

Original Research Article

## Physicians Perspectives on the Preference of Antihyperglycemics for the Management of Diabetes Mellitus in India

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### Article History

Received: 19.12.2023

Accepted: 24.01.2024

Published: 10.02.2024

**Abstract:** As they were commonly prescribed together for blood glucose control, metformin and more recent sulfonylureas, such as glimepiride, have been shown in numerous clinical studies to effectively reverse insulin resistance and promote insulin secretion. In India, primary care physicians and specialists used the fixed-dose combination of metformin and glimepiride in various doses. The results of clinical trials needed to be applied to regular clinical practice in the real world in order to close the knowledge gap. Regarding this, professional opinions will provide insightful information about the use of antihyperglycemics and their combinations, including their safety, effectiveness, and usefulness for a particular subgroup of patients with diabetes. So, a cross-sectional study was conducted on the prescription pattern of oral anti-diabetic drugs for patients with diabetes mellitus. The choice of oral anti-diabetic agents for diabetic patients with comorbidities was analysed by using 26 questions. About 845 physicians participated in the survey by sharing their opinions/views on the questionnaire. Also, 400 physicians out of 845 prefers glimepiride and metformin as the preferred combination to achieve the targeted glycated haemoglobin level. Moreover, 723 physicians out of 845 experienced glycated haemoglobin reduction with glimepiride and metformin for more than 3 years. Maximum glycated haemoglobin reduction with glimepiride and metformin was 1.5%-2% by 383 physicians as per the survey. They also experienced good glycaemic control and good cardiovascular safety with glimepiride and metformin. Thus, the experts recommended glimepiride and metformin very often in elderly individuals. Glycated haemoglobin reduction was more than 3 years with glimepiride and metformin, as per the clinical experience of the experts participated in the survey. They also witnessed good glycaemic control and cardiovascular safety profile with glimepiride and metformin combination.

**Keywords:** Type 2 diabetes mellitus, Glimepiride and metformin, Vildagliptin and metformin, Glycated hemoglobin, Glycemic control.

## INTRODUCTION

With 463 million cases and 4.2 million deaths worldwide, diabetes mellitus has become a global health burden [1]. Due to insufficient glycaemic control, patients with type 2 diabetes mellitus (T2DM) are more likely to experience microvascular complications such as diabetic retinopathy, neuropathy, and diabetic nephropathy, as well as macrovascular complications such as coronary artery disease (CAD), peripheral arterial disease (PAD), stroke, and transient ischemic attack (TIA) [2].

Diabetes is becoming more and more common in India, which increases the financial burden associated with incapacity and deadly complications [3]. To manage T2DM, the armamentarium of oral hypoglycaemic agents (OHA) includes sulfonylureas (SUs) (glipizide, glyburide, gliclazide, glimepiride), meglitinides (repaglinide and nateglinide), biguanides (metformin), thiazolidinediones (rosiglitazone, pioglitazone),  $\alpha$ -glucosidase inhibitors (acarbose, miglitol, voglibose), dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin) and sodium glucose cotransporter-2 (SGLT2) inhibitors (dapagliflozin and canagliflozin) [4].

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**Citation:** Manjula S & Krishna Kumar M (2024). Physicians Perspectives on the Preference of Antihyperglycemics for the Management of Diabetes Mellitus in India. *South Asian Res J App Med Sci*, 6(1), 19-24. 19

The United Kingdom (UK) prospective diabetes study indicated that many patients will inevitably need combination therapy in order to reach their target glucose level because glycaemic management with a single oral hypoglycaemic medication may likely to be inadequate over a longer period of time [5]. In the real world clinical practice, choosing an appropriate OHA and its combination remains a big challenge. To ascertain the merits and demerits of the available OHAs and its combination is of paramount importance. Various clinical studies have proved the combination of metformin and newer sulfonylureas like glimepiride can effectively reverse insulin resistance and promote insulin secretion, as they were frequently recommended together for blood glucose control respectively. Primary care physicians and specialists in India employed the fixed-dose combination of glimepiride and metformin in several strengths [6]. In order to bridge the knowledge gap, there was a need to translate the clinical trial findings in day to day real world clinical practice. In this regard, expert opinions will offer valuable insights into the utilization of OHAs and its combinations including its efficacy, safety, and its utility in specific subgroup of diabetic patients.

