MARKET RESEARCH ON PREFERENCE OF GLIPTINS IN TYPE 2 DIABETES MELLITUS

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

By

Deeksha Singh

Under the Supervision and Guidance of

Dr. Sudhinder Singh Chowhan

2024

MACLEODS

Date: 25th June, 2024

To,

Ms Deeksha Singh,

Dear Ms Deeksha Singh,

We are happy to share that you have completed your internship with us in our Domestic Business Department at our Head Office, Andheri.

The internship duration was of 3 months from 18th March, 2024 to 17th June, 2024.

We appreciate your sincerity and discipline displayed during the internship duration.

We wish you all the best.

For Macleod's Pharmaceuticals Limited.

Saidutta Nanda

President - HRD

Candidate name & sign

DEEKSHA SINGH

Accepted & acknowledged by

MACLEODS PHARMACEUTICALS LIMITED

Regd. Office :
Atlanta Arcade, Church Road,
Near Leela Hotel, Andheri-Kurla Road,
Andheri (East), Mumbai-400 059, India.

Phone : 91 - 22 - 6676 2800
Fax : 91 - 22 - 2925 6599
Email : customercare@macleodspharma.com
Website : www.macleodspharma.com
CIN : U24239MH1989PLC052049

DECLARATION BY STUDENT

I hereby declare that this dissertation titled **"Market Research on Preference of GLIPTINS in Type 2 Diabetes Mellitus"** is the Bonafede record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Deeksha

(Signature)

Name of Student: Deeksha Singh Deeksha

Date: 26 June, 2024

CERTIFICATE BY FACULTY GUIDE

This is to certify that dissertation titled **"Market Research on Preference of GLIPTINS in Type 2 Diabetes Mellitus"** is a record of the research work undertaken by **Deeksha Singh** in partial fulfilment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide

26/06/24

Dr. Sudhinder Singh Chowhan
IIHMR University, Jaipur

School Dean

26/6/2024

Dr. Saurabh Kumar Banerjee
IIHMR University, Jaipur

Date: June 26, 2024

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141-3924700, 2791431- 32, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

CONTENTS

CERTIFICATE BY ORGANIZATION

MACLEODS

Date: 25th June, 2024

To,

Ms Deeksha Singh,

Dear Ms Deeksha Singh,

We are happy to share that you have completed your internship with us in our Domestic Business Department at our Head Office, Andheri.

The internship duration was of 3 months from 18th March, 2024 to 17th June, 2024.

We appreciate your sincerity and discipline displayed during the internship duration.

We wish you all the best.

For Macleod's Pharmaceuticals Limited.

Saidutta Nanda

President - HRD

Candidate name & sign

DEEKSHA SINGH

Accepted & acknowledged by

MACLEODS PHARMACEUTICALS LIMITED

Regd. Office :
Atlanta Arcade, Church Road,
Near Leela Hotel, Ancheri-Kurla Road,
Andheri (East), Mumbai-400 059, India.

Phone : 91 - 22 - 6676 2800
Fax : 91 - 22 - 2925 6599
Email : customercare@macleodspharma.com
Website : www.macleodspharma.com
CIN : U24239MH1989PLC052049

DECLARATION BY STUDENT

I hereby declare that this dissertation titled **"Market Research on Preference of GLIPTINS in Type 2 Diabetes Mellitus"** is the Bonafede record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

(Signature)

Name of Student: Deeksha Singh

Date:

CERTIFICATE BY FACULTY GUIDE

This is to certify that dissertation titled **"Market Research on Preference of GLIPTINS in Type 2 Diabetes Mellitus"** is a record of the research work undertaken by **Deeksha Singh** in partial fulfilment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide IIHMR University, Jaipur

School Dean IIHMR University, Jaipur

Date:

ACKNOWLEDGEMENT

My sincere appreciation goes out to the administration of **Macleods Pharmaceuticals Ltd**, Mumbai, for granting me an opportunity to undergo Dissertation in their esteemed organization. I, hereby also take the opportunity to thanks my organizational mentor Mr. Sandeep Mane Sir who has given me this golden opportunity to get trained at Macleods Pharmaceuticals Ltd. without his active supervision, assistance and encouragement, I would not have made progress in this project. I express my deepest thanks to my mentor Dr. Sudhinder Singh Chowhan Sir and our Dean Dr. Saurabh Banerjee Sir for their guidance and advice which were enormously helpful for my training both theoretically and practically. My sincere thanks to Vinod Tejwani Sir and the Placement Committee team for coordinating the Dissertation and helping us in all possible way. Throughout my dissertation journey, I learned a great deal about many facets of the project and gained a great deal of experience and knowledge that will be useful to me in the future in my work. I'll work to make the most use of the knowledge and abilities I've gained.

.

Deeksha Singh

ABSTRACT

TITLE: Market Research on Preference of GLIPTINS in Type 2 Diabetes Mellitus

AUTHOR NAME: Deeksha Singh

KEYWORD: Market Research, Diabetes, Gliptins, DPP4 Inhibitors.

OBJECTIVE:

i. To Identify the Preference of Gliptins by the Doctors in T2DM.
ii. Based on Different Combinations and patient's portfolio, identify the needs of the Doctors and their Patients.

INTRODUCTION: Gliptins are a notable class of pharmaceutical medicines that have been developed in order to curb the

emerging issues surrounding type 2 diabetes mellitus (T2DM). This study aims at collecting experts'

perspectives about gliptins use in type 2 diabetes through conducting a comprehensive market research survey.

The purpose of the study is to get further insight into the variables that influence the choice of gliptins, such as vildagliptin, linagliptin, and sitagliptin, by endocrinologists, diabetologists, and general practitioners. Among the variables that will be considered are patient comorbidities, renal function, Hypoglycemia risk, cardiovascular profile, weight considerations, and overall views of drug efficacy and safety.

ABOUT THE ORGANIZATION

Worldwide pharmaceutical operations are carried out by Macleods Pharmaceuticals Ltd. The company creates, produces, and distributes a broad variety of pharmaceutical products in numerous important therapeutic areas, such as dermatological, anti-diabetic, cardiovascular, and hormone therapy.[1]

Vision

Our vision is to be a leading global pharmaceutical company by providing high quality, affordable and innovative therapeutic solutions for patients with diverse medical needs.[1]

Mission

To contribute towards improving patients' quality of life across the globe, by providing effective and accessible medicines. [1]

Methodology

Research Design

➤ Type of Research Design

The market survey undertaken is an example of a descriptive research since the overall research design is rigid and pre-planned all throughout our study.

➤ Research Tool

Structured Questionnaire is used and framed in a way so as to derive maximum information from the Consultant Physicians, Endocrinologists, Diabetologists, Cardiologists of Jaipur regarding Preference of Gliptins used in Diabetes.

➤ Data Collection Method

.

Primary Data Collection

- Data was collected through means of a structured questionnaire. The structured questionnaire was designed covering only open ended and questions.
- It was aimed to derive maximum information from the Consultant Physicians, Endocrinologists, Diabetologists, Cardiologists of Jaipur

Secondary Data Collection

Data was also collected from various sites on the internet, the sources are mentioned in the reference section.

Sample Size

100 Consultant Physicians, Endocrinologists, Diabetologists, Cardiologists of Jaipur

➤ Time Period of Project

3 months

➤ Data Analysis Technique

The data was compiled and analyzed in the Microsoft Excel.

What is Diabetes?

Hyperglycaemia, or elevated blood sugar, is one of the strongest indications of diabetes mellitus: a chronic metabolic disease, that results from defective insulin secretion by the pancreas or an alteration in insulin action within cells. As mentioned, insulin is one hormone that controls blood sugar (glucose) levels. [2]

Types of Diabetes:

T1D for type 1 diabetes

- caused when the immune system mistakenly kills the beta cells in the pancreas that make insulin.
- Requires continuous insulin treatment to survive
- Patients are usually diagnosed as young adults and children.

