Original Research Article

Expert opinion on the use of vildagliptin in Indian patients with diabetes mellitus

ABSTRACT

Background: Diabetes mellitus is a prevalent disease, and its burden has increased over the years which is going to cross 134 million cases by 2045, despite the available treatments. This study was carried out to understand the prescribing behaviours in the management of diabetes. **Methodology:** A questionnaire was administered to clinicians focused on diabetes prevalence, symptoms, causes, clinical characteristics, and the utilization of different antidiabetic medications. **Statistical analysis:** The data collected was analysed using descriptive statistics. **Results:** Around 353 clinicians responded with majority from Delhi (8.8%). Most commonly preferred first line drug is metformin (46.5%). Vildagliptin (89%) is the most preferred drug out of the DPP-4 inhibitors that is added to metformin to achieve glycaemic control. Dapagliflozin (87%) is the most preferred SGLT-2 inhibitor. It was seen that 59.2% opted for DPP-4 inhibitor and SGLT-2 inhibitor FDC in 25 to 50% of their diabetic patients. If affordability was not an issue most clinicians (44.2%) preferred vildagliptin, dapagliflozin, and metformin FDC. Insulin usage declined with 38.8% reporting that they used insulin in only 11 to 15% of their diabetic patient pool and 71.4 % reported hypertension as the most common comorbidity with diabetes. **Conclusion:** This study gives a comprehensive view of the perspectives of the medical community with respect to evidence-based change in management trends which will help make strategies to improve patient outcomes. It also sheds light on factors clinicians consider to choose treatment options. One criterion that is as important as efficacy and safety is affordability.

Keywords: Glycaemic control, clinician's perspective, affordability, vildagliptin, dapagliflozin, metformin

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder. It is primarily defined by hyperglycaemia. There are 2 main categories type 1 DM (T1DM) seen in children or adolescents due to lack of insulin production, and type 2 DM (T2DM) which is seen in middle-aged adults due to insulin resistance [1].

DM is a prevalent non-communicable disease. WHO has estimated that around 422 million people have DM worldwide [2]. While in India 77 million individuals had diabetes in 2019, which is expected to cross 134 million by 2045. Since 1990, DM has risen in India, and the prevalence has increased from 7.1% in 2009 to 8.9% in 2019 placing India second after China. Around 57% are undiagnosed, healthcare expenditure per person is 92 US dollars, and the total deaths caused by DM is around 1 million. So, the burden is rising [3].

T1DM is treated with insulin while T2DM is treated with hypoglycaemic agents like metformin, sulfonylureas, meglitinides, glucagon-like peptide 1 receptor agonist (GLP-1RA),

Comment [MWS1]: Consider revising the title to explicitly mention "vildagliptin as an antidiabetic drug" to provide clarity and improve the relevance of the study.

Comment [MWS2]: When exactly did the research begin?Expert opinions may vary depending on the year of the guidelines

Comment [MWS3]: Consider having the manuscript reviewed by a native speaker or a language expert to ensure grammatical accuracy and adherence to accepted language conventions. This will help enhance the overall quality and readability of the manuscript.

Comment [MWS4]: When exactly did the research begin?

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thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium glucose cotransporter -2 inhibitor (SGLT-2i) along with lifestyle modification [4]. Despite the myriad of drugs at hand, the prevalence is rising. There could be many reasons for this like patient compliance, poor lifestyle choices, comorbid conditions, availability, affordability, safety, and efficacy data which affect medication choices [5,6]. Thus, in this study, we have tried to understand the drug preferences and prescribing behaviours of Indian clinicians by making them answer a questionnaire regarding T2DM.

2. MATERIALS AND METHODS

We carried out a cross sectional, multiple-response questionnaire-based study involving clinicians with expertise in managing diabetes mellitus in the major Indian cities from June 2022 to December 2022.

2.1 Questionnaire

The questionnaire booklet named VERDICT (Vildagliptin and its combination Efficacy foR managing DIabetes mellitus and associated Cardio-renal complicaTions) study was sent to the clinicians who were interested to participate. The VERDICT study questionnaire focused on diabetes prevalence, symptoms, causes, clinical characteristics, and the utilization of different antidiabetic medications. The study was carried out after getting approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

2.2 Participants

An invitation was sent to leading practitioners in treating diabetes mellitus in the month of March 2022 for participation in this Indian survey. About 353 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. Participants were asked to complete the questionnaire without discussing with their peers. A written informed consent was obtained from each consultants before initiation of the study.

2.3 Statistical Methods

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).

