Survey Report

Perception Mapping of Indian Physicians to Evaluate the Effectiveness of Combination of Linagliptin 5 mg with Metformin 1000 mg

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 (DM) is a chronic metabolic disorder characterized by elevated blood sugar levels, stemming from impaired insulin secretion, insulin resistance, or both [1]. This condition gives rise to both microvascular and macro vascular complications, including retinopathy, nephropathy, neuropathy, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease, often leading to significant tissue and organ damage [2]. The prevalence of DM, which was 529 million in 2021, is anticipated to rise, with projections suggesting that 1.31 billion people worldwide could be living with diabetes by the year 2050 [3]. India ranks the second-highest global prevalence of type 2 diabetes mellitus (T2DM), with an estimated 74.2 million cases in 2021, and projections anticipate a substantial rise to 124.9 million by 2045 among adults aged 20–79 years. It is the most common type of diabetes, accounting for more than 90% of all diabetes worldwide [4].

T2DM, often termed the "silent disease," progresses steadily without early symptoms, culminating in severe organ damage. Its escalating prevalence is attributed to urbanization, lifestyle changes, and dietary patterns [5]. The risk factors associated with type 2 diabetes, including sleep quantity/quality, smoking, dyslipidemia, hypertension, ethnicity, family history, obesity, and physical inactivity, significantly influence its development [6].

Metformin has long been established as the first-line therapy for T2DM due to its efficacy in improving insulin sensitivity and reducing hepatic glucose output [7]. However, as the disease progresses, many patients require additional medications to achieve and maintain glycemic control. This has led to the development and widespread use of various classes of antidiabetic drugs, including Dipeptidyl peptidase 4 inhibitors (DPP-4) [8]. Linagliptin, a once-daily DPP-4 inhibitor, has demonstrated efficacy across a wide range of patient profiles, including those with renal impairment [9]. Its unique pharmacokinetic profile allows for a single 5mg dose without the need for adjustment in patients with hepatic or renal dysfunction, making it an attractive option for clinicians managing complex T2DM cases [10]. The combination of Linagliptin with Metformin has shown promise in improving glycemic

control while potentially offering additional benefits such as weight neutrality and a low risk of hypoglycemia [11].

Despite the availability of various treatment options, achieving optimal glycemic

control remains a challenge for many patients with T2DM. Factors such as adherence to medication, tolerability, and the presence of comorbidities can significantly impact treatment outcomes [12]. Understanding physicians' perceptions and prescribing patterns is crucial for identifying potential barriers to effective diabetes management and areas for improvement in clinical practice.

In the Indian context, where the burden of T2DM is particularly high, it is essential to explore how physicians approach combination therapy, especially the use of newer agents like Linagliptin in combination with established treatments like Metformin. This study employs a questionnaire-based survey aims to map the perceptions of Indian physicians regarding the combination of Linagliptin 5mg with Metformin 1000mg in T2DM management. By exploring physicians' views on unmet medical needs, prescription patterns, patient selection criteria, and perceived benefits of this combination, we seek to gain insights into real-world clinical decision-making.

2 RATIONALE OF THE STUDY

The rationale for this study was to gather comprehensive insights into the clinical use and efficacy of a combination therapy of linagliptin 5mg with metformin 1000mg in managing T2DM among Indian patients. Understanding the prescribing patterns, treatment preferences, and perceived efficacy among physicians will aid in optimizing therapeutic strategies and improving patient outcomes.

The purpose of this study was to evaluate the protective effect of linagliptin 5 mg with metformin 1000 mg combination therapy in Indian patients diagnosed with T2DM. This investigation aims to assess its efficacy in reducing blood sugar level, improving patient compliance, and determining its long-term safety profile.

3 STUDY OBJECTIVE

The primary objective of the study was to map the perceptions and practices of Indian physicians regarding the use of linagliptin 5mg and metformin 1000mg combination therapy in managing T2DM.

4 METHODS

This cross-sectional, questionnaire-based study involved a sample of Indian physicians managing patients with T2DM. The survey consisted of 14 questions focusing on physicians' clinical experience, prescribing practices, and perceptions regarding the use of the linagliptin and metformin combination for Indian patients with T2DM.

Physicians were identified and invited to participate through professional networks and medical associations. Prior to participation, detailed information about the study was provided to each physician. The survey was administered electronically to ensure convenience. Responses were collected and securely stored to maintain confidentiality. A total of 99 Indian physicians were targeted for the study to ensure a diverse and representative sample, allowing for meaningful statistical analysis.

Ethical approval was obtained from an Independent Ethics Committee, adhering to the ethical principles outlined in the Declaration of Helsinki. 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.

After data collection, statistical analysis was conducted to summarize findings and identify key trends. The results were compiled into a comprehensive report, which was shared through scientific publications and presentations at conferences, where suitable. The study design ensured a systematic and ethical approach to gathering data from a representative sample of Indian physicians. This methodology provided robust insights into the clinical practices and perceptions related to the use of linagliptin and metformin in T2DM. The electronic administration of the survey facilitated high participation rates, and stringent confidentiality measures maintained the integrity of the data collected.

5 RESULTS

A total of 99 HCPs participated in the survey. Below is the summary of the responses.

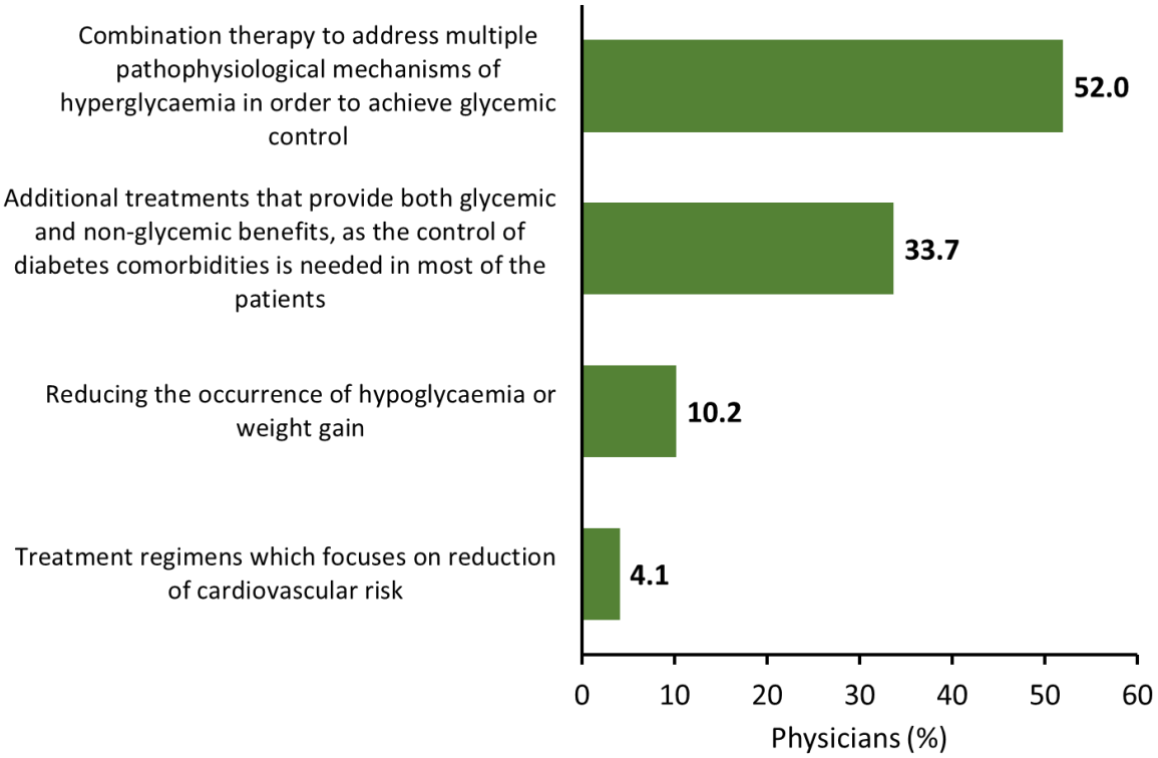
1. As per your opinion, which is the unmet medical need in patients with type 2 diabetes mellitus (T2DM)?