Type 2 Diabetes (T2D),

- The development of type 2 diabetes is caused by a gradual loss of the ability to produce sufficient insulin,
- due to the body becoming resistant to insulin.Often associated with lifestyle variables like genetic constitution,

3. Gestational Diabetes:

a. Occurs during pregnancy and usually resolves after childbirth.

b. Raises the likelihood that both the mother and the child may experience type 2 diabetes in later life.

Common Signs and Symptoms

1. People with diabetes pretty much all have the same symptoms, but depending on who you ask, there are different signs and symptoms of diabetes mellitus. Here are the common warning signs and symptoms of diabetes:
2. Polyuria (urinating more often): This happens when the kidneys are working harder to filter out the extra blood sugar, resulting in more urine being produced. This leads to frequent urination and especially at night (nocturia).
3. Unintended Weight Loss: Without insulin, the body begins to break down muscle and fat for energy which can result in weight loss in type 1 diabetics whereas they eat more.
4. Fatigue: A nonfunctioning body to use glucose for fuel can cause feelings of little to no energy.
5. Vision is finding blurry: Big shifts in your blood sugar stages may purpose short periods fizziness.
6. Polydipsia (Excessive Thirst): o The body experiences increased thirst as a means of replacing fluids lost through excessive urine.
7. Polyphagia (Excessive Hunger): People with diabetes may experience hunger even after eating because their bodies are unable to efficiently use glucose as fuel.
8. Slow Wound Healing: Elevated blood sugar can compromise immune system function and circulation, which can cause wounds, ulcers, and cuts to heal more slowly.
9. Recurrent Infections: People with high blood sugar are more prone to infections, especially skin and urinary tract infections, as it might impair immunity.

Additional Symptoms in Type 1 Diabetes:

- **Sudden Onset:** Type 1 diabetes often presents with sudden symptoms over a short period.

Ketoacidosis: Untreated type 1 diabetes in severe situations can result in diabetic ketoacidosis (DKA), It is defined by breath that smells like fruit, nausea, vomiting, and stomach pain.

Extra Diagnoses of Type 2 Diabetes:

- **Gradual Onset:** Type 2 diabetes symptoms may develop gradually over time and may be less pronounced initially.
- **Hyperosmolar Hyperglycemic State (HHS):** In severe cases, untreated type 2 diabetes can lead to HHS, characterized by extreme dehydration, confusion, seizures, and coma.[2]

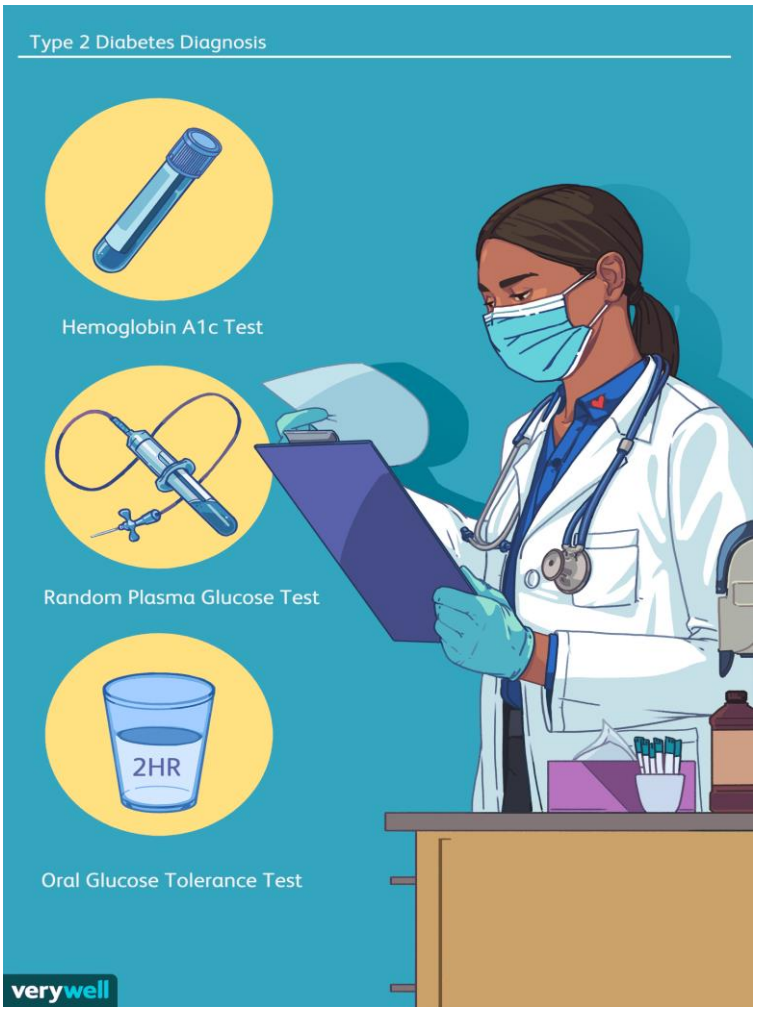
How is diabetes type 2 diagnosed?

Your healthcare professional can diagnose Type 2 diabetes with the help of the blood tests described below:

In a lab environment, the fasting plasma glucose test determines your blood sugar levels. Usually, this test is planned for the morning after an eight-hour fast, during which you only consume water. You have diabetes if your result is 126 mg/dL or above.

Test for plasma glucose at random: This is a lab test that may be obtained at any time that measures blood sugar levels without the need for fasting. You have diabetes if your result is 200 mg/dL or higher.

Your blood sugar levels over the last two to three months are averaged and calculated by the A1C test. You have diabetes if your score is 6.5% or over. [3]



Medications in Diabetes

Drugs used to treat diabetes mellitus fall into a number of types, each of which focuses on a distinct area of insulin and glucose metabolism. The following are the primary drug types used:

1. Oral Antidiabetic Medications:

These oral medicines are frequently utilised in the management of type 2 diabetes. Among them are:

- **Biguanides, such as Metformin:**
  o Mechanism: Enhances insulin sensitivity in peripheral tissues and reduces the synthesis of glucose by the liver.
  o Advantages: Low risk of hypoglycemia, often weight-neutral or may result in a small amount of weight loss [4]
- **Sulfonylureas, like Glipizide and Gliclazide**, work by encouraging the pancreatic beta cells to secrete insulin.
  o Benefits: Effective at lowering blood sugar, but may raise the chance of hypoglycemia and cause weight gain.
  • **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**: Saxagliptin and Sitagliptin o Mechanism: Increases insulin release and suppresses glucagon release by prolonging the action of incretin hormones (GLP-1 and GIP).
- Advantages: Low risk of hypoglycemia, weight-neutral
  - .
- **SGLT-2 Inhibitors (e.g., Empagliflozin, Canagliflozin):**
  - Mechanism: Inhibits SGLT-2 transporter in the kidneys, reducing reabsorption of glucose and increasing glucose excretion in urine.
  - Benefits: Can lead to weight loss, lower blood pressure, and cardiovascular benefits. May increase risk of urinary tract infections and genital fungal infections.
- **Thiazolidinediones (e.g., Pioglitazone, Rosiglitazone):**
  - Mechanism: Improves insulin sensitivity in peripheral tissues (muscle, fat, liver) by activating peroxisome proliferator-activated receptor gamma (PPAR-gamma).
  - Benefits: Effective in improving insulin sensitivity, but may cause weight gain and fluid retention. Use is limited due to potential cardiovascular risks.[4]

2. Injectable Medications:

These medications are administered via injection and are used in both type 1 and type 2 diabetes:

• Insulin (various varieties, including long-acting, intermediate-acting, short-acting, and rapid-acting):

- Mechanism: directly substitutes or enhances the body's natural production of insulin to regulate blood sugar levels.
- Benefits: Essential for type 1 diabetes and often used in type 2 diabetes when other medications are insufficient.