3. RESULTS

The survey was completed by 353 clinicians across India. Geographically, the clinicians were uniformly widespread with most of them hailing from Delhi (8.8%) with a major proportion of clinicians (87%) having 41-60 years of clinical experience with 67.7% of them having both MBBS and MD degrees. Majority of them (44%) preferred following the American Diabetes Association (ADA) guidelines for DM management.

In this study clinicians we asked to which income group most of their diabetic patients belonged to and what their HbA1c was at the time of diagnosis of the disease. It was seen that majority of the clinicians responded (84.7%) that a major chunk of their patients belonged to the middle-income group and majority responded (56.9%) that most of their patients had an HbA1c range between 7.5 to 8.5% during the time of diagnosis (Figure 1).

Comment [MWS6]: Please ensure clarity and consistency in the use of drug types or classes. For example, if referring to drug classes, replace 'Metformin' with 'Biguanide,' followed by DPP-4 Inhibitor, Sulfonylurea, and SGLT-2 Inhibitor. Please check all of this manuscript again.

Comment [MWS7]: Have there been prior studies employing similar methods of research that already conducted this?

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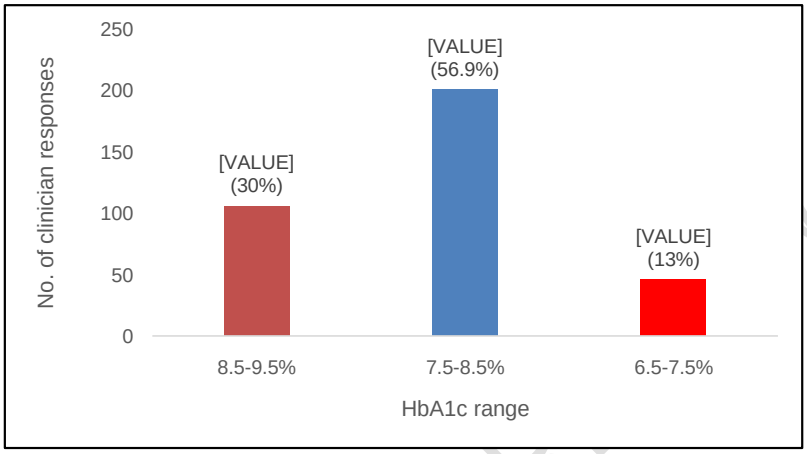
Fig. 1. Clinician response of most common HbA1c range amongst their diabetic patients at the time of diagnosis of disease



Majority of the clinicians (46.5%) prescribed metformin as the first line of treatment followed by DPP-4 inhibitors (DPP4i's) (20.2%), sulphonylureas (7.6%), and the least number of clinicians opted for SGLT-2 inhibitors (5.7%) (Figure 2). When asked what proportion of their patient required the addition of a second drug to achieve glycaemic control majority (43.9%) reported that 26 to 40% of their patient required it. The patients in whom metformin wasn't enough to achieve glycaemic control, the drug most of the clinicians added to metformin was DPP-4 inhibitor (69.1%) followed by SGLT-2 inhibitors (18.7%) and sulphonylureas (11.9%) (Figure 3).

Fig. 2. Clinician response to most commonly used first line drug for diabetes management

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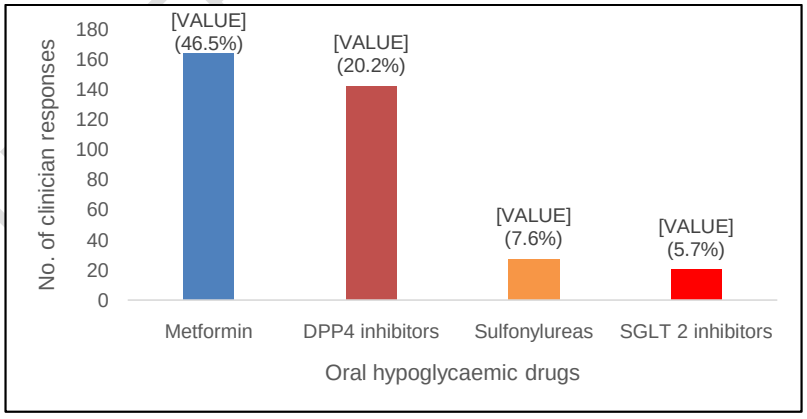
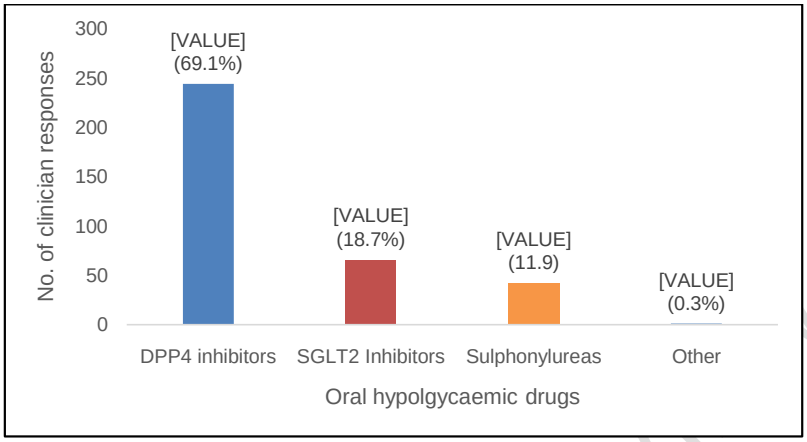


