World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Expert viewpoint on the position of Vildagliptin in a cardiology clinic in Indian clinical settings

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World Journal of Advanced Research and Reviews, 2023, 17(02), 001–009

Publication history: Received on 18 November 2022; revised on 07 January 2023; accepted on 09 January 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.2.1252

Abstract

Objective: To analyze the opinion of Indian clinical experts on the current usage patterns of vildagliptin in the treatment of patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Methods: This report summarizes opinions and discussions that occurred during the 36 virtual round table meetings (May 2021 - March 2022) involving 540 healthcare practitioners (HCPs) across India. The collected data were analyzed and categorized into four grades: Level A, very strong (≥80% responses); Level B, strong (≥50-79% responses); Level C, moderate (25-49% responses); Level D, neutral/no consensus (<25% responses).

Results: Healthcare practitioners gave opinions for the following; Level A (90.9%): time-in-range (TIR) and glycemic variability are important clinical criteria for selecting antidiabetic therapy in patients with risks of macrovascular complications; Level B (70.8%): vildagliptin gives better TIR and less glycemic variability compared to other dipeptidyl peptidase-4 inhibitors; Level A (90.9%): addition of vildagliptin should be considered in patients with T2DM and established atherosclerotic CVD who have uncontrolled glycemia with metformin plus sodium-glucose cotransporter-2 inhibitors treatment; Level B (52.9%): Vildagliptin should be considered as a part of the treatment algorithm only when the patient population is elderly, with long-standing diabetes, newly diagnosed T2DM with prior CVD, patients with obesity, or renal impairment. The majority of HCPs reported clinical benefits including a reduction in the dose of insulin (52.4%) and the number of hypoglycemic incidences (33.3%) with vildagliptin plus insulin.

Conclusion: Indian clinical experts recommended the safe and neutral use of vildagliptin in patients with T2DM and CV risk and/or CVD.

Keywords: CVD; DPP-4 inhibitors; Indian clinical experts; T2DM; Uncontrolled glycemia

1. Introduction

A strong correlation exists between T2DM and cardiovascular disease (CVD), which is the leading cause of morbidity and mortality in patients with diabetes. Cardiovascular (CV) risk factors such as obesity, hypertension, and dyslipidemia are common in these patients, leading to a higher risk of cardiac events [1]. Patients with T2DM frequently have endothelial dysfunction, increased oxidative stress, increased coagulability, autonomic neuropathy, and other conditions that may directly influence the development of CVD [2]. Diabetic patients are more likely to have CVD due to the high prevalence of CV risk factors and direct biological effects of diabetes on the CV system, which further increase the risk of MI, revascularization, stroke, and CHF [3].

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Treatment of T2DM and CVD differs widely across and within countries, and although most of the CVD risk in T2DM can be attributed to the long-term complications of diabetes, interest has been growing in studying the effect of antidiabetic drugs on this risk. In recent years, regulatory authorities have rigorously evaluated the CV safety of newer antidiabetic agents and have provided guidelines for evaluating CV safety outcomes [4, 5]. The patient's needs should be taken into consideration when choosing oral anti-diabetic medicines (OADs). The agents that stimulate insulin secretion (sulphonylureas and rapid-acting secretagogues), reduce hepatic glucose production (biguanides), delay digestion and absorption of intestinal carbohydrate (alpha-glucosidase inhibitors) or improve insulin action (thiazolidinediones) are some of the primary groups of OADs [6]. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely accepted since they were introduced in 2006 due to their favorable safety profile, particularly their lack of weight gain and hypoglycemia risks [7]. When combined with maximal metformin therapy, all classes of non-insulin antidiabetic drugs reduced HbA1c in a comparable way, but varied in how they affected weight gain and the risk of hypoglycemia. Due to the elevated amounts of active glucagon-like peptide 1 (GLP-1), neither the monotherapy nor the combination therapy of alpha-glucosidase inhibitors nor DPP-4 inhibitors cause a statistically significant weight change [8, 9].

