Study Report

Therapeutic Usage of Vildagliptin + Dapagliflozin + Metformin Combination in Indian Patients with Diabetes Mellitus in Current Clinical Scenario

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that is increasingly becoming a major global health challenge, affecting millions of individuals worldwide. India is currently the diabetes capital of the world, with an estimated 77 million people living with the condition [1]. Uncontrolled diabetes is associated with numerous long-term complications, including cardiovascular disease, retinopathy, neuropathy, and nephropathy. These conditions can significantly diminish quality of life and cause early death. Consequently, managing diabetes effectively is essential to prevent these complications and improve overall health outcomes [1].

Effective management of diabetes mellitus requires a comprehensive approach that includes lifestyle modifications, pharmacotherapy, and sometimes insulin therapy. This strategy aims to achieve and maintain glycemic control while reducing the risk of associated complications [2]. Considering the various pathophysiological factors contributing to hyperglycemia, it is important to use a combination of antihyperglycemic drugs with different mechanisms of action. This approach is vital for effectively controlling blood sugar levels and preventing the chronic complications associated with diabetes [3].

The American Diabetes Association recommends metformin as a first-line medication for lowering glucose levels [4]. It is commonly prescribed in conjunction with other antidiabetic medications, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors, to manage blood glucose and lipid levels [5]. Metformin primarily decreases hepatic glucose production and improves insulin sensitivity [6]. Dapagliflozin, a SGLT2 inhibitor, reduces renal glucose reabsorption, leading to increased urinary glucose excretion and lower blood glucose levels [7]. Vildagliptin, among the DPP-4 inhibitors, has undergone extensive clinical research due to its clinical effectiveness. Its efficacy profile, minimal risk of hypoglycemia, avoidance of weight gain, and lack of increased cardiovascular event risk have established vildagliptin as a valuable anti-diabetes medication [8]. The combination of the triple therapy offers a multi-faceted approach to glycemic control, targeting different pathways in glucose metabolism [9].

Therefore, this study aimed to evaluate the therapeutic usage of the vildagliptin, dapagliflozin, and metformin combination among Indian physicians managing patients with T2DM. By employing a cross-sectional, questionnaire-based approach, the study seeks to explore prescribing patterns, perceived efficacy, safety considerations, and the challenges associated with this regimen in real-life clinical settings. The findings are expected to provide valuable insights into the practical application of this combination therapy, thereby informing clinical decisions and optimizing treatment strategies for better health outcomes in Indian patients with T2DM.

2 RATIONALE OF THE STUDY

The rationale for this study was to understand the preferences and practices of Indian physicians regarding the combination therapy of Vildagliptin, Dapagliflozin, and Metformin in T2DM management. By investigating their perspectives and experiences, the study aimed to identify potential barriers and facilitators to the adoption of this combination therapy in clinical practice, ultimately optimizing treatment outcomes for patients. The purpose of this study was to gather insights into the usage of the Vildagliptin + Dapagliflozin + Metformin combination among Indian physicians treating patients with T2DM inadequately controlled on dual combination therapy.

3 STUDY OBJECTIVE

The primary objective of this study was to assess the perspectives, prescribing patterns, and experiences of Indian physicians regarding the usage of the Vildagliptin + Dapagliflozin + Metformin combination in T2DM patients inadequately controlled on dual combination therapy.

4 METHODS

This cross-sectional, questionnaire-based study aimed to gather insights from Indian physicians regarding the combination therapy of Vildagliptin, Dapagliflozin, and Metformin in the management of type 2 diabetes mellitus (T2DM). The study was designed to assess the perspectives, prescribing patterns, and experiences of physicians treating patients inadequately controlled on dual combination therapy.

Physicians who manage patients with T2DM across India were identified and invited to participate through professional networks and medical associations. Participation was voluntary. The study employs a 12-question electronic survey to collect data from participants. The survey included questions related to the following areas: Demographics of the physicians (e.g., age, gender, years of clinical experience); Clinical experience in managing T2DM; Prescribing practices for T2DM, particularly regarding the use of Vildagliptin, Dapagliflozin, and Metformin; and Perceptions and experiences related to the combination therapy of Vildagliptin, Dapagliflozin, and Metformin.

Participants were provided with detailed information about the study and its objectives prior to participation. The survey was administered electronically, and responses were collected and securely stored to ensure confidentiality.

Statistical analysis was conducted to summarize the findings and identify key trends. Descriptive statistics will be used to analyze the demographic data and responses to survey questions. Trends in prescribing patterns and physician perceptions were identified and reported.

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was sought from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without any consequences. All responses were anonymized to ensure participant confidentiality.

5 RESULTS

A total of 83 HCPs participated in the survey. Below is the summary of the responses.