A. Combination therapy to address multiple pathophysiological mechanisms of hyperglycaemia in order to achieve glycemic control

B. Additional treatments that provide both glycemic and non-glycemic benefits, as the control of diabetes comorbidities is needed in most of the patients

C. Reducing the occurrence of hypoglycaemia or weight gain

D. Treatment regimens, which focuses on reduction of cardiovascular risk



- Majority of physicians (52.0%) observed that the unmet medical need in patients with T2DM was combination therapy to address multiple pathophysiological mechanisms of hyperglycaemia in order to achieve glycemic control.

- Around 33.7% of physicians identified the need for treatments that provide both glycemic and non-glycemic benefits, as controlling diabetes comorbidities was essential for most patients.
- While, 10.2% of physicians considered reducing the occurrence of hypoglycaemia or weight gain as necessary.
- However, 4.1% prioritized treatment regimens focusing on the reduction of cardiovascular risk.
- This study reflected the varied perspectives of medical professionals regarding the primary needs in managing T2DM, with a significant majority emphasizing the importance of comprehensive glycemic control strategies.

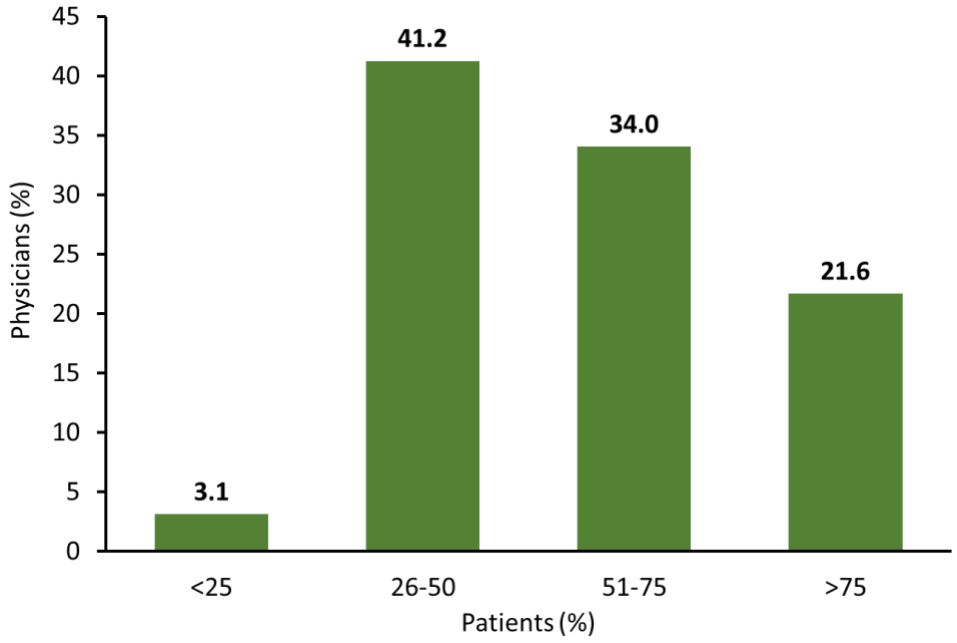
2. In your clinical practise how often do you find the need to initiate therapy for T2DM with a combination?

A. <25%

B. 26-50%

C. 51-75%

D. >75%



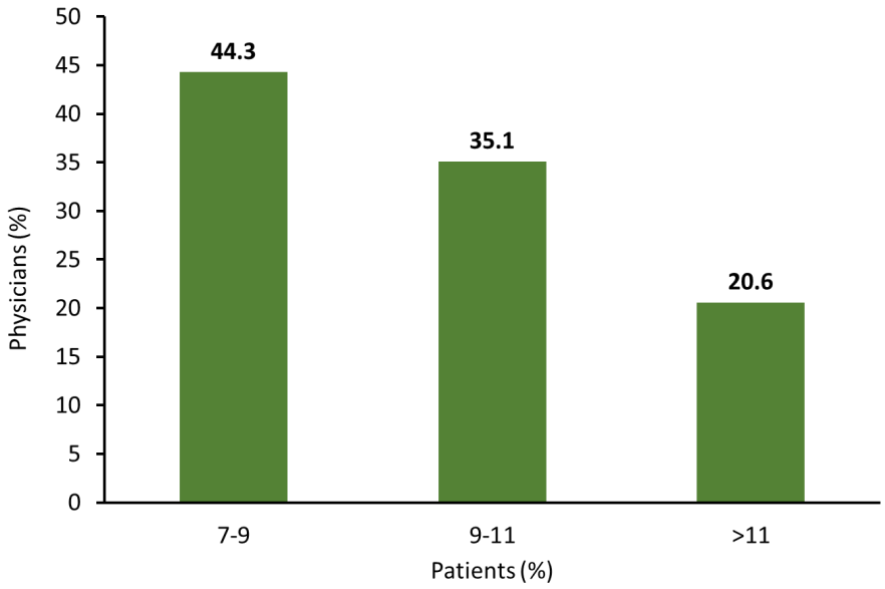
- About, 41.2% of physicians reported that they initiated combination therapy in 26-50% of their patients in their clinical practice.
- Around, 34.0% of physicians stated that they started combination therapy in 51-75% of their patients in their clinical practice.
- While, 21.6% of physicians noted that they started combination therapy for T2DM in more than 75% of their patients in their clinical practice.