Fig. 3. Clinician response to which the most common drug they add to metformin to achieve glycaemic control



Most clinicians responded that they started DPP-4 inhibitors after 1 drug failure (48.7%) followed by being used as first line therapy (41.1%) and after 2 drug failures (10.2%) (Figure 4). Also, the preferred DPP-4 inhibitor was vildagliptin (89%) followed by sitagliptin (7.4%) and teneligliptin (3.4%) (Figure 5). When enquired why they chose vildagliptin most clinicians (74.2%) gave the reason as all of the above, which meant it preserved the beta cell function, caused less glycaemic variation, had weight neutral properties, posed a lower risk of adverse effects, and was affordable. Majority of the clinicians (50.1%) also noticed that vildagliptin caused a HbA1c drop of 1 to 1.5% (Figure 6). When enquired why they chose sitagliptin clinicians claimed its efficacy (33.1%) followed by glycaemic durability (28%), many did not have a clear reason for preference (21.8%), some chose it for its cardiovascular benefit (11%) and lastly few chose (5.9%) it for its renal benefits. Further, when asked which SGLT-2 inhibitor was preferred, majority of the clinicians chose dapagliflozin (87%), followed by canagliflozin (9.3%) and empagliflozin (3.1%) (Figure 7).

Comment [MWS14]: What about other considerations, such as the drug's availability or affordability? Is Vildagliptin prescribed regardless of any economic status due to its efficacy? Please clarify.

Fig. 4. Clinicians response to which stage of diabetes management DPP-4 inhibitors were introduced