- **GLP-1 Receptor Agonists (e.g., Liraglutide, Dulaglutide):**
  - Mechanism: Mimics the action of GLP-1, stimulating insulin secretion, inhibiting glucagon release, and delaying gastric emptying.
  - Benefits: can result in cardiovascular advantages, lowered blood pressure, and weight loss. May cause gastrointestinal side effects.[4]

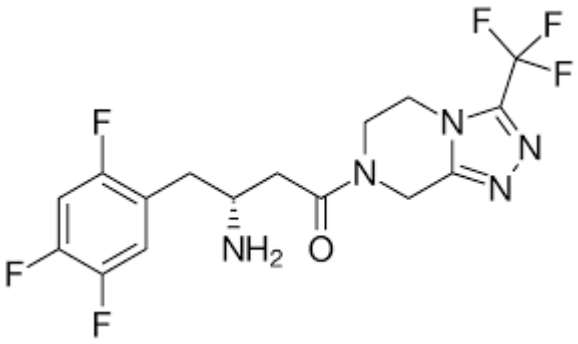
3. Other Medications:

- **Amylin Analog (e.g., Pramlintide):**
  - Mechanism: Mimics the action of amylin, a hormone that slows gastric emptying, suppresses glucagon secretion, and reduces postprandial glucose levels.
  - Benefits: Helps control postprandial glucose levels. Used as an adjunct to insulin therapy.
- **Meglitinides (e.g., Repaglinide, Nateglinide):**
  - Mechanism: Stimulates insulin secretion from pancreatic beta cells, similar to sulfonylureas but with a shorter duration of action.
  - Benefits: Rapid onset of action with a shorter duration, useful for controlling postprandial glucose spikes.[4]

Gliptins

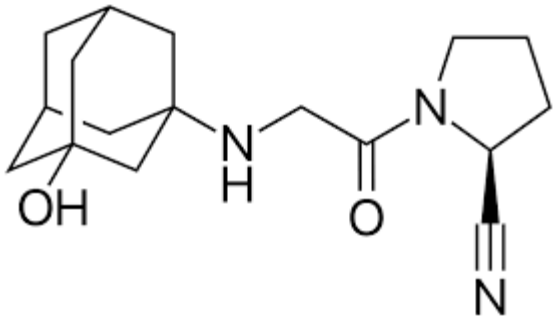
An oral medication class called gliptins is used to treat type 2 diabetic mellitus (T2DM). The term Dipeptidyl Peptidase-4 (DPP-4) inhibitors is frequently used to describe gliptins. They function by stopping the DPP-4 enzyme from functioning, which causes glucagon-like peptide-1, or GLP-1, levels to rise. This process improves blood sugar regulation by increasing insulin secretion and lowering glucagon levels. There is a minimal chance of hypoglycemia and weight gain with gliptins, and they are usually well tolerated. They are frequently taken either by itself or in conjunction with other antidiabetic drugs like metformin. [5]

Sitagliptin



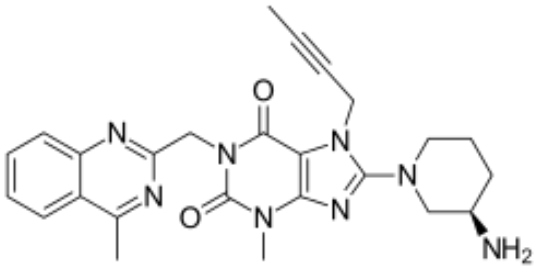
One of the DPP-4 inhibitors that is most frequently used is sitagliptin. It works to reduce blood sugar by supporting the body's natural capacity to control glucagon and insulin levels after meals. Usually taken once daily, sitagliptin can be used alone or in conjunction with other medications that reduce blood sugar levels. Based on clinical research, sitagliptin is generally well tolerated and has a low rate of adverse effects. Though this danger is still being investigated, several findings have indicated a potential link with an elevated risk of pancreatitis.[5]

Vildagliptin



Another DPP-4 inhibitor used to treat type 2 diabetes is vildagliptin. By releasing more insulin and secreting less glucagon, it aids in blood sugar regulation. Vildagliptin can be taken in addition to other antidiabetic drugs and is typically given twice daily. When taken by itself, it is usually well tolerated and does not result in hypoglycemia or weight gain like other gliptins. Though the evidence is inconclusive, there have been concerns over a possible relationship to pancreatitis, similar to sitagliptin. [5]

Linagliptin



Unlike other DPP-4 inhibitors in its family, linagliptin is mainly eliminated unaltered through the bile and stomach instead of the kidneys. Because of this, linagliptin is especially appropriate for those with renal impairment. Linagliptin is a once-daily medication that effectively lowers blood glucose levels when used alone or in conjunction with other antidiabetic medications. Additionally, it has a reduced risk of hypoglycemia and is well tolerated. Patients with kidney problems frequently choose linagliptin because of its distinct excretion pathway.[5]

Mechanism of Action

Gliptins, sometimes referred to as Dipeptidyl Peptidase-4 (DPP-4) inhibitors, enable people with type 2 diabetes mellitus (T2DM) better regulate their blood sugar levels by altering incretin hormones. This is a detailed explanation of how gliptins work:

DPP-4 Enzyme Inhibition: Gliptins work by inhibiting the DPP-4 enzyme, which breaks down incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and glucose-dependent insulinotropic polypeptide (GIP).

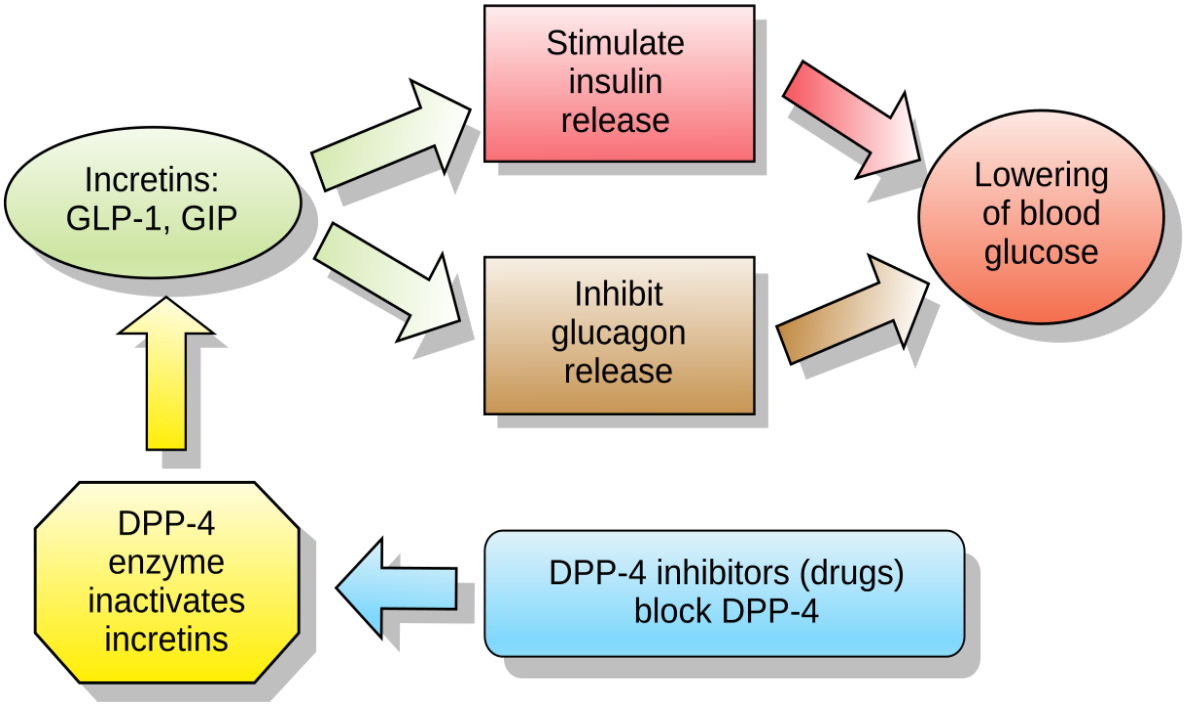
.