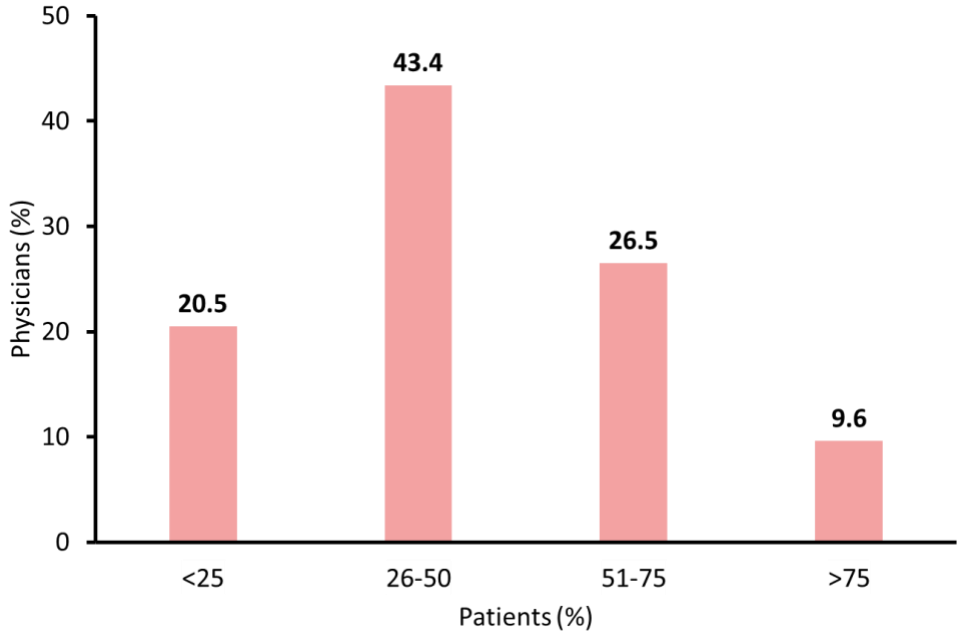
1. In your clinical practice, what is the approximate percentage of T2DM patients usually observed uncontrolled with dual combination therapy?

a. <25%

b. 26-50%

c. 51-75%

d. >75%



- Approximately 43.5% of physicians observed that 26-50% of their T2DM patients were usually uncontrolled with dual combination therapy.
- Additionally, 26.4% of physicians noted that 51-75% of their T2DM patients were uncontrolled with dual combination therapy.
- About 20.5% of physicians reported that less than 25% of their T2DM patients were generally uncontrolled with dual combination therapy, while 9.6% of physicians observed that more than 75% of their T2DM patients are usually uncontrolled with dual combination therapy.

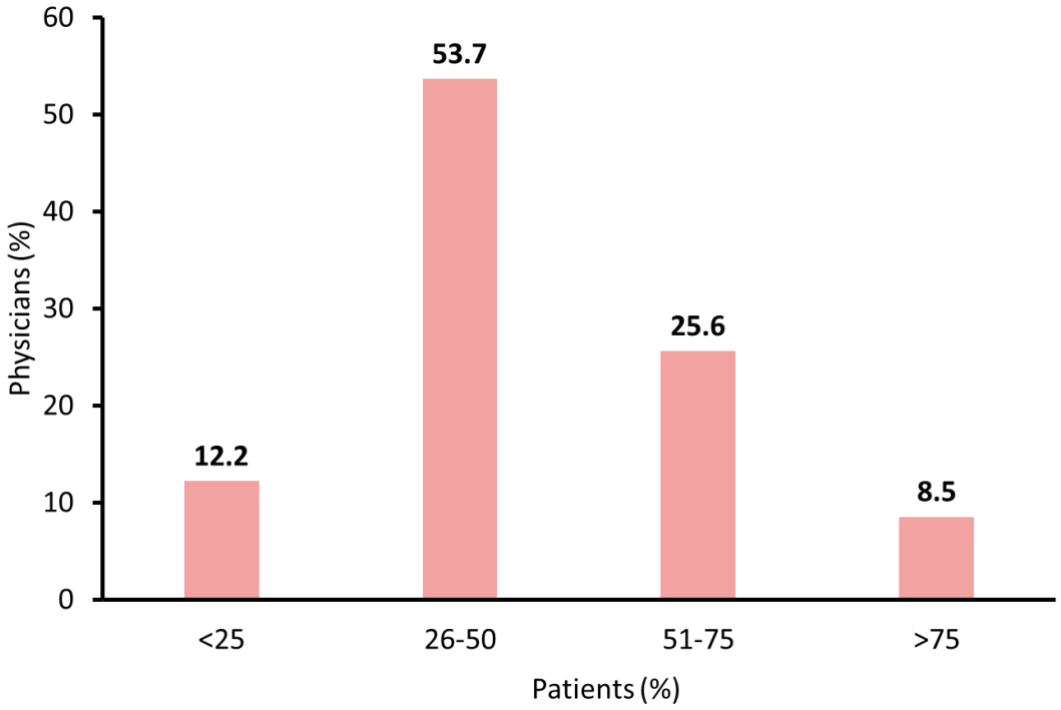
2. In your clinical experience, what percentage of diabetic patients are prescribed with combination of DPP4i + SGLT2i + Metformin?

a. <25%

b. 26-50%

c. 51-75%

d. >75%



- About 53.7% of physicians reported that 26-50% of diabetic patients were prescribed the combination of DPP4i + SGLT2i + metformin in their clinical practice, followed by 25.6% of physicians who reported that 51-75% of diabetic patients were prescribed this combination.
- Additionally, 12.2% of physicians noted that less than 25% of diabetic patients were prescribed this combination, and 8.5% of physicians reported that more than 75% of diabetic patients were prescribed it in their clinical practice.