Compared to other DPP-4 inhibitors, vildagliptin has the highest binding capacity for human DPP-4 enzyme, which induces more levels of active GLP-1 and gastric inhibitory polypeptide (GIP) incretins that substantially enhance the pancreatic islet α- and β-cell responsiveness to glucose, leading to a better time in range (TIR) profile [10]. The TIR, a newly developed metric for evaluating glycemic management, is rapidly being linked to outcomes associated with diabetes. The usefulness of TIR as a surrogate marker of long-term negative clinical outcomes is supported by the known connection between lower TIR and an increased risk of all-cause and CVD death among patients with type 2 diabetes mellitus (T2DM) [11]. Among all the DPP-4 inhibitors, the ability to block the inactivation of GLP-1 and GIP between meals and overnight was only demonstrated by vildagliptin [12, 13]. Moreover, vildagliptin is more potent than other DPP-4 inhibitors, such as sitagliptin, saxagliptin, linagliptin, and alogliptin, in suppressing glucagon, and causes less glycemic variability [14]. This was also evaluated in a study by Kothny et.al. Where vildagliptin showed slightly lower baseline HbA1c level than sitagliptin [15]. Vildagliptin is associated with reduced gastrointestinal adverse effects than metformin, and reduced edema than rosiglitazone. Vildagliptin has been reported to significantly lower HbA1c in patients taking metformin, pioglitazone, glimepiride, and insulin as an add-on combination therapy. Vildagliptin has also been found to significantly lower the frequency of hypoglycemia in patients receiving insulin [16].

Three large prospective DPP-4 inhibitor trials with CV outcomes including the SAVOR-TIMI 53, TECOS and EXAMINE trials, confirmed that there was no increased risk of major adverse CV events [17, 18, 19]. A study by Mclnnes et.al. Showed that vildagliptin has no increased risk of major adverse cardiac events (MACE) relative to comparators, also the number of heart failure hospitalizations is not significant [20]. The patient's adherence to vildagliptin was also higher due to its low risk of hypoglycemia and other adverse effects; which makes vildagliptin a more suitable oral hypoglycemic agent in the elderly population [21, 22]. Vildagliptin exhibits the same metabolic advantages in subjects with impaired glucose tolerance as it does in T2DM. Vildagliptin thereby enhances islet function, which in turn enhances glucose metabolism [23]. This therapy has also been linked to advantageous extra-pancreatic effects, such as enhanced postprandial triglyceride-rich lipoprotein metabolism and enhanced peripheral insulin sensitivity [24]. Additionally, a comprehensive meta-analysis of CV events adjudicated independently has also provided reassurance about the CV safety of DPP-4 inhibitors, particularly vildagliptin [20]. Furthermore, real-world studies indicate that vildagliptin had a good safety profile without increased risk of CVD including chronic heart failure [25, 26] and hospitalization for heart failure (HHF) [27] in patients with T2DM. Overall data indicate that vildagliptin has optimal glycemic control, better TIR, glycemic variability control as well as a CV neutral effect in patients with T2DM.

Despite available evidence for the use of vildagliptin in diabetes management, there is a paucity of data regarding its use, particularly in Indian patients with T2DM and CV risk and/or established CVD. Therefore, this consensus report aimed to analyze the opinion of Indian clinical experts on the use of vildagliptin among patients with T2DM and CVD as well as to understand the practical usage pattern of vildagliptin in the treatment journey of patients with T2DM with CV risk and/or established CVD. This consensus will help to improve the spectrum of usage of vildagliptin in the management of T2DM with cardiac complications.

2. Methods

This consensus report was prepared from discussions that occurred during the 36 virtual round table meetings (RTMs) conducted between May 2021 to March 2022. Healthcare practitioners (HCPs) from the different geographical regions of PAN India sites participated in these RTMs. A standard questionnaire of seven questions pertaining to the usage pattern of vildagliptin in the treatment journey of T2DM patients with cardiovascular risks or complications was prepared, discussed, and evaluated by Indian cardiologists. All the HCPs were independently requested to vote from the given options for each question during the RTMs and their opinions/responses were recorded. To derive key

recommendations for the consensus, the collected data were analyzed and considered for categorization into four grades. Level A as very strong (if ≥80% of responses then experts accepted completely), level B as strong (If ≥50-79% of responses then experts accepted with minor reservation), level C as moderate (If 25-49% of responses then experts accepted with major reservation) and level D as neutral/ no consensus (If <25% responses then experts rejected the statement) (Table 1). These opinion-based recommendations were compiled to prepare this consensus report on the usage pattern of vildagliptin in the treatment journey of Indian patients with T2DM with CV risks and/or established CVD.