Elevated Incretin Levels: Gliptins raise the blood levels of active GLP-1 and GIP by blocking DPP-4. The intestines release these hormones in reaction to food consumption.

Enhanced Insulin Secretion: In a glucose-dependent way, elevated levels of GLP-1 and GIP stimulate the pancreatic beta cells to release insulin. This lowers the risk of hypoglycemia by enhancing insulin secretion solely in response to elevated blood glucose levels.

Diminished Secretion of Glucagon: GLP-1 also inhibits the pancreatic alpha cells' ability to secrete glucagon. By inducing the liver to release stored glycogen into glucose, the hormone glucagon increases blood glucose levels. Decreased hepatic glucose synthesis is the outcome of lower glucagon levels.

Increased Insulin and Decreased Glucagon Together Help Lower Blood Glucose: Insulin and dextrose work together to lower blood glucose, especially postprandial glucose levels during meals.[5]


Stimulate insulin release
Incretins: GLP-1, GIP
Lowering of blood glucose
Inhibit glucagon release
DPP-4 enzyme inactivates incretins
DPP-4 inhibitors (drugs) block DPP-4

Literature Review

K. Gooßen et al (2012): DPP-4 inhibitors, which are oral drugs for type 2 diabetes, show promise in slowing the disease's progression, though their long-term safety remains uncertain. A thorough analysis of randomised controlled trials assessed the safety of long-term DPP-4 inhibitor use. The review included double-blind trials of at least 18 weeks, incorporating 67 studies on various DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin). Adverse events were comparable to placebo, with no significant increase in infection risk. However, there were observed risks of asthenia, cardiac, and vascular disorders. The risk of Hypoglycemia was generally low, except when combined with sulphonylurea or insulin, which significantly increased the risk. The findings support the long-term safety of DPP-4 inhibitors but suggest more research is needed on specific adverse effects and recommend careful selection of agents in combination treatments. [14]

Nicolas Paquot et al (2012): Gliptins, commonly known as inhibitors of dipeptidyl peptidase-4 (DPP-4) offer a special method of treating type 2 diabetes. Unlike other oral diabetes medications, glucagon-like peptide-1 (GLP-1) inhibitors increase blood levels of GLP-1 by blocking the enzyme that breaks it down. Linagliptin, like other DPP-4 inhibitors such as sitagliptin, vildagliptin, saxagliptin, and alogliptin, enhances glucose regulation by raising postprandial insulin secretion and lowering glucagon secretion. Among other oral diabetic drugs, these inhibitors can be administered with or without metformin, sulphonylureas, thiazolidinediones, or even insulin.[15]

Anne Zanchi et al (2012): Patients with diabetes are prone to early decline in kidney function, necessitating annual monitoring of kidney function. The glomerular filtration rate (GFR) can drop below 60 ml/min, which can alter how the body processes antidiabetic medications. When renal impairment is present, the risk of Hypoglycemia from glinides and sulfonylureas therapies is higher. The majority of sulfonylureas ought to be stopped when the GFR falls below 60 ml/min. Certain glinides, most notably repaglinide, may be administered after this, particularly to dialysis patients. If there are no additional health concerns, metformin can be continued at lower dosages until a GFR of 45 ml/min; nevertheless, it should be discontinued during bouts of dehydration or when receiving nephrotoxic medications, such as contrast dye for imaging studies. Glitazones may exacerbate fluid retention in patients with kidney problems. The pharmacokinetics of all DPP-4 inhibitors, except for linagliptin, are altered in renal impairment. Sitagliptin, saxagliptin, and linagliptin are the only DPP-4 inhibitors recommended for use in advanced kidney disease, although their

use remains limited by experience. GLP-1 agonists are not suitable for patients with moderate to severe kidney disease.[17]

Andre Scheen et al (2013): Patients with diabetes have been found to have a higher incidence of pancreatitis than people without the disease. Sitagliptin and vildagliptin have been linked to pancreatitis in a number of clinical cases, and FDA records indicate that sitagliptin has a higher relative risk than other therapies, while bias in reporting cannot be completely ruled out.

However, none of the five commercially available DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin) have demonstrated an elevated risk of acute pancreatitis in relatively short-term clinical trials with carefully chosen diabetic individuals.

Cohort studies conducted in the real world have also shown no increased risk of pancreatitis when using gliptins in comparison to other glucose-lowering drugs; however, a case-control study has recently called into doubt these results. Post-marketing surveillance programmes and ongoing large-scale trials with an emphasis on cardiovascular outcomes are required to validate these findings.[20]

Avivit Cahn Et al (2013): This study concludes that the Gliptins are an alternative second-line treatment after metformin, known for being well tolerated and having a low risk of causing Hypoglycemia. Although different gliptins have varying pharmacokinetic and pharmacodynamic properties, their overall clinical effectiveness is similar. The differences among them mainly arise from their safety profiles and side effects, rather than their ability to lower blood sugar. The currently available gliptins have optimized the clinical benefits of DPP-4 inhibition, and new gliptins in development are expected to be equally effective. Two gliptins in late-stage development are designed for once-weekly dosing, which may improve patient adherence. Additionally, individual gliptins are being tested for use in specific diabetes subpopulations, including type 1 diabetes patients and adolescents.[8]

André J. Scheen (2013): The article concludes that gliptins, or DPP-4 inhibitors, are a novel class of oral drugs for the treatment of type 2 diabetes. They show potential cardiovascular benefits through both GLP-1 dependent and independent pathways. By increasing the concentration of various peptides, DPP-4 inhibitors might offer cardioprotective effects. Clinical research shows that these medications improve blood pressure, improve lipid metabolism after meals, lower inflammation and oxidative stress, increase endothelial function, improve blood glucose control, especially post-meal glucose levels, and are often weight-neutral or slightly weight-loss causing. Further study is necessary, however some studies indicate that they might help

people with heart failure or ischemic heart disease. Phase II–III trial post-hoc studies show a tendency for gliptins to be associated with a lower incidence of major cardiovascular events when compared to other medications or placebos. Nevertheless, conclusive proof is still required to associate DPP-4 inhibition with better cardiovascular outcomes. Extensive clinical trials are being conducted to evaluate these cardiovascular consequences in individuals with high-risk diabetes.[11][12]

Harikrashna B. Bhatt et al (2015): The study found that non-alcoholic fatty liver disease (NAFLD) is highly prevalent in individuals with type 2 diabetes mellitus (T2DM) due to the prevalence of obesity and insulin resistance in this population. NAFLD must be differentiated from glycogen hepatopathy, which is more prevalent and can result in hepatomegaly and impaired liver function in type 1 diabetes mellitus (T1DM). NAFLD can also present in T1DM. For obese patients with diabetes, diet- and exercise-induced weight loss has shown promise in both controlling and preventing non-alcoholic fatty liver disease (NAFLD). NAFLD in people with type 2 diabetes can also be reversed by bariatric surgery, and the effects of recently approved weight-loss drugs on the onset and course of NAFLD should be investigated. There is little proof that some medications used to control blood sugar.[18]