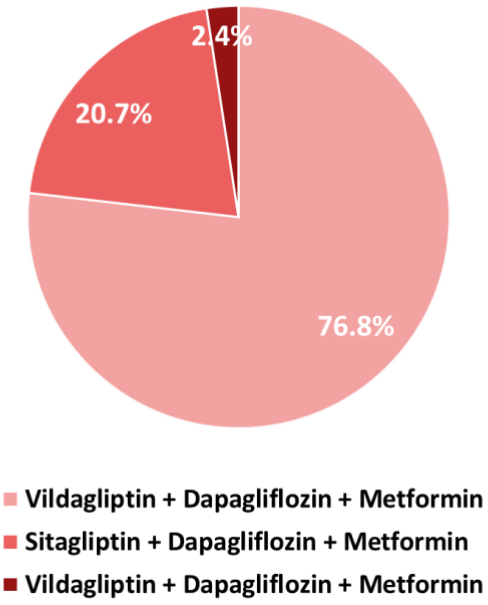
3. Which is the preferred DPP4i + Dapagliflozin + Metformin in your current clinical practice?

a. Vildagliptin + Dapagliflozin + Metformin

b. Sitagliptin + Dapagliflozin + Metformin

c. Vildagliptin + Dapagliflozin + Metformin

d. Teneligliptin + Dapagliflozin + Metformin

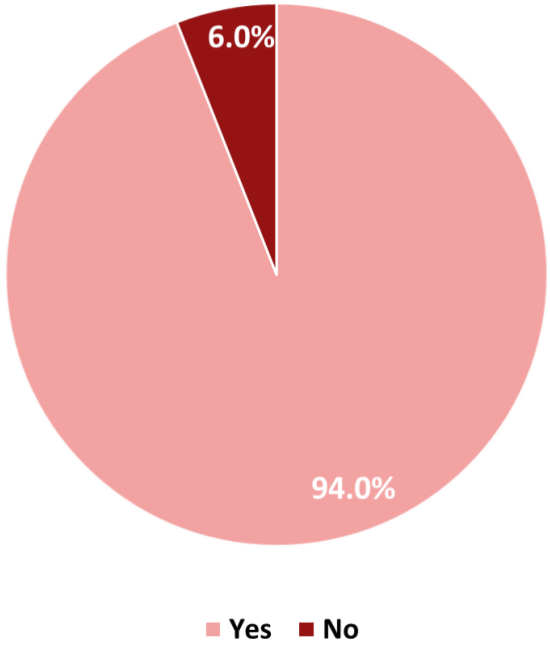


- The majority of physicians (76.8%) preferred vildagliptin + dapagliflozin + metformin for diabetic patients in their clinical practice, while 20.7% preferred sitagliptin + dapagliflozin + metformin, and 2.4% opted for vildagliptin + dapagliflozin + metformin. no physicians preferred teneligliptin + dapagliflozin + metformin

4. Do you concomitantly use Vildagliptin, Dapagliflozin, and Metformin?

a. Yes

b. No



- The majority of physicians (94.0%) concomitantly use vildagliptin, dapagliflozin, and metformin, while 6.0% of physicians do not concomitantly use vildagliptin, dapagliflozin, and metformin.

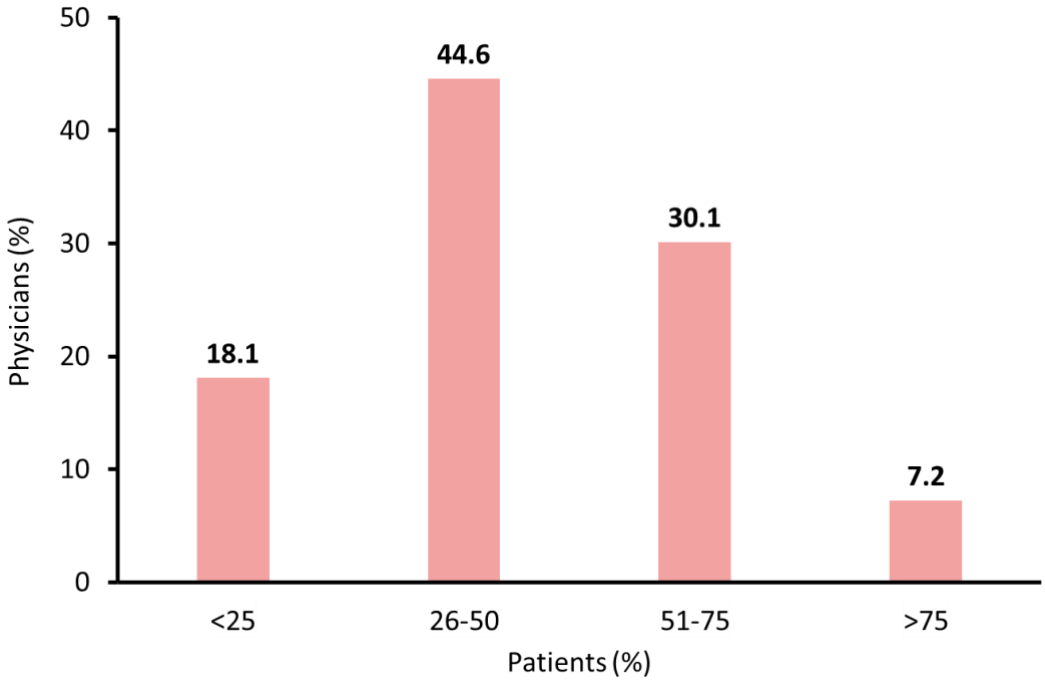
5. In your clinical practice, what percentage of Diabetic patients are prescribed with Vildagliptin + Dapagliflozin + Metformin combination?

a. <25%

b. 26-50%

c. 51-75%

- d. >75%



Approximately 44.6% of physicians reported that 26-50% of diabetic patients were prescribed the combination of vildagliptin, dapagliflozin, and metformin in their clinical practice, followed by 30.1% who reported that 26-50% of diabetic patients were prescribed this combination.