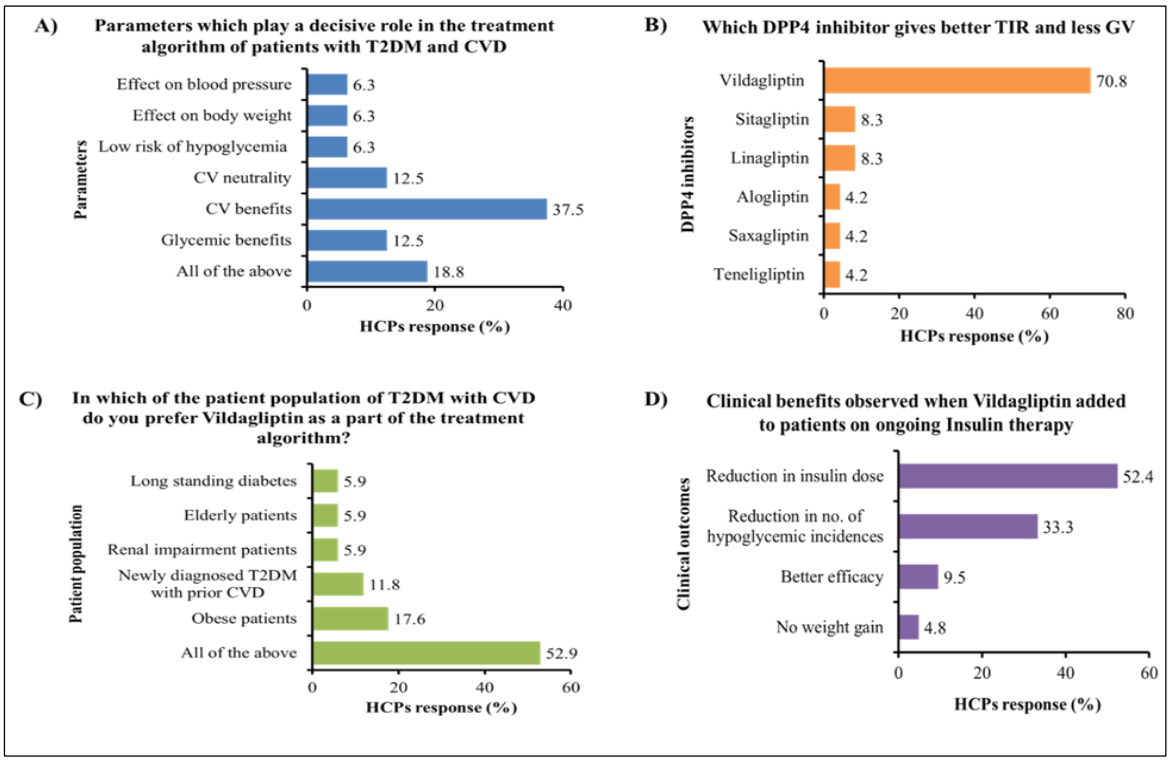
Table 1 Levels of evidence and consensus

Grade	Level of consensus	Voting description	Responses (%)	Description
A	Very strong	Strongly agree + Agree	≥80	Accepted completely
B	Strong	Strongly agree + Agree	≥50-79	Accepted with minor reservation
C	Moderate	Strongly agree + Agree	25-49	Accepted with minor reservation
D	Neutral/ no consensus	Disagree	<25	Rejected

3. Results

A total of 540 HCPs comprising cardiologists from all over India, participated in the RTMs.

A total of 37.5% of HCPs opined that CV benefits play a decisive role in the addition of an antidiabetic agent in the treatment algorithm of patients with T2DM and CVD (Figure 1A). On the other hand, 18.8% of HCPs mentioned that they would consider the addition of a potential therapeutic antidiabetic agent for the treatment of patients with T2DM and CVD only if it has CV benefits, CV neutrality, and effect on blood pressure, effect on body weight, glycemic benefit, and low risk of hypoglycemia (Figure 1A).



