Potential Role of Triple Combination of Sitagliptin + Glimepiride + Metformin in Diabetes Management in Current Era

Content

Background and Objective of the Survey

Over the last several decades, the diabetes landscape has been transformed by an improved understanding of its pathophysiology and the development of an array of antihyperglycemic medications. Despite the number of treatment options, hyperglycemia is still often poorly controlled, chiefly reflecting the limitations inherent in treatment options for T2DM and clinical inertia. After prescribing therapeutic lifestyle changes, there may be delays in initiating monotherapy, often metformin, and physicians may wait long periods of time (even years) before adding additional therapy. In addition, patients with T2DM and chronic kidney disease (CKD) are also at an increased risk of severe hypoglycemia and present a treatment challenge. Thus, a one-size-fits-all approach to treat hyperglycemia is insufficient and a patient-centered approach is necessary.

Sitagliptin/metformin is a single-tablet, fixed-dose combination of the dipeptidyl peptidase-4 inhibitor sitagliptin and the biguanide antihyperglycemic metformin that achieves greater improvements in glycemic control than either component alone in patients with type 2 diabetes mellitus. The addition of sitagliptin 100 mg/day significantly improved glycemic control in patients with type 2 diabetes inadequately controlled on glimepiride 4-8 mg/day with or without metformin ≥1500 mg/day. Sitagliptin decreased HbA1c levels from baseline at 24 weeks by 0.89% relative to placebo when added to glimepiride plus metformin therapy and by 0.57% when added to glimepiride alone. Glimepiride is important for good glycemic control in triple OAD therapy with sitagliptin and metformin. This regimen may be useful for those patients who do not achieve satisfactory glycemic control with dual combination therapy.

The objective of the survey is:

To study the potential role of triple combination of Sitagliptin + Glimepiride + Metformin in diabetes management in current era.

Methodology of the Survey

A survey was conducted to study the potential role of triple combination of Sitagliptin + Glimepiride + Metformin in diabetes management in current era. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Pathophysiology of T2DM
- Treatment guidelines and approaches
- Combination therapy
- Sitagliptin/metformin – pharmacodynamic, pharmacokinetic, therapeutic efficacy, add-on therapy and tolerability
- Glimepiride – pharmacodynamic, pharmacokinetic, therapeutic and clinical efficacy
- Abstract

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction

Over the last several decades, the diabetes landscape has been transformed by an improved understanding of its pathophysiology and the development of an array of antihyperglycemic medications. Yet, diabetes remains a pervasive disease with immense public health consequences and increasing prevalence of type 2 diabetes mellitus (T2DM) in adults. Despite the number of treatment options, hyperglycemia is still often poorly controlled, chiefly reflecting the limitations inherent in treatment options for T2DM and clinical inertia. Lifestyle changes such as diet or exercise are insufficient, and the efficacy of pharmacologic agents is rarely sustained over time and may be limited by side effects. After prescribing therapeutic lifestyle changes, there may be delays in initiating monotherapy, often metformin, and physicians may wait long periods of time (even years) before adding additional therapy. This step-up approach is conducive to treatment failure; evidence from monotherapy studies shows that long-term glycemic control is often not durable.[1]

Several studies have stressed the importance of early treatment, not only to prevent small vessel disease complications, but to prevent cardiovascular (CV) events years after the completion of the trial (a result of the legacy effect) as well. The current therapeutic landscape also results from caution based on potential adverse events with available glucose-lowering agents. For example, insulins and sulfonylureas (SUs) are associated with weight gain and hypoglycemia, the latter being of particular concern in the elderly. The management of T2DM may be facilitated with single-pill combinations (SPC) by enabling patients to take fewer pills per day, which may lead to improved patient adherence. Many combinations include metformin and can be used early in the disease. Two other SPCs, pioglitazone/alogliptin and empagliflozin/linagliptin, have shown good glucose-lowering efficacy when added to metformin. It is important to choose agents that treat the patient as a whole, not just their hyperglycemia. For example, individuals with T2DM are at high risk of CV disease and need aggressive therapy that includes the management of concomitant CV risk factors such as obesity, hypertension, and dyslipidemia.[1]

In addition, patients with T2DM and chronic kidney disease (CKD) are also at an increased risk of severe hypoglycemia and present a treatment challenge. Metformin is not recommended for use in patients with an estimated glomerular filtration rate (eGFR) less than 45

mL/min/1.73^2; however, metformin may be used safely in patients with mild impairment in kidney function and with proper monitoring in patients with moderate impairment in kidney function. As the number of newly diagnosed patients with T2DM increases and patients live longer, CKD needs to be a consideration when choosing antihyperglycemic agents. In the recently published long-term follow-up to the Steno-2 trial of patients with T2DM and microalbuminuria, more intensified, multifactorial, target-driven treatment resulted in an almost 8-year longer survival with fewer CV complications. Thus, a one-size-fits-all approach to treat hyperglycemia is insufficient and a patient-centered approach is necessary.[1]

Pathophysiology of T2DM

T2DM is a complex disease with multiple pathophysiologic components. Elevated blood glucose results from insufficient insulin production and insulin resistance, as well as a closely intertwined dysfunction of many other metabolic and hormonal pathways. Impaired β-cell function and impaired insulin secretion are hallmarks of T2DM. In addition, pancreatic α cells secrete inappropriately high amounts of glucagon in spite of hyperglycemia and hyperinsulinemia, the two major factors that decrease glucagon secretion and endogenous glucose production. As a result, inappropriate endogenous glucose production leads to fasting hyperglycemia and also contributes to postprandial hyperglycemia.[1]

T2DM has evolved into a disorder that now affects a younger population afflicted with central obesity and abnormal adipocyte function. In addition, the gastrointestinal tract exhibits abnormal secretion of incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide. These two hormones account for 90% of the incretin effect, which plays a pivotal role in maintaining normal glucose homeostasis. The kidneys also play a crucial role in glucose homeostasis by releasing glucose into the circulation via gluconeogenesis, particularly during fasting, and reabsorbing all of the filtered glucose, both of which are adaptive mechanisms that ensure sufficient energy is available during fasting periods. The transport protein, SGLT2, is a low-affinity, high-capacity glucose transporter that reabsorbs approximately 90% of filtered glucose, while the high-affinity, low-capacity SGLT1 transporter reabsorbs the remainder.[1]

A maladaptation takes place in individuals with diabetes with increased expression and activity of SGLT2 in the proximal tubule of the kidney. As a result, glucose reabsorption increases by as much as 20% in individuals with poorly controlled diabetes, contributing to hyperglycemia. In T2DM and obesity, the central nervous system fuel feedback is affected by insulin and leptin resistance, further contributing to glycemic dysregulation. Individuals with obesity and T2DM are insulin and leptin resistant and display neurotransmitter dysfunction that alters the normal fuel feedback to the brain, making the central nervous system a critical player in glucose dysregulation. In summary, complex and multiple pathophysiologic disturbances involving different organs and endocrine and neurologic pathways cause hyperglycemia, and therefore it is not surprising that a multitiered treatment approach is necessary.[1]

Treatment guidelines and approaches

Treatment guidelines developed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), as well as by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), recommend metformin as the first-choice pharmacotherapy if lifestyle changes, such as diet and exercise, fail to achieve glycated hemoglobin (HbA1c) goals within 3 months. Metformin does not cause significant hypoglycemia, is weight neutral, inexpensive, and has a long-standing evidence base for efficacy and safety; it may even reduce the risk of CV events. On the basis of the Diabetes Prevention Program study, metformin is also recommended for individuals with prediabetes, particularly those with a body mass index greater than 35 kg/m^2, aged less than 60 years, and women with previous gestational diabetes. If metformin is contraindicated (e.g., because of decreased renal function) or not tolerated, the AACE/ACE guidelines suggest the use of one of the newer agents, such as a GLP-1 receptor agonist, SGLT2 inhibitor, or DPP-4 inhibitor, over older agents (a-glucosidase inhibitors, TZDs, and SUs). The ADA/EASD Position Statement does not prioritize treatments and instead emphasizes patient preference and individualized treatment. Individuals with T2DM benefit from learning about managing their disease, adopting a healthier lifestyle, and understanding the pros and cons of their medications. Well-structured education, such as diabetes self-management education, should aim to support informed decision-making, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and quality of life in a cost-effective manner. Monitoring glycemic goals via determination of HbA1c levels and self-

monitoring of blood glucose (SMBG) varies according to the individual and his or her treatment.[1]

Combination therapy

Current guidelines recommend combination therapy in patients with elevated HbA1c levels at diagnosis (ADA/EASD >9.0%; AACE/ ACE ≥7.5%) or after 3 months of monotherapy if HbA1c goals are not achieved. To address the lack of long-term studies assessing the efficacy and safety of initial combination therapy, the US National Institutes of Health has sponsored the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study. The trial does not compare older combinations, such as TZDs, or newer agents, such as the SGLT2 inhibitors, and is limited to comparing the combination of metformin with DPP-4 inhibitors, GLP-1 receptor agonists, insulin, or SUs. Until the GRADE trial is completed (estimated 2020), only two randomized, controlled, long-term studies (both 5 years) are available. First, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study compared two different strategies, insulin secretagogues (mainly insulin and SUs) versus insulin sensitizers (mainly metformin and rosiglitazone). The study showed that the insulin sensitizer strategy not only achieved better glycemic control but was also associated with less hypoglycemia and less weight gain. The second trial, Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD), compared metformin plus SU with metformin plus rosiglitazone, and also found better glycemic control with the combination of rosiglitazone and metformin. Since these are the only two long-term randomized clinical trials available, treatment decisions should be patient-centered and include considerations such as efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.[1]

Sitagliptin/metformin

Sitagliptin/metformin is a single-tablet, fixed-dose combination of the dipeptidyl peptidase-4 inhibitor sitagliptin and the biguanide antihyperglycemic metformin that achieves greater improvements in glycemic control than either component alone in patients with type 2 diabetes mellitus. Drug therapy for type 2 diabetes is usually initiated with a single agent early in the disease course, but patients inevitably require combination therapy with two or more agents of different classes as the disease progresses. Metformin is recognized as the most favored agent

for commencement of oral drug therapy, with a second agent from another class being added when therapy with metformin alone fails to provide adequate glycemic control. The incretin enhancers (dipeptidyl peptidase-4 [DPP-4] inhibitors) are one such option for add-on therapy, of which sitagliptin was the first to be approved for use in patients with type 2 diabetes.[2]

Pharmacodynamic profile

The individual pharmacodynamic profiles of sitagliptin and metformin are well characterized and have been extensively reviewed, and, thus, are briefly summarized here with a focus on the combined pharmacodynamic effects of the co-administered agents. The effects of combined sitagliptin and metformin administration on glycemic control and related parameters in large, well designed clinical trials have been studied.[2]

Sitagliptin inhibits the serine protease DPP-4, resulting in increased levels of circulating incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide), which are gut-derived hormones that glucose-dependently stimulate the release of insulin from the pancreas. This novel, glucose-dependent mechanism of action of sitagliptin, where insulin levels are only increased in response to the body's requirement for insulin, means that the risk of hypoglycemia is reduced whilst glycemic control is improved.[2]