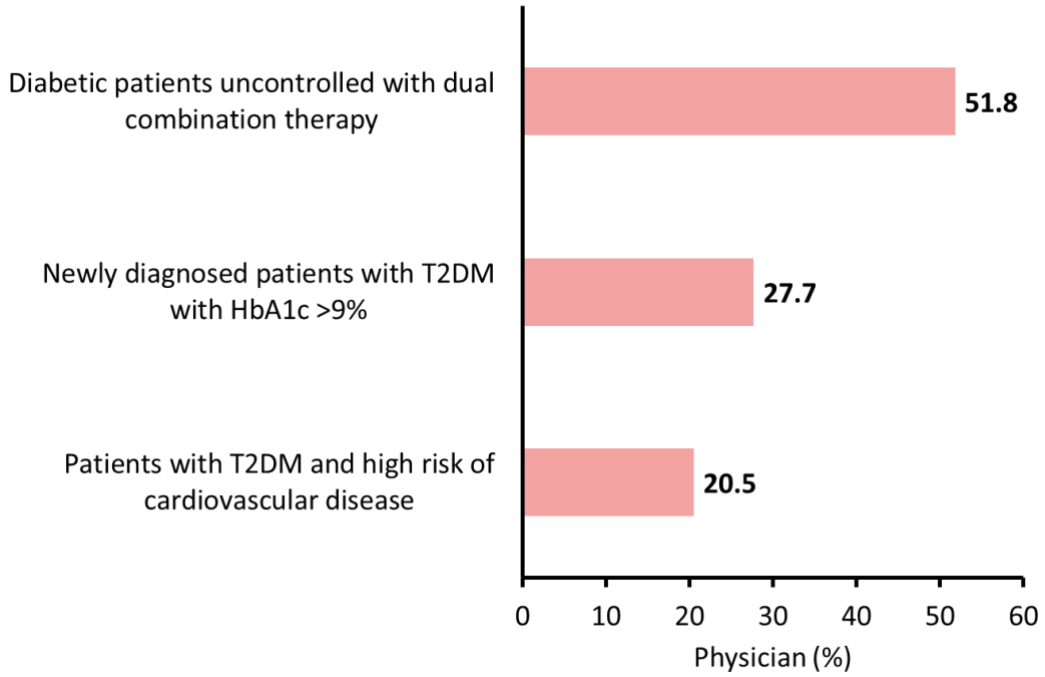
- Additionally, 18.1% of physicians noted that less than 25% of diabetic patients were prescribed this combination of vildagliptin, dapagliflozin, and metformin.
- A total of 7.2% of physicians reported that more than 75% of diabetic patients receive it in their clinical practice.

6. In which patient population would the combination Vildagliptin + Dapagliflozin + Metformin be preferred? (Can mark multiple options, if required)

a. Newly diagnosed patients with T2DM with HbA1c >9%

b. Diabetic Patients Uncontrolled with dual combination therapy

c. Patients with T2DM and high risk of cardiovascular disease



- The majority of physicians (51.8%) preferred the combination of vildagliptin, dapagliflozin, and metformin for diabetic patients uncontrolled with dual combination therapy.
- This was followed by 27.7% of physicians who preferred this combination for newly diagnosed patients with T2DM with HbA1c >9%, and 20.5% of physicians who preferred it for patients with T2DM at high risk of cardiovascular disease.

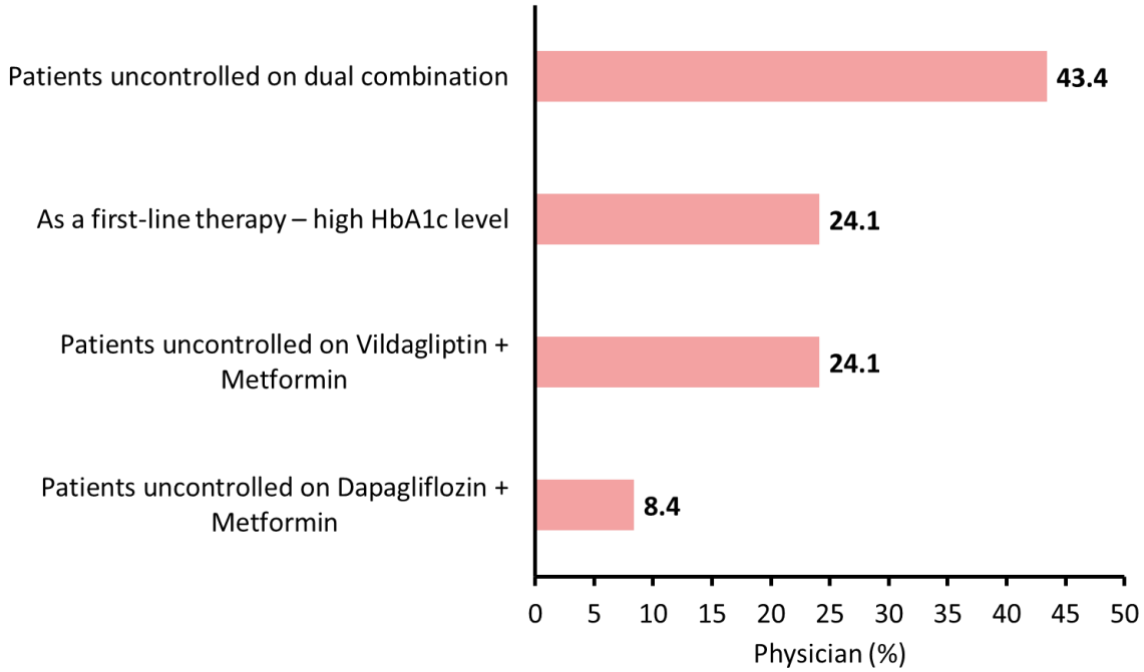
7. Where do you see the place of Vildagliptin + Dapagliflozin + Metformin FDC in obese people with T2DM?

a. As a first-line therapy – high HbA1c level

b. Patients uncontrolled on dual combination

c. Patients uncontrolled on Vildagliptin + Metformin

d. Patients uncontrolled on Dapagliflozin + Metformin



- About 43.4% of physicians preferred the vildagliptin + dapagliflozin + metformin FDC for obese patients with T2DM who were uncontrolled on a dual combination.
- This was followed by 24.1% of physicians who preferred the same FDC for obese patients with T2DM who were uncontrolled on vildagliptin + metformin.
- Additionally, 24.1% of physicians favoured the vildagliptin + dapagliflozin + metformin FDC as a first-line therapy for obese patients with T2DM with high HbA1c levels.
- 8.4% of physicians preferred this FDC for obese patients with T2DM who were uncontrolled on dapagliflozin + metformin.