CV, cardiovascular; CVD, cardiovascular disease, DPP4i, dipepdyl peptidase inhibitor, HCP, healthcare practitioners; T2DM, type 2 diabetes mellitus

Figure 1 Opinion on a spectrum of usage of vildagliptin in the management of diabetes mellitus with cardiac complications

Healthcare practitioners strongly agreed (Consensus level A; 90.9%) with the consideration of TIR and glycemic variability as important clinical criteria for selecting antidiabetic therapy in patients with risks of macrovascular complications (Figure 2). The majority of HCPs (Consensus level B; 70.8%) experienced that vildagliptin gives better TIR and less glycemic variability compared to other DPP4 inhibitors (Figure 1B). Healthcare practitioners (Consensus level A; 90.9%) were in very strong consensus with the idea that the addition of vildagliptin should be considered in patients with T2DM and established atherosclerotic CVD (ASCVD) who have uncontrolled glycemia with metformin plus sodium-glucose cotransporter-2 inhibitor (SGLT2i) treatment (Figure 2). More than half of the HCPs (Consensus level B; 52.9%) considered vildagliptin as a part of the treatment algorithm only when the patient population is elderly, with long-standing diabetes, newly diagnosed T2DM with prior CVD, patients with obesity, or renal impairment (Figure 1C). The majority of HCPs reported clinical benefits including a reduction in the dose of insulin (52.4%) and a reduction in the number of hypoglycemic incidences (33.3%) when vildagliptin was added to patients with ongoing insulin therapy (Figure 1D). A total of 19.5% and 9.8% of HCPs considered vildagliptin in patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) (Consensus level D), however, most HCPs (61.0%) preferred SGLT2i for managing heart failure (HF) in patients with T2DM (Figure 3).