Near maximal DPP-4 inhibition is seen at the recommended sitagliptin dosage of 100 mg/day in patients with type 2 diabetes; corrected percent plasma DPP-4 inhibition was ≈96% at trough 24 hours following once-daily dosing with sitagliptin 100 mg for 7 days, in a randomized, double-blind, crossover study. The precise mechanism by which the biguanide metformin lowers basal and postprandial blood glucose in patients with type 2 diabetes is not completely understood. However, its effects include: reduced hepatic glucose output; increased peripheral glucose utilization; decreased fatty acid oxidation; reduced appetite and weight gain; sensitization of peripheral tissues to insulin; increased functional activity of glucose transporters; and increased insulin-mediated insulin receptor tyrosine kinase activity. Some of the therapeutic effects of metformin are mediated via GLP-1, possibly by increasing GLP-1 secretion.[2]

In healthy volunteers, the effects of combined sitagliptin and metformin administration on active GLP-1 levels were complementary; postprandial GLP-1 levels increased 1.5- to 2-fold with sitagliptin 100 mg/day or metformin 1000 mg/day monotherapy, and >4-fold with the sitagliptin plus metformin combination. Results suggested that the two drugs increase active GLP-1 concentrations by different, but complementary, mechanisms, with sitagliptin inhibiting GLP-1 degradation and metformin increasing GLP-1 release. This complementary activity was also demonstrated in a randomized, double-blind, placebo-controlled, crossover study in 18 patients with type 2 diabetes.[2]

In a nonblind, proof of concept study (n = 48), 4 weeks of adjunctive sitagliptin or exenatide therapy improved postprandial blood glucose control in patients receiving ongoing metformin plus insulin glargine for type 2 diabetes. Statistically significant improvements in almost all parameters of metabolic control were seen, including postprandial glucose excursions, glycosylated hemoglobin (HbA1c), 7-point blood glucose profiles, and fasting plasma glucose (FPG) and lipid levels (all $p < 0.05$ vs metformin plus insulin glargine alone).[2]

After 24 weeks of treatment, sitagliptin 100 mg/day added to ongoing metformin therapy significantly ($p < 0.01$ vs placebo) reduced 2-hour postprandial glucose concentrations in two studies. The effects of combination sitagliptin and metformin were significantly greater than those of either component alone in this regard. Sitagliptin 100 mg/day significantly reduced 2-hour postprandial glucose concentrations compared with placebo when added to metformin plus glimepiride or metformin plus insulin.[2]

In patients with type 2 diabetes, significant improvements in measures of β-cell function (i.e., the homeostasis model of β-cell function [HOMA-β] and proinsulin/insulin ratio) were observed following 18 weeks of treatment with the sitagliptin/metformin fixed-dose combination compared with metformin monotherapy. Combined sitagliptin plus metformin therapy improved HOMA-β and the proinsulin/insulin ratio to a significantly ($p \leq 0.05$) greater extent than either agent alone in several clinical trials with beneficial effects on β-cell function being sustained over treatment durations of up to 2 years. In one trial, the fasting proinsulin/insulin ratio was improved with sitagliptin plus metformin relative to glipizide plus metformin, while increases in HOMA-β were significant in glipizide plus metformin recipients

only. Improvements in β-cell function were also seen with the addition of sitagliptin to metformin plus glimepiride or metformin plus insulin.[2]

Pharmacokinetic profile

The individual pharmacokinetic profiles of sitagliptin and metformin have been extensively reviewed in Drugs and, thus, are briefly discussed.[2]

Sitagliptin/Metformin

Pharmacokinetic studies relating specifically to the sitagliptin/metformin single-pill combination are limited to a single bioequivalence study in healthy volunteers. In this randomized, nonblind, crossover study, the bioequivalence of the sitagliptin/metformin single-pill combination and its individual components was established in 48 healthy volunteers who received single-dose sitagliptin/metformin 50 mg/500 mg or 50 mg/ 1000 mg, and co-administered sitagliptin plus metformin at the corresponding doses.[2]

The steady-state pharmacokinetics of sitagliptin and metformin were not altered to a clinically meaningful extent by their coadministration in another randomized, double-blind, double-dummy, crossover, placebo-controlled study in 13 patients with type 2 diabetes, further supporting the clinical interchangeability of the fixed-dose combination and the concomitantly administered individual components.[2]

Sitagliptin

Sitagliptin is well absorbed following oral administration and has an absolute bioavailability of 87%. The pharmacokinetics of sitagliptin are not altered to a clinically meaningful extent by coadministration with a high-fat meal. After a single oral 100 mg dose in healthy volunteers, the least-squares mean maximum plasma concentration (C_{max}) was 950 nmol/L, mean area under the concentration-time curve (AUC) was 8.52 µmolh/L and time to C_{max} (t_{max}) was 1.3 hours. Dose-proportionality was established for AUC, but not for C_{max} or C24h (the plasma sitagliptin concentration at 24 hours post-dose) in single-dose (1.5-600 mg) and multiple-dose (25-600 mg/day) studies. Only minimal accumulation occurs with multiple dosing and steady-state sitagliptin concentrations are achieved within ≈2-3 days. In patients with type 2 diabetes, sitagliptin pharmacokinetic parameters following the administration of sitagliptin 50 mg twice

daily with and without metformin 1000 mg twice daily for 7 days were as follows: C_{max}, 522 and 498 nmol/L; AUC between zero and 12 hours, 4.04 and 3.95 mmolh/L (least squares mean [LSM] values reported); and median t_{max} 2.0 and 3.0 hours. Sitagliptin has a volume of distribution (Vd) of 198 L following a single 100 mg intravenous dose. The drug is approximately 38% plasma protein bound.[2]

Sitagliptin is metabolized to a minor extent; the primary enzyme responsible for the limited metabolism of sitagliptin is cytochrome P450 (CYP) 3A4, and secondarily, CYP1A2. Sitagliptin is not an inhibitor of the CYP isoenzymes 3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and does not induce CYP isoenzymes 3A4 or 1A2. Sitagliptin is primarily excreted unchanged in the urine, predominantly via renal excretion, but also through active tubular secretion. It is transported by human organic anion transporter-3, organic anion transporting polypeptide-4C1, and multidrug resistance P-glycoprotein. After a single oral dose of radiolabeled sitagliptin in healthy volunteers, ≈13% of radioactivity was eliminated in the feces and 87% was eliminated in the urine within 1 week of administration; ≈16% of the total dose was excreted as metabolites, of which six were detected at trace levels.[2]

In healthy volunteers, the elimination half-life (t½) of sitagliptin was 12.4 hours following a single oral 100 mg dose; the renal clearance (CL) of sitagliptin (pooled across a 25-400 mg dose range) was 344 mL/min. In clinical studies, sitagliptin was shown to have a small effect on plasma digoxin concentrations, but no clinically meaningful interaction with other commonly co-administered pharmacotherapies including glibenclamide, simvastatin, warfarin or oral contraceptives. The pharmacokinetics of sitagliptin were not altered to a clinically meaningful extent with ciclosporin coadministration; relevant interactions with other p-glycoprotein inhibitors are not expected. While it is possible that potent CYP3A4 inhibitors may alter sitagliptin disposition in patients with severe renal impairment or end-stage renal disease, this has not been formally evaluated in clinical studies.[2]

Relative to healthy volunteers, the pharmacokinetics of a single oral 50 mg dose of sitagliptin were not altered to a clinically meaningful extent in patients with mild renal insufficiency (creatinine clearance [CL_{CR}] 50-80 mL/min [3-4.8 L/h]). However, ≈2- and ≈4-fold increases in sitagliptin AUC were seen in patients with moderate (CL_{CR} 30-50 mL/min [1.8-3 L/h]) and

severe (CL_{CR} <30mL/min [1.8 L/h]) renal insufficiencies, the latter including those with end-stage renal disease on hemodialysis. In the EU, sitagliptin is not recommended for use in patients with moderate or severe renal impairment. Patients with mild or moderate hepatic insufficiency do not require sitagliptin dose adjustment. Although not formally established, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin due to its primarily renal elimination.[2]

Metformin

Metformin has a bioavailability of between 50% and 60%. The absorption of orally administered metformin is saturable and incomplete, and is reduced and delayed in the presence of food. The pharmacokinetics of metformin absorption are assumed to be non-linear. Steady-state plasma concentrations are generally under 1 µg/mL and reached within 24-48 hours at usual therapeutic dosages. Even at maximum metformin doses, the Cmax was ≤4 µg/mL in controlled clinical trials.[2]

In 13 patients with type 2 diabetes, metformin pharmacokinetic parameters following the administration of metformin 1000 mg twice daily with and without sitagliptin 50 mg twice daily for 7 days were: Cmax, 2050 and 2130 ng/mL; AUC, 14.9 and 14.6 µg h/mL (LSM values reported); and median t_{max}, 2.0 and 3.0 hours, respectively. Mean values for the metformin Vd range between 63 and 276 L and the drug partitions into red blood cells, which likely represent a secondary compartment of distribution. Plasma protein binding of metformin is insignificant. Metformin is excreted unchanged in the urine and no metabolites have been identified. The drug is eliminated via globular filtration and tubular secretion; the renal CL of metformin is ≈400 mL/min and the apparent terminal elimination t½ is ≈6.5 hours.[2]

The non-absorbed fraction of an oral dose recovered in the feces was between 20% and 30%. Renal CL decreases in proportion to CL_{CR}; thus, increased plasma metformin concentrations may occur in the presence of renal impairment. Potentially, other cationic drugs that are eliminated by renal tubular secretion may interact with metformin. For example, a 60% increase in peak plasma metformin levels has been seen with the coadministration of metformin and cimetidine. Iodinated contrast agents used in radiological studies may lead to renal failure causing metformin accumulation and an increased risk of lactic acidosis. Although no

pharmacokinetic interaction has been observed with concurrent metformin and sulfonylurea administration, their synergistic effects may necessitate dosage adjustments to avoid hypoglycemic episodes.[2]

Therapeutic efficacy

The therapeutic efficacy of sitagliptin and metformin combination therapy in patients with type 2 diabetes has been evaluated in eight randomized, double-blind, multicenter trials. Other clinical studies, including those of open-label design, enrolling <200 patients or comparing the combination with an agent not currently approved for use in the EU have also demonstrated the positive effects of sitagliptin plus metformin on glycemic control in patients with type 2 diabetes.[2]

The trial evaluating the sitagliptin/metformin fixed-dose combination enrolled drug-naive patients (aged 18-78 years) with type 2 diabetes and HbA1c levels of ≥7.5%. The other trials enrolled adults (≥18 years) who had type 2 diabetes (HbA1c levels overall comprising the range of 6.5-11%) inadequately controlled with diet and exercise alone, metformin monotherapy, sulfonylurea (glimepiride) with or without metformin, or insulin with or without metformin at study baseline. In these studies, only patients who had completed an appropriate washout period following discontinuation of prior treatment with other oral hypoglycemic agents and/or been stabilized on the specified baseline regimen for a period sufficient to establish an inadequate glycemic response, entered a 2-week placebo run-in phase and were then randomized to receive double-blind study treatment.[2]