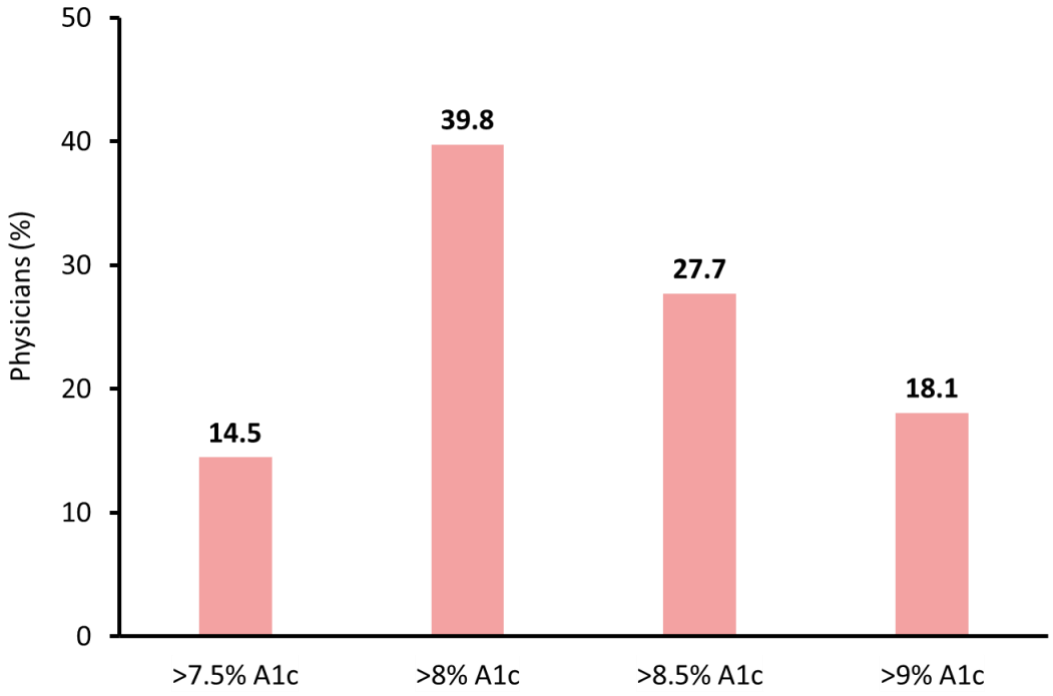
8. At what HbA1c level would you consider prescribing Vildagliptin + Dapagliflozin + Metformin FDC, in patients with T2DM who are on two oral antidiabetic drugs (OADs) and uncontrolled?

a. >7.5%

b. >8%

c. >8.5%

d. >9%



- When prescribing vildagliptin + dapagliflozin + metformin FDC to patients with T2DM who are on two oral antidiabetic drugs and uncontrolled, approximately 39.8% of physicians considered that the patient's HbA1c level was >8%.
- This was followed by 27.7% of physicians who considered the patient's HbA1c level was >8.5% when they were prescribing vildagliptin + dapagliflozin + metformin FDC.
- Additionally, 18.1% of physicians considered that the patient had an HbA1c level of >9% when they were prescribing vildagliptin + dapagliflozin + metformin FDC, and 14.5% of physicians considered that the patient's HbA1c level was >7.5%.

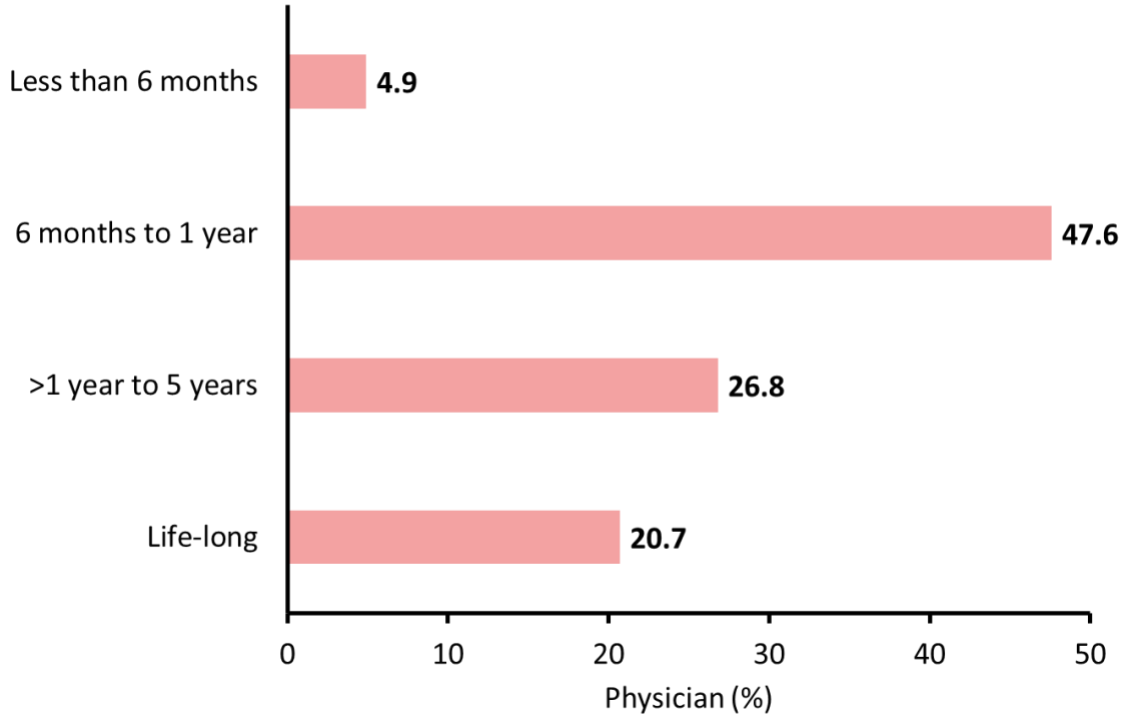
9. As per your opinion, what can be the average duration of Vildagliptin + Dapagliflozin + Metformin Therapy in Diabetes with multiple CV risk factors?