Ricardo Godinho et al (2015): From the study we found that Incretin-based treatments, particularly DPP-4 inhibitors (gliptins), represent recent advancements in managing type 2 diabetes (T2DM). These treatments target high postprandial blood sugar, aberrant gastric emptying, excessive glucagon release, and maybe dysfunctional pancreatic β cells, among other T2DM-related problems. DPP-4 inhibitors correct the "incretin defect" observed in T2DM patients by raising GLP-1 levels, which effectively regulates blood sugar levels with a low risk of Hypoglycemia and other side effects. However, there is currently no proof linking DPP-4 inhibitors to pancreatitis. Studies suggest that DPP-4 inhibitors may safeguard pancreatic function by inhibiting apoptosis and encouraging β cell proliferation. Furthermore, they might offer protective benefits for the heart, kidneys, and retina. This review examines the advantages and challenges of DPP-4 inhibitors, proposing that they could become a leading therapy for T2DM by modifying the disease's course and mitigating complications such as nephropathy, retinopathy, and cardiovascular problems. [13]

Khosro Keshavarz et al (2017): 32 studies totaling 13,747 patients were included in this network meta-analysis. The distributions of the studies were as follows: Linagliptin versus placebo (n = 8), Sitagliptin versus placebo (n = 13), Linagliptin plus metformin versus placebo plus metformin (n = 4), and Sitagliptin plus metformin versus placebo plus metformin (n = 7). Regarding critical safety and efficacy measures, such

as changes in body weight and HbA1c from baseline, the percentage of patients reaching HbA1c levels below 7%, and the incidence of Hypoglycemic events, the results showed no significant differences between linagliptin and sitagliptin ($p > 0.05$). As a result, both medication combinations' efficacy was equivalent.[19]

Lesley J. Scott (2017): This review emphasises on Sitagliptin, known by various brand names such as Januvia and Xelevia, is a DPP-4 inhibitor used in over 130 countries to treat type 2 diabetes (T2D) either alone or with other blood sugar-lowering medications. It has proven effective across a wide range of T2D patients, including those who are obese, older, have kidney issues, or existing heart disease. Generally well tolerated, sitagliptin causes mainly mild to moderate side effects, leading to few discontinuations. It does not raise the risks of hypoglycemia or weight gain. In the TECOS cardiovascular safety study, it was shown to be as safe as a placebo concerning major heart events and did not increase heart failure hospitalizations. There has been significant discussion regarding the possible dangers of pancreatitis and pancreatic cancer with comparable therapies, but no clear cause has been identified. With its easy once-daily oral dosage, minimal drug interaction potential, and strong efficacy and safety, including heart safety, sitagliptin remains a key treatment for T2D.[6][7]

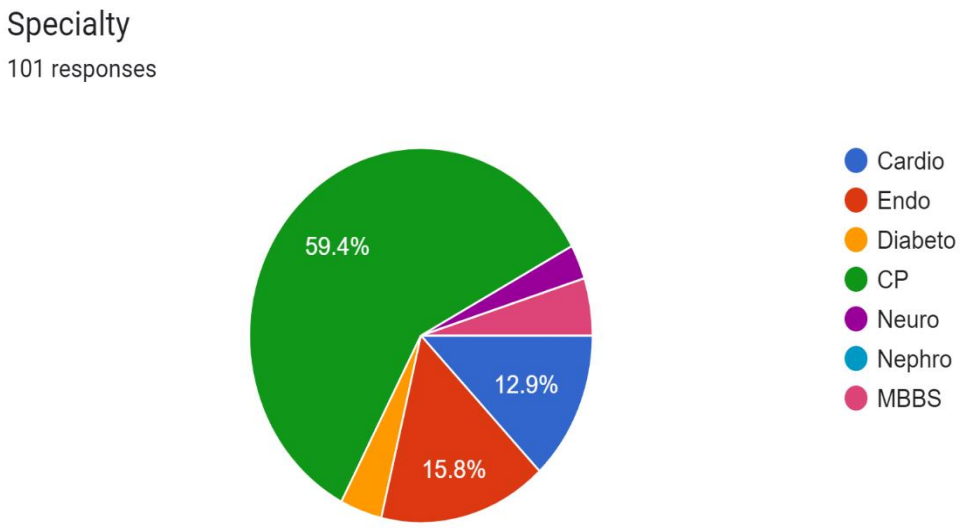
André Jacques Scheen Et al (2018): From the Study we concluded that with no gastrointestinal side effects, little risk of Hypoglycemia, and no tendency to cause weight gain, DPP-4 inhibitors are generally well tolerated. Though this adverse event was uncommon and absent from several observational studies comparing DPP-4 inhibitor users to nonusers, a small increase in acute pancreatitis was observed in cardiovascular outcome trials. Phase III trial meta-analyses and three sizable placebo-controlled studies have demonstrated cardiovascular safety Observational studies suggest that patients with type 2 diabetes may have better cardiovascular outcomes if they use DPP-4 inhibitors rather than sulphonylureas or other glucose-lowering drugs. No further clinical trials or observational studies have corroborated the higher risk of heart failure associated with saxagliptin, as reported in a single research. Research is needed to ascertain the frequency and underlying reasons of recently reported side effects, such as arthralgia.[9][10]

Marta Olivares et al (2024): The relationship between host metabolic health and gut microbiota is becoming more widely recognised, particularly in relation to the therapy of type 2 diabetic mellitus (T2DM). Gliptins, or dipeptidyl peptidase 4 (DPP4) inhibitors, are frequently used to treat type 2 diabetes, yet little is known about how they interact with the gut flora. This work employed computational methods to examine

the binding affinities of several gliptins to DPP4-like homologs generated by gut bacteria. Using computer modelling, we approximated the three-dimensional (3D) structures of DPP4 homologs from gut microbiota species, including Segatella copri, Bacteroides uniformis, Alistipes sp., and Phocaeicola vulgatus. Next, in order to confirm that these anticipated structures were stable, we ran 200 ns of molecular dynamics simulations. Using molecular docking, the stable structures were utilised to forecast binding interactions with recognised gliptins.[16]

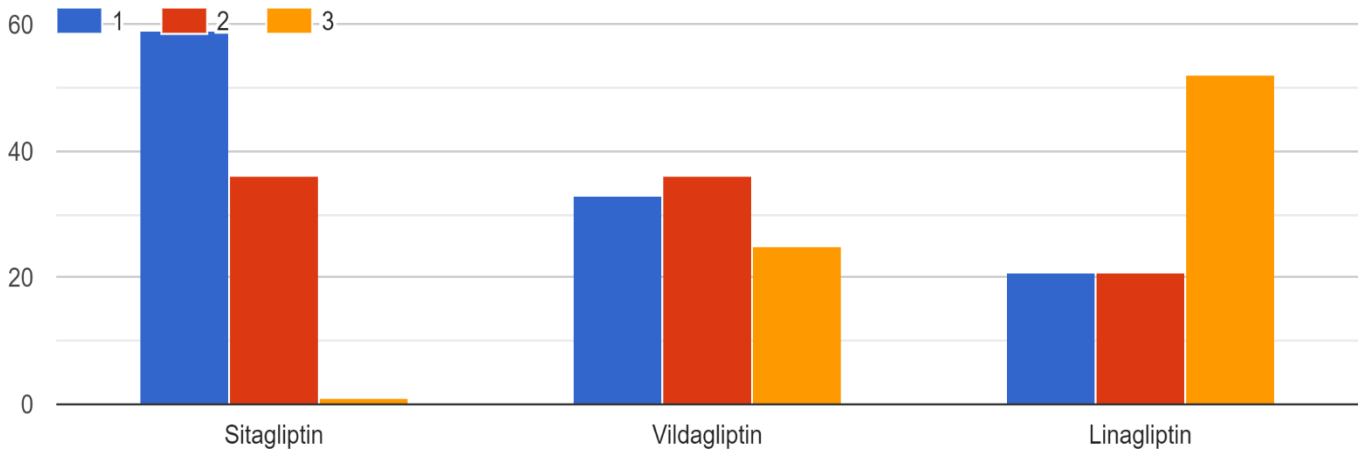
Survey Analysis

“Market Research on preference of GLIPTINS in Type 2 Diabetes Mellitus”



