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Original Research Article

Expert opinion on the prescription practice of dual combination oral anti-diabetic drugs in type 2 diabetes mellitus management

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ABSTRACT

Background: This study aimed to gather the clinicians' perspective regarding the use and prescription practice of dual combination oral anti-diabetic drugs (OADs) in type 2 diabetes mellitus (T2DM) management in Indian settings.
Methods: A cross-sectional study was conducted by using a 29-item structured questionnaire covering factors considered, challenges, preferred indicators of glycemic control, continuous glucose monitoring (CGM) use, and strategies. Additionally, it explored clinicians' feedback and experiences with dual combination oral anti-diabetic drugs in T2DM management.
Results: Seventy percent of clinicians observed improved adherence to dual combination therapy of OAD. The combination of dipeptidyl-peptidase 4 (DPP4) inhibitors and metformin was favored for early initiation and showed better tolerability within the first year according to 42% of clinicians. Approximately 63% of clinicians prefer vildagliptin + metformin for 40–50 year-old diabetics. The combination yields favorable outcomes: 21% in young, 14% in elderly, and 7% in long-standing diabetes cases. After 5 years, 37% of clinicians observed 40-50% of diabetics reaching an HbA1c goal of <7.0% with this combination. Clinicians choose glimepiride + metformin for treatment intensification based on its efficacy, cardiovascular (CV) safety, and fewer adverse events. These factors were collectively recognized by 66.54% of respondents.
Conclusions: This study provided valuable insights into real-world clinical practices and preferences regarding dual combination therapy for diabetes management. Clinicians identified the fixed-dose combination of DPP4 inhibitors and metformin as the preferred choice and highlighted the effectiveness of glimepiride + metformin in overcoming treatment intensification challenges.

Keywords: Dipeptidyl-peptidase 4 inhibitors, Metformin, Oral anti-diabetic drugs, Sulphonylurea, Type 2 diabetes mellitus

INTRODUCTION

The 2023 Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, encompassing 113,043 individuals, reported a weighted diabetes prevalence of 11.4%, affecting 10,151 out of 107,119 individuals.[1] According to the World Health Organization estimates, approximately 77 million Indian adults aged 18 years and older have type 2 diabetes mellitus (T2DM), with nearly 25 million individuals classified as prediabetic.[2] The international diabetes federation (IDF) Diabetes Atlas 10th edition has underscored that the escalating prevalence of global diabetes poses a significant health challenge worldwide. Presently, 537 million adults aged 20-79 have diabetes, projected to increase to 643 million by 2030 and a staggering 783 million by 2045. Alarmingly, over three-quarters of adults with diabetes reside in low- and middle-income countries. Diabetes

claims 6.7 million lives in 2021 alone-equivalent to one life lost every 5 seconds.[3]

Reliance on monotherapy often leads to reduced effectiveness in blood glucose control over time, underscoring the necessity for combination therapy involving multiple antidiabetic medications or insulin.[4] For the past six decades, metformin has remained a cornerstone in the treatment of T2DM as the primary oral hypoglycemic medication.[5] In cases where patients exhibit intolerance to metformin or encounter adverse effects during metformin monotherapy, they often receive fixed-dose combinations (FDCs) comprising a variety of other oral antidiabetic agents (OADs). These combinations comprise various oral antidiabetic agents (OADs), targeting different mechanisms to achieve optimal glycemic control, such as enhancing pancreatic insulin secretion, reducing insulin resistance in body tissues, or increasing levels of glucagon-like peptide-1. Commonly preferred combinations include sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase (DPP-4) inhibitors, thiazolidinediones (TZDs), sulfonylureas (SUs), glucagon-like peptide-1 (GLP-1) receptor agonists, and basal insulin.[6]

The combination therapy involving DPP-4 inhibitors and metformin has shown remarkable tolerability with minimal risk of hypoglycemia. Therefore, pairing DPP-4 inhibitors with metformin emerges as an effective, safe, and well-tolerated treatment strategy for T2DM.[7] On the other hand, the combination therapy of sulfonylurea and metformin, which targets insulin secretion and insulin resistance, respectively, provides a comprehensive approach to address the primary pathophysiological mechanisms of type 2 diabetes. Notably, findings from the United Kingdom Prospective Diabetes Study (UKPDS) and other clinical studies have consistently demonstrated the superior efficacy of this combination therapy over monotherapy in managing T2DM.[8,9]