Amongst patients excluded from the trials were those with pre-randomization FPG levels of >240, >260, >270 or >280 mg/dL, type 1 diabetes, renal function impairment inconsistent with metformin use and use of insulin within 8 weeks of screening. Some studies permitted antihyperglycemic rescue therapy in order to meet increasingly strict glycemic parameters, while in one, patients were discontinued from the study if they did not meet prespecified increasingly strict glycemic parameters. The primary efficacy variable in all trials was the change from baseline at endpoint in HbA1c levels, while secondary outcomes included changes from baseline in FPG levels and the proportion of patients achieving target HbA1c levels of <7%.[2]

Initial combination therapy

As the fixed-dose combination

Sitagliptin/metformin, as the fixed-dose combination, provided greater glycemic improvements than metformin alone in antihyperglycemic treatment-naive patients with type 2 diabetes. LSM reductions in HbA1c levels from baseline at 18 weeks (primary endpoint) were significantly ($p < 0.001$) greater with sitagliptin/metformin 50 mg/1000 mg twice daily than with metformin 1000 mg twice daily. Furthermore, sitagliptin/metformin reduced FPG levels to a significantly ($p < 0.001$) greater extent than metformin alone, and significantly ($p < 0.001$) more fixed-dose combination recipients than metformin monotherapy recipients achieved target HbA1c levels of <7%. By the end of a 26-week continuation phase of this study (results available in a separate abstract), 8.8% of sitagliptin/metformin recipients and 16.7% of metformin monotherapy recipients received additional antihyperglycemic drugs to achieve glycemic goals. After 44 weeks of treatment, in the two respective groups, HbA1c levels were reduced from baseline by 2.3% (95% CI -2.4, -2.1) versus 1.8% (95% CI -1.9, -1.6) [between-group difference of -0.5% in favor of the fixed-dose combination], FPG levels were reduced by 65.0 and 53.4 mg/dL ($p < 0.001$), and 46% versus 30% ($p < 0.001$) of patients reached target HbA1c goals of <7%. A decrease from baseline in bodyweight was seen in each of the two treatment groups (1.1 kg in fixed-dose combination recipients and 1.2 kg in metformin monotherapy recipients).[2]

Add-on therapy

As part of triple combination therapy

The addition of sitagliptin 100 mg/day significantly improved glycemic control in patients with type 2 diabetes inadequately controlled on glimepiride 4-8 mg/day with or without metformin ≥1500 mg/day. In the entire study cohort (i.e., patients treated with glimepiride alone or in combination with metformin), the addition of sitagliptin decreased HbA1c levels from baseline at 24 weeks (primary endpoint) by 0.74% relative to placebo ($p < 0.001$). Sitagliptin decreased HbA1c levels from baseline at 24 weeks by 0.89% relative to placebo when added to glimepiride plus metformin therapy and by 0.57% when added to glimepiride alone.[2]

Sitagliptin 100 mg/day added to ongoing insulin ≥15 IU/day with or without metformin ≥1500 mg/day significantly improved glycemic control in a trial in patients with type 2 diabetes. At

the 24-week endpoint, LSM changes from baseline in both HbA1c and FPG levels were significantly greater with the addition of sitagliptin to ongoing insulin with or without metformin than with the addition of placebo. Furthermore, the proportion of patients achieving HbA1c levels of <7% at 24 weeks in both trials were significantly higher with the addition of sitagliptin to metformin-based therapies (metformin plus glimepiride, metformin plus insulin) than with the addition of placebo.[2]

Tolerability

General profile

Sitagliptin and metformin, as a combination of the individual components or as the fixed-dose combination, was generally well tolerated in clinical trials in patients with type 2 diabetes. The tolerability profile of combined sitagliptin and metformin therapy was generally similar to that of metformin alone, and remained as such after ≤2 years of treatment. Furthermore, the combination of sitagliptin plus metformin was generally well tolerated in patients receiving concomitant insulin or glimepiride in 24-week studies. The proportion of patients reporting at least one adverse event was similar during 18 weeks of treatment with fixed-dose combination sitagliptin/ metformin 50 mg/1000 mg twice daily (271 of 626 patients [43.3%]) and metformin 1000 mg twice daily (303 of 624 patients [48.6%]). In the two respective treatment groups, 17.4% and 18.9% of patients reported adverse events that were considered by the investigator to be possibly, probably or definitely related to study treatment. Adverse events considered to be treatment-related and occurring in more sitagliptin plus metformin than placebo recipients during 24-week trials were nausea (frequency ≥1/100 to <1/100). Likewise, events occurring during triple combination therapy with sitagliptin plus metformin and a sulfonylurea were hypoglycemia (≥1/10) and constipation (≥1/100 to <1/100).[2]

Dosage and administration

In Europe, the sitagliptin/metformin fixed-dose combination is available in 50 mg/850 mg and 50 mg/1000 mg film-coated tablets for twice-daily administration in patients with type 2 diabetes (other fixed-dose combinations are available in other countries). The maximum recommended dosage of sitagliptin is 100 mg/day, and the sitagliptin/ metformin dosage should be individualized, up to this maximum, based upon the patient's current regimen, efficacy and tolerability. It is important that patients continue to adhere to an appropriate diet and exercise

regimen during treatment. Sitagliptin/metformin should be taken twice daily with meals so as to minimize the adverse gastrointestinal effects that may occur with metformin therapy. In patients inadequately controlled with a maximal tolerated dose of metformin alone, sitagliptin/metformin should be initiated to provide a sitagliptin dosage of 50 mg twice daily, plus the metformin dosage already being administered.[2]

In those switching from Coad ministered sitagliptin plus metformin, the single-pill combination should be started to provide the equivalent dosages to those of the individual components. In patients inadequately controlled with the maximal tolerated metformin dose plus either a sulfonylurea, a peroxisome proliferator-activated receptor-g agonist (i.e., a thiazolidinedione) or insulin, a sitagliptin/metformin dosage providing sitagliptin 50 mg twice daily should be given along with a metformin dosage similar to that already being taken; a decrease in the sulfonylurea or insulin dosage may be necessary in order to lower the risk of hypoglycemia. Sitagliptin/metformin should not be used in patients with hepatic impairment, nor in those with moderate or severe renal impairment (CL_{CR} <60 mL/min [3.6L/h]). It should not be used for the treatment of type 1 diabetes or for diabetic ketoacidosis. Local prescribing information should be consulted for details of contraindications, warnings and precautions, and use in special patient populations.[2]

Glimepiride

Sulfonylureas (SUs) are widely used in the management of T2DM as insulin secretagogues and are named for their common core configuration. They are classified as first- and second-generation SUs. First-generation SUs includes long-acting chlorpropamide, tolbutamide, tolazamide, and acetohexamide. Substitutions at either end of the compound result in pharmacologic and pharmacokinetic differences among SUs.11 Second-generation SUs include glyburide (glibenclamide), glipizide, gliquidone, and glimepiride, which vary in duration of action. Glimepiride and glyburide are longer acting agents than glipizide. Glimepiride is the newest second-generation SU and is sometimes classified as a third generation SU because it has larger substitutions than other second-generation SUs. It was first introduced into clinical practice in Sweden. The United States Food and Drug Administration (FDA) approved glimepiride in 1995 for the treatment of T2DM as monotherapy as well as in combination with metformin or insulin. Although other SUs is used with insulin, glimepiride

is the only SU approved by FDA for use in combination with insulin. It is used in more than 60 countries worldwide. Treatment with glimepiride as monotherapy results in a 1.5-2.0% reduction in HbA1c.[3]

Table 1. Pharmacokinetic properties of glimepiride[3]

Absorption	Completely absorbed after oral administration within 1 hour of administration; significant absorption occurs: plasma protein binding is 99.4% and volume of distribution is 8.8 L. Accumulation does not occur after multiple doses.
Metabolism	The drug is primarily metabolized in the liver by CYP2C9 to the active M1 (hydroxyl) metabolite and then to inactive M2 (carboxy) metabolite.
Excretion	The main route of excretion is through kidneys. A total of 60% of the metabolites are excreted in urine (predominantly M_1) and remainder in feces (predominantly M_2).

Pharmacodynamics

Pancreatic effects

Glimepiride acts at ATPase-dependent potassium channels in β cells of the pancreas to stimulate insulin release. Using euglycemic and hyperglycemic clamp studies it has been shown to improve both first- and second-phase insulin secretion. Glimepiride binds to 65-kD proteins on β cells. In healthy volunteers, a linear relationship was shown between serum glimepiride concentrations and insulin release during euglycemia and a nearly linear relationship under hyperglycemic conditions.[3]

Maximal glucose-lowering activity and insulin level in T2DM patients is achieved within 2-3 hours of taking glimepiride and can last for 24 hours.16 In a 14-week clinical study, peak

concentrations 2 hours after administration of 1, 4, and 8 mg doses of glimepiride were associated with decreases in median fasting plasma glucose (FPG) of 43, 70.5, and 74 mg/dL, respectively. Glimepiride reduces blood glucose levels and increases insulin levels in blood. A 3-day study of 14 T2DM patients found greater reductions in blood glucose (4.1 vs 1.9 mmol/L) and increase in C-peptide (1.8 vs 1.4 mg/L) and plasma insulin (41 vs 25 mu/L) with 2 mg/day glimepiride compared to placebo ($P < 0.05$).18 Hypoglycemia after exercise while taking glimepiride was observed in 167 patients with T2DM. This was associated with a greater reduction in insulinemia than glibenclamide during exercise, despite similar reductions in blood glucose. Glimepiride may be taken before or after breakfast with similar results. The efficacy of 2 mg/day glimepiride for 2 weeks on blood glucose levels was not significantly different over a period of 0-4 hours when the drug was given either immediately before breakfast or 30 minutes after breakfast.[3]

Extra pancreatic effects

The extra pancreatic effects of glimepiride are similar to those of other sulfonylureas. Although peripheral tissue response to insulin is potentiated like other SUs, the clinical relevance of this is not yet clear. In in vitro studies, glimepiride was found to be two times as potent as glibenclamide in stimulating lipogenesis and glycogenesis. Studies in cultured skeletal muscle also suggest a sensitizing effect of glimepiride. Possible mechanisms include promotion of GLUT4 transport protein activation and/or translocation in fat and muscle. Glimepiride reduced insulin resistance and increased hepatic glucose disposal in animal models, but showed no effect in glucose utilization in patients with type 1 diabetes.[3]

Clinical efficacy

The drug has been assessed in placebo-controlled studies as monotherapy and compared with other SUs and insulin in T2DM patients. Most studies examined FPG, post-prandial glucose (PPG), and HbA1c. Some studies included plasma lipids, serum insulin, or fasting C-peptide levels.[3]

Glimepiride as monotherapy

To assess the efficacy of glimepiride in T2DM, Goldberg et al randomized 304 patients to receive either placebo or one of the three doses (1, 4, or 8 mg) of glimepiride during a 14-week

study period. All glimepiride regimens significantly reduced FPG, PPG, and HbA1c values (P <0.001) compared to placebo by the end of the study period. Median changes in FPG levels were 43, 70, and 74 mg/dL at glimepiride doses of 1, 4, and 8 mg, respectively. HbA1c levels were lowered by 1.2%, 1.8%, and 1.9%, and the corresponding decreases in PPG were 63, 92, and 94 mg/dL, respectively. The 4- and 8-mg doses of glimepiride were more effective than the 1-mg dose; however, the 4-mg dose provided a nearly maximal antihyperglycemic effect.[3]