3. At what HbA1c level would you consider initiating a dual combination therapy for T2DM? (More than 1 3option can be marked, if required)

A. 7-9%

B. 9-11%

C. >11%



- About 44.3% of physicians considered initiating dual combination therapy for T2DM when the HbA1c level was between 7-9%.
- In comparison, 35.1% of physicians would start dual combination therapy when the HbA1c level was between 9-11%.
- Approximately 20.6% of physicians reported that they would consider initiating dual combination therapy for T2DM if the HbA1c level exceeded 11%.

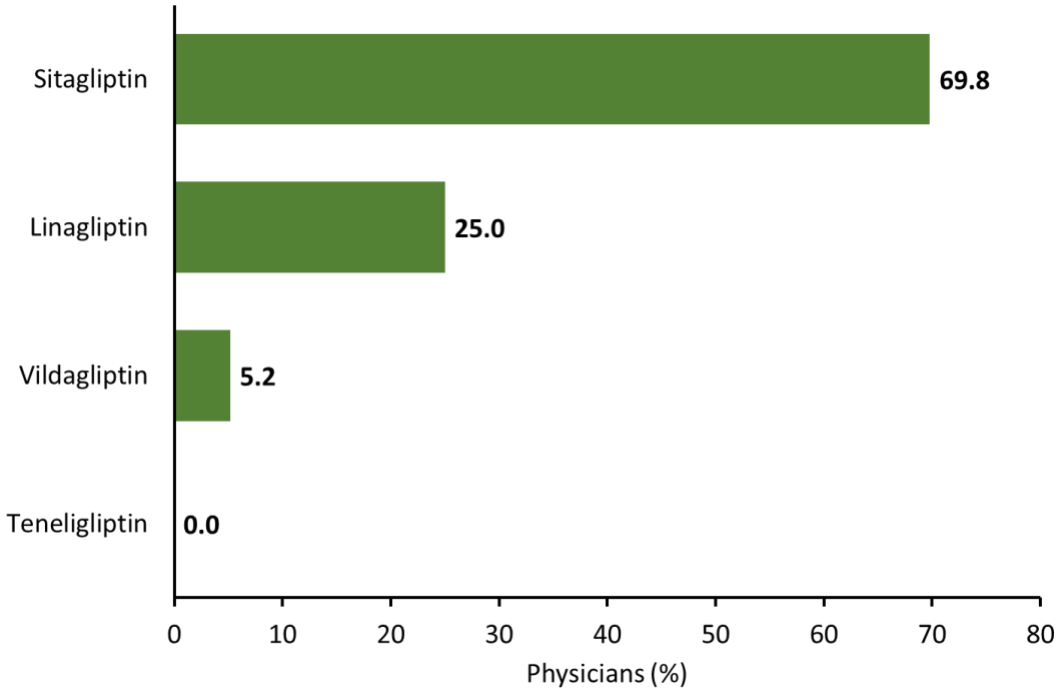
4. Which is the most preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor in your current clinical practice?

A. Linagliptin

B. Vildagliptin

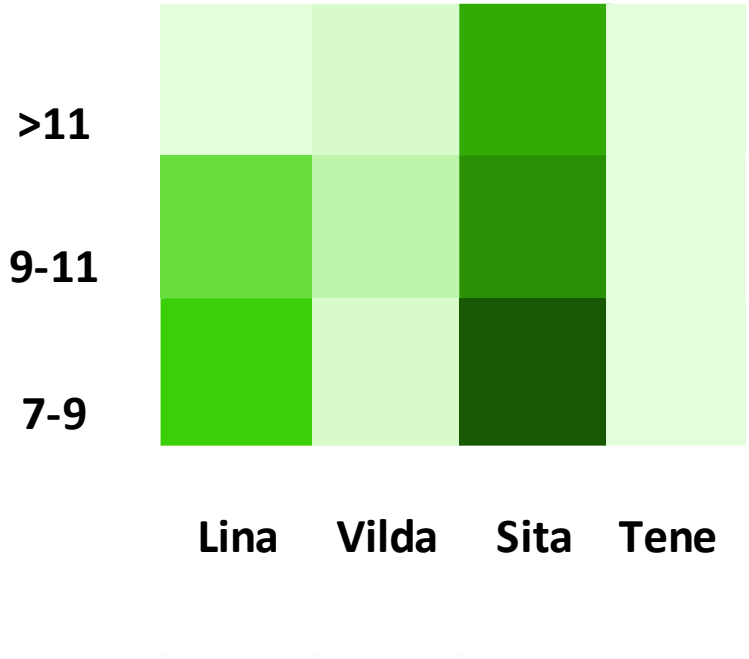
C. Sitagliptin

D. Teneligliptin



- The majority of physicians (69.8%) selected sitagliptin as their most preferred DPP-4 inhibitor in their current clinical practice.
- About 25.0% of physicians preferred linagliptin as the most favored DPP-4 inhibitor in their current clinical practice.
- Approximately, 5.2% of physicians preferred vildagliptin as their most preferred DPP-4 inhibitor in their current clinical practice.
- No physicians reported teneligliptin as their preferred DPP-4 inhibitor, with 0% indicating it as their choice.

Correlation between HbA1c Levels and Choice of Gliptin



- Sitagliptin was the favored DPP-4 inhibitor for all HbA1c levels, with its preference increasing as HbA1c levels decreased, underscoring its perceived effectiveness in managing various glycemic control needs.
- Linagliptin was mainly chosen for moderate HbA1c levels (7-9%) and to a lesser extent for 9-11%.
- Vildagliptin had the lowest preference across all HbA1c levels, indicating it was not a primary option for glycemic control among the surveyed physicians.
- However, no physicians preferred teneligliptin.