The necessity to improve and attain glycated hemoglobin (HbA1c) goals was closely linked to the demand for diverse therapeutic options, particularly in the context of personalized medicine. Presently, clinicians are encountering an expanding array of treatment choices, which can be employed individually or in combination to target specific needs. This survey-based study aimed to gather expert opinion regarding their prescription practices concerning the use of dual combination OADs in the management of T2DM.

METHODS

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians specialized in treating T2DM patients in the major Indian cities from June 2023 to December 2023. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

An invitation was sent to leading clinicians in managing T2DM in the month of March 2023 for participation in this Indian survey. About 523 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. The questionnaire booklet titled INITIATE (Initiation and Intensification- Strategy of Pharmacotherapy of T2DM Management) study was sent to the physicians who were interested to participate. The INITIATE study questionnaire consisting of 29 meticulously crafted questions delved into multifaceted aspects, encompassing factors pivotal during the initiation of pharmacotherapy, encountered challenges, preferred metrics for assessing glycemic control, utilization of continuous glucose monitoring (CGM), and strategies aimed at mitigating clinical inertia. Additionally, it sought to capture current feedback, clinical observations, and specialized experiences regarding the utilization and prescription patterns of dual combination oral anti-diabetic drugs.

Clinicians were provided the option to skip any questions they did not wish to answer and were instructed to complete the questionnaire independently, without consulting their colleagues. Prior to the initiation of the study, written informed consent was obtained from all study participants.

Statistical analysis

The data were analyzed using descriptive statistics. 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. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

RESULTS

According to 42% and 28% of the clinicians, glycemic status and associated complications, as well as family history of diabetes, were the factors usually considered when initiating pharmacotherapy in T2DM, respectively. Approximately 30% of the respondents identified medication cost as the major challenge encountered during the initiation of pharmacotherapy in T2DM, while 24% reported poor adherence to medication. Majority (70%) of the clinicians indicated that HbA1c was the better indicator of glycemic control after the initiation of pharmacotherapy. Additionally, 44% and 26% of clinicians reported that <10% and 11-25% proportion of patients preferred to use CGM as a tool for initiating pharmacotherapy, respectively. Nearly 65% of the clinicians emphasized the comprehensive benefits of CGM, including its ability to identify glycemic

excursions, understand intricate glycemic details, its user-friendly interface, and its assistance in dose titration. Majority of the respondents (70%) noted that clinical inertia in intensifying pharmacotherapy at the patient level can be attributed to poor communication regarding the disease, a lack of awareness about diabetic-related complications, and insufficient financial and family support.

According to 67% of the respondents, the major reasons for clinical inertia in intensifying pharmacotherapy were difficulty in navigating between guidelines and algorithms, lack of clear guidelines for individualized treatment, lack of family and financial support, and poor patient awareness. Majority of the respondents (75%) noted that to address patient-level inertia effectively, awareness programs should prioritize providing an overview of the disease and its complications, offering dietary and exercise counseling, emphasizing the usefulness of medications, and highlighting the importance of regular follow-up consultations with clinicians. According to 74% of clinicians, strategies to overcome clinical inertia at the healthcare professional level include frequent educational meetings, staying updated with articles published in peer-reviewed journals, and engaging in peer-to-peer influencing. The majority (67%) of clinicians reported physical meetings and interactions as the better medium for group consulting meetings for interactive sessions. Approximately 60% of clinicians stated hypoglycemic episodes as a major barrier to intensifying treatment in elderly patients with conventional OADs. Around 37% of the clinicians emphasized the importance of addressing emotional and religious issues when intensifying therapy.