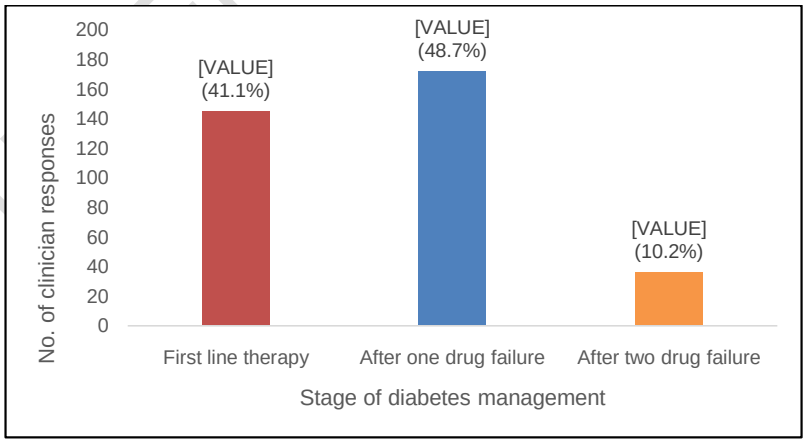


Fig. 5. Clinician response to which DDP-4 inhibitor was most preferred

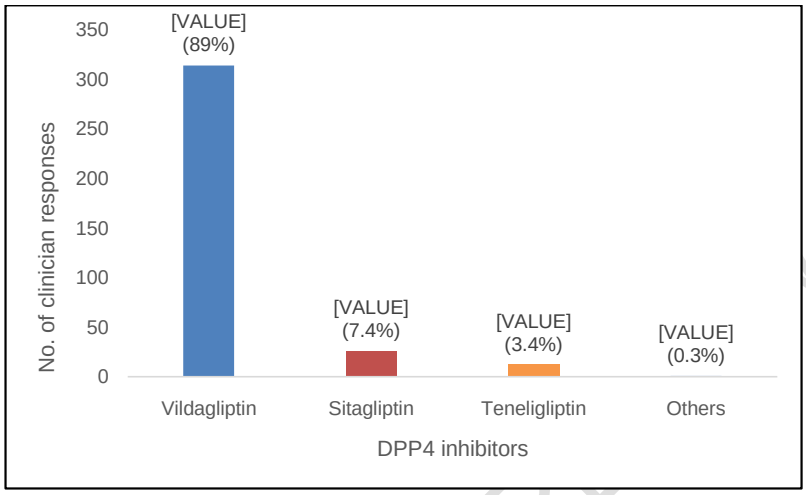


Fig. 6. Clinician response to the fall in HbA1c noticed with vildagliptin

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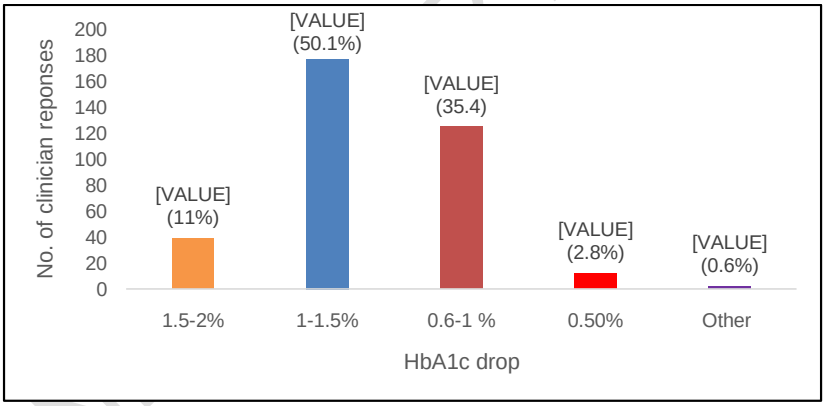
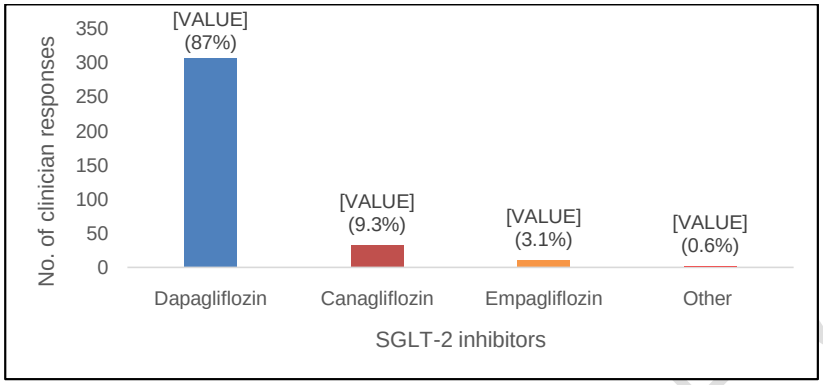


Fig. 7. Clinician response to which SGLT-2 inhibitor is preferred



Amongst the surveyed clinician's, majority (59.2%) opt for SGLT-2 inhibitor and DPP-4 inhibitor in 25 to 50% of their patients. When asked why they chose this combination, majority (80.2%) said it was due to all of the above reasons which included better glycaemic control, patient compliance, and pleiotropic benefits. More specifically 98% of the clinicians were inclined to prescribe the vildagliptin and dapagliflozin fixed-dose combination which has been approved by the DCGI. If affordability was not an issue most clinicians (44.2%) said they would prefer to prescribe dapagliflozin + vildagliptin + metformin combination (Figure 8). When asked in what proportion of their patients do they use insulin, majority (38.8%) reported the usage in 11 to 15% of their patients. There are more responses for usage in less than 20% of their patient pool category indicating a fall in insulin usage. Also, when enquired about which comorbid condition was usually seen along with DM in their patients, most clinicians mentioned hypertension (71.4%), followed by dyslipidaemia (22.1%), ischaemic heart disease (3.7%), and hypothyroidism (2%) (Figure 9).