Another study showed equal effects on FPG, PPG, HbA1c, C-peptide, and insulin levels in a cross-over study of 98 patients treated with glimepiride.31 The only significant difference was observed in glucose levels throughout the day, which were lower with a once daily dose compared to a twice daily dosage. The opposite results were observed by Rosenstock *et al* who found a significant decrease in FPG by 0.6 mmol/L with glimepiride when it was given twice daily compared to once daily dosage. Another multicenter, randomized, placebo-controlled clinical trial by Schade et al studied glimepiride (1-8 mg) titrated over 10 weeks compared with placebo in T2DM subjects who were not controlled by diet alone. In this study, glimepiride lowered FPG by 46 mg/dL, PPG by 72 mg/dL, and HbA1c by 1.4% more than the placebo (P <0.001). Good glycemic control (HbA1c <7.2%) was achieved in 69% of glimepiride subjects compared to 32% of controls. C-peptide levels and non-fasting insulin levels were also increased in the study subjects.[3]

Glimepiride monotherapy reduced both FPG and PPG levels more than placebo and once daily administration is equivalent to twice daily dosing. Studies also suggest that glimepiride controls blood glucose level throughout the day through its effect on stimulating insulin release, which appears to be greater 2 h after meals than under fasting conditions. These findings suggest that glimepiride enhances insulin and C-peptide secretion under physiologic conditions. Combination therapy for treating T2DM is now a recommended practice as the disease progresses. Several studies have examined the combination of glimepiride with other oral hypoglycemic agents with different mechanisms of action for good glycemic control when monotherapy fails. In a study involving 372 patients with poorly controlled T2DM, glimepiride was added to metformin monotherapy. Study subjects were divided into three groups: metformin group, glimepiride group, metformin plus glimepiride group. In this study, a combination of glimepiride and metformin was shown to be more effective for controlling

blood glucose levels compared to the use of either drug alone.33 Combination treatment was significantly more effective in controlling HbA1c (% change +0.07 ± 1.20 for metformin, +0.27 ± 1.10 for glimepiride, -0.74 ± 0.96 for combination treatment, P <0.001). No significant difference was observed between metformin or glimepiride monotherapy with respect to change in HbA1c or fasting blood glucose; however, glimepiride was significantly more effective than metformin in reducing postprandial blood glucose. Episodes of symptomatic hypoglycemia was also higher in the combination group than in either monotherapy group (P = 0.039).[3]

Glimepiride in combination with insulin

Patients who fail to achieve good glycemic control on combination therapy may require insulin.40 Glimepiride is the only SU currently approved by the FDA for combination therapy with insulin. Several studies have demonstrated that a combination of insulin and glimepiride results in a decreased requirement of insulin and good glycemic control. In a 24-week study of obese patients not adequately controlled by maximum doses of SUs, addition of insulin was compared to insulin + placebo.41 Subjects were randomized to receive insulin and either glimepiride 16 mg/day or placebo, and the insulin dosage was titrated to achieve FPG of 100-120 mg/dL. The two groups showed similar HbA1c and FPG at the end of the study period. However, the group receiving insulin + glimepiride required less insulin (48 vs 78 U/day) and FPG was lowered more rapidly after 2 and 4 weeks of treatment than in the insulin/placebo group.41 Thus, insulin sparing properties are greater with glimepiride than with other SUs.[3]

Another study conducted in 695 poorly controlled patients with T2DM assessed the safety and efficacy of glimepiride with NPH or glargine. Patients were divided into three groups to receive bedtime NPH, bedtime glargine, or morning glargine for 24 weeks in addition to 3 mg of glimepiride. HbA1c improvement was observed more with morning insulin glargine than with NPH insulin (P = 0.001) or bedtime insulin glargine (P = 0.008). The study concluded that the risk for nocturnal hypoglycemia was lower with glimepiride in combination with morning and bedtime insulin glargine than with glimepiride in combination with bedtime NPH insulin.[3]

Combination of glimepiride with dipeptidyl peptidase-4 inhibitors

Recently, several new classes of hypoglycemic agents have been introduced, including glucagon like peptide-1 and dipeptidyl peptidase-4 (DDP-4) inhibitors. These agents improved glycemic control in T2DM patients either as monotherapy or in combination with SU, metformin, thiazolidinedione, or insulin.44-46 Glimepiride can be used in combination with metformin and DDP-4 inhibitors if glycemic control is not achieved with a single or with two agents. Studies have reported an equal efficacy for glimepiride plus metformin vs vildagliptin/sitagliptin plus metformin in terms of HbA1c reduction.47-49 Although DDP-4 induces less weight gain and hypoglycemia compared to glimepiride, further long-term follow-up studies are needed to determine their safety and efficacy.[3]

Advantages of glimepiride compared to other SUs

Hypoglycemia and weight gain are two important disadvantages of SU therapy; however, the unique properties of glimepiride may provide advantages over other currently available insulin secretagogues. Glimepiride is generally well-tolerated, and its safety has been reviewed in various randomized clinical studies involving more than 5000 patients. Data from these clinical trials indicate that the overall incidences of adverse events associated with glimepiride are generally lower compared with other SUs.[3]

Dosage and administration

The starting dose of glimepiride is 1-2 mg typically taken before breakfast. The dose is adjusted according to self-monitoring of blood glucose levels and is gradually increased until glycemic control is achieved. The maximum recommended dosage is 8 mg/day, although doses up to 32 mg/day have been used in clinical trials. Typical maintenance dosages are 1-4 mg/day. However, higher dosages (6-8 mg/day) have been found to be associated with reduced mean HbA1c before and after treatment. It may also be combined with other treatment modalities for T2DM, including insulin in patients who are not controlled with SUs. However, the combination of insulin and glimepiride requires a lower initial dose of insulin.[3]

Abstract

Glimepiride strongly enhances the glucose-lowering effect in triple oral antidiabetics therapy with sitagliptin and metformin for Japanese patients with type 2 diabetes mellitus[4]

Background

After approval of sitagliptin and >750 mg of metformin in Japan, a triple oral antidiabetes drug (OAD) regimen including sulfonylurea, metformin, and sitagliptin was sometimes described. However, in the real world of clinical practice, the daily dose of sulfonylurea tended to be decreased according to the warning from the Japan Diabetes Society for avoiding hypoglycemia, instead of increasing the dose of metformin for maintaining hemoglobin A1c (HbA1c) levels with this regimen. This study examined the impact of either a small dose of glimepiride or a high dose of metformin on HbA1c in triple OAD therapy with sitagliptin in a 3-month, single-center, open-label, randomized controlled study.

Subjects and Methods

Fifty-six type 2 diabetes mellitus patients who had been treated with 50 mg of sitagliptin, ≥1000 mg of metformin, and ≤1 mg of glimepiride with an HbA1c level of <7.4% during at least 3 months were enrolled in the study. The patients were randomly assigned to two treatment groups who either received a 50% reduced dose of metformin (n = 27) or discontinued glimepiride (n = 29), while sitagliptin administration continued in both groups. Twenty-six patients from the reduced metformin group and 27 patients from the discontinued glimepiride group completed the study.

Results

Significantly greater changes were observed in HbA1c and glycated albumin levels in patients who discontinued glimepiride than in patients with a 50% reduced metformin dose, during the 2-3-month period than in the 1-3-month period.

Conclusions

Glimepiride is important for good glycemic control in triple OAD therapy with sitagliptin and metformin. This regimen may be useful for those patients who do not achieve satisfactory glycemic control with dual combination therapy.

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2. Chwieduk CM. Sitagliptin/Metformin Fixed-Dose Combination. Drugs. 2011;71(3):349-61.
3. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations. *Vascular Health and Risk Management*. 2012;8:463-72.
4. Arai K, Maeda H, Sirabe S, *et al*. Glimepiride Strongly Enhances the Glucose-Lowering Effect in Triple Oral Antidiabetes Therapy with Sitagliptin and Metformin for Japanese Patients with Type 2 Diabetes Mellitus. *Diabetes Technology & Therapeutics*. 2013;15(4):335-41.

Survey Form

1. **As per your opinion which unmet medical need to be taken care with in current T2DM management? (Can mark more than 1 option, if required)**

a. Combinatorial approach to address multiple pathophysiological mechanisms of hyperglycemia
b. Treatment to achieve aggressive glycemic control
c. Additional treatments that provide both glycemic and non-glycemic benefits
d. Therapy reducing the occurrence of hypoglycemia or weight gain

2. **How often do you prefer to prescribe the Combination therapy in patients with T2DM?**

a. Frequently
b. Not much frequently

3. **In which patient profile do you consider the triple combination therapy? (Can mark more than 1 option, if required)**

a. Patients not controlled with the dual combination therapy
b. Newly diagnosed patient with HbA1c ≥9%

4. **Do you concomitantly prescribe Sitagliptin with Glimepiride and Metformin?**

a. Yes
b. No

5. **How often do you prefer Sitagliptin concomitantly with Glimepiride and Metformin in patients with type 2 DM?**

a. Frequently
b. Not much frequently

6. **What will be advantage(s) of concomitant prescription of Sitagliptin + Glimepiride + Metformin?**

a. Aggressive glycaemic control
b. Reduced risk of hypoglycaemia
c. Weight neutrality
d. Cardiovascular benefits

7. **In your clinical practice, which patient profile benefits the most from administration of Sitagliptin concomitantly with Metformin and Glimepiride in diabetes management?**

a. Newly diagnosed patients
b. Patients with cardiovascular comorbidities
c. Patients requiring aggressive glycemic control
d. Elderly patients
e. Patients with kidney impairment

8. **How do you perceive the efficacy of administering Sitagliptin concomitantly with Metformin and Glimepiride compared to other available conventional Oral Antidiabetic Drugs (OADs)?**

a. Superior
b. Comparable
c. Inferior
d. Uncertain

9. **In your experience, how often do you observe hypoglycaemic events in patients administered with Sitagliptin concomitantly with Metformin and Glimepiride?**

a. Never
b. Occasionally

10. How do you perceive the long-term safety profile of administering Sitagliptin concomitantly with Metformin and Glimepiride as compared to other available triple combination therapies (conventional) for diabetes management?

a. Superior
b. Comparable
c. Inferior
d. Uncertain

11. In your current clinical practice, in which T2DM cases do you consider to step-down in antihyperglycemic treatment? (Can mark more than 1 option, if required)

a. With significant weight reduction irrespective of its origin
b. With complex insulin regimens where re-evaluation of this treatment was missed
c. With continuously decreasing renal function
d. Among elderly patients with comorbidities

12. In your clinical practice, in T2DM management with step-down approach will you prefer to use Sitagliptin concomitantly with Metformin and Glimepiride?