According to 38% of clinicians, DPP4 inhibitors are the class of OADs that exhibit greater glycemic durability as monotherapy. Majority (42%) of the clinicians preferred combination therapy of OADs for initiating pharmacotherapy in young patients with T2DM. Nearly 44% of the clinicians noted that 41-60% of patients are on combination therapy in newly diagnosed T2DM individuals. Majority of the experts (63%) noted that clinicians commonly opt for combination therapy due to its facilitation in achieving glycemic goals, minimizing adverse events, and delaying disease progression.

A significant proportion (70%) of clinicians observed better adherence to dual combination therapy of OADs after initiation (Table 1). The majority of clinicians (67%) cited glycemic efficacy, extensive clinical experience, and well-known adverse events as reasons to opt for traditional (time-tested) OADs like sulphonylureas and their combinations when initiating pharmacotherapy in individuals with T2DM.

According to 42% of clinicians, the combination of DPP4 inhibitors and metformin was the most preferred fixed-dose combination therapy for early initiation, with 48% noting its better tolerability at the end of the first year of initiating dual combination therapy (Table 2).

Table 1: Distribution of response to therapy which showed better medication adherence after initiating combination therapy.

Type of therapy	Response rate (n=523)
Monotherapy of OAD	70 (13.38)
Dual combination therapy of OAD	364 (69.6)
Triple combination therapy of OAD	69 (13.19)
Insulin	20 (3.82)

Table 2: Distribution of response to the (a): most preferred fixed-dose combination therapy for early initiation in T2DM, (b): Dual combination therapy with better tolerability at the end of 1st year of initiation.

Combination therapy	Response rate (n=523) (%)	
	a	**b**
Sulphonylureas+ metformin	189 (36.14)	158 (30.21)
SGLT2i+metformin	48 (9.18)	44 (8.41)
DPP4i+metformin	222 (42.45)	254 (48.57)
Pioglitazone+metformin	7 (1.34)	6 (1.15)
SGLT2i+DPP4i	57 (10.9)	61 (11.66)

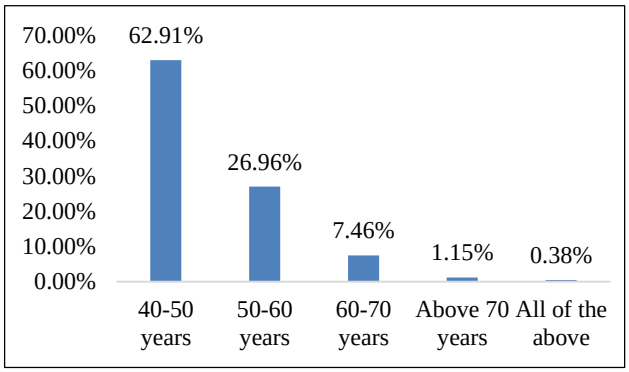

Figure 1a: Distribution of response to preferred age groups for vildagliptin + metformin combination therapy.

Nearly 63% of clinicians preferred using vildagliptin + metformin combination therapy in the 40-50 years' age group of diabetic individuals (Figure 1a). Furthermore, 57% of clinicians concurred on its effectiveness across all three demographics: young, elderly, and long-standing diabetic individuals (Figure 1b). According to 37% of clinicians, 40-50% of diabetic individuals achieve the target HbA1c goal of <7.0% after initiating a fixed-dose combination of vildagliptin + metformin after 5 years (Figure 1c).

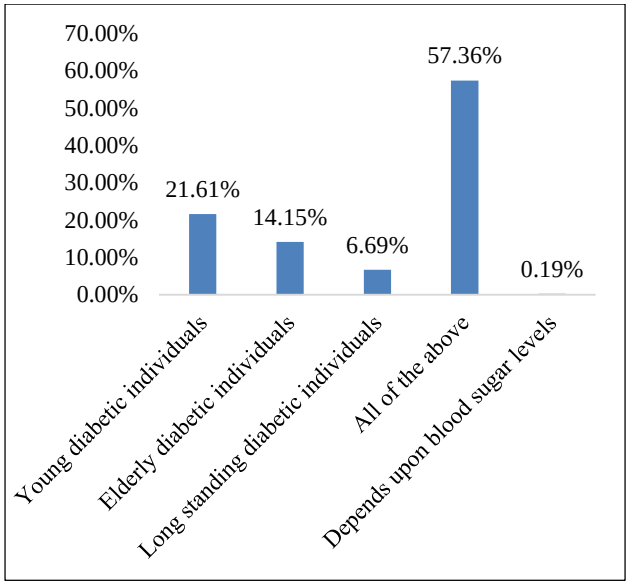

Figure 1b: Distribution of response to patient groups where glycemic efficacy of fixed dose combination of vildagliptin + metformin was better experienced as an initiation strategy.