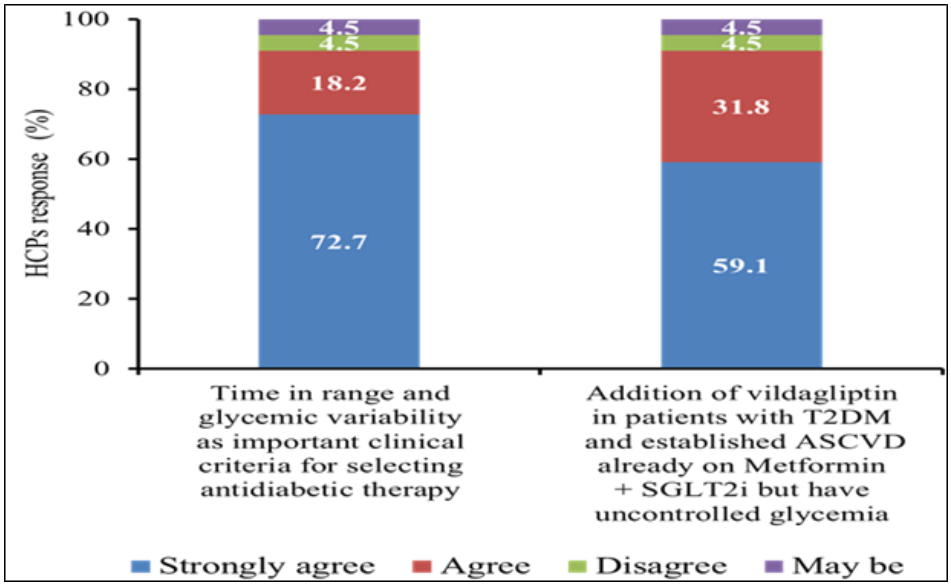


Figure 2 Opinion on criteria for selection of antidiabetic therapy

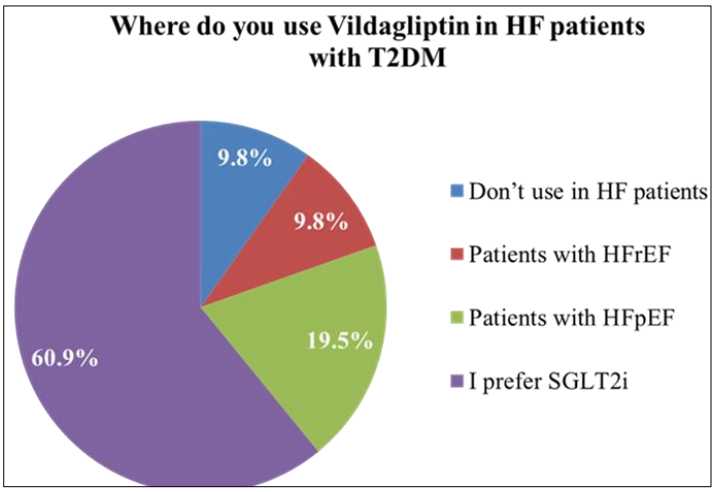


Figure 3 Opinion on use of vildagliptin in HF patients with T2DM

4. Discussion

It is well known that treating conventional CV risk factors such as hypertension and dyslipidemia plays a pivotal role in improving long-term survival of patients with diabetes irrespective of their diabetes status. The primary outcomes used to evaluate optimal care of a patient with T2DM have evolved over the past four decades from optimal glycemic control (i.e., glycated hemoglobin [HbA1c]) to preventing macrovascular diseases, cerebral and cardiac events. In response, several new classes of T2DM medications have been developed in recent years, some of which have been linked to reductions in CV outcomes. This consensus report attempted to present the opinions of Indian clinical experts on the use of vildagliptin among patients with T2DM and CVD.

The key observations of this survey highlight the position of vildagliptin in current clinical practice and further emphasizes on the spectrum of usage of vildagliptin in the management of T2DM with cardiac complications.

According to the present survey, one-third of participants opined that choosing an antidiabetic drug with CV benefits is essential in the treatment of patients with T2DM and CVD. However, about 18% of HCPs opined that they would consider addition of a potential therapeutic antidiabetic agent for the treatment of patients with T2DM and CVD only if it has CV benefits, CV neutrality, effect on blood pressure, effect on body weight, glycemic benefit, and low risk of hypoglycemia. This is in line with the previously published update on the management of T2DM for cardiologists where it highlighted that an optimal antidiabetic agent should be able to produce optimal glycemic control, low risk of hypoglycemia, reduce CVD risk, preferably no weight gain and optimal control of blood pressure [28].

Modern glucometrics including TIR, one of the emerging metrics for assessing glycemic control, and glycemic variability allow the management of diabetes with individualized and personalized glycemic control. There is growing evidence supporting the association between TIR, and diabetes-related outcomes. A large prospective cohort study has found that TIR as measured by CGM during hospitalization was found to be inversely linked with long-term risks of all-cause and CVD mortality in patients with T2DM. These findings back up the efficacy of TIR as a predictive marker for long-term adverse clinical outcomes. In both type 1 and type 2 diabetes, TIR has been linked to microvascular complications as diabetic retinopathy, microalbuminuria, nephropathy, and neuropathy [29, 30, 31]. Poor or low TIR has been found to be associated with high rates of total mortality as well as CV mortality [11]. Therefore, achieving a greater TIR is an important goal for patients with diabetes to reduce the risk of adverse clinical outcomes. In the present survey, HCPs reached to a consensus level A with the statement that TIR and glycemic variability are important clinical criteria for selecting antidiabetic therapy in patients with risks of macrovascular complications and further believed that vildagliptin had a better TIR profile with less glycemic variability compared to other DPP-4 inhibitors (Consensus level B). This is in agreement with a multicentric, prospective, randomized study comparing the continuous glucose monitoring profile of patients with inadequately controlled T2DM receiving either vildagliptin or sitagliptin in addition to metformin. The results indicate that there was no difference between the two drugs in the reduction of glycemic variability. However, patients on vildagliptin spent an additional 13% (3 Hours) of time in the target range (70-180 mg/dL) when compared to sitagliptin [32]. A significant reduction in glycemic variability was seen with vildagliptin, including the mean amplitude of glycemic excursion, a standard deviation of 24 hours glucose measured by continuous glucose monitoring, as well as HbA1c and fasting prandial glucose [33]. Consequently, glucose excursion may be attenuated glucose-dependently with DPP-4 inhibition, thus reducing glycemic variability markers.