a. Yes
b. No

Survey Findings

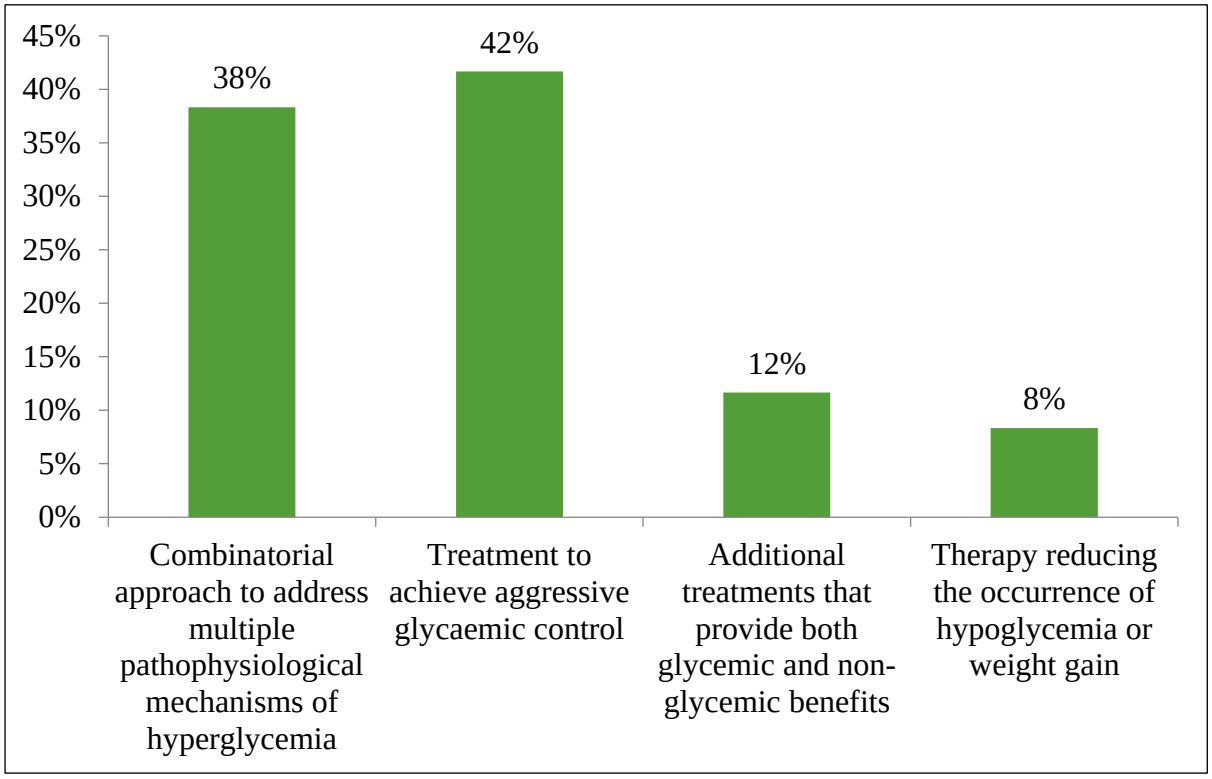
1. **As per your opinion which unmet medical need to be taken care within current T2DM management? (Can mark more than 1 option, if required)**

a. Combinatorial approach to address multiple pathophysiological mechanisms of hyperglycemia

b. Treatment to achieve aggressive glycemic control

c. Additional treatments that provide both glycemic and non-glycemic benefits

d. Therapy reducing the occurrence of hypoglycemia or weight gain

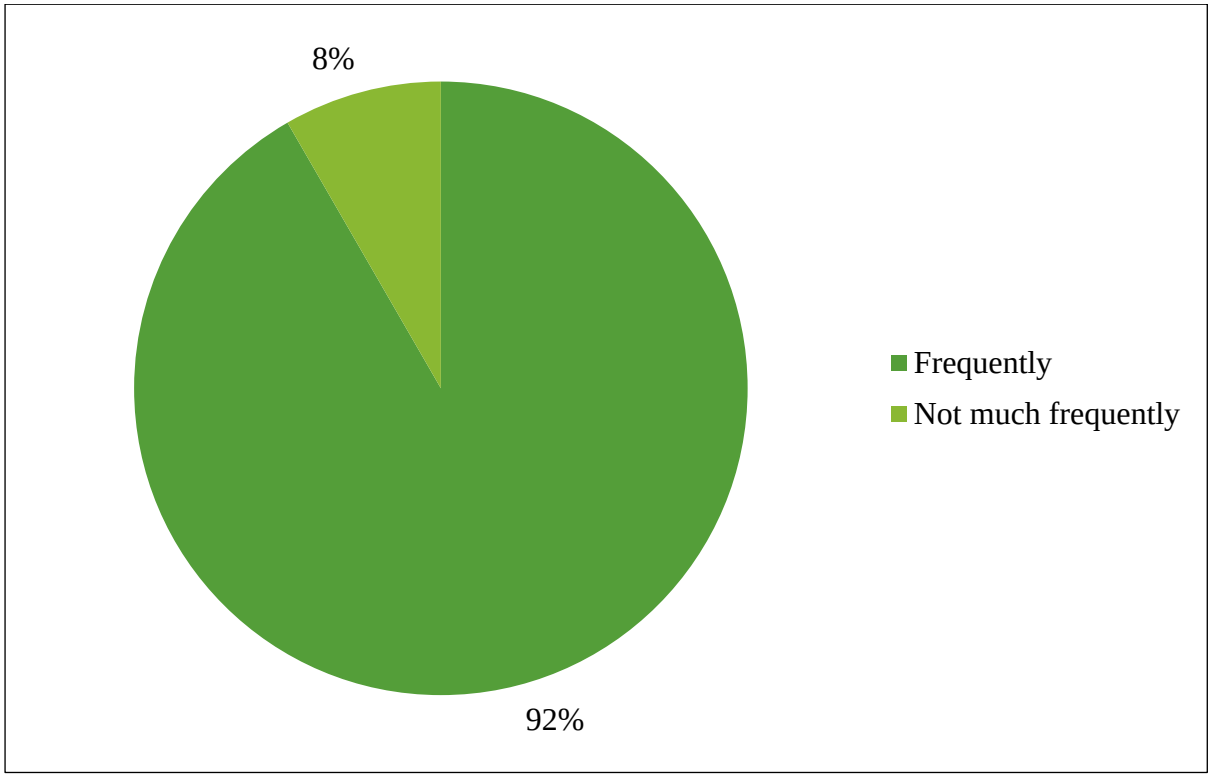


According to 42% of doctors, the unmet medical need that needs to be addressed within current T2DM management is treatment to achieve aggressive glycemic control.

2. How often do you prefer to prescribe the Combination therapy in patients with T2DM?

a. Frequently

b. Not much frequently

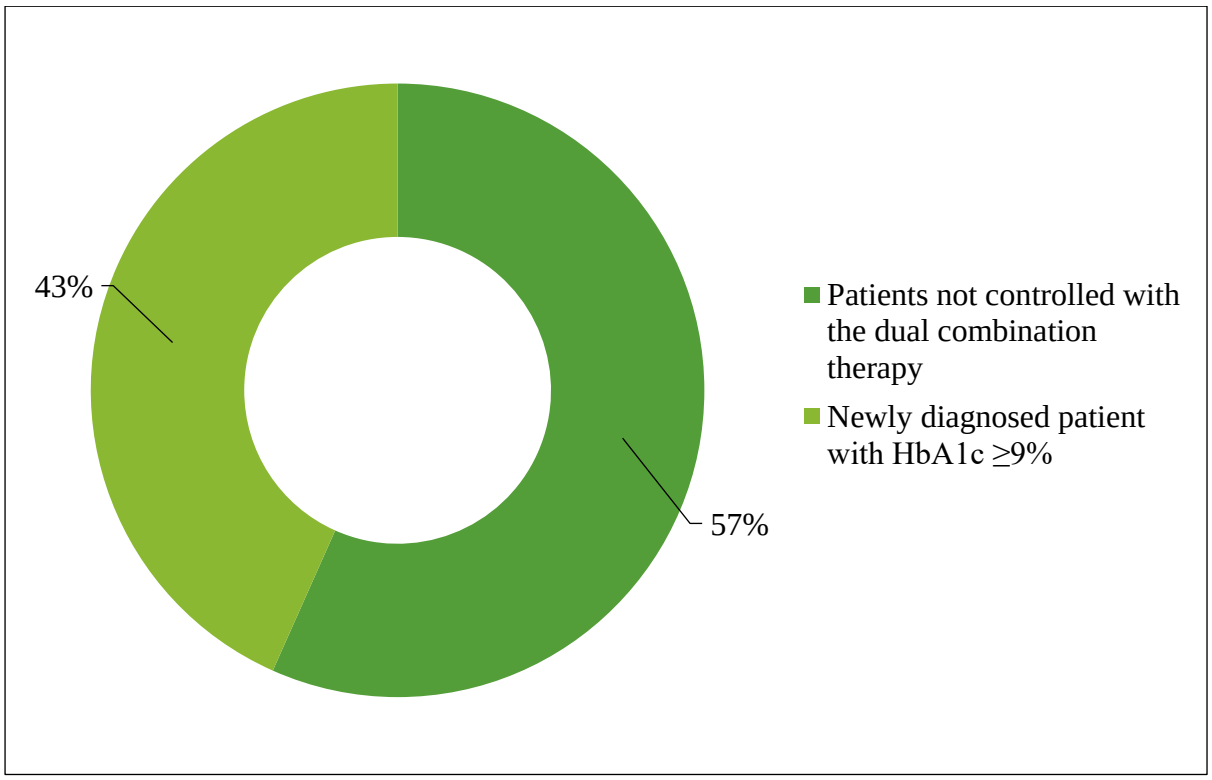


A majority of doctors, 92%, mentioned that they frequently preferred to prescribe the Combination therapy in patients with T2DM.