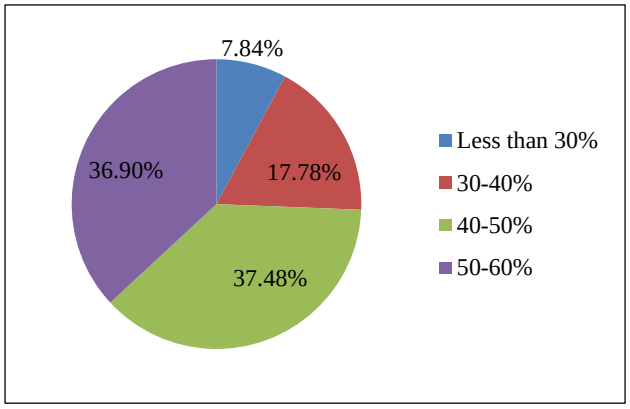

Figure 1c: Distribution of response to the proportion of diabetic individuals who achieve target HbA1c goal of <7.0% after initiating a fixed dose combination of vildagliptin + metformin after 5 years.

Table 3: Distribution of response to advantages of bedtime insulin daytime sulphonylurea as an initiation strategy.

Advantages	Response rate (%)
Helps to achieve target glycemic goals faster	91 (17.4)
Delays long-term complications	34 (6.5)
Preserves beta cell function	48 (9.18)
All of the above	349 (66.73)
Never used this formula	1 (0.19)

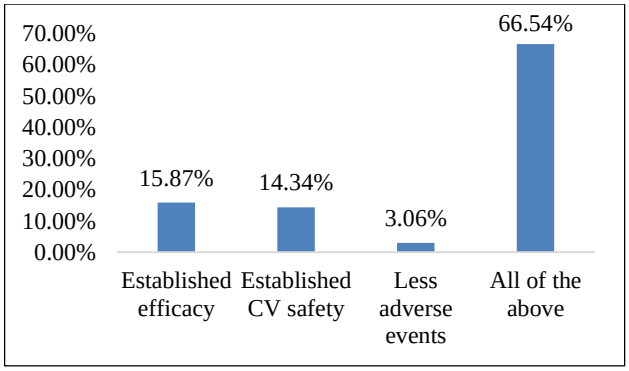

Figure 2: Distribution of response to reasons for choosing glimepiride + metformin combination for treatment intensification.

Table 4: Distribution of response to (a) most preferred combination in overcoming treatment intensification, (b) most preferred combination along with insulin.

Combination therapy	Response rate (%)	
	a	b
Glimepiride + metformin	251 (47.99)	245 (46.85)
DPP4i + metformin	152 (29.06)	205 (39.2)
SGLT2i + metformin	33 (6.31)	59 (11.28)
SGLT2i + DPP4i	86 (16.44)	12 (2.29)
All of the above	1 (0.19)	1 (0.19)

Majority of the respondents (66%) identified the advantages of bedtime insulin daytime sulphonylurea (BIDS) initiation therapy as achieving target glycemic goals faster, preserving beta cell function, and delaying long-term complications (Table 3). When selecting the glimepiride + metformin combination for treatment intensification, the majority (67%) of respondents cited established efficacy, established CV safety, and fewer adverse events as reasons for choosing this combination therapy (Figure 2).