Vildagliptin add-on to insulin therapy can improve glycemic control with minimal hypoglycemic risk when used in conjunction with self-monitoring of blood glucose [34, 35, 36]. Moreover, this combination reduces the dose of insulin [37, 38] and was found to be well-tolerated when followed up for two years [39]. In line with the previous evidence, the majority of HCPs in their cardiology practice experienced that vildagliptin add-on to insulin treatment reduced insulin doses and number of hypoglycemic incidences.

In the present survey, Indian clinical experts strongly agreed with the idea that the addition of vildagliptin will be beneficial for the management of CV complications and to meet glycemic goals in patients with T2DM and established ASCVD who were already on metformin and SGLT2i combination but have poor glycemic control. On the other hand, in diabetes patients who have established CVD or high CV risk, SGLT2i CV outcome trials have consistently shown a reduction in HHF and secondary renal outcomes, such as the incidence or progression of nephropathy [40, 41, 42, 43, 44]. Among SGLT2i, empagliflozin and canagliflozin have significant benefits in reducing MACE events in patients with T2DM and established CVD. Moreover, empagliflozin is associated with a significantly reduced risk of CV death in this population [40, 41]. The earlier expert opinion panel supports the early use of SGLT2i and DPP-4 inhibitor combination therapy for the management of Indian patients with T2DM [45]. However, among DPP-4 inhibitors, vildagliptin does not have any profound CV benefits but its CV neutrality is proven which may help physicians to consider it as an add-on

therapy with metformin and SGLT2i to achieve the glycemic target in T2DM patients with ASCVD who still have uncontrolled glycemia.

Evidence from a meta-analysis involving 17,000 patients suggested that vildagliptin can be used in a broad variety of patients with T2DM including a history of CV events or two or more concomitant risk factors such as hypertension and/or dyslipidemia [46]. The safety and efficacy of vildagliptin in elderly patients with T2DM and mild renal impairment have already been demonstrated [47, 48]. Furthermore, regardless of the well-known elevated CV risk in T2DM patients with reduced renal function, vildagliptin therapy is associated with a CV-neutral effect. In this expert opinion panel, the majority of HCPs reported that they consider vildagliptin as a part of the treatment algorithm in a broader variety of T2DM patients with high CV risk or prior CVD. Vildagliptin treatment with proven benefits may be preferred for patients with obesity, renal impairment, long-standing diabetes, older age, and newly diagnosed diabetes with prior CVD.

5. Conclusion

The participating HCPs came to a consensus that the use of vildagliptin in patients with T2DM and CV risk and/or CVD is highly recommended. Vildagliptin may not reduce the complications; however, over time it has demonstrated its potent efficacy and safety. Vildagliptin has many advantages including low hypoglycemic risk, reduced gastrointestinal complications, good adherence in patients, improved glycemic index, and no weight gain; which makes it advantageous for treatment in CVD patients. Overcoming glycemic variability and ensuring maximum time to be spent in the target range are important aspects for optimization of better clinical outcomes; Vildagliptin is the current choice of treatment that can help to address these aspects. Furthermore, Vildagliptin can be preferred in all patient profiles with T2DM and CVD.

Key recommendations

- Time-in-range and glycemic variability are important clinical criteria for selecting antidiabetic therapy in patients with risks of macrovascular complications.
- Addition of vildagliptin will be beneficial in managing the CV complications and achieving the glycemic goals in patients with T2DM and established ASCVD who were already on metformin plus SGLT2i combination therapy but have uncontrolled glycemia.
- Vildagliptin can be a preferred choice of treatment in all patient profiles with T2DM and CVD.
- Vildagliptin as an add-on drug choice to insulin therapy can improve glycemic control with reduced insulin doses and minimal hypoglycemic risk.

Compliance with ethical standards

Acknowledgments

The medical writing support was provided by from Sqarona Medical Communications LLP (Mumbai) and Dr Sona Warrier from the scientific services team of USV Pvt Ltd.

Authorship

All named authors take the responsibility for this integrity of the work as a whole and have given their approval for this version to be published. The contents published herein represents the views and does not necessarily represent the views or opinions of USV Pvt Ltd. and/or its affiliates. The details published herein and intended for discrimination of educational, academic, and/or research purposes and are not intended as a substitute for professional medical advice, diagnostic or treatment.

Disclosure of conflict of interest

There are no conflicts of interest. Dr. Sona Warrier is the employee of USV Pvt Ltd.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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