The purpose of the current study was to understand how OHAs were preferred to treat uncontrolled T2DM and their benefits with a special focus on metformin and glimepiride combination among clinicians.

## **MATERIALS AND METHODS**

A cross sectional, questionnaire based survey was carried out among clinicians in treating diabetes mellitus in the major Indian cities from June 2022 to December 2022.

### **Questionnaire**

The questionnaire booklet named VICTORY (A Report on Views In Current Treatment Options & Recent trends in Diabetology) study was sent to the clinicians who were willing to participate in this study. The VICTORY study questionnaire included 26 questions on the prevalence of diabetes, common causes, clinical manifestations, available drug therapy combinations and its effectiveness in the management of uncontrolled diabetes. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

### **Participants**

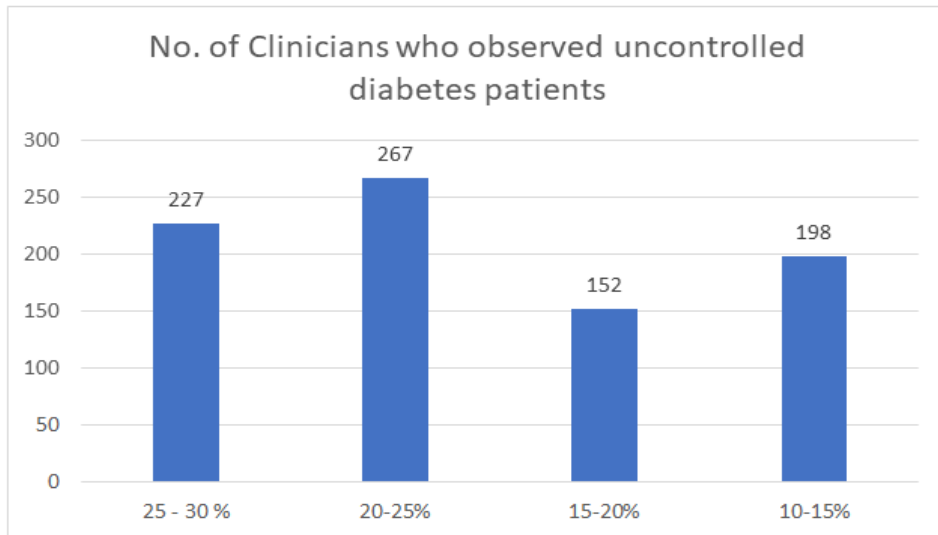
An invitation was sent to leading physicians in managing diabetes mellitus in the month of March 2022 for participation in this Indian survey. About 845 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Doctors were requested to complete the questionnaire without discussing with peers. A written informed consent was obtained from each clinician before initiation of the study.

### **Statistical Analysis**

The data were analyzed using descriptive statistics where the categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. Microsoft Excel was used to visualize the distribution of the categorical variables, pie, and bar charts.