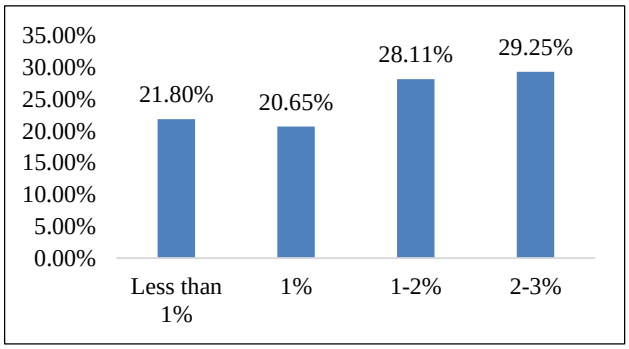

Figure 3: Distribution of response to incidence of hypoglycemia observed with glimepiride + metformin fixed-dose combination.

Around 48% of the clinicians reported glimepiride + metformin as the most preferred combination therapy for

overcoming treatment intensification, and 47% noted it as the preferred therapy in combination with insulin (Table 4). Nearly 29% of clinicians observed a 2 to 3% incidence of hypoglycemia with glimepiride + metformin FDC (Figure 3). Majority of the clinicians (47%) recommended the combination of glimepiride + metformin in elderly individuals (Figure 4).

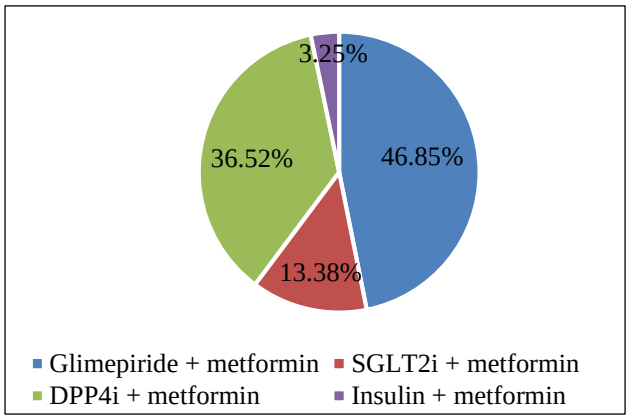

Figure 4: Distribution of response to most preferred combination among elderly individuals.

DISCUSSION

The current study contributes to the expanding body of evidence advocating the use of dual combination therapy for managing T2DM. Specifically, a notable proportion of clinicians in this study reported an increase in adherence to dual combination therapy of OAD following its initiation.

Majority of the current survey respondents favored the FDC of DPP4 inhibitors and metformin as the preferred choice for combination therapy, citing its preference for early initiation and improved tolerability by the end of the first year of treatment. Moreover, the majority of clinicians opted for vildagliptin + metformin combination therapy for individuals aged 40 to 50 with diabetes. Additionally, clinicians widely observed favorable outcomes across various demographics, including young and elderly diabetic individuals, as well as those with longstanding diabetes, with approximately 40-50% of diabetic individuals achieving the target HbA1c goal of <7.0% after five years of initiating this regimen.

In line with these findings, Ahrén et al concluded that the concurrent administration of DPP-4 inhibition and metformin demonstrates remarkable tolerability and presents a notably low risk of hypoglycemia. The synergistic effect of DPP-4 inhibition in conjunction with metformin emerges as a proficient, secure, and well-tolerated therapeutic approach for addressing T2DM.[7] A meta-analysis conducted by Cheng et al. highlighted that the combined utilization of DPP-4 inhibitors and metformin surpasses the efficacy of metformin alone in regulating blood glucose levels and enhancing pancreatic islet β-cell function throughout the treatment of T2DM.[10]

Das et al reported that the combination therapy of vildagliptin and metformin proved to be an efficacious approach in reducing HbA1c levels, facilitating the attainment of target glycemic control, and demonstrating favorable tolerability among Indian patients with long-standing T2DM.[11] In a multicenter, double-blind trial spanning 5 years, conducted by Matthews et al, it was observed that early intervention with a combination therapy of vildagliptin plus metformin offers superior and sustained long-term advantages when compared to the current standard-of-care approach of initiating metformin monotherapy for patients with newly diagnosed T2DM.[12] A meta-analysis conducted by Ding et al, which encompassed 11 randomized controlled trials (RCTs) and involved 8533 patients, demonstrated that vildagliptin in combination with metformin led to significant reductions in fasting plasma glucose (FPG), HbA1c levels, and body weight compared to metformin alone.[13] Numerous additional studies have highlighted the early initiation of a combination therapy involving metformin and vildagliptin as superior to metformin monotherapy in achieving enhanced glycemic control. Furthermore, this combination has been associated with notable and clinically significant reductions in HbA1c levels, while also being well tolerated without inducing hypoglycemic events.[14-18]