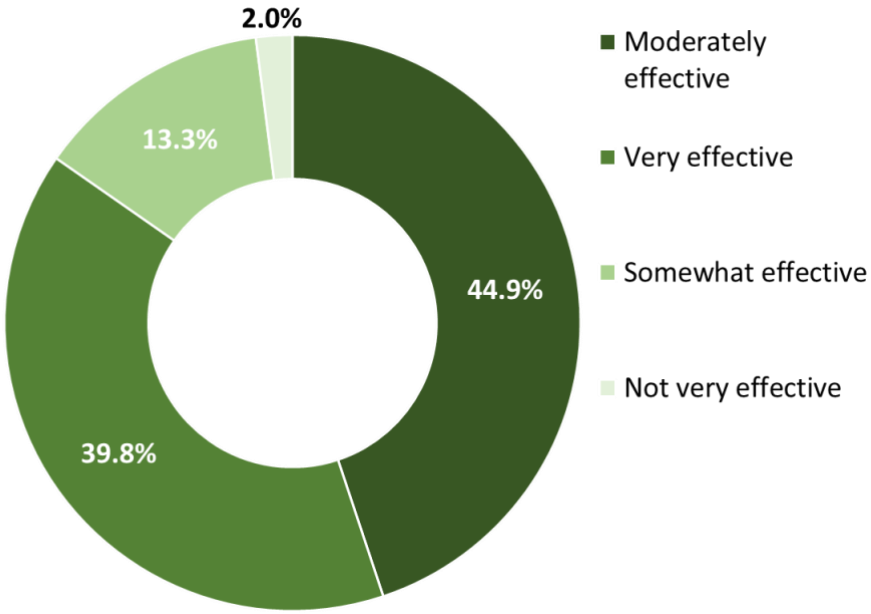
5. In your opinion, how effective is Linagliptin in terms of glycemic control for patients with diabetes?

A. Very effective

B. Moderately effective

C. Somewhat effective

D. Not very effective



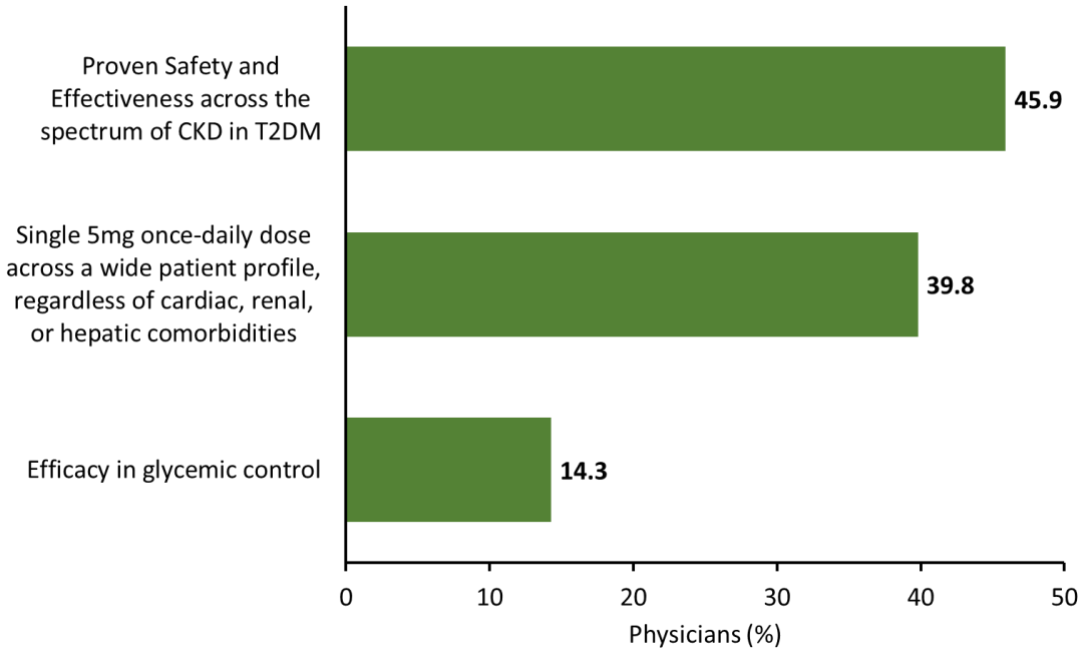
- Around, 44.9% of physicians considered linagliptin to be moderately effective for glycemic control in diabetic patients.
- About 39.8% of physicians believed that linagliptin was very effective in terms of glycemic control for patients with diabetes.
- Approximately 13.3% of physicians found linagliptin to be somewhat effective in managing glycemic control.
- Only 2.0% of physicians felt that linagliptin was not very effective for glycemic control in patients with diabetes.

6. What factors influence your preference for Linagliptin over other DPP4 inhibitors?

A. Efficacy in glycemic control

B. Proven Safety and Effectiveness across the spectrum of CKD in T2DM

C. Single 5mg once-daily dose across a wide patient profile, regardless of cardiac, renal, or hepatic comorbidities



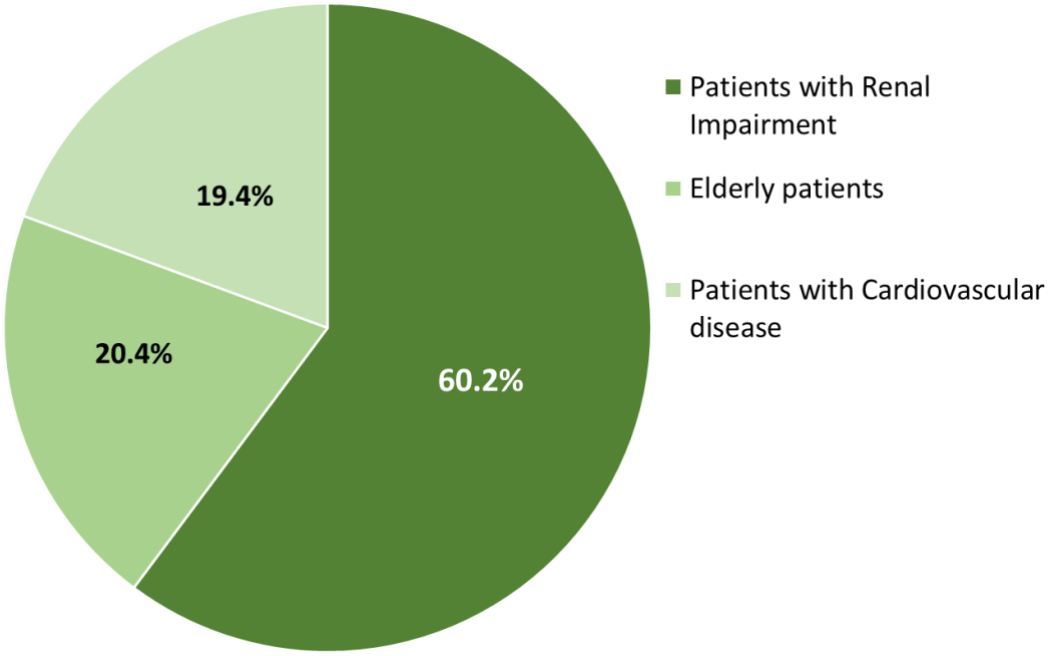
- About. 45.9% of physicians preferred linagliptin due to its proven safety and effectiveness across the spectrum of chronic kidney disease (CKD) in T2DM over other DPP-4 inhibitors.
- Around, 39.8% of physicians preferred linagliptin over other DPP-4 inhibitors due to the single 5 mg once-daily dose of linagliptin, which is suitable across a wide patient profile, regardless of cardiac, renal, or hepatic comorbidities.
- Approximately, 14.3% of physicians indicated that the efficacy in glycemic control influenced their preference for Linagliptin over other DPP-4 inhibitors.