Fig. 8. Clinician response to which combination they would prefer if affordability wasn't an issue

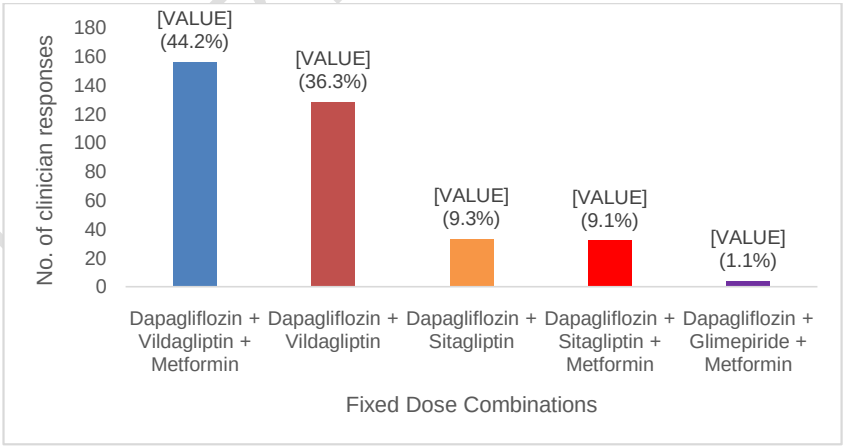
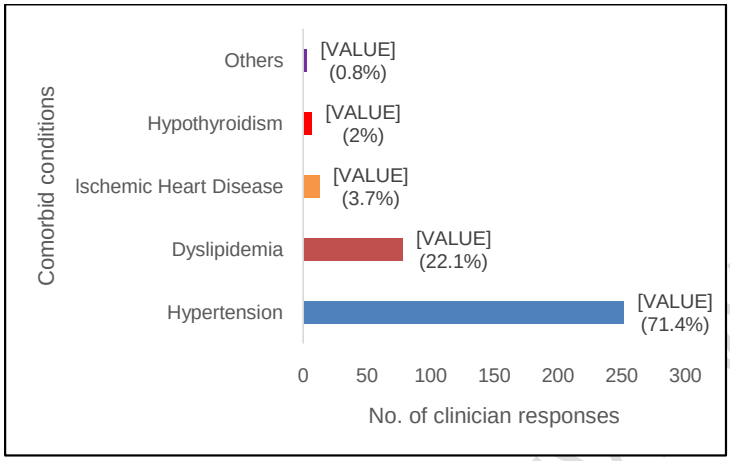


Fig. 9. Clinician's response to which comorbidity was most commonly associated with DM



4. DISCUSSION

A total of 353 clinicians responded to the survey. Most responses came from Delhi (8.8%), but overall, there was a uniform response across major cities in India. Therefore, the results of this study gives an insightful portrait of the landscape with a generalised picture of the prescribing behaviours of Indian clinicians in the management of diabetes. Most of the clinicians who responded had 41 to 60 years of clinical experience (87%), completed both MBBS and MD degrees (67.7%), and preferred to follow ADA guidelines(44%). What this signifies is that those who are vested with the responsibility to cater to public health needs are well trained, qualified, and follow scientifically centered and medically sound approaches to deal with diabetes among their patients. The American Diabetes Association guidelines are an evidence-based recommendation for the detection, prevention, and treatment of prediabetes, T1DM, T2DM, gestational diabetes, associated comorbidities, and mitigation of complications [7]. These recommendations are based on the latest scientific research and clinical trials. The remaining clinicians followed EASD, IDF, and AACE guidelines. So, following the guidelines implies that clinicians are in line with the latest trends in the management of diabetes.

It was seen that 84.7% of the clinicians reported that their diabetic population was from the middle income group. In accordance with this study, the study done by A Misra et al., also states that the prevalence of diabetes is increasing all over the world with 75% of the burden in low to middle income groups [8].This also brings to light that in India, clinicians have to factor in patient's financial affordability while prescribing medications to manage diabetes. When asked which fixed dose combination (FDC) the clinicians preferred if affordability was not an issue 44.2% chose a fixed dose combination of vildagliptin, dapagliflozin, and metformin. Unfortunately, in India, the out of pocket expenditure is the highest in the world which is around 62.6% of the total health expenditure, due to inadequate health insurance coverage [9]. So, affordability becomes a significant criterion based on which treatment is guided.

An HbA1c >6.5% is considered a diagnosis of diabetes and an HbA1c level >9% is dangerous with a rise chance of developing long term complications like nerve damage, kidney damage, and blindness [10,11]. In this study, 56.9% of the clinicians responded that their patient's HbA1c at the time of diagnosis of diabetes was between 7.5 to 8.5%. This indicates that most patients are getting diagnosed late and are at risk of developing these

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Comment [MWS18]: The discussion about HbA1c should be introduced in the introduction section to help readers better understand the results.

long term complications. Which implies having to use more drugs to manage the situation. Close to 50% of the clinicians preferred metformin as the first line treatment for diabetes. Similar findings were obtained in a survey done by A Agarwal et al., wherein the prescribing pattern and efficacy of anti-diabetic drugs in 100 diabetes patients attending medicine outpatient departments were assessed which found that the most commonly prescribed drug was metformin as monotherapy [12].