a. Less than 6 months

b. 6 months to 1 year

c. >1 year to 5 years

d. Life-long



- According to 47.6% of physicians, the average duration of vildagliptin + dapagliflozin + metformin therapy in diabetes with multiple CV risk factors is believed to be 6 months to 1 year, followed by 26.8% who believed it to be >1 year to 5 years, 20.7% who believed it to be lifelong, and 4.9% who believed it to be less than 6 months.

10. What is the observed clinical advantage(s) with the usage of the combination of Vildagliptin + Dapagliflozin + Metformin?

a. Significant reduction in hyperglycaemia.

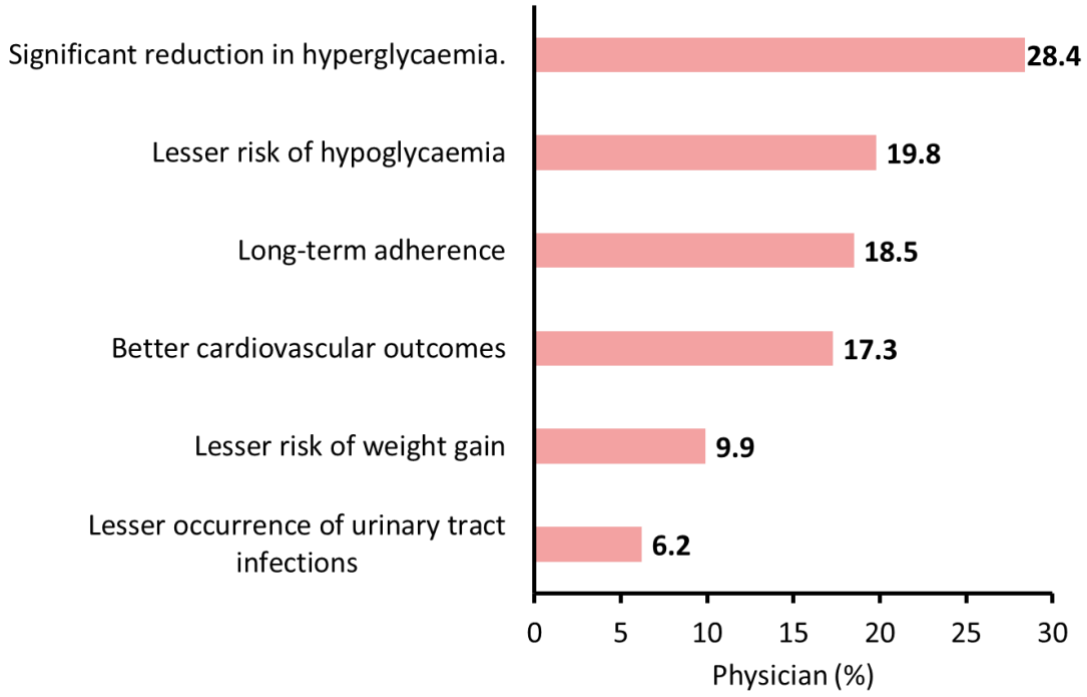
b. Better Cardiovascular Outcomes

c. Lesser risk of weight gain

d. Lesser risk of hypoglycaemia

e. Lesser occurrence of urinary tract infections

f. Long-term adherence



- According to 28.4% of physicians, significant reduction in hyperglycemia was the primary clinical advantage of using the combination of vildagliptin, dapagliflozin, and metformin.
- This was followed by 19.8% citing a lesser risk of hypoglycemia, 18.5% noting improved long-term adherence, 17.3% recognizing better cardiovascular outcomes, 9.9% observing a lesser risk of weight gain, and 6.2% reporting a reduced occurrence of urinary tract infections.