## **RESULTS**

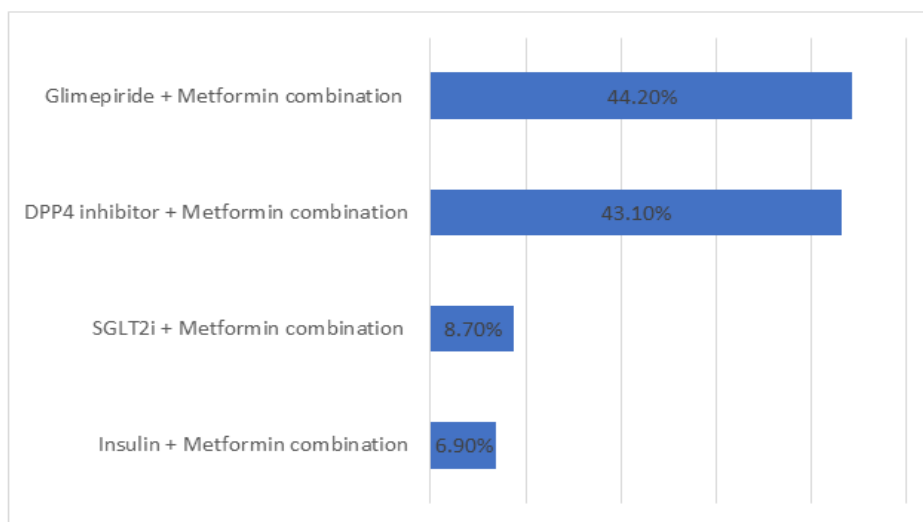
The clinicians observed the proportion of patients with uncontrolled diabetes in their practice was described in Figure 1. According to the participants, 39% of physicians seen 50-55% of newly diagnosed diabetic patients, approximately 26% of them treat 65-70% of new T2DM patients and only 25% of them seen 60-65% of new diagnosed T2DM individuals. Majority of doctors stressed the need for periodic screening and regular awareness. Further, nearly 44% of physicians reported that poor patient adherence to diet and medication was the primary reason for uncontrolled diabetes whereas 41% of them highlighted sedentary lifestyle and 28% of them reported irregular follow-up visits to the doctor. Also, most of the practitioners (86%) recommended self-screening of blood glucose level for people with long standing diabetes. In that, 44% of respondents reported diabetes individuals should perform 2 tests per day while 30% of them suggested 3 tests per day.



**Figure 1: Distribution of percentage of patients with uncontrolled diabetes**

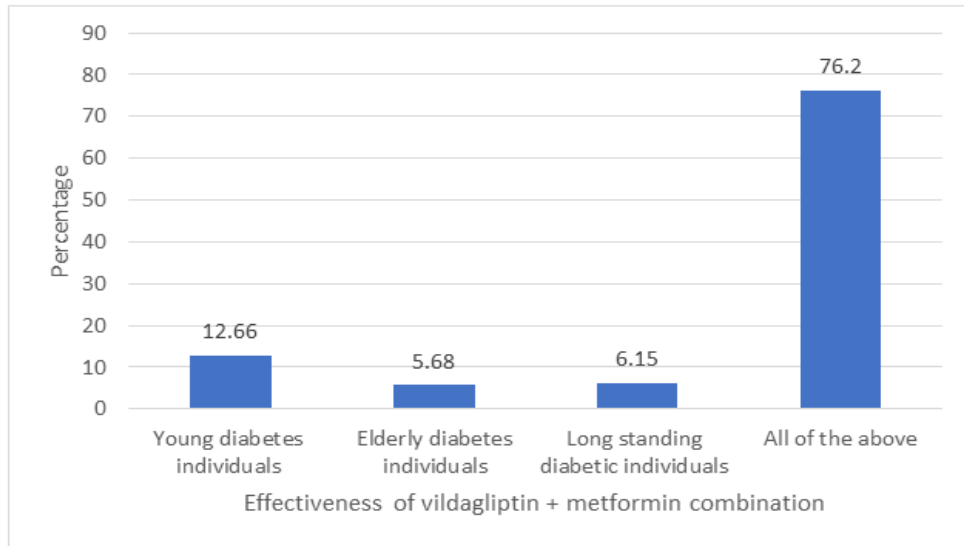
In a month, 39% of clinicians prescribed vildagliptin and metformin combination as a first line therapy in newly diagnosed individuals of more than 10 patients whereas 27% of them prescribed in 6-8 individuals and 23.5% of them in 8-10 patients. According to their clinical experience, nearly 48% of doctors noted 1 to 1.5% reduction in glycated haemoglobin (HbA1c) with vildagliptin and metformin combination, 28.5% of them observed 1.5 to 2% HbA1c reduction and only around 21% of them experienced 0.5 to 1% HbA1c reduction. Further, the glycaemic durability with vildagliptin and metformin combination was 3-5 years as mentioned by 43% of clinicians, more than 5 years by nearly 25% of doctors and 2 to 3 years by 23.5% of doctors.