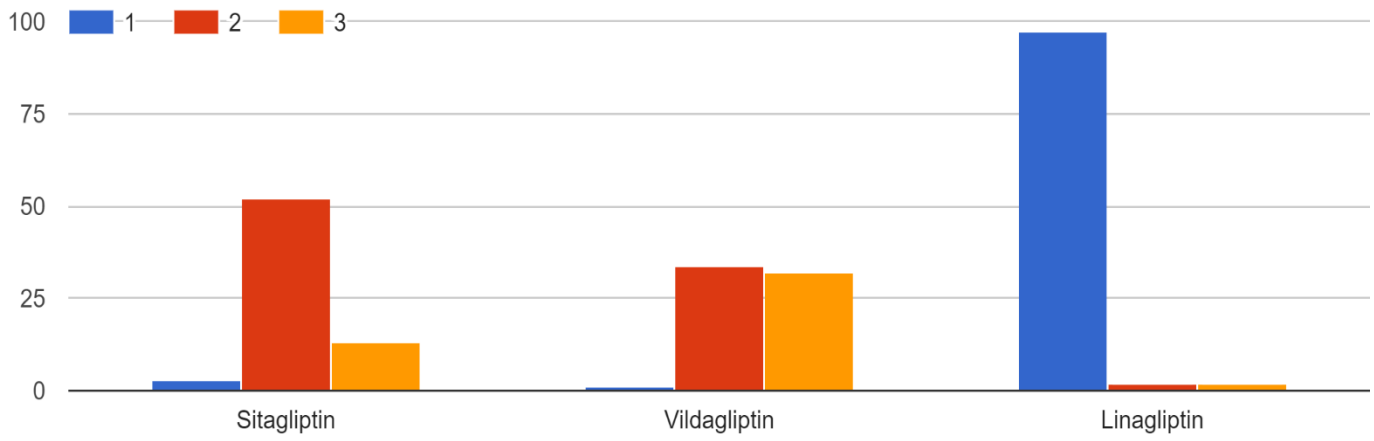
The Survey Covered almost 59% of Consultant Physicians, 15.8% of Endocrinologist, 12.9% of Cardiologist.

1. Which Gliptin do you prefer as the first choice for T2DM, followed by the second and third choices?



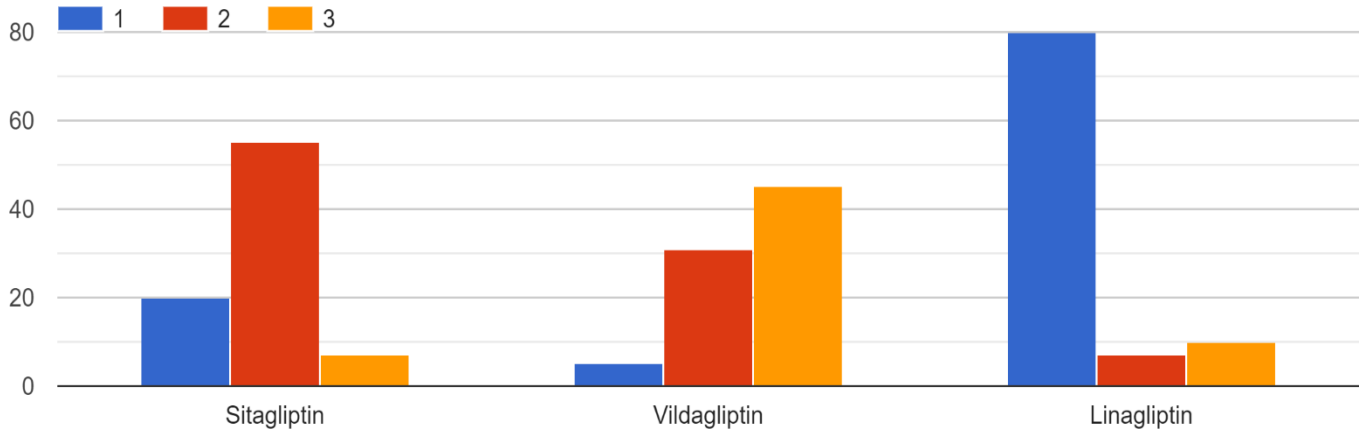
After asking doctors that which gliptin they preferred for T2DM, majority of them chose Sitagliptin as their 1st choice, then Vildagliptin as their 2nd choice and then Linagliptin as

2. Among Gliptins, what is your preferred choice during worsening renal function in the sequence of 1st to 3rd?



After asking doctors that which gliptin they preferred during worsening renal function for T2DM, majority of them chose Linagliptin as their 1st choice, then Sitagliptin as their 2nd choice and then Vildagliptin as their 3rd choice.

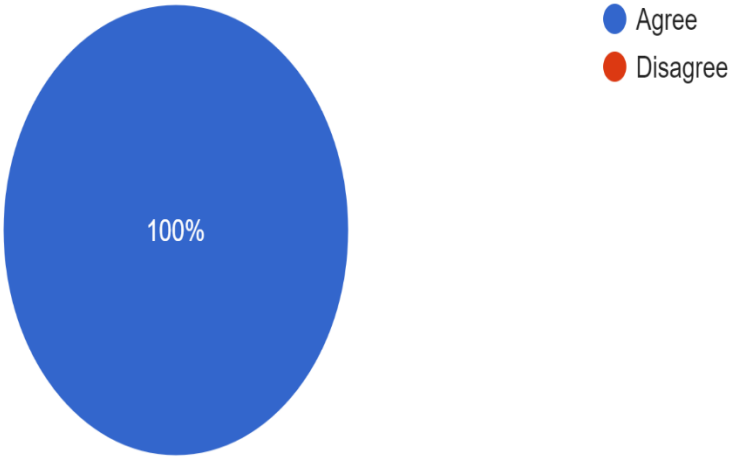
3. Among Gliptins, what is your preferred choice during hepatic impairment in the sequence of 1st to 3rd?



After asking doctors that which gliptin they preferred during hepatic impairment for T2DM, majority of them chose Linagliptin as their 1st choice, then Sitagliptin as their 2nd choice and then Vildagliptin as their 3rd choice.

4. In your practice is there a shift in prescription from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin?

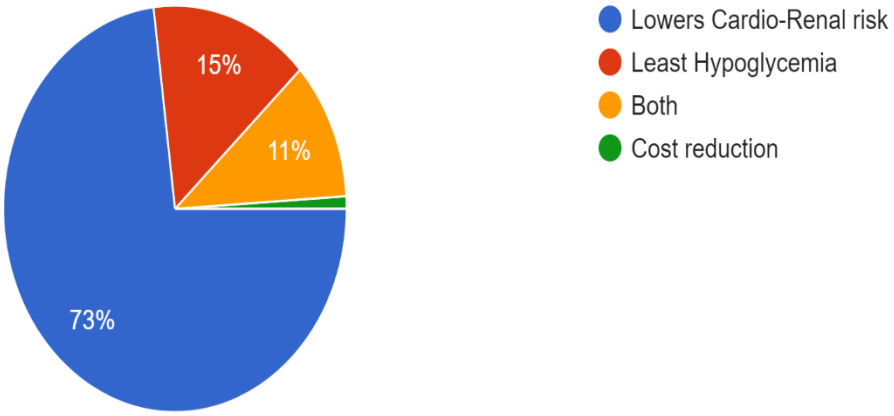
100 responses



Almost all Doctors agreed that there is a shift in prescription from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin.