In the current survey, majority of the clinicians recognized the benefits of initiating BIDS therapy, including its ability to achieve target glycemic goals more rapidly, preserve beta-cell function, and postpone the onset of long-term complications. Miller et al reported that the addition of BIDS enhances glycemic control in individuals with uncontrolled type 2 diabetes.[19]

In the present survey, majority of the respondents reported considering various factors, including demonstrated efficacy, established CV safety profile, and reduced incidence of adverse events when contemplating the use of the glimepiride + metformin combination for treatment intensification. Clinicians favored this combination therapy for overcoming treatment intensification challenges, making it the preferred option, especially when used alongside insulin and in elderly individuals. Additionally, clinicians noted a modest incidence of hypoglycemia, ranging from 2 to 3%, associated with the glimepiride + metformin fixed-dose combination.

A real-world study conducted in the Indian clinical setting, involving 4858 patients with T2DM, revealed widespread utilization of glimepiride and metformin FDC for managing patients with comorbidities such as hypertension, dyslipidemia, and diabetes complications. These FDCs were considered suitable for both early and long-standing diabetes management.[20] Additionally, the FDC therapy of glimepiride and metformin proved to be more effective in glycemic control compared to metformin up titration, and it was well tolerated among

patients with T2DM who had inadequate control with low-dose metformin monotherapy.[21]

A retrospective, multicenter study conducted in India, involving 7058 patients, demonstrated significant reduction in HbA1c levels with the combination therapy of glimepiride and metformin alongside insulin, ensuring favorable clinical outcomes. The treatment exhibited good to excellent efficacy and tolerability across various age groups of patients with T2DM, irrespective of the duration of the disease, whether it was early or long-standing.[22] Kumar et al documented a noteworthy reduction in HbA1c levels, as well as FPG, and postprandial glucose (PPG) levels, following treatment with glimepiride-metformin therapy in individuals newly diagnosed with T2DM.[23] The combination therapy of metformin and glimepiride, along with glargine insulin, exhibited a notable enhancement in overall glycemic control compared to regimens involving insulin glargine plus either metformin or glimepiride alone.[24] Jain et al showed that a low dose of 0.5 mg of glimepiride in combination with metformin FDC effectively achieves glycemic control by reducing levels of HbA1c, with satisfactory safety outcomes.[25]

The present survey offers valuable insights into prescription practices tailored specifically to the Indian context, offering guidance to clinicians and researchers for informed decision-making regarding the use of dual combination OADs. This research aims to refine patient care strategies and contribute to the development of evidence-based guidelines to optimize treatment outcomes. The study highlighted the significance of utilizing dual combination OADs in managing patients with T2DM. One notable strength of this study lies in the meticulous design and validation of the questionnaire used for gathering expert data. However, it was important to recognize that individual perspectives and preferences may have influenced the study's conclusions, potentially introducing bias. Therefore, it was essential to interpret the results while taking these limitations into account. Further research endeavors should focus on corroborating and expanding upon the findings presented in this study.

CONCLUSION

This study highlighted the favorable outcomes and benefits associated with the use of various combination therapies for diabetes management. Clinicians emphasized the significance of early initiation and personalized treatment plans to achieve target glycemic goals and reduce long-term complications. Notably, the fixed-dose combination of DPP4 inhibitors and metformin emerged as the preferred choice for combination therapy, whereas vildagliptin + metformin was favored for individuals aged 40 to 50 with diabetes. Additionally, the efficacy of glimepiride + metformin combination therapy in overcoming treatment intensification challenges was underscored, particularly in elderly individuals and when used alongside insulin.

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