Moreover, 69% of the clinicians preferred vildagliptin sustained release once daily formulation for all age groups, only 11% and 12% of them preferred for elderly and long standing diabetic individuals. About 44% of endocrinologists opted glimepiride + metformin combination as the first-line of therapy for newly diagnosed diabetics, 43% of them opined DPP4 inhibitors + metformin and only around 9% of them prescribed SGLT2 inhibitors + metformin (Figure 2). Among DPP4 inhibitors + metformin combinations, vildagliptin + metformin combination was prescribed by 83.5% of endocrinologists, followed by 10% of clinicians prescribed sitagliptin + metformin combination and nearly 6% of them opted teneligliptin + metformin combination.



**Figure 2: Distribution of preference of first-line of therapy for newly diagnosed diabetics**

As well, 76% of respondents reported vildagliptin + metformin combination was effective in all patient groups. Only nearly 13% of them highlighted that it was effective in young diabetic individuals and 6% in long standing diabetic individuals (Figure 3). In addition, 36% of participants noted 50-60 mg/dl post-prandial blood glucose (PPBG) reduction, 29% of them marked 40-50 mg/dl PPBG reduction and only 18% with 60-75 mg/dl reduction in PPBG.

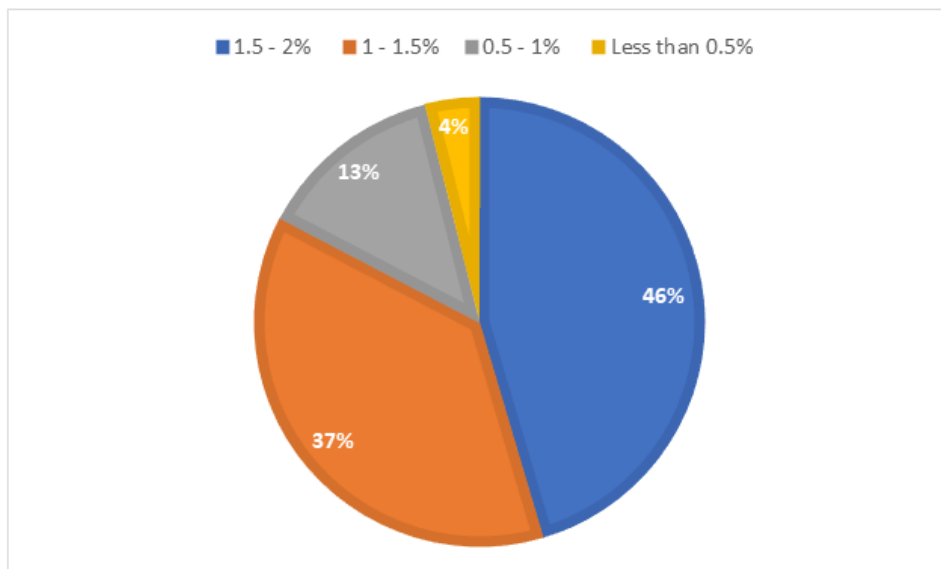


**Figure 3: Distribution of effectiveness of vildagliptin + metformin combination**

The advantages of vildagliptin + dapagliflozin combination as highlighted by participants include 9.5% for complementary action and better glycaemic control, 7.4% for end organ protection, 5% for preserving beta cell function and decreasing insulin resistance and almost 79% of them for all the effects. Among the participants, vildagliptin scored over other drugs of their own class in glycaemic variability as marked by 79% of doctors, sitagliptin by 18% of clinicians and 3% each with teneligliptin and linagliptin. About 37% of respondents recommended patient education sessions of once in 3 months to increase awareness of uncontrolled diabetes and its complications and 31% of clinicians stressed once monthly patient education and 23% of them necessitated bimonthly patient education. In that, one to one patient education was recommended by 47% of clinicians, 36% of them denoted patient group meeting and 14% of them pointed patient education along with their caregivers.