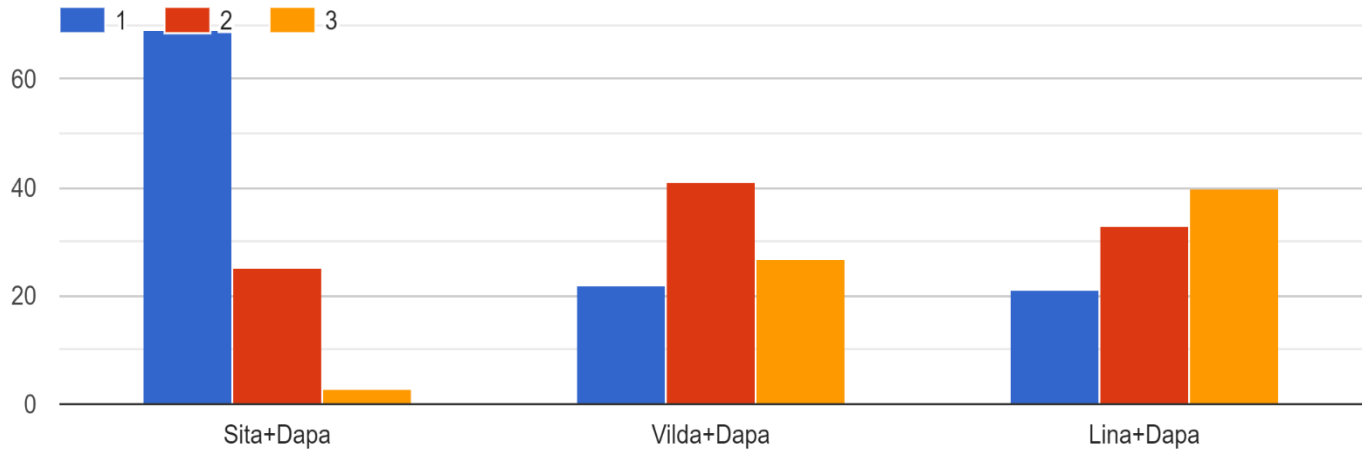
5. What is the main reason to shift Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin?

100 responses



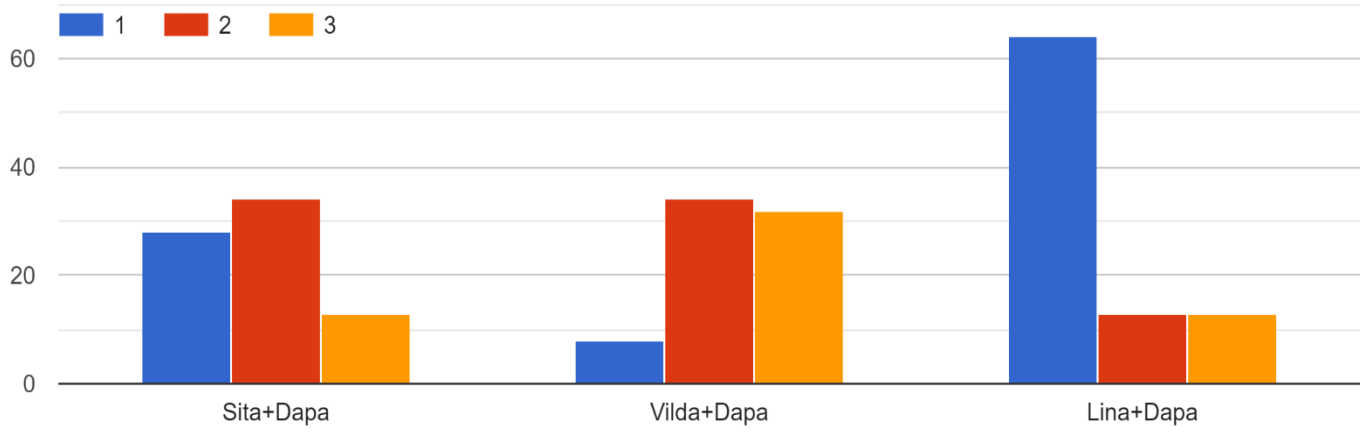
73% Doctors believes that the main reason to shift from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin is Lower Cardio-Renal risk and 15% Doctors believes it is least Hypoglycemia and 11% believes it is both.

6. In SGLT2i+DPP4i combination, what is your preferred choice for T2DM to prolong treatment failure in the sequence of 1st to 3rd?



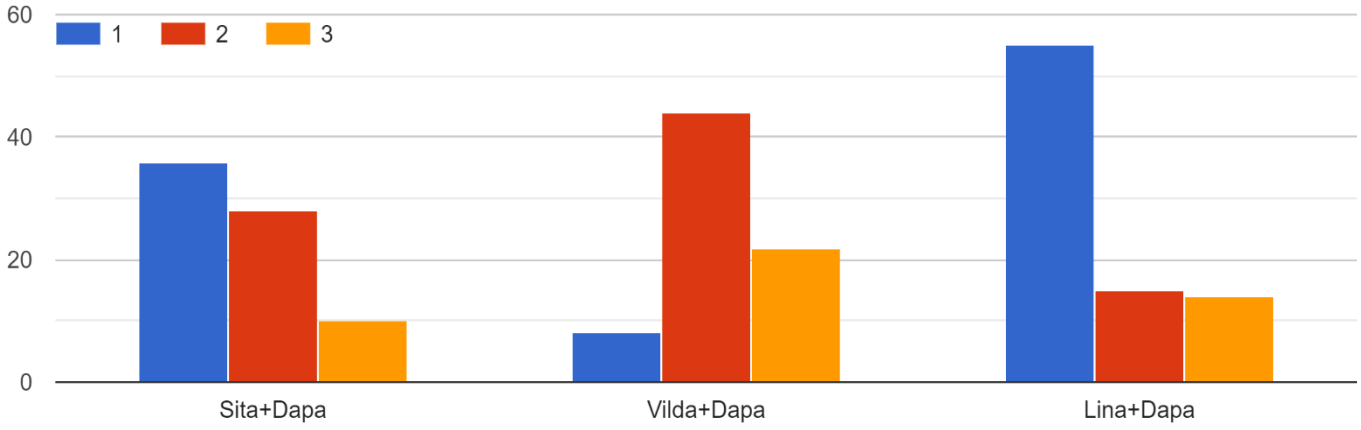
According to the doctors their 1st preference was Sita+Dapa, then 2nd preference was Vilda+Dapa, then 3rd preference was Lina+Dapa.

7. In SGLT2i+DPP4i combination, what is your preferred choice with lower UTI side effects incidences in the sequence of 1st to 3rd?



In SGLT2i+Dpp4i Combination, Doctors considered Dapa to be causing UTI so they Didn't prefer Dapa, but based on Gliptins Doctors preferred LINA+Dapa as their 1st preference, SITA+Dapa as their 2nd preference and VILDA+Dapa as their 3rd preference.