3. In which patient profile do you consider the triple combination therapy? (Can mark more than 1 option, if required)

a. Patients not controlled with the dual combination therapy

b. Newly diagnosed patient with HbA1c ≥9%

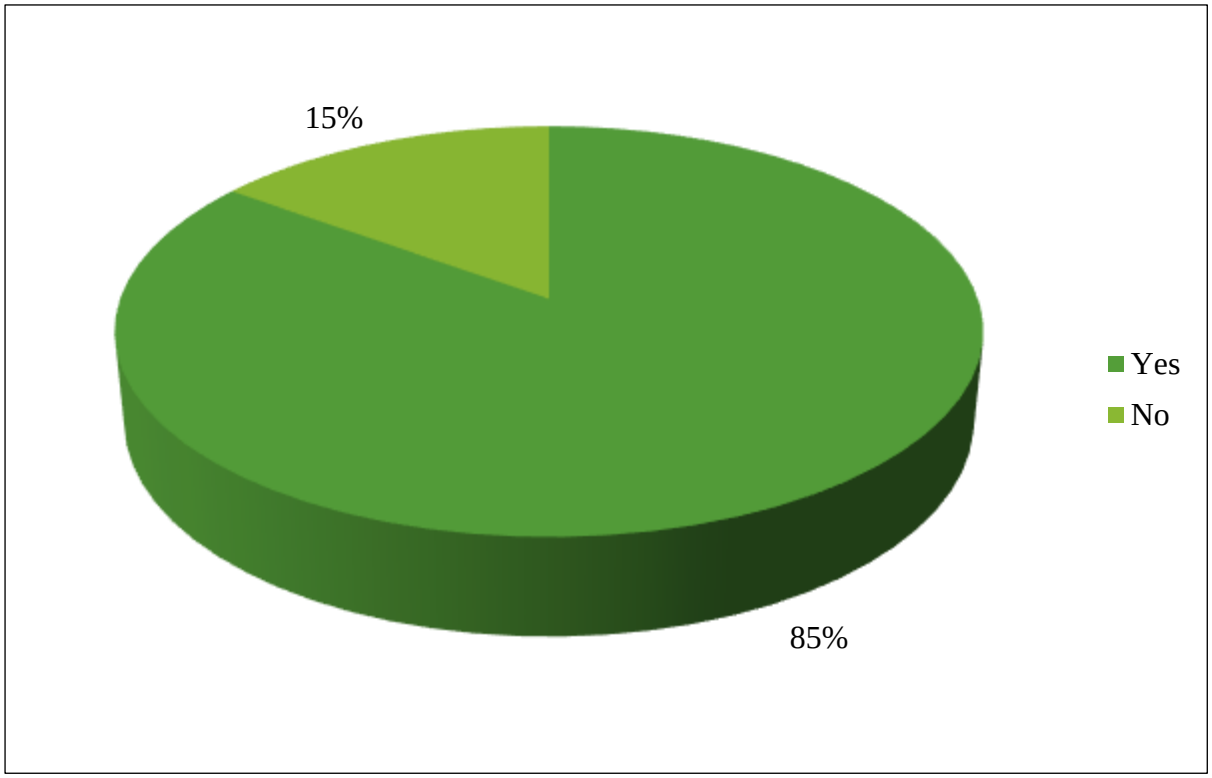


As per 57% of doctors, the triple combination therapy is considered in patients who are not controlled with dual combination therapy.

4. Do you concomitantly prescribe Sitagliptin with Glimepiride and Metformin?

a. Yes

b. No

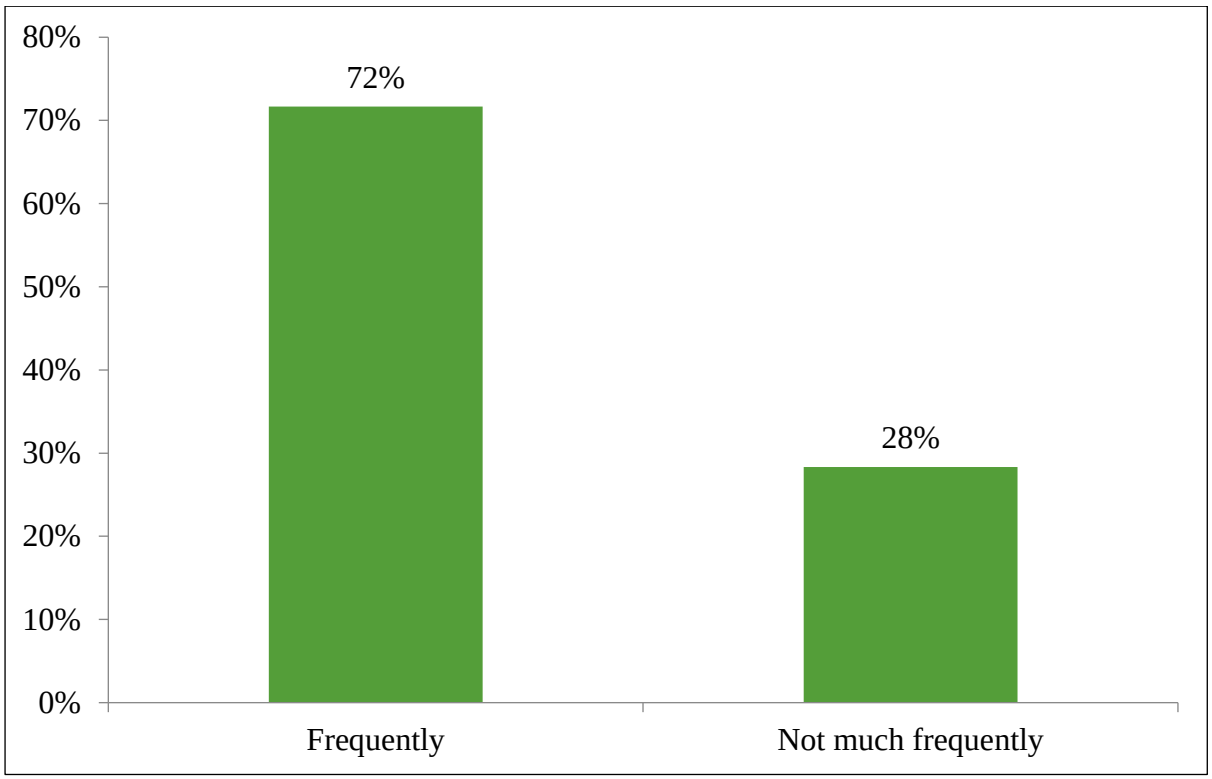


Around 85% of doctors concomitantly prescribe Sitagliptin with Glimepiride and Metformin.

5. How often do you prefer Sitagliptin concomitantly with Glimepiride and Metformin in patients with type 2 DM?

a. Frequently

b. Not much frequently



As per 72% of doctors, Sitagliptin concomitantly with Glimepiride and Metformin in patients with T2DM is frequently preferred.

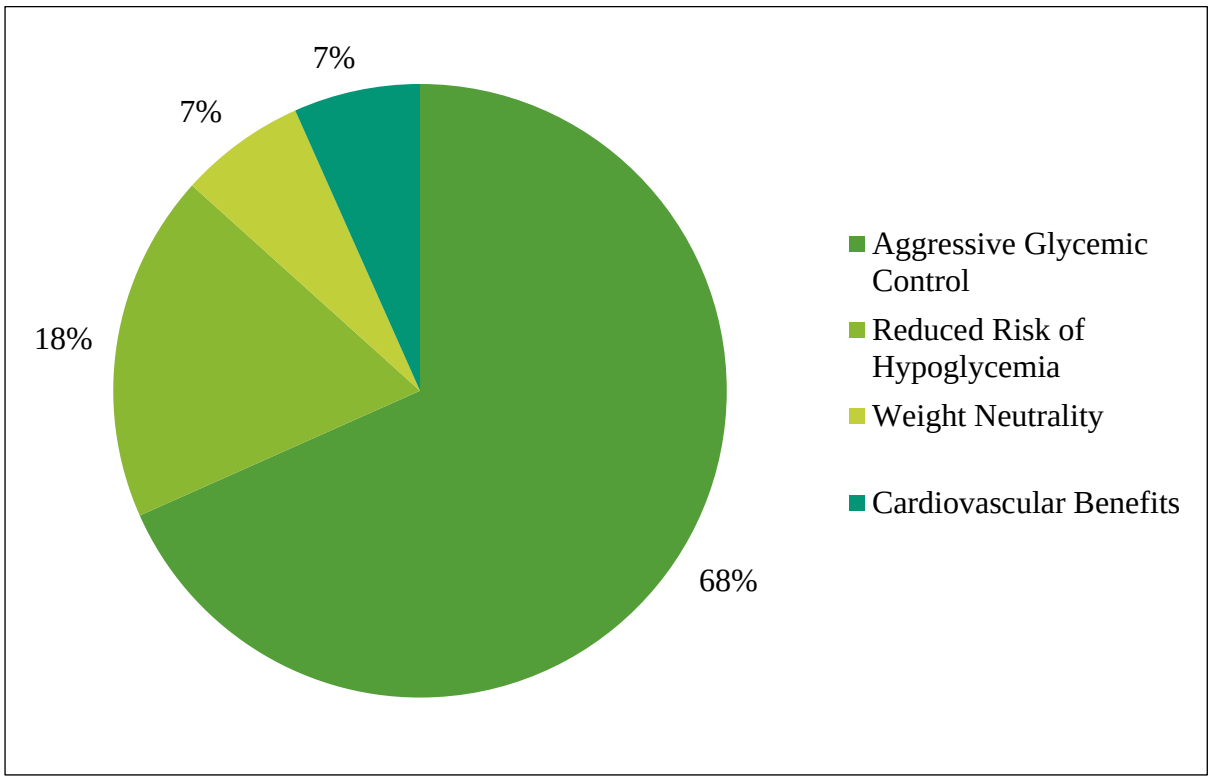
6. What will be advantage(s) of concomitant prescription of Sitagliptin + Glimepiride + Metformin?

a. Aggressive glycemic control

b. Reduced risk of hypoglycemia

c. Weight neutrality

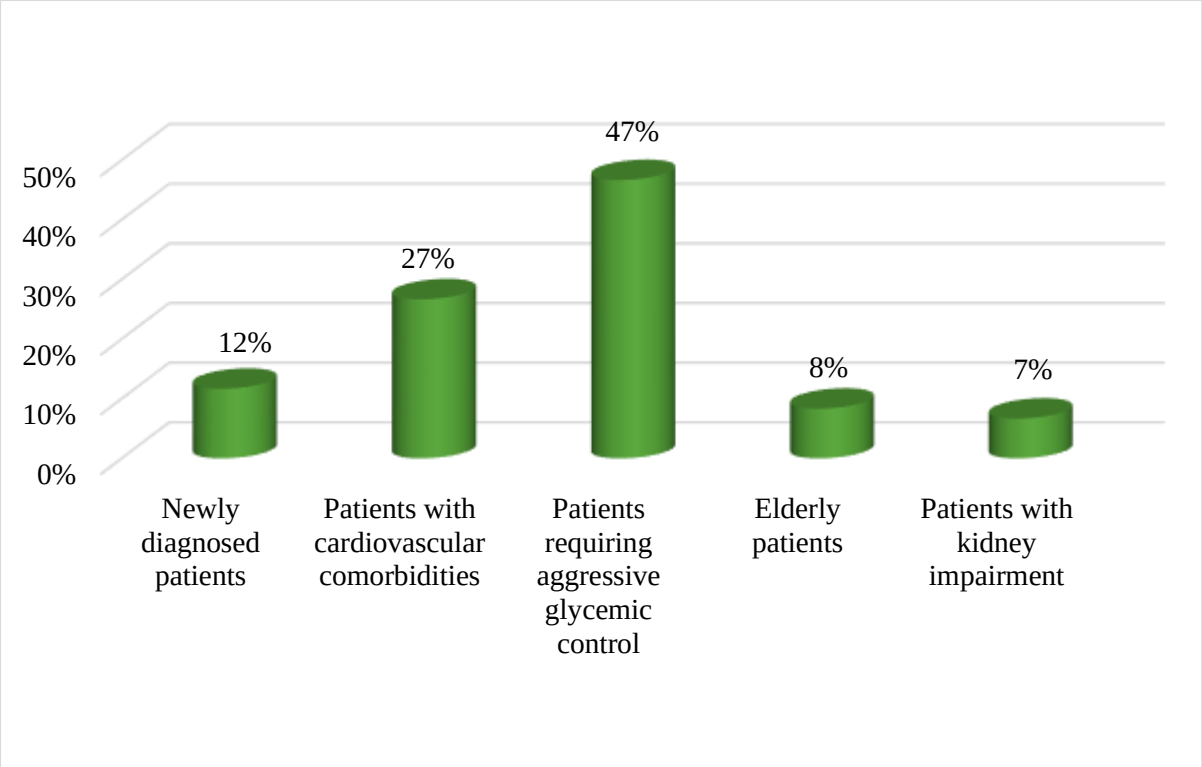
d. Cardiovascular benefits



According to 68% of doctors, the advantage of concomitant prescription of Sitagliptin + Glimepiride + Metformin is aggressive glycemic control.