7. In your opinion, which of the following patient profiles is most suitable for Linagliptin therapy?

A. Patients with Renal Impairment

B. Patients with Cardiovascular disease

C. Elderly patients

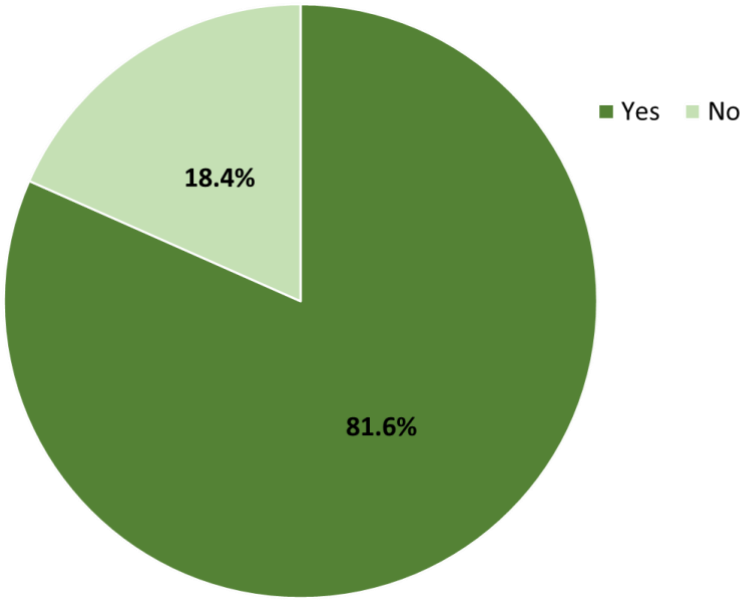


- The majority of physicians (60.2%) considered patients with renal impairment to be the most suitable profile for linagliptin therapy.
- About, 20.4% of physicians believed that elderly patients were the most suitable profile for linagliptin therapy.
- Approximately, 19.4% of physicians felt that patients with cardiovascular disease were the most suitable candidates for Linagliptin therapy.

8. Have you previously used Linagliptin and Metformin concomitantly?

A. Yes

B. No



- Majority of physicians (81.6%) reported that they had previously used linagliptin and metformin concomitantly.
- In contrast, 18.4% of physicians indicated that they had not used linagliptin and metformin concomitantly.

9. Which patient profile do you consider most appropriate for the Linagliptin and Metformin combination therapy?

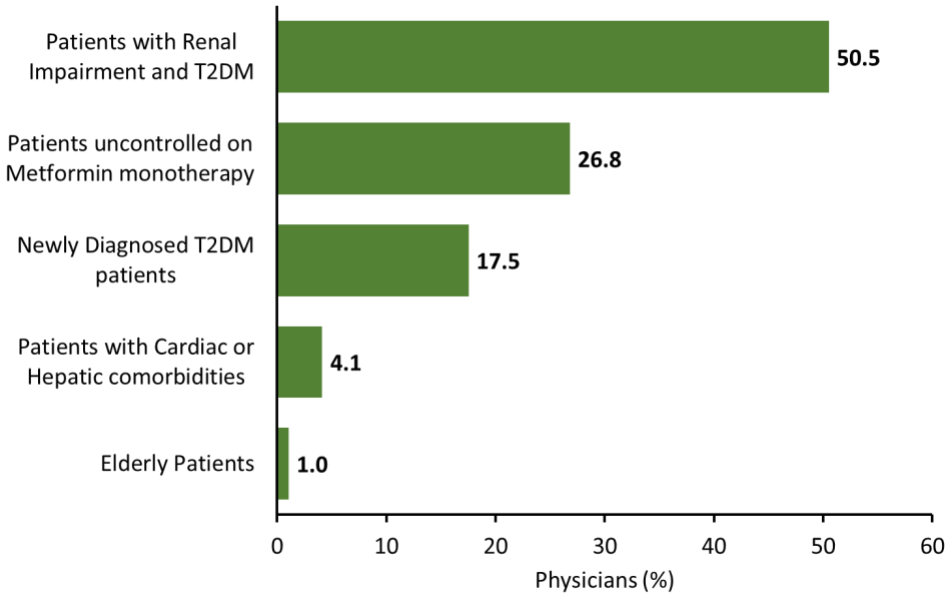
A. Newly Diagnosed T2DM patients

B. Patients uncontrolled on Metformin monotherapy

C. Patients with Renal Impairment and T2DM

D. Patients with Cardiac or Hepatic comorbidities

E. Elderly Patients

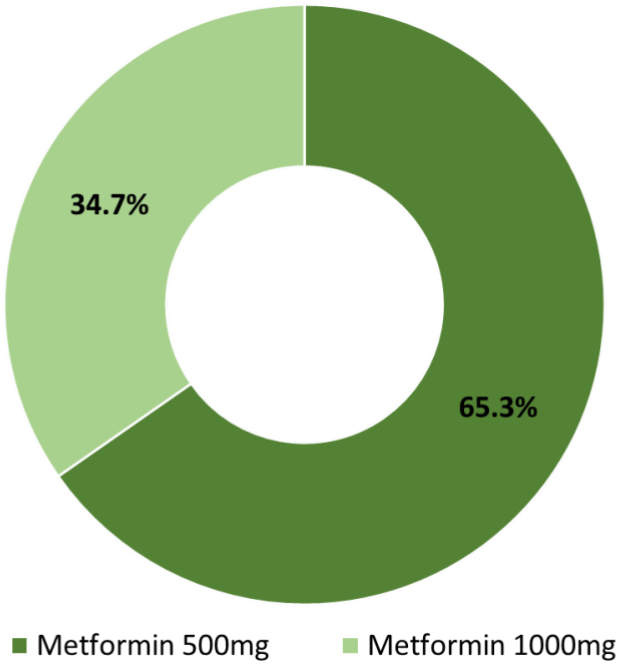


- Majority of physicians (50.5%) considered patients with renal impairment and T2DM as the most appropriate candidates for linagliptin and metformin combination therapy.
- Approximately 26.8% of physicians considered that patients uncontrolled on metformin monotherapy were the most suitable for this combination therapy.
- About 17.5% of physicians considered newly diagnosed T2DM patients as the most appropriate profile for linagliptin and metformin combination therapy.
- However, 4.1% of physicians considered that patients with cardiac or hepatic comorbidities were the most suitable for this combination therapy.
- A small 1.0% of physicians considered elderly patients as the most appropriate profile for linagliptin and metformin combination therapy.

