sharing does not apply to this article, as no datasets were generated or analyzed during the current study.

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