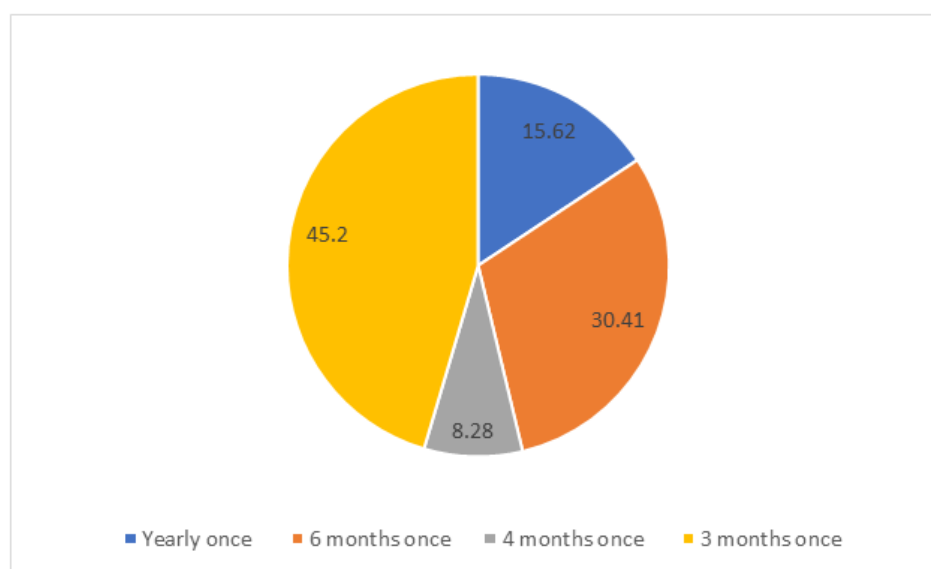
Further, the CAROLINA (The Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes) trial proved the cardiovascular safety outcome with glimepiride and metformin combination where 87% of the clinicians adhered that it has good glycaemic control and cardiovascular safety profile.

Nearly 46% of respondents observed 1.5 to 2% of maximum HbA1c reduction with glimepiride and metformin combination, 37% of them with 1 to 1.5% reduction and 13% with 0.5 to 1% reduction in HbA1c (Figure 4). Also, in their clinical practice, 3 to 4 years of HbA1c reduction with glimepiride and metformin combination by nearly 33% of participants, 4 to 5 years by 28% of clinicians and more than 5 years by 24% of them.



**Figure 4: Distribution of proportion of HbA1c reduction with glimepiride and metformin combination**

In the management of diabetes, 8% each of the participants reported the patient centric approach should be glycaemic control and end organ protection. Interestingly, 84% of them reported both glycaemic control and end organ protection approach in managing diabetes. Nearly 48% of the clinicians preferred glimepiride and metformin combination to achieve the targeted HbA1c goal, 40% of them opted DPP4 inhibitors + metformin and only 10% of them recommended insulin + metformin. Along with that, 45.2% of clinicians titrated the dose of glimepiride and metformin once in 3 months, 30.41% of them titrated once in 6 months and 15.62% of them increased the dose once in a year (Figure 5). About 45% of the doctors prescribed glimepiride and metformin combination in elderly T2DM patients and 35% prescribed very often and only 13% of them recommended occasionally. Almost 70% of the clinicians recommended DPP4 inhibitors as an add-on treatment with glimepiride and metformin combination and 16% of them mentioned SGLT2 inhibitors and 14% of them prescribed voglibose along with the combination.