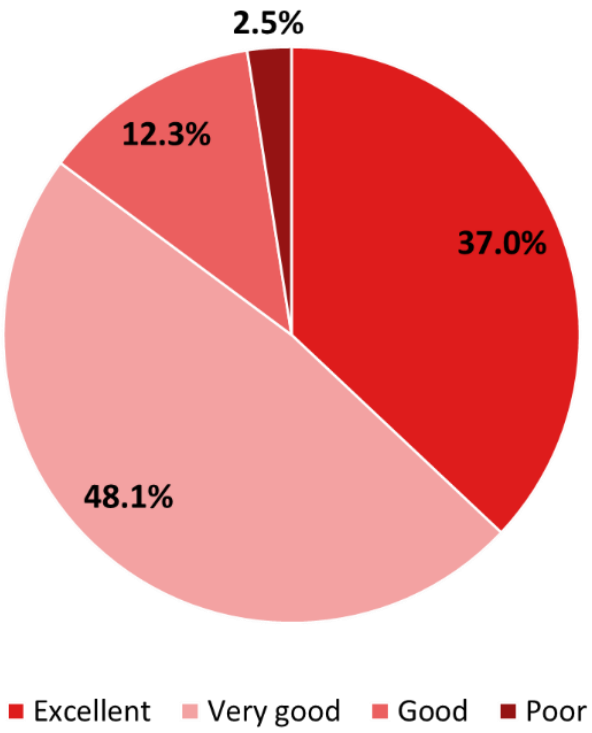
11. In your opinion, how is the long-term safety profile of Vildagliptin + Dapagliflozin + Metformin?

a. Excellent

b. Very Good

c. Good

d. Poor

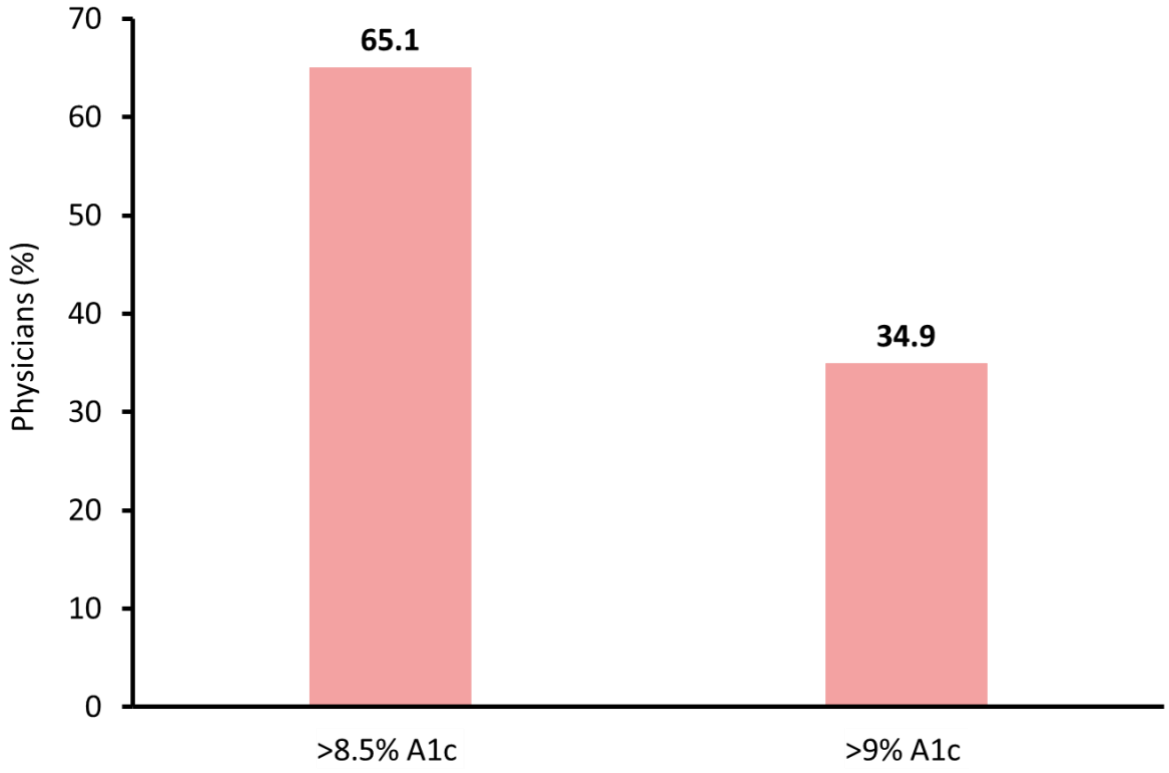


- About 48.1% of physicians believed that the long-term safety profile of vildagliptin + dapagliflozin + metformin was very good while 37.0% believed that the long-term safety profile of vildagliptin + dapagliflozin + metformin was excellent.
- Additionally,12.3% of physicians believed that the long-term safety profile of vildagliptin + dapagliflozin + metformin was good and only 2.5% of physician considered poor long-term safety profile of vildagliptin + dapagliflozin + metformin.

12. Which of the following can be the ideal patient profile for initiating with the FDC of Vildagliptin + Dapagliflozin + Metformin therapy?

a. Treatment naïve patients with HbA1c >8.5

b. Treatment naïve patients with HbA1c >9



- The majority of physicians (65.1%) considered that treatment-naive patients with HbA1c > 8.5 can be the ideal patient profile for initiating the FDC of vildagliptin + dapagliflozin + metformin therapy.
- While 34.9% of physicians considered treatment-naive patients with HbA1c >9 can be the ideal patient profile for initiating with the FDC of vildagliptin + dapagliflozin + metformin therapy.

6 SUMMARY

The survey revealed that a significant portion of T2DM patients remain uncontrolled on dual combination therapy, with 43.5% of physicians noting that 26-50% of their patients are usually uncontrolled. The combination therapy of DPP4i + SGLT2i + metformin is commonly prescribed, with 53.7% of physicians using it for 26-50% of their patients. Vildagliptin + dapagliflozin + metformin is highly preferred by 76.8% of physicians, with 94.0% using it concomitantly. This combination is frequently prescribed to 26-50% of patients (44.6%) and is favored for uncontrolled T2DM patients (51.8%), newly diagnosed patients with HbA1c >9% (27.7%), and those at high cardiovascular risk (20.5%). For obese T2DM patients, 43.4% of physicians preferred this combination when uncontrolled on dual therapy. Physicians consider initiating therapy at different HbA1c thresholds, primarily >8% and >8.5%. The majority believe the treatment duration is 6 months to 1 year (47.6%), and the therapy offers significant reduction in hyperglycemia (28.4%) with a very good to excellent safety profile (85.1%). The ideal patient profile for initiating this combination is treatment-naive patients with HbA1c >8.5% (65.1%).