10. In your opinion, what would be the ideal strength of Metformin to be added to Linagliptin 5mg?

A. Metformin 500mg

B. Metformin 1000mg



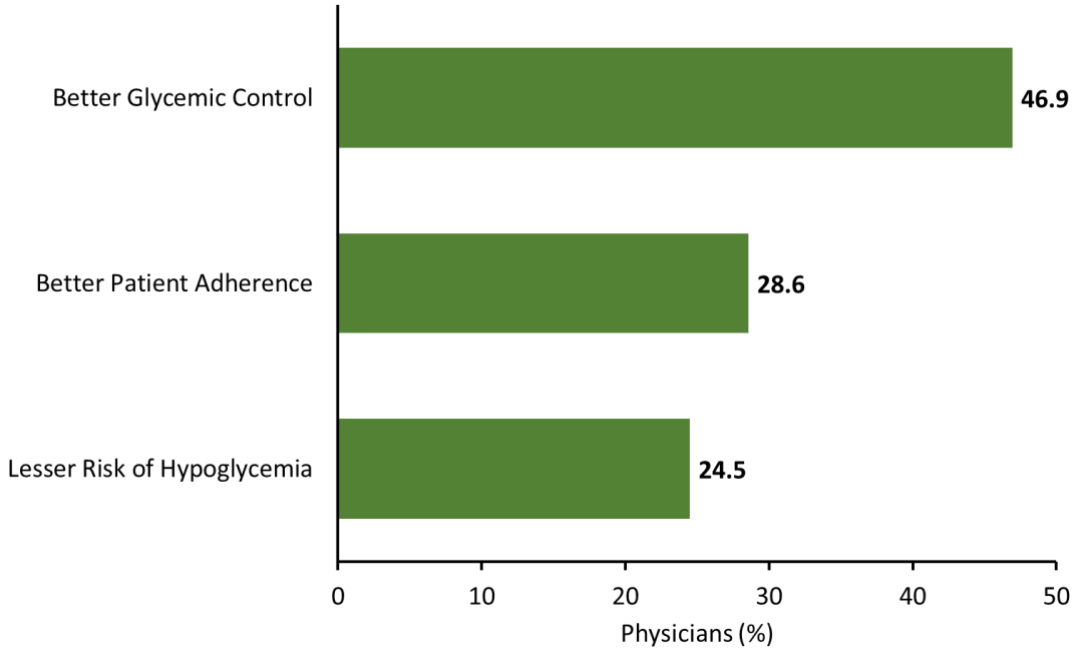
- Majority of physicians (65.3%) considered metformin 500 mg to be the ideal strength to be added to linagliptin 5 mg.
- In contrast, 34.7% of physicians preferred metformin 1000 mg as the ideal strength to combine with linagliptin 5 mg.

11. In your opinion, what is the benefit of a higher dose of Linagliptin 5mg and Metformin 1000mg FDC?

A. Better Glycemic Control

B. Lesser Risk of Hypoglycemia

C. Better Patient Adherence



- About, 46.9% of physicians believed that the benefit of a higher dose of linagliptin 5 mg and metformin 1000 mg fixed-dose combination (FDC) was better glycemic control.
- Around, 28.6% of physicians believed that a higher dose of linagliptin 5 mg and metformin 1000 mg FDC would lead to better patient adherence.
- Approximately 24.5% of physicians noted that a higher dose of this linagliptin 5 mg and metformin 1000 mg FDC would result in a lesser risk of hypoglycemia.

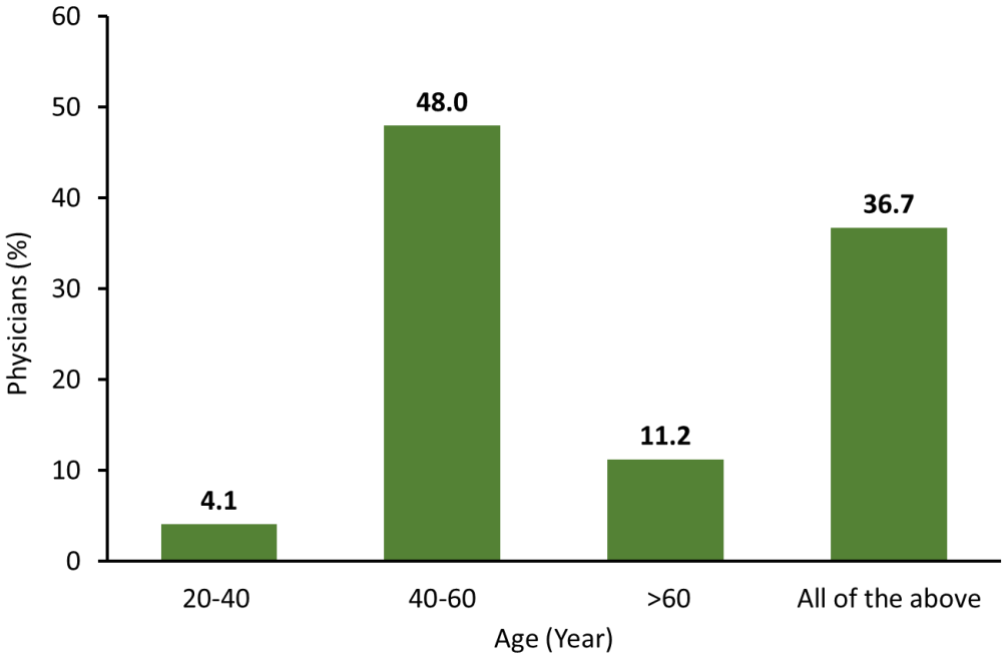
12. In your opinion, in what age group can the combination of Linagliptin 5mg + Metformin 1000mg be preferred?

A. 20-40 years old

B. 40-60 years old

C. >60 years old

D. All of the above



- About, 48.0% of physicians preferred the combination of linagliptin 5 mg + metformin 1000 mg for patients aged with 40-60 years.
- Around, 36.7% of physicians preferred the combination of linagliptin 5 mg + metformin 1000 mg for patients aged with 20-40, 40-60 years and older than 60 years.
- While, 11.2% of physicians considered the combination appropriate for patients older than 60 years.
- However only 4.1% of physicians preferred the combination of linagliptin 5 mg + metformin 1000 mg for patients aged with 20-40 years.