**Figure 5: Distribution of frequency of titration of glimepiride and metformin combination dosage**

## DISCUSSION

Glimepiride and metformin combination was the most preferred choice to achieve HbA1c goal followed by DPP4i and metformin combination. Because of the combination therapy's effectiveness and affordability, doctors in India frequently prescribe glimepiride and metformin together, citing all of its advantages [7]. Moreover, as per 374 physicians, Glimepiride and Metformin is preferred as the first line therapy amongst newly diagnosed diabetes individuals with HbA1c >9%. In line with the findings of the study by Kalra S *et al.*, the current study results showed good glycaemic control across all age groups and a persistent legacy impact maintained for a longer duration of diabetes [8].

Studies indicated that glimepiride has neutral CV effects while traditional sulfonylureas are reported to have negative effects on the cardiovascular system. A three-point major adverse cardiovascular event (3P-MACE) and four-point MACE (4P-MACE) safety comparison of glimepiride and linagliptin was shown in the CAROLINA (Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Type 2 Diabetes) trial, which was conducted in patients with T2DM at an elevated cardiovascular risk [9]. According to a consensus statement of the South Asian Federation of Endocrine Societies (SAFES), contemporary sulfonylureas, like glimepiride, should be chosen over traditional sulfonylureas due to their improved cardiovascular results and decreased mortality (both all-cause and CV mortality) [10]. As per the survey conducted, 732 physicians noted good glycaemic control and CV safety profile with glimepiride and metformin which was in accordance with the CAROLINA Trail.

Vildagliptin decreased glycaemic variability in people with type 2 diabetes whose metformin monotherapy did not sufficiently control their condition, however pioglitazone did not [11]. The response was in accordance with this survey where 667 Physicians out of 845 believe vildagliptin scores over other gliptins in addressing glycaemic variability.

The combination of vildagliptin and dapagliflozin was a good choice for T2DM patients in India because it synergistically helps people reach their glycaemic goals more effectively and has a number of additional glycaemic benefits, such as lowering blood pressure, reducing body weight, and having cardio protective properties [12]. In this survey, out of 845 physicians, 670 physicians believe the complimentary action of vildagliptin and dapagliflozin and better glycaemic control with vildagliptin and dapagliflozin combination.

In Indian patients with T2DM, vildagliptin, either with or without metformin, was a well-tolerated treatment that effectively lowered HbA1c and assisted in reaching target glycaemic control [13]. In accordance with this, the physicians also prefer vildagliptin and metformin as the most preferred combination in the DPP4i and metformin combination category.

The results of the current survey may help physicians make decisions that will improve routine patient care and outcomes, particularly in light of the growing difficulties that diabetic patients' cardio-renal complications in place. The study emphasizes the value of tailored treatment plans and medication adherence in the management of diabetic patients who have complications with their kidneys and hearts. It was critical to recognize some of the study's limitations. The study's reliance on expert judgment raised the possibility of bias since various viewpoints and preferences might have affected the survey results. It was crucial to take these restrictions into account when analysing the data and to carry out additional research to corroborate the conclusions.

## CONCLUSION

Even after introduction of many molecules and its combination therapy, glimepiride and metformin was still preferred as the most preferred choice by the physicians who participated in the survey to achieve the HbA1c goal. Moreover, majority of the physicians experienced vildagliptin as the most preferred gliptin among other gliptins in addressing glycaemic variability. In addition, vildagliptin was the most preferred DPP4i in combination with metformin as reported by majority of the physicians participated in the survey.

**Acknowledgement:** We would like to thank all the doctors who were participated in this study.

## DECLARATIONS

**Funding:** No funding sources

**Conflict of Interest:** None declared

**Ethical approval:** This study was approved by the Independent Ethics Committee.

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