7. In your clinical practice, which patient profile benefits the most from administration of Sitagliptin concomitantly with Metformin and Glimepiride in diabetes management?

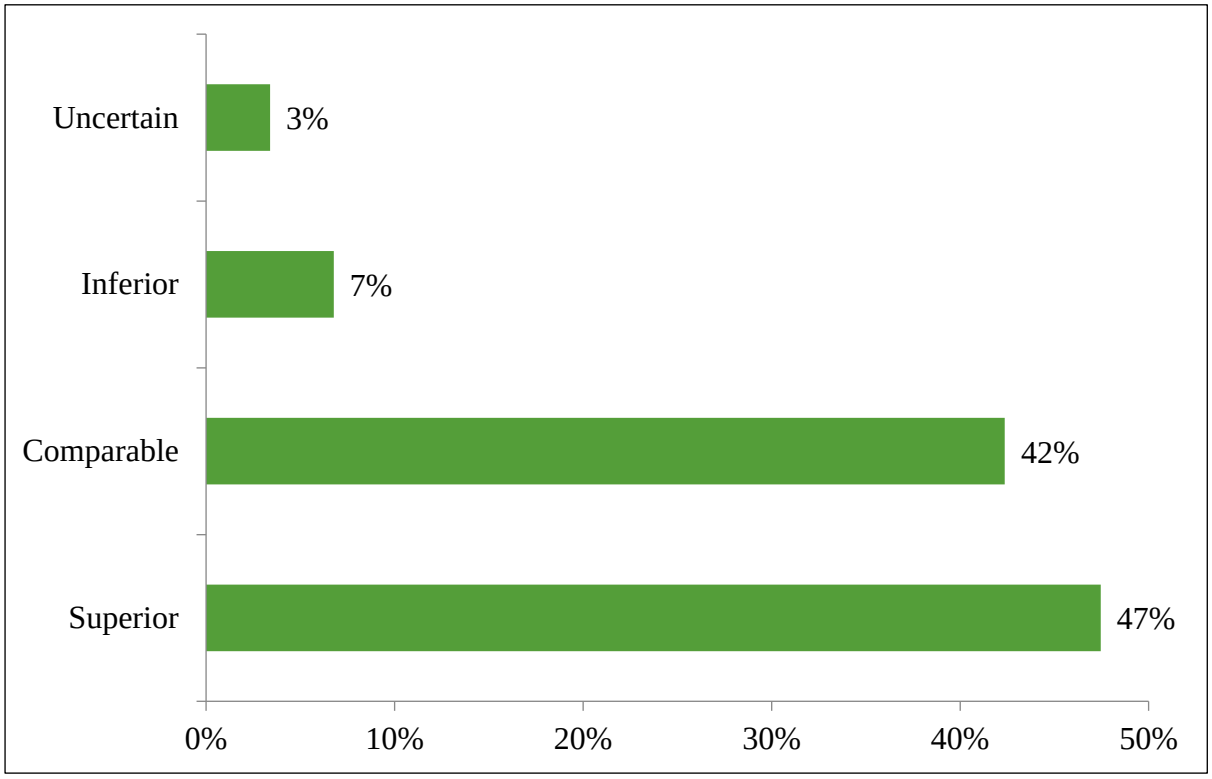
a. Newly diagnosed patients
b. Patients with cardiovascular comorbidities
c. Patients requiring aggressive glycemic control
d. Elderly patients
e. Patients with kidney impairment



Around 47% of doctors reported that patients requiring aggressive glycemic control benefit the most from the administration of Sitagliptin concomitantly with Metformin and Glimepiride in diabetes management.

8. **How do you perceive the efficacy of administering Sitagliptin concomitantly with Metformin and Glimepiride compared to other available conventional Oral Antidiabetic Drugs (OADs)?**

a. Superior
b. Comparable
c. Inferior
d. Uncertain

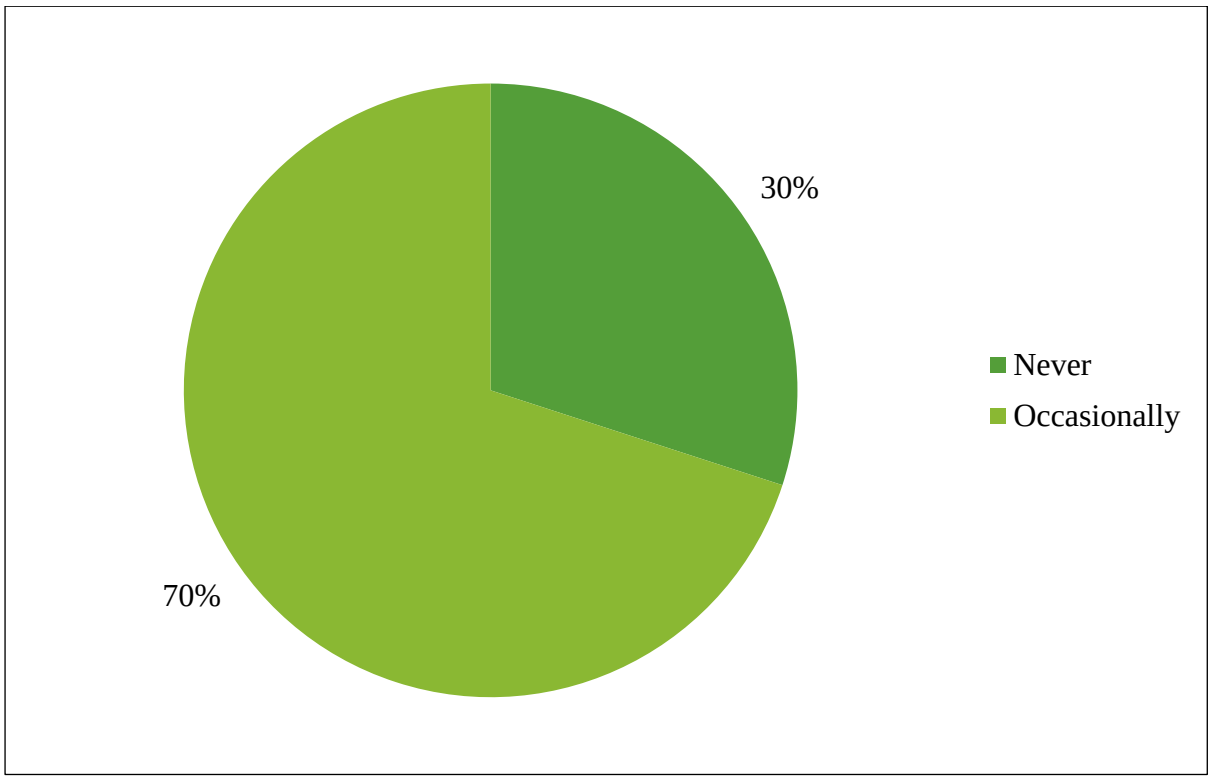


According to 47% of doctors, administering Sitagliptin concomitantly with Metformin and Glimepiride is perceived as superior in efficacy compared to other available conventional OADs.

9. In your experience, how often do you observe hypoglycaemic events in patients administered with Sitagliptin concomitantly with Metformin and Glimepiride?

a. Never

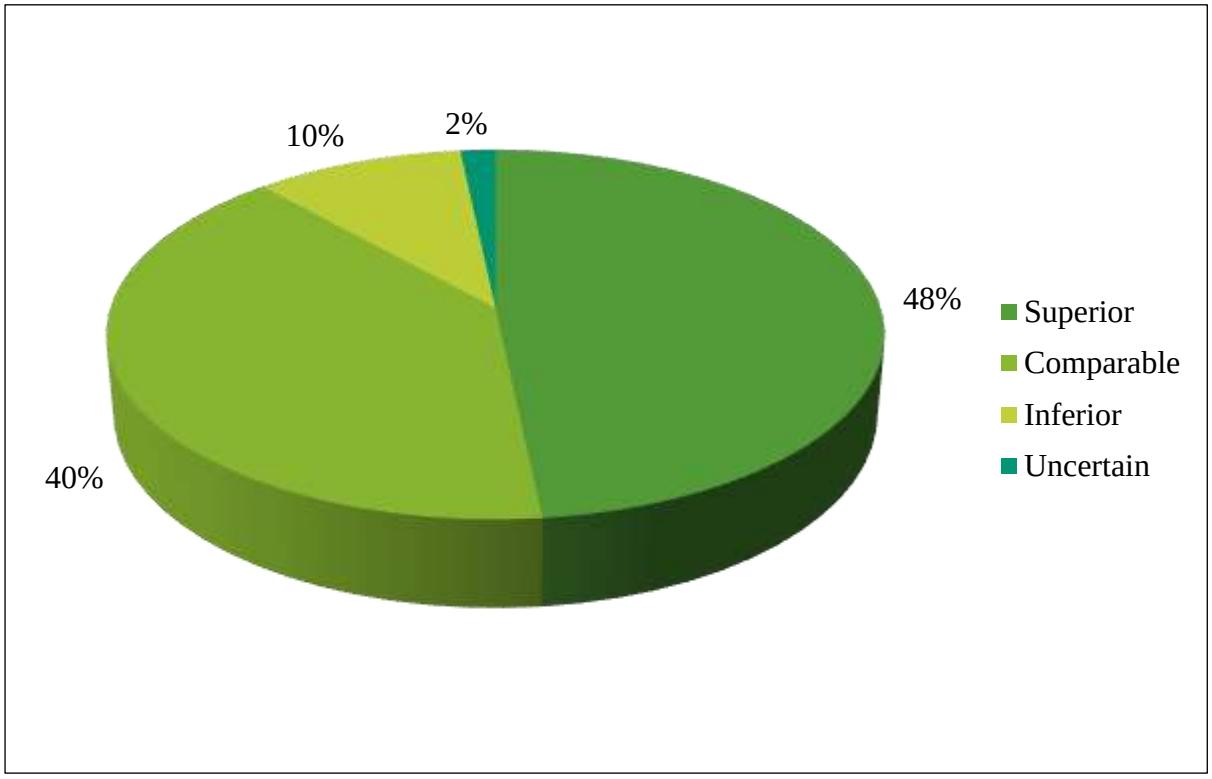
b. Occasionally



As per 70% of doctors, hypoglycemic events are observed occasionally in patients administered with Sitagliptin concomitantly with Metformin and Glimepiride.