To achieve glycaemic control, most clinicians (69.1%) preferred adding DPP-4 inhibitors to metformin, that is most clinicians (48.7%) preferred to add the DPP-4 inhibitor after failure of first line therapy, and of all DPP-4 inhibitors 89% of the clinicians preferred vildagliptin followed by sitagliptin (7.4%). Around 74.2 % of clinicians preferred vildagliptin for reasons like better glycaemic control, better β-cell preservation, and more tolerable and affordable. Also, 50.1% of the clinicians noticed that vildagliptin reduced HbA1c levels by 1 to 1.5%. Studies claim that the most commonly added drug to metformin is sulphonylureas in T2DM, due to its cheap cost and known data but unfortunately, it has a higher risk of severe hypoglycaemia, and also many secondary failures have occurred [13].Various studies have shown metformin plus vildagliptin is better than metformin and sulphonylureas in terms of a better quality of life, and fewer incidences of hypoglycaemia, also some studies have shown adding vildagliptin to metformin improves beta cell function, shows better glycaemic control, and does not increase weight as well [14,15,16]. In accordance with the results of the above studies we see that there is alignment of responses of the clinicians in this study. This implies they are aware of newer treatment modalities, and trends, and are up to date with recent evidence.

Of the SGLT-2 inhibitors that remove glucose from the body by allowing it to be lost in the urine, 87% preferred dapagliflozin followed by canagliflozin (9.3%), and empagliflozin (3.1%). Studies have shown dapagliflozin has reduced fall in GFR, end stage kidney disease (ESKD), and renal or all-cause mortality in patients with diabetes [17,18]. In this study, the preference for dapagliflozin by the clinician's sheds light on their updated medical knowledge. Majority of the clinicians opted for SGLT-2 inhibitor plus DPP-4 inhibitor FDC in 25 to 50% of their diabetic patient pool. Nearly 80% said they chose this FDC because of better glycaemic control, patient compliance, and pleiotropic benefits, 98% of them specifically were inclined to use dapagliflozin and vildagliptin FDC which is also DCGI approved. A systematic review done by SH Min et al., the combination therapy of SGLT-2 inhibitor and DPP-4 inhibitor reduces weight, shows better glycaemic control, has a lesser incidence of hypoglycaemia, and reduces urinary tract infection in uncontrolled T2DM patients [19]. This is in accordance with the responses of the clinicians in our study again giving an insight into the prescribing trend and the current evidence based knowledge of the practitioner.

Of the clinicians who responded 38.8% of them said insulin was needed in 11 to 15% of their diabetic patient pool. More than 50% of the clinicians claimed that insulin is needed in less than 20% of the diabetic patient pool. This shows that insulin usage has fallen. In type 2 diabetes mellitus, insulin is initiated when HbA1c is more than equal to 7% after 2 to 3 months of dual oral antidiabetic therapy [20]. Thus, in this study, the reduced insulin usage reflects that the newer treatments such as DPP-4 inhibitors, SGLT-2 inhibitors, FDCs, were being used and they were effective and helping achieve glycaemic control.

In this study, 71.4% of the clinicians said that hypertension was the most common comorbidity associated with their diabetic patients. Pathologically, inflammation, oxidative stress, activation of immunity, and kidney damage that stimulates the renin-angiotensin-aldosterone system which leads to increased saltwater retention contribute to the close link between hypertension and diabetes [21]. Also, the San Antonio heart study showed that 85% of those with T2DM developed hypertension while 50% of individuals with hypertension experienced impaired glucose tolerance or T2DM [22].

5. CONCLUSION

This study gives a comprehensive view of the perspectives of the medical community when it comes to the management of diabetes mellitus. It shed light on how up to date the clinicians were with respective new emerging evidence based changing trends in the management. It showed what was actually being implemented in the clinic by practitioners. The pharmaceutical realm is continually innovating, and this study shed light on how clinicians' knowledge of the innovations was to par. It also brought into the picture that there are many factors clinicians consider before choosing a treatment plan. One criterion was identified which is as important as the safety and efficacy of the drug which was its affordability by the patients.

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Comment [MWS19]: Pay attention to the publication year of cited journals, with a maximum gap of 5 years from the current year, and for books, a maximum of 10 years from the current year. Revision needed.

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