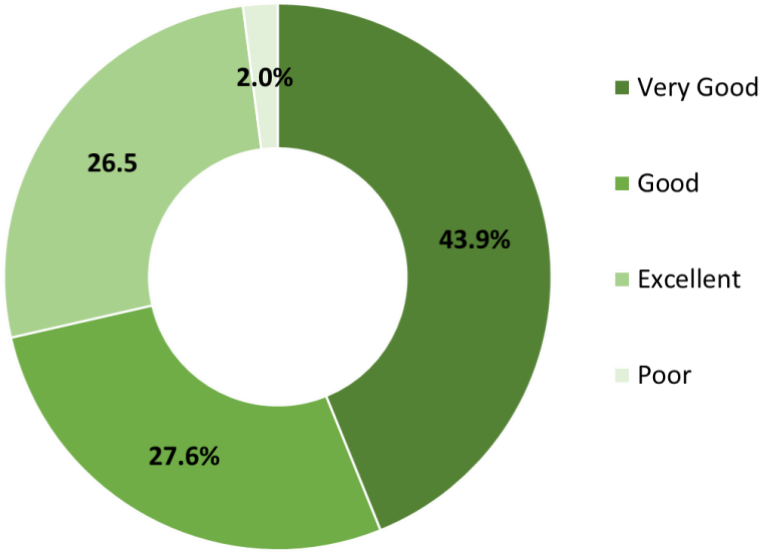
13. In your opinion, how is the long-term safety profile of Linagliptin 5mg + Metformin 1000mg combination?

A. Excellent

B. Very Good

C. Good

D. Poor



- About, 43.9% of physicians considered the long-term safety profile of the linagliptin 5 mg + metformin 1000 mg combination to be very good.
- Around, 27.6% of physicians considered the long-term safety profile of the linagliptin 5 mg + metformin 1000 mg combination to be good.
- Approximately, 26.5% of physicians rated the long-term safety profile of the linagliptin 5 mg + metformin 1000 mg combination as excellent.
- Only 2.0% of physicians rated the long-term safety profile of the linagliptin 5 mg + metformin 1000 mg combination as poor.

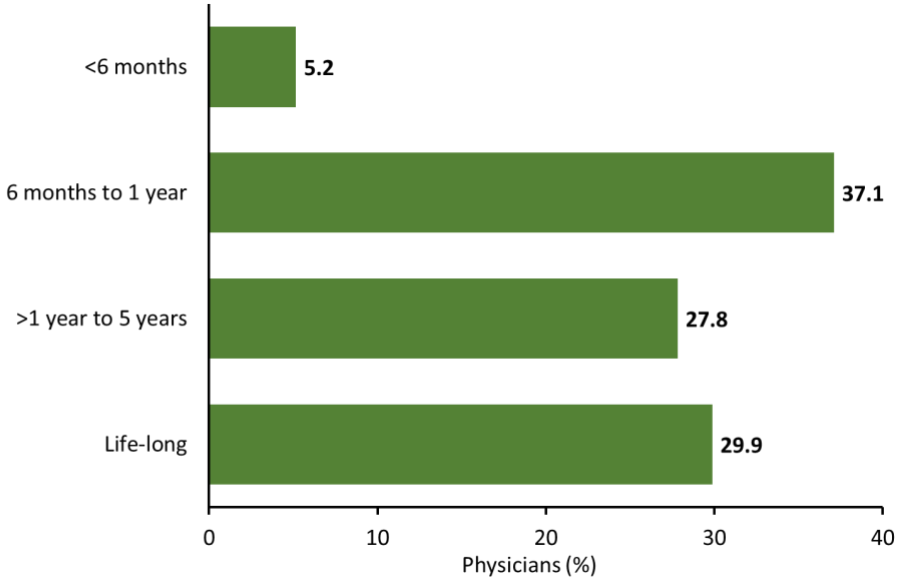
14. As per your opinion, what could be the average duration of Linagliptin 5mg + Metformin 1000mg combination therapy in patients with T2DM?

A. <6 months

B. 6 months to 1 year

C. >1 year to 5 years

D. Life-long



- Around 37.1% of physicians believed that the average duration of linagliptin 5 mg + metformin 1000 mg combination therapy would typically last from 6 months to 1 year.
- About 29.9% of physicians estimated that the average duration of linagliptin 5 mg + metformin 1000 mg combination therapy would be life-long for patients with T2DM. Approximately 27.8% of physicians believed that the average duration of linagliptin 5 mg + metformin 1000 mg combination therapy to continue for more than 1 year but less than 5 years.
- About 5.2% of physicians estimated that the average duration of linagliptin 5 mg + metformin 1000 mg combination therapy in patients with T2DM would be less than 6 months.

6 SUMMARY

The survey of physicians regarding the management of T2DM, several key findings emerged. The majority of physicians (52.0%) identified the need for combination therapy to address multiple pathophysiological mechanisms of hyperglycemia as the most significant unmet medical need in T2DM management. This was followed by 33.7% who emphasized the importance of treatments providing both glycemic and non-glycemic benefits due to the need to manage diabetes comorbidities. Only 10.2% prioritized reducing hypoglycemia or weight gain, while 4.1% focused on reducing cardiovascular risk. When it came to initiating combination therapy, 41.2% of physicians reported starting it in 26-50% of their patients, and 34.0% initiated it in 51-75% of their patients. A smaller proportion, 21.6%, began combination therapy in more than 75% of their patients, while 3.1% used it in less than 25% of their patients. Physicians also indicated that dual combination therapy was most often considered when HbA1c levels were between 7-9%, with 44.3% preferring this range.

Sitagliptin was the most preferred DPP-4 inhibitor for 69.8% of physicians, while 25.0% preferred Linagliptin, 5.2% preferred Vildagliptin, and none preferred Teneligliptin. Regarding Linagliptin's effectiveness, 44.3% of physicians considered it moderately effective, and 39.8% found it very effective for glycemic control. The preference for Linagliptin was primarily due to its proven safety across CKD in T2DM (45.9%) and its single daily dose convenience (39.8%). For Linagliptin and Metformin combination therapy, 81.6% of physicians had used it concomitantly, with 50.5% finding it most appropriate for patients with renal impairment and T2DM. In terms of strength, 65.3% preferred Metformin 500 mg combined with Linagliptin 5 mg. A higher dose of Linagliptin 5 mg + Metformin 1000 mg was seen as beneficial for better glycemic control (46.9%), better patient adherence (28.6%), and a lesser risk of hypoglycemia (24.5%).

In terms of patient profiles, 48.0% of physicians preferred the combination therapy for patients aged 40-60 years, while 36.7% found it suitable across all age groups, and 11.2% for those older than 60 years. The long-term safety profile of the combination therapy was rated as very good by 43.9%, good by 27.6%, and excellent by 26.5%, with only 2.0% rating it as poor. The average duration for the

combination therapy varied, with 37.1% of physicians expecting it to last 6 months to 1 year, 29.9% estimating it could be life-long, and 27.8% believing it would continue for more than 1 year but less than 5 years. Only 5.2% anticipated a duration of less than 6 months.