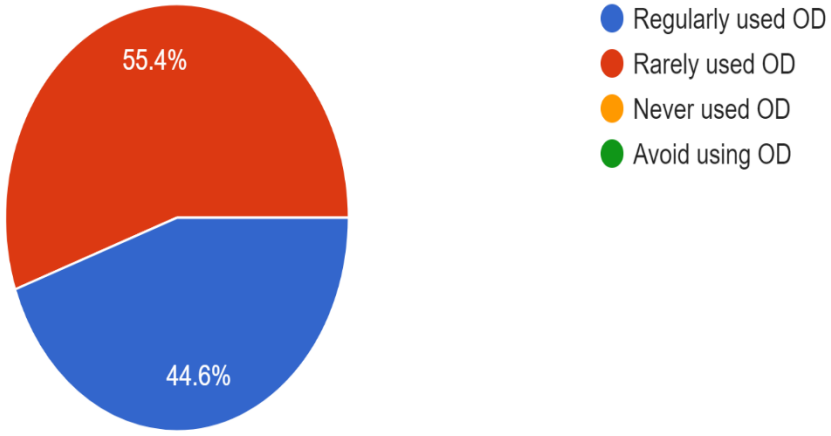
8. In SGLT2i+DPP4i combination, what is your preferred choice for uncontrolled T2DM with Edema or unknown history in the sequence of 1st to 3rd?



For uncontrolled T2DM with Edema, majority of them chose Linagliptin as their 1st choice, then Sitagliptin as their 2nd choice and then Vildagliptin as their 3rd choice

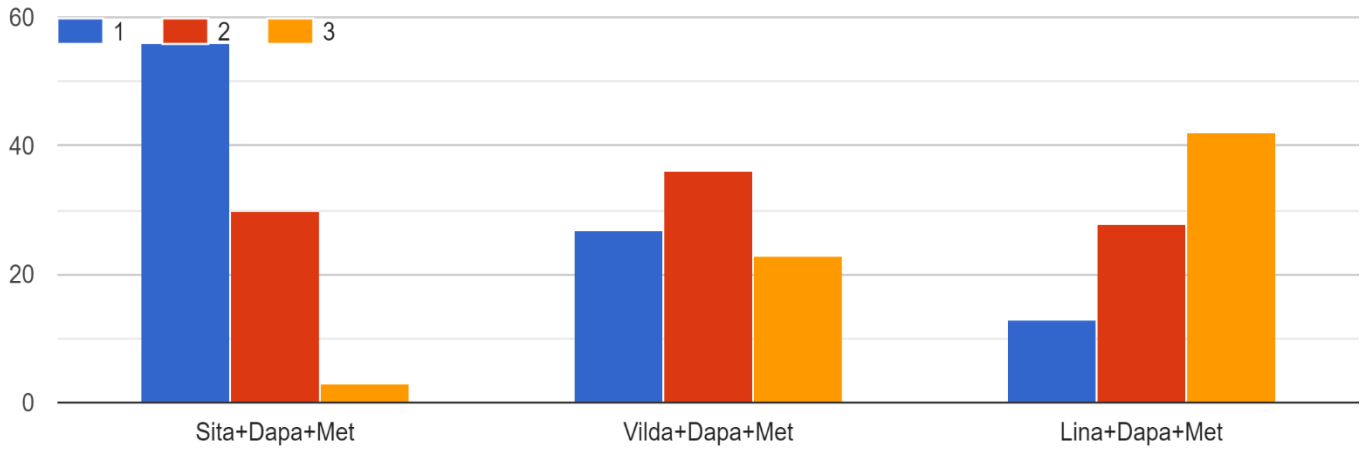
9. Is there any scope for Vildagliptin OD and Vildagliptin OD +Metformin SR (once daily) in your routine practice?

101 responses



55.4% people rarely used Vilda OD and Vilda OD+ Metformin SR in their routine practice and 44.6% people regularly used this comibination.

10. Among triple combination of gliptins what is your preferred choice in the sequence of 1st to 3rd?



In triple combination of Gliptins, Doctors preferred Sita+Dapa+Met as their 1st preference, Vilda+Dapa+Met as their 2nd preference and Lina+Dapa+Met as their 3rd preference.

Findings

1. Doctors are shifting in prescription from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin.
2. Maximum Doctors believes that the main reason to shift from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin is Lower Cardio-Renal risk.
3. Doctors considered Dapa to be causing UTI so they Didn't prefer Dapa, but based on Gliptins Doctors preferred LINA+Dapa as their 1st preference, SITA+Dapa as their 2nd preference and VILDA+Dapa as their 3rd preference.
4. In triple combination of Gliptins, Doctors preferred Sita+Dapa+Met as their 1st preference, Vilda+Dapa+Met as their 2nd preference and Lina+Dapa+Met as their 3rd preference.
5. Almost all Doctors agreed that there is a shift in prescription from Vildagliptin and Glimepiride to Sitagliptin, Linagliptin, Dapagliflozin.
6. During worsening renal function for T2DM Doctors Preferred Linagliptin the most.

Reference

1. https://www.macleodspharma.com
2. https://my.clevelandclinic.org/health/diseases/7104-diabetes
3. https://www.verywellhealth.com/signs-of-diabetes-diagnosing-type-2-diabetes-1087272
4. https://www.healthline.com/health/diabetes/medications-list.
5. Geelhoed-Duijvestijn P. H. L. M., Incretins: a new treatment option for type 2 diabetes?, Netherlands Journal of Medicine. (2007) 65, no. 2, 60–64.
6. Lyseng-Williamson KA. Sitagliptin. Drugs. 2007;67(4):587–97.
7. Bloomfield DM, Krishna R, Hreniuk D, et al. A thorough QTc study to assess the effect of sitagliptin, a DPP4 inhibitor, on ventricular repolarization in healthy subjects. J Clin Pharmacol. 2009;49(8):937–46.
8. Kazuki Orime & Yasuo Terauchi. (2020) Efficacy and safety of saxagliptin for the treatment of type 2 diabetes mellitus. *Expert Opinion on Pharmacotherapy* 21:17, pages 2101-2114.
9. André J. Scheen. (2023) The current role of SGLT2 inhibitors in type 2 diabetes and beyond: a narrative review. *Expert Review of Endocrinology & Metabolism* 18:4, pages 271-282
10. Ping Zou, Mingxing Guo & Jingbo Hu. (2022) Evogliptin for the treatment option for type 2 diabetes: an update of the literature. *Expert Review of Clinical Pharmacology* 15:6, pages 747-757.
11. Seshasai, S. R. *et al*. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N. Engl. J. Med.* **364**, 829–841 (2011).
12. Scheen, A. J. Current management strategies for coexisting diabetes mellitus and obesity. *Drugs* **63**, 1165–1184 (2003).
13. Mcintyre N., Holdsworth C. D., and Turner D. S., New interpretation of oral glucose tolerance, The Lancet. (1964) 284, no. 7349, 20–21,
14. Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994–2007
15. **Addition of incretin therapy to metformin in type 2 diabetes.** *Lancet.* 2010; **375**: 1410-1412
16. Carpio, L.E.; Olivares, M.; Benítez-Paez, A.; Serrano-Candelas, E.; Barigye, S.J.; Sanz, Y.; Gozalbes, R. Comparative Binding Study of Gliptins to Bacterial DPP4-like Enzymes for the Treatment of Type 2 Diabetes Mellitus (T2DM). *Int. J. Mol. Sci.* **2024**, *25*, 5744. https://doi.org/10.3390/ijms25115744.
17. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004;291:844–50.

18. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. Hepatobiliary Surg Nutr. 2015 Apr;4(2):101-8. doi: 10.3978/j.issn.2304-3881.2015.01.03. PMID: 26005676; PMCID: PMC4405411.
19. Wong J, Constantino M, Yue DK. Morbidity and mortality in young-onset type 2 diabetes in comparison to type 1 diabetes: where are we now? Curr Diab Rep. 2015;15(1):566
20. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705