10. How do you perceive the long-term safety profile of administering Sitagliptin concomitantly with Metformin and Glimepiride as compared to other available triple combination therapies (conventional) for diabetes management?

a. Superior
b. Comparable
c. Inferior
d. Uncertain



According to 48% of doctors perceive the long-term safety profile of administering Sitagliptin concomitantly with Metformin and Glimepiride as superior compared to other available triple combination therapies (conventional) for diabetes management.

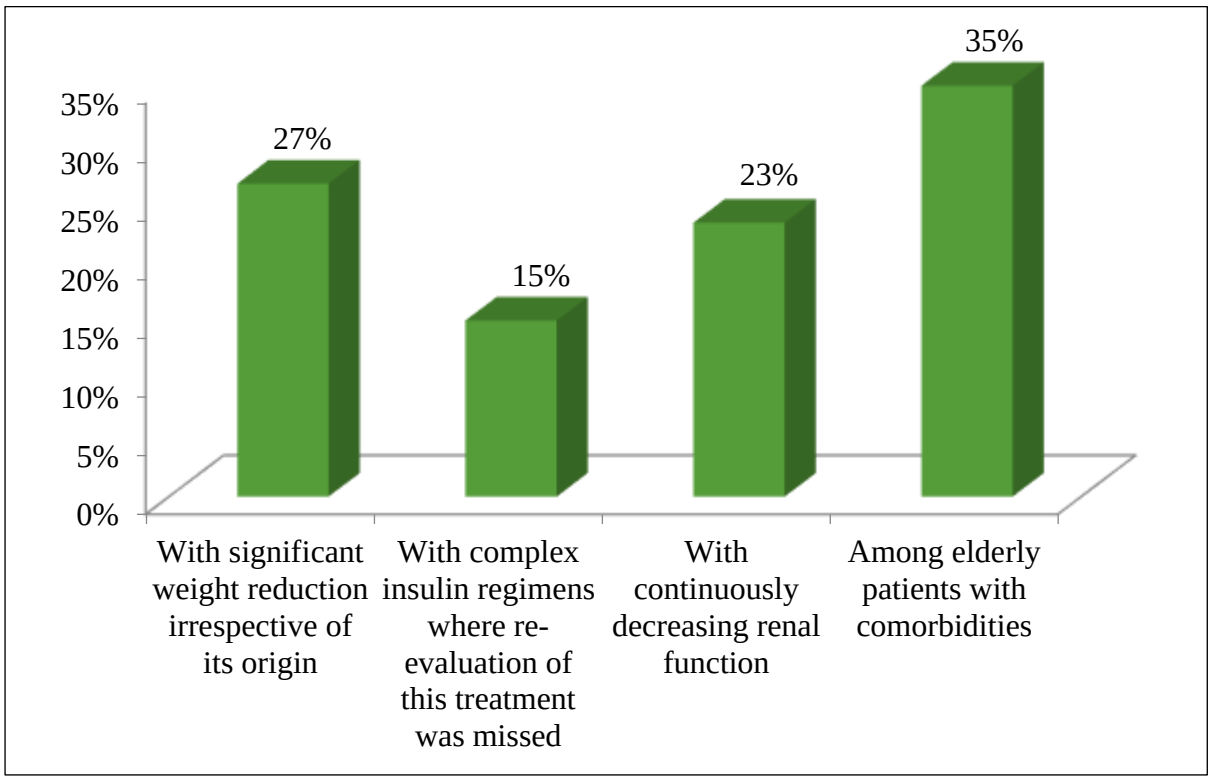
11. In your current clinical practice, in which T2DM cases do you consider to step-down in antihyperglycemic treatment? (Can mark more than 1 option, if required)

a. With significant weight reduction irrespective of its origin

b. With complex insulin regimens where re-evaluation of this treatment was missed

c. With continuously decreasing renal function

d. Among elderly patients with comorbidities

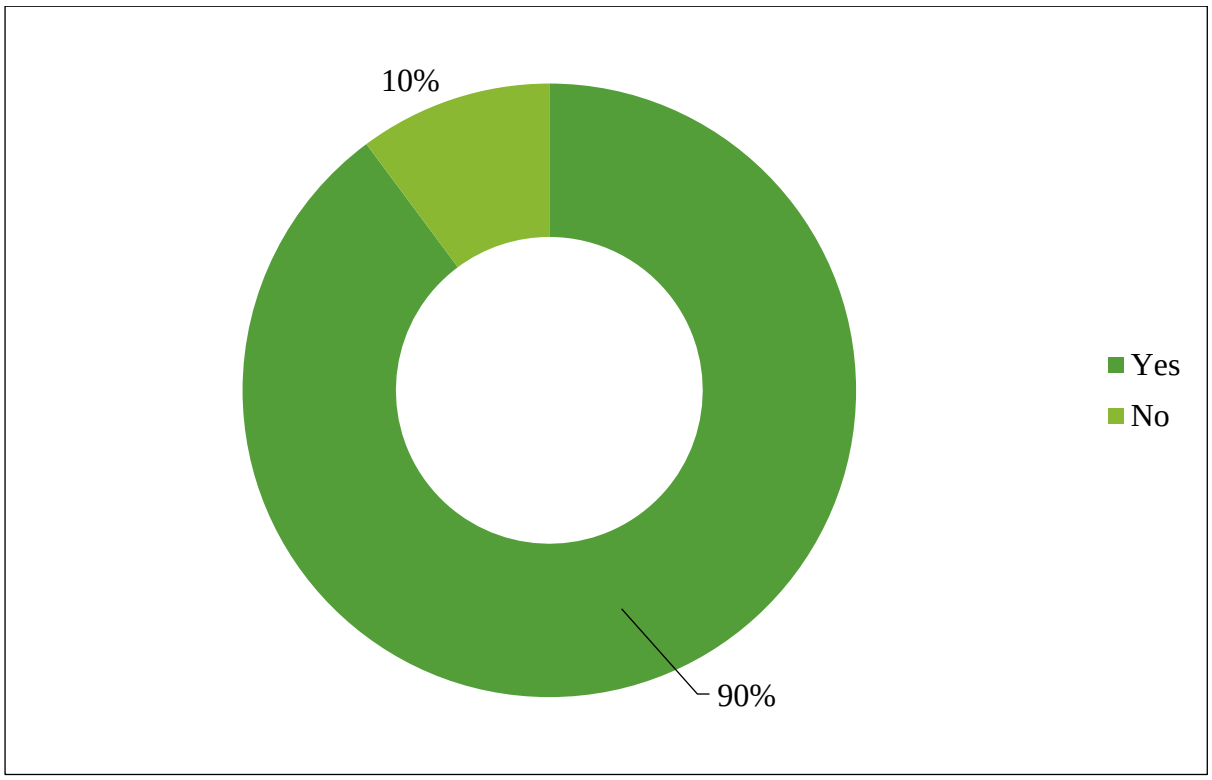


As per 35% of doctors, stepping down in antihyperglycemic treatment is considered among elderly patients with comorbidities.

12. In your clinical practice, in T2DM management with step-down approach will you prefer to use Sitagliptin concomitantly with Metformin and Glimepiride?

a. Yes

b. No



A majority of 90% of doctors prefer to use Sitagliptin concomitantly with Metformin and Glimepiride in T2DM management with a step-down approach.

Summary

- According to 42% of doctors, the unmet medical need that needs to be addressed within current T2DM management is treatment to achieve aggressive glycemic control.
- A majority of doctors, 92%, mentioned that they frequently preferred to prescribe the Combination therapy in patients with T2DM.
- As per 57% of doctors, the triple combination therapy is considered in patients who are not controlled with dual combination therapy.
- Around 85% of doctors concomitantly prescribe Sitagliptin with Glimepiride and Metformin.
- As per 72% of doctors, Sitagliptin concomitantly with Glimepiride and Metformin in patients with T2DM is frequently preferred.
- According to 68% of doctors, the advantage of concomitant prescription of Sitagliptin + Glimepiride + Metformin is aggressive glycemic control.
- Around 47% of doctors reported that patients requiring aggressive glycemic control benefit the most from the administration of Sitagliptin concomitantly with Metformin and Glimepiride in diabetes management.
- According to 47% of doctors, administering Sitagliptin concomitantly with Metformin and Glimepiride is perceived as superior in efficacy compared to other available conventional OADs.
- As per 70% of doctors, hypoglycemic events are observed occasionally in patients administered with Sitagliptin concomitantly with Metformin and Glimepiride.
- According to 48% of doctors perceive the long-term safety profile of administering Sitagliptin concomitantly with Metformin and Glimepiride as superior compared to other available triple combination therapies (conventional) for diabetes management.
- As per 35% of doctors, stepping down in antihyperglycemic treatment is considered among elderly patients with comorbidities.
- A majority of 90% of doctors prefer to use Sitagliptin concomitantly with Metformin and Glimepiride in T2DM management with a step-down approach.

Consultant Opinion

Market opportunities

The market for pharmacologic interventions to optimize glycemic control in diabetes management, particularly with triple combinations like Sitagliptin, Glimepiride, and Metformin, presents significant opportunities for pharmaceutical companies to develop and market effective treatments.

Value for healthcare professionals

Healthcare professionals recognize the efficacy of triple combinations such as Sitagliptin, Glimepiride, and Metformin in achieving glycemic targets, indicating the value of these medications in clinical practice for diabetes management.

Adverse effect management

Considering the usual dose preferences and duration of therapy with triple combinations like Sitagliptin, Glimepiride, and Metformin, there may be opportunities for pharmaceutical companies to focus on minimizing adverse effects associated with long-term use, such as hypoglycemia, weight gain, and gastrointestinal discomfort.

Withdrawal management

The usual duration of therapy with triple combinations like Sitagliptin, Glimepiride, and Metformin in patients with stable diabetes suggests the need for strategies to manage withdrawal and transition to alternative treatments when necessary, ensuring continuity of care and optimal patient outcomes.

Market positioning

Pharmaceutical companies can position triple combinations like Sitagliptin, Glimepiride, and Metformin as preferred options for glycemic control in diabetes management, highlighting their efficacy, tolerability, and potential benefits in patients with varying treatment needs and comorbidities.

Personalized treatment decisions

The preference for specific triple combinations and the consideration of clinical benefits in patients with diabetes underscore the importance of personalized treatment decisions tailored to individual patient characteristics and needs.

Improving patient outcomes

Continued research and development efforts focusing on optimizing dosing regimens, improving efficacy, and minimizing adverse effects of triple combinations like Sitagliptin, Glimepiride, and Metformin can contribute to better patient outcomes and overall management of diabetes. Additionally, education initiatives targeting healthcare professionals can enhance awareness and understanding of the clinical benefits of these combinations in diabetes management.

In summary, the analysis highlights the potential role of triple combinations like Sitagliptin, Glimepiride, and Metformin in optimizing glycemic control in diabetes management. Pharmaceutical companies can leverage this opportunity by developing and marketing innovative treatments that address the specific needs and preferences of healthcare professionals and patients, ultimately improving patient care and outcomes in the management of diabetes in the current era.

Notes

Notes

Notes

For the use or a Registered Medical Practitioner or a Hospital or a Laboratory only

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