7 DISCUSSION

The survey revealed that physicians predominantly recognized the need for comprehensive combination therapies in managing T2DM, with a focus on addressing multiple aspects of hyperglycemia and related comorbidities. The preference for Sitagliptin as the leading DPP-4 inhibitor aligns with its established efficacy and safety profile. Linagliptin's perceived effectiveness and safety, especially in patients with CKD, highlight its role in complex cases. The high rate of usage of Linagliptin and Metformin combination therapy among physicians indicates its acceptance in clinical practice. The preference for Metformin 500 mg and the focus on better glycemic control and patient adherence reflect practical considerations in treatment regimens.

Age considerations and long-term safety evaluations show that physicians are balancing efficacy with safety and patient-specific factors. The varied anticipated duration of therapy underscores the individualized approach required in T2DM management. Overall, the data suggests a strong inclination towards therapies that offer comprehensive benefits and align with patient needs across different demographics.

8 CLINICAL RECOMMENDATIONS

- Combination Therapy as a Primary Need: Majority of physicians identified combination therapy as essential to address multiple pathophysiological mechanisms of hyperglycemia in T2DM patients. This suggests that clinical practice should prioritize therapies that target various aspects of diabetes management to achieve optimal glycemic control.
- Initiation of Combination Therapy: Physicians initiate combination therapy in 26-50% of their patients, indicating that a significant portion of practitioners recognize the need for combination therapy in a substantial subset of their patients. Practitioners should consider this approach for patients with moderate to severe hyperglycemia.
- HbA1c Thresholds for Therapy: Physicians would start dual combination therapy when HbA1c levels are between 7-9%, aligning with recommended practices for initiating more intensive treatment strategies in cases of inadequate glycemic control.
- Preference for DPP-4 Inhibitors: Physicians preferred Sitagliptin over other DPP-4 inhibitors, suggesting that it is the most trusted and effective option in current practice. Clinicians may consider Sitagliptin as a primary choice for patients requiring DPP-4 inhibitors.
- Effectiveness of Linagliptin: Physicians rated Linagliptin as either very effective or moderately effective for glycemic control, highlighting its role as a reliable therapeutic option.

9 CONSULTANT OPINION

Based on the survey data, regarding T2DM management, a clear emphasis emerges on the need for combination therapies to tackle the multifaceted nature of hyperglycemia. The majority of physicians (52.0%) highlight combination therapy as the most pressing unmet need, reflecting a consensus on the necessity of addressing various pathophysiological mechanisms to achieve comprehensive glycemic control. This is further supported by the 33.7% of physicians who stress the importance of treatments offering both glycemic and non-glycemic benefits, underscoring the broader goal of managing diabetes comorbidities. The survey indicates a significant preference for initiating combination therapy in a substantial proportion of patients, with 41.2% and 34.0% of physicians starting it in 26-50% and 51-75% of their patients, respectively. This reflects a proactive approach to managing complex cases of T2DM. When considering HbA1c levels, a majority prefer initiating dual combination therapy when levels are between 7-9%, aligning with established guidelines for intensifying treatment.

Sitagliptin is overwhelmingly favored (69.8%) as the preferred DPP-4 inhibitor, with Linagliptin also being a significant choice due to its proven safety profile in CKD and convenient dosing. The widespread use of the Linagliptin and Metformin combination (81.6%) highlights its established role in managing patients, particularly those with renal impairment, as indicated by 50.5% of physicians.

Regarding the combination’s dosage, 65.3% of physicians prefer Metformin 500 mg with Linagliptin 5 mg, although higher doses are valued for better glycemic control and adherence. Patient age does not significantly limit the therapy's applicability, with 48.0% of physicians recommending it for those aged 40-60 years. The long-term safety profile is largely viewed positively, with a majority rating it as very good to excellent. The anticipated duration of therapy varies, with many physicians expecting it to last from 6 months to life-long, reflecting its integral role in long-term T2DM management. Overall, these insights underscore the importance of individualized, multi-faceted treatment approaches in effectively managing T2DM.

10 MARKET OPPORTUNITIES

The survey reveals significant market opportunities in the management of T2DM, particularly concerning combination therapies and specific patient needs. A substantial majority of physicians (52.0%) emphasize the need for combination therapy to address multiple hyperglycemic mechanisms, highlighting a robust demand for integrated therapeutic solutions. The high preference for Sitagliptin (69.8%) indicates a strong market position for this DPP-4 inhibitor, while Linagliptin also shows notable interest due to its safety profile in CKD patients and convenience in dosing.

The considerable use of Linagliptin and Metformin combination therapy, reported by 81.6% of physicians, underscores a growing market for fixed-dose combinations, particularly for patients with renal impairment (50.5%). The preference for Metformin 500 mg combined with Linagliptin 5 mg (65.3%) suggests a targeted opportunity for formulations catering to this strength. Moreover, the recognition of benefits associated with higher doses of Linagliptin and Metformin for better glycemic control and patient adherence (46.9% and 28.6%, respectively) reflects potential for product differentiation.

The positive long-term safety profile ratings and varied duration expectations (ranging from 6 months to life-long) further support the development and marketing of durable and reliable diabetes management solutions. Addressing these insights can align products with the specific needs and preferences of healthcare providers and patients, creating a substantial market opportunity.

11 MARKET POSITIONING

- The need for combination therapy to address multiple pathophysiological mechanisms of hyperglycemia is a significant unmet medical need. This highlights a strong market opportunity for therapies that effectively target various aspects of diabetes management.
- Physicians commonly initiate combination therapy in a substantial proportion of their patients, with a notable frequency occurring in those with moderate to severe hyperglycemia. This indicates a robust market for combination therapies that can be integrated into standard treatment regimens.
- Dual combination therapy is primarily considered when HbA1c levels are elevated, reflecting an opportunity for products that can effectively manage higher levels of glycemic control.
- Sitagliptin is the most favored DPP-4 inhibitor among physicians, establishing it as a dominant product in the market. Linagliptin also has a significant share due to its perceived benefits, including safety across chronic kidney disease and convenience with a single daily dose.
- The combination of Linagliptin and Metformin is widely used, particularly in patients with renal impairment. The preference for Metformin 500 mg as the ideal strength for this combination highlights the need for tailored dosing options in the market.
- Higher doses of Linagliptin and Metformin are valued for their potential to improve glycemic control, patient adherence, and reduce the risk of hypoglycemia. This underscores the importance of offering combination therapies with optimized dosing strategies.
- The combination therapy is preferred for a broad age range, with a positive long-term safety profile reported by the majority. The duration of therapy varies, with expectations ranging from short-term to potentially life-long, suggesting flexibility in treatment plans.

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