7 DISCUSSION

The results from the survey of physicians reflect a strong preference for the combination therapy of vildagliptin, dapagliflozin, and metformin in the treatment of T2DM patients in India, particularly for those who are not adequately controlled on dual therapy. A significant proportion of physicians (76.8%) prefer this combination due to its efficacy in managing hyperglycemia and its beneficial impact on long-term adherence and cardiovascular outcomes.

Physicians also reported that the combination is widely prescribed, with 53.7% indicating that 26-50% of their patients receive this therapy. The preference for this combination is underscored by the clinical advantages reported, such as significant reduction in hyperglycemia, lesser risk of hypoglycemia, and better cardiovascular outcomes. Moreover, the long-term safety profile of the combination is deemed very good to excellent by the majority of respondents (85.1%).

For patients with higher HbA1c levels, particularly those above 8.5%, this combination is often initiated, aligning with the recommendations of 65.1% of physicians. This approach is further supported by the 51.8% of physicians who favor the combination for patients uncontrolled on dual therapy, highlighting its role in intensifying treatment regimens for better glycemic control.

8 CLINICAL RECOMMENDATIONS

- Initiate vildagliptin + dapagliflozin + metformin in treatment-naive patients with HbA1c >8.5%.
- Consider this combination for patients uncontrolled on dual therapy, especially those with HbA1c levels >8%.
- Regularly monitor HbA1c levels to assess the efficacy of the combination therapy.
- Evaluate cardiovascular risk factors and adjust therapy accordingly to maximize cardiovascular benefits.
- Focus on patient education to improve adherence, emphasizing the benefits of combination therapy in managing hyperglycemia and reducing cardiovascular risks.
- Monitor patients for potential side effects, including urinary tract infections and weight gain, and manage these proactively.

9 CONSULTANT OPINION

Conduct randomized controlled trials comparing the efficacy of vildagliptin + dapagliflozin + metformin with other combination therapies, including different DPP4i and SGLT2i combinations. Investigate the long-term outcomes of vildagliptin + dapagliflozin + metformin therapy on cardiovascular events, renal function, and overall mortality in T2DM patients. Perform subgroup analyses to identify specific patient populations that may benefit the most from this combination, such as those with varying degrees of obesity, different baseline HbA1c levels, and different comorbidities. Collect real-world evidence to supplement clinical trial data, providing

insights into the effectiveness and safety of this combination in diverse clinical settings. Explore patient-reported outcomes to better understand the impact of this combination therapy on quality of life, treatment satisfaction, and adherence. By addressing these areas, future research can provide a more comprehensive understanding of the benefits and limitations of vildagliptin + dapagliflozin + metformin combination therapy, ultimately guiding more effective and personalized treatment strategies for T2DM patients.

10 MARKET OPPORTUNITIES

The combination therapy of vildagliptin, dapagliflozin, and metformin presents a significant market opportunity in the management of T2DM, particularly in the Indian context. Given the high percentage of patients who remain uncontrolled on dual therapy, there is a substantial demand for more effective treatment options. The survey indicates that a majority of physicians (76.8%) already prefer this combination, highlighting a ready market that can be further expanded.

With 43.5% of physicians reporting 26-50% of their patients are uncontrolled on dual therapy, there is a clear need for more effective treatment regimens. Vildagliptin + dapagliflozin + metformin addresses this gap by offering improved glycemic control and other clinical benefits. This combination therapy is particularly effective for patients with high HbA1c levels (>8.5%) and those at high cardiovascular risk. By targeting these specific patient segments, the therapy can position itself as a specialized solution for difficult-to-control diabetes cases.

The preference for this combination therapy in obese T2DM patients who are uncontrolled on dual therapy (43.4%) presents a niche market opportunity. The therapy can be marketed as an effective first-line treatment for obese patients with high HbA1c, addressing both glycemic control and weight management concerns.

The combination's very good to excellent safety profile (85.1%) and benefits like reduced risk of hypoglycemia, better cardiovascular outcomes, and long-term adherence (18.5%) make it an attractive option for long-term therapy. This can be

leveraged to promote the therapy as a reliable, long-term solution for managing T2DM.

11 MARKET POSITIONING

Superior combination therapy

Position vildagliptin + dapagliflozin + metformin as the superior combination therapy for T2DM, emphasizing its efficacy in controlling blood glucose levels where dual therapies fail. Highlight the significant reduction in hyperglycemia and the clinical advantages reported by physicians.

Ideal for high-risk and difficult-to-control patients

Market the therapy as the ideal choice for high-risk patients, including those with high HbA1c levels, cardiovascular risks, and those who are obese. Emphasize the tailored benefits for these groups, such as improved cardiovascular outcomes and better weight management.

Endorsed by physicians

Leverage the high preference and endorsement by physicians (76.8%) to build credibility and trust. Highlight the widespread adoption and positive feedback from the medical community to reassure patients and healthcare providers of its effectiveness and safety.

Long-term safety and adherence

Promote the combination's excellent safety profile and the potential for long-term adherence. Use this to differentiate it from other therapies that may not offer the same level of safety or patient compliance over time.

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